Beans, roots and leaves

A History of the Chemical Therapy of Parkinsonism

by

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Irrtum verläßt uns nie,
doch zieht ein höheres Bedürfnis
immer den strebenden Geist
leise zur Wahrheit hinan.

Johann Wolfgang von Goethe
(Vier Jahreszeiten: Sommer)
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Gutachter: Professor Dr. Dr. Gundolf Keil
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Foreword

The subject of the current work is the history of the chemical and pharmacological treatment of parkinsonism until 1980. Several choices have been consciously made in the delineation of the scope and nature of this work. Firstly, I have restricted my discussion to chemical therapy on the grounds that inclusion of surgical, physical, psychological-psychiatric and other approaches would have involved an intolerable expansion of an already lengthy treatise. Such therapies have been considered briefly in the appropriate places, but could not be discussed here in detail. Secondly, the arbitrary limit of 1980 as the end of the history was selected for two reasons. Most importantly, the significance of innovations and discoveries made during this period cannot yet be judged; they do not yet belong not to ‘history’, and as such could not be validly considered here without reducing the end of the book to an extended review article. Almost as important is the fact that developments in the process of pharmacological and neurochemical investigation have led to an enormous increase in the amount of published material in these areas; to have consulted and assessed all this material could not have been achieved in a reasonable time frame. For similar reasons, animal experiments are only discussed where they were directly invoked by contemporary workers in conjunction with the practical therapy of parkinsonism. Thirdly, I have not discussed in detail the history of ideas relating to what actually constitutes ‘parkinsonism’ or ‘Parkinson’s disease’; this issue has already been investigated in detail by others (especially Keppel Hesselink), and there was no point in increasing the size of my manuscript by repeating what had already been published.

What I present here is thus the story of the chemical therapy of parkinsonism as it was actually practised. My aim is to demonstrate that, while previous therapeutic approaches may today appear questionable or even ludicrous, the treatment of parkinsonism since 1817 has been anything but an ‘irrational’ or haphazard affair. It was shaped by the desperation of those confronted by a disorder whose primary symptoms – rigidity and tremor – were unexpectedly difficult to alleviate, let alone to explain. I wish to present the reasons behind the therapeutic choices made, describe the degree of success which rewarded these efforts in each case, and to discuss reasons for this success and to explain the promising failures. My initial interest concerned only L-DOPA therapy, especially as most articles on the history of antiparkinsonian therapy paint a picture of despair for the period before 1968 with regard to this subject. My intention to append a short chapter to the beginning of the L-DOPA therapy, briefly recounting the pre-1960s ‘dark ages’ of antiparkinsonian therapy, foundered, however, on the discovery that contemporary neurologists and other physicians did not regard themselves as living in a ‘dark age’. Indeed, reports describing the benefits of scopolamine, stramonium, harmine, the Bulgarian treatment, benzhexol or any of a number of other substances rival the early reports on L-DOPA for exuberance and confidence. The history of antiparkinsonian therapy, not previously described in its entirety in detail, was clearly more than a long vale of tears, even if each new hope gradually gave way to more sober views and, in many cases, to disappointment. ‘Rational’ approaches to the design of specific antiparkinsonian drugs in the 1950s were ultimately superseded as the result of an unexpected paradigm shift not only with regard to parkinsonism but also the mechanisms of brain function and its modulation in general. Nonetheless, the efforts and achievements of the pre-L-DOPA era were anything but minor, especially in light of the fact that the physician who cared for his
patient, lacking in many cases a secure theoretical foundation for his treatment options, was entirely dependent on his own observational skills and those of his colleagues and staff.

I have attempted to describe the history of antiparkinsonian therapy in the context of developments in both laboratory and clinical pharmacology. These developments, however, could only be discussed with respect to their impact on the principle subject of my manuscript; to while consideration of the impact of these developments on antiparkinsonian therapies is appropriate here, their detailed exploration would have increased the mass of the work intolerably. I have also provided biographical sketches of many of the participants in this history in order to underscore the fact that medical research and scientific investigation in general is conducted by human beings with idiosyncratic strengths, weaknesses and approaches to their work. Some advances were subsequently forgotten, or at least remained largely unknown outside their country or field of origin, and required re-discovery; in other cases, the same insight emerged in two or more places simultaneously. Progress has thus been achieved by varying combinations of the conditions regarding medical knowledge and philosophy which prevailed at any particular time; the insights, discoveries and curiosity of individual investigators; and blind luck. For this reason, broad based fundamental scientific research is the key to advances in medical research, not narrowly focused industry-driven projects.
Explanatory notes

1. Pharmaceutical preparations

In the first sections of the work, a number of different pharmaceutical preparations of vegetable material are mentioned. The most important are defined here for purposes of clarity.¹

Decocta (Decoctions): the plant material is boiled in water, normally for from five to twenty minutes, in order to liberate constituents not separable at a lower temperature. Decoctions were unstable and needed to be prepared immediately before use.

Emplastra (Plasters): pasty preparation on the plant based on litharge (a lead oxide) and oleic, margaric and stearic acids, stored in rolls and applied directly to the skin. They served either the external administration of an agent or the stimulation of blister formation. One of the most important was the emplastrum belladonnae, prepared from the plant extract.

Extracta (Extracts): prepared from a particular part of the plant (root, leaves, flowers, bark, etc.). After preliminary mechanical preparation (such as crushing, bruising), the extraction could be conducted by any of several means:

- **fresh or green extract**: simple squeezing out of the juice followed by evaporation.
- **aqueous extract**: maceration in cold or decoction, infusion or digestion in boiling distilled water; recovery via pressure or displacement.
- **alcoholic extract**: maceration in rectified, proof or dilute alcohol, followed by recovery by press or percolation and distillation.
- **ethereal extract**.
- **acetic extract**.

The extraction itself was a simple process; the recovery of an active ("uninjured") extract was more difficult and demanded the skill and patience of the apothecary, and, apart from the quality of the initial plant material, was the greatest source in the variability in the final product.

Infusa (Infusions): similar to decoction, but without boiling. This was preferred where the active principles were available at lower temperature, or where preservation of other aspects of the drug, such as aroma, was considered desirable.

Linimenta (Liniments): similar to tinctures, but of greater strength and generally prepared in an oily base in order to allow convenient external application. Linimentum belladonnae, however, relied upon the camphor of the plant itself for its oiliness, and therefore required careful application with a brush or in combination with other liniments in order to avoid injury.

¹ Based principally upon Scoresby-Jackson, 1880, pp. xlvi-xcii.
Explanatory notes

Pilulae (Pills) had long existed, but were an especially favored form of administration from the end of the 19th century.

Succi (Juices): freshly expressed juice of plant, usually of leaves or fresh flowers.

Tincturae (Tinctures): extraction of the active principles in rectified or proof spirit, aromatic spirit of ammonia or spirit of ether. Two processes were employed for this purpose: either the maceration (the older of the two methods) or percolation; it later became normal to combine the two processes. The most common method employed in Britain at the end of the 19th century was as follows:

Macerate for forty-eight hours, with fifteen ounces of the spirit, in a close vessel, agitating occasionally; then transfer to a percolator, and when the fluid ceases to pass, pour into the percolator the remaining five ounces of the spirit. As soon as the percolation is completed, subject the contents of the percolator to pressure, filter the product, mix the liquids, and add sufficient spirit to make one pint.2

Variations on this method continued to be employed until the middle of the 20th century.

Unguenta (Ointments): The British Pharmacopoeia employed this term to indicate an oily or paraffin preparation of a drug used externally, either as vehicle for a potent agent (such as atropia or belladonna) or as an emollient.

2. Weights and measures

In general, I have converted most measurements to their metric equivalents. The following is offered as a guide to the weights and measures employed in most publications until the middle of the 20th century.

1 grain (gr.) = 0.0648 gram
1 ounce (oz.) = 437½ grains = 28.3495 gram
1 pound (lb.) = 16 ounces = 453.5925 gram
1 minim (ml or min.) = 0.059mL
1 fluid drachm (fl. dr.) = 60 minims = 3.549mL
1 fluid ounce (fl. oz.) = 8 fluid drachms = 28.40mL
1 pint (O) = 20 fluid ounces = 567.9mL

These weights and measures, known as the Imperial system, were adopted by the British Pharmacopoeia in 1864 (following the lead of the Dublin College of Physicians),3 and were officially declared as standard for all purposes in the British empire in 1878. It should be noted that the weight system adopted elements of two older systems, the avoirdupois system, based on the ounce and pound, and the troy or apothecaries’ systems, based on the grain and ounce. For completeness, the apothecaries’ system, which can be traced back to the Salerno medical school in the 12th century, is also summarized here:

3 British Pharmacopoeia, 1864, xvi-xix. It was also at this time that the Pharmacopoeia adopted the chemical symbols for denoting compounds.
Explanatory notes

1 grain (gr.)
1 ounce (3) = 480 grains
1 pound (lb) = 12 ounces

3. Writing conventions

I have attempted to make the work readable, in some cases departing from conventions for biological works. Firstly, I have employed footnotes liberally in the manner of a historical work, not only to remove the names of cited authors from the text itself (while retaining their proximity), but also to add details which would otherwise interrupt the flow of the story. These details include, for example, the chemical names for the drugs discussed in the second and third parts. Footnotes are also employed to accommodate brief biographical sketches of the more important persons in the story. A history such of this should also convey the fact that the history of neither medicine nor science is populated by white-coated monomaniacs, but is rather filled with the same vast array of characters and events as political or cultural history. While these details are not always indispensible to advancement of the narrative, I felt that the whole would the weaker for their absence.

I have not employed the registered trademark sign (®) in this work for the simple reason that it was not always clear which brand-names were actually registered marks and which not, especially for drugs marketed before 1970. Rather than risk the implication that a particular name was not protected or to use the sign inappropriately, I have simply enclosed all brand-names in single quotation marks (for example, ‘Artane’). In any case, I have generally employed the generic name for a substance, except where it was being introduced for the first time. Patent information was generally derived from the Merck Index, Chemical Abstracts and Kleeman et al. (1999).

All translations were made by the author except where otherwise noted; for Italian and French papers, the assistance of computer translation programs was employed.
I. Parkinsonism before Parkinson

Parkinson indicated in the pamphlet on the disorder named for him that he was by no means describing a new disease, but rather one which had until his time been comparatively neglected. Nevertheless, the question of the existence of parkinsonism before 1817 has often since been posed, and not only out of idle curiosity. The major factor which has impeded the development of an effective therapy for parkinsonism has been ignorance of its etiology. It is therefore of importance to know whether parkinsonism has long been one of the problems associated with ageing, or whether it emerged only recently with the development of specific environmental, nutritional or social conditions. What appears to be clear is that parkinsonism is a purely human disorder, or at least restricted to the higher primates; it has proved very difficult to produce convincing models of the disorder in lower mammals. The disease appears to be geographically widely distributed, so that it would appear unlikely that any single causative agent will suffice as an explanation for all cases of parkinsonism. But the temporal distribution of the disease in history is also important, as it might relate the disorder to a particular set of conditions with respect to climate, other disorders or social and industrial development. This issue was involved in the once broadly held view that mid-20th century parkinsonism was almost entirely attributable to encephalitis epidemica immediately after the First World War, and should thus be fairly extinct by the 1970s. This view was supported by the fact that many authorities before the encephalitis epidemic had described paralysis agitans as a rare disease, and that many of the cases described in the literature could be ascribed with hindsight to various known causes – carbon monoxide or manganese toxicity, trauma to the basal ganglia, arteriosclerosis – excluding them from the category of “true” paralysis agitans, while other cases clearly involved quite distinct disorders, such as multiple sclerosis and essential tremor. That Parkinson’s disease has not disappeared is thus both tragic and significant. It should also be noted that it cannot be supposed without further ado that the viral epidemic leading to post-encephalitic parkinsonism was either the first or the last incidence of such a disaster, so that some knowledge of the frequency and patterns of such epidemics is of more than academic interest.
There is a great deal of tantalizing evidence suggesting the existence of Parkinson’s disease before Parkinson, and, indeed, that it existed whenever life expectancy allowed its presentation. John Aubrey actually used the term “shaking Palsey” in his description of the progressive disability which afflicted the philosopher Thomas Hobbes (1588-1679) during the last thirty years of his life:

He had the shaking Palsey in his handes; which began in France before the year 1650, and has growne upon him by degrees, ever since, so that he has not been able to write very legibly since 1655 or 1666 . . . Mr Hobbs wase for several yeares before he died so Paralyticall that he wase scarce able to write his name.1

The famous case of Lord L. reported by John Hunter in his Croonian lecture of 1776 is also quite reminiscent of paralysis agitans:

Lord L’s hands are almost perpetually in motion, and he never feels the sensation in them of being tired. When he is asleep his hands, &c., are perfectly at rest; but when he wakes in a little time they begin to move.2

But hints that parkinsonism is not only a recent scourge are also found in ancient medical texts. A disorder known as ‘Kampavata’ was described in Indian medical texts dating back to at least the end of the second millennium B.C.; this disorder, which resembles parkinsonism in many respects, will be discussed below, as not only the disorder but the therapy is of particular interest in light of recent developments. Often cited as a possible reference to parkinsonism is the following depiction of old age in the Old Testament:

Remember your Creator in the days of your youth, before the evil days come, And the years approach of which you will say, I have no pleasure in them; . . . When the guardians of the house tremble, and the strong men are bent, . . . When one waits for the chirp of a bird, but all the daughters of song are suppressed; And one fears heights, and perils in the street; . . . the locust grows sluggish . . .3

The woman who “for eighteen years had been crippled by a spirit . . . bent and completely incapable of standing erect” (Luke 13:11) has also been interpreted by some as a victim of parkinsonism.4 On the other hand, an otherwise comprehensive catalog of the afflictions of old age in a Chinese medical text attributed to Huang Ti Nei Ching Su Wên (supposed to have lived 2697-2597 B.C.) omits reference to motor dysfunction:

When a man grows old his bones become dry and brittle like straw, his flesh sags and there is much air within his thorax, and pains within his stomach; there is an uncomfortable feeling within his heart, the nape of his neck and the top of his shoulders (are contracted), his body burns with fever, his bones are stripped and laid bare of flesh, and his eyes bulge and sag.5

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1 Cited in Freedman, 1989.
2 Cited in Currier (1996), who noted that Parkinson may have attended this lecture.
3 Ecclesiastes 12: 1-5. Senior et al. (1990), the editors of the version cited here, interpret “guardians of the house” as ‘arms’, “the strong men” as legs, “daughters of song” as the voice and “the locust grows sluggish” as a metaphor for creeping stiffness, although akinesia could also be read into the phrase.
4 Gillingham, 1975. The woman is described as follows in the Vulgate: “et ecce mulier quae habebat spiritum infirmitates annis decem et octo et erat inclinata nec omnino poterat sursum respicere.” The passage, however, included no useful information on therapy.
5 Huang Ti Nei Ching Su Wên, 1966, pp.182. This master was quite merciless in his depiction of the decline of life; the editor of the translation from which I have cited summarized the fate of a man thus:
In the *Iliad*, the current version of which was probably prepared in the eighth century B.C., the septuagenarian King Nestor remarks that, despite the fact he still partakes of the armed struggle, he can no longer compete in athletic contests:

> my limbs are no longer steady, my friend, nor my feet, neither do my arms, as they once did, swing light from my shoulders.\(^6\)

Hippocrates recognized that certain disorders were peculiar to the aged, or were at least more common in older persons. This he attributed, according to his humoral pathology, to a decline in the essential internal heat with aging. But there is a certain problem which concerns the interpretation of Greek and Roman medical texts with respect to looking for occurrences of parkinsonism. Parkinson’s breakthrough was not to discover a new disorder, but to define one which already existed. It has often occurred in the history of medicine that certain diseases have not been distinguished from one another; this was necessarily the case for the greater part of history, as disorders were defined according to their symptoms, not according to their etiology. A recent example of discrete disorders being regarded as variations of a single disease would be typhus (caused by *Rickettsia prowazekii*) and typhoid fever (caused by *Salmonella typhus*), defined as separate clinical entities only at the end of the 19th century. A more pertinent example is the confusion of paralysis agitans and multiple sclerosis into the early 20th century.

The relevance of this problem at this point is that the ancient authors spoke of two related disorders, κάτοχη and κατάληψις, the descriptions of which included features which could be identified with any of a number of modern clinical entities, including parkinsonism. As the present work is concerned with the therapy of parkinsonism, I will not discuss here these ancient disorders at length, but not only that tremor and rigidity were associated with these disorders. Even more interesting is the fact that later Roman authorities and, to a certain extent, the Hippocratic texts associate such disorders with febrile illnesses, often of an epidemic nature, which initially caused great somnolence in the sufferers; *katalepsis* was the condition which ensued in those patients who survived the initial crisis but did not fully recover their health. The resemblance to encephalitis lethargica is enticing, but discussion of this issue must be reserved for a later date.\(^7\)

The Latin author Aurelius Cornelius Celsus (ca 25 B.C.-ca A.D. 50) was the first ancient author to devote much specific attention to diseases of the aged, and also provided advice on their treatment. He advised against administering those who suffered tremor of the sinews (τρόμως) with emetics or drugs which promoted urination, and also against baths and dry sweating; relief from worry, rubbing of the limbs and their exercise by ball games and walking were indicated. The patient could eat whatever he wanted, but sexual activity should be restricted; if he should succumb, he should afterwards be rubbed in bed with olive oil, by boys, not men.\(^8\) This discussion of “tremor of the sinews” follows a longer discourse on “relaxing of the sinews” (resolutio nervorum), which he notes by called *apoplexia* by Hippocrates, but was now

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\(^6\) *Iliad*, XXIII 627-628.  
\(^7\) See discussion in Baumann, 1938; Siegel, 1973, pp.258-262.  
\(^8\) *De medicina*, III, 27.3.
designated *paralysis*. While loss of tone seems unlikely to refer to parkinsonism, the following passage is nonetheless interesting:

Those who are gravely paralyzed in all their limbs are as a rule quickly carried off, but if not so carried off, some may live a long while, yet rarely however regain health. Mostly they drag out a miserable existence, their memory lost also.\(^9\)

The treatment in this case was blood-letting, which was expected to either kill or cure; if neither of these outcomes occurred, the case was hopeless anyway. Where only one limb was affected, some benefit could be achieved by being “carried about in a litter or rocked in his bed”, reminiscent of Charcot’s *chaise trépidante*. The limb should be exercised by the patient himself or by an assistant; it could be further stimulated by whipping with nettles or the application of mustard plasters until the skin reddened. Other options included plucking the skin, applying crushed squills or onions in frankincense and anointing with a mixture of old olive oil, soda mixed with oil and vinegar or sea-water. Natural or artificial baths were also to be recommended.\(^{10}\)

Galen (A.D. 129- c.200) wrote extensively on disorders of motor function, including the book *On tremor, palpitation, convulsion and shivering*.\(^{11}\) In contrast to later writers, Galen did not regard *katoche* as a purely post-febrile disorder, although it could occur subsequent to such an illness. More importantly, Galen distinguished between several forms of shaking of the limb on the basis of both appearance and origin. That which he named τρόµος (Latin: *tremor*) was a rapid vibratory motion in an entire body part which arose through diminution of the power to voluntarily lift and move the part appropriately; this unstable motion resembled in appearance the tremor exhibited by someone who was compelled to lift a weight which exceeded their capacity, or in certain cases of fear or psychic disturbance. It was an involuntary shaking which arose during voluntary motion, and thus bore some relationship to intentional tremor. The aged, noted Galen, exhibited tremor precisely because a similar decline in their power to control motion of their limbs. The key to overcoming *tremor* was to abolish the proximal cause; for the aged, this was somewhat impractical.\(^{12}\) This comparatively fine tremor was distinguished from παλµός (Latin: *palpitatio*), a coarser shaking which was independent of voluntary motion; it thus resembled resting tremor. It could be alleviated by the application of heat and by bloodletting. Finally, σπασµός (Latin: *convulsio*) conveyed the idea of the English word ‘spasm’, while ρίγους (Latin: *rigor*) described the shivering due to coldness, whether environmental or internal. These forms are not related to the symptoms of parkinsonism.\(^{13}\)

Galen later relates in this book that a person suffering from *katoche* regards the physician with wild, wide open eyes which do not shut even as the patient speaks. Further, the sufferer lies rigid and stretched out in bed, as if he himself were made of wood. Tremor, constipation and certain psychiatric symptoms are also part of the

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9. Ibid., III, 27.1.
10. Ibid.
12. Perhaps the most famous Latin quotation regarding ageing is that of Terence in his comedy *Phormio*: “Senectus ipsast morbus” (“Age itself is a disease.”). Seneca remarked similarly in Ep. 108, 28: “senectus enim insanibilis morbus est” (“age is namely an incurable disease”). These citations are often falsely attributed to Cicero; in *De senectute*, on the contrary, he emphasizes the positive aspects of a mature age.
clinical picture. Galen had thus described phenomena which can be related without a
great deal of speculation to parkinsonian symptomatology; he did not offer a great deal
of hope, however, with regard to therapy.\textsuperscript{14}

Caelius Aurelianus (4th or 5th centuries A.D.? ) prepared a work which is principally
the reproduction of the writings of Soranos of Ephesos (end of the 1st-beginning of the
2nd centuries A.D.), \textit{Eight books on the acute and chronic diseases}. He also discussed
the disease which he called \textit{catalepsis}, but which he also knew as \textit{aphonia} and \textit{catoche}.
Caelius made the interesting comment:

\begin{quote}
The ancient physicians did not pass over this disease in silence but easily confused it
with lethargy, as very many do even now. . . . But no one identified this disease as such
until the time of the Methodists. . . . And whoever it was who first gave a separate name
to the disease cannot also be said to have correctly recognized its characteristics.\textsuperscript{15}
\end{quote}

Cognizance of difficulties of clinical definition thus existed at this time. The confusion
with \textit{lethargia} is interesting. The term generally referred to a disorder involving
sleepiness, but the concept varied from author to author; prior to Galen, it was often
used to describe a post-febrile state, while Galen noted that it occurred in the course of
any of a number of disorders, and did not necessarily involve fever. Caelius himself saw
it as a general decline in physiological activity, often accompanied by fever.\textsuperscript{16} Mettler
drew the speculative (but obvious) conclusion that the term referred to encephalitis,
providing another tenuous link to parkinsonism.\textsuperscript{17} Aretaeus of Cappadocia (fl. A.D.150)
had also written of a post-febrile lethargic disorder accompanied by tremor; his
recommendation was to place the patients in sunlight and to ensure that they remained
awake.\textsuperscript{18} An alternative conjecture would be that \textit{lethargia} might refer to the akinesia
and bradyphrenia of the parkinsonian patient. In any case, Caelius’ description of
\textit{catalepsis} includes a number of interesting points:

\begin{quote}
face red, eyes staring without any blinking, hands haphazardly stretched out and cast
about, gnashing of the teeth, twitching of the limbs, convulsive movement of the muscles
controlling the jaws (Greek \textit{siagonitae}), and chill in the extremities, since pneuma has
entered the veins.\textsuperscript{19}
\end{quote}

\begin{quote}
Inactivity and sluggish motion of the body, absence of complaint about their pains, . . .
a kind of sleep excessively protracted and heavy, and slow response when we address
them. . . . saliva flowing copiously, pulse prominent and full, feces retained or else
poured out in a fluid mass. . . . eyes staring steadily and without motion, as if longing
for something while gazing intently at it . . . And if we move our fingers before their
eyes, they blink and follow the movements of the hand with their gaze.\textsuperscript{20}
\end{quote}

He also makes mention in another section of a case described by the famous
Alexandrian physician Erasistratus:

\begin{quote}
\textit{Erasistratus terms} paradoxos a type of paralysis in which a person walking along must
suddenly stop and cannot go on, but after a while can walk again.\textsuperscript{21}
\end{quote}

\begin{enumerate}
\item Galen (Kühl), 1965, vol. 7, pp.683-686.
\item Caelius, pp.160-161.
\item Ibid., pp.120-121.
\item Mettler, 1947, pp.508-509.
\item Ibid.
\item Ibid., pp.160-163.
\item Ibid., pp.166-169.
\item Ibid., pp.574-575.
\end{enumerate}
This passage also underscores the fact that *paralysis* cannot always be interpreted in its modern sense. Not everything which Caelius describes in relation to *catalepsis* is consistent with parkinsonism; but the caution made above regarding the fact that the author may not have distinguished between apparently related disorders must be heeded, especially as Caelius was essentially listing the descriptions made by a number of separate physicians, leading the author himself to the comment:

*In view of the situation and the diversity of written opinion, it would be wrong to put our reliance on any of these authors.*

It is also interesting that Caelius mentions, in contrast to Galen, that the disorder is not uncommon amongst children, although it is not absolutely clear whether these juvenile cases are associated with febrile disease. Caelius’ therapeutic approach was to have the patient fast, if possible, to apply warmed sweet olive oil to the limbs, head and trunk, and to apply clysters if necessary to evacuate the patient.

It is thus possible that parkinsonism was described ancient authorities; it is not possible, however, to be conclusive at this distance. Siegel has made the interesting suggestion that manganism may have been observed in ancient Rome; manganese was widely used in cosmetics and in glass-making. Therapy of *catoche/catalepsis*, whatever its real identity, was largely physiotherapeutic: massage and exercise of the limbs. I have encountered no clear indication that pharmacological approaches of any sort were broadly employed. The solanaceous plants which would play a great role in antiparkinsonian therapy were certainly known to the ancients, but were not employed in the disorders discussed here. Gaius Plinius Secundus (Pliny the Elder; A.D. 23–79), knew what has been identified as *Atropa belladonna* under several names, including trychno, but dismissed its medical qualities on the basis that “remedies should not be described the use of which involves the danger of a yet more serious evil.” He knew hyoscyamus by the name *apollinaris*; this he also regarded as a dangerous medicine, while noting that it was formerly made into a wine for reducing fever. The seed was generally used, but Pliny was of the opinion that it had “the character of wine, and therefore injures the head and brain.” He approved, however, its application as an emollient to the sinews. A poisonous oil could also be prepared from the seed which was poured in the ear to derange the brain. The mydriatic effects of mandragora are also described. But nowhere in his vast compendium of *materia medica* have I found reference to what might be interpreted as an antiparkinsonian agent. Pliny also gently mocked the fact that the Greeks not only enjoyed eating cabbage, but also applied it in a wide variety of diseases.

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22 Caelius, in fact, understood *paralysis* as a partial or complete loss of function of any body part or organ, whether permanent, intermittent or transitory. He objected to the attempt by some to introduce the term *paraleipsis* to denote complete loss of function, as the concepts implied in the two words differed in degree, not quality; *ibid.*, pp.564-567.


24 Siegel, 1973; p.262. For further information on early neurology, see Creutz, 1934.

25 Pliny, XXI, 180.


27 *Ibid.*, XXII, 124; XXIII, 94.


29 *Ibid.*, XXV, 147-150. Some authorities believe that Pliny’s *mandragora* should also be understood as *Atropa belladonna*.

30 Plinius, XX, 84-89.
I. Parkinsonism before Parkinson

era) mentioned at the head of his entry in *De materia medica* for the common cabbage (*Brassica oleracea*) that:

\[
\text{Being eaten, it helps such as are dull-sighted, and such as are troubled with tremblings; being taken after meate, it doth extinguish the maladies that come of gluttony, and wine.}^{31}
\]

Dioskorides also noted that beaver testes, prepared with vinegar and roses was helpful not only for the “lethargicall” but was:

\[
good also for tremblings & convulsions, & for all ye diseases of the Nerves, being either dranck or anointed on, and generally it hath a warming facultie.\]^{32}

The beaver would remain popular in the treatment of tremor diseases into early modern times, although the secretion of its anal gland (*oleum castoreum*) was more commonly generally employed.

In the early Middle Ages, Paul of Aigina (c.600-650) noted in his work *On trembling* that tremor was characteristic of alcoholism and what Mettler interpreted as “*senile paralysis agitans*”.\]^{33} A medical-botanical glossary in a manuscript dated to the 10th century contains a number of tantalizing entries:

\[
\text{paralisis solutio membrorum et nervorum contracto} \\
\text{rigor extensio nervorum} \\
\text{tetanus nervorum tensio et dolor cervicis} \\
tremolosus paralisis^{34}
\]

Medieval sources also provide a few clearer references to possible antiparkinsonian agents, the most famous being the passage in the *Regimen sanitatis Salernitanum*, the collection of dietary and hygiene rules composed in poetic form in the 12th century:

\[
\text{Why should one die, if one has sage growing in the garden?} \\
\text{Against the power of death there is no medicine from the garden.} \\
\text{But sage soothes the nerves and relieves the hands of tremor,} \\
\text{before its might, sharp fever takes flight.} \\
\text{Sage, castoreum, lavender, cowslip, watercress, tansy:} \\
\text{these make whole paralytic limbs.} \\
\text{Sage the redeemer, nature’s intermediary (Salvia salvatrix, naturae consiliatrix).}^{35}
\]

Sage (*Salvia officinalis*; German *Salbei*) was long highly regarded throughout western Europe in the treatment of nervous disorders. An English proverb advised that “*He that would live for aye/Must eat Sage in May*”, while the third and fourth lines of the cited poem entered French as a saying.\]^{36} The so-called *Salbeitraktat* (*Wazzer der tugent,

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31 Dioscorides II, 146.
32 Dioscorides II, 26.
33 Mettler, 1947, p.533.
34 Goetz, 1888, pp.604-606.
35 Caput LX. Based on text available at http://accademia.home.it/bibvirt/regnmain.html; accessed 10.02.01.
36 Grieve, 1931, p.701.
tranc der jugent = ‘Water of power, drink of youth’), a popular treatise dating back to the 14th century, lists a broad range of benefits conferred by the herb. Amongst the indications for its application were apoplexy (§II, 10), paralysis (§II, 12) and “deterioration of the brain” (§II, 18); it was also reported to have euphoric effects, improve the intelligence and memory and to be anti-manic (§II, 22). Gerard wrote in his Herbal:

Sage is singular good for the head and braine; it quickneth the senses and memory, strengthneth the sinewes, restoreth health to those that have the palsie upon a moist cause, takes away shaking or trembling of the members; and being put up into the nosthrils, it draweth thin flegme out of the head.

The chief constituents of sage leaf are a yellow volatile oil (1-2.5%), resin, tannin, thujone and bitter principles. It was listed in many pharmacopoeias as late as the 20th century; its major use in recent times was as a mouth and throat wash. Sage tea has enjoyed perennial popularity as a calmative in nervous disorders, but also as a stimulant in digestive disorders. It has been employed, as such remedies to be, in a number of other complaints; interestingly, its final official therapeutic classification was as an anti-secretory agent and emmenagogue. With regard to humoral pathology, sage had nothing in common with other plants used in antiparkinsonian therapy; whereas most solanaceous plants were cold in the fourth degree, sage was hot and dry at the lower end of the third degree. Nicolas Culpeper (1616-1654), publisher of another popular herbal, also recommended sage for “sinews, troubled with palsy and cramp”.

Sage was not the first plant mentioned by medieval authorities in connection with tremor. Ibn Sina (Avicenna; 980-1037) discussed the various forms of motor unrest in his chapter on nervous disorders of the Canon of Medicine. The description of tremor is not unexpectedly similar to that of Galen. A range of measures are proposed for its therapy, the approach differing according to the cause of the disorder (cold, over-indulgence in alcohol, humoral imbalance and so on). Bathing in sea-water or in mineral baths (nitrate, arsenic, asphalt, sulphur) was recommended, as was the ever popular evacuation; composite preparations including made from the excretion of the anal gland of the beaver (oleum castoreum) – a common spasmolytic – mixed with honey and cold oil, to which pills formed from rue (Ruta graveolens) and scolopendrium (Scolopendrium vulgare; hart’s tongue). Apart from the baths, I am not aware of these agents being used elsewhere in the treatment of tremor or other disorders related to parkinsonism. A Syrian medical text from the early medieval period lists among its prescriptions for nervous diseases a complex unguent for “pains in the excretory organs and in the joints, and in cases of gout and palsy, and for those who have the tremors, and for all the pains which take place in the nerves”. It consists of no less than thirty-five components, including frankincense, rosemary, several types of

37 Hlawitschka, 1990.
38 Gerard, 1633, p.766. Gerard’s Herbal first appeared in London in 1597, and was basically a translation of a 1583 Latin herbal illustrated with the woodcuts from the 1588 Neuw Kreuterbuch of Tabernaemontanus (1520-1590). Full of errors, it was heavily amended by the apothecary Thomas Johnson and released in 1633; the rushed release of the new edition was provoked by the expected publication of a better herbal by John Parkinson (which did not ultimately appear until 1640). Despite its faults, Gerard’s book was immensely popular; it is still available in reprint today.
40 Gerard, 1633, p.766.
41 Culpeper, p.312.
42 Avicenna, Book III, Fenster II, xi-xii.
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cypress, cardamom, pepper corns, myrrh, mandragora and frogs; it was to rubbed on the paralyzed or rigid limb.\textsuperscript{43}

Two plants were listed beside sage and cabbage in Gerard’s \textit{Herbal} as useful in treating trembling of the sinews were pellitory (\textit{Anacyclus pyrethrum}) and mugwort (\textit{Artemisia vulgaris}; German: \textit{Beifuß}).\textsuperscript{44} Pellitory was used until this century in Britain to promote salivary flow and to relieve toothache; Culpeper regarded it as “\textit{one of the best purges of the brain that grows}”, useful in ague, epilepsy and lethargy.\textsuperscript{45} The presumed active components of the plant, the pyrethrins, are now widely used as insecticides. Mugwort continued to be used for many years both as an emmenagogue and as a nerve tonic in palsy; it was an especially popular folk medicine for the treatment of epilepsy. It had formerly been used as a flavoring in beer before the introduction of hops. Apart from the fact that it contains a volatile oil, acrid resin and tannin, little has been reported of its chemical characteristics.\textsuperscript{46}

Culpeper also recommended cowslips (\textit{Primula veris}):

\begin{quote}
\textit{An ointment being made with them . . . [remedies] all infirmities of the head coming of heat and wind, as vertigo, ephialtes, false apparitions, frenzies, falling sickness, palsies, convulsions, cramps, pains in the nerves; . . . Because they strengthen the brain and nerves, and remedy palsies, the Greeks gave them the name paralysis.}\textsuperscript{47}
\end{quote}

Amongst the author plant remedies recommended by Culpeper for palsy and trembling were bilberries (\textit{Vaccinium myrtillus}), briony (\textit{Bryonia dioica}; called ‘English mandrake’, but not a solanaceous plant) and mistletoe (\textit{Viscum album}).

The 1696 \textit{Pharmacopoeia Londinensis}, a comprehensive catalog of \textit{materia medica} from the animal, vegetable and mineral kingdoms, offered a variety of items useful in the treatment of “palsies”, the “dead palsy”, “convulsions” and “tremblings”. Amongst the recommended vegetable remedies were sage (“\textit{hot and dry in 2°}”),\textsuperscript{48} capers, costus (\textit{Saussurea lappa}; a Kashmiri plant), cowslip (“\textit{herba paralytica}”), marjoram and primrose; the fruit of the linden and black cherry trees; the gum of the spurge (\textit{Euphorbia resinifera}) and the Persian sagapenum (\textit{Ferula persica}); an ointment prepared from garden rue (\textit{Ruta graveolens}); and laudanum (tincture of opium). In addition, mineral (various silver, antimony and copper preparations) and animal remedies (for example, “\textit{oil of winged ants}” and several preparations involving earthworms), as well as the traditional “\textit{Oleum de Castoreo composita}” were listed. Amongst the composite prescriptions recommended by the author, the following was specifically designated “\textit{Unguentum Paralyticum Mynsichti. An Ointment for the Palsy}”:

\begin{quote}
\textit{Take oils of amber rectified, and of Bricks, A.3 jûs. Oils of Juniper, of Myrrh, of Turpentine, A.3 i. Oils of Bays and Spike, Petroleum, A.3 jûs. Oils of Castor and Pepper, A.3 ii. Spiritus paralyticus 3 iv. mix, and boil to the consumption of the spirit; after add plumous Alum prepared 3 i. distilled Oil of Rosemary, Nutmegs, Cloves, Originum,}
\end{quote}

\textsuperscript{43} Budge, 1913, pp.159-160.
\textsuperscript{44} Gerard, 1633, pp.759 and 1104.
\textsuperscript{45} Grieve, 1931, p.621.
\textsuperscript{46} \textit{Ibid.}, pp.556-557.
\textsuperscript{47} Culpeper, p.101. ‘Ephialtes’ are nightmares.
\textsuperscript{48} Salmon, 1696, p.126.
The rationale for this prescription cannot be discussed here. It is also clear that not all palsies were parkinsonism, but, assuming its existence before Parkinson, parkinsonism would be expected to be included amongst the disorders often nominated collectively as ‘palsies, convulsions and tremblings’.

Further evidence for the existence of parkinsonism in early modern times has been found in sources such as Leonardo da Vinci and Shakespeare and in paintings such as Rembrandt’s The Good Samaritan – although such citations are, of course, inconclusive.\(^{50}\) It is also possible to interpret the disorder described by Cheyne in the first part of chapter XII of his The English Malady (1734) as parkinsonian. The subject of his discussion is the vaguely defined “Palsy”, or “Paralytick Symptoms”. It must be remembered that ‘palsy’ is simply the Anglicization of ‘paralysis’, and that this term did not receive its current meaning until the middle of the 19th century. Middleton’s Complete Dictionary of the Arts and Sciences (1780), for example defined ‘palsy’ as:

\[\text{a disease wherein the body, or some of its members, lose their motion, and sometimes their sensation of feeling. The disease is never acute, often tedious, and in old people, almost incurable; and the patient for the most part drags a miserable life. . . . he totters and shakes, and becomes a dismal sight; as if no longer a man, but an animal half dead.}\] \(^{51}\)

As late as 1834, Roche defined ‘paralysis’ as “\textit{diminution or total loss of motility or sensation}”.\(^{52}\) Such a symptomatic definition could be applied to a variety of etiological entities. In any case, Cheyne described a disorder which could have a number of causes – coldness, exposure to the north-east wind or to mercurial or antimonial vapors, a blow to some part of the body, but “\textit{chiefly from some Obstruction of the Blood Vessels}” – and to which those in the “\textit{Decline of Life}” were particularly prone. It could affect the whole body, one side or individual members. Medical intervention, if it were to be successful, was to commence as soon as the case was diagnosed with bleeding, blisters (initially on the head, and gradually extended to the rest of the body), and then warm purges prepared from hellabore (\textit{Veratrum album}) or senna (\textit{Cassia acutifolia}) as a vinous extract, applied as often as is tolerated. Cordial medicines (such as a sassafras electuary washed down with a “\textit{nervous Julep, mix’d with Volatile Spirits}”\(^{53}\)) were also to be administered, as were a course of chalybeates (iron-containing drinks), aromatics and bitters, accompanied by the application of warm oils and ointments (especially opodeldoc)\(^{54}\) and stimulating warm compresses (fomentations) to the affected parts. Cold bathing might also be useful. Should this course of therapy fail, concluded

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\(^{49}\) Salmon, 1696, p.768. Adrian von Mynsicht (c.1588-1638), apothecary and poet laureate in Mecklenburg-Schwerin, was influenced by Paracelsus and opposed a chemical explanation of disease to the then prevalent humoral pathology in his much cited \textit{Thesaurus medicus-chymicus} (1631).

\(^{50}\) An example from Shakespeare: “Dick: \textit{Why dost thou quiver, man? Say: The palsy, and not fear, provokes me. Cade: Nay, he nods at us, as who would say, I’ll be even with you.}” \textit{Second Part of King Henry VI}, IV vii. See Calne et al., 1989; Stern, 1989. For earlier discussion of the \textit{Good Samaritan} see Embden, 1922.

\(^{51}\) Cited in Berrios, 1995, p.106.

\(^{52}\) \textit{Ibid.}, p.96.

\(^{53}\) Cordial: aromatic, syrupy drink designed to stimulate the heart; electuary: paste composed of the extract mixed with honey or syrup; julep: vehicle composed of water and syrup or sugar.

\(^{54}\) Saponaceous camphorated liniment favored (and named) by Paracelsus.
Cheyne, the case was probably incurable; this was, however, no great problem, if the patient could overlook the loss of function of the limb involved.55

Prior to Parkinson, François Boissier de Sauvages de la Croix (1706-1767) provided one of the clearest descriptions of a parkinsonism-like condition in 1763. He spoke of a condition which he named “sclerotyrbe festinans” in which decreased muscular flexibility led to difficulties in the initiation of walking; both the cases he observed were in elderly persons.56 Gaubius described at about the same time a man who could run, but not walk; this he attributed to the impulse directed by the will to the muscles suddenly escaping the control of the will. There was, however, no mention of other symptoms and, in particular, no reference to the tremor which attracted Parkinson’s attention. Further, Gaubius noted that the condition he described more commonly affected speech than any other motor activity.57 Somewhat earlier, the Dutchman Franciscus de le Boë (generally known as Sylvius; 1614-1672) had distinguished between resting tremor (tremor coactus) and that which occurred during voluntary motion.58 These were the three authorities quoted at length by Parkinson in his 1817 pamphlet as having partially pre-empted his awareness of the disorder, so I will not reproduce their comments here. It is sufficient to remark that all three authors noted symptoms which are consistent with the disorder described by Parkinson, but none described the complete syndrome, the description of which led to the disorder being named for Parkinson.

Two conclusions may be drawn from this cursory examination of the literature: firstly, parkinsonism-like disorders have probably attended old age at most periods in human history when people lived long enough to develop the disorder; and secondly, no therapy had ever emerged or been developed which exerted any great impact on the disorder. It should also be noted that tremor is the easiest symptom to find in the medical literature, as it is much more obvious than either rigidity or akinesia to define, let alone to detect. This was especially true before the manual examination of the patient became normal in diagnosis; Parkinson’s description of the disorder was incomplete precisely because he did not undertake such examinations. Mettler commented that Sylvius’ insight regarding resting and active tremor should have assisted an even closer analysis of tremor types, especially as this symptom attracted some attention in the 17th century, but:

\[
\text{there was no category into which the extrapyramidal dyskinesias and parakinesias might be dropped, so, from age to age, they were repeatedly rediscovered and forgotten. One is likely to find more light shed upon such atypical (for the period) categories in the lay than professional literature.}^{59}
\]

As would later prove to the case for L-DOPA therapy, the appropriate conceptual framework must be available if a new idea is to take root. Von Economo expressed the same idea with respect to encephalitis lethargica in particular:

55 Cheyne, 1734, pp.238-243. Cheyne also discussed palsies which afflicted persons of other otherwise sound constitution; they could benefit from treatment with mercury or any of a number of herbal remedies, including quinquina (source of quinine), oak bark, mistletoe, mustard seed, horse radish, pellitory, juniper berries and zedoary (prepared from turmeric).
57 Ibid., p.24.
58 Ibid., pp.20-21.
59 Mettler, 1947, p.546. Mettler cited references concerning palsy in Don Quixote and Measure for Measure.
How comes it about that a disease which has exited since the days of Hippocrates should only have been discovered nowadays, or, after having been repeatedly observed, how came it again to be forgotten? I think that at the time of the great encephalitis epidemics our knowledge, particularly of pathology, bacteriology, and anatomy, was not sufficiently advanced to enable us to understand scientifically and to demonstrate the common basis underlying the different clinical pictures presented by the protean character of this form of encephalitis. Even Parkinson’s pamphlet had been largely forgotten at the time Charcot rescued it and brought it fame; it is not inconceivable that James Parkinson could have ended up as nothing more than a curious footnote to the history of paralysis agitans, rediscovered only after the disorder had been named for, perhaps, Charcot, or even Lewy.

On the other hand, there were commentators as distinguished as William Heberden who dismissed the significance even of tremor; in 1802, he wrote:

A trembling of the hands, or a shaking of the head, may be judged to have some alliance with paralytic and apoplectic maladies; yet it has been found by experience, that such a tremor has often continued for a great part of a person’s life, without any appearance of further mischief; and therefore, if it have a tendency to palsies, it is a very remote one, and the inconvenience is far more considerable than the danger. Hypochondriac persons are troubled with frequent fits of it; hard drinkers have it continually; and some degrees of it usually attend old age.

This could also be interpreted as the dawning of the realization that the symptom is not significant in itself; the underlying disorder to which the symptom points is what must be addressed, and thus requires definition. It was with this work that not only Heberden but a great many workers in the 19th century would concern themselves.

Defining “parkinsonism”

This is related to a problem which even today has not been completely resolved: that of defining what actually constitutes parkinsonism. The subject of this essay is the chemical treatment of parkinsonism; the development of concepts regarding what constitutes “parkinsonism” can therefore only be treated to the extent that it illuminates the rationale behind the various therapeutic approaches adopted. After Parkinson had named the disorder ‘paralysis agitans’ or ‘shaking palsy’, tremor was long regarded as the major symptom of the disorder, leading to much diagnostic confusion, as will be seen in the next chapter. Parkinson did not remark upon the rigidity of parkinsonism, partly because he observed most of his ‘subjects’ from a distance, and partly because it was not usual to examine this aspect in the early 19th century; in fact, the only examination involving contact was often the feeling of the pulse.

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60 Von Economo, 1931, p.9. Von Economo was actually repeating a question posed by Smith Ely Jelliffe, who in turn was repeating that asked by Charcot upon the discovery of muscular dystrophy by Duchenne.

61 Parkinson’s rehabilitation in the English-speaking world occurred even later, with Leonard Rowntree’s article on “an English physician and scientist, forgotten by the English and the world at large”. He cited large sections of Parkinson’s treatise on the understanding that most physicians were unfamiliar with the text: Rowntree, 1912. The most recent biography of Parkinson was published by Roberts in 1997.

62 Heberden, 1802, p.429.

63 The development of concepts of parkinsonism and of knowledge regarding its neurological substrate has been treated in great depth by Hesselink in his book De Ziekte van Parkinson: Hesselink, 1986.
But even after Charcot and his school had largely clarified the definition of parkinsonism by the 1880s, and reports pointing to its neurological basis had accumulated by the turn of the century, much remained unresolved; as late as 1913, Hermann Oppenheim, the first to emphasize the vegetative aspects of parkinsonism, commented that "the essential nature of the disease is completely unknown to us".64 With the anatomical studies undertaken by Hunt, Wilson, Trétiakoff, Lewy, the Vogts and others in the second and third decades of the 20th century, however, a change began to occur. In the words of Lewy, the concept developed that "the clinical picture of paralysis agitans is a question of localization in particular regions of the central nervous system".65

Ironically, this placed paralysis agitans in danger of extinction as a distinct disorder: ‘parkinsonism’ as a term was increasingly used to denote not a disease but a syndrome which depended on the site and extent of specific lesions, but was not related to a specific disease process. This view was particularly nourished by the obvious similarities of paralysis agitans and post-encephalitic parkinsonism. From the time of the encephalitis epidemica until the 1960s, classification of parkinsonism usually employed the three categories paralysis agitans or idiopathic parkinsonism (= Parkinson’s disease), post-encephalitic parkinsonism and arteriosclerotic parkinsonism;66 other forms, such as post-meningitis parkinsonism and syphilitic (post-luetic) parkinsonism were also described, but were rare in comparison with the three major forms. The first comment which must be made is upon the use of the word ‘parkinsonism’ as opposed to ‘paralysis agitans’ or ‘Parkinson’s disease’. It was apparent to many workers from the time of encephalitis lethargica that symptoms similar to those of paralysis agitans might be presented in disorders of different etiology. It must also be remembered that it was only just before the First World War that the distinction between paralysis agitans and multiple sclerosis was generally recognized as clinically significant; symptomatic definition of disease retained its hold on the thinking of many workers, primarily because symptomatic treatment was often the only option. Nevertheless, the work of many authorities pointed to at least some similarities in the neuropathological substrates of most cases of parkinsonism, and it was implicitly accepted that the various forms might have different origins, but were essentially similar disorders and, with respect to therapy, could be treated as such. There were characteristics in each case which distinguished one form from the other, but these were viewed largely as variations on a theme. This attitude is reflected in the reports on antiparkinsonian therapy in the literature; most clinicians happily mixed patients of different types (if, indeed, the type of parkinsonism was mentioned at all), and comments on differential responses to a given therapy were more the exception than the rule. As noted with consternation by Critchley, there was a tendency in the 1920s and 1930s to collapse the idiopathic and arteriosclerotic cases into one class; as late as the 1960s, some authors felt the need to defend their distinction of these two separate classes.67

This situation only changed in the late 1960s and 1970s with the rise of new techniques in clinical neuropathology. This led to the recognition that ‘parkinsonian’ signs were presented in a number of distinct nosological entities, including progressive

64 Cited in Gamper, 1936, p.758.
65 Ibid.
supranuclear palsy, motoneuron disease, olivo-ponto-cerebellar atrophies and Creutzfeldt-Jakob disease.\footnote{Creutzfeldt (1920) and Jakob (1921) commented on the parkinsonian symptoms of their patients in the original papers on the disorder.} Further, even ‘arteriosclerotic parkinsonism’ came to be regarded less as a form of parkinsonism as a form of generalized arteriosclerosis with parkinsonian symptoms; other workers found that even this was too generous, and noted that the arteriosclerosis of arteriosclerotic parkinsonian patients was no greater than that of non-parkinsonian patients of similar age. Finally, a rare condition known as ‘striatonigral degeneration’\footnote{Adams \textit{et al.}, 1961, 1964; see also Jellinger and Danielczyk, 1968. Retrospective identification of earlier cases have also been reported: see Berciano \textit{et al.}, 1999; Wenning \textit{et al.}, 2000. Richter and Klüver also reported in 1944 a case of spontaneous striatal degeneration in a monkey.} was first described by a Belgian group in 1961,\footnote{A debate was conducted throughout the first two thirds of the 20th century as to whether a lesion in the striatum or the substantia nigra was responsible for the major parkinsonian symptoms. The substantia nigra lesion was more frequently observed, but the role of the striatum in the regulation of motor activity suggested that the lesion should be located in this region. This issue will touched upon several times in succeeding chapters.} in which neurodegeneration is initiated in the pallidum; histologically but not clinically distinct from idiopathic parkinsonism, it actually corresponds closely to earlier views on the pathology of paralysis agitans.\footnote{Izumi \textit{et al.}, 1971; Rajput \textit{et al.}, 1972; Sharpe \textit{et al.}, 1973.} Given the almost total loss of caudate dopamine in such cases, it is not surprising that L-DOPA is usually of no benefit for such patients.\footnote{Parkinson, 1817, p.1.}

The magnitude of the conceptual change involved can be gauged by comparing Parkinson’s original definition of paralysis agitans with a modern definition of the disorder:

\begin{quote}
\textit{Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to running pace: the senses and intellects being uninjured.}\footnote{Parkinson, 1817, p.1.}
\end{quote}

\begin{quote}
\textit{[Parkinson’s disease] is a disorder primarily of adult life whose major manifestation is a progressive disturbance in motor function produced by a characteristic pattern of neuronal cell loss in the zona compacta of the substantia nigra with the formation of Lewy bodies.}\footnote{Yahr, 1993.}
\end{quote}

While the classic symptoms remain important for the diagnosis, the precise definition is now essentially one of pathological substrate, not the visible signs of the disorder, and this despite the fact that the disease can thus only be definitively diagnosed through the use of highly expensive imaging techniques or post mortem. This exemplifies the general shift from identifying disorders with their major symptoms, as was customarily practised by physicians until the 19th century, to defining and demarcating diseases according to their etiology. Another characteristic of the disorder which has been used in its definition is the response to therapies which elevate central dopamine levels; this approach is not unproblematic, but indicates the degree to which pathology and therapy have grown together since the 1960s. Hornykiewicz suggested in the early 1970s that the term “striatal DA deficiency syndrome” might be a more appropriate designation for “parkinsonism” of any origin, but the clumsiness of the term prohibited its acceptance. It is also less clear now what position the striatal dopamine deficiency actually occupies in the chain of events which constitutes the natural history of the
disorder; other regions and transmitters are certainly involved, but the relationships between these many changes remain to be established. Finally, the presentation of Lewy bodies is now regarded as one of the hallmarks for Parkinson’s disease, but is not specific to this disorder; the suggestion has thus been made that Parkinson’s disease be considered one of a greater class of related disorders, the “Lewy body diseases”. The apparent fragmentation in the nosology of parkinsonism has thus been overcome to a certain degree by recognition of the similarities of disparate neurological disorders.

**India: parkinsonism and *Mucuna pruriens***

As the reader will be aware, the standard therapy for parkinsonism by the end of the 20th century was L-DOPA. An interesting and very early episode in the history of antiparkinsonian therapy concerns the occurrence of this amino acid in a plant which is native to India and also found in south-east Asia, Malaya and central west Africa. *Mucuna pruriens* Linné (also: *Mucuna prurita* Bak, *Dolichos pruriens* L., *Stizolobium pruriens* Pers.) is called cowage (that is, cow-itch) in English, a corruption of the Hindi name *Kawanch* or *Kiwich* (Bengali: *Kámách*) influenced by the properties of the plant; Chopra and Nadkarni list several other names in use in India, including the Sanskrit *Atmagupta* (= “having hidden properties”). Neuwinger lists over fifty names used in central Africa, differing from tribe to tribe. In India, the plant grows on the Punjabi plains, from the base of the Himalayas as far as Sri Lanka and Burma; in tropical Africa, it is widely distributed, being found particularly in savanna, forest edges and galley forest. The seeds of *M. pruriens* were often sold in Africa as calabar beans until the turn of the century; the toxic constituent of this plant is physostigmine (eserine).

*M. pruriens* is a climbing plant which exists as a number of varieties, but it generally presents a hairy stem, trifoliate leaves which fold together at night and deep purple to almost black flowers. Most interesting is the pendulous, slightly S-shaped pod (generally 5-9cm long). It is covered in urticating (itching) hairs, each about 2mm long; these spicules are dry when the fruit is ripe and fall off, but otherwise cause pruritis on contact with the skin (hence the name). The pods contain 3-6 bean-shaped, green-olive to black seeds.

*M. pruriens* is used in a number of traditional medicines in both India and Africa. In their catalog of the “principle drugs of vegetable origin met with in British India” (1890), Dymock and colleague noted firstly that the decorticated seeds could be prepared as a powerful aphrodisiac or as a spermatorrhœa. Further, the root was used as a “nerve tonic” and prescribed in “paralysis”. The use of the pod hairs as a vermifuge, on the other hand, was said to have originated in the West Indies, as this application was unknown in India. It was this property, however, which saw *Mucuna*, however, find its way into the Edinburgh (1783) and London *Pharmacopœias* (1809). Two interesting

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74 Smith and Prayson, 1996.
75 Nadkarni and Nadkarni, 1926, pp.818-820; Chopra et al., 1956, p.171. The explanation of the name *Atmagupta* is given in Dymock et al., 1890, pp.447-449; I have also encountered the interpretation “able to defend itself”. I have not been able to ascertain at this point which is correct, but I have no printed source for the second explanation. It should be noted, however, that the different names for the plant in the various Indian languages have different meanings.
77 Ibid., p.687.
chemical properties were noted in light of further history: the cortical portion of the seeds contained high levels of manganese, while the alcoholic extract was yellow and darkened somewhat on exposure; it gave a green reaction when treated with ferric chloride, as do catecholamines.

In 1956, Chopra and associates listed the following applications of the plant: the seeds as an aphrodisiac, nerve tonic and in the treatment of scorpion sting; the pods as an anthelminthic; the root as a purgative for use in fever, mixed with honey for cholera, or powdered and made into a paste for dropsy. Other indications given by Sivarajan and Balachandran include cholera, malignant ulcers and urogenital problems. The hairy covering of the seeds was long held to be responsible for the effect of *M. pruriens* against worms, although it was recognized that it was more effective against roundworm than tapeworm. The mechanical irritation no doubt plays a role in this effect, but it was demonstrated in 1955 by Shelley and Arthur that an alkaloid,

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79 Dymock *et al.*, 1890, pp.447-449. Interestingly, Vulpian, who played an important role in the history of parkinsonism (see page 78), had described this color reaction in the adrenal medulla in 1856.
80 Chopra *et al.*, 1956, p.171; Sivarajan and Balachandran, 1994, pp.67-68.
mucunain, was also anthelminthic. Neuwinger related this phenomenon to the recognition in the 1920s in America that proteinolytic components of certain plants, such as the *Caraya papaya*, were capable of partial digestion of intestinal worms.81

The use of *M. pruriens* in Africa was similar in many respects: many tribes use the fruit hairs (in honey or molasses) as an anthelminthic or to treat intestinal worms; the powdered seed is used as an aphrodisiac in Zaire. In Senegal, leaf and bark preparations are used to stimulate uterine contractions, often for the purpose of abortion, while on the Ivory Coast and in East Africa the leaf juice is used for a number of anti-inflammatory purposes. The spicules are also employed as an arrow and general poison. For the latter purposes, the spines are usually mixed with the victim’s food, who dies after experiencing severe stomach pain and blackened urine or paralysis; the employment of other *Mucuna* species for this purpose has also been described in Indonesia.82 The plant is now also grown in Central and South America, where it is employed for a variety of medical purposes, but mostly as a vermifuge; in Mexico, its seeds are used to prepare coffee, explaining its popular name ‘Nescafé’.83

*M. pruriens* first came to the notice of Western science in 1937 when Manayath Damodaran and Raghaviah Ramaswamy (University Biochemical Laboratory, Chepauk, Madras) isolated l-DOPA from its seeds. They had examined a number of plant extracts for the presence of l-DOPA, using the green response given by treatment with ferric chloride and the reduction of silver nitrate and potassium permanganate as indicators, but had identified genuine l-DOPA only in the seeds of *M. pruriens*. They had been searching for a native source of the amino acid following its isolation from the broad and Georgia velvet beans (which belong to the same family as *Mucuna*) in Europe and America respectively, with an interest in its relationship to both adrenaline and melanin. The authors noted that the plant was famous for its irritating bristles and that the seeds, root and legume were used in a number of traditional medicines. Using Guggenheim’s purification protocol, the yield was impressive: the Indians gained about 30g l-DOPA from 2kg raw beans, about six times the yield achieved by Guggenheim.84

Between 1944 and 1956, the Indian biochemist D.N. Majumdar isolated a series of alkaloids from the seeds of *M. pruriens*, including nicotine;85 Bowden and associates reported the presence of 5-HT in the bristles in 1954.86 It was not until 1971-72 however, that S. Ghosal demonstrated the presence of a number of psychoactive indolealkylamines, including 5-hydroxy-*N*,*N*-dimethyltryptamine (5-hydroxy-DMT; bufotenine)87 and 5-methoxy-*N*,*N*-dimethyltryptamine (5-methoxy-DMT; O-methylbufotenine) in all parts of the plant, as well as choline; it was to these alkaloids that he attributed most of the physiological effects of *M. pruriens*; 6-methoxyharman is contained in the leaves.88

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81 Neuwinger, 1996, p.693.
82 Ibid., p.688-689.
84 Damodaran and Ramaswamy, 1937.
85 Majumdar and Zalani, 1953; Majumdar and Paul, 1954.
86 Bowden et al., 1954.
87 Bufotenine is secreted by the Queensland cane-toad, for which reason the skins of this animal have been exploited for recreational hallucinogenic purposes; it is a controlled substance in the United States.
88 Ghosal, 1972. For detailed discussion of pharmacology of *M. pruriens* alkaloids, see Neuwinger, 1996, pp.690-693. Harmine, discussed as an antiparkinsonian agent in chapter V, is 7-methoxyharman.
Interest in the L-DOPA content of *M. pruriens* was stimulated again in 1971 by E.A. Bell (Department of Botany, University of Texas, Austin) and D.H. Janzen (Department of Biology, University of Chicago). They noted that the accumulation of L-DOPA in plant tissues could occur because the balance between the activities of hydroxylase and decarboxylase enzymes does not favor the rapid formation of dopamine as it does in animal tissues. They reported that the seeds of five further *Mucuna* species from Colombia were also rich in L-DOPA, with the percentage weight accounted for by L-DOPA in the range 5.9-9.0%, a level which would permit industrial extraction. They also speculated on the biological role of L-DOPA in legumes, and noted that *Mucuna* seeds were particularly free from insect and small mammal attack. The incredible commitment of the plant to the production of L-DOPA suggested to the authors that the biological role of L-DOPA in legumes is, in fact, a protective one. Small seed-eating mammals in areas of *Mucuna* growth in central America were found to accept immature seeds but to quickly reject those containing higher levels of L-DOPA.89 Daxenbichler and colleagues (Agricultural Research Service, U.S. Department of Agriculture) reported in the same year that they had examined 724 plant species from 135 families and 447 genera from various parts of the world (central America, southern U.S.A., Africa, Japan); only four species, all *Mucuna* species of the division *Stizolobium*, contained appreciable amounts of L-DOPA.90

A group of Indian scientists (a collaboration from the Department of Clinical Research at Ciba-Geigy, Bombay; the R.A. Podar Ayurvedic Medical College, Bombay; and the Department of Neurology, J.J. Hospital, Bombay) then reported in 1978 their experiences using the powdered seeds of *M. pruriens* as an alternative to commercial L-DOPA in the treatment of Parkinson’s disease in twenty-three patients (age: 35-69; duration of disease: 0.5-10 years). The seeds were purchased from the local market by a botanist who ascertained their identity, following which they were powdered and the L-DOPA content assessed by column chromatography with fluorescent detection; batches with a content of 4.5-5.5% were used in the trial. The initial dose of 15-40g per patient per day (in divided doses) was gradually increased; the maximum dose used was 4×15g/day and the average duration of treatment twenty weeks. The Northwestern University Disability Score (NUDS) was used to assess parkinsonian symptoms. The results were encouraging: the total morbidity score (NUDS plus assessment of physical signs) was reduced in all but one patient (mean NUDS before treatment: 32.3 ± 3.4; after treatment: 17.0 ± 3.1; p<0.01), the mean NUDS dropped from 18.4 ± 2.3 to 9.6 ± 1.8 (p<0.01). Significant improvement in all major symptoms were recorded. The powder was well tolerated with only minor incidence of side-effects; the main desire of the patients was “a reduction in its bulk and a more positive flavour and taste”. Bioavailability studies indicated that peak plasma L-DOPA values (ca. 0.7µg.ml⁻¹) were achieved about an hour after ingestion of the powder. The authors noted that van Woert had communicated to them that the use of velvet beans in a similar manner had previously not met with this success.91

The authors doubted that the beneficial effects of the powder could be entirely attributed to L-DOPA; the doses administered corresponded to maximally 3g L-DOPA/day, and the side-effects associated with commercial L-DOPA preparations were absent. This was an interesting observation, especially given the fact that *M. pruriens*

89 Bell and Janzen, 1971.
90 Daxenbichler et al., 1971.
91 Vaidya et al., 1978a.
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doctor, indeed, possess an extremely interesting pharmacological profile. On the other hand, Ciba-Geigy researchers in Bombay had also noted that the powder was effective in relieving chlorpromazine-induced hyperprolactinemia, pointing to its effectiveness as a dopaminomimetic agent.92 In conclusion, the authors recommended that traditional plants might provide an alternative to expensive commercial pharmaceuticals in countries where these plants were native; they also pointed to the successful introduction of active extracts of the Indian Rauwolfia into the clinic in the 1950s.93

More recently, Bala V. Manyam (Neurology, Southern Illinois University; Plummer Movement Disorders Center), in co-operation with K. M. Parikh (Zandu Pharmaceutical Works, Bombay; manufacturers Ayurvedic products), has promoted the employment of the M. pruriens extract HP-200 (essentially the powdered seeds mixed in water) for the treatment of Parkinson’s disease. In a multicentre open trial in India, sixty parkinsonian patients received the extract orally for twelve weeks (mean dose: 45 ± 22g); significant improvement of motor scores was reported.94 The pharmacokinetic profile of HP-200 (30g in 50ml water) in five normal volunteers was found to be similar to that of synthetic L-DOPA, with plasma peak levels of 1.6 ± 0.2µg.ml⁻¹, achieved after about 1½ hours; the half-life was estimated to be 102 ± 2min. The authors compared these results to the effect of a single Sinemet tablet, but also suggested the presence of active substances other than L-DOPA.95 HP-200 received the approval of the Indian Food and Drug Administration, and is now available as ‘Zandopa’ (Zandu Pharmaceutical Works); in the United States, it has received approval for clinical trials.

There have also been studies which have been interpreted by their authors as indicating that substances contained in M. pruriens other than L-DOPA contribute to the pharmacological qualities of the plant. Nath and colleagues (Neuro-Pharmacology Unit, Pharmacology, K.G.’s Medical college, Lucknow) reported that both seed powder and an alcohol-insoluble methanol extract (‘M1’) were more effective than L-DOPA in the inhibition of oxotremorine-induced tremor in mice and reserpine-induced rigidity, hypokinesia and “catatonia” in rats. This “antiparkinsonian” activity was also exhibited by an L-DOPA-free extract (‘M3’).96 At the 12th International Symposium on Parkinson’s Disease in London in 1997, Manyam reported that M. pruriens seed powder was twice as effective as synthetic L-DOPA in the 6-hydroxydopamine rat model of Parkinson’s disease; further, short-term and long-term toxicity studies of HP-200 in rats and rabbits revealed no untoward physiological, behavioural or hematologic effects (maximum bolus dose in rats: 10g.kg⁻¹). Further, the drug extract was considerably less expensive than synthetic L-DOPA and stable at 37°C for at least three years, both important considerations for a drug intended for use in India.97

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92 Vaidya et al., 1978b, 1978c.
93 Vaidya et al., 1978a.
94 HP-200 in Parkinson’s Disease Study Group, 1995.
95 Mahajani et al., 1996. L-DOPA levels were estimated at 4% in the whole bean, most of which was in the endocarp, where the level was about 5.3%.
96 Nath et al., 1981. None of the extracts antagonized oxotremorine-induced analgesia, suggesting they did not possess anticholinergic activity. It should, however, be noted that L-DOPA, in contrast to adrenergic β receptor blockers, is usually reported as not inhibiting (oxo)tremorine-induced tremor: see, for example, Watanabe et al., 1971.
Nagashayana and associates (Department of Kayachikitsa, Government Ayurveda College, Thiruvananthapuram) recently reported that administration of an Ayurvedic “concoction in cow’s milk of powdered Mucuna pruriens and Hyoscyamus reticulatus seeds and Withania somnifera and Sida cordifolia roots” to thirteen clinically diagnosed parkinsonian patients for fifty-six days following ‘Ayurvedic cleansing’ (twenty-eight days) achieved significant improvement in activities of daily living and as assessed by the Universal Parkinson’s Disease Rating Scale (UPDRS), with alleviation of tremor, bradykinesia, rigidity and cramps noted. This improvement was not seen in five patients who received the medication without prior cleansing. Interestingly, sialorrhea was exacerbated in all patients. Analyses of powdered samples in milk, as administered to patients, indicated that each dose contained about 200mg L-DOPA.98

It is naturally interesting that Hyoscyamus reticulatus (Paraseekayavanee, ‘Indian henbane’) is closely related to Hyoscyamus niger, widely employed in European antiparkinsonian therapy in the 19th and 20th centuries. Withania somnifera (Aswagandha, ‘Indian ginseng’; German: Schlafbeere), also a solanaceous plant, is extensively employed in Indian medicine, principally as a sedative and anti-inflammatory agent, but has also been advertised recently as the ‘Indian Viagra’; it is currently a very popular herbal remedy, especially for the relief of stress.99 In East Africa, it has been used as a narcotic and anti-epileptic agent; interestingly, two workers who examined the plant in the 1930s and 1940s were unable to detect the usual solanaceous alkaloids.100 Sida cordifolia (Bala) has also an extensive tradition in Ayurvedic medicine, and is associated with diaphoretic, diuretic, central nervous system stimulating and anti-asthmatic properties. The most important component of the stem is the alkaloid content of 1-2%, mostly ephedrine and pseudoephedrine, with the ephedrine contribution lying between 30 and 90%, depending on the source.101

The use of M. pruriens in the clinic, however, appears to have not been intensively pursued in western clinics. The plant was, however, not completely ignored. Several groups investigated the viability of callus cultures of M. pruriens and similar species, either on solid culture or in suspension, during the first half of the 1980s. For example, Huizing and colleagues (Laboratory for Pharmacognosy, Gröningen) described a suspension culture system in which the accumulation of L-DOPA (0.5-2.0%) could be demonstrated.102 A group from the same institution reported an improved version of this technique in 1993,103 but there have been no more recent reports on this approach.

What renders M. pruriens especially interesting is that references to a disorder similar to Parkinson’s disease can be found in the Ayurveda, a series of ancient Indian medical texts which form the basis of an alternative health system still practiced today on the Indian subcontinent.104 The basis of this system is the principle of the three doṣas, or dhātus, of the human body:

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98 Nagashayana et al., 2000.
100 Cited in UNESCO, 1960, p.82.
101 Kapoor, 1990, p.303; Sivarajan and Balichandran, 1994, pp.70-72. For overview of Indian plants in modern medicine, see Vaidya, 1997.
102 Huizing et al., 1985.
103 Pras et al., 1993.
104 Versions of the system are also popular in the west as “alternative” or “complementary” medicine.
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- vāyu, vāta, māruta, anīla, samīrana: dry, cold, light, delicate, moving, clear, raw.
- pitta: greasy, hot, sharp, fluid, acrid.
- slesman, kapha: heavy, cold, mild, oily, sweet, stable.\(^{105}\)

According to Manyam and other commentators, the respective association of the three doṣas with wind, bile and phlegm (as made by Jolly)\(^{106}\) is false, probably the result of an overdrawn analogy with the four humores of the Hippocratic-Galenic tradition of the West.\(^{107}\) Blood is sometimes also regarded as a doṣa. There is no place here to enter into a detailed discussion of Ayurvedic medicine; it suffices here to note that the term doṣa (= ‘defect’) emphasizes their need to be treated in disease, whereas dhātu underscores their being elements of the normal body. As with the Greek humores, specific personal character types are associated with specific doṣas. The coordination of the three elements underlies all aspects of human physiological and psychological function.\(^{108}\)

Vāta, associated with psychomotor activities but also regarded as being the dominant doṣa in old age, occurs in five forms. Different texts ascribe the functions of bodily movement (internal and external) either to a single form which pervades the entire body (vyāna) or describe this function as being distributed over all five forms. It is also seen as being the supreme element, and the result of simultaneous derangement of the five forms is fatal: “man is no more.”\(^{109}\) Aspects of the other doṣas, however, are also important for movement: slesana (a form of pitta, generally associated with metabolic activities), for example, is responsible for flexibility of the joints. “Derangements” of vāta are mostly nervous diseases, often involving loss of some aspect of motility; the specific manifestation of disease, depends, however, on the organ or tissue in which the vāta is lacking. The vātāvyādhī, or diseases of vāta include a variety of specific and general paralyses and other disorders of movement; most interesting for the present discussion is the form vepathu, which Jolly identified without further comment as paralysis agitans,\(^{110}\) also known as kampavāta; kampa means tremor. The Basavarajiyam (A.D. 1400) described kampavāta thus:

> Tremors of hand and feet, difficulty in body movements, disturbed sleep and dementia are symptoms of kampavāta.\(^{111}\)

The Mādhava-Nidāna (c. 8th century) lists a similar vāṭika disorder:

> Generalized involuntary movements of all parts of the body or of the head only is known as vepathu; it is due to (vitiated) vātu.\(^{112}\)

The editor noted that vepathu was commonly known as kampavāta. Amongst the other symptoms associated with this disease in various Indian texts are stiffness, reduced desire for movement, depression, excessive salivation, sleepiness and fixed stare.\(^{113}\)

\(^{105}\) The discussion of Ayurvedic medicine here is based upon Kutumbiah, 1962; Kapoor, 1990, pp.347-352; Singhal and Patterson, 1993.

\(^{106}\) Jolly, 1951, pp.59-60.

\(^{107}\) For a comparison of humoral models in different cultures, see Shah, 1966, pp.xiii-xxvi.

\(^{108}\) See footnote 105.

\(^{109}\) Bhāvaprakāśa (16th century), cited in Jolly, 1951, p.60.

\(^{110}\) Ibid., p.59.

\(^{111}\) Cited in Manyam and Sánchez-Ramos, 1999.

\(^{112}\) Singhal et al., 1985, p.414.

\(^{113}\) Manyam, 1990; Gourie-Devi et al., 1991; Manyam and Sánchez-Ramos, 1999.
Interestingly, despite the use of Rauwolfia extracts (Sanskrit: Sarpaghanda; Hindi: Chotachand) as a sedative, febrifuge, antidote to snakebite and scorpion stings and to induce uterine contractions, reserpine-induced parkinsonism appears to have been unknown, perhaps because only whole root extracts were employed.

Even more interesting was the recommended therapy for kampavāta. In order to reestablish the balance of vāta in the body, internal and external application of a number of plant drugs was prescribed – amongst others, the seeds of M. pruriens. Toxic effects of atmagupta included headache, dystonia, fatigue, syncope and tremors, not unfamiliar in modern l-DOPA therapy. Manyam reported that several Ayurvedic preparations which included employed the bean were also used to treat kampavāta. Further, he noted that Jatipatadi churna and Parasikyavani churna are currently used for parkinsonian tremor, but their alkaloid and other chemical content has not been analyzed.

There thus appears to existence some evidence that parkinsonism is not only an ancient disorder, but that the pharmacological treatment was empirically derived several thousand years ago. Of thirty-five formulations for kampavāta listed in Ayurvedic texts, at least eighteen contained atmagupta. Further research by those competent in both Sanskrit and medical botany is required to this interesting question. Some would even detect a certain irony in the fact that plants containing pharmacological levels of reserpine and l-DOPA should be found in such close geographical proximity to one another. It should, however, be recognized that not all Indian medical texts employed by the practitioners of Ayurveda are as ancient as the original treatises; the Caraka Samhita, for example, while drawing on older texts, probably dates from the early part of the second century. Further, atmagupta was employed in a variety of capacities, and in many authoritative handbooks on traditional Indian medicine, its use for a trembling disorder is not mentioned. The use of M. pruriens in “parkinsonism” in ancient India should thus not be overstated, interesting as the possibility is, and worthy of further investigation.

Extracts and seeds of M. pruriens are sold today by various Ayurvedic and other alternative medicine companies for a variety of indications; its actions in Parkinson’s disease are invariably mentioned, but it is usually sold on the basis of its alleged aphrodisiac or muscle-enhancing qualities (which it is reputed to elicit via stimulation of testosterone release). These properties were also recognized in India, where ascetics are supposed to have been afraid of even uttering its name because of its powerful sexual properties. The beans are also used for this purpose in central Nepal – in buffaloes: 25-35g of the root paste is administered with their other cooked food twice a day “for as many days as necessary”.

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115 Manyam, 1990.
116 Ibid.
119 I do not feel it appropriate to advertise for these companies by listing their web addresses here.
120 Sivarajan and Balachandran, 1994, p.67.
121 Bhattarai, 1992.
Interestingly, it was recently reported that immunization against cobra venom using *M. pruriens*-derived serum immunoglobulins proved highly protective in mice.\(^ {122}\)

Aqueous extracts of *M. pruriens* leaves have traditionally been used in Africa as antidote to snakebite by prolonging blood-clotting time.\(^ {123}\)

**Other traditional antiparkinsonian therapies**

Wherever a disease occurs and is recognized, some attempt will be made to develop a method which affords at least some relief from the worst effects of the disorder. Some of the traditional attempts to treat parkinsonian symptoms will be discussed at the appropriate place in the course of this work. At this point, I will restrict myself to a brief reference to Chinese herbal therapies, as they are unrelated to anything which will be discussed in the remainder of this book. Chinese medicine regards disease as the result of imbalance between the opposing processes understood in the terms *yin* and *yang*. Parkinsonism, seen by Chinese medicine as a trembling and convulsive disorder, results from excessive wind (*yang*) in the liver and deficient *yin* in liver, spleen and kidney, leading to muscular malnutrition through blockage of ‘energy channels’ (*qi*) with mucus. The complex solution for this problem was examined by Genghe during three months in fifty parkinsonian patients. He employed a vast range of herbal components in the medications employed in the therapy as well as acupuncture (as required); I could discern nothing in his approach which paralleled Western phytotherapeutic treatment of parkinsonism. Genghe reported that he achieved marked improvement in 30% of patients, some improvement in 48% and no benefit in 22%.\(^ {124}\)

Herbal therapy firms often offer advice regarding parkinsonism, but respectable members of the branch emphasize that conventional (dopaminergic and related) therapies are indispensable; herbal therapies are proffered as adjuncts for the relief of particularly troublesome symptoms. With respect to Chinese herbs, combinations which include liquorice (*Glycyrrhiza uralensis*), rhubarb (*Rheum palmatum*), peony (*Paeonia officinalis*) and magnolia bark (*Magnolia officinalis*) are recommended for tremor and rigor. Passionflower (*Passiflora incarnata*) is also said to reduce tremor if employed together with levodopa, as is evening primrose oil (*Oenothera biennis*).\(^ {125}\)

There is little in Western phytomedicine which would suggest the employment of liquorice, rhubarb or magnolia bark in parkinsonism (although rhubarb has been used in mixtures administered to those suffering delirium tremens). Evening primrose oil has long been popular as a sedative in a variety of medical situations. Peony and passion flower, on the other hand, are a little more interesting. Felter and Lloyd noted for peony:

> Peony is antispasmodic and tonic. It is asserted to have been successfully employed in chorea, epilepsy, spasms, and various nervous affections. . . . An infusion may be made by adding 1 ounce of the root, in coarse powder, to 1 pint of a boiling liquid, composed of 1 part of good gin, and 2 parts of water, which maybe sweetened. Dose, 2 or 3 fluid ounces, 3 or 4 times a day.\(^ {126}\)

\(^ {122}\) Aguiyi *et al.*, 1999.

\(^ {123}\) Cited in Neuwinger, 1996, p.693.


\(^ {125}\) This paragraph is based on information gleaned from a number of internet herbal therapy firms. Please note that these herbal remedies are not Chinese.

\(^ {126}\) Felter and Lloyd, 1898, www.ibiblio.org/herbmed/eclectic/kings/paeonia.html. The version of the book available at this website was employed in the absence of access to a printed copy.
The same authors noted that the passion-flower, native to the southern United States and Mexico, had found application in spasmodic and convulsive disorders and as a sedative, especially in the alleviation of restlessness and sleeplessness, “when these are the result of exhaustion, or the nervous excitement of debility”; it was also used to relieve tetanus “both in man and the horse”. It was also reputed to ward off epilepsy if taken during the aura, and to effectively manage spasms secondary to meningeal inflammation. It appears not to be contraindicated in any form of spasm. Further, the “remedy has given good results in chorea, especially in girls approaching the menstrual age”. Grieve noted that.

The drug is known to be a depressant to the motor side of the spinal cord, slightly reducing arterial pressure, though affecting circulation but little, while increasing the rate of respiration.

She noted its serviceability, in combination with bromides, in epilepsy, as well as its function as a sedative. The use of the passion flower thus has some basis in traditional Western phytotherapy. Its major constituents are reported to be flavonoids (up to 2.5%), including a number of C-glycosyl-flavones and the benzodiazipine ligand, chrysín (5,7-dihydroxyflavone); the cyanogenic glycoside, gynocardine (< 0.1%); and, most interestingly, several harmaline alkaloids (< 0.03%). In animal tests, passion flower extracts have proved to be hypotensive but to stimulate respiration; sedative, anxiolytic and spasmytic effects have also been reported. Nevertheless, association of any of these properties with identified constituents in the plant has been difficult. The herb has been approved in Germany by the Commission E for the treatment of nervousness and insomnia.

It has been reported that embauba (Cecropia palmata) is employed in Colombia in antiparkinsonian therapy, while the bark of pau d’arco or lapacho (Tabebuia impetiginosa) has been used in South America for “thousands of years” to treat a variety of conditions, including “lupus, diabetes, Hodgkin’s disease, osteomyelitis, Parkinson’s disease and psoriasis”. There is no information about their chemical constituents which provides a link with European phytopharmacology of parkinsonism. A recent guide to herbal remedies asserted that gotu kola or hydrocotyle (Centella asiatica) was a traditional central nervous system stimulant “with historic use in Parkinson’s”; I have, however, found no further reference to the employment of this plant in the disorder. The same source recommended the use of gingko or maidenhair tree (Gingko biloba) and hawthorn (Crataegus oxyacanthus) as circulatory stimulants and anti-oxidants; it was also recorded that homeopaths employed 30C preparations of various metals, including silver nitrate, mercury, lead and zinc. The homeopathic preparation ‘elhapargen’ (elha Fabrik (Karl Hubener), Oberursel), drops and ampoules for injection), employed in disorders of the central and peripheral nervous systems, including parkinsonism, contains extracts from a number of plants, amongst them arnica (Arnica montana), gelsemium (Gelsemium nitidum), St. John’s wort (Hypericum...
perforatum), grass pea (or chickling vetch: Lathyrus sativus), poison ivy (Rhus toxicodendron) and Strychnos nux vomica, as well as arsenous acid, lead acetate, fly agaric and “causticum Hahnemanni”.133

Vicia faba134

The plant most closely associated with antiparkinsonian therapy at the end of the 20th century, however, was the broad bean, original source of L-DOPA. The usefulness of this bean (also: fava or horse bean) for the management of Parkinson’s disease has naturally also been investigated. The bean has been part of the diets of many parts of the world for thousands of years, and is believed to have originated in the region south of the Caspian Sea or in North Africa; it still grows wild in Iran. It was already cultivated around the Mediterranean in prehistoric times; Homer mentions the “black-skinned bean” in the Iliad,135 and it was considered a specialty in Rome (the name of one of the leading Roman families, the Fabii, is said to derive from the Latin faba for ‘bean’). Nevertheless, Dioskorides considered the ‘Greek bean’ as “windy, flatulent, hard of digestion, causing troublesome dreams”.137 It could be rendered palatable by soaking the beans and discarding the water used for this purpose; then it was useful in a variety of conditions, including the prevention of flows of all sorts (vomiting, dysentery, milk), in which capacity it was reasonably regarded until recent times.

The Pythagoreans, who were otherwise model vegetarians, were not permitted by their beliefs to consume fava beans. The reasons for this tabu have been much debated, especially as even their contemporaries were not certain about the reasons. One possibility was the prevalence in magna Graecia (now southern Italy) of a hereditary form of glucose-6-phosphate deficiency which causes hemoglobinuric jaundice following consumption of fava beans; in a minority of cases, the resulting shock is sufficient to cause death through anoxemia or acute renal failure, especially in the very young or old. “Favism” is thus probably not linked to the L-DOPA content of the bean, although this cannot be excluded; the component of the bean responsible for the reaction has not been conclusively identified. It is, however, recognized that the toxin is located in the skin of the bean, is heat-stable and its toxicity increases when the beans are dried. The disorder appears to confer a certain degree of immunity to malaria, explaining the genetic persistence of an otherwise unfortunate trait.138

Both Gerard and Culpeper listed a variety of uses for the bean as medication, but noted that in England they were rarely seen.139 The bean also plays a role in the traditional medicine of several parts of the world. In the d’El-Bayadh region of Algeria, the leaf and seed are used as antifungal and antipyretic agents;140 in Assam (India), a juice extracted from the leaves is used to treat otorhea;141 according to Nadkarni’s

133 Information supplied at www.gelbe-seite.de, accessed 12.04.01. ‘Causticum Hahnemanni’ is a tincture employed as a cautery in homeopathy.
134 Illustration on page 381.
135 Iliad XIII, 589.
136 Plinius, XVIII, 10. He also noted that ‘Cicero’ derived from cicer (‘chick-pea’).
137 II, 127.
138 For discussion of favism and the various other theories proposed to explain the Pythagorean prohibition, see Grmek, 1989, pp.210-244. See also Bottini et al., 1970; Lattanzio et al., 1982.
139 Gerard, 1633, pp.1208-1211; Culpeper, pp.41-42.
140 Cheriti et al., 1995.
Indian Materia Medica, the shoots “are efficacious in arousing a drunkard from stupor”.142

Natelson suggested in 1969 that problems with the synthesis and the cost of \( \text{L-DOPA} \) could perhaps be overcome by commercial plantations of \( \text{Vicia faba} \), citing the claim by Sealock that 25g \( \text{L-DOPA} \) could be extracted from a kilogram of the beans, so that 250g would provide the required daily dose.143 Most of the \( \text{L-DOPA} \) is present in the free form, although a \( \text{DOPA} \) glucoside has also been detected.144

The fresh pods and the dry seeds are today especially popular in countries of the eastern Mediterranean, where they are cooked in olive oil and served after the main meal.145 Spengos and Vassilopoulos presented anecdotal reports concerning the benefits of \( \text{Vicia faba} \) for parkinsonian patients at the 9th International Symposium on Parkinson’s Disease in Jerusalem in 1988, finding subsequently corroborated by several groups. After withdrawing their normal medication (‘Dopicar’, Assia, Israel; = 10:1 \( \text{L-DOPA} \)/carbidopa, as well as bromocriptine or lisuride) for twelve hours, Korczyn’s group (Departments of Neurology and Pharmacology, Sackler Faculty of Medicine, Tel-Aviv University) served six parkinsonian patients 250g cooked broad beans; substantial clinical improvement (accompanied by severe dyskinesia in three subjects) was paralleled by significant rises in plasma \( \text{L-DOPA} \) levels corresponding to the effects of 137.5mg Dopicar. The authors recognized the limits imposed by varying levels of \( \text{L-DOPA} \) in broad-beans, but suggested that they might be a useful adjunct to therapy in patients with mild to moderate motor disability.146 Kempster and associates (Neuroscience, Medicine and Biochemistry, Monash Medical Centre, Melbourne) and Vered and colleagues confirmed that the effect of \( \text{Vicia faba} \) ingestion upon plasma \( \text{L-DOPA} \) levels was sufficient to make them a viable therapeutic option.147

Apaydin and his colleagues in the Department of Neurology of the Cerrahpasşa Medical School (Istanbul University) recently examined the long-term effects of broad bean consumption in eight patients suffering from disabling motor fluctuations. Medication was not withdrawn; the patients were simply required to consume two portions (each 250mg) of broad beans per day for one to three months. The major effect, which surprised the authors, was a marked prolongation of the “on”-periods in these patients and a shortening of the “off” periods. This was not attributable to increased \( \text{L-DOPA} \) levels alone, as the patients had previously been treated with high \( \text{L-DOPA} \)/carbidopa doses in an effort to control their condition. It was concluded that, despite lack of knowledge concerning the mechanism involved, the preliminary results justified further investigation of the bean as adjunct therapy in Parkinson’s disease.148

It has also been reported that \( \text{L-DOPA} \) occurs at 1.7% of the fresh weight of latex prepared from the unrelated \( \text{Euphorbia lathyris} \) (caper spurge, petroleum or mole plant). The other constituents of the plant, including auculetin, would render its direct employment as a drug, however, extremely unpleasant, especially for the digestive tract;

142 Nadkarni and Nadkarni, 1926, p.1272.
143 Natelson, 1969.
144 Andrews and Pridham, 1965; see also 1967 paper by same group on plant melanins.
145 For sample recipe, see Apaydin et al., 2000.
146 Rabey et al., 1993a, 1993b.
147 Kempster et al., 1993; Vered et al., 1997.
148 Apaydin et al., 2000.
it has been employed in French folk medicine as a purgative similar to castor oil, but it is also emetic, diuretic and vesicant.\textsuperscript{149} 

The problem with any herbal medication is that quality control of the product is not as convenient, nor indeed normally as rigorous as for synthetic pharmaceuticals. Further, extracts of \textit{Vicia faba} and \textit{M. pruriens} are available freely via mail order and from internet firms (as is L-DOPA itself) without the need for medical competence on the part of the supplier or awareness on the part of the “patient”; a disclaimer to the effect that the supplier does not assert that the product possesses specific effects in specific medical disorders suffices in many countries to absolve the manufacturer of responsibility for its use. The increasing demand for “natural” medications and therapies ensures, however, that such suppliers are eagerly sought both by sufferers of chronic disorders who have lost faith in conventional medicine (for any of a variety of reasons) and by those who believe that they one day might fall victim to such illnesses. This demand is also supplemented by the claims frequently made for many traditional remedies that they have also been traditionally employed as aphrodisiacs, muscle enhancers or nerve tonics. What is generally forgotten is that the success of the modern pharmaceutical industry is largely due to the rigorous standards of safety and efficacy to which it is subject; active agents of vegetable origin are separated from potential or actual toxins and supplied in a pure form, or further developed to yield more effective therapeutic agents. This does not, of course, eliminate all risk, but at least ensures that maximal efforts are taken to reduce the residual risk to the patient, who will normally receive the medication following consultation with an accredited medical practitioner. That there are examples where this responsibility has been overlooked or appears to have been overlooked, or where unforeseen side effects of an agent have later emerged, does not invalidate the basic observation that the controls imposed by the state on the pharmaceutical industry are there to protect the patient, not to entrench any system of “school medicine”. 

This is particularly relevant with respect to the current discussion. \textit{M. pruriens} is not usually grown locally in western countries but imported from India or Africa. The health authorities in Mozambique reported in 1990 an outbreak of acute toxic psychosis which they attributed to \textit{M. pruriens} (local name: \textit{feijão macaco}), eaten as a result of the famine conditions then prevailing in part of the country. The toxicity of the seed is usually avoided by repeated boiling in water and the discarding of this water; unfortunately, water was also a problem during this crisis. It was not clear whether L-DOPA was responsible for this toxic response; it was noted, however, that \textit{M. pruriens} is also a rich source of the hallucinogens DMT and 5-methoxy-DMT.\textsuperscript{150} Vijayakumari and colleagues found that the L-DOPA content of \textit{M. pruriens} pods was not significantly reduced by a number of processes (including soaking, cooking, autoclaving) which rid the pulse of toxins such as phenols, tannin and cyanide.\textsuperscript{151} Finally, Roy’s group measured aflatoxin levels of 1.16µg.g\textsuperscript{-1} seeds in \textit{M. pruriens} collected from an Indian storehouse.\textsuperscript{152} Without wanting to exclude a renewed role for vegetable extracts in medicine, natural is clearly not always safer.

\textsuperscript{149} Duke, 1985, p.189. 
\textsuperscript{150} Infante \textit{et al.}, 1990. 
\textsuperscript{151} Vijayakumari \textit{et al.}, 1996. 
\textsuperscript{152} Roy \textit{et al.}, 1988.
Both the beginnings of antiparkinsonian and its current leading pharmaceutical agent thus lie in beans and seeds – and, as will be seen, most of what has been tried in the meantime has also been derived from plants. There is a certain irony in finding solutions for motor problems where mobility is so limited. This serves to illustrate both the ubiquity of certain metabolic pathways and the different functions they can support.
Part I

The alkaloid therapies

Oculus itaque patients plantae fabricum, judicium autem optimum vires expendat sedulis experimentis.

Scopoli, Foreword to Flora carniolica
II. Therapy of parkinsonism in the first half of the nineteenth century

The history of the therapy of parkinsonism has been the history of palliative therapies which attempt the mitigation of the worst symptoms of the disorder. In the absence of precise knowledge regarding the etiology of idiopathic parkinsonism, this has been necessarily so in this form of the disorder. The ideal solution would naturally be the elimination or correction of the causes underlying the disorder, or at least an intervention which halted the progression of the disease at a given point. Until the 1930s, many workers were hopeful that the required knowledge for such a curative therapy would be available in the near future, and often apologized that any proffered treatment was not this ultimate therapy, but rather an interim solution. It was nevertheless hoped that these provisional answers might at least provide clues as to the identity of the final “cure”. As late as 1965, the neurologist Boshes compared the chemical therapy of parkinsonism with doing something to a “black box”: the clinician administered a drug he did not completely understand to patients whose disease he understood even less, and simply hoped for the best.

James Parkinson, noting this conundrum early, wrote in his booklet on paralysis agitans that:

Until we are better informed respecting the nature of this disease, the employment of internal medicines is scarcely warrantable; unless analogy should point out some remedy the trial of which rational hope might authorize.

Despite the justifiably cautious note, Parkinson suggested in the same paragraph that:

the intelligent will never fail to avail themselves of the opportunity of making a trial of the influence of mercury, which has in so many instances, manifested its power in correcting derangement of structure.

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1 Boshes, 1965.
2 Parkinson, 1817; p.62.
Parkinson’s admonition would also be disregarded by many others who followed him; the disease named for him was to become the target of many would-be miracle-workers, so that by the second half of the twentieth century each new “breakthrough” would be greeted by the skeptical coolness which resulted from more than one hundred and fifty years of disappointments.

Parkinson was reasonably confident that “some remedial process may ere long be discovered, by which, at least, the progress of the disease may be stopped.” He was clear about the fact that he was not describing a new disease; it had simply been disregarded up until his time as being the “irremediable diminution of the nervous influence, naturally resulting from declining life.” This attitude had led to the disease being neglected and remedies not being sought; it was perhaps the fact that the patients concerned were in the twilight of their years that enabled so many physicians to experiment with speculative cures in the years following the appearance of Parkinson’s book.

Before criticisms of “quack physicians” are too loudly raised, a little thought should, however, be directed to the state of medical knowledge at the time. The pharmacopoeia of the mid-nineteenth century doctor contained little more than iron as a general tonic, mercury for syphilis and ringworm, digitalis for the weak heart, amyl nitrate for angina, quinine for malaria and colchicine for gout; he could also dispense a wide variety of purgatives. Roy Porter cited the report of a visitor to St Bartholomew’s Hospital in London in 1869:

120 patients were seen by the physician and dismissed in an hour and ten minutes. . . . [Each received] a doubtful dose of physic, ordered almost at random, and poured out of a huge brown jug.6

The two ruling principles of medicine: “elimination, and the supply of some elements to the blood.”7 Apart from this, there flourished a trade in the plethora of snake-oil and home remedies with which people sought to cure themselves without the doubtful aid of professional advice, which at best were harmless and at worst highly dangerous. Finally, it should be remembered that at Parkinson’s time the “doctrine of the nerves” had not yet assumed the dominance in neurology which it would later assert; the question of the localization of specific brain functions was still too much a passionately contested issue that speculation over the mechanisms operative within a particular brain region could be useful. The fact that Parkinson’s acute observations led him to the hypothesis of a specific anatomic lesion which was responsible for the symptoms of paralysis agitans while sparing other motor and psychic functions was, in fact, a bold step at the time it was made.8 With regard to paralysis agitans, Parkinson stood at that point which marks the beginning of all scientific achievement: careful observation and collation of the available facts. Other tools and methods would be required, not to mention a more detailed conception of the nature of brain function, before the talk could be of “rational hope” in the treatment of parkinsonism.

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5 Ibid.; p.64.
6 Porter, 1999; p.674.
7 Ibid.
8 See also Riese and Hoff, 1951, especially pp.455-457.
Parkinson had speculated that the immediate cause of the disorder was a:

*diseased state of the medulla spinalis, in that part contained in the canal, formed by the superior cervical vertebrae, and extending, as the disease proceeds, to the medulla oblongata.*

He based this premise on the belief that the disease involved derangement of nervous transmission to the affected limbs; at the same time, he conceded that the six cases which he had described had provided no evidence which corroborated this opinion. The controversy over Parkinson’s disease secondary to mechanical trauma would continue until the present day; evidence for its accounting at best for more than a vanishingly small number of cases, however, has never been reported. Parkinson’s preferred option for the treatment of victims was phlebotomy, which by this time was generally falling out of favor: to relieve the pressure on the medulla, blood should be taken from the upper part of the neck, followed by the application of vesicatories (cupping glasses used in venesection) and the encouragement of pus production (suppuration) by use of the Sabine liniment. Parkinson was still under the influence of medieval ideas of the influence of digestive processes on nervous function, and had also noted the bowel problems experienced by parkinsonian patients; he therefore treated the trembling of one patient with a dose of calomel (mercurous chloride) and Epsom salts (magnesium sulphate); the opening of the man’s bowels resolved his physical situation within ten days. Parkinson, however, did not advance this as a cure for paralysis agitans, but rather as an example of the unlikely influence of the intestines upon nervous function.

The first review of Parkinson’s booklet appeared in the *London Medical Repository* in July 1817. Its one-and-one-half pages (including several direct citations) was warm in its praise; the fact that Parkinson had brought precision to the term “palsy” and defined paralysis agitans as a specific disease was a tribute to “the acuity of his observation.” Interestingly, it was noted that the treatment of the disease, due to its progressive nature, was unlikely to meet with great success, and, if at all, only during its early stages. The *Medico-Chirurgical Journal and Review* devoted a total of six and one-half pages to Parkinson’s work, and was confident that his reputation as man and physician should ensure that he was secure from “censure which the precipitate publication of mere conjectural suggestions may incur.” As well as including case-reports from other physicians, the journal recommended the pamphlet highly. Parkinson’s tract was also greeted with praise by the *London Medical and Physical Journal* in two articles which appeared in 1818. An anonymous reviewer remarked that its “confined size . . . will bring it within the reach of every Practitioner, and we heartily recommend it to universal perusal.” It is also reported that a positive review appeared in 1817 in the Swedish journal *Ars-Berättelse om Svenska Läkare-Sällskapets Arbeiten.*

9 Parkinson, 1817; p.33-34.
11 Prepared from the tops of the savine (*Juniperus sabina*; a conifer); also used to treat syphilitic warts. Occasionally used internally as an emmagogue or abortifacient, but can cause death through severe gastrointestinal irritation.
12 Parkinson, 1817; p.56-66.
13 Murrows and Thomson, 1817.
14 Cited in Herzberg, 1990.
15 Anonymus, 1817.
16 Cited in McMenemey, 1955, p.126.
II. Therapy of parkinsonism in the first half of the nineteenth century

But the disorder appears to have received little attention during the following half century. This is probably to be attributed to the reasons advanced above for its having been ignored thus far; the advanced age of most sufferers dissuaded physicians from all too great efforts in searching for a cure.\(^{17}\) There is also the fact that it was described by most 19th century authorities as a rare disease; whether the word “rare” should be replaced with “unrecognized” or “disregarded” is another question. It was also due to the fact that Parkinson’s booklet was only printed in limited numbers; by 1922, only five copies were known to exist.\(^ {18}\) In any case, Parkinson’s observations were cited by a number of British textbooks in the two following decades without much novel information being added. He was quoted at length, for example, in what is often considered the first textbook specifically devoted to neurology, John Cooke’s (1756-1838) *A treatise on nervous disorders*.\(^{19}\)

The first original contributions were the publications of John Elliotson (1791-1868; St Thomas’s Hospital, London) in the *Lancet*.\(^{20}\) Elliotson acknowledged in 1830 that most of his information about the disorder stemmed from Parkinson’s pamphlet, and noted that cases were more commonly encountered in the private practice than in the hospital.\(^ {21}\) His own publications appeared in the years 1827 to 1831 as transcripts of clinical lectures, and consist largely of case reports; many of these, however, would now be interpreted as different neurological diseases, but a number were probably what we term Parkinson’s disease. The rather vague nature of paralysis agitans is indicated by this definition by an anonymous writer in the *Lancet* in 1831:

> When an universal or partial muscular tremor prevails as a chronic affection, and not as a symptom of acute disorder, it is termed shaking palsy. It is a disease of the nervous system, the proximate cause of which we are unacquainted . . . The trembling hand of the drunkard is a minor degree of this affection.\(^ {22}\)

Elliotson distinguished between “organic paralysis agitans”, which was a disease of old age and could not usually be treated with any success, and traumatic paralysis agitans, which resulted from stress or shock.\(^ {23}\) Nevertheless, it is not always certain that he was describing what we would regard as Parkinson’s disease. For instance, the case he introduced in his 1830 lecture was a 38 year old man with tremor of the right arm; but the disease was reported to have begun in his head and tongue: on attempting to speak, *“the tongue begins to quiver like the tongue of a serpent”*.\(^ {24}\) A number of possibilities were considered as causes of the disorder in this case: a fall, mercury exposure, anxiousness, alcoholism, or a combination of any of these moments.

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\(^{17}\) One of the discoverers of the L-DOPA therapy, Walther Birkmayer, often noted that various disorders of advanced age were popularly attributed to “*calcium in the brain*”; that is, as the inevitable companions of the ageing brain.

\(^{18}\) Osthoeimer, 1922.

\(^{19}\) Cooke, 1824; p.207.

\(^{20}\) Elliotson, 1827, 1830, 1831a,b,c.

\(^{21}\) Elliotson, 1830.

\(^{22}\) Anonymus, 1831.

\(^{23}\) At least in the popular mind, these two causes could be linked; Horowski and colleagues (1995), for instance, have presented evidence that the German academic Wilhelm von Humboldt (1767-1835) suffered from Parkinson’s disease during the last seven years of his life, which condition he described not as a disease but as accelerated ageing following the death of his wife in 1829.

\(^{24}\) Elliotson, 1830.
Amongst his preferred methods of treatment were bleeding, induction and maintenance of pus building (with setons and issues), cauterization, purging, low diet and mercurialization, as well as the administration of iron, silver nitrate, arsenic, zinc sulphate and copper compounds. As a nerve tonic, iron was preferred to arsenic, both for its safety and its lesser propensity to irritate the stomach, and silver, which tended to blacken the skin. As an adjunct to iron therapy, Elliotson allowed a “certain allowance of porter”, a popularly recognized tonic until very recent times. One of his cases was particularly interesting, as it represents the first claimed cure of a parkinsonian patient:

*I have never been able to cure a person of [paralysis agitans] at or after middle life. I cured one between thirty and forty years of age, but he was the oldest. In this case it came on from fright, and therefore there may be nothing organic.*

Elliotson indeed noted that many young patients could be cured. The “cure” in this case consisted of the carbonate of iron, widely employed in various nervous diseases at this time, apparently with beneficial effect, although a rather unreliable one. On another occasion, he reported that the “disease instantly and permanently gave way” when he treated with iron a patient who had proved resistant to all other forms of therapy.27

The great English physiologist and brain researcher Marshall Hall (1790-1857), author of the reflex theory of nervous function,28 described in 1841 the case of a 28 year old man who suffered from “hemiplegic paralysis agitans”:

*[he] is affected by weakness and agitation of the right arm and leg; augmented on any occasion of agitation, and on moving.*

This may, however, have been multiple sclerosis.30 Hall was also responsible for firmly establishing paralysis agitans as the recognized term for the disorder. Several reports of probable parkinsonian patients are found in the reports of Guy’s Hospital for 1853,31 and the description by G.E. Paget of a case of “involuntary tendency to fall precipitately forward”32 is also reminiscent of Parkinson’s disease, as is Toulmouche’s case of an elderly gentleman with tremor and problems with balance and walking.33 There are, however, clear indications that, in the half century after the warning in Parkinson’s pamphlet that tremor could arise from any of a number of etiologic causes, the term “shaking palsy” was applied to most disorders in which tremor or impaired motor performance was the dominant feature, including cases of “intermittent paralysis agitans” and cases in which spontaneous recovery of function was observed.34 The use of the term “paralysis agitans” would continue to be employed into this century for any case involving tremor, whether as the result of physical or emotional shock, disease or sexual incontinence.35 This confusion of definition was not assisted by the fact that

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25 Elliotson, 1831b.
26 Anonymus, 1831; Elliotson, 1827; 1830; 1831b,c.
27 Elliotson, 1830.
28 Expounded in *The reflex function of the medulla oblongata and medulla spinalis* (1833).
29 Hall, 1841; p.320-321.
30 Hesselink, 1996.
32 Paget, 1855.
33 Toulmouche, 1833.
34 For instance, Gowry, 1831; see other examples cited in Louis, 1997.
35 As late as 1910, a “typical” case of paralysis agitans in a 33 year old beer carter could be unequivocally attributed to shock ensuing from the loss of a sum of money: Lowinsky, 1910.
many workers tended to see the tremor of paralysis agitans, fatigue, old age, drunkenness and of other causes as essentially manifestations of a common physiological phenomenon. It was also not until Handfield Jones (1864) and Charcot (1868) that at least a theoretical distinction was drawn between paralysis agitans and “juvenile paralysis agitans” (multiple sclerosis), a distinction which was still debated in the early part of the 20th century. Such problems, of course, confound epidemiological and therapeutic interpretations of reports from this period.

This illustrates the problems relating to definition of ‘parkinsonism’ to which I alluded in the previous chapter. As concluded by Hesselink in his excellent review of the development of the concept of parkinsonism, Parkinson’s disease was in the period 1817 to 1867 “relatively unknown and not distinguished from multiple sclerosis, chorea, senile tremor, tremors caused by mercury and other neurological conditions.”

On the other hand, it was also recognized by some physicians that paralysis agitans without tremor was also possible; indeed, Charcot argued that the term paralysis agitans should be abandoned, as the trembling was the most striking feature of the disorder, but neither always present nor essential for the diagnosis. The appropriateness of the term ‘paralysis’ was also contested, and at the end of the 19th century the term ‘paresis’ was often substituted in cases where total loss of movement was not involved; Gowers disdained this as an affectation for the benefit of the patient, noting that ‘paralysis’ referred only to a partial or complete loss of control of voluntary movement, and was thus quite justified in parkinsonism. As discussed in the opening chapter, this terminological difficulty reflected only the shift in the meaning attached to ‘paralysis’.

**Therapy for parkinsonism from the middle of the 19th century**

Understandably, the confused situation regarding the clinical entity ‘parkinsonism’ was not conducive to the development of rational therapies for the disorder. The first clear recommendation of a pharmacological agent following Elliotson’s iron cure was that of ergot of rye (*Secale cornutum*) by the English “Surgeon &c.” J.B. Thompson in 1842, which he successfully employed in St Vitus’ dance patients. Thompson had been prompted to try it in the latter cases on two grounds: firstly, because of its well-known stimulating effect on the uterus, which effect seemed desirable in his cases of female chorea patients; and secondly, because it had recently been discovered to help in cases of lead-induced paralysis, and in “the paralysis agitans or tremens in advanced life, where I have seen it of considerable benefit recently myself.” Thompson supposed that

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36 Ordenstein, 1867; Charcot, 1868 (in Sigerson, 1877; p.133-4, p150); Jones, 1864, 1873. Even after this time, the distinction was seen by many clinicians as rather theoretical: see Manschot, 1904.

37 Hesselink, 1986; p.48. Handfield Jones was one of the earliest authorities to plead specifically for a distinction between mercurial tremor and paralysis agitans; his comments indicate that his was a view not widely shared at the time. Jones, 1864, pp.267-269. At the same time, his definition of ‘paralysis agitans’ remained broad: he described the case of a man cured fifteen days after contracting the disorder by a series of hourly applications of a 120-link Pulvermacher’s chain (p.264). For a depiction of the Pulvermacher’s chain, see http://www.collectmedicalantiques.com/quk_26.html (accessed 12.02.01).

38 Cited in Hesselink, 1991. See also Charcot (Goetz), 1987, pp.123-130; this is the English translation of an 1888 lecture in which he described a case of Parkinson’s disease in which tremor was absent. Interestingly, the presented patient was 31 years old and had suffered from parkinsonism for five years; it had, however, been developing for twelve years following successive bouts of rheumatism. Charcot devoted a great deal of attention to the differential diagnosis of tremor: see Charcot, 1889, pp.183-197. See also Beevor, 1885, Bramwell, 1905/06.

39 Gowers, 1885; p.49.
it must act directly on the muscles, as its effect was too rapid to be accounted for by 
circulation; more he was not willing to hypothesize. In paralysis agitans, it conveyed “a 
more fixed steadiness and firmness”, and could be “given to a larger amount than is 
generally supposed”; he was, however, aware of the risks of accumulation, the danger 
of which appears to have blocked its more widespread application.40

The Berlin Professor of Medicine Moritz Heinrich Romberg (1795-1873) saw 
paralysis agitans as a type of tremor which he discussed with but distinguished from 
mercurial, febrile and senile tremors, and also distinct from “tremor potatorum”. He 
noted the view of Volkmann that tremor in animals could be elicited by interruption of 
the normal train of stimulation to the affected organ, but did not involve this finding in 
his therapeutic approach. Romberg regarded paralysis agitans as a “neurosis of 
motility”, “a bridge which conducts from the region of convulsions to the paralyses”.41
It should be noted that ‘neurosis’ in the 19th century referred generally to any disorder 
of affect or motor performance in which a neurological basis was presumed but not 
apparent. Romberg had seen many cases of paralysis agitans, for which he knew no 
definite cause, but:

All the remedies had proved fruitless; issues ordered by another physician to be applied 
to the spinal column, together with the endermatic application of strychnia, had only 
increased the intensity of the disease.42

In another case, he had achieved some success with warm baths, with cold affusion to 
the head and neck, and carbonate of iron; it was doubtful, however, that this woman was 
suffering from paralysis agitans, although it is interesting that she had suffered a 
“nervous fever” thirty years earlier.43 It should, however, be noted that ‘meningitis’ was 
associated in the first half of the 19th century with a variety of conditions, including 
gastrointestinal conditions; Mettler noted that parkinsonism was often attributed to 
“‘chronic’ meningitis”.44

Many of the cases reported in the second half of the 19th century did not indicate 
whether any treatment at all was attempted, simply recording in impressive detail the 
nature of the presented symptoms, the character of the patient affected (often stated was 
the fact that the case involved a man of temperate habits and good character, who had 
ever drunk strong tea or coffee, etc.) and anecdotal information on other family 
members who had suffered nervous disorders; a hereditary component to the disorder 
was suspected from the time the disorder had been recognized as a distinct nosological 
entity. It was often noted that the disorder was manifested initially as a unilateral 
complaint, but physicians generally expected that it would eventually spread to the 
other side.45 The rather alarming nature of the cures attempted is exemplified by the 
means adopted by William Sanders in 1865 for a case of “dystaxia, or pseudo-paralysis 
agitans”:

40 Thompson, 1842.
41 Romberg, 1853, p.230.
42 Ibid.; p.234.
43 Ibid.; p.235. Romberg was not sure “whether these circumstances and eleven confinements, and a life 
worn out by anxiety and care” could be held responsible for the disorder.
44 Mettler, 1947, pp.568-569.
45 For example, Haynes, 1869.
The treatment has been conducted on the tonic plan, together with narcotics; the principal means employed were, good diet, steel, quinine, zinc, arsenic, iodide of potassium (which last made him worse), belladonna, henbane. Warm poultices to the spine were of marked benefit; counter-irritation did no good. . . . On the whole, no single remedy except belladonna and chloroform has exerted any marked beneficial effect, but the general tonic treatment has been of advantage. 

Sanders was unusual in that he explicitly complained about the careless employment of the term paralysis agitans; as defined by Parkinson, he said, paralysis agitans is a disease of old age characterized by two clinical symptoms:

- “tremor coactus”, which gradually develops, initially in the arms, and occurs “in parts not in action, and even supported”;
- “sclerotyrbe festinans”, or the propensity to bend the trunk forwards “and to pass from running to a walking pace.”

This was the reason for the title of Sanders’ paper; he recognized that his patient, who was 35 years old, did not fully meet these criteria; he suggested that true paralysis agitans be termed “paralysis agitans Parkinsonii” or “senilis”, as non-senile cases of the disorder, of unknown etiology, were also seen.

Sanders mentioned in this paper that the application of “galvanism” was without benefit for his patient. The utilization of electrical means for the diagnosis and therapy of motor disorders had been popularized around the middle of the century by the French doctor Guillame Benjamin-Amand Duchenne de Boulogne (1806-1875) with his 1855 publication *On localized electrification, and on its application to pathology and therapy*. Duchenne was the first to describe a number of motor disorders, including progressive bulbar paralysis, hypertrophic muscular paralysis and the progressive muscular atrophy which bears his name. According to Charcot, his friend Duchenne had reported a case in which he had cured paralysis agitans by application of galvanism. The approach was popularized in Germany by Wilhelm Erb, one of the most prominent neurologists of his time, with his book *Handbook of Electrotherapeutics* (1882). Electrotherapy was more popular on the continent than in the English-speaking world – both Hughlings Jackson and William Gowers, who tried it in paralysis agitans, were unstinting in their deprecation of the practice as “useless” – but even there it found adherents. An amusing case was reported by the Dublin physician U.S.L. Butler in 1869:

*While occupied some few days ago in preparing an electromagnetic machine for application to a patient, an old servant (upwards of 80 years), who had long been subject to violent spasmodic tremblings of both arms, chanced to enter the room. More I must confess in the spirit of levity than either philanthropy or philosophy, I asked her to...*

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46 Sanders, 1865.
47 Ibid.
48 Original title: *De l'electrisation localisée, et de son application à la pathologie et à la thérapeutique.* Electricity, however, had been applied “in the form of sparks” (for example: Elliotson, 1831) since the first quarter of the 19th century, and was applied to disorders ranging from chronic pain to insanity.
49 Charcot, 1868 (in Sigerson, 1877); p.155.
50 Original title: *Handbuch der Elektrotherapie.* Erb had written on the subject for at least fifteen years; see, for example, *Galvanotherapeutische Mitteilungen* in the *Deutsches Archiv für klinische Medizin* (III, 1867).
51 Gowers, 1893; p.656-657.
take hold of the electrodes of the machine, at the same time pressing the bundle of soft wires some distance into the centre of the helix, so as to give her a pretty sharp shock.52

The experiment, which had not been approved by an ethics committee, resulted in the cure of her paralysis agitans, so that her greatest pleasure became the demonstration of “her powers as an equilibrist to any one who may feel an interest in the matter.” It should be noted, however, that the editor of the journal appended the comment that he believed this example of “the disappearance of a singularly incurable disease” was the result of emotion, not of electrical effects. The application of electrical stimulation in Parkinson’s disease continued to be employed into the 20th century, though rarely with such marked success. In the 1924 edition of his handbook on electrotherapy, Toby Cohn (Berlin) commented that “remarkable results could not be expected”; early cases might benefit from galvanization of head or neck, but in advanced cases the best which could be achieved was some relief of tremor by application of galvanic baths. Even in these cases, however, he considered the benefit to be largely psychological.53

There was thus little comfort to be drawn from school medicine at this stage for the parkinsonian patient. It is probable that most patients, whatever their social standing, were seen as suffering the ravages of advanced age, and never came to the professional attention of a physician; indeed, it is generally only those physicians who worked in large public institutions or polyclinics, such as Charcot and Romberg, who claimed that they had seen many cases of the disorder. Traditional popular remedies and tonics were undoubtedly applied in most cases by relatives and friends of the victims, but there is certainly no indication that any such alternative met with great success.

52 Butler, 1869.
53 Cohn, 1924, pp.140-141, 150. Electrotherapy of parkinsonism was not completely unknown as late as the 1930s; in his 1941 review of the “modern treatment of parkinsonism” (1941), Critchley specifically warned against strychnine, electricity and “dietetic and other spurious claims of ‘curing’ this disease.” As electrotherapy is only tangentially relevant to the current work, a discussion of the various techniques employed would be inappropriate here; these issues are discussed in detail in Cohn’s book. It suffices here to note that galvanic methods exposed the patient directly to the battery current, faradization employed induced current and ‘sparks’ or ‘franklinization’ employed static electricity.
III. The solanaceous alkaloids

The importance of plant-derived substances in the history of medicine cannot be overestimated. Until the advent of modern synthetic agents, many of which are ultimately derivatives of vegetable substances, vegetable products dominated non-surgical therapy of most disorders. It is interesting to note that even in English the word ‘drug’ corresponded to the German ‘Droge’ until at least the Second World War; that is, it denoted a plant extract used for pharmacological purposes. This distinction, which points directly to the botanical origins of modern medicine, was only lost in the course of the 1950s.1

For the therapeutics of parkinsonism, those plant constituents designated as ‘alkaloids’ would play a major role for one hundred years. The definition of the term ‘alkaloid’ is problematic. It is usually employed to refer to nitrogen-containing bases which have a limited distribution in plants; Pelletier further specified that it should include a cyclic structure with nitrogen in a negative oxidation state.2 In general, this term has included any compound isolated from a plant which has at some time been described by an investigator as an alkaloid.3 Most alkaloids are colourless crystalline substances composed of carbon, hydrogen, oxygen and nitrogen; the few which do not include oxygen are colorless liquids (such as coniine and nicotine). Hegnauer (Pharmacognosy and Experimental Plant Taxonomy, University of Leiden) suggested a classification of such substances into three classes:

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1 Both words are derived from the French ‘drogue’, which itself was loaned from Lower German ‘droge’ or Dutch ‘droog’, meaning ‘something dried’. For the more recent shift in the meaning of the English word, see Parascandola, 1995: The drug habit: the association of the word ‘drug’ with abuse in American history. For recent discussion of role of alkaloids in the development of the pharmaceutical industry, see Parascandola, 1997.
3 The vagueness of the term is indicated by the fact that Thudichum, regarded by man as the father of neurochemistry, could speak of “the simpler alkaloids of the brain” (Grundzüge der anatomischen und klinischen Chemie, Berlin, 1886; p.172); that reference to animal ‘alkaloids’ was considered unusual at the time is indicated, for example, by the enclosure of the term in quotation marks by Gulewitsch (1899) when discussing Thudichum’s work. It has since been recognized that certain alkaloids can be synthesized by animals; these are termed ‘leukomaines’.
III. The solanaceous alkaloids

- **Protoalkaloids**: simple bases which arise through either the decarboxylation (biogenic amines) or N-methylation of amino acids, or which are choline derivatives.
- **Pseudoalkaloids**: bases which are clearly related to non-alkaloid plant constituents; these include, for example, various terpene-based molecules, and simple derivatives of nicotinic acid.
- **True alkaloids**: plant constituents of limited distribution in which the nitrogen-containing element is derived from an amino acid, but by a multistage process rather than simple decarboxylation.\(^4\)

Hegnauer divided the true alkaloids into biogenetic families according to the parent amino acid: phenylalanine, tryptophan (subdivided into simple and complex derivatives), ornithine, lysine and anthranilic acid. Most of the alkaloids to be described in the current work – namely those extracted from solanaceous plants – belong to the ornithine family (figure 3-1), which includes the tropine and ecgonine subtypes.

Now recognized as alkaloids are substances which are not derived from amino acids and would have been rejected by Hegnauer’s classification; for example, steroid and diterpene alkaloids, in which the nitrogen atom is incorporated at a late synthetic stage into an existing molecule. Various plant peptides are also classified as alkaloids.\(^5\)

The physiological function of plant alkaloids remains somewhat unclear. The production of alkaloids by plants is restricted to a few dicotyledon orders, and the characteristic presence of specific alkaloids or alkaloid types by particular orders, genus or even species has been exploited for taxonomic purposes.\(^6\) Most alkaloids occur as salts of organic acids, such as malate, succinate or citrate; some are found only in certain parts of the plant in which they occur, others are distributed in all tissues. Variations in alkaloid content have also been noted with stage of growth, conditions of cultivation and even with time of day.\(^7\) Some alkaloids, such as L-DOPA, appear to serve protective functions, in that they render the plant unpalatable for potential predators. Alkaloids might also serve as waste products of nitrogen metabolism, consistent with their occurrence in tissues which are shed, such as seeds and fruit; this appears to be the case for the opium poppy alkaloids. Alternatively, the solanaceous alkaloids are tropane esters which appear to be transported from the roots to aerial parts, where hydrolysis of the ester and breakdown of the acid component ensues; the alkaloid may thus serve to dispose of metabolic acids. Alkaloids could also serve as nitrogenous intermediates in general metabolism. On the other hand, neither allographic manipulations which result in the absence of alkaloids in plants which normally produce them, nor the administration of alkaloids to plants in which they do not occur appear to compromise the viability of the plant; it may thus be that plant alkaloids are, to certain extent, chance products of ubiquitous reaction pathways, the innocuous nature of which has protected them from elimination by natural selection. Whatever the reason for their presence, it certainly has little to do with their actions in man.\(^8\)

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\(^6\) Hegnauer, 1963.
\(^7\) A particularly spectacular example of this phenomenon was reported in 1961 by Fairbairn and Suwal, who found that the conine content of the fruit of *Conium maculatum* varied on a diurnal basis from 8µg/fruit at 4 p.m. to 226µg/fruit at 4 a.m. See also Boshart, 1931.
\(^8\) Reviews: Waller and Nowacki, 1978 (pp.143-182); Trease and Evans, 1983 (pp.540-541); Schlee, 1985.
III. The solanaceous alkaloids

Figure 3-1: Postulated synthetic pathway for plant alkaloids derived from ornithine. The conversion of the N-methyl-4-pyrrolinium salt to the hypothetical intermediate hygrine-carboxylic acid involves reaction with acetoacetate, followed by spontaneous decarboxylation to hygrine. For further details, refer to the sources upon which this figure is based: Trease and Evans (1983; pp.546-547) and Liebisch and Schütte (1985; pp.108-111).

Whatever the definition of the term ‘alkaloid’, Wootton could confidently assert in 1910 that the three great achievements of 19th century pharmacy were the discovery of alkaloids at the beginning of the century, of anesthetics in its middle, and of synthetic organic compounds towards its end. Further:

The alkaloids extracted from vegetables are the ideal quintessences which the alchemical pharmacists of the sixteenth and seventeenth centuries sought so eagerly to obtain.⁹

⁹ Wootton, 1910, p.243.
This enthusiasm for the use of extracts, let alone purified chemical substances, in place of the original plant has not always received universal applause; some pharmacists and others argued (and argue) that if the plant itself is sufficiently potent, there existed no need to remove the active constituents from their natural environment. A certain Fischer from Erfurt, for example, argued in 1837 that the various German pharmacopoeias had become swollen with unnecessary extracts of various forms of dubious quality:

I evaporated equal quantities of opium tincture from six otherwise very good pharmacies and found in each case a different amount of dry residue. I dissolved in water the hyoscyamus extract from three different but equally good pharmacies. One solution was bright green, another dark green and the third brown.10

The separation of alkaloids only exacerbated this situation in Fischer’s eyes; he saw this process not so much as the purification of active principles but as the disintegration of an effective medicinal herb into disparate components, none of which could be identified with the properties of the whole plant. In the same article, however, he delivers the very argument which partly motivated the search for the essential elements of medicinal plants:

The digitalis and the belladonna which grow in our Thuringian forest and on the northern Alps are much more potent as those from lower regions. In an area of the local government district which is of neptunian origin, hemlock grows which surpasses that of all others in its effect; not to mention other potent herbal drugs from foreign countries, even the age of which is unknown.11

The author was particularly distrustful of the ‘narcotic drugs’ – those derived from the poppy and the solanaceous plants –, precisely those which attracted most attention in the early days of alkaloid discovery.

The first alkaloid to be isolated was morphine (“principium somniferum”), prepared in 1806 by the Eimbeck pharmacist Friedrich Wilhelm Sertürner (1783-1841); until this point, the active principles of plant drugs were thought to be exclusively acids.12 The Halle pharmacist Karl Friedrich Wilhelm Meissner (1792-1853) coined the term ‘alkaloid’ in 1819:

It actually appears to me appropriate that the hitherto recognized alkaline plant substances be termed not ‘alkalis’, but rather ‘alkaloids’, for they differ greatly in many respects from alkalis; they would then assume their place in plant chemistry before the plant acids.13

10 Fischer, 1837.
11 Ibid.
12 Sertürner, 1806. For biography of Sertürner, see Krömeke, 1925. Sertürner was a controversial character – he had no formal training as a chemist and was psychologically labile – and his claim to priority in the discovery of morphine was fiercely contested but ultimately recognized in France. The French chemist Derosne chemist had achieved the same feat in 1803, but had not recognized what he had done, attributing the alkaline nature of his isolate to residual preparative alkali; Seguin reported a process for the preparation of morphinum in 1804 but, for unknown reasons, did not publish his report until 1814. In any case, the news from both France and Hanover passed largely unnoticed. It was only with the publication in 1817 of Sertürner’s proof that ‘morphium’ formed salts with acids that the significance of his earlier discovery was recognized; his priority was officially recognized by the French Institute in 1831. He also correctly identified the means by which cholera was communicated, but was ignored. Wootton, 1910, pp.243-245; Partington, 1964, p.240; Hosztafi, 1997.
13 Meissner, 1819; the paper described his isolation of the alkaloid veratrine. For biography of Meissner, see Friedrich and von Domarus, 1998.
The term was, however, not immediately adopted by the chemical world. In the fourth edition of Ure’s chemical dictionary (1835), the “vegetable alkalis” constituted the third class of alkalis (the others were metal bases combined with oxygen (potash, soda and lithia) and those lacking oxygen (such as ammonia); the author noted that this class, which included at least nine members (amongst others, ‘hyoscyamia’ and ‘datura’), were “called by the German chemists alkaloids.” He also noted, however, that certain authorities regarded their presence in vegetable extracts as an artifact of the preparative process. The Swedish chemist Berzelius (1779-1848) used the term ‘vegetabilische Salzbassen’ or ‘alcalis végétaux’ in his authoritative Lehrbuch der Chemie and Traité de chimie; this marked the official acceptance of bioactive alkaline plant substances. The French chemist Dumas (1800-1884) employed the term ‘alcaloïde’ in his Traité de chimie appliquée aux arts.

It was initially assumed that the alkaline nature of these principles was due to the presence of ammonia, but this was subsequently disproved by Justus Liebig (1803-1873), who also proposed a hypothesis for their mechanism of action:

*If we reflect that this action is exerted by substances which are material, tangible and ponderable; that they disappear in the organism; that a double dose acts more powerfully than a single one; that, after a time, a fresh dose must be given, if we wish to produce the action a second time; all these considerations, viewed chemically, permit only one form of explanation; the supposition, namely, that these compounds, by means of their elements, take a share in the formation of new, or the transformation of existing brain and nervous matter.*

Liebig was aware that this model was “strange”, but noted that the brain and nerves themselves were composed of materials supplied by vegetables. It must also be remembered that the hypothesis was expressed at a time when localization of function in the cerebral ‘organ’ was still controversial, and the nerves emanating from it regarded as endless bifurcating ribbons – analogous to the increasingly small branches and anastamoses of the circulatory system – which conducted ‘force’ to and from the brain. By the end of the century, investigators were employing concepts closer to those which are now current, but even by this point the mechanisms involved were perceived only vaguely:

*When considering more closely the actions of toxins which modulate sharply defined functional areas, one is again and again drawn to the idea that the elementary organs associated with those functions – the protoplasm of the nerve cells – must exert a sort of attractive force on the toxins, which generally circulate at extremely small concentrations in the blood of the living organism. The nature of this attraction is obscure.*

This ignorance regarding their mode of action was initially inconsequential. The identification of new alkaloids by chemists and pharmacists was pursued throughout the

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14 Ure, 1835, p.135.
15 Ibid., p.805.
16 Berzelius, 1827, III/i, p.238 (German); 1831, V, p.118 (French).
17 Dumas, 1835, V, p.724.
18 Liebig, 1833b.
19 Liebig, 1843; pp.182-183.
21 Boehm, 1895.
19th century with great vigor; between 1817 and 1835 the majority of the most important plant bases had been isolated, including strychnine (1818), caffeine, quinine (1820), nicotine (1828), conine (1831), codeine (1832) and colchicine (1833). By 1904, Pictet listed about 200 alkaloids, although the structure of most was still unknown.

The chemist Philipp Lorenz Geiger (1785-1836) made an especial study of the plant alkaloids (then still generally designated ‘organic alkalis’) at the beginning of the 19th century in Heidelberg, being the first to described in detail the properties of a number of poisonous extracts, including belladonna, hyoscyamine, daturine, colchicine and aconitine. Despite their role as toxins, Geiger noted:

The organic alkalis are amongst the most powerful medicaments and their study is thus also for the doctor of the greatest importance.

These prophetic words would prove to be particularly relevant to the treatment of parkinsonism: almost all medications for the disorder would be solanaceous plant extracts until the 1950s.

The firm Merck (later E. Merck) played an distinguished role in the history of the development of alkaloid pharmacology. The Merck family, which originated in the Franconian towns of Hammelburg and Schweinfurt, had long been involved in the apothecary business in Darmstadt – Friedrich Jacob (1621-1678) acquired the Engel-Apotheke (Angel Pharmacy) in 1668 – by the time Heinrich Emanuel (1794-1855; great-great-great-grand nephew of Friedrich Jacob) founded the firm bearing the family name. Emanuel trained at Trommsdorf’s famous Chemical, Physical and Pharmaceutical School for Young Men in Erfurt, followed by work in Eisenach, Frankfurt and Strassburg and further study in Berlin and Vienna, and assumed control of the family pharmacy in 1816. He directed his attention to the large scale purification of phytochemical products, particularly of plant alkaloids; his skills in the laboratory bestowed success upon his preparation of alkaloids, and in 1826 he published his method for the preparation of morphine in the 

Magazin für Pharmacie. In 1827,

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22 Pictet, 1904; pp.3-4; Partington, 1964; pp.241-245.
23 Pictet, 1904; p.4. Mothes and Luckner suggested in 1985 that “about 7000 more or less well-characterized alkaloids may be known.”
24 Geiger became an apprentice apothecary at the age of 14 years; from 1814 he operated the University Pharmacy in Heidelberg, and from 1816 held private lectures on botany, pharmacognosy and pharmaceutical chemistry. He never achieved a Chair in Pharmacy; he was appointed to a Chair in the Medical Faculty in 1824 by Grand Duke Ludwig I of Baden against the wishes of the University, as a result of which he was not paid until 1826. He received an honorary Doctorate of Medicine from Marburg in 1828. Obituary: Dierbach, 1836.
25 Geiger expressed the hope that his results would inspire others to further the investigation of the alkaloids; this was the purpose of his publication of his preliminary results: “For I am not infected with that ridiculous mad lust for priority which might lead me to claim discoveries to which I am perhaps not entitled or even to announce something which later proves to be wrong. Insufficiencies and mistakes are actually so easily possible in chemistry, especially in the investigation of organic substances, and they can often only be corrected through research from many laboratories. . . . What a loss this is for science, and not seldom also for their practical branches which have an impact on our lives.” Geiger, 1833a; pp.279-280.
26 Merck, 1826; see also Merck, 1830. The Magazin für Pharmacie was acquired by Liebig from Geiger in 1831 and renamed Annalen der Pharmacie (from 1840: Annalen der Chemie und Pharmacie; 1873: Annalen der Pharmacie and Justus Liebigs Annalen der Chemie); this journal published many of the significant German language papers on plant alkaloids throughout the 19th century.
Merck described methods for the preparation of all sixteen known alkaloids (including atropine) in the *Cabinet of Pharmaceutical and Chemical Innovations*, simultaneously announcing his intention to produce “this class of medications” in bulk, commencing with the industrial production of opium alkaloids. His products and methods were soon widely recognized, as from the beginning he had laid great emphasis on the purity of his products; as a result, he erected an enlarged laboratory outside Darmstadt in 1840, and this in turn was converted to the Merck factory in 1850.

While working in the laboratory of Justus Liebig, one of Heinrich’s sons, Georg, discovered the alkaloid papaverine, later extensively employed as an antispasmodic. The rapid growth of the company began during the tenure as manager of Georg’s son Emanuel August (1855-1923). He also stimulated the further refinement of stringent quality control of the firm’s products, culminating in the publication in 1888 of *Controlling chemical reagents for purity* by Carl Krauch, a chemist employed by Merck, and the establishment of the purity guarantee for the firm’s products under the label “pro analysi”. As a consequence, Merck chemicals acquired a reputation for absolute reliability, and, as will be seen several times below, were routinely used as reference materials in the analysis of new alkaloids. At the same time, Emanuel increased the range of items offered by Merck; 800 products were listed for sale in 1860, about 10,000 in 1900. The number of employees at Merck also rose: from about 55 in 1855 to over one thousand in 1900. At the commencement of the 20th century, the firm was amongst those chemical firms which successfully established themselves in the new era of “pharmaceutical firms”, which saw the demise of the centuries-old preparation of medications by individual apothecaries. Amongst the items appearing on the first “Patented and Special Preparations List” (1904) was the first commercial barbiturate, ‘Veronal’ (barbital).27

**John Harley and The Old Vegetable Neurotics**

The first detailed descriptions of the use of plant alkaloids in parkinsonism appeared in the volume *The Old Vegetable Neurotics* published by the London physician John Harley (King’s College Hospital, London Fever Hospital) in 1869. Harley discussed in this book the physiological actions and therapeutic applications of the traditional medicinal plants hemlock (conium), belladonna, opium and henbane (hyoscyamus). Belladonna was described as a “direct and powerful stimulant to the sympathetic nervous system”, by which he meant that it was a potent cardiovascular stimulant, and as a “valuable antispasmodic.”28 Its use in various fevers and nephritis was extensively

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27 Most of the biographical information presented here derives from *Neue Deutsche Biographie* (1994; XVII, pp. 118-121), supplemented by Merck (1968), Posselh (no date) and information at www.merck.com.au/about_history.htm. There exists a certain degree of confusion regarding the name “Merck”. Emanuel August’s cousin Georg (later: George) established a branch of the firm in New York in 1887; as a result of World War I, however, the firm was expropriated by the American Government as an enemy alien company. The firm later resumed business as an American company, still managed by George. This company retains the rights to the trademark “Merck & Co.” in North America; in Europe, it operates under the title of the conglomerate “Merck, Sharp & Dohme” (except in Germany: “MSD Sharp & Dohme”). The German company now employs the name “Merck KGaA” in Europe and as “EM Pharma”, “EM Industries” and “EM Science” in the United States (and as “BDH” in Canada). This information appears on the website www.merck.de/english/corporate/culture/ukname.gb.html.

28 Harley, 1869; p.244. Harley recorded that the antagonism between belladonna and opium, noted at least as early as 1570, was not absolute, which had consequences for the traditional treatment of opium poisoning with belladonna; pp.303-311.
discussed, and the side effects associated with atropine described in detail, but its application in paralysis agitans was not yet known. In fact, Harley commented:

*The action on the motor centres and the spinal cord is comparatively slight. The corpora striata participate in both the hypnotic and in the excitant effects. Giddiness and muscular weakness, from inability for exertion, rather than any real loss of motor power, accompany the hypnotic effect... The spinal cord is least of all affected by the action of belladonna. The truth appears to be that it is only when the voluntary control over the muscular movements is weakened, that any effect on the cord is observable. When the movements become feeble and tremulous, it is then that jactitation appears and feeble convulsive movements are apt to intervene.*

Henbane was seen by Harley as a cardiac sedative, useful for various neuralgic complaints, and in spasmodic affectations of the uterus, bladder and urethra, as well as in “epilepsy arising from emotional disturbances”, but in other varieties of the disease and in any convulsive disorder was found to be without effect:

*The plant undoubtedly exercises a considerable depressing influence on the corpora striata, but fails to diminish the excitability of the spinal centres, if it does not actually exalt it. As the will loses much of its directing power under the influence of henbane, the conditions induced by the drug are generally favourable for the development of convulsive action.*

The value of these two plants for parkinsonian patients thus awaited discovery. Hemlock (*Conium maculatum*), on the other hand, was found to be of benefit in paralysis agitans:

*Conium...exerts its power chiefly, if not exclusively, upon the motor centres within the cranium. And of those the corpora striata of course are the parts principally affected.*

He noted the rapid action of conium, and likened its effects to putting the entire motor system to sleep:

![Figure 3.2: Coniine (2-propylpiperidine)](image)

*just as opium tranquillises and refreshes the over-excited and weary brain, so does conium soothe and strengthen the unduly excited and exhausted centres of motor activity.*

Harley, however, saw the effect as not being a depression of vigor, but a tonic for over-stimulated areas of the nervous system; its effects were proportional to the motor activity of the individual. The plant was thus recommended for situations involving convulsions or tetanus, for epilepsy, chorea and “paralysis agitans”. Two cases of the latter treated with conium were described: one involving “general paralysis agitans from defective

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29 Ibid., pp.239-240.
31 This plant was often confused (not always inadvertently) with water hemlock (*Cicuta virosa*); indeed, leaves of the true (or spotted) hemlock were sometimes adulterated with those of the cheaper plant. Note that even the authoritative pharmacologist Sollmann appears to have confused the two plants: Sollmann, 1935, p.412.
32 Harley, 1869; p.11.
33 Ibid., p.12.
nutrition or atrophy of the motor centres, probably excited by ague”, in which the
tremor was exacerbated by conium, and one of “local paralysis agitans” (left arm only)
in a smith suffering from rheumatism and lead exposure (his gums were blue), in which
the tremor was resolved by a combination of succus conii, potassium iodide and
potassium bicarbonate. Harley saw the latter case as representing an early form of full
blown parkinsonism, encouraging his faith in the agent. He emphasized that the
physician must be sufficiently courageous to administer an adequate dose; the
employment of small amounts of conium was equivalent to giving “repeatedly the
hundredth of a grain of morphia to one dying for want of sleep, or a grain of quinine to
cure an ague fit.”

The active alkaloid of hemlock, D,L-coniine (figure 3-2), was first isolated by A.L.
Giesecke (as the sulphate) and by Geiger in 1831. It was also the first alkaloid to be
synthesized in the laboratory (by Ladenburg from picolic acid in 1886; complete
synthesis, however, only in 1906). It occurs at highest concentrations in the unripe
fruit of the hemlock plant, where the content reaches 0.2-0.725%; total alkaloid content
of the young fruit ranges up to 3%. Coniine is only sparingly present in other parts of
the plant. Its pharmacological profile is similar to that of nicotine; it acts as a local
anesthetic when applied externally by paralyzing sensory nerve endings, while internal
use results in inhibition of the motor and (later) sensory nerves. Regarded by ancient
and medieval authorities as extremely toxic, it was not widely used medicinally, and
was thus absent from many medieval herbals. It found limited use, however, as a
narcotic and sedative. It was first brought to prominence in modern medicine by Anton
Störck in Vienna in the second half of the 18th century, as he controversially claimed
great success in the employment of the herb for treating cancer. Conium was used as a
sedative and antispasmodic from the middle of the 19th century, but was virtually
obsolete by the 1920s. As late as 1931, however, Grieve listed succus conii for the
purposes given by Harley; that is, conditions of undue nervous excitability, such as
teeathing in children, acute mania and early paralysis agitans; the French author Leclerc
also saw it in 1927 as valuable in the management of parkinsonism and cramp. Madaus also recommended its employment in the alleviation of parkinsonian rigidity in
1938. Its primary use by this stage, however, was as an external agent in the control of
scabies and as an anodyne and internally to relieve chronic pain in neuralgia and
conditions such as stomach cancer. The major problem with conium itself was the
highly variable alkaloid content of both leaves and fruits and the rapid loss of alkaloid
content in leaf preparations following collection (dried leaves are virtually alkaloid-

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34 Ibid., pp.45-48.
36 Also: conicin or cicutine.
37 Ladenburg, 1886.
39 Schwepe und Probst, 1987. Anticarcinogenic alkaloids have been identified, but not in hemlock;
Solanum dulcamara, for instance, produces the steroid glycoalkaloid β-solamaryne, which has been
shown to suppress sarcoma 180 growth in mice. Interestingly, extracts of this latter plant had been
recommended by Galen for the treatment of warts and tumors; Roddick, 1991.
40 See, for example, Scoresby-Jackson, 1880, pp.258-260.
41 Grieve, 1931, p.393. See also Maric and Boulter, 1921.
42 Madaus, 1938, p.1083. Radaus also cited Potter as listing paralysis agitans under the indications for
coniun (p.1082); this recommendation, however, is not to be found in the 1904 edition of Potter’s
Compendium of materia medica.
43 Ibid.
free), rendering the potency of any sample highly variable. Pure coniine, on the other hand, is one of the most potent known toxins, so that the use of less dangerous alternatives was to be preferred.44

**Alkaloids from the solanaceous plants**

A single family of drugs would play the major role in the attempted therapy of parkinsonism until the 1950s: alkaloids derived from the solanaceous plants. It is remarkable that the drugs which should dominate the therapy of parkinsonism, and which I will therefore introduce in the following pages, for a century should all derive from a plant family whose diverse members were scattered across the planet, and which had been familiar to mankind in various capacities since at least ancient times. As a guide, I will list here the major plants will be discussed, together with their relevant constituents:

- Henbane (*Hyoscyamus niger*): hyoscyamine, scopolamine, atropine.
- Deadly nightshade (*Atropa belladonna*): hyoscyamine, atropine.
- Australian cork-tree (*Duboisia myoporoides*): scopolamine.
- Datura (*Datura stramonium*): hyoscyamine, atropine, scopolamine.
- Scopola (*Scopola carniolica*): scopolamine, atropine.45

Confusion regarding the identity or even existence of individual alkaloids was caused in the 19th century by the expectation that geographically separated plants were unlikely to contain identical alkaloids, which, it seemed, were not crucial to the general physiology of the plant. The major alkaloids isolated from a plant thus tended to be named after their source: scopolamine from *Scopolia*, daturine from *Datura*, hyoscyamine from *Hyoscyamus*, and so on. The situation with respect to the solanaceous alkaloids only began to be resolved by workers such as Albert Ladenburg (1842-1911)46 and Ernst Schmidt (1845-1921)47 in the last third of the century as exact

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44 Tschirch, 1923, pp.216-217.
45 For detailed discussions of the distribution of alkaloids in *Solanaceae*, see Hegnauer, 1963; Evans, 1979; Trease and Evans, 1983, pp.541-562; Roddick, 1991.
46 Ladenburg originally studied physics, but was persuaded by Bunsen to switch to chemistry. His investigations of aromatic compounds (*Die Theorie der aromatischen Verbindungen; 1876*) was initiated by his contact with Kekulé from 1865; his first major achievement was the ‘prism formula’ for benzol, superior to Kekulé’s ring formula in some respects. His two-year sojourn in Paris (1866-1867) contributed significantly to the establishment of silicon-based organic chemistry. His investigations of the alkaloids commenced as he was Professor in Kiel (1872-1889), one of high points in this period being the premier synthesis of an alkaloid (coniine) in 1886. Ladenburg published lectures on the history of chemistry and a thirteen volume chemical dictionary; his 1902 lecture at the meeting of the German Researchers and Doctors on the ‘Influence of the natural sciences on our conceptions of the universe’, a vigorous advancement of materialism, was a source of extensive controversy, despite his unchallenged status as one of the greatest chemists of the day.
47 Schmidt was widely known for his *Lehrbuch der pharmazeutischen Chemie*, regarded by the leading pharmacognosist Tschirch as “the pharmacists’ bible”. He commenced his apprenticeship as an apothecary in 1861, passed the state exam in pharmacy in 1870 (which allowed him to participate in the Franco-Prussian War as a field apothecary) and achieved his doctorate in 1871; only after this time did he complete his high school studies (*Gymnasium*; he had previously attended a *Realschule*), allowing him an academic career. After a period in Halle, he was appointed Professor of Pharmaceutical Chemistry in Marburg, which position he occupied for 30 years. His major research interest concerned the alkaloids, particularly those of the *Solanaceae* and *Papaveraceae*. As editor of *Archiv der Pharmacie*, he was not averse to adding his own footnotes to other workers’ papers. See Thoms, 1921.
chemical analysis of the isolated alkaloids revealed that in most cases the active components were all atropine, hyoscyamine and hyoscine.\textsuperscript{48}

The \textit{Solanaceae}, a family which also includes the potato and tomato, were known as medicines, psychoactive agents and poisons in many parts of the world since ancient times; the name derives from the Latin \textit{solamen}, for ‘comfort-giver’. The \textit{Solanaceae} were classified in Greek medicine as two groups:

- the \textit{στρύχνος} or \textit{στρύχνον} plants: Dioskorides listed four plants which have been identified as \textit{Solanum nigrum} (black or garden nightshade), \textit{Physalis alkekengi} (winter cherry) or \textit{Physalis somnifera}, \textit{Solanum dulcamara} (woody nightshade) and \textit{Datura stramonium} (with which Dioskorides apparently confused \textit{Atropa belladonna});
- the \textit{υοσκύα µος} plants: Dioskorides knew three – the black (\textit{Hyoscyamus niger}), yellow (\textit{Hyoscyamus aureus}) and white (\textit{Hyoscyamus albus}; Russian henbane). The related \textit{Atropa mandragora} was also recognized as belonging to the same group.\textsuperscript{49}

In terms of medieval humoral pathology, all the major \textit{Solanaceae} discussed here were regarded as being cold in the fourth degree.\textsuperscript{50} The Germanic peoples employed the smoke produced by the burning of these agents (\textit{Qualmkräuter}) as sedatives in conditions of agitated excitement. Fühner noted in 1926 that members of the family were used across the globe as psychotropic agents by primitive peoples in a manner analogous to the European use of alcohol, morphine and cocaine.\textsuperscript{51} Similar uses were not unknown in Europe. Beer in medieval Germany was fortified by the addition of henbane,\textsuperscript{52} in China and amongst the Cossacks stramonium seeds, in Siberia henbane or \textit{Hyoscyamus physaloides}. The addition of such substances was recognized as both potent and dangerous, and was eventually forbidden in most places; the earliest record of such a ban appears to be that of the central Franconian town of Eichstätt in 1507.\textsuperscript{53} The use of various solanaceous plants, especially belladonna, in the “witches’ brews” of the Middle Ages is well known; the involvement of their mind-altering effects in such phenomenon as flying and lycanthropy, while interesting, cannot be discussed in the present work. Finally, the use of extracts of these plants as potent toxins also has widespread temporal and geographic distribution.\textsuperscript{54}

\textsuperscript{48} Ladenburg, 1880a,c,d; 1881. For a contemporary discussion of the confusion regarding nomenclature, see Sharp, 1897, who concluded that there existed at most two major solanaceous alkaloids, atropine and (perhaps) hyoscyine.

\textsuperscript{49} Gunther, 1934, pp.464-474 (= Dioskorides IV,69; 72-76); Tschirch, 1931, III, p.267.

\textsuperscript{50} Gerard, 1633.

\textsuperscript{51} Fühner also noted that hashish, widely used in Asia and Africa, was relatively unimportant in Europe, but had recently been forbidden in California due to its rising popularity.

\textsuperscript{52} Hartmann von Aue, \textit{Iwein}: “\textit{wînes ein becher vol/der gît, das si tu geseit,/mêre rede und manheit/dan vierzec unde viere/mit wazzzer ode mit biere}” (818-822: “I tell you truly, a beaker of wine elicits more talk and bravado than forty-four of water or beer.”)

\textsuperscript{53} Marzell, 1922, p.170. This thus preceded the Regensburg law, the famous German Beer Purity Law, of 1516. Interestingly, in 1649 the Bavarian Land and Police Ordinance was altered to allow “\textit{the addition of a little salt, juniper berry and caraway to beer; whoever, however, adds other herbs and seeds, especially henbane, shall, along with the seller of such herbs, be punished harshly}” (cited by Fühner). The practice was not entirely extinguished until the end of the 17th century as the production of stronger beer became possible and the production of distilled alcohol began its expansion; Fühner, 1925.

\textsuperscript{54} Cooper, 1974; Holzman, 1998; Müller, 1998.
III. The solanaceous alkaloids

The persistent significance of the Solanaceae in medicine, magic and folklore is attributable to the presence in these plants in varying quantities of atropine, hyoscyamine and hyoscine (figure 3-3):

They all possess the ability to elicit disturbances of brain function which are evident as excitement of a particular hue followed by depression. . . . Beside other unpleasant symptoms, the nightshades and also their active principles — above all, atropine, and to an even greater extent, scopolamine — induce visual, aural, gustatory hallucinations and illusions, which, unlike those induced by other hallucinogens, are not of a pleasant, but rather of a terrible and frightening nature.

The re-introduction of these and other ancient plant agents into modern medicine thus had to overcome not only the objections of those who questioned the use of poisons as medicaments, but also their history as witches’ tools and agents of mischief. Much of the credit for overcoming these objections is owed to the Viennese physician and investigator Anton Störck (1731-1803), who operated under the motto “The dose alone makes the medication to a poison”. Störck was a member of the “Old Viennese Medical School” led by Baron Gerard van Swieten (1700-1772), whom he succeeded as Court Physician to the Empress Maria Theresa. Störck thus oversaw the final design and implementation of the famous reforms of the Austrian medical system. Between 1760 and 1771, Störck published a series of treatises on his investigations of the medical properties of a number of plants, including stramonium, henbane, aconite, meadow saffron, clematis, burning bush and bastard dittany. Störck’s work attracted a great deal of attention throughout Europe, not least because of his meticulous examination of drug effects and the determination of their toxicity in experiments on

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56 This maxim is generally attributed to Paracelsus (1493-1541), who wrote: “If you want to properly explain every poison, what then is not a poison? All things are poisons and nothing is free of poison, it is only the dose which determines that something is not a poison (...alein die dosis macht das ein ding kein gift ist)”; from Sieben Defensiones, in Sämtliche Werke (ed. Sudhoff, 1928), vol. XI, p.138. Cf. Deichmann et al., 1986.
III. The solanaceous alkaloids

both dogs and himself before testing these potentially dangerous substances on patients. Sir John Pringle, for example, lobbied (with great success) for the immediate inclusion of all of Störck’s plants in the 1774 Edinburgh Pharmacopoeia.

The concentration of the various alkaloids in the solanaceous plants varies according to plant, part and stage of growth. Belladonna, scopola (which was not much used after the First World War) and stramonium were long regarded as being equipotent with regard to atropine content, while hyoscyamus was considered weaker. In more recent times, Clair and colleagues reported that the alkaloid content of various belladonna varieties varied with no apparent pattern, and also with the age of the plant. The scopolamine:hyoscyamine ratio decreased with growth due to an increase in the hyoscyamine content. They also noted that the apoatropine content increased with time, and probably that of other demethylation and N-oxidation derivatives.

Belladonna (*Atropa belladonna* Linnaeus), atropine and hyoscyamine

One plant in particular would dominate the therapy of parkinsonism until the 1950s: the deadly nightshade (*Atropa belladonna*; figure 3-4). This plant unites in its scientific name references to its two most famous and contrasting applications: its exceptional toxicity (Atropos, the “unturnable” or “inflexible”, was the Fate in Greek mythology who severed the thread of life) and its supposed cosmetic use by Venetian and Paduan women for dilation of their pupils and for skin rejuvenation. It is a shrub-like plant growing to about 1.5m in height, with a smooth, pale purplish stem. The leaves on the upper stem, which on top are brown-green and under grey-green, are paired, so that a large and a small leaf stand opposite one another. Up to 20cm long and 10cm wide, they are elliptical or pointed, exhibit conspicuous veins and a purplish centre vein, as well as small white spots. Individual bell-shaped, five-lobed brown-purple or white flowers, up to 3cm long, bloom from June to August. After the flowers fall, egg-shaped berries (initially green, later deep purple to glossy black) containing a dark purple juice appear in the calices. The plant is extensively distributed in Europe and Asia, and is cultivated especially in central Europe, England, India and America; apart from cultivated forms, it is generally found in forests, paddocks and amongst ruins and other abandoned sites. The plant has only a faint odor, but is bitter to the taste, a typical characteristic of alkaloid-containing medicinal plants.

Despite ambiguous references in ancient authors, the belladonna was first definitely mentioned in the French “*Grand Herbier*” in 1504, at which time it was a popular poison. The German botanist Leonhard Fuchs described the toxic effects of “*Solanum*...
somniferum” in detail in 1542. As already noted, the pupil-dilating effects were known from at least the 16th century (first reported in a scientific work by Rajus in 1686); Reimarus (d. 1814) was reported by Tschirch to have been the first to have exploited this property to render cataract operations easier.64 Linné gave the plant its current Latin name in 1753, which also led to the acceptance of the common name “belladonna”. A veritable profusion of medical and scientific treatises on the plant appeared during the 18th century, and it first appeared in pharmacopoeias (in Württemberg and Switzerland) in 1771.65

*Folium belladonnae* was listed in most pharmacopoeias from this period onwards, mostly for purposes also served by atropine, but also as an ingredient in cigarettes prepared for asthmatics. Its use as an anodyne appears to have commenced about 1860. Brown-Sequard’s pills for neuralgia, a popular remedy in the late 19th century, included

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64 The mydriatic properties of belladonna appear to have been ‘discovered’ many times throughout the centuries: see Himly, 1843; Kobert, 1916.

65 Niederkorn et al., 1905; Tschirch, 1923, p.282. Tschirch also refers to an Egyptian manuscript which he interpreted as indicating that the use of mandragora for this purpose was known in ancient Egypt (p.264). This is false; his citation indicates the adulteration of beer with solanaceous drugs to increase its potency was also practiced at this time, as, indeed, it also was in Babylon and China.
not only belladonna, but also a number of other solanaceous and other plant extracts,\textsuperscript{66} together with potassium bromide, it was used in epilepsy in the United States.\textsuperscript{67} Belladonna was regarded as a powerful narcotic, and especially valuable in the management of spasmodic and convulsive disorders, and of "diseases having their seat chiefly in the nervous system".\textsuperscript{68} In Germany, it was also used to treat scarlet fever.\textsuperscript{69}

The mean alkaloid content of belladonna leaf was about 0.4\% (range: 0.14-1.32\%;\textsuperscript{70} more recent estimate: 0.2-2\%\textsuperscript{71}), consisting mostly of hyoscyamine and some atropine. The alkaloid content was highest from the flowering period in summer until the fruit production, and was especially high in younger leaves. \textit{Radix belladonnae} was listed in the pharmacopoeias of many European countries (but not of France or Germany) and in the USA, essentially as an alternative to leaf preparations; the alkaloid content of 0.31-0.64\% consists mostly of hyoscyamine and a level of atropine which increases with age of the plant, together with some scopolamine and apoatropine.\textsuperscript{72} Its clinical indications have since ranged from asthma and sea-sickness to neurosis and parkinsonism. Atropine itself was increasingly employed from the middle of the 19th century principally for its mydriatic effects but also as a general anodyne.\textsuperscript{73}

All parts of the plant are poisonous due to its alkaloid content, which consists to 99\% of atropine and hyoscyamine, although the relative amounts of each have varied according to report. Atropine has been the most widely clinically used of the alkaloids derived from the solanaceous plants, explaining their collective designation as the "belladonna alkaloids". Nonetheless, the reputation of belladonna as a poison and the presentation of a disturbing 'atropine delirium' tending to frank acute psychosis in cases of accidental overdosage often inhibited its employment as an internal medication.\textsuperscript{74}

The isolation of atropine in the early 19th century was a somewhat confused story. It was purportedly first isolated (in impure form) from belladonna leaves in 1809 by the French chemist Vauquelin.\textsuperscript{75} This, however, was only the first 'isolation' of the active narcotic principle of the belladonna, a fact noted with irritation by the German chemist\textsuperscript{76}

\textsuperscript{67} Ibid., p.66.
\textsuperscript{68} Squire, 1866, p.51.
\textsuperscript{69} Fischer, 1837.
\textsuperscript{70} Tschirch, 1923, pp.276-277; Brandt and Wasicky, 1929, pp.1547-1550.
\textsuperscript{71} Lindequist, 1992.
\textsuperscript{72} Tschirch, 1923, pp.276-277; Brandt and Wasicky, 1929, pp.1550-1552. More recent estimate: 0.3-1.2\%, of which 68.7\% is hyoscyamine, 17.9\% apoatropine; Lindequist, 1992. The same author reported an alkaloid content of 0.1-9.6\% in the ripe fruit.
\textsuperscript{73} Squire, 1866, pp.38 (mydriatic); Squire et al., 1882, pp.69-70 (hypodermic injection for relief of pain due to neuralgia or spasm); Martindale and Westcott, 1888, p.89 (also to suppress secretion of all types); Niederkorn \textit{et al.}, 1905. It was considered a cleaner agent than extract of belladonna. For comprehensive cultural, botanical and medical history of belladonna: Schwamm, 1988.
\textsuperscript{74} For interesting self-experiment with belladonna fruits: Kanngiesser, 1911. See also de Boor (1956), pp.161-166, and references therein.
\textsuperscript{75} Nicolas Louis Vauquelin (1763-1829) commenced his career as a pharmacist's assistant and was appointed Professor of Chemistry in Paris in 1809. He discovered chromium (1798), was the first to isolate an amino acid (asparagine from asparagus in 1805) and identified the presence of nicotine in tobacco (1809). Together with Sigismund Friedrich Hermbstaedt (1760-1833) and Johann Bartholomäus Trommsdorff (1770-1837), he was considered one of the most important investigators of the chemical composition of plants prior to the alkaloid era.
Friedlieb Ferdinand Runge (1795-1867) in 1820.\textsuperscript{76} The Salz-Uffeln (Lippe-Detmold) pharmacist and founder of the North German Pharmacist Association, Rudolph Brandes (1795-1842), then isolated a substance to purity in 1819 or 1820 which he named ‘atropine’;\textsuperscript{77} the vapors of its salts induced dilatation of pupils, and when on one occasion he taste atropine sulphate (finding it salty rather bitter), the dilatation lasted twelve hours.\textsuperscript{78} In 1833, however, he conceded that the extract prepared by his method did not exert the classic mydriatic effects of belladonna preparations, and thus did not earn the name of atropine.\textsuperscript{79} A similar fate befell his reported isolation in 1832 from the henbane of what he called ‘hyoscyamine’.\textsuperscript{80} Pure atropine thus seems to have been first isolated from the dried root of the belladonna by the apothecary Mein (Neustadt-Göders) in 1831, but the report was published only in 1833, and then at the behest of a friend of Geiger.\textsuperscript{81} By this time, atropine had been isolated from the leaves by Geiger and his student Hesse;\textsuperscript{82} Geiger also isolated hyoscyamine (as a “sticky, evil-smelling mass”) from hyoscyamus seeds in the same year.\textsuperscript{83} These two workers then provided Liebig with samples of atropine for the determination of its chemical composition and undertook their own extensive series of investigations of the chemical and pharmacological properties of atropine, including self experimentation:

\begin{quote}
We ourselves experienced equally clearly [as the animals in the previous experiments] the toxic effect of this substance in the necessary tasting of it. One of us, who gradually brought \(\frac{1}{10}\) grain to the tongue, but each time spat out as much as possible, suddenly felt unusually dry in the mouth, all salivation was suddenly inhibited, at the same time he experienced a tightening of the throat; he could only eat with some difficulty, his pupils were markedly dilated; an unpleasant sensation with numbness, later headache, lasted for about 5 hours, but the symptoms were only completely gone after 12 hours.\textsuperscript{84}
\end{quote}

\textsuperscript{76} Runge, 1820; p.121. Runge himself succeeded in isolating a “belladonna base” in 1819, but could not purify it; \textit{ibid.}, pp.120-132; also his 1819 dissertation (Jena): \textit{De novo methodo venficium un belladonnae, daturae, nec non hyosciami explorandi}.

\textsuperscript{77} Brandes, 1820a, b; 1832a, b.

\textsuperscript{78} Brandes, 1820a, b.

\textsuperscript{79} Brandes, 1833. In his 1820 report, Brandes had described mydriatic effects of atropium salts, but: “I neither wish nor could carry out further experiments into the effects of atropium in animals. In a small hamlet (‘kleines Landstädtchen’) such as mine, suitable animals for such experiments are not always available. I am pleased to yield this field to those who are doctors, physiologists or anatomists by profession.” Brandes’ fragile health also suffered from the effects which long-term exposure to the vapors of atropine salts caused, including intoxication, violent headaches and back pain.

\textsuperscript{80} Brandes, 1832b. Despite these misadventures, Brandes was a well-respected chemist; he also discovered the alkaloids delphinine (1819) and daturine (1819).

\textsuperscript{81} Mein, 1833.

\textsuperscript{82} I have found no further biographical information for either Mein or Hesse (including their given names). Contrary to Leake (1975; p.121) and Holzman (1998), Hesse is almost certainly not the chemist Henri Germain Hesse (1802-1850), who was resident in Russia from the age of three; in 1833, he was Professor of Chemistry in St Petersburg. According to Poggendorf (1863), his first publications appeared in 1836, and he never wrote on alkaloids.

\textsuperscript{83} Geiger and Hesse acknowledged the controversy concerning the isolation of atropine in their opening sentences: “We see the reader of the Annals start and hear them call out, ‘Yet another atropine? After we have read in the previous article [by Brandes] that the same substance has already been discovered twice and then disappeared again? What are we supposed to think? Will this New Year’s gift not also disappear into nothing by the end of the year or even sooner, like last year’s? ’ In no way can we hold it against the reader if he greet this new announcement with skepticism after two disappointments; . . . may the facts themselves determine whether we have captured the deadly Atropos (of the belladonna) or not.” Geiger and Hesse, 1833a, 1833b; Geiger, 1833.

\textsuperscript{84} Geiger and Hesse, 1833b.
These detailed investigations have earned Geiger and Hesse the deserved credit for the first significant examination of belladonna and hyoscyamus in modern medicine; they were also deeply interested in the alkaloids isolated from other solanaceous species. Geiger recommended that, despite the difficulty of purification, atropine should be used in place of belladonna because it could be more accurately dosed and was safer to employ. His advice, however, was initially observed only with respect to the preparation of mydriatic solutions.

The relationship between atropine and hyoscyamine should be explained here. The belladonna alkaloids are ester-like combinations of particular bases with aromatic acids. Lossen had shown in 1864 that atropine could be hydrolyzed to tropic acid and tropine;\textsuperscript{85} in 1880, Ladenburg demonstrated that atropine and hyoscyamine are optical isomers, and that hyoscyamine could be converted into atropine.\textsuperscript{86} In 1897, Willstätter corrected Ladenburg’s incorrect suggestion for the structure of tropine by determining that it consists of fused pyrrole and pyridine nuclei, and that atropine was the ester of this bicyclic moiety and the aromatic tropic acid, as depicted in figure 3-5. This allowed him to undertake the complete synthesis of atropine in eighteen steps.\textsuperscript{87} Atropine is thus a tropeine, an acidic ester of tropine. The asymmetric carbon of tropic acid (marked with an asterisk in figure 3-5) means that three optical forms are possible: L-hyoscyamine (or, simply, hyoscyamine), D-hyoscyamine (which does not occur alone in nature) and the optically neutral mixture of the two forms, D,L-hyoscyamine, or atropine.\textsuperscript{88}

It should also be noted that hyoscine (scopolamine) is not, as originally believed, an isomer of atropine or hyoscyamine, although the name hyoscine is based upon this misunderstanding. The oscinees are esters in which the base scopine replaces tropine; the name derives from the fact that oscine was originally found following hydrolysis of hyoscine, but it was later demonstrated by Willstätter and Berner (1923) that the initial product is the relatively unstable scopine. The tropic ester of scopine is hyoscyine or scopolamine, which also occurs in two isomeric forms: the racemic form atroscine (cf. atropine) and the levorotatory scopolamine proper. Both atropine and atroscine are more stable than their levorotatory counterparts. Commercial preparations of scopolamine were often contaminated by atroscine, but this does not appear to have altered their therapeutic benefit; in fact, some authorities attributed the pharmacological power of hyoscine to atroscine.\textsuperscript{89} Schmidt argued that scopolamine was isomeric with cocaine, but it would prove that they were structurally distinct, though sharing a common empirical formula.\textsuperscript{90} Cushny and Peebles found the same relative responsiveness of various tissues to the L- and D-isomers as for hyoscyamine.\textsuperscript{91}

\textsuperscript{85} Lossen, 1864.
\textsuperscript{86} Ladenburg, 1880c,d.
\textsuperscript{87} Willstätter, 1901. Richard Willstätter (1873-1942) also synthesized the related ecgonine in 1901 and its derivative cocaine in 1923; Partington, 1964, p.161.
\textsuperscript{88} See Amenomiya, 1902.
\textsuperscript{89} Martindale and Westcott, 1901, pp.282-283; Thoms, 1927-29, VI, p.1956.
\textsuperscript{90} Schmidt, 1892a.
\textsuperscript{91} Cushny, 1903; Cushny and Peebles, 1904. It was the data in this latter paper with which Student conducted the first (illustrative) $t$-test in 1908. Interestingly, Student actually misread the data published by Cushny and Peebles, so that his conclusion was invalid; see Senn and Richardson, 1994. The total synthesis of scopolamine was first achieved in 1956 by Fodor and colleagues at the University of Szeged in Hungary (1956, 1957).
The presence of atropine in the belladonna root was doubted, however, by the end of the 1880s, as the Marburg chemist Ernst Schmidt had shown that hyoscyamine was easily converted into atropine by heating,\(^92\) and W. Will (Chemical Laboratory DXCCIII of the First Berlin Chemical University and the firm E. Schering) argued that well-preserved belladonna root contains only hyoscyamine (‘light atropine’), and was converted to atropine (‘heavy atropine’) only in case of bad storage and during extraction.\(^93\) W. Schütte, aware of these problems, had carefully examined the atropine content of a range of solanaceous plants (mostly collected by himself), and found that atropine was present only in the roots of older belladonna plants, wild or cultivated, and then only in very small quantities; the major alkaloid was hyoscyamine.\(^94\) In 1892, Julius Oswald Hesse (1835-1917)\(^95\) assayed various samples of “atropinum naturale” extracted from belladonna root and concluded that it consisted to large part of hyoscyamine, but noted that the preponderance of this alternative alkaloid did not appear to alter its pharmacological characteristics.\(^96\) As late as 1938, the assay of

\(^{92}\) Schmidt, 1888.
\(^{93}\) Will, 1888.
\(^{94}\) Schütte, 1888. Further: the ripened fruit of the cultivated black belladonna contained a mixture of atropine and hyoscyamine, of the wild variety only atropine; the unripe fruit contained only hyoscyamine. There was little atropine in the leaves. The stramonium seed contained hyoscyamine with small amounts of atropine and scopolamine.
\(^{95}\) Hesse was supposed to have become a farmer, but was stimulated by the apothecary Reichel to study chemistry. As director of the Feuerbach branch of the United Quinine Works Zimmer & Co., he concerned himself extensively with alkaloid research; amongst his achievements were the first isolation of a \textit{Rauwolfia} alkaloid, the identification of several new opium alkaloids and the discovery of physostigmine; he was also regarded as the leading authority on quinine. Effler and Effler (1972) paid particular tribute to his innovations in the industrial production of alkaloid products. The United Quinine Works was absorbed by Merck in 1927.
\(^{96}\) Hesse, 1892, 1893.
atropine in pharmaceutical preparations was regarded as problematic, primarily due to the instability of atropine in standard solvents. By the beginning of the 20th century, it was generally agreed, however, that the greater part of the alkaloid content consisted of the more stable hyoscyamine, and that racemization to atropine occurred principally during the preparation of the drug. In 1903, Arthur R. Cushny (Pharmacological Laboratory of the University of Michigan) dismissed most of the earlier investigations of hyoscyamine on the basis that the substance used was in the most cases “merely a purified extract of hyoscyamus”, thereby including a mixture of alkaloids; this explained the similarity of the pharmacological properties of “hyoscyamine” and simple belladonna extracts. Cushny found in mammals that purified hyoscyamine (from *Scopola carniolica*) was somewhat more potent than atropine (from belladonna) with respect to its parasympatholytic effects in the periphery but the effects of the two agents on the central nervous system were about equal.

A number of other alkaloids (including apoatropine and belladonnine, to be discussed below), glucosides (especially methyl-aesculin, or scopolin) and choline are also found in various parts of the belladonna plant. The leaves also contain sugar, succinic acid, an oxidase and a renninase; the root also contains lower amounts of the latter. It is perhaps significant that in considering the action of extracts of belladonna root (in particular), only the major alkaloids were considered; these other substances were rarely even mentioned except in detailed volumes on plant physiology. The contribution of these “minor” constituents to the pharmacological effects of belladonna preparations remains largely unknown. Commission E, which evaluates phytochemical therapies on behalf of but independently of the German Health Department, classified both leaf and root of belladonna in 1985 as “approved herbs” for the relief of spasms and colic-like pain of the gastrointestinal tract and bile duct; the only constituents listed by the Commission were hyoscyamine, atropine and scopolamine.

**Henbane or Hyoscyamus (Hyoscyamus niger Linnaeus)**

Hyoscyamine was later usually isolated from the dried leaves and flowering tops of the henbane (‘Bilsenkraut’; figure 3-6) – the yield is 0.05-0.2% – but is also found in a number of other plants. The henbane, which grows as a weed in Eurasia, was known from ancient times as the source of a potent sedative, and was also employed in ocular disease. Pliny considered it a dangerous drug, causing insanity, insomnia and dizziness. The name is usually said to derive from the Greek for ‘hog-bean’ – swine

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97 Fricke and Kaufman, 1938.
98 This phenomenon was sufficiently controversial and significant to merit an explanatory footnote which occupied the greater part of a page in the 1901 edition of the Extra Pharmacopoeia: Martindale and Westcott, 1901, p.88.
99 Cushny, 1903. These experiments were also interesting in that Cushny succeeded in demonstrating that certain mammalian tissues were capable of distinguishing between the two isomers of a pharmacologically active substance, whereas this was not the case in the frog, except in the spine. Stereoselectivity in nature had been first described by Pasteur with respect to the metabolism of tartaric acids by bacteria; this was one of the earliest descriptions in higher organisms.
100 For example, Tschirch, 1923, pp.276-278; Brandt and Wasicky, 1929, pp.1547-1552.
102 Including *Datura stramonium*, *Mandragora officinarum* and *Scopola carniolica*. It was first isolated from the belladonna root by Ladenburg in 1880(c).
103 Pliny, XVIII, 118; XXIII, 94; XXV, 35-37; Dioskorides, IV, 69. Pliny listed a variety of antidotes for poisoning with hyoscyamus, leading him to a comment which was interesting in light of
can supposedly eat the plant with impunity – but Tschirch noted that the plant is clearly not bean-like.\textsuperscript{104} It is an annual or biennial plant with a spindle-shaped root which is turnip-like in the upper part (which has led to most cases of accidental poisoning with henbane). Its upright stem can be 20-100cm tall. In the biennial plant, the leaves spread out from the corona like a rosette, greyish green and covered in hairs. These leaves disappear with winter; in the following spring, the stalk develops from the root corona and produces stemless, pale green, sticky leaves (up to 20cm long). The dingy yellow, pitcher-shaped flowers are crossed by a network of purple veins. The fruit is curiously constructed, consisting of a lid-covered capsule filled with tiny black seeds. The plant blooms from June till October and is marked by a strongly nauseous scent. It was originally native to southern and central Europe and in Asia as far west as India and Siberia, but was naturalized in North America by 1672, having been inadvertently introduced at the commencement of white settlement; it was also common in England by Elizabethan times, perhaps more so than it is now.\textsuperscript{105}

developments initiated by Störck and others: “no possible experiment has been omitted, so that even poisons are forced to be helpful remedies.” (XXV, 37).

\textsuperscript{104} Tschirch, 1923, p.283. He suggested a derivation based on ‘Dios-kyanos’ (the plant was called ‘Dioskyamos’ by Apuleius, who also called it ‘Apollinaris’), referring to its magical or divine powers and its color (κυάνεος = blue-black).

\textsuperscript{105} Tschirch, 1923, pp.283-290; Grieve, 1931; pp.399-402; Brandt and Wäsicky, 1929, pp.1553-1556.
III. The solanaceous alkaloids

The major alkaloid of *Folium hyoscyami* is hyoscyamine (the content varies considerably: 0.017-0.29%). Leaves of related species, such as *H. muticus* of Egypt, Persia and India, contain much higher levels (up to 1.7%), which fact has been exploited for commercial hyoscyamine preparation.\(^{106}\) Alkaloid content decreases with distance from the stem; further, it is higher in root and highest in seeds of the plant, except in *H. muticus*, where highest levels are uniquely found in the flowers.\(^{107}\) Other alkaloids are present at lower levels, including scopolamine (this is absent from the Egyptian plant), as are choline and a number of lipids. Hyoscyamine concentration increases with the age of the plant at the expense of hyoscine.\(^{108}\) Biennial henbane was traditionally regarded as the superior medicinal plant, but Gerrard remarked in 1890 that this prejudice was not justified by the relative alkaloid content of the two plants.\(^{109}\)

Hyoscyamus has been used since time immemorial in medicine in both Europe and India.\(^{110}\) The root and seeds were also formerly used as nerve tonics, but in more recent times the leaves and flowering tops have been more important in medicine. In Ayurvedic medicine, it is prescribed largely as a sedative, especially in cases of excitement, paralysis agitans, and in irritation of the bowels, urinogenital tract, kidney or uterus.\(^{111}\) Henbane has been used since Babylonian times to treat toothache in most regions of the Middle East and Europe. In Greece, it was sacred to Herakles, and the dead were said to be crowned with henbane as they wandered beside the Styx,\(^{112}\) whereas Josephus noted that one of the ornaments of the Jewish High Priests’ headdress was modelled on the seed capsule.\(^{113}\) Dioskorides valued it as an anodyne and for the induction of sleep, while recognizing its propensity for inducing sensory disturbances;\(^{114}\) Pliny described it disapprovingly as having the character of wine, only more powerfully.\(^{115}\) It is, however, probable that Dioskorides was more acquainted with the Russian (white) henbane, which in most respects is pharmacologically equivalent to the black species. Avicenna certainly valued the white henbane as a safer alternative to the black version; he recommended it for all forms of sedation and for treatment of ocular pain.\(^{116}\) Hyoscyamus was well known throughout the Middle Ages (under the names *caniculata* and *simphoniaca*, amongst others) for both its narcotic and toxic properties; burning henbane was used, for instance, in *The Thousand Nights and One* to

\(^{106}\) Tschirch, 1923, p.291; Amor et al., 1946; see also Chopra et al., 1960, p.40; Paris and Dillmann, 1961, p.81.
\(^{107}\) Misra et al., 1992.
\(^{109}\) Gerrard, 1890b. The root of the annual henbane was too small for practical purposes, but it was the leaf which was used for medical purposes; but it was interesting that Gerrard also wrote: “Whether the roots may supersede the leaves it is not in my power to say, but if the question between them were one of strength and elegance of preparation then the root must win”; Gerrard, 1890a. This would later prove to be the case with respect to belladonna. See also Gilmour, 1884, who discussed methods for distinguishing between tinctures prepared from the annual and biennial plants.
\(^{110}\) Sanskrit: Yavani; Hindi: Khurasani ajvayan.
\(^{111}\) Kapoor, 1990, p.211.
\(^{112}\) Hocking (1947) suggested that the Homeric drug of forgetfulness, *nepenthe*, was probably *H. niger*.
\(^{113}\) Grieve, 1931, p.400.
\(^{114}\) Dioskorides, IV, 69.
\(^{115}\) Pliny XXV, 69.
\(^{116}\) Avicenna, 1507, II, 360.
‘knock out’ inconvenient guards. Older authors noted that its name in most European languages includes the Indo-European element ‘bal’, ‘to kill’. The plant was particularly popular in England throughout the Middle Ages as a pain reliever (under the name Henbell), but its toxic effects were more greatly emphasized; according to Gerard:

To wash the feet in the decoction of Henbane causeth sleepe; or given in a clister it doth the same: and also the often smelling to the floures. The leaves, seed, and juyce taken inwardly causeth an unquiet sleepe like unto the sleepe of drunkennesse, which continueth long, and is deadly to the party [patient].

Hyoscyamus was one of the plants used in the soporific sponges (spongia somnifera) and pomanders (sleeping apples) used in the absence of surgical anesthesia during the Middle Ages. The crushed seeds of the plant were often used in parts of Germany to increase the potency of beer; as noted above, this dangerous practice was forbidden by a purity law enacted in Eichstätt in 1507. Employment of the plant alone for intoxicant purposes was also widespread. Accidental poisoning by the plant is unusual due to the pungent smell emitted by the plant (most commonly compared to that of fresh tobacco or musk); contamination of poppy-seed with henbane seed and confusion of the plant with black salsify (Tragopogon porrifolius, Schwarzwurzel) has, however, led to occasional poisonings.

According to Hartmann-von Monakow, henbane was used to treat tremor (Zitterkrankheit) in Lithuania in the 17th century, but its use as medication had generally been forgotten in Europe by the end of the 16th century. Hyoscyamus was re-introduced into modern medicine by the Jena physicians Wedel (De Hyoscyamo) and Slevogt (De virtute Hyoscyami cathartici) in 1715 and by Störck in 1762 (Libellus, quo demonstratur Stramonium, Hyoscianum, Aconitum etc. esse remedia salutifera) as a hypnotic, but this application appears to have become unusual by the early 1800s. Ure noted in 1835 that the newly isolated alkaloid hyoscyamine was particularly “prejudicial” to the eyes and the “smallest morsel put upon the tongue” was dangerous. Its pharmacological career had, however, been established by 1875, when the English physician Lawson promoted the use of purified hyoscyamine as a

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118 Tschirch, 1923, p.283. More recent etymologists derive the name from *bhel-, which referred to any form of bulging or inflated object (the word ball is derived from the same source), perhaps a reference to its seed capsule. The plant was already known in Old High German as bil(i)sa. Rätsch (1998, p.278) notes that the Gauls called the plant belinuntia, ‘herb of the sun-god Bel’, but also that bil in early German could mean ‘vision’ or ‘magical power’.
120 Theodoric of Cervia (1205-1296) listed opium, the juice of unripe mulberry, hyoscyamus, spurge flax, mandragora, ivy, lettuce seed, lapathum seed and hemlock as being used in the sponge employed by Hugh of Lucca (1160-1252). Roger of Salerno mentioned such sponges in 1170, but not their composition. Hirschlauff, 1918; Holzman, 1998; Kuhlen, 1983; Müller, 1998.
121 Fühner, 1926. Pilsen in Bohemia (and several other place-names in central Europe) may owe its name to its being a henbane-growing area.
122 Lewin, 1924, p.129; Fühner, 1926; Sands and Sands, 1976.
123 Tschirch, 1923, p.293.
125 It was not listed in London of Pharmacopoeias of 1746 and 1788, but returned in 1806; Hocking, 1947.
126 Ure, 1835, p.526. Hyoscyamine was first isolated (in impure form) from henbane by the Geneva pharmacist Peschier in 1821 (cited in Seguin, 1880); Geiger reported its crystallization in 1833.
hypnotic. In 1879, Mendel found that thrice daily subcutaneous application of 3×10mg crystallized hyoscyamine pacified manic patients, which response he attributed to depression of motor centres. Application of the purified salts of hyoscyamine as a "chemical restraint" in mania, a somewhat more effective alternative to the bromides, quickly spread; hyoscyamine salts, which were preferred to the plant itself, were also employed "to quiet the insane and nervous", to ease the cough of tuberculosis, and to relieve sea-sickness. It also found limited application as a narcotic, sedative and pain reliever. 

Semen hyoscyami was much less used in modern medicine. Although it was largely supplanted after 1901 in most roles by hyoscine and atropine, for reasons which will be discussed below, hyoscyamine sulphate was still listed in the Martindale Extra Pharmacopoeia of 1941 as relieving the tremor, rigidity and excessive salivation of paralysis agitans. Henbane extracts and hyoscyamine sulphate remained officially listed in many countries as late as the 1990s, but rarely used in the conventional clinic. Henbane leaf was classified in 1988 by the German E Commission as an approved herb for the treatment of spasms of the gastrointestinal tract; relief of centrally determined muscular tremor was also noted as possible.

Another member of the Solanaceae family, the mandrake (Atropa mandragora) long played a role in European medicine and magic, but dropped from use before the modern era. The fear attached to this plant played a major role in the popular resistance to the introduction of the potato to Europe in the 17th and 18th centuries. The root contains, amongst other alkaloids, hyoscyamine (~0.36%) and some scopolamine. Leclerc recommended its employment as a sedative in the 1920s, and wrote in his 1927 Précis de Phytothérapie that the hyoscyamus plant represented the most appropriate therapy for parkinsonian tremor, mercury toxicity and hysterical chorea. The Israeli pharmaceutical-chemical firm Tamar (Rehovot) marketed a total alkaloid extract of mandragora in the 1950s under the name ‘Scopanin’, with indications including post-encephalitic parkinsonism and motion sickness.

**Duboisia (Australian corkwood; Duboisia myoporoides Robert Brown)**

The latest addition to the Solanaceae family was identified in an unlikely corner of the world. Joseph Bancroft (1836-1894), the first of a family line of medical naturalists, had been intrigued by the properties of *pituri*, or “native tobacco”, a product of the Central Desert tree Duboisia hopwoodii. Pituri was (and is) used by Aborigines as a

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127 Kobert and Sohrt, 1887. Merck had made amorphous hyoscyamine commercially available in 1856.
128 Mendel, 1879.
129 Merck & Co., 1899, pp.41-42; see also Brower, 1880; Browne, 1882; Ewart, 1884; Thompson, 1888; Squire, 1899. Combination preparations of impressive composition were also used: Gray described pills containing strychnine, morphine, hyoscyamine and black pepper (1880).
130 Vol. I, p.617. This was the last edition in which it was accorded an independent entry; thereafter it was discussed under ‘atropine’, where it was described as having “been used” in the treatment of paralysis agitans, noting at that the same time that it was now “seldom used”; Extra Pharmacopoeia, 24th edition, 1958, p.207.
133 Cited in Madaus, 1938, p.158; see also Leclerc, 1927.
134 Ludwig *et al*., 150, p.286.
135 *Duboisia* was named in 1810 by Robert Brown (*Prodromus Florae Novae Hollandiae*, 1810), who collected samples of *D. myoporoides* in his 1802-05 expedition, for the French botanist Dubois.
chewed intoxicant and to allow long periods of work without food or rest, similar to the chewing of coca in central America. *D. hopwoodii* was found to contain a number of alkaloids, including ‘piturine’ (initially identified with nicotine, later (1934) with D-nor-nicotine, which is four times as potent as nicotine),\(^{136}\) isolated by Gerrard in 1878. A sample of pituri had been brought in 1863 to Tasmania by the sole survivor of the Burke and Wills expedition, which led to its investigation by Bancroft in Australia and by a number of workers in England and France.\(^{137}\)

The Rostock-born botanist Baron Ferdinand von Mueller (1825-1896) had in the meantime suggested to Bancroft that *D. myoporoides* (figure 3-7) might also be of

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\(^{136}\) Hicks, 1963.

\(^{137}\) Bancroft, 1877a,b; Anonymus, 1878b; Ringer and Murrell, 1878; Murray, 1879; Petit, 1879; Maiden, 1888a, b; Lewin, 1924, pp.138-140; Johnston and Cleland, 1933/34; Aiston, 1937; Barnard, 1951; Peterson, 1979; Lassak and McCarthy, 1997, pp.22-25. Further Australian solanaceous species containing belladonna alkaloids were subsequently identified, including yellow tail (*Anthocercis littorea*) and sticky tail (*Anthocercis viscosa*). Many *Solanum* species are also traditionally employed as “bush food”, including bush tomatoes, bush sultanas and other equivalents of European or American species.
interest, as he had found the leaves to possess stramonium-like properties. *D. myoporoides* is most common on the east coast of Australia between 15° and 30° S. latitude, but is also found in a number of other Southeast Asian countries. It had originally been allocated to the *Scrophulariaceae*, but had been reclassified under the *Solanaceae* by the 1870s on account of its regular corolla; the correctness of this decision was confirmed by the finding that the *Duboisia* species contained belladonna-type alkaloids. The sap of the tree had long been employed by the Aborigines as a stupefacient, but more dramatically as a hunting poison; added to a billabong (water-hole), it causes eels and fish to float to the surface in a dazed condition and stuns emus which drink from it, while not poisoning the flesh of the animal. Aborigines use the leaves – thin, fragile, up to 12 cm long, 3 cm broad, odorless but bitter to the taste – to treat allergies and colds, and to inhibit bodily secretions.

In 1877, Bancroft established the mydriatic effect of duboisia leaf extracts in his house pets; he also noted the fatal effect on cats and dogs of intravenous administration of the substance. He then applied it as a mydriatic in human patients and dispatched samples to various ophthalmologists; Holmes reported in 1878 that in Sydney and Brisbane it had already supplanted atropine as routine mydriatic. It was also used in this capacity in America and Europe by 1880; its mydriatic action was generally found to be more rapid of onset and longer in duration than that of atropine. Ringer and Murrell commented in 1878 that the alkaloid extract was remarkably similar in its pharmacological effects to atropine, although the duboisia extract was far more potent than any belladonna preparation, and placed it in the same class as gelsemine and muscarine. Bancroft took samples of pituri and *D. myoporoides* to England in 1878 to place at the disposal of a number of analytical chemists. In 1879, Fauqué published a doctoral thesis on his investigations of the pharmacological properties of duboisine in animals; he recorded mydriasis and quickening of respiration in all examined species, followed by delirium and stupor, and suppression of sweating and salivation. These effects he attributed to “a paralysing action on the excito-sudoral nervous fibres.” Duboisine was first isolated in the same year by Gerrard (Pharmacy, University College Hospital) as a sticky yellow mass which chemically resembled atropine but was more soluble in water; it was independently crystallized in 1880 by Gerrard and Duquesnel as fine, colorless needles of limited water solubility. The first medical use of duboisine was reported as early as 1879 by Soelberg Wells (Ophthalmology, King’s College Hospital, London), who treated spasm of the ciliary muscle with a solution

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138 Holmes, 1878; Anonymus, 1878a.
139 The first report of its narcotic action appears to have been that of the Richmond minister Woolls in 1867 (pp.178-206).
141 Bancroft, 1877; see also Holmes, 1878.
142 Norris, 1879; Anonymus, 1880.
143 Ringer and Murrell, 1878, 1879; Tweedy and Ringer, 1878; Ladenburg, 1880b.
144 Anonymus, 1880. He also found that duboisine accelerated the heartbeat in mammals, but slowed it in frogs.
145 Gerrard found the chemical characteristics of the isolated alkaloid to be so similar to those of atropine, that he suspected the identity of the two alkaloids; the morphological differences between *Duboisia* and the European *Solanaceae*, however, were sufficient to at least suggest that the products were different. He also noted that treatment of duboisine with baryta water evolved an odor of butyric acid, whereas the same treatment of atropine resulted in the aroma of oil of gaultheria or of hawthorn.
146 Gerrard, 1880; see also Mendel, 1893. That Duquesnel crystallized duboisine was stated by many contemporary authors, but the exact citation was never given; nor does Duquesnel’s 1882 report on the crystallization of hyoscyamine mention duboisine.
provided by the Sydney doctor Fortescue; he found it more effective than atropine but could not yet predict whether it would have the same glaucoma-inducing effects of the traditional agent. Duboisine intolerance was occasionally reported, with one patient experiencing a condition mimicking alcohol intoxication; a rash also developed on the hands and voluntary movement was temporarily lost.

In 1879, Ladenburg announced the identity of duboisine and hyoscyamine. Duboisine was commercially prepared by the firm E. Merck, which supplied it principally for use as a stronger mydriatic than atropine, and as an injected sedative and narcotic in psychiatric and neurological patients. As with many solanaceous alkaloids of this period, commercial duboisine was actually a mixture of hyoscyamine and hyoscine (and possibly other undefined alkaloids), but, on Ladenburg’s authority, ‘duboisine’ came to be regarded in a practical sense as being identical with ‘hyoscyamine’, despite frequent observations that duboisine was much more potent than commercial hyoscyamine. Ladenburg re-examined the question together with Petersen in 1887; he found that commercial duboisine (E. Merck), a yellow-brown syrupy mass, was, in fact, mainly hyoscine. The firm Schering, on the other hand, also addressed the issue and found that duboisine prepared as described by Bancroft consisted of nothing but hyoscyamine.

By 1895, it had been established that the alkaloid content of *D. myoporoides* leaves from young plants consisted mostly of hyoscine, while older specimens principally contained hyoscyamine. The issue was further clouded by the fact that leaves of *D. myoporoides* and *D. hopwoodii* were long sold in Europe indiscriminately as ‘Duboisia’. This confusion of the two species, facilitated by the fact that most European workers had never seen fresh source plants, was not entirely eliminated until the early 20th century. Barger’s group noted in 1937 that an alkaloid extract they had prepared from *D. myoporoides* material contained no hyoscyamine but was rich in hyoscine, whereas commercial ‘duboisine’ (*Duboisinum purum crystallisatum*; Merck) was almost pure hyoscyamine. At about the same time, Thoms recorded that the amorphous duboisine samples from this company consisted of racemic scopolamine (as did amorphous hyoscyamine). The result of this confusion, which was not unusual at this point in the history of alkaloid chemistry, is that the popular identification of hyoscyamine and duboisine was an accident resulting from the selection of raw materials and the preparative processes employed at E. Merck. By 1940 a number of other alkaloids had been identified in the plant, including nor-hyoscyamine, valeroidine, poroidine and tigloidine.

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147 Wells, 1879; see also Lauterer, 1895. Scopolamine was later also associated with glaucoma: see Hirschlaff, 1918.
148 Anonymus, 1896b.
149 Ladenburg, 1880b,c; also Ladenburg and Meyer, 1880.
150 Ladenburg and Petersen, 1887.
151 Anonymus, 1890. This controversy was separate from the confusion of ‘pituri’ and ‘duboisine’ (and of their source plants) which persisted for some time in England; see Dixon, 1883. Von Mueller also made this mistake: Mueller and Rummel, 1879.
152 This confusion is still referred to in the review article published in *Mercks Jahresbericht* for 1916 (pp.3-12); the author noted that Gerrard had isolated ‘piturine’, an alkaloid not identical with ‘duboisine’, from *Duboisia*.
153 Barger *et al.*, 1937; see also Barger *et al*., 1938.
154 Thoms, 1927-9, VI, p.1956.
155 Lauterer, 1895; Barger *et al*., 1937, 1938; Griffin *et al*., 1975; Cougoul *et al*., 1979; Trease and Evans, 1983, p.561.
III. The solanaceous alkaloids

The entire story underscores the uncertainty which prevails when employing plant extracts and explains the perceived need by some workers to develop therapies involving defined quantities of specific alkaloids rather than the plants themselves.\textsuperscript{156} It should also be noted that the literature on \textit{Duboisia} is confused by the fact that many authors, including recent authorities who would be expected to know better, have not distinguished between \textit{D. myoporoides} and \textit{D. hopwoodii}. This necessarily leads to confounding in these depictions of the associated alkaloids and the pharmacological effects of the plants.

In any case, commercial plantations of \textit{Duboisia} as sources of both scopolamine and atropine were planted soon after Barger’s discovery of the high hyoscine levels of \textit{D. myoporoides}. This, however, was less the result of immediate recognition of the value of \textit{Duboisia} as of historical necessity. The Dresden firm Gehe & Co. had already noted in 1891 that the price of duboisine was leading to a decline in its use; as it was principally employed in ophthalmology, and had shown here no advantage over atropine, the high cost of the raw material was prohibiting its application.\textsuperscript{157} But most of the scopolamine used in Australia and America before the Second World War had been imported from Germany. Large quantities of the agent were required during the War both as a sedative (including pre-surgical anesthesia) and to manage the sea-sickness which was a major problem in the wars in the Pacific and Atlantic, and supplies were quickly depleted. Wilfred Russell Grimwade (1879-1955), as official botanical advisor to the Australian Army, accordingly oversaw the introduction of the commercial production of hyoscine in south-east Queensland and northern New South Wales by Felton, Grimwade & Duerdins Pty Ltd.\textsuperscript{158} Australia became thereby the sole supplier of the drug to the Allied forces during the second half of the war; vast quantities were employed for the preparation of the troops participating in D-Day;\textsuperscript{159} it was also useful in the treatment of bomb shock. It is said that the 7000 ounces hyoscine produced from this source during the War exceeded all previous production. Commercial extraction of hyoscyamine for conversion to atropine proved more difficult, but also commenced following the War. The related \textit{D. leichhardtii} is also a useful source of scopolamine. In contrast, attempts to cultivate belladonna or \textit{Datura} species met with disappointing results, with viral and insect attack representing problems which did not affect \textit{Duboisia} to the same degree.\textsuperscript{160}

\textsuperscript{156} The name ‘duboisine sulphate’ is still employed by the firm Ciba Vision Ophthalmics for their preparation of hyoscyamine (for use as mydriatic in those who respond poorly to atropine).

\textsuperscript{157} Maiden, 1893. Rabow (1893), however, noted that duboisine was cheaper than hyoscine; as he regarded hyoscine and scopolamine as distinct alkaloids, however, it is difficult to interpret this statement.

\textsuperscript{158} Rosenblum, 1945. Felton, Grimwade & Duerdins later became Drug Houses of Australia (Victoria). Grimwade investigated the cultivation of a number of plant drugs on his property ‘Westerfield during the War; he also developed a method for extracting oil from apricot seeds as an alternative to olive oil.

\textsuperscript{159} Blainey, 1977: “Here, in 1944, was the greatest armada in the history of man, setting out towards a turning point in history; and much of the success of that armada depended on a drug which had been discovered by forgotten men and women in ancient Australia.” Another curiosity: “Hyoscine” was the American naval codeword for Adelaide (South Australia) during the War.

\textsuperscript{160} Ralph and Willis, 1944; Barnard and Finnemore, 1945; Barnard, 1951. Initial attempts to cultivate belladonna in the United States were also frustrated by low yields: Woodward, 1947. See also Annual Reports of the Council for Scientific and Industrial Research 15 (1940/41) to 21 (1947/48) and Annual Reports of the Commonwealth Scientific and Industrial Research Organisation 1 (1948/49) to 4 (1951/52).
III. The solanaceous alkaloids

Plantations of *D. myoporoides* and *D. leichhardtii* and of hybrids of the two species (which have the dual advantages of higher tropane alkaloid levels and virtually no nor-nicotine)\(^{161}\) on the east coast of Australia have since remained major world sources of scopolamine and atropine (derived from hyoscyamine); the leaves have an alkaloid content of to 7% by dry weight, of which about half is hyoscine. Scopolamine production was formerly performed locally, but the raw product is now largely exported to Germany for extraction; interestingly, Maiden as early as 1893 noted that most exported *Duboisia* leaf was sold in Germany. The alkaloid content of *Folium Duboisiae* is exceptionally high (1.95%-2.18%), and includes hyoscyamine, pseudohyoscyamine, scopolamine and tigloidine, amongst other alkaloids.\(^{162}\) For this reason, accidental poisoning through exposure to aerosols during harvest of the plant has been a constant problem.\(^{163}\) Research into the biochemistry of alkaloid production in *Duboisia* was pursued in Australia during the post-War period, particularly by Trautner’s group it was found, for example, that alkaloid production occurs principally in the roots, from whence the compounds are transported to the aerial parts of the plant, in a fashion similar to that since described in European Solanaceae.\(^{164}\)

**Hyoscine: the “second alkaloid” of hyoscyamus**

Hyoscine was originally also isolated by Ladenburg from henbane in 1880 as a thick, colorless syrup, which he named hyoscine in the false belief that it was an isomer of hyoscyamine.\(^{165}\) E. Merck commenced commercial production shortly after Ladenburg succeeded in producing several salts of the base, thus making its use in medicine feasible (1882). Despite theoretical problems with some of his results, Ladenburg and many others remained convinced until the early 1890s that hyoscine was isomeric with atropine, which contributed to the first major controversy regarding the alkaloid.

It was recognized in retrospect by many workers that many of the effects attributed to hyoscyamine were in fact attributable to hyoscine, the “second alkaloid” of hyoscyamus. For instance, the Philadelphia neurologist H.C. Wood noted in 1885:

> Every reader of the therapeutic literature must have noticed the great diversity of experience and sentiment which exists in regard to the therapeutic effect of hyoscyamia. By some physicians it is believed to be of great value as a calmative and hypnotic remedy, whilst others have found it almost inert; and others, equivalent in its influence to atropia. Its commercial form is almost as various as its action; . . . and when . . . very extended trial shows that the most reliable form is Merck’s uncrystallized hyoscyamine, suspicion is at once aroused, because crystalline principles are, as a rule, much purer than amorphous ones.\(^{166}\)

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\(^{161}\) Luanratana and Griffin, 1980.

\(^{162}\) Tschirch, 1923, pp.203-204; Carr, 1974; Cribb, 1985. Pseudohyoscyamine: Merck, 1893.

\(^{163}\) Pearn, 1981.

\(^{164}\) Hills et al., 1946.

\(^{165}\) Ladenburg, 1880e. Höhn and Reichardt (1871) had originally used the name ‘Hyoscin’ for the base produced by the decomposition of hyoscyamine; after Ladenburg had shown that this was, in fact, tropine, he applied the name to the new alkaloid.

\(^{166}\) The Merck alkaloids generally enjoyed the most widespread approval amongst both pharmacologists and physicians in the 19th and early 20th centuries. There were clearly differences in the composition of ostensibly identical products marketed by different chemical firms; see, for example, the comparison of the physical properties of atropine and daturine produced by Merck, Trommsdorf, Schuchardt and Gehe in Schmidt, 1881.
Wood correctly assumed that a contaminant of amorphous hyoscyamine was, in fact, responsible for most of its beneficial actions. He found it remarkable that American physicians, aware of this phenomenon, should have largely ignored the work of Ladenburg, especially as two salts of purified hyoscine (hydrobromate and hydroiodate) were commercially supplied by Merck in America. He did also note, however, that the drug was quite expensive. Wood had conducted his own investigations into the pharmacological effects of hyoscine, and found that in mammals it was primarily a “spinal depressant” which, at sufficient doses, induced death by asphyxia. In experiments in humans, however, the central hypnotic-narcotic effects of the agent predominated, which led him to try the agent successfully in a number of patients suffering from excitement of various types (mania, dementia, delirium tremens); he also found it useful in the relief of spasm.

The first comprehensive investigations of the pharmacology of hyoscine were reported in 1886 by Rudolf Kobert (1854-1918) of the Pharmacological Institute in Dorpat; his report concerned the material contained in the doctoral thesis of August Sohrt, Assistant in the Psychiatric Clinic. Kobert noted that this was the first report concerning the alkaloid in Naunyn-Schmiedeberg’s Archiv; he had suggested two years previously, however, that many of the effects attributed to hyoscyamine might in fact be due to contamination by hyoscine. This was indicated by the clinical differences in the effects of atropine and ‘extractum hyoscyami’; the latter was sedative, the former not. Merck also marketed a product at this time under the name ‘amorphous hyoscyamine’, the pharmacological effects of which were clearly distinct from those of both hyoscyamine and atropine; it was from this amorphous product that Ladenburg had isolated hyoscine in 1880. Kobert’s laboratory explored the effects of hyoscine on a variety of physiological functions in frogs, mammals and in man. It was established that hyoscine exerted the following effects in humans:

• It was excreted unchanged in the urine.
• It had no effect on the normal pulse or blood pressure, nor on respiration, but inhibited vagal inhibition of the heart.
• Hyoscine inhibited sialorrhea in paranoid patients and sweating in phthisics; it was tolerated better than atropine.
• Like atropine, it was mydriatic, but the effect was achieved more quickly and was of shorter duration; it could also be more easily reversed with physostigmine.
• Sohrt experienced in self-experiments the profound sedative and hypnotic effects of 0.5-1mg administered subcutaneously. Another doctor accidentally consumed a small amount of a strong solution of hyoscine hydrobromide; apart from an irresistible urge to sleep, he was affected by vertigo, nausea, restlessness, disturbing dreams and unpleasant feelings.

Kobert thus regarded the alkaloid as a mild narcotic which could possibly find application in the clinic. He noted that between 1879 and 1882 a number of English and American papers had reported that the amorphous hyoscyamine was a better sedative than the crystallized form. This attracted particular attention as the amorphous version was much cheaper than the purer preparation. The amorphous form had already been applied with some success in a number of neurological conditions:

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167 ‘Amorphous hyoscyamine’ was a thick, syrupy liquid; Squire noted in 1899 that the prices of the two forms of hyoscyamine were similar (p.363).
168 Including one case where, while “assisting [Wood] in the laboratory, Dr. F. E. Stewart accidentally swallowed a small quantity of a strong solution.”
169 Seguin (1880) cited prices of 15c/grain for the amorphous form and 75c for crystalline hyoscyamine.
1880 Mania: Therapeutic Society of New York.
1880 Agitated conditions, including chorea, paralysis agitans, epilepsy: Seguin.
1880 Epilepsy, mania: Reinhard.
1881 Mania; sleeplessness, paranoia, destructive mania; also as an antispasmodic in paralysis agitans, epilepsy, chorea, tabes dorsalis: Sepilli.\textsuperscript{170}

Kobert interpreted these reports as possibly indicative that hyoscine, not hyoscyamine, was the effective component of the extract. Schüle, on the other hand, advised against the use of hyoscyamine in 1882 on the grounds that it not only induced xerostomia to a degree which hindered ingestion of food, but also because it produced, agitation, disturbances of sensory perception, hallucinations, muscular pain in the legs and emaciation. These contrasting responses to ostensibly the same agent certainly appeared to indicate that different active principles might actually have been involved.

In general, the description by humans of the effects of hyoscine corresponded to those described eloquently by Lewin in 1924:

\begin{quote}
They feel a pressure in their head, as if a heavy body had been laid upon it. At the same time, they begin to feel as if an invisible power was forcing their eyelids shut. Objects appear to the blurry eye as if stretched into the distance. Eyes wide open, all sorts of visual hallucinations appear: for example, a black circle on a silver background, or a green on a golden. Then the lids close for sleep. Smell and taste also experience changes. Visions haunt the slumbering individual.\textsuperscript{171}
\end{quote}

The first clinical trials with purified hyoscine in psychiatric patients were those of Rudolf Gnauck in the Psychiatric Clinic of the Charité in Berlin in 1881/2. Gnauck noted that there few reliable hypnotics for use in psychiatric patients, so that the finding that hyoscine, which he believed to be a decomposition product of hyoscyamine, possessed both calmative and sleep-inducing properties was highly welcome. The subcutaneous administration of 1-2mg hyoscine elicited sedation and analgesia within twelve minutes, accompanied by pupil dilatation, dryness of mouth, motor unsteadiness and a sense of mental confusion and vertigo which was still apparent after sleep. Gnauck was impressed with hyoscine as a sedative, but regarded it less suitable as a hypnotic, due to the frequency of unpleasant side effects which the required doses elicited. He noted that sensitivity to the effects of hyoscine was highly variable, but that his psychiatric patients appeared to be particularly sensitive to its effects.\textsuperscript{172}

Other reports of its use in psychiatric patients and delirium tremens followed. For example, Kraepelin’s student Sohrt treated twelve clinic patients (dementia, paranoia, mania, paralysis progrediens) with 0.5-1mg hyoscine; selected were those who had always responded well to amorphous hyoscyamine but were refractory to the effects of conventional hypnotics. In each case, sleep was induced without the production of serious side effects, so that Kobert recommended the use of the alkaloid in all cases of agitation. He also noted that the sedative effect of the drug was curiously far less marked in normal persons than in agitated patients; this may simply reflect the greater potential for sedation in such patients.\textsuperscript{173} Kraepelin himself regarded hyoscine a

\textsuperscript{170} All cited in Kobert and Sohrt, 1887.
\textsuperscript{171} Lewin, 1924, p.129. See also extensive examination of the effects of hyoscine in Heimann, 1952.
\textsuperscript{172} Gnauck, 1882; also see Wood, 1885; Robdeau, 1887.
\textsuperscript{173} Kobert and Sohrt, 1887.
valuable addition to the pharmacopoeia of the psychiatric clinic, a reliable and rapid sedative exhibiting few if any negative long term effects.\(^{174}\)

**Scopolamine**

Ernst Schmidt isolated scopolamine from *Scopolia atropoides* (scopola; figure 3-8)\(^{175}\) and *S. japonica* (‘Japanese belladonna’) in 1888, and immediately concluded that it was identical with hyoscine;\(^{176}\) indeed, the term ‘scopolamine’ was not employed by Schmidt, but was introduced by those who did not accept that he had isolated hyoscine from these plants.\(^{177}\) This was unsurprising, as *Scopolia* species were already regarded as occupying a position intermediate between *Atropa* and *Hyoscyamus*. Scopolamine was also shown by Schmidt to be present in differing amounts in belladonna, mandragora, dubyosia and a number of *Datura* species.\(^{178}\) The identity of hyoscine and scopolamine was accepted early by most workers, but a debate between Schmidt and Ladenburg on this point was carried out in the pages of the leading German chemical journals from 1890 to 1894;\(^{179}\) as late as 1904, the second edition of Pictet’s *The vegetable alkaloids* declared the issue still unresolved.\(^{180}\) The question turned on the fact that Ladenburg had determined C\(_{17}\)H\(_{23}\)NO\(_3\) as the molecular formula for hyoscine, and thus regarded it as isomeric with atropine, whereas Schmidt had found C\(_{17}\)H\(_{21}\)NO\(_4\) for scopolamine, but also determined that both bases shared near-identical physical properties. The debate was also fostered by the common feeling that it was unlikely that two geographically separated plants would yield the same alkaloid, a prejudice which would later figure in the harmine/banisterine controversy. The argument was effectively decided when Schmidt demonstrated that scopolamine could be prepared from preparations of hyoscine hydrobromide (Merck), in the course of which he also found that the commercial salt was not entirely pure.\(^{181}\) Kobert (Dorpat) confirmed that hyoscine and scopolamine were pharmacologically indistinguishable.\(^{182}\) Oswald Hesse, who had supported Schmidt’s position in the hyoscine debate, nevertheless opposed Schmidt’s suggestion that hyoscine be henceforth designated scopolamine in order to

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\(^{174}\) Kraepelin, 1903, p.398. Employment of hyoscine as a ‘chemical restraint’ in psychiatric patients and prisoners has long been the subject of critical discussion: see Näcke, 1892; Schwarz, 1984.

\(^{175}\) Native to Bavaria, Austria, Hungary and southern Russia; identical with *S. carniolica*. *Scopolia* was named by Linné for the Tyrolean botanist, physician and apothecary Johann Anton Scopoli (1723-1788); the Linnean name was *Hyoscyamus scopolii*. The current name was later introduced by Jacquin. After an adventurous life as physician, Scopoli was appointed Professor of Chemistry and Botany at Pavia in 1776. His most important botanical works were *Flora Carniolica* (1766; re-issued in 1772 in accordance with the Linnean classification system) and *Anni Historica Naturalis* (1769-1772); he also wrote on physics, metallurgy and chemistry. His death in 1788 was attributed to the sharpness of a public rebuke from the Emperor Josef II following Scopoli’s denouncement of a famous colleague as a thief.

\(^{176}\) Schmidt and Henschke, 1888; Schmidt, 1890; confirmed by Siebert, 1890.

\(^{177}\) These plants also contained choline. Martin (1878) had reported that Japanese belladonna was devoid of atropine but contained solanine. Langgaard had isolated two alkaloids from *S. japonica* (‘onishirikusa’ or ‘rōto’): he named them ‘scopoleîne’ and ‘rotoine’; the latter was only present in small quantities, but appeared to be mydriatic, whereas scopoleîne acted in an atropine-like fashion (see also Dupuy, 1889, II, pp.497-498). Scopoleîne was apparently commercially available in Germany, as Schmidt concluded in his 1888 paper that it consisted of a mixture of hyoscynamine, hyoscine and atropine.

\(^{178}\) Schmidt, 1881, 1892a, 1892b, 1894.

\(^{179}\) See especially: Schmidt 1892a, 1892b, 1894; Ladenburg, 1892.

\(^{180}\) Pictet, 1904, p.194.

\(^{181}\) Schmidt, 1892a.

\(^{182}\) Schmidt, 1892a, pp.217-218.
avoid confusion with hyoscyamine; he argued that it was more important that the errors which led to the name had been resolved, and that the name hyoscine was already established in pharmacy. The name scopolamine would have first to become familiar were it to be adopted, and it was “doubtful whether that would ever happen.”

183 Louis Merck offered a similar explanation in 1897:

> It is only for the purpose of obviating misunderstandings in commercial and medical circles, where a change of name is apt to create great confusion, that our house has retained in its trade-list the designation of "hyoscine" for the base from hyoscyamus, while applying that of "scopolamine" to the base from scopolia atropoides.

184 Hesse, 1892. Hesse also opposed Schmidt’s use of the term scopoline for oscine, as there already existed a glucoside with this name. Schmidt’s views eventually prevailed but in both cases, Hesse was involved in a number of such identity controversies; for instance, he did not accept the equivalence of atroscine and i-scopolamine (i.e. d,l-scopolamine; see Gadamer, 1898, 1901 and Kunz-Krause, 1901), nor of atropamine and apoatropine (Hesse, 1891, 1892, 1893); in both cases, he proved to be in error. The latter controversy led to the unhappy circumstance that scopolamine proper (the L-isomer) and the racemic mixture (properly atroscine, in analogy to atropine) were both referred to as ‘scopolamine’. See also Anonymus, 1896a, for the continuation of the debate.

184 Merck, 1897.
Ladenburg’s reputation was such that even Merck was not willing to dismiss the possible existence of "hyoscine $C_{17}H_{23}NO_{3}$", even if the efforts of his firm to isolate such an alkaloid had proved fruitless. That the similar names of hyoscine and hyoscyamine caused confusion even amongst the initiated is exemplified by the fact the *Journal of the Chemical Society* in 1887 (p.740) and the *Year Book of Pharmacy* for 1888 (p.62) cited Ladenburg as having demonstrated the identity of the alkaloid duboisine with hyoscyamine; these were misreadings of the original article, the major point of which was that duboisine was identical with hyoscine, not hyoscyamine. Physicians of the time also treated hyoscine and hyoscyamine as either identical or isomeric; for example, a physician wrote in the *British Medical Journal* in 1888 that he knew “that hyoscyamine is identical with hyoscine, light atropine, and light daturine”, with consequences for the use of the two drugs. At the same time, there were those who declared that “it has been demonstrated that the value of hyoscyamine really depends on the hyoscine it contains”.

The two names ‘hyoscine’ and ‘scopolamine’ continued to be used for many decades, seemingly dependent on the application of the drug and the nationality of the writer; English-speaking authors tended to prefer ‘hyoscine’, German speakers ‘scopolamine’. By the mid 1920s, hyoscine was abandoned as the name for the alkaloid except in England and associated countries.

Scopolamine was initially used in the clinic as a mydriatic, although its employment as a sedative was also quickly recognized. Scopolamine had probably been employed as an anesthetic and narcotic since the Middle Ages as a component of the ‘narcotic sponges’ discussed above. Its use in combination with morphine in surgical anesthesia was suggested by Schneiderlin and Korff at the turn of the 20th century. Scopolamine was thus used in the early part of the 20th century to induce pre-anesthetic sedation and even true anesthetic narcosis (lasting 45 minutes to 14 hours); the individual variability in sensitivity to the drug, however, made its use difficult. The most famous example of this role was its application during childbirth, where it was used together with morphine to induce the “twilight sleep” (*Dämmerschlaf*), introduced by von Steinbüchel in 1902 and popularized by the report by Carl Gauß in Freiburg in 1905 of its successful application in 500 cases. Gauß used scopolamine in both powdered and tablet form, and prepared and sterilized the morphine and scopolamine solutions separately by careful boiling. Not only was the birth thereby accelerated, but the mother generally neither experienced nor remembered the associated pain. This was not accepted by all with the anticipated gratitude, as it seemed to run contrary to the divine punishment meted out to Eve and all subsequent mothers at the time of the

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185 Squire, 1890.
186 Sinclair-Thompson, 1888; see also West, 1888.
187 Piteain, 1888.
188 But as late as 1918, Hirschlaff, while noting that many regarded hyoscine, scopolamine and duboisine as identical, treated hyoscine and scopolamine separately in his review of scopolamine research.
189 The United States Pharmacopoeia adopted ‘scopolamine’ as the official designation in 1916. The usual arguments pertaining to plant drugs – that the species of origin determined the potency of the alkaloid – also applied in the hyoscine/scopolamine debate for many years. See Gerlach, 1948.
190 See, for example, Peters, 1894.
191 Review: Hirschlaff, 1918.
192 Korff, 1901; von Steinbüchel, 1902; Gauss, 1906. See also Schneiderlin, 1903; Kochmann, 1905; Hellman, 1915, pp.1-33; Thearle and Pearn, 1983; Marx, 1987; Soban et al., 1989. Schneiderlin’s original paper appeared in *Aerztliche Mitteilungen aus und für Baden* on 31 May 1900.
expulsion from the Garden of Eden. Kröning lectured on the method in Sheffield in 1908, after which it was gradually accepted in England; the British Medical Journal noted the insistence of the professor upon the name ‘scopolamine’ which no doubt contributed to its acceptance in this application.

It is now recognized that scopolamine impairs short term memory processes and reduces the ability to focus attention, both of which contribute to its pseudo-anesthetic effect. A more controversial application of the alkaloid was introduced in the 1920s in the United States: the use of scopolamine as a ‘truth serum’ for extracting confessions from recalcitrant suspects; it has also been used to ameliorate the withdrawal symptoms experienced by heroin addicts.

The role of the Scopolia species in the history of scopolamine was restricted largely to its eponymic role. The genus Scopola has been compared to both Atropa and Hyoscyamus, with the leaf, flower and root reminiscent of the former and the fruit that of the latter. Radix scopoliae had an alkaloid content of 0.2-0.5% (the European version contained twice as much as the Japanese), but it consisted mainly of hyoscyamine. It was noted in the Münchner medicinische Wochenschrift of 31 December 1889 that British pharmacologists had recently identified the root as a particularly rich source of hyoscyamine, and indeed in purer form than in other solanaceous plants. The Scopola extract exerted all the pharmacological effects associated with other atropine-containing plants. The root was accepted into the United States Pharmacopoeia, but was not widely used in Europe. As belladonna and scopolia preparations were regarded as completely interchangeable, there appeared no reason to introduce a new plant agent. Hyoscine/scopolamine was thus usually prepared from hyoscyamus or stramonium as a byproduct of atropine isolation, or from the Indian plant Datura metel, the leaves and seeds of which contain about 0.5% hyoscine as the principle alkaloid. Podack reported that the dried root of S. carniolica was employed in southern Lithuania both as a sleeping drug and in paralysis agitans, as did Fühner; experiments in his clinic, stimulated by his observation that one patient had used pieces of the root as his only medication for thirty years without developing symptoms of intoxication, found that an extract of the root was as effective as scopolamine or hyoscyamine from Merck, but less liable to induce toxic effects. Von Ketly of Ofen-Pest also reported in 1903 that he had achieved good results with the root of S. carniolica, administered as a powder (0.3-0.4g/day), in paralysis agitans patients. It was also used as an intoxicant, an aphrodisiac and an abortificant, and

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193 Scopolamine was said to have still been used in 60% of births in America in 1958: figure cited in Geis, 1959.
194 Anonymous, 1910.
195 Van Leeuwen and Györgi, 1921; for recent discussions of the central effects of scopolamine see Safer and Allen, 1971; Flicker et al., 1990.
196 Geis, 1959, 1961. Belladonna is reported to have been employed in a similar manner in Prussia in the 19th century: Schwamm, 1988, p.270.
197 Geis, 1959. Higier mentioned in 1905 that hyoscine was employed in English-speaking countries in the treatment of alcoholism; he himself had used it to treat morphine addiction (see also Hirschaff, 1918). Scopolamine has also been used in recent years to adulterate heroin supplies: see Kaa, 1994; Centers for Disease Control and Prevention, 1996.
198 Grieve, 1931, p.722.
199 Anonymous, 1889.
200 Tschirch, 1923, pp.308-309; Brandt and Wasicky, 1929, pp.1552-1553.
201 Podack, 1897; Fühner, 1919.
202 Von Ketly, 1903; see also E. Merck’s Annual Report (English version) for 1902, pp.175-176.
III. The solanaceous alkaloids

popular for inducing temporary madness as a form of joke and for expediting the demise of aged relatives.203

Table 3-1: Summary of the identification of the solanaceous alkaloids discussed in this work.

<table>
<thead>
<tr>
<th>“Alkaloid”</th>
<th>Year named</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atropine</td>
<td>1820</td>
<td>Brandes</td>
</tr>
<tr>
<td></td>
<td>(isolated 1831)</td>
<td>Mein</td>
</tr>
<tr>
<td>Daturine</td>
<td>1832</td>
<td>Bley</td>
</tr>
<tr>
<td>Hyoscyamine</td>
<td>1833</td>
<td>Geiger and Hesse</td>
</tr>
<tr>
<td>Belladonnine</td>
<td>1868</td>
<td>Hübbschmann</td>
</tr>
<tr>
<td>Duboisine</td>
<td>1878</td>
<td>von Müller and Rummel</td>
</tr>
<tr>
<td>Hyoscine</td>
<td>1880</td>
<td>Ladenburg</td>
</tr>
<tr>
<td>Scopolamine</td>
<td>1890</td>
<td>Schmidt</td>
</tr>
<tr>
<td>Atropamine</td>
<td>1891</td>
<td>Hesse</td>
</tr>
<tr>
<td>Pseudohyoscyamine</td>
<td>1892</td>
<td>Merck</td>
</tr>
<tr>
<td>Atroscine</td>
<td>1898</td>
<td>Gadamer</td>
</tr>
<tr>
<td>Meteloidine</td>
<td>1908</td>
<td>Pyman and Reynolds</td>
</tr>
</tbody>
</table>

203 Fühner, 1925.
IV. Alkaloids in the therapy of parkinsonism: From Charcot to the outbreak of encephalitis epidemica

ALTHOUGH PARALYSIS AGITANS had been recognized quite early as a distinct nosological entity by certain authors in continental Europe, its general acceptance by the French medical community was reached only in 1859, when Armand Trousseau (1801-1867) published a lecture on the disorder as part of his work on chorea, discussing the rigidity and bradykinesia of parkinsonism for the first time. The ultimate breakthrough, however, was made by the group around Jean Martin Charcot (1825-1893) at the Salpêtrière Hospital in Paris.

"Among the multitude of names that illumine the pages of neurology none shines with greater brilliance than that of Charcot." He was the son of a wagon-builder, and had initially considered a career as an artist. Charcot described chronic joint rheumatism so well in his doctoral dissertation (1853) that it was named after him (Charcot’s joint). He became medical superintendent at the Salpêtrière in 1862, the turning point in his career; he succeeded Vulpian in the Chair of Pathological Anatomy in 1872, which he occupied until his appointment to the newly created Chair of Diseases of the Nervous System in 1882. Amongst his pupils were many who continued his work: Pierre Marie (1853-1940), Dejerine (1849-1917) and Babinski (1857-1932).

At the Salpêtrière Charcot found five to eight thousand welfare patients suffering from a wide variety of neurological, psychiatric and other disorders, most of them

1 Trousseau, 1862.
3 De Morsier, 1956; Wechsler, 1970; Capildeo, 1982.
unclassified. Charcot became determined to create some form of system from this chaotic group of patients. As noted by his student Sigmund Freud, Charcot complemented his sharp observational skills with the desire to define what he saw:

*He called this form of intellectual exercise, in which he had no equal, “doing nosography”, and was proud of it.*

Charcot regarded the Salpêtrière as "a sort of living pathological museum whose resources are almost inexhaustible", and shared Claude Bernard’s belief that the study of pathological states and their modification by therapy as the key to the advancement of physiology itself. Edmé-Félix Alfred Vulpian (1826-1887), who had been appointed to the Salpêtrière (as Professor of Pathological Anatomy) at the same time as Charcot arrived, collaborated with him in this massive work of classification, which they pursued until the breakdown of order in Paris in 1870/71. Together, they described Parkinson’s disease in a series of articles in the French journal *Gazette de Hebdomadaire Médecine et Chirurgie* in 1861-2; more importantly, Charcot included lectures on the subject in his much translated *Leçons sur les maladies du système nerveux faites à la Salpêtrière*, published after he succeeded to Vulpian’s chair in 1872.

The third member of the Paris group who is important to the present discussion was Leopold Ordenstein (1835-1902), a German student who prepared the thesis for his doctorate in medicine in Paris; the tract (*Sur la paralysie agitante et la sclérose en plaques généralisées*) was published in December 1867. Together, the publications on Parkinson’s disease by the three workers would shape medical views of the disorder until after the First World War.

This is not the place to discuss Charcot’s depiction of Parkinson’s disease in detail; it suffices to note that his description of the disorder is regarded as one of his major contributions to neurology, a large claim, given the magnitude of his other achievements. The major symptoms of the disease were recognized by Charcot, including tremor, rigidity, postural problems and bradykinesia. Another doctoral student, Claveleira, drew further attention to the slowness of movement in his 1872 thesis. Charcot classified Parkinson’s disease, as he preferred to term the disorder, as a ‘névrose’ on the basis that there were no obvious causal anatomic lesions. The major immediate causes of the disorder were identified as prolonged exposure to a cold, damp environment, and emotional trauma of an extreme nature. These two causes were both involved in Romberg’s famous case of a man stripped of his clothing by Cossacks and left lying on damp ground for an extended period.

Charcot was primarily a nosologist, and only secondarily interested in treatment:

*He disdained therapeutic intervention, regarding the imperfections of the human body as an astronomer would the motions of the stars.*

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4 Cited by de Morsier, 1956, p.40.
6 Charcot and Vulpian, 1861, 1862.
7 Charcot, 1877, pp.129-156 (= Charcot, 1892, pp.155-188) and 317-320. Vulpian transferred to the Chair of Experimental Pathology with the aim of promoting in France the microscopic anatomy then pursued with remarkable results by Virchow in Berlin.
8 The second post mortem case described in the thesis exhibited some deterioration of the substantia nigra, but did not attract further attention.
9 Romberg, 1853, p.235.
This attitude was undoubtedly supported by the impotence of the physician before the neurological diseases with which Charcot was confronted in the Salpêtrière; particularly in the case of Parkinson’s disease, Charcot was convinced that pharmacological intervention was largely fruitless, and that any cures which were achieved were effected by other means:

*It is an incontestable fact that paralysis agitans is sometimes cured. . . . These instances prove that paralysis agitans is not incurable. But we must confess that we are ignorant of the means employed by nature to produce this result. Everything, or almost everything, has been tried against this disease.*

In their 1862 publication on the disorder, he and Vulpian had concluded that the doctor “was powerless against the progression of the disease.” The inconsistent experiences of Romberg and Elliotson with iron salts were reviewed; Basedow had reported one case in which the symptoms were suspended for a few months following treatment with Töplitz alkali. Sulfurous baths were also found to be of benefit by two other doctors, but it is not clear to the modern reader that paralysis agitans was actually the problem in these cases. In his lectures on paralysis agitans, Charcot listed the substances which had been “extolled”, but in Charcot’s hands had brought no success:

- Strychnine: despite positive reports from Trousseau, exacerbated the trembling.
- Ergot of rye and belladonna: anti-convulsive, but no effect in paralysis agitans.
- Opium: despite its analgesic capacity, heightened reflex excitability.
- Calabar bean (contains physostigmine): used by Ogle “without advantage.”
- Silver nitrate: exaggerates the convulsive condition, although it is calming in disseminated sclerosis.
- Barium chloride: recommended by Brown-Séquard.
- Electricity: Charcot cited two cases in which direct current from a galvanic pile had been reported as beneficial; he emphasized that neither alternating current nor static electricity should be tried. In his previous article, Charcot and Vulpian observed that, while ineffective in paralysis agitans, electricity might be of benefit in chorea.

The editor of Charcot’s lectures, Bourneville, noted that camphor bromide had also proved disappointing. Ordenstein discussed the therapy of paralysis agitans in his 1867 thesis, noting that even temporary success had been evasive in the management of the symptoms; he suggested that the advanced nature of the cases treated may have precluded a positive result. He mentioned, however, that his mentor had tried a novelty which appeared to be worth pursuing:

*Since the beginning of this month, M. Charcot has prescribed two or three granules of hyoscyamine, approximately one milligram each. New observations are clearly necessary to permit one to give an opinion about this last medication.*

11 Charcot, 1877, p.155.
12 Charcot and Vulpian, 1862.
14 Charcot, 1877, p.156.
15 Ordenstein, 1867; cited in Sourkes, 1999. Sourkes has noted that the frequent citation of ‘Ordenstein, 1867’ as the first reference to hyoscyamine therapy has led to the widespread misconception that Ordenstein himself was the originator of the idea.
The rationale underlying the treatment was presumably that sedation of the patient and the control of excessive salivation evident in the disorder were worthy goals.\textsuperscript{16} Hyoscyamine was, in any case, already recognized for its value as an antispasmodic and a sedative, especially in cases of nervous excitement; it was perhaps as such that it was first administered to Charcot’s patients, and he noticed subsequently the calming effects on the symptoms of those exhibiting parkinsonism. Certainly by 1880, hyoscyamine was viewed as a suitable substitute for both belladonna and opium in many of their clinical roles.\textsuperscript{17} Charcot himself noted that “some patients have obtained relief; its action, however, is simply palliative.”\textsuperscript{18} Despite Charcot’s deprecatory remark, this marked the introduction of the anticholinergic agents, in the form of what came to be known as the belladonna alkaloids, to anti-parkinsonian therapy.

It should, however, be noted that this was not the first employment of hyoscyamine in the treatment of paralysis agitans. Belladonna preparations had been recommended by Hecker in 1814 for a variety of nervous complaints, including chorea and epilepsy, and Hufeland (1762-1837) saw the belladonna root as especially useful in brain disorders and as an antispasmodic.\textsuperscript{19} With respect to paralysis agitans itself, the English physician Handfield Jones (1819-1890) had previously registered some success with the use of the alkaloid in a 47-year old man with tremor in one arm and both legs which disappeared only during sleep, and a panel of other symptoms, including excessive sweating. Jones attempted a variety of agents:

\begin{quote}
I gave him at first strychnia, iron and ether, and faradized his arm. This treatment especially the electricity was rather injurious than otherwise. I changed it after eight days for \textit{tr. hyoscyami 5 ss. ter die [~1.85mL, three times per day], under which he rapidly improved and ceased attendance in fortnight.}\textsuperscript{20}
\end{quote}

No explanation was provided for his use of henbane, except that in consequence of its beneficial effect Jones concluded that paralysis agitans, which he regarded as only superficially different to chorea, probably depended:

\begin{quote}
in some instances at least on increased excitability of the nervous centres of such a quality that it will not tolerate tonics, and requires rather calmants.\textsuperscript{21}
\end{quote}

There was no indication by Jones that the use of henbane in such patients was a novelty. Despite the promising result recorded, Jones’ report appears to have had little influence on the therapy of paralysis agitans, and Charcot was generally attributed with the introduction of the therapy by contemporaries. In any case, Jones recorded the opinion a decade later that the most appropriate agents for the management of paralysis agitans

\begin{itemize}
\item \textsuperscript{16} Geiger and Hesse (1833b) were presumably the first to note the inhibitory effect of atropine on salivation, but Heidenhain (1872) was the first to systematically investigate the action of this and certain other alkaloids on the nerves of the submaxillary salivary glands. This soon led to the use of atropine sulphate to control sialorrhea in a variety of clinical conditions; see, for example, Oettinger, 1878. Belladonna itself had been employed for centuries as an antisecretory agent.
\item \textsuperscript{17} Squire \textit{et al.}, 1882, pp.178-180.
\item \textsuperscript{18} Charcot, 1877, p.155.
\item \textsuperscript{19} Madaus, 1938, p.678.
\item \textsuperscript{20} Jones, 1864; pp.266. The tinctura of hyoscyamus was prepared slightly differently at this point to that employed in the early 20th century; amongst other differences, proof spirit was used in place of 45% alcohol, and the final dilution of crude henbane extract was 1 in 8 instead of 1 in 10; in both cases, the process yielded a brown-green fluid.
\item \textsuperscript{21} Ibid., p.267.
\end{itemize}
IV. From Charcot to the outbreak of encephalitis lethargica

were sedatives and mild tonics: and here he listed henbane without special distinction together with:

\[
\text{conium, chloral, subcutaneous opiates, bromide of potassium, belladonna, hypophosphites or phosphorus, cod-liver oil, carbonate of iron, and sulphuret of potassium baths, with electricity in one or other of its three forms.}^{22}
\]

Cases detected early offered good hope of recovery, according to Jones; otherwise he concurred with Trousseau’s adage, “À longue maladie, longue traitement”.

In America, Seguin championed the employment of hyoscyamine as antispasmodic and “depresso-motor” in a variety of motor disorders, including paralysis agitans. In his 1880 review of the “seldom used alkaloid”, he remarked that the French physician Oulmont was “often referred to as having been the first to use Hyoscyamia in [paralysis agitans]”, but noted that Oulmont had had some success in managing mercurial tremor with hyoscyamina, but had never had the opportunity to treat parkinsonism. Seguin was aware of Charcot’s use of hyoscyamine in paralysis agitans, and regarded Robert Lawson’s reports (in the West Riding Asylum Reports of 1875 and 1876) on his employment of the alkaloid in chorea and locomotor ataxia as the first English language descriptions of its usefulness in motor disease. Seguin himself had examined its effect in one paralysis agitans patient; he had: “told the patient frankly that nothing would cure him, but proposed a trial of hyoscyamia as a means of relief.”^{23}

Seguin filtered a preparation of one grain hyoscyamine in 100mL each of glycerine and distilled water with a half-drop of carbolic acid, and injected an amount corresponding to \(\frac{1}{50}\) grain into the patient’s arm; tremor was abolished within 30 minutes, and the effect persisted for 2-4 hours. After a few weeks, an increase in dose to \(\frac{1}{25}\) grain could be tolerated; the patient was thereafter maintained by the administration of two \(\frac{1}{30}\) grain pills per day (manufactured by Caswell & Hazard). Nevertheless, Seguin was well aware of the limitations of the therapy, noting with the same frankness he had shown his patient: “The usual progressive development of the disease has not been prevented.”^{24}

**Duboisine**

As discussed above, duboisine was originally applied to the alkaloid mixture obtained from *D. myoporoides*, and then to the mixture of hyoscyamine and hyoscine, and only finally to hyoscyamine alone.^{25} Only two years after its first isolation, Merck was able to provide Ladenburg with two grams of the sulphate for his experiments.^{26} Ostermayer appears to have been the first who recommended the use of the yellow hygroscopic powder duboisine sulphate as a rapid and intensive sedative and hypnotic which was safer to use in treating excited states in psychiatric patients than hyoscine.^{27} A number of other European authors similarly applied it subcutaneously, although a few also found it to be effective as an oral medication.^{28} During the 1890s, when many physicians did not rigorously distinguish between hyoscyamine and hyoscine, it was simply seen as an alternative to hyoscyamine as a sedative or atropine as a mydriatic.

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22 Jones, 1873.
23 Seguin, 1880.
24 Ibid.
25 See discussion in Barger et al., 1937.
26 Ladenburg, 1880c.
27 Ostermayer, 1891.
28 See references in Squire, 1899; Martindale and Westcott, 1901.
Pharmacological investigations of hyoscymine or duboisine were rare before the early 1890s. In animals, dilation of the central vasculature and contraction of peripheral vessels, leading to no marked change in blood pressure, had been observed following administration of duboisine, while in man 1mg of the substance produced “sleepiness, delirium, twitching of the limbs, visual hallucinations, increase in pulse and respiration lasting for 10 hours.”

The sedative properties of duboisine in maniacal delirium had been recognized as early as 1879; its sedative and hypnotic properties achieved greater attention, however, following the publication in 1890 by Nicolaus Ostermayer (Budapest) of a study comparing the effects of atropine, hyoscine and duboisine which found that the latter agent exhibited certain advantages with respect to the alternatives. In Germany, duboisine was recommended by Gellhorn (Pierson’s Sanatorium, Píma, Saxony) in 1891 as a rapid and safe sedative for psychotic patients; by 1893, it had entered both the Spanish pharmacopoeia and the Prussian Arzneitaxe.

Emanuel Mendel (1839-1907) applied duboisine in the treatment of parkinsonism in 1893 on the basis of its sedative effects in his psychiatric patients; he had noted that muscle relaxation preceded the onset of sleep. Mendel initially applied duboisine in patients whose motor unrest prevented sleep; muscular relaxation ensued five to ten minutes after injection, and sleep rapidly followed. He noted that it was not a true hypnotic, such as chloral or morphine, as this effect was not seen in patients whose insomnia was of psychiatric origin, as in depression or paranoia. Toxic signs appeared even at doses of 0.2mg (Mendel exceeded 1mg only rarely), and included pupil dilatation, dryness of the mouth and increased pulse. As the major problem in paralysis agitans, according to Mendel, was rigidity, he also tried the drug in these patients. He had treated twelve cases with duboisine (he noted that that he could not yet bring himself to try the drug in the polyclinic), rarely without success; within fifteen minutes, tremor was usually reduced to the extent that writing was again possible, and this effect lasted for three to five hours. Mendel had abandoned the use of hyoscine in favour of duboisine because of the less marked toxic effects and because of the lower required dose (2-3 × 0.2-0.3mg/day).

Duboisine was also a popular antiparkinsonian agent in France, but appears not to have been adopted to any great degree outside continental Europe. The activity of

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29 Studies cited by Mendel, 1893. See also Anonymus, 1880.
30 Gellhorn, 1891; further references in Mercks Jahresbericht for 1916, pp.3-12. In an afterword to his report, Gellhorn noted that duboisine in tablet form for injection (tablettae hypodermicae; à 1mg) had recently become available from Dr Oetker of Bielefeld, and that he found it a useful addition to the clinic. August Oetker (1862-1918) had recently commenced his work concerning the improvement of American baking powder which would lead to the success of the now famous cooking ingredient firm.
Duboisine was employed in a similar capacity in other countries, including Switzerland and Russia: see Rabow, 1893; Chimelovski, 1895.
31 Mendel, a Silesian Jew, spent most of his career in Berlin. He was politically active both within various medical associations, including the Berlin Medical Chamber, and as a member of local councils and the Reichstag (member for Potsdam, 1877-1881; Progress Party). His medical lectures, in which he promoted the unity of psychiatry and neurology and the empirical basis of scientific work, were popular, with Virchow, he opposed the anti-vivisectionist movement; he was also instrumental in framing legislation regarding the rights of the ill. Particular interests included progressive paralysis and epilepsy. Obituaries: Kron, 1907; Laquer, 1907.
32 Mendel, 1893.
33 For example, Francotte, 1896, 1899.
duboisine, when not attributed to an autonomous alkaloid of that name, was generally linked with the hyoscynamine content of the preparation. The therapies introduced by Jones and Charcot and by Mendel were actually equivalent, and the differing names of the drugs employed reflected only the different plant sources.

**Wilhelm Erb and hyoscine**

The clinical use of hyoscine had been delayed by difficulties in its preparation and the difficulty of its handling, hyoscine itself being a thick, largely insoluble syrup. The pure alkaloid was thus abandoned in favour of its salts, including the hydrobromide, hydrochloride and hydroiodide, which were initially used as a sedative and to induce sleep in psychiatric patients, as well as in the relief of chorea and other spasmodic conditions. Because of its potency, it was particularly popular in the management of manic patients; the dose recommended by the 1899 Merck Manual was up to three times higher for the “insane” than the sane. It was noted by a German physician in 1888 that, apart from its pharmacological properties, the chief advantages of hyoscine in comparison with other currently employed sedatives were its lack of taste and its inexpensiveness. The Leeds physician Gordon Sharp, who also believed that hyoscine to be an isomer of atropine and hyoscyamine, tested its clinical effects in three tremor patients (two of them males suffering from delirium tremens) in 1894, and concluded that it resembled atropine in its actions. He treated two cases of delirium tremens with hyoscine injected into the gluteal muscle, one with ½ grain, the other with ⅙ grain, and was alarmed by the partial paralysis of speech, swallowing and respiratory organs; the second patient died. A third patient, an anemic woman, received ½ grain to help her sleep, but it instead induced delirium and motor disturbances. Under these circumstances, concluded Sharp hyoscine could not be recommended as a hypnotic.

A recurring problem with hyoscine/scopolamine was the high variability of individual responsiveness to the drug. This was often ascribed to contamination with atropamine or apoatropine, or to general deterioration on storage. It seems, however, more likely that untoward effects experienced by some patients simply reflected their idiosyncratic sensitivity to the drug. The leader of the Merck Pharmacological Department, Kreitmair, indeed demonstrated that ephedrine counteracted the toxic effects of scopolamine in animals without negating its narcotic effect.

Wilhelm Heinrich Erb (1840-1921) was a highly respected figure in neurology during the last quarter of the 19th century, and was sometimes referred to as the “German Charcot”; his major achievements were generally regarded as being the distinction of dystrophia musculorum progressiva from other forms of muscular dystrophy and the establishment of the syphilitic etiology of tabes. The son of a forester, the acerbity and earthiness of his language, combined with his love of argument, were attributed to this unusually ordinary background for an academic; his dislike of the

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34 Merck duboisine, however, was found in some cases to be racemic scopolamine; see above (p.66) and Thoms, 1927-29, p.1956.
35 See also Martindale and Westcott, 1910, p.281-284.
36 Kny, 1888; 1889. Kny noted that many patients, for example, rejected the Bayer product ‘Sulfonal’ (sulfonemethane), even when mixed with food, because of its unpleasant bitterness.
37 Sharp, 1894. For contemporary review of the role of hyoscine in the clinic, see Cramer, 1889.
39 Kreitmair, 1926; for successful implementation of this finding in patients: Guttmann, 1926.
“Berlin” establishment, “with which Erb, being the classic Southern German of the best type, was deeply imbued”, was only mitigated by his elevation to the inaugural chairmanship of the Society of German Neurologists. He regarded himself more as an internist than a neurologist, and regarded the closer affiliation of neurology to psychiatry and its drift from inner medicine as damaging to the clinic of neurological disorders. His obituary noted that his character was shaped by a strength and will which were inspirations for both students and patients. During or shortly after attending a performance of the Eroica, he lapsed into a coma from which he never awoke.

Erb (from 1883: Internal Medicine, Heidelberg) is usually credited with introducing hyoscine into the therapy of parkinsonism in 1898 (although it does not appear to have become known to the English-speaking world until its publication in Deutsche Klinik am Eingange des Zwanzigsten Jahrhunderts in 1906). But Erb’s first publication on its use was in the Therapeutische Monatshefte of July 1887. Further, as just mentioned, Mendel had obviously seen it as the drug of choice before 1893. This probably indicates that the drug was not widely used in paralysis agitans before the turn of the century, and that Mendel’s employment of the agent was a personal choice, typical of the idiosyncratic manner with which clinicians selected a treatment at a time when there were no clear guidelines as to what was to be preferred. Significant is also the fact that the first edition of the Merck Manual (1899) lists as the only indication for hyoscine: “To quiet and give sleep to insane and others.”

Erb emphasized from the beginning the incredibly small doses of hyoscine (which he, like Kobert and many others at this point, regarded as being an isomer of atropine) which were required in the clinic for the production of sedation; he preferred the subcutaneous route to internal administration as more rapid and reliable, and had thereby never exceeded 0.8mg as a single dose. Erb had noted that many of the side effects of atropine – dilatation of the pupils, vasomotor responses resulting in facial reddening – were less marked with hyoscine, while suppression of sweating and salivation was still pronounced. The sedative and narcotic effects of hyoscine were also observed, which motivated Erb to try the alkaloid in patients exhibiting motor restlessness of various types, including twelve parkinsonian patients. These severe cases of paralysis agitans responded especially well to the agent: the tremor was markedly reduced and even disappeared for up to half a day, the rigidity was reduced, the patients enjoyed both freer movement and increased self-satisfaction; sialorrhea was also suspended for the duration of the motor effect. In short, the patients were able to attend to their own needs as long as the drug effect persisted, usually after what Erb regarded as remarkably small doses (0.2-0.3mg). The benefit for the motor symptoms outweighed the unwanted side effects, but Erb conceded that the drug was a palliative not a cure:

it is at least a pleasant palliative for the disturbing tremor and rigor which seems to afford more relief than most other agents which have been employed for this purpose until now.

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40 Schoenborn, 1921.
41 For biography, see Nonne, 1900; Schoenborn, 1921; Nonne, 1956 (Nonne was one of his students).
42 For example: ‘hyoscine . . . had been discovered about 1895 by Erb, although he appears to have described the treatment for the first time in 1906’; Hurst, 1934a. See also Hall, 1926.
43 Hyoscine was first mentioned in Squire’s Extra Pharmacopoeia in 1899.
44 Erb, 1887.
Erb was thus highly impressed with the effects of hyoscine both against motor restlessness and sleeplessness. The major problem in his opinion was the low dose at which toxic reactions were manifested; despite reports that animals tolerated hundreds of milligrams without lethal effects, Erb noted that fractions of a milligram were sufficient to elicit certain effects which, “apart from upsetting the patient, make a thoroughly disturbing impression [on the physician]”. Hyoscine also brought relief in a case of torticollis, but the effect seen in paralysis agitans patients could not be reproduced in most cases of localized cramp or spasm.45

In his 1901 lecture on paralysis agitans, Erb noted two features of the disorder which were characteristic of discussions of parkinsonism at this time: the fact that the disorder was infrequent and that it was only neurologists and hospitals for the chronically ill that saw any number of cases; and that at least twice as many males presented with the disease as females.46 According to Erb, heredity played a minor role in the presentation of paralysis agitans; the major risk factor was age, with the majority of cases commencing beyond the fifth decade of life. It should be noted that, contrary to current popular opinion, the life expectancy for an adult was only a few years lower than it is today. Life expectancy at birth was much lower in the 19th century due to high infant and child mortality, but once these periods were survived, it was not unusual to achieve what we consider a “ripe old age”.47 Erb noted in an aside the interesting observation that influenza was perhaps not unrelated to the disorder, but did not indicate why he had said this. Erb was also of the opinion that both psychic and physical trauma could induce the disease.48

Erb commenced his recommendations with the observation that a causal therapy was not possible:

*Heredity cannot be overcome, psychological and physical traumas cannot be undone, even worries and cares can rarely be mitigated, and other causes are generally not to be found.*49

Nor was a cure likely; Erb suggested that, where claims of such were reported, the case had probably been misdiagnosed in the first place. The two major symptoms which required treatment were tremor and rigidity, although he noted that about 20% of his patients lacked tremor. In fact, since Béchet had declared in 1892 that all other symptoms of parkinsonism were secondary to rigidity, this had become accepted as the major symptom.50 In contrast to Gowers, Erb attributed the stiffness not to a decrease, but rather an increase in muscular tone. He recommended in the first instance regulation

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45 Ibid.
46 That the majority of parkinsonian patients are male was often been reported until the 1960s (see, for example, Selby, 1968); this has often been interpreted by more recent commentators as reflecting lower access of women to health services in the past. A new study, however, indicates that the differential risk may, in fact, be real: see Baldereschi *et al.*, 2000.
47 For example: life expectancy at birth in Sweden was 38 years in 1780 and 76 years in 1965; life expectancy at the age of 50 was about 20 years in 1780 and 28.6 years in 1965. Similarly, the life expectancy of 60 year old Austrians increased by only 3 years between the 1870s and the late 1960s. Drawing a longer bow, the anthropologist Kenneth Weiss estimated that, since primitive times, the life expectancy of an infant has increased by 50 years, that of a 15 year old by 30 years, and that of a 50 year old by 12 years. Kertzer, 1995.
48 Erb, 1906.
49 Ibid.
of the lifestyle, relaxation, massage, exercise, baths and summers in the south. Three therapies had proved their worth in his eyes:

- **arsenic**, which as a nerve tonic was "undoubtedly the supreme drug for a number of neuroses, chorea, tics, Basedow's, etc."; it was not only good against tremor, for which it was first recommended, but of general benefit for the metabolism and function of the nervous system. The form was unimportant, but Erb used a mixture of *solutio Fowlerii*, *aqua foeniculi* and *tinctura nucis vomicae* (6-15 drops). The use of sodium cacodylicum, or dimethylarsinic acid, allowed the subcutaneous administration of arsenic in larger quantities (50mg/day).
- **electricity**, preferably in the form of bipolar Faradic baths, 3×15min/week. Galvanization of head, neck and sympathetic was also of some use. Erb had himself published a volume on the medical use of electricity which had attracted widespread praise.
- **hydrotherapy**, preferably in a mountain or forest environment. Bath temperature should never, however, exceed 33.5°C.

Apart from these approaches, the use of iron, quinine, strychnine, glycerophosphate, silver nitrate, bismuth, valerian and other agents could be tried. All these measures are designed to treat the disease as a whole; it is for the specific symptomatic treatment of rigor, tremor and limb restlessness, the "classic triad" of symptoms at this time, that Erb had introduced *hyoscinum hydrobromicum* (Merck). He emphasized the potency of the agent – "so be careful when writing a prescription!" – and applied once or twice daily injections of 0.2-0.4mg. He noted that Mendel had recommended *duboisine*, but the effects of the drugs appeared to be quite similar. Erb felt the need to defend his promotion of a substance which was merely a palliative, not a cure, and was either remarkably modest or unaware of the significance of hyoscine; in the 1901 work it is discussed only at the very end of a long presentation on paralysis agitans, and without special emphasis or drama. The introduction of hyoscine into antiparkinsonian therapy was also regarded as insufficiently important in comparison with his other achievements to mention in any of his biographical sketches.

By the turn of the century, hyoscine/scopolamine had established itself in the therapy of parkinsonism. Higier (Warsaw) placed this role at the head of his review of hyoscine in neurology and psychiatry. He himself had achieved success in more than fifty cases of "*PARQUINSON's (sic) tremor disease*"; the symptoms of one patient had been managed alternately with hyoscine and *duboisine* for seven years. Higier made the interesting observation that, where the patient complained of intolerance for oral or injected hyoscine (Higier recommended the use of pills where possible), it was possible to administer the agent via the eye without optometric effects. He commented that untoward side effects were uncommon if the dose was not excessive; development of tolerance was not observed, but isolated cases of dependence were observed.

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51 10g L⁻¹ arsenic anhydride, 10g L⁻¹ potassium (bi)carbonate, 3% v/v compound tincture of lavender. The lavender was not an active constituent, but its aroma served to identify the solution for safety reasons. British Pharmacopoeia, 1898, p.178.
52 Fennel water: to relieve the gastrointestinal discomfort caused by the other ingredients. Scoresby-Jackson, 1880, p.252.
53 = *Semen strychni*: Prepared from the poison nut (*Strychnos nux-vomica*). The major constituents of the seeds are the alkaloids strychnine and brucine. The tincture of the British Pharmacopoeia was an alcohol extract containing 0.125% w/v strychnine.
54 Erb, 1883.
55 The dose required for *duboisine* was slightly higher: 0.6-1.2mg/day; Erb, 1898.
56 Higier, 1905.
Roussy (Pierre Marie’s clinic, Bicètre) reported in 1910 the case of a patient whose parkinsonism had begun at the age of twenty years. Tremor, however, had only become a problem in the past five years (the patient had been presented by Charcot in an 1888 lecture; he must therefore have been at least 42 years old), and had resisted therapy with hyoscynamine, hyoscine and atropine; he had consequently been unable to move at all. High doses of scopolamine (up to 2mg/day; stabilized at 2mg every second day) had restored his mobility to the extent that he was able to walk around the clinic garden:

*The injection initially elicits clouding of his consciousness, followed by nausea, often proceeding to emesis. 3 hours after the injection, tremor disappears completely and muscular rigidity is significantly reduced. This improvement lasts for 12 to 18 hours.*

This therapy had been successfully employed for five years. Souques commented that he had been achieving similar or better results during the past four years with the subcutaneous injection every second day of ½mg scopolamine. Leo Hirschlaff (Berlin) recommended the employment of a morphine/scopolamine mixture (‘Morphosan-Euscopol Riedel’) in many neurological and psychiatric disorders, including paralysis agitans, clonic and spastic tics, bronchial asthma, morphine addiction and psychotic agitation. The employment of hyoscine in paralysis agitans had also won supporters in England by the early 20th century.

In 1913, Roche introduced ‘Pantopon-Scopolamine’, which combined 40mg.mL\(^{-1}\) of the existing product ‘Pantopon’, a total alkaloid extract of opium, including about 50% morphine; introduced 1909), with 0.6mg mL\(^{-1}\) scopolamine. The product was chiefly designed for application as an anesthetic and as a sedative in the mentally ill; it was initially regarded as an alternative to scopolamine-morphine for inducing surgical narcosis, but was associated with severe respiratory abnormalities. Stiefler reported in 1914 the successful treatment of five cases of paralysis agitans with the agent; 1.1mL was applied subcutaneously twice a week, while 1.5mL ‘Pantopon’ was administered on the other days. This combination treatment, however, was not widely adopted, presumably because of the mentioned respiratory problems.

The use of hyoscine for parkinsonism also established itself quickly in England. Judson Bury (Physician to Manchester Royal Infirmary) certified in 1902 that hyoscine:

*is probably the most useful drug that has hitherto been tried in the treatment of paralysis agitans. As a rule, it diminishes or arrests the tremor, checks the troublesome restlessness and the desire to change position, and relieves the “hot flushes” and unpleasant sensations of heat.*

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57 Roussy, 1910.
58 Ibid. The fact that ‘scopolamine’ succeeded where ‘hyoscine’ failed underscores the uncertain composition of pharmaceutical agents employed at this time. Roussy had employed scopolamine in paralysis agitans for some time by this stage, having made a presentation on the therapy to the Neurological Society in Paris on 8 June 1905; see Mercks Jahresbericht for 1905, p.180.
59 Hirschlaff, 1918.
60 Rose, 1903.
61 Ibid.
62 Stiefler, 1914.
63 Bury, 1902.
He favored its oral administration to injection, and advocated use of the Merck preparation hyoscine hydrobromide, diluted in chloroform water (¼ grain in six ounces; \( \sim 8 \text{ mg in 180 mL, } 3 \times 2-6 \text{ tsp/day}. \))

But hyoscine was best known in England as the poison used by Dr Hawley Crippen to murder his wife, for which crime he was hanged in 1910. The equivalent of ½ grain hyoscine hydrobromide was identified in the woman’s corpse, leading the coroner to the assumption that at least ½ grain (injected into ready-made sugar disks; \( \sim 32 \text{ mg} \)) had been employed by Crippen. Crippen had duly registered his purchase of 5 grains in the official Poisons Book. The case was discussed in the Martindale Pharmacopoeia of 1912, which advised retailers to exercise greater caution in the sales of the drug; contrary to popular belief at the time, the drug was not only used for the treatment of maniacs. In a review of cases during the previous half century in which vegetable alkaloids had been employed as poisons, the *British Medical Journal* noted in 1910 that “much of our knowledge of their properties is due to homicidal instances of their use”. It was also remarked with surprise that hyoscyamine had not yet figured in a criminal trial. Interestingly, however, the drug had been utilized in the 1870s as a murder weapon in the sensational novel *A Wingless Angel*; the author “Dick Donovan” (J.E.P. Muddock) had consulted a physician with respect to a suitable toxin, and was told of hyoscyamine, at the time virtually unknown in England.

**Hyoscyamine or hyoscine therapy?**

Before passing to alternative means of therapy, the question must be addressed as to whether ‘hyoscyamine’ and ‘hyoscine’ as used in paralysis agitans were two different therapies or merely variations on a theme. Firstly, it should be noted that the alkaloids employed in the 19th century cannot be assumed to be identical with the commercial product which be purchased today. Despite the efforts of companies such as Merck, the standards of chemical purity which are expected today could not be met in the late 1800s. This is exemplified by the fact that it is now understood that the methods employed at this time to produce the alkaloid ‘solanine’ resulted in a mixture of not only the three forms of solanine proper, but also its hydrolytic product solanidine and a number of other minor alkaloids. Similarly, the debates over the relationships between atropine and hyoscyamine, hyoscine and scopolamine, atroscine and \( \alpha \)-scopolamine are all attributable to the fact that physical methods of chemical identification available at this point were often not capable of decisively settling such questions. The major means of defining the identity of an alkaloid were to determine the physical characteristics of its crystalline form, particularly its degree and direction of light polarization – and it

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64 The case reported by Bury was also interesting, in that it was a miller who first exhibited symptoms at 35; his sister had commenced showing similar symptoms at 18. Another report in 1903 of the beneficial effects of hyoscine was prefaced by the remark that “One does not see many cases of Parkinson’s disease in general practice.”
65 Crippen had dissected his wife and buried her in his cellar before attempting to flee to Canada with his secretary (disguised as a boy). The suspicious captain telegraphed Scotland Yard, the first use of radio to solve a murder case; the employment of the pathologist Spillsbury to analyze the victim’s tissue content of toxin was one of the earliest examples of forensic pathology.
67 Anonymus, 1910.
68 Aconitine, strychnine, digitalin, morphine and atropine had all been used as murder weapons in cases heard in English courts; the use of atropine for homicide, on the other hand, was surprisingly rare given the frequency of accidental poisonings: Anonymus, 1910.
proved difficult or even impossible to prepare crystals of many alkaloids – and to
determine the melting and boiling points and other features of specific salts prepared
from the raw alkaloid. These methods were not always sufficiently precise for an
indubitable answer as to the identity of two substances. Even where the absolute
formula of an alkaloid had been ascertained with reasonable security, the actual
structure was often not amenable to elucidation with the techniques which were
employed. For example, strychnine was first isolated in 1818, but its structure would
not be fully elucidated until the 1950s. With respect to the solanaceous alkaloids, the
structure of tropane was not correctly determined until the opening year of the new
century, the structure of scopolamine would not be determined until after the deaths of
most of the major alkaloid researchers of the 19th century, and well after it had
established itself as an invaluable addition to the world’s major pharmacopoeias.

It can thus not be assumed that the physician was administering the substance which
he believed to be administering. This is particularly the case in the
hyoscyamine/hyoscine question. It is difficult to know what Handfield Jones or Charcot
were using in terms of ‘hyoscyamine’; what is clear is that later workers noted a great
deal of variability in the effectiveness of various preparations of ‘hyoscyamine’,
although not as great as that experienced with the use of freshly prepared henbane or
belladonna extracts, and that a consensus emerged to the effect that the ‘amorphous
hyoscyamine’ was generally more potent than the presumably purer ‘crystalline
hyoscyamine’, with respect to both its sedative properties and its use in the management
of motor disorders. These two features, incidentally, were closely allied in the minds of
19th century doctors; the treatments for motor unrest and psychic unrest were generally
regarded as interchangeable, and terms such as ‘antispasmodic’ were applied post hoc
to brandmark those agents were particularly effective in motor disorders. It
subsequently proved that, amongst other components, ‘amorphous hyoscyamine’ (and,
indeed, ‘amorphous duboisine’ and ‘amorphous daturine’) consisted in large part of
hyoscine. It is therefore not unreasonable to suppose that early successes with
hyoscyamine in paralysis agitans, which were only rarely reported in the 20th century,
can be fairly attributed to the presence of contaminating hyoscine. Consequently, it can
also be fairly asserted that there existed a single solanaceous alkaloid therapy for
paralysis agitans at this point, despite the fact that this was not (and could not be)
recognized by its various proponents.

As a concluding note, it is interesting that the alkaloids ‘hyoscyamine’ and
‘hyoscine’ entered Squire’s Companion to the British Pharmacopoeia in the same year
(1899); but the entry for hyoscyamine already concluded with the remark that

*it has been used for calming the excitement of delirium tremens and acute mania, but
for this purpose it is superseded by the salts of Hyoscine.*

Hyoscine, on the other hand, was “*highly recommended in all forms of violent mania
and cerebral excitement*” while henbane leaves were listed as a milder alternative to
belladonna and stramonium leaves for a variety of purposes, including the treatment of
spasmodic disorders. Martindale and Westcott’s Extra Pharmacopoeia had
recommended hyoscine for the treatment of paralysis agitans since at least 1884; hyoscine was introduced for this purpose in 1901.

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69 Squire et al., 1899, p.365.
70 Ibid., p.363.
71 Ibid., p.360.
72 This was the oldest edition (the Third) to which I had access.
Other agents employed in the therapy of parkinsonism in the 19th century

The great English clinician William Richard Gowers (1845-1915) regarded paralysis agitans as a malady related to “changes in the finer nutrition of the nerve-elements, which have no tendency to proceed to the degree of destructive degeneration”, and should, as such, be amenable to therapy. However, the fact that the disorder did not exhibit “spontaneous variations”, and that it was generally a geriatric disease, challenged this hope, so that, according to Gowers, “relief or retardation” was the best that could be expected. Other possible triggers for parkinsonism were malaria, typhus and chronic rheumatic disease. Lifestyle was correspondingly the most important factor:

All causes of mental strain and of physical exhaustion should, as far as possible, be prevented. Life should be quiet and regular, freed, as far as may be, from care and work.\(^\text{73}\)

Of the many medications which had “been praised by some and found to fail by others”, morphine, conium, hyoscyamine, hyoscine, solanine\(^\text{74}\) and Indian hemp controlled tremor, at least temporarily; iron carbonate, barium chloride and strychnine had limited value as nerve tonics. Strychnine and oral arsenic met with his approval, while curare and bromides were “valueless”, as were all forms of electrotherapy and “nerve stretching”. Gowers’ recommendation was a combination of Indian hemp and arsenic, with opium added later.\(^\text{75}\) Once again, however, doubt is warranted about the disorder being treated; while Gowers presented an impressive description of paralysis agitans, and how it could be distinguished from other forms of tremor, the case he mentions in this connection was a railway worker in whom unilateral tremor in both the arm and leg had commenced following an accident. This would be a recurring problem in the history of the therapy for Parkinson’s disease, and one which has certainly not yet been completely resolved: the obfuscation of the value of any therapy on “parkinsonism” through the failure to delineate between various disease entities.

The general attitude of most clinicians remained extremely skeptical concerning the therapy of parkinsonism; in Germany, Rosenthal wrote in his textbook on neurology

Therapy manages in most cases only to limit or relieve individual symptoms. The exceptional successes are almost always nothing more than temporary.\(^\text{76}\)

Eulenburg was similarly pessimistic, having encountered no positive results with hyoscyamine, nor with morphine, curare, calabar, potassium bromide, Fowler’s solution or chloral hydrate; his recommendation to Charcot to try potassium arsenate was

\[^{73}\text{Gowers, 1893, pp.656-657.}\]

\[^{74}\text{Solanine is a mixture of three glycoalkaloids consisting of the steroid alkaloid solanidine and three sugar moieties (figure 4-1). It can be isolated from any of a number of Solanum species (also members of the Solanaceae), such as S. nigrum (garden nightshade), from which it was first isolated in 1821 by Desfosses, and S. dulcamara (woody nightshade). In the potato (S. tuberosum) it is found in especially high concentrations in the fruit and the chlorophyll-free shoots. The solanines are potent brainstem depressants; they have also been employed as natural insecticides. Thoms, 1927-29, pp.2017-2018.}\]

\[^{75}\text{Indian hemp is reported to have some anticholinergic properties, and to stimulate catecholamine release; Pertwee, 1983.}\]

\[^{76}\text{Rosenthal, 1870, p.401.}\]
equally unrewarding for both workers. Hesselink mentions that the Dutch literature of this period was full of reports of the benefits of different sorts of mineral and other baths. The first edition of the Merck Manual (1899) listed as treatments for paralysis agitans (apart from the solanaceous compounds) arsenic, arsen-hemol, borax, cannabis indica, chloral hydrate, cocaine, conium, gelseminine, glycerinophosphates, hypophosphites, Levico water, opium, picrotoxin, phosphorus, potassium iodide, sodium phosphates, spermine. At this stage, anything might be tried at least once in this disorder, as there existed no clear indications as to which direction would prove fruitful.

The question arises as to what guided the selection of drugs used in parkinsonism at this time. Although the choices in the late 19th century were certainly limited, and physicians were entitled to attempt anything in order to combat this puzzling disorder, it should not be assumed that agents were tried at random. Physicians, then as now, were guided by their own experiences and those of others regarding the effects of various medications, and chose to act accordingly. Certain agents appear repeatedly in the lists of those investigated in the therapy of parkinsonism. Most were found to be ineffective in the disorder; nevertheless, a brief overview of such choices and the rationale underlying their application is appropriate here.

- **Arsenic** (usually in the form of *Liquor arsenicalis* (Fowler’s solution) or sodium arseniate (Na$_2$HAsO$_4$.7H$_2$O) was long regarded as a tonic for spasmodic disorders; it was seen as the best treatment for chorea, and from here its use spread to spasmodic asthma, paralysis agitans and chronic diarrhea. It was regarded as a general physiological stimulant, with benefits for cardiac, neural and sexual functions.

- **Barium chloride** was occasionally used for the same purposes as arsenic, but its toxicity rendered it an unpopular choice.

- **Bromides** (and a short time later, *iodides*) were seen as agents with which central nervous system overactivity could be depressed. By the 1880s, potassium bromide was one of most frequently employed medications; it was introduced into the psychiatric clinic by Locock in 1853 as therapy for epilepsy and nymphomania. By 1890, Potter noted that its “use is terribly abused, by patients, nurses, and even by physicians.” Following rapid intestinal absorption, first the psychic functions, then motor activity and finally the medulla and cord were affected, depending on the dose administered. Unlike the effect of alcohol, the depression of higher centres did not appear to release lower drives from inhibition. The use of these agents in parkinsonism was due to their “great diminution of excitability of the motor area”, especially if administered on a chronic basis; it had been found to be virtually impossible to elicit epileptic seizures by cortical stimulation in dogs treated in this manner.

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78 Hemoglobin reduced by zinc in 1% arsenous acid; Merck’s 1899 Manual, p.20.
79 An alkaloid isolated from the American yellow jasmine; further discussed below.
80 From the Tyrol; noted for its content of arsenic (179mg.100kg$^{-1}$ Na$_2$AsO$_3$), iron (125g.100kg$^{-1}$ FeSO$_4$.7H$_2$O, 27g.100kg$^{-1}$ Fe(SO$_4$)$_3$), and copper (813mg.100kg$^{-1}$ CuSO$_4$.5H$_2$O) salts; full analysis in Frerichs et al., 1925-27, p.505.
81 The information presented here is compiled from the following sources: Scoresby-Jackson, 1880; Squire et al., 1882; Potter, 1890; Merck’s 1899 Manual; Squire, 1899; Martindale and Westcott, 1901. Only direct citations are directly referenced; further, most of these agents were also employed in a wide variety of other disorders which, being irrelevant to the present object, will not be discussed here.
82 Scoresby-Jackson, 1880, p.16.
IV. From Charcot to the outbreak of encephalitis lethargica

- **Camphor** was useful as an antispasmodic for the treatment of delirium tremens and hysterical convulsions, but found little use in paralysis agitans; as noted above, it had been dismissed by Charcot’s editor as disappointing. Cassin and Girard noted as late as 1909, however, that the subcutaneous administration of a 10% solution of camphor bromide in olive oil was useful in paralysis agitans and other instances of “psychic excitability”.

- **Cannabis** (as extract or tincture of the flowering tops of the female plant) was noted for its intoxicating capacity, and was employed in the clinic as an alternative to opium. It had also found application as a tonic and antispasmodic in disorders such as tetanus, chorea, delirium tremens, neuralgia, migraine and hysteria, and was occasionally applied in paralysis agitans, especially for the control of tremor. It had also been employed as a surgical anesthetic. By the 1890s, it had become unfashionable and largely abandoned.

- Preparations of root of *Gelsemium* (*Gelsemium sempervirens* Aiton *seu nitidum* Michaux; yellow jasmine or jessamine), native to the southern USA, had been identified as a febrifuge and sedative in the middle of the 19th century, and was subsequently found to also be useful for dysmenorrhea and spasmodic disorders, such as whooping cough and localized muscle spasm. The alkaloid content of the root is 0.15-0.5%, consisting mostly of gelseminine and gelsimoidine (= sempervirine). The actions of gelseminine are similar to those of conine and nicotine, inducing a sensation of muscular relaxation and general languor, accompanied by suppression of pain sensation. Lethal doses exert their effect by depression of the medullary respiratory centre. It was thus tried in epilepsy, chorea and paralysis agitans, as ‘spasm’ and ‘tremor’ were not strictly demarcated by general physicians at this point, but without convincing success. It would nonetheless remain popular until the 1920s.

- **Glycerophosphates** and **hypophosphites** were believed to possess the stimulant properties of phosphorus without eliciting its toxic side effects. Phosphorus was believed to stimulate not only bone development, but also to promote nutrition of the nervous system, and was thus especially popular in disorders associated with functional derangement of the brain and spine, and in nervous exhaustion of any etiology. Phosphorus compounds were thus applied not only in paralysis agitans, but also in chronic neuralgia, paraplegia and during convalescence from nervous or other illness.

- **Iron** “was probably the first used of any of the minerals in medicine.” Iron carbonate was probably the most popular treatment for paralysis agitans before the advent of solanaceous alkaloid therapy, often mixed with sugar to render it more palatable. Hoppe-Seyler identified the central function of hemoglobin in respiration in 1862, but the essential nature of blood iron for nutrition had long been recognized, so that it was only natural to employ the metal in diseases characterized by nervous exhaustion. Iron salts were used in recognition of the fact that iron was inert in the metallic state.

- **Morphine** remained one of the most employed agents in advanced parkinsonism well into the 20th century. Although it also exhibited antispasmodic characteristics, its use owed more to its sedative and pain-relieving properties.

- **Nitrites** (especially sodium and amyl nitrite) were employed as motor depressants. Amyl nitrite by inhalation was more rapid in its action, but shorter in duration; it was more commonly used in epilepsy and migraine than in paralysis agitans.

- **Physostigmine** or **eserine**, an alkaloid isolated from the Calabar or ordeal bean (seed of *Physostigma venenosum*), was found to paralyze spinal and motor nerves, commencing in the peripheral extremities, similar to conium and curare. It was therefore tried in spasmodic disorders, including paralysis agitans, but proved to be of worth only in tetanus.
IV. From Charcot to the outbreak of encephalitis lethargica

Figure 4.1: Representative alkaloids of therapies used in the treatment of paralysis agitans in the 19th century. Cevadine and jervine are regarded as the most important examples of two alkaloid classes found in Veratrum viride. Solanidine is the base molecule for a number of closely related alkaloids which are collectively referred to as "solanine" with the following sugar additions: (a) Solanidine: $R = H$; (b) $\gamma$-Solanine: $R = \beta$-D-Galactose; (c) $\beta$-Solanine: $R = \beta$-D-Glucose(1→3)$\beta$-D-Galactose (1→); $\alpha$-Solanine: $R = \beta$-D-Glucose(1→3)$\beta$-D-Galactose (1→)

$\alpha$-L-Rhamnose (1→2)
Quinine, the chief alkaloid isolated from the bark of the yellow cinchona, was, alongside, one of the “wonder drugs” of the 19th century; the first facilities for the industrial production of alkaloids, established in the early 1820s, were devoted to quinine (Pelletier in France; Koch in Oppenheim). Apart from its major role as antimalarial therapy, quinine was also regarded as a brain tonic, although its chronic application could lead to a cerebral syndrome (cinchonism) characterized by sensory disturbances, headache and nausea, and could end fatally following paralysis of cardiac and respiratory function. The use of quinine in paralysis agitans was also suggested by analogies drawn between malarial and parkinsonian tremor. Quinine would be again suggested as therapy for parkinsonian in the 1930s, when chemical similarities to harmine were noted.

Silver nitrate was often tried in the treatment of spasmodic disorders, including epilepsy, chorea, whooping cough and paralysis agitans, although in most cases it was admitted that its employment was purely empirical and without marked success. A disturbing side effect of long-term silver nitrate therapy was the irreversible discoloration of the skin, commencing with a blue tinge of the gums.

Solanine (or infusion of dulcamara) was employed as a nerve sedative in neuralgia and for the treatment of epileptoid tremors, and occasionally in paralysis agitans. Its action was, however, regarded as obscure and unreliable. It was reported by Martin (1878) to be the principle alkaloid in Scopolia japonica.

Strychnine, especially in the form of Tinctura nucis vomicae, was one of the most employed agents in the 19th century. In therapeutic doses, the alkaloid acted as a tonic, stimulating nervous and gastrointestinal function; it was believed to exert an especial influence upon the medulla oblongata and spine; higher doses induced spasms in the voluntary musculature, including paralyzed limbs, without affecting cognitive function. For this reason, strychnine preparations were used in the therapy of paralysis, as also in other motor disorders, including paralysis agitans.

Valerian root (as infusion or tincture) was utilized as a stimulating antispasmodic in cases of nervous exhaustion, including cases of typhoid fever, hysteria, mania and epilepsy. Its use in paralysis agitans was occasionally recorded. A number of mildly tranquilizing constituents have since been identified (‘valepotriates’).

Preparations of Veratrum viride root (American or green hellabore; Liliaceae) were used by native North Americans long before the tincture was introduced to England in 1862; it was recommended for use internally in nervous palpitations and other spasmodic disorders. The European or white hellabore (Veratrum album) had been used for similar purposes, but was considered too dangerous for protracted internal use. Each plant contains a complex range of steroidal alkaloids, including the anticholinesterase sempervirine. Older texts refer to the white, but not the green hellabore containing the analgesic ‘veratrine’, but this reflects the differing constituents of the two plants; ‘veratrine’ as such does not exist, although still occasionally used as a synonym for cevadine, the chief alkaloid of Veratrum sabadilla. The tincture prepared from the American plant was repeatedly tried in paralysis agitans, but with only chequered success; this based on its reputation against “undue excitement of the spinal nervous system, in spinal irritation, spinal convulsions, cerebro-spinal meningitis, and acute mania, all with excited circulation”. The side effects (nausea, severe pain) elicited by the American hellabore, while generally milder than those of European hellabore, prompted Scoresby-Jackson to comment that “the therapeutic value of this drug has undoubtedly been overrated.”

Felter and Lloyd, 1898, *Veratrum viride*. Both plants are now used as sources of alkaloidal insecticides. Interest in these plants revived in the 1950s following the (re)discovery that a number of their alkaloids are hypotensive; partially purified alkaloid extracts of the American hellabore are commercially available for this indication (‘Veriloid’/Riker and ‘Vergitryl’/Squibb). Protoveratrine A, the hypotensive constituent of European hellabore, is similarly available (‘Pro-Amid’/Amid). Tyler et al., 1981, pp.251-252; Trease and Evans, 1983, pp.627-628.

Scoresby-Jackson, 1880, p.367.
This catalog is by no means exhaustive, only listing those therapies which were mentioned most frequently. It should be clear, however, that most hypnotics, sedatives and antispasmodics were regarded as worth trying in the therapy of paralysis agitans, an unsurprising philosophy given the vague notions regarding the essential nature of the disorder at this time. Nor should it be understood that a physician would restrict himself to a single agent. Albrecht Erlenmeyer, for instance, described the therapy he had implemented in a patient whose tremor was so severe as to disturb sleep:

- To procure sleep: chloral hydrate (7.5g), morphine hydrochloride (50mg), arrac (50g) in 150mL water. This was sufficient for 14 days.
- To alleviate tremor: infusion of valerian (20g in 200mL water) including 25g potassium bromide. Four tablespoons (~60mL) were taken per day.
- For temporary relief of tremor: galvanic current from eight cells applied for fifteen minutes to forehead (anode) and neck (cathode).
- For longer term relief of tremor: 500mg curare in 15g water including two drops of hydrochloric acid. Having gradually raised the dose, a syringeful of the solution was administered every five days, the effect lasting three.
- For control of sweating and with some effect on tremor: thirty pills were prepared from 30mg atropine sulphate, 1g extract of ergot and sufficient extract of liquorice, and taken one per day. This had to be terminated after nine days due to the toxicity of the atropine, but later re-instituted with the same effect.

Crystallized hyoscyamine and silver nitrate had both proved to be of no benefit for this patient.

Amongst the more unusual therapies suggested by chance which should be mentioned was an approach introduced by Charcot at the end of the 1880s. His patients had reported to him that they felt better during long train journeys; he therefore constructed a shaking chair (chaise or fauteuil trépidant), with which he claimed some success. He also employed a harness (the Sayre device, used for the donning of corsets) which suspended the patient in order to stretch the spinal column; this was said to improve rigidity, but had little effect on tremor. Most other clinicians, however, found no success with such methods, although a “careful vibration massage” was found by some to be of benefit.

Perhaps the most bizarre approach was formic acid therapy practised in France. According to the Lancet in 1905, the acid was derived from the red ant (Formica rubra), and was often used in cases of gout and paralysis; one form of administration involved exposing the affected limb to steam emanating from a boiled ant-hill. It was

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92 The literature abounds with sedative-hypnotic compounds which were reported to alleviate tremor or to at least overcome insomnia in paralysis agitans patients; most of these reports, however, were of purely anecdotal character.
93 Erlenmeyer, 1884.
94 See Erb, 1906, who gives as reference the Leçons du Mardi I., 1892, 2nd edition; p.331. I have not obtained a copy of this volume; but for abstract, see Charcot, 1893. See also Glorieux, 1893; Williamson, 1900.‘Vibratory massages’ were also employed by some physicians for a number of disorders; de la Tourette introduced a ‘vibratory helmet’ for direct stimulation of the head; Charcot, 1893.
95 Charcot spoke on the method, originally developed in Odessa by Motschoutkowski, in his Tuesday lecture on 15 January 1889; Goetz, 1987, pp.63-65. See also Charcot, 1889; Eulenburg and Mendel, 1889; Russell and Taylor, 1890; de la Tourette, 1890.
96 Strümpell, 1917.
suggested that the rationale underlying the therapy related to the prodigious physical strength of ants; an ant elixir was peddled in France which purported to confer increased physical prowess on those who employed it. Sodium formate and formic acid itself were also reported to be beneficial as a general muscular tonic and in many forms of tremor, including that of paralysis agitans.\textsuperscript{97}

**Hypotheses regarding the cause of parkinsonism at the turn of the century**

In the period following Charcot’s lectures in Paris, the search began for both the neurological basis of Parkinson’s disease and for the ultimate cause of the disorder. There were opinions based on the symptom of tremor which did not differ significantly from that of Galen eighteen centuries previously:

In paralysis agitans the whole nervous system does its work badly; there is a great and general loss of nervous vigour; that is, there is evidence of slackened accumulation of tension in the nerve-cells. And in paralysis agitans there is tremor. In drunkenness there is tremor, and tremor is worst at the time that every symptom points to the lowest ebb of nervous energy – in the early part of the day.\textsuperscript{98}

Despite the objections of authorities such as Sherrington that the tremor of paralysis agitans and of delirium tremens could not be compared with one another, this simplification is often encountered in the medical literature at the end of the 19th century. This is not surprising, given the state of knowledge concerning nerve and muscle function. One reads constantly of electrical fields sweeping the brain, of the conveyance of force by nerves to muscles, simplifications rendered understandable by the lack of neurochemistry. The just cited author proposed that every nerve cell exerts both excitatory and inhibitory effects on its neighbours, and that the failure of the inhibitory principle at some point is responsible for motor disorders – an impressive hypothesis in light of current knowledge, although incorrect in its detail.\textsuperscript{99}

But even such a failure would not explain the ultimate cause of parkinsonism. A number of hypotheses were circulated in this regard:\textsuperscript{100}

- **Endocrine hypothesis**: arguments were advanced for an association of paralysis agitans with either hypo- or hyperthyroidism; disturbances of parathyroid function were also proposed. This direction has been linked to the rise of endocrinology as a recognized specialty within inner medicine in the second half of the 19th century. The hypothesis was first proposed by Möbius (1883), who noted that many symptoms of paralysis agitans were also presented in Basedow’s disease (tremor, hyperthermia, restlessness, influence of mood, sweating crises), and last defended as a primary explanation by Lewy (1923).\textsuperscript{101}

- **Myogenic hypothesis**: the hypothesis that the problem was one of muscle function was especially promoted by Gauthier (1888) and was discussed until the end of the

\textsuperscript{97} Anonymus, 1905a; 1905b; *Mercks Jahresbericht* for 1906, pp.9-10; 1907, pp.6-7 (both: English editions). Formic acid was still listed in the 1952 Extra Pharmacopoeia with comment that the “formates were at one time thought to stimulate mental activity, but there is no scientific evidence in support of this.” (p.33).

\textsuperscript{98} Mercier, 1888.

\textsuperscript{99} Ibid.


\textsuperscript{101} Möbius cited in Manschot, 1904; Lewy, 1923, p.607-624.
1920s. It was suggested by the fact that parkinsonism was a purely motor disorder characterized by muscular rigidity; further, no specific brain lesions had been identified, but structural changes in the muscle spindle and elevated levels of urinary phosphates had been described.  

- **Cerebral vascular insufficiency**: first proposed around 1875, the concept remains current with respect to so-called “arteriosclerotic parkinsonism”. The concept is closely allied to that of deficient nutrition of the brain, whether as a natural consequence of aging or the result of a pathological process, underlying the disorder, as proposed by Handfield Jones in 1873.

- **Neuritis ascendens**: that parkinsonism could result from inflammation in or damage to peripheral nervous tissue enjoyed a brief popularity before being abandoned by the First World War. The possibility that trauma could lead to parkinsonism, however, first suggested by Parkinson himself, has never been definitively excluded, although it probably accounts for only a small proportion of all cases, head trauma has recently been identified as a risk factor for parkinsonism in the British military.

But from at least the turn of the century, there was general agreement that, whatever the ultimate cause of the disorder, paralysis agitans involved an anatomic lesion somewhere in the central nervous system, although some commentators continued to regard the primary problem as being in the muscle nerve endings. Lesions were identified in various parts of the parkinsonian brain, but none with convincing consistency. The first autopsy of a parkinsonian patient appears to have been that by Johannes von Oppolzer (1808-1871) in Vienna in 1861, who was particularly impressed by the rigidity exhibited by his patient during life. He noted “an apoplectic cyst in the right optic thalamus the size of a pea, with a pigmented lining”; further, he noted “opaque scratches” in the medullary substance. Interestingly, however, it was taken that the actual presentation of symptoms was precipitated by the traumatic experiences of the patient during the siege of Vienna in 1848. The paper was considered so important by Charcot that he translated it into French; it formed the basis of the first part of his famous 1861 article series on paralysis agitans. Theodor Meynert (1833-1892), also of Vienna, suggested that both Parkinson’s disease and Sydenham’s chorea might be due to dysfunction of the basal ganglia. Virchow and Leyden published reports of similar cysts in cases of hemiparkinsonism in 1864, while Bouchut observed complete destruction of the optic thalami in an otherwise normal brain of a paralysis agitans patient in 1874. Hughlings Jackson hypothesized in 1877 that a progressive degeneration of the motor cortex was responsible for the symptoms of parkinsonism, which he essentially regarded as “double hemiplegia”; in the absence of cerebral control, cerebellar input to the motor system was inhibited, leading initially to tremor and, finally to rigidity. By 1899 he had seen no reason to alter this opinion.

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102 See, for example: Gauthier, 1895; Dana, 1899; Kolliker, 1900, p.865; Byrnes, 1926.
103 Krafft-Ebing, 1899; Lewy, 1912, p.920; Factor et al., 1988; Hesselink, 1989. See also the recent paper by Morris et al. (1998) regarding parkinsonian tremor subsequent to electrical injury to the hand, references therein, and discussion by Quinn and Maraganore (2000).
104 Wiener Medizinische Wochenschrift, 1861, issues 36 and 38; French translation in Charcot and Vulpian, 1861a.
105 Meynert, 1871.
107 Jackson, 1899.
In his 1940 review of the history of investigations of the striatum, Lewy noted that research was hampered in the 19th century by technical questions; the major staining method available was the Weigert method for the medullary sheath, so that neurons and glia were not stained. Only with the regular use of the Nissl stain in the second decade of the twentieth century did it become possible to identify changes in the basal ganglia not amenable to detection in unstained sections. Lewy thus dated the period of the modern investigation of the striatum from 1912, when he published his examination of the pathology of the basal ganglia in Lewandowsky’s handbook.

One of Charcot’s successors at the Salpêtrière, Édouard Brissaud (1852-1909) extended the observations made by Charcot respecting Parkinson’s disease, being the first to use the term ‘masque’ to describe the faces of its victims, and also paid more attention to the psychic aspects of the disorder than his predecessor. Perhaps most significantly, he reviewed the reports concerning the pathological brain changes which had been detected in Parkinson’s disease, and was particularly impressed by a case reported by Paul Blocq (1850-1896) and the eminent Rumanian neurologist Georges Marinesco (1864-1938) in 1893 of a hemi-parkinsonian patient who, on autopsy, proved to have a tumor in the contralateral peduncle which had destroyed most of the substantia nigra. These authors, as did many others at the time who reported similar findings, suggested that the superior cerebral peduncle was the critical site in the disorder. Brissaud, however, while conceding that the function of the substantia nigra was obscure, speculated that this nucleus might be involved in voluntary movement and the control of muscular tone, the elevation of which he regarded as one of the significant signs in paralysis agitans. Further:

*a lesion of the locus niger could very well be the anatomic substrate of Parkinson’s disease.*

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108 Lewy, 1942.
109 Lewy, 1912. Alzheimer had published in 1911 his employment of the technique in the investigation of Huntington’s disease.
110 A more detailed description of the case was included in the doctoral thesis of E. Bechet, *Formes cliniques et diagnostic de la maladie de Parkinson* (Paris, 1892; cited in Duvoisin, 1987).
111 Blocq and Marinesco, 1893; Halbern and Infeld, 1902; see also Carpenter et al., 1950.
112 Brissaud, 1895. Paget had reported a case in 1855 of a man who had the “involuntary tendency to fall precipitately forwards”; the autopsy revealed a mass which encroached upon the substantia nigra and surfaced near the left oculomotor nerve. The small size of the nigra, however, was regarded as excluding it from a major role in motor regulation.
At the same time, he remarked that paralysis agitans was “so utterly inexplicable . . . that we are constantly drawn to it by the lure of the mysterious.”

In any case, the “substantia nigra hypothesis” did not immediately contribute to the improvement of therapy for the disorder. The major reason was that in 1895 the knowledge that degeneration of a specific central nucleus “caused” Parkinson’s disease yielded no clues as to how the problem might be addressed; if anything, it rendered the situation of the patient more hopeless. Another important reason was that the hypothesis was not generally accepted by the neurology community. Although appropriately located with respect to Parkinson’s original conjecture, the evidence from a single case lent no great weight to the argument, especially as few other neurologists had seen a lesion in the substantia nigra. The most common sites for lesions were, in fact, the spinal cord and peripheral nerves. The substantia nigra theory also competed directly with that proposed by the Austrian Theodor Meynert that a lesion in the corpus striatum was better supported by animal experiments (particularly in the dog) which showed that this region was vital for motor function. The involvement of the striatum in control of at least some aspects of movement had first been proposed by Willis in 1664, and had become generally accepted in the first half of the 19th century as a result of the first successes of the brain localization theorists. Its involvement in parkinsonism was thus to be expected, despite the lack of specific knowledge of its function. Support for this view was provided by the first large systematic investigation of the lesions in Parkinson’s disease by Lewy (1913): in 60 cases, the most consistent findings were lesions in the striatum and the globus pallidus and the presence of dark bodies in various nuclei (substantia innominata, dorsal motor nucleus of the vagus) which now bear his name. Others, such as Kurt Mendel, were led by the symptomatology of the disorder to assume a primarily cerebral localization. In his exhaustive review of the literature, the Dutch worker Manschot came to the conclusion:

Although muscle spindles, nerves, spine and the contents of the skull have been thoroughly investigated, one does not yet detect trace of consensus with regard to the nature, the site or the occurrence of the changes which are encountered in paralysis agitans.

This, then, was the situation with respect to the neuropathology of parkinsonism at the turn of the century. It is interesting to note that the symptom which was most noticed at this time was the tremor, which had also motivated Parkinson to name the disorder ‘paralysis agitans’ (table 4-1). Charcot preferred the term Parkinson’s disease, precisely because he believed that he had recognized cases of the disorder in which the tremor was minimal or even absent. For him the rigidity of the patient was of greater concern, but this would not generally be recognized until the 1920s. This had two consequences for therapy: the first was that the effectiveness of treatment was assessed according to its effect on tremor. The second was that a range of disorders were collected together under the name ‘paralysis agitans’, when “disorders in which tremor

114 Meynert, 1871.
115 Reviews of basal ganglia function: Lewy, 1942; Greenfield, 1956; Schiller, 1980; Yanagisawa, 1996.
116 Edinger, 1911, p.408: “We lack all knowledge of the function of the corpus striatum and of the symptoms following its stimulation or destruction.”
118 Mendel, 1911, p.77.
119 Manschot, 1904, p.666.
is a major symptom” would have been more accurate. Idiopathic or toxic Parkinson’s disease was regarded as part of a spectrum which included ‘palsy’, ‘intermittent paralysis agitans’, traumatic limb injuries and even delirium tremens. As noted many years later:

_The common practice of referring to tremor as the hallmark of Parkinson’s disease is unfortunate; like all reductionist thinking, it does not simplify but only complicates the work of diagnosis. Since tremor is symptomatic of a wide variety of disorders, using this as the sole identifier of a given disease is like calling any red fruit a tomato simply because it is red. Parkinson’s disease is a multifaceted disorder; as such, it cannot be defined by tremor or any other single finding._

The third member of the now “classic parkinsonian triad”, akinesia, was rarely mentioned at this time. If, indeed, there was a typical triad of symptoms before the First World War, it consisted of tremor, rigidity and abnormal gait; interestingly, the neurosurgeon Cooper nominated the same three symptoms as typical of Parkinson’s disease in 1961.

### Pharmacological therapy at the beginning of the 20th century

Therapy of the disorder thus continued to be an empirical exercise; whenever a new treatment suggested itself, either by analogy with its effect in another disorder or purely by chance, it was attempted, often with mixed results. Pessimism was experienced by even the leading workers in the field; in 1911, Kurt Mendel declared that the situation regarding the therapy of paralysis agitans was completely hopeless. There was no shortage of possibilities, only of results, and opinion regarding these possibilities varied widely from clinic to clinic. Mendel himself recommended a combination of subcutaneous hyoscine or duboisine, warm baths, vibration massages and physiotherapy. The situation regarding physical therapy at the turn of the century was summarized by the German physician Hermann Oppenheim (1858-1919) as follows:

- **Massage**: Light massage was recommended by some authors, but was generally regarded as ineffective.
- **Hydro- and balneotherapy**: Bathing cures were especially popular in Germany, probably as a result of the Kur-culture which still persists today. All varieties were suggested by one authority or another: cold, lukewarm or warm baths, carbonated, herbal and mineral, immersion baths and showering. Erb had named a number of bath resorts which had produced good results, although Oppenheim regarded these recommendations as less than enthusiastic; Mendel was rather of the opinion that the stress of travel involved more than cancelled any benefit that the baths might produce.
- **Movement therapy**: Passive gymnastic movements for up to ten minutes at a time, several times a day, were seen as useful for temporary relief of tremor, a moderate but lasting effect on rigor, and for their assistance of patient confidence. Where such activity was still possible, active gymnastics were also advocated in some cases.
- **Electrotherapy**: According to Oppenheim, Erb was impressed by the effects of direct current applied to the neck, head and other places, but he had always been disappointed

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120 Yahr, 1981.
121 Cooper, 1961, p.4. The term ‘akinesia’ appears to have been first used in a textbook description of parkinsonism by Jaccoud in 1873 (p.448). The history of the concept of akinesia was reviewed in 1971 by de Ajuriaguerra (English translation: 1975).
122 Mendel, 1911, p.85. In his extensive paper (nearly 200 pages) on the disorder, the Dutch author Manschot (1904) offered only a half page on therapy; rest and baths were his preferred approaches.
## IV. From Charcot to the outbreak of encephalitis lethargica

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Resting tremor</th>
<th>Rigidity</th>
<th>Akinesia or hypokinesia</th>
<th>Reduced muscular power</th>
<th>Progressive nature</th>
<th>Postural abnormalities</th>
<th>Intellect intact</th>
<th>Propulsion</th>
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**Table 4.1:** The major symptoms of parkinsonism as defined by authors between 1817 and the outbreak of encephalitis lethargica. The table is based partly on those appearing in Hesselink, 1986, pp.265-266. 1817 and the outbreak of encephalitis lethargica. The table is based partly on those appearing in Hesselink, 1986, pp.265-266.
with the results in paralysis agitans. “Electrical baths”, on the other hand, had their use; Oppenheim had seen impressive results in many cases, but the effect of the therapy waned with time. A number of other workers had reported benefit from application of current to the spine.

- **Vibration therapy, suspension therapy, nerve-stretching**: These practices were recommended by Charcot but generally ill-regarded outside France; Oppenheim declared that they could be regarded as “definitely rejected”.

- **Lifestyle adjustment**: All authorities were agreed that stress of all types should be avoided, including work of any sort; the practicality of this advice no doubt depended on the social status of the patient concerned. Oppenheim even supported the isolation of the patient from social interaction, but at the same time noted that this advice must be adjusted according to the nature of the individual. Ideal was the withdrawal to a rural setting of relaxing nature, the mountains being particularly suitable for this purpose. The parkinsonian patient, however, should not be burdened with rules or excited in any way.

- **The diet** should consist of easily digested, not overly spiced food, including much fruit, only a little meat, little or no coffee or alcohol, and a moderate use of tobacco. Jelliffe and White later advised (1923) against an overly strict application of dietary regulations lest “the patients, already suffering from irritating conditions, . . . become further annoyed thereby”; in any case, “fussy dietaries are superstitious nonsense for the most part.”

- **Psychotherapy**: Oppenheim admitted that the suggestion that psychotherapy might play a role in the therapy of paralysis agitans sounded a little strange, but he noted that there were also psychological aspects of the disorder, including the development of inhibitions and phobias; he therefore emphasized its role in therapy. Hypnosis was successfully employed by Gumpert.123

Oppenheim recognized the limited potential of such therapies and had concluded by 1905 that it was pharmacological therapy which offered the most hope for the management of the disorder. He noted that a plethora of such medications were applied in paralysis agitans; perhaps surprisingly, he stated that the most commonly applied remedies were the bromide preparations and arsenic (the latter as tablets or in the form of Fowler’s solution); also recommended were the tinctures of *Nux vomica* (~0.125% w/v strychnine), *Gelsemium sempervirens* and *Veratrum viride*.124 Oppenheim conceded, however, that he could not recommend these agents with the authority of someone who was convinced of their power.

Hyoscine was also the drug which found most favour by Oppenheim:

> Erb has certainly performed a great service by introducing hyoscine into the therapy of paralysis agitans. And duboisine, recommended by Mendel, has also proved to be useful. I myself was at first disturbed by the toxic effects of these substances – perhaps I had no access to pure preparations – but in the second edition of my textbook I have spoken of successes . . . and may now, on the basis of broad experience, present myself as an advocate of this therapy. Certainly, it still often fails me and is not tolerated by many patients, but the number of cases in which it is effective is not inconsiderable.125

The symptoms controlled best by hyoscine were tremor, to a lesser extent the rigor, and, as a result of the decrease in the latter, the akinesia. Oppenheim emphasized that the

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123 Oppenheim, 1905. See also Kölliker, 1900, Mendel, 1911, Strümpell, 1917.
124 It is interesting that Oppenheim should nominate two plants native to North America, while the strychnine plant was imported from India.
125 Oppenheim, 1905, p.1710.
drug solution should be prepared fresh from the purest available stock of scopolaminum hydrobromicum, and that a clean needle be used for the subcutaneous injection. The initial dose should be small – of the order of 0.1mg – and then increased in 0.05mg increments until an effective dose which did not elicit signs of intoxication was reached; Oppenheim found 0.2-0.3mg daily to be effective. Some doctors administered the drug subcutaneously every second or third day and orally on the other days. It was possible to use hyoscine for a year without its effectiveness diminishing significantly. Oppenheim preferred hyoscine to duboisine, except in patients who did not tolerate it as well; the dose required was also twice as high with duboisine. This concords with the assumption that duboisine was a mixture of hyoscyamine and hyoscine. Interestingly, Oppenheim mentioned that Podack employed similar doses of the rhizome Scopoliae carnioleae (sic); he himself had no experience in the use of this plant. The oral application of hyoscine was not as effective as the injected route, but for precisely this reason it was preferred by many clinicians, as the risk of intoxication was also reduced in this manner.

Finally, Oppenheim noted the inevitable end of the disorder:

I don’t need to mention that in the end-stages and worst cases one cannot do without morphine. Against the often quite irritating salivation I have employed gurgling of a few drops of iodine in a glass of red wine with success. Other authorities were similarly acquainted – and disappointed – with a range of approaches. Mendel advised against the use of arsenic, as it led to a decline in the mood of the patient, and helped neither the tremor nor the rigidity; nor did gelsemium or veratum attract his approval. Strümpell, on the other, still recommended arsenic and bromide preparations as the most reliable pharmacological agents for paralysis agitans in 1917; he acknowledged that hyoscine was praised by many, but its toxicity rendered it a dubious choice in his eyes. He also recommended ergotamine, physostigmine and curare. The English physician Williamson had tried and ultimately discarded arsenic, quinine, atropine, strychnine, potassium bromide, Calabar bean, cocaine, cannabis, caffeine, silver nitrate, codeine, gelsemium, butyl choral, chloral hydrate, potassium iodide, piscidia “and many others” as therapies; opium, morphine and duboisine were also accompanied by side effects which rendered any benefit useless. The only drug he found useful was the hyoscine of Professor Erb, and used only that imported from Merck, Darmstadt. A similar list was provided by Peterson in America; he, too, was only impressed by the effects of the belladonna alkaloids, and indicated that he had used hydrobromate of hyoscine since at least 1885, usually in combination with

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126 See Hirschlaff (1918) for discussion of the stability of scopolamine solutions.
127 Ibid.
128 Mendel, 1911.
129 Strümpell, 1917.
130 The bark of Piscidia erythrina Jacq. (Jamaica dogwood) produced ataxia similar to that elicited by cannabis and was used as a hypnotic, antispasmodic and analgesic. Although extolled in late 19th herbal texts (for example, Felter and Lloyd, 1898), its worth is perhaps best indicated by its disappearance from major pharmacognostic handbooks by the middle of the 20th century; Sollmann dismissed it curtly as “practically useless”, citing a paper published by Tyrode and Nelson in 1905. It continued to be used occasionally in the treatment of dysmenorrhea into the 1950s; Extra Pharmacopoeia, 1952, p.632. Its constituents included a toxic, non-nitrogenous compound, ‘piscidin’ and an aromatic dicarboxylic acid (‘piscid acid’).
131 Williamson, 1900. Williamson’s positive experiences with scopolamine were reported in the Mercks Jahresbericht for 1908; p.294.
codeine. Peterson regarded the opiates as required by the discomfort and restlessness of paralysis agitans patients, and employed codeine as a safer adjunct to hyoscine therapy than morphine, which was particularly popular in Germany for this indication.132 Bramwell was also of the opinion that hyoscine was by far the most effective remedy, although by no means curative; he specifically warned against high doses of chloral hydrate or bromides as, in his experience, they contributed more to the general decline of the patient than to his recovery.133

**Organotherapy**

Another approach which shares features with the pharmacological approach to the disorder was organotherapy. This included the administration of brain extracts, such as ‘Poehl’s Opocerebrin’, consisting of “a mixture of three brain cerebrosides” and initially promoted at the beginning of the century as an internal agent for the therapy of epilepsy.134 Subcutaneous administration of pituitary extract was reported in England to bring some relief in paralysis agitans, amongst a broad range of other conditions; the primary effect of the extract was presumed to be a rise in blood pressure subsequent to vasoconstriction.135

But more important for the therapy of parkinsonism were the thyroid and parathyroid glands. Möbius and others, on the basis of the endocrine hypothesis, had unsuccessfully attempted to treat the disorder with thyroid gland extracts and thyroid hormone. There was some small support for the approach provided by, for example, Karl Cori (Pharmacological Institute, University of Vienna), who reported in 1904 that a deficient sympathetic effect could be enhanced or an existing parasympathetic effect suppressed by atropine, adrenaline or thyroid substances. Erb noted that Dana appeared to have pursued this approach with particular vigor: extracts of thyroid, thymus, pituitary, brain, testis, adrenal gland were all tried without success; thyreoidine was the only agent to elicit a change, and this was a deterioration of the parkinsonian symptoms.136 Oppenheim similarly reported a complete lack of success with hormone preparations.137

But this did not dissuade the adherents of the hypothesis. Hormone treatments for many neurological disorders received increasing attention during the first quarter of the twentieth century. At the turn of the century, Hermann Lundborg (Lund) had studied a family in the Swedish countryside which suffered from “familial myoclonus”; he had noted, however, that no less than five cases of paralysis agitans were presented in this family, and suggested that the parkinsonism, like the myoclonus, might be attributed to hypothyroidism which was endemic in the region. Two clinic patients were subsequently treated with thyroid extracts; one showed no response, one deteriorated. By no means discouraged, Lundborg then described in detail the history and post mortem examination of a woman suffering from concurrent paralysis agitans and myxedema. He hypothesized that the secretion of the undersized thyroid was

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132 Peterson, 1891.
133 Bramwell, 1905/06.
135 Williams, 1910.
136 Erb, 1906.
137 Oppenheim, 1905, 1908. Parhon and Urechic (1908) reported in Paris that a preparation of four hypophyses in 30g glycerine (dose: two coffee-spoons) achieved an improvement of tremor but not rigidity in a single case of paralysis agitans.
insufficient, and that this might be linked to the motor disorder. In this connection, he noted the work by Frenkel which described the unusual characteristics of the skin of patients with paralysis agitans, a report which was subsequently dismissed by many workers. In a subsequent paper, Lundborg proposed that the parathyroid gland was responsible for the maintenance of normal neuromuscular activity, and that varying degrees of thyroid and hypothyroid hypo- or hyperfunction were associated with a spectrum of motor disorders.

William Berkeley subsequently reported improvements and even some cures in sixty-five patients treated with parathyroid extracts, as did Decrum, Alquier and the Italians Marogna and Massaglia. Berkeley emphasized that the source of the parathyroid cells was important: only those obtained from humans at autopsy or from cattle were useful. Equine preparations were too expensive, those from rabbits and sheep too small. Further, many of the available commercial preparations were, in fact, inactive. Berkeley used only dried preparations of bovine parathyroid, and had achieved satisfactory relief from rigidity, sialorrhea and muscular pain in 80% of his patients. His approach employed chronic administration of relatively small amounts of the expensive extract; notable results were only seen three months after the beginning of treatment. Early cases of paralysis agitans responded best, but even bed-ridden patients also experienced significant improvement. Other gland preparations were ineffective, thyroid extract elicited a deterioration in his patients. At about the same time, it was reported that the serum of parkinsonian patients included a substance which metabolized secretions of both the thyroid and parathyroid glands.

Roussy believed that parathyroid overactivity underlay paralysis agitans and applied radium to his patients’ necks, with success in three cases. In 1912, Gjestland reported a case of paralysis agitans with hypertrophy of the gland, but was not willing to propose a definite causal connection. Cornil and colleagues reported in 1934 that unilateral parathyroidectomy achieved reduction of both rigidity and tremor in one patient.

In July 1921, Walter Kühl (Altona), drawing on the work by Lundborg and others, implanted the parathyroid glands from two calves under the abdominal skin of a patient with “typical paralysis agitans”. A dramatic improvement in the motor performance of the patient was noted:

It is thus proved that the muscular rigidity of paralysis agitans is attributable to a failure of the parathyroid gland. . . . I feel justified in recommending such a safe intervention to relieve what has hitherto been regarded as an incurable disorder, even if from time to time, as the effectiveness of the transplant wanes, the operation must be repeated.

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138 Frenkel, 1899.
139 Lundborg, 1901.
140 Lundborg, 1904. Most workers have erroneously cited Lundborg’s 1901 paper as the basis of Kühl’s parathyroid transplant therapy; Kühl himself did not give an exact reference for Lundborg in his paper, citing only his name.
141 Berkeley, 1905, 1910, 1925; Alquier, 1909; Decrum, 1918. Marogna (1908) and Massaglia (1909; both Gazzetta degli ospedali e della cliniche) cited in Mercks Jahresbericht for 1909, pp.220-221.
142 Berkeley, 1912.
143 Marinesco and Papazolu, 1913.
144 Roussy and Clunet, 1910.
145 Cornil et al., 1934.
146 Kühl, 1921. See also Kühl, 1922a.
Excluding the possibility of a psychosomatic effect, he urged the investigation of both the role of calcium in paralysis agitans and its significance for the function of the motor endplate. At the presentation of these results to the annual meeting of the Northwest German Psychiatrists and Neurologists (November 1921), the audience reaction was aggressively skeptical; most questioned the diagnosis, suggesting that the absence of tremor indicated that the patient probably suffered ‘Rigor post encephalitidem’, and that the possibility of spontaneous remission could not be excluded. This differentiation of paralysis agitans and post-encephalitic parkinsonism, especially with respect to prognosis and therapy, would later assume a reduced importance in neurological thinking. More significantly, a number of audience members (including Alfons Jakob) objected that it had become clear that the seat of paralysis agitans lay in the central nervous system, and specifically in the extrapyramidal system; the role of peripheral factors in the etiology of the disorder was thus regarded as minor by this stage, and the view of paralysis agitans as a strio-pallidal disorder had gained the ascendancy.147

Nevertheless, Kühl pursued the approach further. In 1924, he reported that he had opened the parathyroid gland of a number of other paralysis agitans patients (he specifically excluded post-encephalitic parkinsonian patients) and implanted a section of bovine or equine parathyroid (‘allographic transplantation’). The hope was that the grafts would resolve the parathyroid deficiency of the patient and thus their motor disorder. He emphasized in this second report, however, that he did not see his approach as practical therapy, but rather as a means for investigating the hypothesis that hyposecretion of the gland was responsible for the symptoms of paralysis agitans. Kühl saw the hypothesis confirmed by the results of his operations: the patients showed a partial recovery of motor function which lasted about six weeks. The decline in effect was correlated with necrosis of the implant, commencing from its outer edges. Several other surgeons had followed Kühl’s lead, and in his 1924 paper he summarized what he saw as their confirmation of his success. Most, however, regarded the benefit of any parathyroid treatment, including the Kühl approach, to be largely psychosomatic.148

No effect on the course of paralysis agitans had, however, been demonstrated, apart from the extremely temporary effect which Kühl had described.149 It may well be possible that homologous grafts (human tissue), which may have had a greater chance of survival, might have exerted a long-lasting effect; the practical problems for such an approach are, however, clear. In any case, Wilmoth described the whole approach in 1925 as a failure, and it was gradually abandoned as more effective pharmacological methods emerged. Guillain and Marqery described a case in 1924 which involved Basedow’s disease combined with unilateral parkinsonism; following resection of the thyroid, the former was resolved, the latter continued its course unabated.150 In England, injections of Collip’s parathyroid extract were employed at the end of the 1920s to improve akinesia, the psychic aspects (especially bradyphrenia) and, to a lesser extent, rigidity in post-encephalitic patients; reduced blood calcium had been found to be associated with bradyphrenia in post-encephalitic parkinsonism.151

147 Kühl, 1922b.
148 For example, Madlener, 1922. Bergman (1923) described a less invasive approach, whereby calf parathyroid cells were applied subcutaneously, with about the same success.
149 Kühl, 1924.
150 Cited in Gamper, 1936, p.799.
151 Collip, 1925; Worster-Drought and Hill, 1930. On the other hand, Hühnerfeld (1930, 1931) reported that blood calcium levels were increased in ten of eighteen post-encephalitic parkinsonian patients, as were cerebrospinal fluid levels in eight patients.
Sex hormone therapy in paralysis agitans and post-encephalitic parkinsonism was also reported, albeit usually in litanies of agents which failed to make an impact upon the disorder. The psychoanalyst Cohen-Booth, however, regarded the use of ‘Testes siccati Merck’ (3×2-4 dragees à 25mg) in men and ‘Hormofollin’ (Labopharma, Berlin; 100-300U follicular hormone/day) in women as appropriate, given the decline in endogenous hormone levels in the age group most afflicted by paralysis agitans, and he even believed that the “most significant goal of this treatment, to halt the central degenerative process, appears to be achievable by these means.”152 And this despite the fact that he regarded the disorder as essentially being the consequence of inappropriate psychiatric responses to childhood trauma. He noted that one patient treated with testicular extract had maintained reasonable condition since 2¼ years. Another, who had been treated concurrently with the extract and atropine for a year, was similarly well until he abandoned the testicular extract for financial reasons; within a year, his deterioration had led to his suicide.153

In contrast to attempts to supplement hormonal function was an approach briefly mentioned by Gamper in his 1936 review of antiparkinsonian therapy:

And naturally the ‘puberty gland’ [interstitial cells of the testes] must be invoked in therapy; according to SKALA, its dysfunction is supposedly one of the first signs of the disease. The result: Steinach operation [occlusion of the vas deferens] and – as to be expected – “significant” improvement, and over the further course of the patient, silence.154

By 1936, Gamper could comment that the initial hopes attached to the treatment of paralysis agitans with hormone extracts and preparations had faded.155 During the 1930s, hypothyroidism became more closely linked with schizophrenia (and later with depression), whereas hyperthyroidism was associated by some with Parkinson’s disease. This hypothesis was still current as late as 1958: Bartels and Rohart reviewed the similarities of hyperthyroidism and parkinsonism, and suggested that thyroid dysfunction should be suspected in every case of the Parkinson’s disease; they presented details of twelve patients with concurrent hyperthyroidism and idiopathic parkinsonism.156 Four years earlier, Schwab and Chapman had reported some success in six of nine euthyroid parkinsonian patients by using 131I to induce a hypothyroid state; subjective improvement was registered by the other three patients. The authors concluded, however, that there was no evidence “that lowering the thyroid function did anything more than make the Parkinsonism more tolerable to the individual.”157 Barbeau mentioned in 1962 unpublished results which indicated that protein-bound iodine levels were often at the higher end of the normal range or slightly increased in parkinsonian patients. It was reported in 1974 that intravenous thyrotropin-releasing hormone (200µg in saline) did not elicit any motor improvements in parkinsonian patients, but did achieve an improvement in mood in two of three patients receiving L-DOPA.158 French workers recently reported once again an association between

152 Cohen-Booth, 1935.
153 Ibid. Interestingly, neuroprotection of mesencephalic dopaminergic neurons has been reported (Sawada and Shimohama, 2000).
155 Ibid.
156 Bartels and Rohart, 1958.
158 McCaul et al., 1974.
hypothesis and Parkinson’s disease; this was linked to the lack of the stimulatory effect of dopamine on TSH release.\textsuperscript{159} Finally, in a somewhat complex analysis of the epidemiology of Parkinson’s disease in the United States, Foster found that the two variables “percentage of state with sodium-deficient soil” and “thyroid disturbances in White male selective service registrants during World War II” accounted for two-thirds of variance in the data (nearly 50\% was attributed to the factor ‘sodium’ alone); the author noted that the same factors which were significant for Parkinson’s disease were also predictive for the distribution of multiple sclerosis, suggesting a similar etiology.\textsuperscript{160}

The present discussion, however, must return to the first quarter of the 20th century and the outbreak of a neurological epidemic which altered forever the attitude to parkinsonism.

\textsuperscript{159} Guerin \textit{et al.}, 1990 and references therein.

\textsuperscript{160} Foster, 1992. As the consequence of his study, Foster suggested that increasing the iodine content and decreasing the levels of sodium, strontium and phosphorus in the diets of patients might be useful, as also perhaps the diet advocated by Swank for multiple sclerosis patients.
V. Encephalitis lethargica: New strategies in the therapy of parkinsonism

In 1915, the first of a series of epidemics of what appeared to be a new and mysterious disease began to sweep Europe and, ultimately, the world. Both the very young and the old were particularly prone to the disorder, which presented initially as an influenza-like fever, followed by a syndrome which was characterized by somnolence (hence the alternative designation “European sleeping disease”), oculogyric signs and a palette of neurologic symptoms of almost all types, ranging from headache, depression, delirium, confusion and motor disturbances to full-blown psychosis and stupor. Around 40% of patients died during the acute phase of the disease, usually by respiratory failure. The important aspects of the epidemic for the present discussion are, in fact, the sequelae exhibited by survivors of its acute phase: up to four in five patients may have exhibited parkinsonian symptoms at some time following the initial crisis.¹ Duvoisin has calculated that the incidence of such signs was about 30% within 3 years and 50% within 5 years.² Robb reported in 1927 the condition of 141 patients 2½ years after their apparent recovery: only thirteen were regarded as being completely healthy, while 58% suffered from parkinsonism. In most countries, the worst years of the pandemic were 1920 and 1921; the severity of the epidemic waves petered out after 1926, although new cases of post-encephalitic parkinsonism continued to be reported as late as the 1940s.

Epidemic encephalitis and its parkinsonian consequences were first specifically described by the colorful Austrian neurologist Constantin von Economo (1876-1931), recently returned to Vienna from service as a reconnaissance pilot in Tyrolia, in a series

¹ Freeman, 1927.
² Duvoisin, 1992.
of papers in the *Wiener Klinische Wochenschrift* in 1917; his papers on the subject were so complete that the disorder was frequently referred to as *von Economo’s disease*. At about the same time, the Frenchman René Cruchet reported the appearance during 1915/16 of a similar disorder on the battlefields in France, but without immediately recognizing it as a distinct nosological entity. The earliest reference in English to post-encephalitic parkinsonism which I have found was a short paper by Arthur J. Hall in the *Lancet* of April 20, 1918. In July of the same year, Kinnier Wilson attempted a classification of types of the encephalitis; the “paralysis agitans” type was the seventh and final category.

The cause of the epidemic has never been satisfactorily explained; von Economo wrote in his original paper:

> We have the histologic picture of a polioencephalitis cerebri, pontis et medullae oblongatae, with a slight poliomyelitis of a perivascular, inflammatory and diffusely infiltrative but not hemorrhagic and only slightly neuronophagic character. . . . the remarkable paucity of the general symptoms of ‘grippe’ and the severity of the cerebral symptoms indicate a specificity for central nervous tissue, similar but not identical to the virus of poliomyelitis.

The most widely accepted explanation, despite certain epidemiologic problems raised as early as the 1920s, is that the major responsible agent for encephalitis lethargica was the influenza virus which ravaged the world at about the same time, although the involvement of a herpes-type virus was also argued. For this reason, Ravenholt recently urged that the epidemic encephalitis not be relegated to the scrapheap of curious but trivial medical curiosities, but rather be more closely investigated for clues to the etiologies of neurological disorders such as Alzheimer’s disease and, of course, Parkinson’s disease. It was remarked by contemporaries of the epidemic that almost any disease of the central nervous system could follow infection with influenza. Von Economo himself referred to similar, although less extensive, outbreaks in Italy and Hungary in 1890 (the “nona”) and a famous epidemic of ‘sleeping sickness in Tübingen in 1712; the Frenchman Arnold Netter published a review in 1929 of the occurrences

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3 The most important papers: Economo, 1917a, 1917b, 1919a, 1919b, 1921. His monograph on the subject appeared in 1929, the English translation in 1931. A useful biography was published in 1979 by van Bogaert and Théodoridès; it includes English translations of the four crucial papers. See also biography by his wife and von Wagner-Jauregg, 1934 (English translation: 1937).

4 Economo first spoke of ‘Encephalitis lethargica’ in a paper read to the Viennese Psychiatric Society on 17 April 1917 (von Economo, 1931, p.168). During the 1920s, a debate as to the priority of the discovery of encephalitis lethargica was largely fought on nationalistic grounds; cf. Cruchet, 1929; von Economo, 1929; von Economo, 1931, pp.v, 1-6.

5 The parkinsonian symptoms in the ten cases described, however, seemed temporary, and Hall noted a difference between the tremor of paralysis agitans and that of the new disease. On the same page, Wilfrid Harris described the new disease as “acute infectious ophthalmoplegia” or “botulism”. See also Buzzard, 1918.

6 Economo, 1917a.

7 Crookshank, 1919. See also discussions in Ebstein, 1921; Schuster, 1931b. For contemporary discussion of alternative theories regarding the infectious agent, see von Economo, 1931, pp.17-24.

8 For example, by Doerr and Schnabel (Hygiene Institute, Basel University), 1921.

9 Ravenholt, 1993; see also Ravenholt and Foege, 1982.


11 Economo, 1917b, 1919b. The relationships between the epidemics of the Australian “mysterious” or “X disease”, Japanese B encephalitis (which occurred immediately prior to the encephalitis lethargica epidemic) and encephalitis lethargica remain to be clarified.
of similar epidemics throughout history. Von Economo had been impressed by the vegetative symptoms and disturbances of muscle tone, especially of the eye muscles (but not restricted to them), which were often observed at an early stage of the disease; this had motivated his successful search for lesions in the brainstem.

The importance of encephalitis lethargica for the present discussion is that it led to a huge increase in the number of patients with parkinsonian symptoms, and to a shift in the demographics of this group to a lower age of onset. As already remarked, Hall noted a case in which parkinsonian symptoms were presented as early as 1918. The leading French neurologists Jean Athanase Sicard (1872-1929) and Achille Alexandre Souques (1860-1944), however, were the first to emphasize the frequency of this syndrome in recovering encephalitics and to use the term ‘parkinsonism’ (‘parkinsonnisme’, in distinction to ‘maladie de Parkinson’) to describe it. Sicard and Paraf posed the question early of whether the prognosis for post-encephalitic parkinsonian patients, and thus the therapy, would be similar to those who suffered ‘true’ Parkinson’s disease. Two thirds of parkinsonian patients treated in clinics in the 1920s were encephalitis lethargica victims, and their number would still represent a significant proportion of cases into the 1960s, especially in Europe. There was some disagreement as to whether the parkinsonian symptoms should be regarded as “after-effects” of the encephalitis, or simply as its chronic phase; this confusion was aided by the fact that the appearance of parkinsonian symptoms could appear as late as 16½ years after the acute phase of the illness. Meggendorfer had already categorically stated in 1920 that the parkinsonian symptoms were the chronic phase of the disease, an opinion also widely held in France; Felix Stern had also been clear in 1921:

the chronic myostatic conditions represent a chronic disease process which is the chronic form of encephalitis.

For a time, some workers attempted to replace the term ‘post-encephalitic’ with ‘metencephalitic’, but without success. The “senseless” term ‘post-encephalitic parkinsonism’ had established itself early and continues to be employed today, even by most who accept the unitary nature of the disorder. In any case, it had become clear by 1921 at the latest that the sequelae of the epidemic were to be a long term public health problem, even though the active infectious phase seemed to have passed. Heinrich Pette, of Nonne’s clinic in Hamburg-Eppendorf, wrote at the beginning of 1922 that the view that the worst phase of the epidemic and its consequences had passed was no longer tenable. The horror induced by a disease which not only claimed a massive death toll during its acute phase, but seemed capable of returning for a second cull was expressed clearly in the dawning realization of the progressive nature of its after-effects:

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12 Bogaert and Théodoridès, 1979, pp.39-40; the precise reference is not given. A brief review is given in Netter, 1920a. See also the critical history of ‘sleep fevers’ by Ebstein (1921) and the historical survey in von Economo, 1931, pp.6-9.
13 Sicard and Paraf, 1920. See also Froment and Magnet, 1921; Lhermitte and Cornil, 1921; Souques, 1921b.
14 12% in 1964; Hoehn, 1976. Duvoisin has co-published a number of reviews on the subject, including Duvoisin et al., 1963, Duvoisin and Yahr, 1965 and Duvoisin and Schweitzer, 1966.
15 Witzleben, 1938a. Pohlmeier and Matussek reported in 1965 the case of a patient who developed parkinsonism symptoms twenty-six years after the encephalitis.
16 Cited in Witzleben, 1938a.
17 Witzleben, 1938a.
If the view is correct, that the pathogen underlying the encephalitis can still be present in the organism as a virulent seed years after the infection, there would be significant consequences for the prognosis of our encephalitis patients. Each person who had survived the encephalitis epidemic would then be bearing within themselves a volcano which could erupt again at any time with dire consequences for the carrier.  

Dimsdale reviewed in 1946 the 320 cases of parkinsonism seen at the Maida Vale Hospital between 1900 and 1942. She noted that paralysis agitans accounted for almost all of the 100 cases up to 1919, for 34 of the 100 cases between 1920 and 1930, and for 52 of the 120 cases after 1930. Further, she could distinguish post-encephalitic from idiopathic cases by the more common presentation of mental symptoms, salivation and ocular problems by the former. She noted, however, another interesting difference within the post-encephalitic group: those reporting by 1930 had experienced the onset of parkinsonian signs within two years of encephalitis, and the clinical picture was dominated by rigidity. Those reporting after 1930 showed a long latency and gradual onset of parkinsonian symptoms, the major complaint being tremor; the progressive character of the disorder in this group was thus much more similar to that of the idiopathic patients.

It was a common view at this time that the original disease process must still be active to explain the progression of the disease. The Executive Secretary of the Matheson Commission for Encephalitis Research in New York, Josephine Neal, wrote in 1934 that it was “now generally believed that the chronic stage of the disease is caused by the continued activity of the infecting agent.” There were also voices, however, which suggested that the initial damage sustained during the acute infection might be sufficient to produce a progradient lesion. As it would turn out, the disagreement was unimportant; the disease was incurable and demanded lifetime symptomatic management. On the other hand, the difference was important, because the first view implied that treatment should aim at controlling the infectious agent, even years after the initial illness; this was the official view in England. Arnold Netter, for instance, regarded the excessive salivation in encephalitis lethargica as a physiological attempt to excrete the virus via the salivary glands, as in rabies; hence his use of pilocarpine to increase sialorrhea. A variety of measures which aimed to control the infectious process were investigated, as will be discussed below; but it little real progress was to be made in this direction, so that there remained no option but to instigate symptomatic treatment.

The parkinsonism of encephalitis lethargica was not identical with the idiopathic disease: tremor was not as striking, bradykinesia and rigidity, however, more so, and the wide variety of accompanying extrapyramidal symptoms – particularly the oculogyric crises, characteristic for encephalitis lethargica but not seen in the idiopathic disorder – and psychological phenomena demarcated the disease from that described by ‘paralysis agitans’. In particular, bradyphrenia, the slowness of cognition in

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18 Pette, 1922.
19 Dimsdale, 1946.
20 Hill, 1929c.
21 Bing, 1921; Pette, 1922, 1923.
22 Ministry of Health, 1924.
23 Netter, 1920b.
24 Cruchet indicated that he coined the term ‘bradykinesia’ in 1906: see Cruchet, 1925; 1931.
25 See, for example, Cruchet, 1925; Lotmar, 1926.
parkinsonism, was first described in post-encephalitic patients and long regarded as a hallmark of this form; it is now regarded, however, as also typical for the idiopathic disease. Further, the tremor was less a resting than an intention tremor. There were however, also different levels of incapacity observed in post-encephalitic parkinsonian patients. Some attributed these variations to the differential effectiveness with which the immune system of a particular had dealt with the infectious agent. It is certainly curious that many patients developed parkinsonian symptoms almost immediately after the encephalitic attack, while in others an apparently uneventful interim of several years occurred between the emergence of progressive symptoms; incapacity was generally greater and life expectancy shorter in the former group. It would almost appear that post-encephalitic parkinsonism consisted, in fact, of at least two distinct though related disorders. The discussion of this question must be deferred to a later time.

The etiology of parkinsonism: neuropathology of the extrapyramidal system

The similarities were sufficiently striking, however, to provide new impulses for localizing the seat of the disorder; there was explosion of publications of the histopathology of paralysis agitans after 1920. Von Economo noted in his volume on encephalitis lethargica:

The sorry fact of the helplessness of our medical art in chronic cases of encephalitis lethargica has been in some measure compensated amongst the scientifically minded by the immense gain which our knowledge of pathological and nervous mechanisms has derived from our acquaintance with this disease, and by the justified hope that, in days not too far ahead, this knowledge will open up new avenues towards the discovery of means of remedial aid.

Von Economo remarked that both the acute and chronic forms of encephalitis lethargica presented a vast array of motor, vegetative and psychiatric symptoms which had previously proved difficult to definitively associate with an organic basis. It was now clear that an infectious agent acting upon the central nervous system could elicit such symptoms, confirming that, in each case, they did possess an organic origin. Further, post mortem examination of encephalitis lethargica victims had allowed some association of particular symptoms with damage to discrete brain regions. Von Economo compared the revolution in thinking provoked by encephalitis lethargica to the “proof that living organisms cause infectious diseases and the discovery of cerebral localizations as a consequence of brain-injuries caused by the war of 1870”.

By the time of the epidemic encephalitis, innovations in histological techniques (table 5-1) had led to the general acceptance that one or more anatomical lesions could be identified, at least in principle, as underlying the symptoms of parkinsonism. The challenge of defining which lesion was consistently associated with which deficit, however, remained. This, in turn, depended on an understanding of the appearance and function of the healthy brain and, in particular, of the extrapyramidal system. Interest in the neurology of the this system had long been overshadowed by that of the neocortex,
especially after Fritsch and Hitzig had excited interest with their electrical stimulation of the cortex and demonstration of the existence of a ‘motor cortex’ (1867-1870).31 Prior to these experiments, it was thought that any effect of electrical stimulation of the cortex on movement was attributable to current overflow into the basal ganglia or cerebellum; now the situation was reversed, with all interest focused upon the higher centres.

The revival of interest in the striatum was triggered by the appearance in 1911 of both Alzheimer’s paper on striatal changes in Huntington’s chorea and Wilson’s thesis on those in the disease named for him. A flurry in activity devoted to the normal and pathological anatomy of the striatum and associated nuclei, only some of which can be discussed here, culminated in the most significant conceptual innovation of the period, the definition of the ‘extrapyramidal motor system’ by Hugo Spatz in 1922 on the basis of metabolic similarities, especially iron content, in the various constituent nuclei; he included the striatum, pallidum, subthalamic nucleus, substantia nigra, nucleus ruber and dentate nucleus in this system.32 One of the first chemical changes identified in the brains of patients who had suffered from parkinsonism or other extrapyramidal disorders was an increase in reactive iron levels.33

One report which made an essential contribution to this development was a doctoral thesis published in Paris in 1919. Constantin Trétiakoff (Faculty of Medicine, Paris) is generally regarded as having provided the evidence which cemented the substantia nigra hypothesis of parkinsonism proposed a quarter of a century earlier by Brissaud (see page 98). Trétiakoff described two cases of encephalitis lethargica with parkinsonism who presented at autopsy with inflammation of the substantia nigra; degeneration of the nucleus was also noted in nine cases of paralysis agitans. In one case of unilateral parkinsonism, the substantia nigra was affected only on the side contralateral to the symptoms. Arteriosclerosis was found in only three cases; there was no evidence for inflammatory damage. Trétiakoff also noted the following changes in paralysis agitans:

31 The key paper was Fritsch and Hitzig, 1870. Golgi had seen degeneration of the lenticular nucleus in Huntington’s disease in 1874 (reprinted in Golgi, 1903); the elaboration of this finding, however, awaited Meynert’s pupil Anton (1896) and Alzheimer (1911). Wilson described the disease named after him in his doctoral thesis of 1911 (most significant parts reproduced in Wilson, 1912). See discussion and further details in Schiller, 1980.

32 Spatz, 1922a,b,c; see also Spatz, 1927. Jan Prus (Lemberg), however, had introduced the term ‘extrapyramidal’ in 1898, and the concept of ‘extrapyramidal tracts’ was familiar to the Vienna school in the first decade of the 20th century. For further details, see Eicke, 1968 and Schiller, 1980.

33 For example, see Kingo, 1935.
Throughout the 1920s, a number of workers confirmed Trétiakoff’s findings in paralysis agitans. Although the damage sustained in encephalitis lethargica tended to be diffuse, involving all major structures of the brain (Economo had, however, early noted a preference for grey matter), a constant finding was the almost total destruction of the substantia nigra. Lesions of the substantia nigra were also observed in other diseases in which muscular tone was affected, including chorea, multiple sclerosis and certain forms of hemiplegia. Others remained doubtful, most famously Lewy, who argued that lesions in the striatum and vagal nucleus were more important in parkinsonism, and James Ramsay Hunt (1872-1937), who contended that the primary lesion was located in the pallidum. Trétiakoff, amongst others, pointed out that the substantia nigra might be regarded ontologically a part of the pallidum, so that his lesion was reconcilable with Hunt’s view. Yet others confirmed the lesion in the substantia nigra, but regarded its clinical significance as secondary to that in the pallidum. The most significant adherents of this view were Cécile (née Maugnier; 1875-1962) and Oskar Vogt (1870-1959), who had published a number of papers on the striatal system and its pathology between 1918 and 1925, including the exhaustive paper on the subject which appeared in 1920. The pair had also detected lesions in the substantia nigra of parkinsonian patients, but deferred the discussion of this finding to a later date. Until they became aware of Trétiakoff’s work, they tended to the interpretation that the anatomical substrate of paralysis agitans was what they described as a “status desintegrationis” of the striatum and pallidum.

In 1921, a symposium was held by the French Neurological Society in Paris at which the issue was debated, with a slight tendency towards acceptance of the substantia nigra hypothesis. Kinnier Wilson (1877-1937) stated in the introduction to his Croonian lectures of 1925 that he had thus far not seen any reason to move from the position advanced in his 1911 doctoral thesis that paralysis agitans, like lenticular degeneration, was a progressive degeneration of the striatum and some of its fibre systems; he ascribed the rigidity to a pathway distinct from that of the classical pyramidal motor pathway. He did not, however, attribute all parkinsonian symptoms to the striatum; indeed, he emphasized that it was a simple structure in comparison to the cerebellum or thalamus, and could be held responsible only for regulation of muscle tone and the control of involuntary movements, not for direction of voluntary motor activity. Certain other aspects of the disorder could be attributed to loss of cortical functions, but much remained unclear.

34 Trétiakoff, 1919; partial translation in Marks, 1974.
35 Economo, 1917a.
36 Lewy, 1923.
37 Hunt, 1916; 1917; 1933.
39 Souques, 1921a.
40 Wilson, 1925a, 1925b; see also Doshay et al., 1947. Critchley noted in his tribute to Wilson in 1988 that Wilson was appointed by the Kings’ College Hospital as the first “pure neurologist” in the United
Foix and Nicolesco published an extensive examination of the lesions in the parkinsonian brain in 1925; they did not, however, describe their methods or patient material. Lesions were located in various parts of the brain and spinal cord, leading them to the conclusion:

*The lesions are much more diffuse than it had at first appeared; in its detail, the parkinsonian process resembles in many ways the usual process of senile cerebral disintegration. . . . It is not to be doubted that the clinical signs of Parkinson’s disease do not depend on the special localization of the lesions. The diffuse lesions are, indeed, completely banal. The specific lesions, on the contrary, are not found with the same intensity in any other disease of the nervous system. In short, the disease seems to be a quite regional affection, but to a certain extent also systemic, involving at the same time the simultaneous attack on a certain number of synergistic centers and secondary deteriorations following the lesions of these centers.*

Their description of parkinsonism as a “systemic” disorder sounds very modern. The French authors were prepared to accept that both the striatum and the substantia nigra were involved in the disease process; the reduced volume of the latter, however, was an absolute constant in the disorder.

By the 1930s, an increasing number of investigations had shown that pathology of the substantia nigra – including neurodegeneration and the presentation of Alzheimer-type neurofibrillary inclusions, which had previously only been observed in the elderly – was a constant feature in post-encephalitic patients with parkinsonian symptoms, although cortical abnormalities were also noted. The doctoral student Rolf Hassler (Kaiser Wilhelm Institute for Brain Research, Berlin-Buch, and Institute of the German Society for Brain Research, Neustadt/Black Forest; 1914-1984) described the pathology of the brain in all three major forms of parkinsonism in 1938/39 in a series of classic papers, which also described finer subdivisions of the substantia nigra in detail for the first time. His conclusion was clear: the lesion in the substantia nigra was the pathologic-anatomic substrate of all forms of parkinsonism. There were differences between the magnitude and the precise localization of this lesion in paralysis agitans and post-encephalitic parkinsonism, but the major lesion was definitely in this nucleus. He also noted the specific vulnerability of the melanin-containing cells of certain regions of the substantia nigra pars compacta, as well as that of the locus ceruleus and perhaps the dorsal vagus nucleus. Hassler attributed the tremor of parkinsonism to unspecific lesions in the striatum, the vegetative symptoms to damage of the dorsal vagus nucleus; the other movement abnormalities were functions of the nigral lesion. Even at this stage, however, the substantia nigra hypothesis was not accepted without reservations; workers such as Leo Alexander were not alone in regarding degeneration in this region as characteristic of post-encephalitic parkinsonism, but not of paralysis.
agitans, where many workers observed major pallidal lesions. There were still others who were still not convinced that the nigral lesion was the crucial problem in parkinsonism.⁴⁶

There were a number of competing neuropathological models of the etiology of parkinsonian symptoms at this time, none of which made a major impact on the therapy of the disorder, for which reason they will not be discussed in detail here. An excellent contemporary summary of the various models is found in the monograph by Lotmar of the University of Bern;⁴⁷ an English language précis of the situation somewhat later is included in the paper presented by Russell Meyers to the Association for Research in Nervous and Mental Disease in 1940. The state of knowledge was perhaps best summarized by the latter author in the opening of his review:

_A survey of the various views that have been advanced concerning the physiology of those parts of the nervous system which in disease are generally considered to produce the symptom-complex of parkinsonism discloses with forceful emphasis the morass in which we now stand._⁴⁸

Halpern had expressed the same concerns in his review of antiparkinsonian therapy a decade earlier:

_It is precisely knowledge of the physiological basis which is the immediate prerequisite for treatment. It is thus all the more regrettable that this necessary connection between pathological anatomy and clinical symptomatology is often lacking in neurology, even if there have recently been indications of a change in this situation. That is equally true for Parkinson’s syndrome, which . . . has been the subject of physiological investigation only to a limited degree and has largely been the preserve of pathological anatomy. This one-sided conception of the Parkinson problem, together with the changing views with time of the location of the lesion – in the muscle, in the peripheral nerves, in the hormonal system and finally in the substance of the brain – could not contribute a great deal to the physiological underpinning of a Parkinsonian therapy._⁴⁹

The Vogts had also seen therapy as the ultimate rationale of their neuropathological investigations. After pleading for more precise definitions of the _essential_ symptoms of particular basal ganglia disorders in order to allow their closer correlation with neuropathological changes, the Vogts had concluded that the striatal system was especially prone to particular types of damage, and that these lesions could be caused by different noxious causes. The explanation for this particular vulnerability, they proposed, was not due to differential perfusion, as commonly supposed, but was instead attributable to specific chemical characteristics of the striatal system which differentiated it from other central nervous system regions:

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⁴⁶ See also Benda and Cobb, 1942; Heath, 1947. Leo Alexander (1905-1985), a Viennese Jew, trained with Oskar Vogt in Berlin and Karl Kleist in Frankfurt before taking a postgraduate teaching position at the Peking Union Medical College. Choosing not to return to Germany in 1933, he moved to the United States. At the end of the War, he returned to Germany as a major in the U.S. Army, and was responsible for the preparation of the Combined Intelligence Operative Sub-Committee reports on the neuropsychiatric work of German agencies during the National Socialist years. Shevell, 1996.

⁴⁷ Lotmar, 1926.

⁴⁸ Meyers, 1942.

⁴⁹ Halpern, 1931. Halpern advanced this argument to emphasize that the new harmine therapy was, in fact, physiologically justified, as it was supported by the ‘double lesion’ model of parkinsonism promoted by Halpern (see below). Nevertheless, harmine, as with all other antiparkinsonian agents at this point, had been introduced empirically, not as the result of a physiological model.
By recognizing this non-homogenous chemical constitution [Chemismus], we have, however, established the necessary prerequisite for its detection, and further – as we have emphasized many times – will have thus also laid the essential basis for chemotherapy, which we believe appears to promise more success in the control of striatal disorders than any other therapeutic approach.\(^{50}\)

This was written forty years before the biochemical basis of parkinsonism was uncovered.

It was not only the fact that the site of the lesion in parkinsonism was disputed; it was also the confusion as to the organization of the motor system in general and the extrapyramidal system in particular. Ramsay Hunt, for example, conceptualized the large cells of the caudate nucleus, pallidum and putamen as forming the “paleostriatum” or “pallidal system”, while the smaller cells of these structures formed the “neostriatum”; the former managed automatic movements, while the latter maintained the muscles in a state of preparation an regulated to an extent the paleostriatum.\(^{51}\)

Kinnier Wilson, in contrast, rejected separate functions for different parts of the basal ganglia, and insisted that the striatum, a much simpler organ than either the cerebellum or thalamus, simply controlled muscle tone and inhibited the rhythmic movements inherent in the “old motor system” (cerebello-mesencephalo-thalamo-ponto-spinal complex, as opposed to the “new” or pyramidal motor system).\(^{52}\) Wilson denied also that the striatum was involved in affective functions, in which he was opposed by workers such as Papez, who, like the Vogts, saw the striatum primarily as a motor integration centre, but also regarded it as being concerned with limbic functions.\(^{53}\) Some workers believed that somatotopic localization in the basal ganglia was unlikely, while others were convinced that it existed, but disagreed on whether the orientation was oral-caudal or dorso-ventral. This was quite apart from questions of whether, for instance, the dentate and red nuclei should be considered part of the basal ganglia.\(^{54}\)

These discussions concerned the organization of the healthy basal ganglia, although based almost entirely on the correlation of functional deficits and neurological findings in pathological cases; it is thus no surprise that ideas concerning the neurological bases of various motor signs were also confusing. This was partly because investigators were extrapolating from their usually limited number of sections to the disease in general; further, without prior agreement as to what constituted a particular disorder, it was difficult to judge how much emphasis should be given to a particular finding. Most theories posited more or less focal lesions in the central nervous system, perhaps the most elaborate being that advanced by Kleist on the basis of his experiences with soldiers suffering head injuries during the First World War; for example, loss of the nigral pars reticulata resulted in akinesia, general rigidity and loss of associated movements, while tremor was the consequence of losses in the pars compacta.\(^{55}\) Other workers proposed different classifications.\(^{56}\) The numbers of exceptions to any model, however, and the failure to reproduce symptoms in laboratory animals with similar lesions reduced the credibility of any single model. This problem, the lack of an

\(^{50}\) Vogt and Vogt, 1920.

\(^{51}\) Hunt, 1916, 1917.

\(^{52}\) Wilson, 1924, 1925a, 1925b.

\(^{53}\) Papez, 1942.

\(^{54}\) Meyers, 1942.

\(^{55}\) Kleist, 1925.

\(^{56}\) Lotmar, 1926, Meyers, 1942.
adequate animal model of parkinsonism, has until the present not been entirely solved; the best which had been reported by the 1940s was the induction of a parkinsonism-like state in monkeys with manganese, but the shortcomings of this study were too severe for it to attain much significance. The production of lesions in the animal brain by various means – zinc chloride, chromic acid, implanted radium – had been tried since the middle of the 19th century, but the specificity of these lesions in most cases was doubtful and the results therefore ambiguous. Even the electrolytic lesions produced by Wilson while employing the recently devised Horsley-Clark stereotactic device had failed to produce functional deficits in monkeys which could be compared with those of any extrapyramidal disease.

Neurosurgical approaches to parkinsonism

A consensus with regard to the normal and pathological physiology of the basal ganglia was thus impossible; it was often prevented not only by scientific considerations but also by national differences of interpretation. The final consequence for the chemical therapy of parkinsonism was that neuropathology offered little in the way of insight into the most effective manner in which to approach the disorder or any of its symptoms. Perhaps surprisingly, however, this was precisely the point in time at which neurosurgical intervention began to play a major role in the therapy of parkinsonism. This development was partially facilitated by the failure of any form of medication to provide lasting symptomatic relief, and partly because individual clinicians felt justified in applying the insights they had gained from their neuropathological studies. In this sense, there was indeed an impact of anatomical knowledge upon the therapy of parkinsonism, although even here a certain degree of empiricism was involved. As basic knowledge concerning the disorder was so uncertain, the development of effective

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57 Mella, 1924.
58 For example: Edwards and Bagg, 1923; Morgan, 1927. See also Meyers, 1942.
59 Horsley and Clarke, 1908; Wilson, 1914.
V. Encephalitis lethargica: new strategies in the therapy of parkinsonism

Surgical interventions required experimentation directly on the patient: This was also the case with conservative pharmacological therapy of the disorder, but with neurosurgery there existed greater potential for a disastrous, irreversible outcome. The surgical approach, however, was complicated at this stage not only by uncertainties with regard to the function of individual central nuclei, but also because the innervation of the muscle was itself still a topic of controversy, with a double (sympathetic and parasympathetic) innervation model competing with single and triple innervation models.60

The approach was thus reserved for only the most serious cases – Meyers spoke of the "abject condition of the sufferer and his forlorn life-outlook"61 – and was indeed associated with a high mortality rate. The fact remains, however, that neurosurgery achieved impressive gains in the relief of neurological symptoms in parkinsonism and other disorders, achievements which increased with time as techniques were refined and experience in their application gained. Further, advanced tremor is regarded by most patients as the most disabling, both from a performance and a psychological point of view. This problem has, until the present time, proved particularly resistant to chemical therapy, but can be ameliorated or even completely abolished for a considerable period by a variety of neurosurgical approaches. Ultimately, however, neurosurgery began its ascent because neurology was essentially based upon neuroanatomical (as opposed to neurochemical) foundations at this point.

Neurosurgical intervention in parkinsonism is a broad theme in its own right and cannot be treated here in detail. The history of this approach was reviewed in detail by Robert Redfern in 1989, and more briefly by Speelman and Bosch.62 The latter authors have defined a number of periods in the history of the neurosurgery of parkinsonism:

**Open functional neurosurgery**

- **1912-1939** Ganglionectomy, thyroidectomy and various lesions of the spinal cord. The first specific attempt to treat parkinsonism surgically was reported by Leriche in 1912, via section of the posterior roots; the intervention was variously reported as relieving tremor or rigidity. Delmas-Marsalet also claimed success in the treatment of rigidity with lesions of the cerebellum.
- **1937-1954** Cortex and spinal tract. Improvements in tremor were achieved by cortectomy, but often at the price of other functional losses. Cordotomy was directed against unilateral tremor and rigidity, and associated with fewer side effects.
- **1939-1949** Basal ganglia and efferents. Meyers experimented with various lesions over twelve years, and reported in 1951 that the sectioning of pallidofugal fibres achieved the best results for relieving tremor and rigidity; his success rate was 60%, the mortality rate 15.7%. Other authors reported fatality rates of up to 41%. Most surgeons chose to undertake a more direct attack on the pallidum, with equal success and fewer deaths (7.5%).63

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60 Brücke, 1932; Tiegs, 1935; Bülbring and Burn, 1941; also Scheifărth, 1939 and references therein.
61 Meyers, 1942.
63 An interesting sidelight to this discussion was the suggestion by Walter Edward Dandy (1886-1946) in 1946 that the centre of human consciousness was located in anterior striatum. This hypothesis, based on his surgical experiences dating back to 1930 (when he reported the almost complete extirpation of both frontal lobes without apparent damage to mentation of any sort; the corpus callosum could also be
Stereotactic (closed) functional neurosurgery

- 1947-1969 Pre-levodopa era. The publication of the first stereotactic atlas of the human brain by Spiegel and Wycis in 1952 increased the popularity of stereotactic surgery. Initially, the major targets remained the inner segment of the pallidum and the ansa lenticularis, but the thalamus gradually became the preferred target, as the impact on tremor was greater and the operation was associated with fewer risks. By 1969, 37000 stereotactic operations had been reported, mostly in parkinsonian patients; although only 15% of such patients were suitable candidates for such interventions, up to 90% of this selected group could expect relief from tremor and rigidity (but not akinesia). Stereotactic devices had reduced the rate of serious complications to about 10%, and mortality to less than 1%.

- 1969-present Levodopa era. After a sharp decline in the number of stereotactic interventions, thalamotomy was revived in the 1970s for patients whose tremor was not helped by L-DOPA therapy. Laitinen and colleagues resumed operations on the medial pallidum in 1985, while deep brain stimulation (of the thalamus) for movement disorders was introduced in the 1970s, but refined for parkinsonian patients by Benabid and colleagues at the end of the 1980s.64

An alternative surgical approach was described by Myerson and Berlin (Tufts College Medical School, Boston) in 1934. They believed that basal metabolism was increased in post-encephalitic parkinsonism by up to 60%, and therefore undertook a total thyroidectomy in one of their patients. The required hyoscine dose after the operation was reduced by 75%, but in the absence of the drug, the tremor was at least as severe as before the operation. The administration of thyroid extract was naturally also necessary.65

During the period before the War, neurosurgical approaches to parkinsonism were thus highly experimental and attended by significant risks of further incapacitation and even death. Open functional surgery on the brain was of its nature a perilous undertaking, especially during its pioneer period; but controversies regarding the functions of various brain regions rendered the approach even more hazardous. There was no controversy, however, about the severity of the parkinsonism which followed encephalitis lethargica; descriptions such as the following describe graphically the situation in which the unexpected invalids found themselves:

*With their marked motor and psychic inhibitions, the fixed, mask-like face, the lack of all impulses of will, the strong flow of saliva, the frequently existing tremor, the torturous sleeplessness of the night and increased need for sleep during the day, patients at the peak of the illness present a terrible sight which provokes sympathy, Moreover, in the vast majority of cases a continuous progression of the disorder is to be noted.*66

Further, some authorities regarded the true extent of post-encephalitic parkinsonism as being even greater than the apparent toll indicated by presentations in clinics; Stemplinger, for example, noted in 1930 that most cases were not found in institutions but in the family home, so that the general practitioner must be astute to recognize the
problem which confronted him. He also noted that this lack of recognition led to many not receiving any form of treatment, so that the sick were forced to lead “an absolutely miserable and pitiful martyr’s existence”, accentuated by the heightened feelings of infirmity characteristic of those with severe neurological disorders. The increased number of patients and the expanded knowledge of the histological basis of the disorder produced no progress in the therapy of the disease.

These remarks should not be interpreted, however, as indicating that physicians and pharmacologists were ignorant or dismissive of anatomical findings. Worster-Drought and Hill, for example, incorporated such knowledge into their discussion of the effects of belladonna alkaloids in 1930. They assumed that the failure of paralysis agitans cases to respond to belladonna alkaloids to the same extent as post-encephalitic patients was due to a combination of difference in anatomical lesion (pallidum in paralysis agitans, substantia nigra in post-encephalitic parkinsonism) and the generally reduced responsiveness of the generally older idiopathic patients to alkaloids. They also addressed the fact that atropine was not the complete solution in a similar manner. The authors accepted Hughling Jackson’s dictum that central structural loss could not lead directly to the production of ‘positive neurological symptoms’, and assumed that the action of hyoscine was to depress a centre which was normally responsible for the physiological suppression of stimulation leading to hypertonia. This explained, on the other hand, its lack of impact on the ‘negative symptom’, bradykinesia. Noting further that bradyphrenia was unknown at the time in paralysis agitans but characteristic for post-encephalitic states, they proposed that the benefit of atropine-class drugs was the result of their rectification of a centrally disturbed autonomic system.

The initial responses to post-encephalitic parkinsonism: attempts to address the viral disorder

Encephalitis epidemica provided an unprecedented stimulus for the investigation of a range of novel approaches to the therapy for parkinsonian syndromes. Felix Stern (Kassel) noted in 1930:

As epidemic encephalitis . . . cut a swathe across the planet, it also provided the impetus for a neurological mass experiment which provided science with a number of extremely curious impulses, and indeed in most areas which concern neurology and psychiatry.

The initial strategy was to devise a vaccine for the underlying viral disorder, according to Ehrlich’s principle of “therapia sterilisans magna”, but the lack of success in this direction led to its being quickly abandoned, although isolated successes with a number of speculative vaccines were claimed. For example, Levaditi prepared a vaccine by injecting rabbits with a herpes virus recovered from a case of epidemic encephalitis, after the animals recovered, the brains were emulsified, sterilized and used as vaccine. Gay’s hyperimmune rabbit brain vaccine was produced in a similar fashion; Gay and Holden also employed formalized herpes virus in this capacity. Neal obtained somewhat encouraging but far from indubitable results with vaccine F, also consisting of formalized herpes-type virus.
V. Encephalitis lethargica: new strategies in the therapy of parkinsonism

Von Economo recommended a variety of measures for the acute phase of the disease which he retained as the more chronic aspects of the disease began to manifest themselves. He was the most prominent representative of the school which saw the sequelae of encephalitis lethargica as evidence of the continued presence and virulence of the pathogenic agent. Until his death in 1931, von Economo valued the intravenous administration of large iodine doses (preferably in the form of 10% sodium iodide or Pregl’s solution) as the optimal approach in both acute encephalitis and during the subsequent parkinsonism. Treatment with iodine had been regarded since the 19th century as appropriate for stimulation of general metabolism; its disinfectant properties (usually as a topical solution) remain its most common application today. Von Economo’s method began with intramuscular or intravenous (of the diluted preparation) administration of the non-specific vaccineurin in saline solution the vaccineurin concentration was gradually raised from 1:250 to 1:10, with a total of twelve injections on alternate days. 1-2g hexamine was administered daily per os. 20mL Pregl’s solution was initially administered; after gradually raising this level, 100mL was injected three times per week until a total of 1000-2000mL had been received. Other forms of iodine could also be employed, with the exception of potassium iodide, which von Economo had found to damage the heart.

This combined iodine-vaccineurin-hexamine therapy was regarded by von Economo as the “classical treatment” in the acute phase of encephalitis lethargica, and he found that it was quite successful, and certainly far superior to any alternative; other remedies, such as trypaflavin or fixation abscess, were tried only if the iodine therapy failed to elicit improvement, and then only in conjunction with its continuation. The iodine treatment was also to occur first place in the therapy of the sequelae, including parkinsonism, in which case it was to be repeated once or twice a year. The method was most effective when the inflammatory process was more dominant than the degenerative, but, as said, von Economo regarded this approach as suitable at all stages of parkinsonism. “If iodine produces no effect”, he concluded, “the hope of arresting or influencing the pathological process is but small”. As adjuncts, arsenic preparations, trypaflavin, radium, colloidal silver, calcium chloride, antiseptics, various hormones, diathermy, injection of air or own serum into the lumbar spine, X-rays, implantation of epithelial (parathyroid) cells as adjuncts could also be tried. The von Economo approach was not associated, however, with great symptomatic relief, and appears to have been employed by other workers only as an adjunct to alkaloid therapy. Von Economo, 1928; 1929; 1931, pp.64-68.  

intrauterine transmission to the fetus of the virus responsible for epidemic encephalitis; this was suggested to him by the case of a 10 year old boy who had developed the full clinical picture of parkinsonism during the previous six years, after having been born eight weeks prematurely in December 1919 to a mother suffering a severe lung inflammation.

Pregl’s solution was prepared according to a “secret formula”, but was supposed to contain about 0.04% free iodine, as well as sodium iodide, sodium iodate and sodium hypoiodite; Frerichs, et al., 1925, p.1541. Lugol’s solution (Liquor iodo compositus) was used similarly, containing 5% w/v iodine and 10% w/v potassium iodide.

Economo, 1928; 1929; 1931, pp.64-68.

Prepared by the Swiss Serum and Immune Products Institute (Bern) from autolyzed Streptococcus pyogenes and Bacillus prodigiosus; Bacillus pyocyaneus was sometimes also used to increase the potency of the preparation. Ludwig et al., 1948, p.982.

Also known as methenamine and urotropine (amongst other names); a urinary tract antiseptic related to formaldehyde, it was commonly applied at this time as a general antiseptic and antibiotic; it is still employed today in urinary tract infections.

Von Economo, 1931, p.151.

“One will quite frequently fail to achieve any success with this method.” Economo, 1928.
Economo was aware that no method offered more than temporary relief, but argued that it was better to attempt anything than "to increase the abulia and akinesis of the patient by leaving him to his fate and thus depriving him of any hope". From the beginning, von Economo was acutely aware of the suggestiveness of encephalitis lethargica victims, and vigorously promoted physical and psychological therapy as an urgent strategy in the prevention of their further decline.

Felix Stern proposed an alternative strategy: He believed that the intramuscular or intraspinal injection of convalescent serum, supplemented by trypaflavin, arsenic or milk injections not only reduced mortality in the acute phase but also hindered progression to the chronic phase of the disorder. He saw no benefit in iodine solutions of any type. Stern claimed that 70% of patients treated in this manner were still working three years after the acute infection; this, however, must be evaluated in the context that the normal mortality rate of encephalitis lethargica was 25-40%, and that the onset of the chronic phase could, even without medical treatment, be delayed by many years. Once the chronic phase had been reached, Stern employed the conventional belladonna alkaloids in combination with large doses of sodium cacodylate. In attempting to reconcile the approaches of the two leading central European authorities on the disorder, the Matheson commissioner Neal concluded that both philosophies could be regarded as forms of "shock therapy".

Treatment with induced fever

Patients suffering general paresis or progressive paralysis had been found in the first quarter of the century to recover a great deal of function following infection with malaria; deliberate inoculation with the causative agent was thus introduced with some success as a treatment for such disorders. Lust treated sleep disturbances in post-encephalitic children with fever therapy in 1921, but Embden appears to have been the first to treat parkinsonian patients with malarial therapy (in 1926), and with some success, although his brief presentation lacked detail. The patients proved resilient to infection, and often required repeated inoculation. Two English clinics reported in 1927 that they had treated a number of post-encephalitic patients with induced malaria on the basis of his experience with the use of the approach in paresis. The neurological rationale for the approach is also interesting:

'It is possible that the after-effects of encephalitis, such as the Parkinsonian state, are due to damage of the basal nuclei and great correlating centres in the mid-brain during the acute phase of the disease. If this is so, no improvement could be hoped for by treatment, as the damage has already been done. On the other hand, there is a feeling that the Parkinsonian state may be due to a gradual invasion or extension of the disease into the mid-brain, and that the disease is still active.'

This early clinical expression of the dynamic nature of the disease aroused the hope in the author that more than palliative treatment of the disorder might be possible. In both experiments, patients were directly inoculated by *Anopheles* mosquitoes, as the authors

77 Von Economo, 1931, p.154. Abulia: loss of will power. Von Economo regarded akinesia as a lack of volition, but also believed that this was an organically determined deficit.
78 Stern, 1928; 1930; 1935.
79 Neal and Bentley, 1932. They also commented: "Moreover, since neither author used controls, it is impossible to draw definite conclusions in regard to the value of either method."
80 Craig, 1927.
were not convinced that injection of infected blood was as efficient. Craig saw no improvement in the motor symptoms of his eight treated patients, but noted some relief from the sialorrhea and depression; McCowan and Cook saw no benefit at all in fifteen patients, and terminated the experiment early due to the rigors of malaria in already enfeebled patients.\textsuperscript{81} Only isolated successes were reported by other workers who tried this approach, and then usually only in single patients. Von Witzleben reviewed the literature concerning this approach in 1942; of 100 cases treated with malaria, one recovery, nine marked improvements and eight deaths (including three of twelve patients in his own care) had been reported.\textsuperscript{82} Malarial therapy was thus abandoned by the end of the 1920s as an option in parkinsonism.

Several similar approaches were also tried. Febrile responses were elicited in post-encephalitic parkinsonian patients (and occasionally in idiopathic parkinsonian patients) by the induction of relapsing fever with \textit{Treponema duttoni} or the administration of influenza antigen.\textsuperscript{83} A similar approach was the induction of protein shock by injection of nonspecific protein, sterile milk or various milk proteins, peptone solutions, typhoid, influenza or diphtheria vaccine, or sulphur compounds, with mixed but ultimately unconvincing results.\textsuperscript{84} The stimulation of artificial fever in paralysis agitans cases with non-specific protein had, indeed, been reported as early as 1914 by Buiä in France, who reported that both tremor and mood had been rapidly improved in five patients by this means. Various combination therapies were also described by individual workers. German doctors in Czechoslovakia, for instance, recommended a therapy which commenced with wafers prepared from powdered root of \textit{Scopolia} and calcium lactate; after 3-6 days, fever (39.5°C) was induced with ‘Phlogetan’ (plant protein), \textsuperscript{85} ‘Xifalmilch’ (fat-free milk containing bacterial protein)\textsuperscript{86} or plain milk. This was followed by concurrent treatment with intramuscular calcium injections (5-10×10mL at 2-3 day intervals) and oral ‘Bellafolin’ (if the patient could afford this very expensive belladonna leaf alkaloid preparation).\textsuperscript{87} Stransky administered typhoid vaccine together with 200mg sodium caffeine benzoate on the basis that caffeine would accelerate the elimination of the infectious agent.\textsuperscript{88} The production of a “fixation abscess” by subcutaneous injection of turpentine or some other irritant in order to elicit fever was also practiced,\textsuperscript{89} not differing a great deal from Elliotson’s cultivation of pus production with setons almost a century earlier. Netter had discussed a version of this therapy before the Academy of Medicine in Paris as early as 1920; after methenamine had been administered, the patient is treated with “jaborandi salivary secretions, which contain considerable proportions of a pathogenic agent”. In more severe cases, “heroic measures” had to be taken; ‘terebenthine’ (turpentine oil) was employed to elicit an

\textsuperscript{81} McCowan and Cook, 1927.
\textsuperscript{82} Witzleben, 1942, pp.69-71.
\textsuperscript{83} For example, Höglund and Sjögren, 1931.
\textsuperscript{84} Freeman, 1927; the discussion of this paper is especially interesting, as various physicians describe the different approaches they have tried in post-encephalitic parkinsonism. See also Schrøder, 1929; Abramson, 1935; and review in Neal and Bentley, 1932.
\textsuperscript{85} Pharmazeutische Werke “Norgine”, Prague.
\textsuperscript{86} Sächsisches Serumwerk, Dresden.
\textsuperscript{87} Lampl, 1928; 1929. ‘Bellafolin’, introduced by Sandoz in 1924, was the first commercial total alkaloid extract of the leaf, analogous to ‘Pantopon’ (Hoffmann-La Roche), a total poppy extract. It was recommended as a general parasympatholytic agent, particularly in instances of spasm, hypersecretion or extrapyramidal motor disturbance; it was, as mentioned, extremely expensive, to the point that this drawback was mentioned in many of the published reports of its use.
\textsuperscript{88} Stransky, 1931.
\textsuperscript{89} Darrach \textit{et al.}, 1929, pp.151-152.
artificial abscess “which concentrates all septic matter in the body”. Interestingly, Trousseau had achieved some improvement of parkinsonian symptoms with high doses of turpentine oil and hydrotherapy, although conceding that he had never actually cured a patient by these means.

Fever production by hot baths (43.3°C; mean 45min/day for 14-28 days) was also employed. Body temperatures of 41°C could be achieved in this manner; tremor and oculogyria, but all parkinsonian symptoms were reported to be significantly reduced thereafter.

Wielinski introduced a method in 1927 for the production of fever by electrical means (electropyrexia), a method further developed in America by Neymann. The approach was not without danger, particularly in patients with heart disease or arteriosclerosis, but some success in the control of rigidity, tremor and oculogyric crises was claimed: “the progress of the disease is delayed or may even be checked after twenty treatment sessions with electropyrexia.”

Post-encephalitic patients were treated twice a week; their body temperature was raised to 40°C, which was claimed to improve cerebral circulation and thus antibody transport to the brain. No success was found in the treatment of paralysis agitans.

The emphasis then moved from cure and acute therapy to symptomatic treatment, although there could be an overlap between the two approaches: Eden and Yates (Queen’s and Nerve Hospitals, Birmingham and General Hospital, Wolverhampton), noting the florid nasal discharge in post-encephalitic syndromes, assumed that the causative catarrhal virus remained in the nasal passages of victims, and was constantly being resorbed across damaged epithelium. They therefore washed the sphenoidal and posterior ethmoidal sinuses with saline (following anesthesia with 5% cocaine in 1:1000 adrenaline), administered a medicine dropper of a mixture composed of menthol (130mg), eucalyptol (1.23mL) and liquid paraffin (120mL) to each nostril three times a day, and inoculated the patient with vaccines directed against nose and throat organisms. They claimed some success against some parkinsonian symptoms with this method.

**Radiation therapy: X-ray and ultraviolet therapy**

Roentgen therapy has been tried several times in post-encephalitic parkinsonism. The rationale behind this approach was that irradiation improved cerebral perfusion, particularly in the basal ganglia, and suppressed inflammatory processes. Marburg and Sgalitzer published a volume in 1930 on the treatment of central nervous disease with

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90 Netter, 1920b; see also Netter, 1920a It was reported in the *New York Times*, 1 April 1920: “Treats sleeping sickness. French doctor has new method based on discovery by Hippocrates”; Netter had been inspired to employ abscess therapy by Hippocrates’ use of the technique in the ancient disorder lethargos, which Netter identified with encephalitis lethargica. Passages cited by Netter are actually from the *Prognoses of Kos* (II, V), a pre-Hippocratic text noted to be confused with the more famous *Prognostikon*.
92 Pouppirt, 1929.
93 Neymann, *Artificial fever produced by physical means; its development and application* (Springfield, 1938), cited in Witzleben, 1942, p.73.
94 Witzleben, 1942, pp.72-73.
95 Eden and Yates, 1927.
X-rays; they reported that irradiation has a beneficial effect on inflammatory diseases, including those of the brain, despite the fact that this tissue is highly resilient to the effects of X-rays.96 It had also been noted by several authors that the skin of post-encephalitic patients is unusually sensitive to X-rays.97 Some workers also believed that irradiation increased the “bactericidal power of the blood serum” and destroyed white blood cells at the inflammation site.98

The method developed by the Viennese radiologist W. von Wieser for the treatment of post-encephalitic parkinsonism was commonly used in the German-speaking world and elsewhere. X-rays of 180-200 kilovolt were filtered through 0.5mm zinc and 1mm aluminium; skull areas of 6-8cm diameter and 6cm wide along the vertebral column were irradiated with a focal distance of 30-50cm. A treatment series consisted of up to 12 sessions; in each session, one exposure area was irradiated (30-60 rads), or two in milder cases (150-200 rads); irradiation of skull and spinal areas was alternated. Rest periods of 2-3 months were interposed after an 8-10 week course.99 Radiotherapy enjoyed a brief vogue in France around 1923, but the results were inconsistent, and the method abandoned.100 The results in Germany were similarly disappointing; for example, Kürbitz and Lange reported mild success in four of nine patients treated according to the von Wieser method.101 As late as 1939, however, Günther vor der Brück (Psychiatric and Neurological Clinic, Cologne) reported that his clinic had used high dose radiation therapy to stimulate atrophic ganglion cells in most post-encephalitic patients since 1933, with some success. Variations on the von Wieser method were also reported; for example, Kohlmann achieved success in four of seven paralysis agitans patients but none at all in post-encephalitic cases,102 while Kiss and Szirmák targeted the superior thoracic ganglion and elicited improvement in rigor, tremor, akinesia and sialorrhea in six post-encephalitic and two paralysis agitans cases.103

X-ray treatment of post-encephalitic parkinsonism was tried in America in the 1930s without notable success.104 Goldberg, Baker and Hurff (Presbyterian Hospital, Newark), on the other hand, reported some success with the treatment of the acute phase of encephalitis lethargica using the technique; the rationale for their approach was their belief that the essential lesion of the infection was the perivascular mantling by small cells and that the early symptoms were due to central circulatory consequences of perivascular lymphocytic infiltration, cells which are highly sensitive to the effects of radiation.105 Rubenfeld and Wolf (Bellevue Hospital, New York) hypothesized that irradiation might be of benefit in the advanced stages of the disease if vascular

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96 Marburg and Sgalitzer, 1930.
97 For example: Appelrath, 1924, Witzleben, 1942, p.77.
98 Pansdorf and Trautmann, Ueber die entzündungswidrige Bestrahlung des Gehirns (Röntgenpraxis 2: 393ff., 1930), cited in Witzleben, 1942, p.79. Panegrossi, who introduced the Bulgarian therapy to western Europe (see next chapter), supported electrotherapy as providing at least temporary relief; Panegrossi, 1940, p.37.
99 Von Wieser, 1929.
100 L.R., 1949.
101 Kürbitz and Lange, 1932.
102 Kohlmann, 1931.
103 Kiss and Szirmák, 1934.
104 Meyers, 1942.
105 Goldberg et al., 1934. The authors recorded their belief that their investigation represented the first trial of X-ray therapy in encephalitis lethargica.
hyperemia and dilatation could be achieved; the application of up to 400 rads twice weekly to seven patients, however, resulted in nothing more than loss of scalp hair.\textsuperscript{106}

Two French groups re-examined X-irradiation therapy in 1948. Both groups adopted the same protocol: penetrating rays of 200 kilovolt, filtered by 0.5mm copper and 2mm aluminium (for rigidity: 160kV, 5mm aluminium); current, 4-8mA; focal distance, 40-60cm; irradiation of entire head from various angles, with an a dose of 50-150 rads per session, twice a week, rising to a total of 1000 rads per field if tolerated. Tardieu achieved good results in 11 of 15 patients and slight improvement in a further two; May and Adam achieved clear benefits in 5 of 12 patients and slight improvements in a further three. Post-encephalitic patients responded better than idiopathic or arteriosclerotic cases, the rigidity better than the tremor; the improvement was maintained in some cases for six months. A commentator in the \textit{Presse médicale} noted that much higher doses of radiation were tolerated in the treatment of brain tumours, so that the therapy, which could be combined with pharmacological treatment, could be recommended as safe.\textsuperscript{107}

Bruce noted in 1954 that should sialorrhea not be controlled by belladonna alkaloids, it could be reduced by X-ray irradiation of the salivary glands.\textsuperscript{108} This had first been demonstrated by Manfred Fraenkl during the First World War, and employed by him to reduce sialorrhea in post-encephalitic parkinsonism; he noted, however, that it did not modulate the motor symptoms of the disorder.\textsuperscript{109}

Ultraviolet radiation was also investigated in the treatment of parkinsonism. Jaffé (Nottingham Sun-Ray Clinic) treated 40 post-encephalitic patients with “general body radiation” in the 15 months from January 1926. The patients were exposed front and back to mercury vapour lamps (10 minutes, twice weekly) for a period of six to seven weeks; the course was repeated as necessary at monthly intervals. Thirty-five cases were claimed to exhibit marked improvements in muscular co-ordination and control.\textsuperscript{110} Fawcitt also reported improvements in “gait, feeling of well-being, diminution of salivation, and relaxation of the fixed expression of the face” in a number of patients similarly treated; he supplemented the usual sun-room treatment in some patients with local applications to nose and throat.\textsuperscript{111}

\textbf{Serum therapies}

Animal experiments had indicated that the injection of own serum irritated the meninges, resulting in hyperemia and thus better perfusion of the adjacent parenchymal tissue, and an increase in cell numbers in the cerebrospinal fluid; such an effect was most noticeable precisely in those areas damaged in post-encephalitic parkinsonism. Pette inactivated 30mL of the patient’s blood and injected 10mL of sterile serum into the spinal canal; a small rise in temperature (38C) and increase in leucocyte number (4000.µg–1) persisted for about a week following treatment. Improved speech and mobility accompanied these changes in eleven of twenty-three patients.\textsuperscript{112}

\textsuperscript{106} Rubenfeld and Wolf, 1939.
\textsuperscript{107} L.R., 1949.
\textsuperscript{109} Fraenkel, 1923.
\textsuperscript{110} Jaffé, 1927.
\textsuperscript{111} Fawcitt, 1927.
\textsuperscript{112} Pette, 1926.
technique was reported by several workers to be useful at the early stage of chronic encephalitis, but the best effects were inevitably achieved in the years immediately following infection. The approach gradually fell into disuse during the 1940s as the mean age of the post-encephalitic patient population increased.

Injection of convalescent serum had been employed by some physicians since the beginning of the epidemic, but, as noted by Neal (Neurological Institute, New York) was conceptually flawed, as it was clear that ‘recovering’ encephalitis patients were scarcely able to produce sufficient antibody to protect themselves; further, their immune system was often, in fact, severely compromised. Injection of serum from animals inoculated with a “somewhat peculiar streptococcus” from the tonsils, teeth and nasopharynx of encephalitis lethargica patients (‘Rosenow’s serum’ or of Gay’s herpes hyperimmune rabbit serum was employed by those who subscribed to either of the related etiological theories of encephalitis lethargica. Neal reported that a comparison of the effectiveness of the various sera in 500 patients treated for up to five years – at the commencement of the trial, a control, non-immune rabbit brain serum was also used – indicated that no spectacular successes could be achieved, but some improvement was noted in patients receiving either Gay’s or Rosenow’s preparations, with the former marginally more effective. The benefits obtained, however, were not sufficient to counteract the disenchantment which most physicians developed with respect to this approach by the end of the 1930s.

Miscellaneous therapies directed against the presumed viral basis

A number of strategies derived from current views on the management of viral or inflammatory illnesses were also tried in an effort to reduce the effects of the unknown virus or at least to contain its access to the brain. As none proved to a consistent success, I list them here briefly for the sake of completion:

- **Hexamine** (i.v. and intrathecal): as mentioned above, a urinary tract antiseptic related to formaldehyde, it was popularly applied at this time as a general antiseptic and antibiotic. An investigation into the treatment of post-encephalitic patients criticized the use of hexamine on a routine basis as being based on nothing more substantial than habit.

- **Trypaflavin** (= acriflavin): this antiseptic dye was initially employed in the treatment of cystitis, pyelonephritis, influenza and pneumonia. Its use was extended by analogy to encephalitis lethargica. Lasting improvements in akinesia, rigidity and bradyphrenia were reported as its most consistent effects, tremor and salivation were less responsive. Its effect was attributed to its bactericidal effects, although some regarded it rather as a non-specific irritant.

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113 See Tucker, 1924; Witzleben, 1942, pp.55-58.
114 For example: Marinescu and Drăgănescu, 1921.
115 Neal and Bentley, 1932.
116 Rosenow, 1923. Rosenow believed to have replicated some of the symptoms of encephalitis lethargica in animals by infection with this streptococcus (S. viridans). Evans and Freeman isolated the same organism from post-encephalitic patients in 1926; cited in Freeman, 1927.
117 See Neal, 1934.
118 Neal, 1934.
119 Darrach et al., 1929, pp.176-177.
120 Buß and Peltzer, 1924; Marx, 1927.
sodium salicylate (i.v.): salicylate had been first prepared from a glycoside of the European willow by Piria in 1838, and both sodium salicylate and other derivatives (most notably acetylsalicylate, prepared in 1859) were regarded as panaceas. Manschot had recommended salicylates for pain associated with paralysis agitans as early as 1904 (indeed, as the only drug he suggested for the disorder). Sodium salicylate was generally employed as a means of reducing fever and as an antiseptic. Several workers reported that the salicylates were of benefit for tremor if rigidity was absent, but it was generally not regarded favorably by the 1930s.

colloidal gold and silver; ‘Sanocrysin’ (gold plus sodium thiosulphate) was used for rheumatism and syphilis, but also for a number of neurological diseases, including multiple sclerosis. Felix Stern lamented in 1933 that it had largely been ignored in the treatment of post-encephalitic conditions.

magnesium chloride (i.m.) was found to reduce muscle tone without otherwise benefiting parkinsonian patients. Magnesium sulphate (i.m.) and magnesium thiosulphate together with calcium chloride (i.v.) were also reported to be of some benefit.

repeated lumbar puncture and drainage or intravenous administration of hypertonic dextrose or iodide solution aimed to reduce intracranial pressure.

‘Metrazol’ shock therapy: the Ziskinds improved oculogyric crises in a single patient through the induction of five successive epileptic seizures.

Intralumbar injection of any of the above agents was also undertaken in an effort to bring the substance in direct contact with the brain tissue. Lumbar anesthesia, suboccipital injection of air into the brain, and the intralumbar injection of serum or cerebrospinal fluid were all tried with the aim of improving cerebral circulation. Some positive results were reported, especially with respect to rigidity, but not sufficiently consistent as to justify such invasive and often dangerous means. Endolumbar injection of the patient’s own serum or cerebrospinal fluid was also investigated by those who sought a causal therapy but regarded antiviral or antibacterial approaches as futile:

According to our view, we can not reasonably expect in the vast majority of cases success from an antibacterial or immunologically based therapy. More appropriate here is rather a therapy which aims to improve the circulatory system in those brain regions which are anatomically damaged and thus function only inadequately.

Amongst other substances injected intralumbarly in the therapy of post-encephalitic were phenolsulphonphthalein, normally employed as a diagnostic aid in nephrology, and tetrahydroatophan (dihyronaphtacridine carbonic acid, tetrophine or ‘Tetrophan’; Riedel-Häen, Berlin-Britz). The aim was to induce a sterile meningitis, so that these approaches might be seen as allied to induced fever therapies.

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121 Issekutz, 1971, pp.50-51.
122 Epstein et al., 1927/28; Lévy and Pierffa, 1934.
123 Dansk Chemo-Therap. Selskab, Copenhagen; usually used in tuberculosis, asthma and joint rheumatism; Ludwig et al., 1948, p.824.
124 Fuller, 1926; Stern, 1933.
125 Reviewed: Durrach et al., 1929; Neal and Bentley, 1932; Witzleben, 1942.
127 Hall, 1926.
128 Stark, 1932; Boschi, 1937; Mercks Jahresbericht for 1938, p.252.
A number of substances regarded as general tonics were also tried in post-encephalitic parkinsonism without great success. Arsenic preparations were especially popular in the 1920s. Sodium cacodylate, sodium arsanilate (‘Atoxyl’) and ‘Salvarsan’ \(^{129}\) (i.m.), much used in the 1920s in the treatment of syphilis, were the preferred forms of arsenic for the treatment of post-encephalitic conditions. The doses employed in paralysis agitans, however, were much higher than for syphilis; intravenous doses of 100mg.kg\(^{-1}\) body weight were usual, leading, not unexpectedly, to toxic symptoms including emesis, delirium and even hallucinations. Although not undangerous, many workers reported positive experiences with the agent.\(^{130}\) A few years later, however, the number of deaths resulting from the therapy caused a shift from high dosage schemes.\(^{131}\) Until the early 1930s, arsenic cacodylate was nevertheless praised by some as relieving rigidity and sialorrhea and improving mood and weight.

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\(^{129}\) Arsenamine or diamino-dioxyarsenobenzol hydrochloride (patent to Hoechst: 1911). Introduced by Ehrlich in 1909 for the treatment of syphilis, he renamed what was hitherto known as ‘Ehrlich-Hata 606’ with the title ‘Salve Arsen’ (healthy-giving arsenic); popularly known as the ‘magic bullet’.

\(^{130}\) In the *Mercks Jahresbericht* for 1917-21 (English edition; pp.85-86), it was concluded in summary of a list of reports that the “initial results . . . were almost invariably good”, but were not sustained after withdrawal of the drug.

\(^{131}\) *Mercks Jahresbericht* for 1924, pp.148-149.
but was regarded by others as further undermining a compromised nervous system.\textsuperscript{132} Orbach (Neurology, Friedrich Wilhelm Hospital, Berlin), who achieved satisfactory results with 0.25-1g of a 50\% solution (i.v., 3 times per week), suggested that its benefits were achieved via induction of local venous hyperemia in damaged brain tissue, facilitating possible repair processes. Alternatively, it might be acting upon the autonomic nervous system, as both “paralysis agitans and parkinsonism . . . are ultimately disorders of the vegetative nervous system”\textsuperscript{133}.

Other chemical therapies employed at this time included:

- \textit{Calcium preparations}: injected together with parathyroid extract, vaccineurin and sodium cacodylate,\textsuperscript{125} or with phenobarbital.\textsuperscript{134} “Calcibronat” (calcium bromolactobionate; introduced by Sandoz in 1933) was reported to be especially useful for the relief of oculogyria.\textsuperscript{135}

- \textit{Mercury preparations}: first recommended for parkinsonism by Parkinson himself and one of the oldest medications in Europe, often used in the 1920s for the treatment of syphilis, especially in the form of mercuric cyanide or mercurchrome-220 soluble. Mercury salicylate, also used to treat syphilis, had been suggested for paralysis agitans as early as 1970.\textsuperscript{136} Paasche (Warstein) recommended intragluteal injection of 1mL 1\% mercuric oxycyanide, a highly toxic topical antiseptic, on alternate days for twenty days, the course to be repeated after a two week pause.\textsuperscript{137}

- \textit{Oxygen}: 300mL was injected into the thigh, into which was also injected 1mL of 1\% potassium permanganate; oxygen was also inhaled three times a day (‘oxytherapy’). The author claimed improvement of movement and delayed progress of the disorder.\textsuperscript{138}

- \textit{Strontium bromide} was administered intravenously (10-20mL of a 10\% solution or 5-10mL of a 20\% solution) by Mann to post-encephalitic patients suffering tremor, rigidity or clonus; relief lasting a few hours was reported.\textsuperscript{139} Alwens (Sandhof City Hospital, Frankfurt am Main) noted that, like magnesium, strontium exerted a curare-like action on peripheral nerve endings, although not aspotently; a mild influence on cortical excitability had also been demonstrated.\textsuperscript{140}

Froment and colleagues reported great success in 1930 with the use of insulin in post-encephalitic parkinsonism. The basis for this approach was an assumed acidosis in post-encephalitic parkinsonism; insulin (10-15 units per day) was hypothesized to correct this situation and to restore normal basal metabolism. This allowed the relaxation of muscular rigidity, which the workers believed to underlie the entire symptomatology of parkinsonism. The effect on the general health of the patient was salutary, and it may have acted synergistically with hyoscine in the relief of rigidity.\textsuperscript{141}

\textsuperscript{132} Reviewed: Porro, 1920; Boveri, 1925; Durrach et al., 1929; Neal and Bentley, 1932; Witzleben, 1942.
\textsuperscript{133} Example of individual study with moderate success: Mella, 1922.
\textsuperscript{134} Orbach, 1924.
\textsuperscript{135} Reviewed by Loew, dismissed by Curschmann: cited in Gamper, 1936, p.801.
\textsuperscript{136} Duensing and Meyer, 1939.
\textsuperscript{137} Mercks Jahresbericht for 1907, p.131.
\textsuperscript{138} Paasche, 1925. See also Ornstein and Orestianu, 1930 (with a success rate of one patient from sixteen).
\textsuperscript{139} Sepp, 1927.
\textsuperscript{140} Mann, 1924.
\textsuperscript{141} Reviewed in Alwens, 1924.
\textsuperscript{142} Froment and Mouriquand, 1929; Froment et al., 1929, 1930; Froment, 1930. See also Pfanner, 1931; this worker applied 10IU ‘Iloglandol’ (Hoffmann-La Roche) per day with some success.
Vitamin therapy was attempted in parkinsonism for the first time at the end of the 1930s. The employment of pyridoxine will be discussed in the next chapter, as it became more popular in the 1950s. In 1939, Gangl and Lucksch (German Psychiatric and Neurological Clinic, Prague) noted that the regions affected in post-encephalitic parkinsonism were also those which had recently been identified as being richest in vitamin C. It was reported that a patient who had suffered attacks of oculogyria, rigidity, anxiousness and stupor 5-6 times per month following encephalitic fever had been successfully cured with calcium supplements; even the previously reduced stomach acidity was restored to closer to normal levels. This impressive result, however, remained anecdotal.\(^{142}\)

In brief, however, none of these often imaginative approaches proved to be of long term benefit for any of the parkinsonian symptoms of post-encephalitic patients. They continued, however, to be employed in clinics in the absence of alternatives and as a means of maintaining both the general well-being and morale of the patient. This lack of success was registered with disappointment, but was hardly surprising; as noted by Neal, there was no indication that any intervention was particularly capable of reducing the mortality associated with the acute phase of the infection, so that arresting the further, unpredictable progression of the disease represented a Herculean task.\(^{143}\)

**Pharmacological intervention in post-encephalitic parkinsonism: symptomatic treatment**

There no notable innovations in the pharmacological therapy of parkinsonism during the first five years of the epidemic encephalitis. In general, clinicians applied the same drugs which they had been employing in paralysis agitans with limited success since the previous century; conversely, each new suggestion for post-encephalitic parkinsonism was also tried in paralysis agitans patients, with varying degrees of success.\(^{144}\) In a 1923 presentation, Nonne could discuss the therapy for post-encephalitic parkinsonism in just a few words: scopolamine and atropine were the major available choices, but their effects faded rapidly, while Pregl’s solution, nonspecific protein therapy and von Economo’s urine vaccine treatment were all ineffective.\(^{145}\) In a paper read to the Ulster Medical Society in 1925, Gardner Robb noted with astonishing frankness:

> Many of the treatments suggested, and even enthusiastically recommended, can only be described as weird in the extreme. Yet I fancy most of us who have been called upon to treat any considerable number of cases have, doubtingly, employed some of these extraordinary treatments, the rationale of which we could not see, only quickly to abandon them.\(^{146}\)

Robb then mentioned a number of “weird” therapies which he had tried for the acute phase of the disorder, amongst them frequently repeated lumbar puncture and drainage

\(^{142}\) Gangl and Lucksch, 1939.  
\(^{143}\) Neal and Bentley, 1932.  
\(^{144}\) For example, Wilson tried lecithin, phytin, phosphorus and gonadal extracts, all of which experienced renewed interest following the encephalitis lethargica epidemic, in paralysis agitans cases, in each case without success; he also had acquaintances who had similarly failed with ligation of the vasa deferentia or the compound lymph serum of Loewenthal. He regarded paralysis agitans as essentially incurable, and also saw the potential for symptomatic relief as limited. Wilson, 1954b, pp.938-939.  
\(^{145}\) Cited in von Witzleben, 1938a.  
\(^{146}\) Robb, 1925.
and injection of the patient’s own cerebrospinal fluid, and concluded that only hyoscine
\((3 \times 1/100 \text{ grain/day})\) relieved the symptoms, and then only temporarily. The Rostock
neurologist Hans Curschmann introduced his discussion of therapy with the comment
that “In the majority of cases, therapy has proved to be useless” and concluded with
“Morphine, in not too small doses, will be a ‘solamen miseris’ towards the end.”
In between, the same remedies listed by Oppenheim in 1905 continue to find less than
enthusiastic endorsement; only the effect of hyoscine on tremor is mentioned with
praise, and then only if the patient can tolerate the toxic side-effects which accompany
long-term use, such as dryness of the mouth and visual disturbances. Curschmann
recognized that parkinsonism secondary to encephalitis lethargica was not identical
with paralysis agitans; the therapy for both disorders, however, was both similar and
similarly ineffective.

The comprehensive results of the New York Matheson Commission investigation
into the etiology, treatment and epidemiology of epidemic encephalitis published in
1929 listed over 70 types of therapy which had been tried at various stages of the
disease. It is clear from the summary of the evidence for each therapy that most reports
concerned only single cases; the authors of the report adopted a somewhat wry attitude
to the standard of scientific work adopted by many workers, as illustrated by the
following example:

\textit{ARNICA (TINCTURE OF): There was only one reference to this drug, and it was
apparently used in only one case. The effect was not stated. The conclusions to be
drawn are obvious.}\footnote{Durrach \emph{et al.}, p.141. Arnica, which is highly irritant, was traditionally employed in some parts of
Europe for adynamic fevers, chronic rheumatism, in nervous and paralytic disorders, and for cases of
general debility; Scoresby-Jackson, 1880, pp.279-280.}

Many of the treatments tested around the world seem quite bizarre in retrospect:
there were, for example two cases of subcutaneous administration of turpentine (without
the intention of procuring a fixation abscess), and one of its being applied intraspinally
– with fatal results. The intradermal application of phenol (1mL of a 3% solution) along
the spine and the use of picrotoxin were both described by the commissioners as
\textit{‘without logical foundation’}.\footnote{Durrach \emph{et al.}, pp.162 and 163; one case each.}
The most employed agent in encephalitis lethargica
was hexamine (331 reports), more in the early phase than the chronic phase of the
disease; of these, 166 reports were positive with respect to outcome and 101 were
unfavorable or doubtful.\footnote{Ibid., pp.176-177. For reasons which are not clear, the sum of ‘favorable’ and ‘unfavorable’ reports
did not always equal the total number of reports examined; the sum could be greater or lower than the
total number.} Nevertheless, the Commission regarded the use of this agent
as largely a matter of habit and suspected that it might be acting only as a placebo.\footnote{The term ‘placebo’ referred since at least 1811 to a drug intended to placate rather than treat the
patients (Oxford English Dictionary). It thus differs from the modern use of the term; Gaddum, in
fact, objected in 1954 to the growing use of the term to describe what he termed ‘dummy’ tablets used
in clinical trials. The term ‘placebo’, incidentally, has little direct connection with its Latin meaning
(‘I shall please’); it had entered English in the 12th century as a colloquial reference to prayers for the
dead (‘\emph{Placebo Domino in regione vivorum . . .}’), but by the 14th century had also come to mean
‘flattery’. By the end of the 18th century, it indicated an act which aimed to placate. From here it
the basis of the number of reports available, the numbers of patients involved and the apparent quality of work, the Commission could only recommend, with reservations, atropine (54 of 75 references positive), bulbo-capnine (for tremor; 7 of 9 positive), hyoscine (66 of 88 positive), phenobarbital (17 of 28 positive), “physiotherapy” (34 of 73 positive), scopolamine (101 of 131 positive; the Commission ranked it equally with hyoscine, seemingly unaware of their identity) and stramonium (13 of 15 positive). Four positive reports of the influence of nicotine on tremor at the expense of increased rigidity were balanced against the fact that its beneficial effect was no more impressive than that of hyoscine. The use of intravenously injected iodides in various forms was widespread, but the Commissioners found the results inconclusive; they recommended that it be further investigated with better controls. It will be noted that the agents recommended by the Commission applied principally to the parkinsonian signs of the chronic phase of the disease. Only the salicylates were regarded as useful in the acute phase of the disorder, maintaining "their reputation for universal service in the treatment of a wide range of symptoms." The Commission lamented the lack of appropriate controls in the vast majority of studies and noted that detailed records of patients and responses were usually published only for agents used in the treatment of parkinsonism.

The second report of the Matheson Commission (1932) noted that nothing new had been added to knowledge of the disorder since the first; longer experience meant, however, that the drugs of choice had been reduced to belladonna and allied agents, hyoscine, scopolamine, bulbo-capnine and stramonium.

**Psychological factors and antiparkinsonian therapy**

It is appropriate at this point to address two aspects of the treatment of parkinsonism which would be significant in the coming years. The first was the idea that parkinsonian patients, particularly post-encephalitic patients, were especially susceptible to the power of suggestion. This confounded the interpretation of drug trials, as it was often suggested that patients were responding more to the hope of a cure than to an actual effect of the particular agent. This was also the reason why so much effort was devoted by some workers to devising an “objective means” of defining the response to any drug; that is, an appropriate means by which tremor or rigor could be measured before and after treatment. The identification of a particular sign which could be employed to measure the effect of a drug was also tried; for example, J.S. Harris found that the patellar reflex was abnormal in post-encephalitic patients, but was normalized by hyoscine (but not by stramonium). Beyerman and Leicher (Provincial Hospital, Santpoort) described a study in which seven parkinsonian patients were subjected to a panel of motoric (ergogram curves, dynamometric assessment of grip, speed of movement) and psychological tests. The motor tests indicated that greater improvement was achieved by hyoscine than by ‘Bellafolin’ or atropine therapy; an impact of alkaloid therapy on psychological parameters was not noted except with regard to the

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153 Including: 8 of 28 for electrotherapy, 12 of 20 for radiotherapy, 7 of 11 for X-ray therapy and 7 of 14 for hydrotherapy; the Commission noted that benefits seemed mostly linked with "general exercise, swimming and reéducation of muscles"; Durrach et al., p.163.
154 Ibid., pp.165-166.
155 Ibid., pp.136-178.
156 Reviewed in Anonymous, 1932a.
157 Harris, 1927.
speed with which mathematical subtractions were performed. Novel devices for measuring the severity of parkinsonian symptoms have continued to be introduced and abandoned until the present. Many workers, in the absence of such a tool which was accepted by more than a small group of workers, abandoned the idea of “objective measurement” entirely, and simply assessed in a subjective fashion the ability of patients to perform normal tasks of daily living. Yet other workers, denied that suggestibility was a positive factor; these patients had suffered so many disappointments, they argued, any new therapy was approached with the greatest skepticism:

*In order to score the results in as objective a manner as possible, it was necessary to eliminate or temper the rather prevalent factors of wishful enthusiasm in those attempting the use of a new drug, or the cynical attitude of futility observed in some patients and their families.*

One of the earliest clinicians to express definite thoughts on the suggestibility of his post-encephalitic parkinsonian patients was Arthur J. Hall (Medicine, Sheffield University). In 1926, he wrote that the belladonna alkaloids undoubtedly had physiological effects on his patients, but that psychological factors were also involved:

[*I*]t must be admitted that the bulk of the improvement is something inherent in the patient’s nervous system – an auto-suggestion set going by a feeling of release from some constant oppression. In these cases the oppression is described by the patients as the effort required to perform any action. Directly even the slightest relief is felt from that a condition of ‘euphoria’ is produced, which extends its beneficent influence over every part.

Hall thus saw a part of the action of the medicinal agent as consisting of a change in the morale of the patient brought about by a subjective or objective improvement in physical condition. From the 1930s onwards, it was often noted that amphetamine and related agents, best known for their euphoric effects, were relatively ineffective in the treatment of parkinsonism as monotherapies, but were useful as mood-altering adjuncts to anticholinergic therapy. Vollmer noted in his examination of the Bulgarian treatment that the first symptoms to respond were the rigidity and the mood of the patient, and that relief from rigor was clearly accompanied by a significant rise in spirits.

Hall also appears to have been one of the first to emphasize the akinesia of the disorder. In fact, he stated explicitly that “the most characteristic feature of Parkinsonism is the extreme slowness of action.” He noted that in cases where the parkinsonism was unilateral, the patient was usually aware of the deficit on the afflicted

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158 Beyerman and Leicher, 1929.
159 For assessment of tremor: Edwards and Bagg, 1923; Agate *et al.*, 1956; Brumlik *et al.*, 1964; Clarke *et al.*, 1966; Shahani and Young, 1976; see also the device described and depicted in the discussion by Goetz of Charcot’s 1888 lecture on parkinsonism without tremor (Charcot, 1987, pp.132-133). For rigidity: Carmichael and Green, 1928; West, 1932; Agate *et al.*, 1956; Brumlik *et al.*, 1964. For bradykinesia: Hall, 1927. For history of methods for assessment of muscle tone, see Walsh, 1992. See also discussion in Schwab and Prichard, 1951.
160 Moore, 1951; see also Budnitz, 1948.
161 Hall, 1926.
162 Vollmer, 1940.
163 Hall, 1926. As already mentioned, Jaccoud used the term ‘akinesia’ with respect to parkinsonism in 1873, but it was the attention given it by Wilson in the symptom (1925a) which revived active recognition of the symptom.
side, as the healthy side served as a gauge for comparison; in bilateral parkinsonism, however, it was quite common that the patient was completely unaware of the degree of bradykinesia which affected them, despite the fact it was often the sorry lot of a member of their household to assist them perform their normal activities. Hall investigated this problem by constructing a device for measuring the speed with which a patient repeatedly moved their arm from side to side over a distance of 45cm, with an obstacle of about 12cm height between the two endpoints. He established by these means that slowness of movement was detectable even in an arm in which tremor and rigidity were absent; this implied that the presentation of akinesia was independent of hypertonia. This was of crucial importance: the “condition of the peripheral motor apparatus” (Hall) might exacerbate the effects of akinesia, but the latter symptom was in principle determined centrally and independently of rigidity. Wilson and Cruchet had argued similarly. Nevertheless, this acute observation, while often cited in handbooks, does not appear to have had much impact on those investigating the therapy of parkinsonism; akinesia, when considered at all, is treated either as a minor symptom or as secondary to muscular stiffness. Interestingly, Hall found that the effect of belladonna or hyoscine on akinesia was small (maximal increase in speed: 25%), but was usually equal in both arms.

Given that the patient was unlikely to complain about this aspect of the disorder, and that akinesia could in any case be conceptually subsumed by the physician under the aspect of rigidity, it is perhaps understandable that this symptom was overlooked for so long. On the other hand, it is probably no coincidence that the symptom which derived least benefit from drug therapy before the arrival of L-DOPA was akinesia, often described as a “negative symptom” of the disorder. The remark by Medawar that “present skills are sufficient for present ills” might be pressed into service here: akinesia was not only more difficult to understand, but also nigh impossible to treat, and was therefore largely ignored in the assessment of new agents. England and Schwab wrote in 1959 that akinesia was actually the most disabling feature of the disorder, although not as spectacular as tremor; it was the symptom which rendered the patient dependent on outside support, and was also the least responsive to any form of therapy. It must also be remembered, however, that tremor was reported by most patients as the symptom which detracted most from their quality of life; many were totally unaware of their a- or bradykinesia until it was brought to their attention by relatives or their physician. The neurosurgeon Meyers rated the importance of the various symptoms to the post-encephalitic patient in the following order: tremor, oculogyric crises and other involuntary movements, disturbance of speech and writing, bradykinesia and rigidity, weakness, mask face, sialorrhea, drowsiness, depression and muscular pain. His major complaint about pharmacological approaches was that tremor was less amenable to chemical treatment than rigidity.

**Hyoscine/Scopolamine**

The same solanaceous alkaloids were applied to the therapy of the parkinsonian sequelae of encephalitis lethargica during the early 1920s; ‘hyoscyamine’ (as noted above, consisting in large part of hyoscine) continued to be the drug of choice in many

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164 Cruchet, 1925; Wilson, 1925b.
165 Hall 1926.
166 Martin et al., 1962.
167 Meyers, 1942.
countries for the management of tremor and rigor. ‘Scopolamine’ as a drug for use in parkinsonism was first mentioned by this name in a publication by Guido Avezzù in 1921, who introduced it into the therapy of post-encephalitic parkinsonism; he thought it natural that a drug which worked in paralysis agitans would also benefit similar symptoms in post-encephalitic cases. Scopolamine had been recommended by himself and A. Spanio at the recent medical congress in Naples as the ideal choice for improving both the motor symptoms of parkinsonism and elevating the morale of the patient, and Avezzù reported in this paper on his experiences in thirty patients, an unusually high number at this time. He noted that it was not a new drug, but had in the past been generally reserved for the psychiatrist and the ophthalmologist, as well as for surgery; he lamented the fact that both the dangers and the benefits of the drug had been exaggerated, leading to its neglect; its identity with hyoscine was taken as given by Avezzù. Since its introduction to the clinic by Gnauck in 1882, it had been used especially in all forms of motor restlessness in the insane and in tremor of all types (paralysis agitans, delirium tremens, senile and essential tremor, multiple sclerosis). 0.25-1mg/day p.o. or 0.25-0.5mg/day s.c. was found to also control saliva flow, sweating and the subjective sense of heat, as well as tremor; its narcotic action was also a welcome relief for the sleepless post-encephalitic patients. Avezzù avoided accumulation of the drug in his patients by substitution of coniine or gelseminine bromide for 5-6 days each month. Avezzù did not know why scopolamine worked in his patients; he regarded parkinsonism as a hyperparasympathetic syndrome, but he recognized that only further work and the careful observation of unusual symptoms and responses to the drug would reveal whether it was acting peripherally or directly in the brain.168

The form of ‘hyoscine’ which had established itself in the clinic by this stage was the hydrobromide derivative of the L-isomer (that is; scopolamine hydrobromide), and was used in a wide variety of circumstances where sedation of one type or another was desired, including acute mania, delirium tremens, chorea, pertussis and asthma. It could be administered orally or via hypodermic injection, but the latter route was found by most physicians to be more effective; it was thus difficult to utilize on an ambulant basis. Although it rapidly depressed motor activity and elicited sleep, it was regarded as a less reliable hypnotic than morphine or chloral hydrate. Nevertheless, it was often used in combination with atropine and morphine as part of the basal narcosis cocktail prior to an operation (“pre-anesthetic”). It achieved greater prominence in parkinsonism as the drug of choice in post-encephalitic parkinsonism and, consequently, paralysis agitans. Babinski and Souques appear to have been the first to report its successful application under this name in post-encephalitic patients in 1921, but its application quickly spread.169 Hyslop reported in 1922 in a review that hyoscine relieved rigidity in six of eight patients, a result later repeated by his group.170 By the middle of the 1920s, a number of groups had reported the benefit of the agent for the rigidity of post-encephalitic parkinsonism, and hyoscine had established itself as the drug of choice in this condition. Further positive experiences with hyoscine in post-encephalitic parkinsonism were reported in England (“Hyoscine is of undoubted value in the Parkinsonism following encephalitis lethargica”)171 and France.172 By 1925, the Italian

168 Avezzù, 1921.
169 Babinski, 1921; Paulian and Bagdasar, 1921; Souques, 1921a; Clymer, 1923. Hohmann (1924) reported that he first used it at the Johns Hopkins Hospital in April in 1921.
170 Kennedy et al., 1922.
171 McCowan et al., 1926a.
worker Boveri spoke of scopolamine as being “the morphine of the extrapyramidal and vegetative systems”.\(^{173}\) The major subsequent modification of the therapy was the addition by A.F. Hurst (“who never shrank from prescribing drugs in high doses”)\(^{174}\) of pilocarpine nitrate (together with liquor strychniniae) in 1926 to relieve the dryness of mouth and paralysis of ocular accommodation associated with hyoscine; this allowed him to increase the dose of the latter to \(\frac{1}{8}\) grain (\(~8\text{mg}\)), 3-4 times per day.\(^{175}\)

Despite occasional dissenters,\(^{176}\) 0.3-0.6mg hyoscine, 3 or 4 times a day per os (although hypodermic administration was employed at the commencement of treatment), was generally found to greatly relieve tremor and rigidity; simultaneous use of 3-6mg pilocarpine allowed the dose to be increased to as high as 8mg thrice daily.\(^{177}\) Despite the high variability in the responsiveness of patients to scopolamine, the greatest difference noted by some workers was between normal persons and post-encephalitic parkinsonians: whereas the former reacted to 0.6mg scopolamine with disturbed visual reflexes, slurring of speech, dryness of mouth and, ultimately, several hours of deep sleep, the post-encephalitic patient experienced only slight side effects during the relief of his motor symptoms. This was despite the fact that many reported that parkinsonian patients were, in fact, less tolerant of scopolamine, so that careful control of dosage was required.\(^{178}\) Other workers, however, detected no differences between responses to scopolamine of healthy and afflicted persons, at least at doses of up to 0.6mg (\(\frac{1}{100}\) grain), except that its depressant effects were much reduced in post-encephalitic patients.\(^{179}\)

The New York Matheson Commission into the etiology and treatment of encephalitis lethargica concluded in 1929 that:

Evidence shows hyoscine to be one of the most reliable drugs in the symptomatic treatment of epidemic encephalitis. It acts in the early stage to quiet delirium and mental excitement, and to arrest myoclonic twitchings. It is especially useful in late stages to control tremor, especially of the Parkinsonian type, and to lessen the intensity of myoclonic and ocular spasms. There is no evidence that it has specific influence on the process of the disease.\(^{180}\)

Of eighty-eight references cited by the Commission, sixty-six had reported positive experiences. Interestingly, scopolamine was assessed separately in the report; not surprisingly, the Commission concluded that “scopolamine ranks about the same as hyoscine”. One hundred and one of one hundred and thirty-one reports assessed scopolamine positively in the treatment of post-encephalitic parkinsonism.\(^{181}\) The effect

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\(^{172}\) Delmas-Marsalet, 1925; Cruchet, 1927, 1931. Delmas-Marsalet, who studied under Cruchet, regarded the suppression of postural reflexes as one of the most significant mechanisms of scopolamine in parkinsonism, as did Marinesco in Rumania (1928a; 1928b).

\(^{173}\) Boveri, 1925.

\(^{174}\) Critchley, 1958; see also Hurst, 1934b.

\(^{175}\) Hurst, 1926. Hurst attributed the original employment of pilocarpine for this purpose to Erb (“about 1895”).

\(^{176}\) For example, Meerloo (1935) found scopolamine useful in paralysis agitans but not in post-encephalitic parkinsonism.

\(^{177}\) Such a high dose, however, was unusual.

\(^{178}\) Witzleben, 1942, pp.96-98.

\(^{179}\) McCowan et al., 1926a.

\(^{180}\) Darrach et al., pp.153-154.

\(^{181}\) Ibid., p.167-168.
of hyoscine/scopolamine was, however, only ever temporary, and the symptoms returned at their former intensity almost immediately on the cessation of therapy. There was also some concern that habituation to scopolamine could develop.\textsuperscript{182}

Nevertheless, the effects of hyoscine could be dramatic, as illustrated in a letter to the\textit{British Medical Journal} in 1935. A 44 year old man in the Star and Garter Home for Disabled and Sailors Soldiers in Surrey had been disabled by post-encephalitic parkinsonism for ten years and bed-ridden for six; further, he had not spoken since being confined to bed. He had recently received $\frac{1}{100}$ grain hyoscine twice daily for excessive salivation, whereupon he had resumed talking:

\begin{quote}
This has cheered him up and made him feel very much better. He is still confined to his bed and is unable to move his limbs, . . . I am not a neurologist, but record this most unusual happening in the hope that possibly somebody may be able to produce an explanation.\textsuperscript{183}
\end{quote}

Similarly impressed was an American physician reported in 1927:

\begin{quote}
I have seen patients who were tremulous, drooling at the mouth, and almost unable to walk, improve to such an extent that they were able, in part, to resume useful occupations. Some may hesitate to use scopolamine over long periods; but in a case of paralysis agitans in which I gave tablets of $\frac{1}{100}$ grain four times daily for more than nine years, there was no apparent injury and the effect was still good at the end of that time, when the patient died.\textsuperscript{184}
\end{quote}

The fear of using too much hyoscine inhibited many physicians from adopting the therapy, particularly in post-encephalitic parkinsonism, where the patient faced the prospect of many decades of remaining life and therapy; Arthur Hall, for instance, conceded that his treatment failure with the drug might be attributable to his lack of boldness in its application.\textsuperscript{185} The Polish physician Karol Zahorski, on the other hand, reported success in the treatment of hypertonia and tremor with massive doses of scopolamine (10mg/day).\textsuperscript{186} A German reviewer accompanied his digest of this paper with a warning against using it as a model, noting that he had employed much lower doses with success since 1905; he advised that higher doses tended to be accompanied by motor restlessness and hallucinations.\textsuperscript{187} Patry recommended relatively high doses of scopolamine (up to 4mg/day) during ultraviolet therapy.\textsuperscript{188} The record for boldness in the deployment of scopolamine, however, must be awarded to the English physicians Cohen and Craw, who treated the severe oculogyria of a 28 year old woman suffering advanced post-encephalitic parkinsonism patient with increasing doses of intravenous hyoscine; by May 1937 she was receiving 130 to 195mg per day. There were no apparent signs of toxicity; mydriasis was managed with eserine (physostigmine) drops.\textsuperscript{189} These instances of high dose scopolamine therapy remained, as far as I can determine, without great echo in the literature, and much lower doses were employed with satisfactory results.

\textsuperscript{182} Schaltenbrand, 1924; see also Stalker, 1929.
\textsuperscript{183} Gowlland, 1935.
\textsuperscript{184} Discussion in Freeman, 1927.
\textsuperscript{185} Hall, 1926.
\textsuperscript{186} Zahorski, 1925.
\textsuperscript{187} Ibid.
\textsuperscript{188} Patry, 1929.
\textsuperscript{189} Cohen and Craw, 1937.
It was not known why scopolamine exerted its benefits in parkinsonism. French authorities believed it depressed activity in the extrapyramidal system, so that the pyramidal system was freed to function normally. Marinesco’s group in Bucharest hypothesized that problems of tonus were the results of disturbances in the vegetative system. They found that the pH of the blood increased by about 0.05 following administration of scopolamine; they hypothesized that hyoscine stimulated the release of potassium ions by the muscle, leading to its increased excitability (as indicated by reduced chronaxia) and the alkalinization of the blood. Ross concluded in 1926 that the drug effect was real and could not be attributed to suggestion; there were also several reports in which the mechanical assessment of rigidity, tremor and speed of movement were employed to objectivize the effect of scopolamine in post-encephalitic parkinsonism.

The use of scopolamine as a diagnostic aid was suggested by Rosenfeld. He noted that agitated psychiatric patients invariably responded to 0.5-1mg scopolamine with a strong Babinski reflex (dorsal flexion of the big toe), even before changes in consciousness or perception were evident. This was also the case in patients with brain tumors or multiple sclerosis; flexion of the toe was often observed normally in these patients, but this flexion was further increased by scopolamine. In paralysis agitans and post-encephalitic patients, in contrast, doses as high as 1.3mg failed to elicit a Babinski response, so that the possibility existed for distinguishing between pyramidal and extrapyramidal motor disorders.

McCowan, Harris and Mann (Maudsley Hospital (London) and West Park Mental Hospital) also regarded encephalitis lethargica as an opportunity to gain insights into the neurological aspects of psychosis and neurosis, and reported extensively in 1926 on their experiments with hyoscine in normal persons and in post-encephalitic patients. The effect on rigor in parkinsonian patients was impressive, although the authors were careful to allow for the role of suggestion in its effects. The beneficial psychic effects were attributed to the improved motor performance, after the motto “mens sana in corpore sano”.

This group also investigated one of the first metabolic abnormalities to be reported in parkinsonism. Dresch and Lewy had reported in 1922 that glucose metabolism was abnormal in paralysis agitans patients. McCowan and colleagues now found that post-encephalitic patients showed a marked and sustained hyperglycemia following the ingestion of glucose; further, stupor and depression in these patients was associated with the greatest abnormalities in the blood-glucose response curve. No evidence of enduring hepatic insufficiency was detected. Administration of atropine or hyoscine to normal persons reduced the gradient of the rise in blood glucose levels following ingestion of 50mg glucose; this was interpreted as depression of glycogenolysis and a variable glycogenetic response. In post-encephalitic parkinsonian patients, hyoscine shifted the prolonged hyperglycemia exhibited by these patients following glucose intake towards a more normal curve; that is, the blood glucose curve resembled more

190 Freeman, 1927.
191 Marinesco et al., 1928a; 1928b. It was noted that that the effect of scopolamine on nerve excitability was much less than on that of the muscles.
192 Delmas-Marsalet, 1925; Hall, 1927; Harris, 1927.
193 Rosenfeld, 1921.
194 As an aside, the citation is “Orandum est ut sit mens sana in corpore sano”; Juvenal was actually deprecating the emphasis on gymnastic ability over intellectual pursuits.
closely that of a normal person who had not received the alkaloid. Interestingly, non-parkinsonian post-encephalitic patients did not show this improvement after hyoscine. The authors concluded from this “objective” evidence that hyoscine exerted a specific but undetermined metabolic effect on the parkinsonian patient.\textsuperscript{195} It might be noted in passing that intravenous injections of hypertonic glucose solutions was popular in the 1930s as a means for reducing cramp and, in particular, vasoconstriction; isolated reports of success with this approach were reported for parkinsonism, amongst other conditions.\textsuperscript{196}

By 1928, the recommended pharmaceutical agents in the Martindale Extra Pharmacopoeia had been reduced from the previous range to just a handful: tincture of belladonna, hyoscine hydrobromide, strammonium (sic) and nicotine injections.\textsuperscript{197} The 1928/29 report of the Metropolitan Asylums Board in London recorded that:

\textit{It is fortunate that in the treatment of Parkinsonian rigidity, we possess one group of drugs, the atropine group, which have specific symptomatic action. Atropine, belladonna, hyoscyamus, stramonium, and hyoscine all exert this effect and when given in adequate doses greatly diminish the rigidity, lessening the patient’s discomfort and increasing the ability to walk, look after themselves, and to pursue their occupations. The most beneficial of these is hyoscine.}\textsuperscript{198}

Nicotine, gelsemium, cicutine (= conine) and tincture of arnica were dismissed as ineffective in this report, as was ultraviolet radiation therapy. Belladonna extracts in various forms were also found to be of some benefit. The plant was cultivated in Europe at this time, but most drug derived from wild sources; in 1917, the leading suppliers were Hungary, Croatia (which exported 12 tonne leaf and 16 tonne root per year), Bosnia, Istria and Galicia, with Italy and Russia also supplying significant quantities. In contrast, most belladonna used in America was cultivated.\textsuperscript{199} The commercial cultivation of the plant was necessary in Europe by the 1920s in order to supply the rapidly expanded market for both plant extracts and pure alkaloids; the required quantity in Germany prior to the Second World War was estimated at 13 tonne per year.\textsuperscript{200} By this time, most belladonna was derived from Hungary and central Europe; the renewed outbreak of hostilities led to its cultivation in Australia, New Zealand, America and Britain, the increased significance of Indian supplies, and the exploitation of alternative plants, such as \textit{Duboisia} species (Australia), \textit{Hyoscyamus muticus} (Egypt) and \textit{Atropa acuminata} (‘Indian belladonna’).\textsuperscript{201}

\textsuperscript{195} McCowan \textit{et al.}, 1926a. See also Froment and Corajod, 1929; Hühnerfeld, 1931. Von Pákozdy (1928) found changes in creatinine metabolism in post-encephalitic paralysis agitans; Scheffärth (1939) reported that a number of metabolic changes in post-encephalitic patients (blood cholesterol, calcium, potassium, sodium, chloride, lymphocyte numbers) had been measured and were influenced by therapy with belladonna alkaloids. As an example of an earlier report on metabolic changes in parkinsonism: Schäfer (Jena) reported in 1893 reduced nitrogen excretion and normal urinary phosphate levels in an atypical paralysis agitans patient (25 years old, co-existent chorea hereditaria).

\textsuperscript{196} Mercks Jahresbericht for 1933, p.106-107. See Westphal (1932) for discussion of glucose injections (as more effective alternative to blood-letting) in stroke victims.

\textsuperscript{197} Volume I, p.1082.

\textsuperscript{198} Hill, 1929a, p.287.

\textsuperscript{199} Tschirch, 1923, III, pp.271-272.

\textsuperscript{200} Wetzel (1936), cited in Schwamm, 1988, p.306. See also Boshart, 1931; and Esdorn, 1935, for role of the chemical industry in culture and collection of medicinal plants.

\textsuperscript{201} See references at Henry, 1949, pp.64-65.
One of the most impressive case reports of its use in parkinsonism was from Kennedy, Davis and Hyslop in 1921:

A woman of middle age who had been unable to articulate, chew, or move the arms and legs on volition — so intense was the Parkinsonian spasm — after a suppository of belladonna, was able to talk fluently, move quickly and with grace, and express emotion easily by gesture and facial expression. Congealment of function gradually returned, but temporary dramatic amelioration has always been possible by the rectal use of belladonna in tolerance dosage.  

The dominance of what were subsequently termed belladonna alkaloids had thus been established by this point in the therapy of post-encephalitic parkinsonism, but the patients were not generally restored to a capacity approaching full functionality, let alone cured.

‘Eustateina’ (Reale Farmacia Toschi, Bologna) was an Italian variation of the hyoscine theme. Two solutions were used in the treatment:

Bottle No.1: Acidum sclerotinicum (= acidum secale amidosulfonicum) 4.1%, hyoscine bromide 0.063%, bitter almond water 1.38%, veratrine root 6.0%.

Bottle No.2: Hyoscine bromide 0.126%, cherry laurel water 1.38%, laurocereasine 3%, alcoholic tincture of aconite root 0.5%, total alkaloids 1.8%, organic arsenic 0.0013%.

According to von Witzleben, who was citing Franchini, 20 drops of solution 1 were initially administered in sugar water in the morning and the same amount from No.2 at night; the dose was slowly increased until the optimal effect was achieved. Benefits were said to be noticeable soon after the initiation of treatment, including the relief of oculogyric crises. Veratrine was supposed to increase the functional capacity of the muscles, while aconite decreased sensory irritability. Amongst the few references to this product in non-Italian journals was a paper by the Assistant Seckbach (University Medical Polyclinic III, Berlin) in 1931, who reported that it successfully controlled the rigidity but not the tremor of post-encephalitic parkinsonism, even if those cases where atropine and scopolamine had failed. Römer regarded ‘Eustateina’ as valueless in the therapy of parkinsonism; he claimed that even in its country of origin it was regarded as less than effective.

Genoscopolamine, the N-oxide of hyoscine first synthesized by Polonovski in 1925, was preferred by some clinicians, particularly in France, because it was said to be less toxic and addictive than hyoscine itself (figure 5-2). A number of N-oxides of plant alkaloids were synthesized by workers in the early 1920s in the search for less toxic but...
fully active derivatives of the parent compounds; the first had been génserine, synthesized by Polonovski and Nitzberg in 1915.\textsuperscript{208} The names for these compounds derived from the assumption that they exerted their effects by being reduced in the organism to the active agent (\textit{γεννάω} = “I generate”), but in a gradual manner. Genoscopolamine was \( \frac{1}{200} \) as toxic as the parent compound in dogs, which could tolerate 1.25g of the derivative (s.c. or i.v.). Polonovski and Colleagues (Medical Faculty, Lille) first tried the agent in post-encephalitic parkinsonism in 1926 in six patients, and found it to be a less toxic substitute for the usual belladonna alkaloids.\textsuperscript{209} In his thesis at the University in Lyons in 1927, J. Lardos reported that the major symptomatic effects were relief of tremor, reduction of muscular hypertonia and the associated discomfort, reduction in sialorrhea, and an increase in muscular strength and the presentation of natural accompanying movements; no toxic effects were observed.\textsuperscript{210}

Elsewhere in Europe, genoscopolamine found application in the roles normally occupied by scopolamine, including the “twilight sleep”. In America, John Scharf (Neurological Hospital, Welfare Island, New York) administered up to 80mg genoscopolamine per day to 22 parkinsonian patients, and reported essentially the same results as the French workers a decade earlier: toxic side effects were completely lacking, although polyuria was noted in a number of cases; the effects of genoscopolamine could be increased by combination with small doses of atropine. Arteriosclerotic patients did not derive as much benefit from the drug.\textsuperscript{211} Despite such promising results, genoscopolamine does not appear to have been able to compete with stramonium in the 1920s and the Bulgarian cure of the 1930s, although Wilson’s Neurology remarked the usefulness of the compound was “beyond question”.\textsuperscript{212}

As an interesting aside, it was discovered later that fresh samples of \textit{Atropa}, \textit{Datura}, \textit{Hyoscyamus} and \textit{Scopolia} species contain the two isomeric \( N \)-oxides of hyoscyamine and one of the two possible \( N \)-oxides of hyoscine. Concentrations of \( N \)-hyoscyamine are highest in the developing fruit, but there is otherwise no indication as to the role of these molecules. Technical limitations had prevented their earlier identification in solanaceous plants.\textsuperscript{213}

\textsuperscript{208} Polonovski, 1926.
\textsuperscript{209} Polonovski \textit{et al.}, 1926.
\textsuperscript{210} Contribution à l’étude du traitement du syndrome Parkinsonism postencéphalitique par l’aminoxide de scopolamine (Genoscopolamine), Thèse de Lyons; cited in Scharf, 1939.
\textsuperscript{211} Scharf, 1939.
\textsuperscript{212} Wilson, 1954a, p.160. It is not clear whether the comments in this book were those of Wilson himself (and thus dating from the 1930s), those of the editor Bruce in 1954, or views held by both men.
\textsuperscript{213} Phillipson and Handa, 1975; 1978.
A further derivative of scopolamine, $N$-butylscopolammonium bromide (‘Buscopan’; Boehringer Ingelheim; figure 5-3) found some application in the therapy of parkinsonism in the 1950s, but was more useful as a ganglion blocking agent. $N$-methyl-scopolamine, like $N$-methyl-atropine, proved effective as a spasmylytic, but the conversion of the basic ester into the corresponding quaternary base rendered it unsuitable for the therapy of parkinsonism.

**Gelsemium**

The urgency of the encephalitis lethargica situation led to the reconsideration of many therapies for paralysis agitans which had been largely discarded; amongst these was the use of extracts of the gelsemium root (see page 92). Sollmann noted in 1943 that the use of gelsemium in any disorder was purely empirical; the root was official only in England, Switzerland and a few South American countries. George Hyslop (Bellevue Hospital, New York) found gelsemium root extracts to be as useful as hyoscine in postencephalitic parkinsonism (6 of 8 patients showed improvement with hyoscine, 12 of 15 with gelsemium (3×7 minims/day) or gelsemine (3×$\frac{1}{30}$ grain/day p.o. or s.c.); four patients receiving the latter showed “marked improvement”). He even noted two possible “cures” with gelsemium. Hyslop also noted a certain synergism between the effects of the two drugs. Interestingly, atropine (5×$\frac{1}{100}$ grain/day) and tincture of belladonna were found to have no effect or to exacerbate the symptoms. Gelsemium continued to find limited use in the United States throughout the 1920s, but was never as popular as stramonium. Nevertheless, Wilson’s *Neurology* indicated that tincture of gelsemium and gelsemine hydrochlorate had a “similar if less marked effect” to genoscopolamine.

**Stramonium**

The thorn apple (*Datura stramonium*; figure 5-4) is another member of the *Solanaceae* which also contains atropine, hyoscyamine and scopolamine; all parts, but especially the seeds, are thus highly poisonous. The *Datura* species are distributed throughout the tropical and subtropical regions of the world, and are employed similarly as medicinal agents in most indigenous cultures. The stramonium grows to about a metre in height, has a rather bushy appearance and a very long root; the latter, however, is not used in medicine. Stramonium leaves were long official in most pharmacopoeias. They are about 12-15cm long and 7-10cm broad, ovoid or heart-shaped with a wavy...

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214 Wick, 1951; Stefan, 1953.
215 Roost and Schindler, 1947.
216 Sollmann, 1943, p.413.
217 Hyslop, 1922.
218 Gelsemium was still official in Britain in the 1950s for the treatment of neuralgia and migraine; Extra Pharmacopoeia, 1952, pp.561-562.
220 Also known as Jimson weed, stink weed, devil’s apple, apple of Peru, herbe des magiciens, Teufelskraut. Stramonium is reputed to be a contraction of the Greek στρύχνον μάνικον.
edge, and deep grey-green in color. The plant exudes a narcotic odor and is extremely bitter and salty to the taste, particularly when dried; the seeds, in contrast, are slightly sweet, which has led to numerous poisonings in children. The seeds have been used as medicinal agents in some countries, but without the same popularity as the leaves.221

‘Datura’ is derived from Sanskrit; plants of this genus served as poisons in India since ancient times in much the same way as belladonna in early modern Europe. It is not clear whether stramonium was known to pre-modern Europe, with some evidence suggesting that it first arrived there, probably from the Caspian region, in the 16th century; the plant was unknown to Linné. References in some earlier works to ‘stramonia’ (for instance, by Hildegard of Bingen) probably refer to the very similar *D. metel*. Stramonium poisoning has been reported from all parts of the world, with a particularly amusing case being reported by an early American historian for 1676: soldiers had used the plant in a salad, “the effect of which was a very pleasant Comedy” which lasted for eleven days before the men “return’d themselves again, not remembering anything that had pass’d.”222 According to Duke, the medicinal

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222 Hughes and Clark, 1939.
applications of stramonium have been various, indications for its use ranging from baldness and earache to spasm and cancer; its seeds have also proved popular with homicides and suicides, and as a component of “knockout drops”.  

The major alkaloid of both leaves and seeds is hyoscyamine (up to 0.5%), with some atropine and scopolamine. The scopolamine level is greater in the cultivated than the wild plant due to greater light exposure. Stramonium was introduced into modern clinic in 1762 by Störock after it had enjoyed a period of notoriety due to its involvement in a number of poisonings. It was used for a period as in the therapy of epilepsy and manic states, but its major use at the beginning of the 20th century was in the form of cigars for asthmatics; stramonium leaves were usually soaked in an opium tincture for this purpose; leaves of other plants (henbane, belladonna, tobacco, lobelia, tea, cannabis, digitalis) were often also added. The German E Commission published a monograph in 1990 in which doubt was cast on the claimed benefits of the plant for this indication, and noted that the erratic alkaloid content of both seed and leaf rendered the risks involved in employment of the drug unacceptable. Other constituents identified in the seeds included a number of saturated and unsaturated fats, the rennin enzyme and hemagglutinin. In contrast, the major alkaloid of the D. metel (broadly distributed in Asia, Africa, South America and the Mediterranean region) is scopolamine (average 0.55%), with a little hyoscyamine and atropine in the seeds. The South American tree D. sanguinea, formerly cultivated by Andean natives for its hallucinogenic properties, has recently been suggested a commercial source of scopolamine, with a leaf content of up to 0.5%. Samuel Cooper (Pennsylvania Hospital) introduced stramonium into clinical practice in America in 1779 or 1797 for mania, epilepsy and nervous fevers.

It was apparently also tried for parkinsonism in nineteenth century America; Hammond reported the case of a United States senator who was cured by the plant, and specifically mentioned the increased strength of both his handwriting and his voice. But the employment of the leaves of Datura stramonium in antiparkinsonian therapy achieved its greatest prominence in France during the 1920s, primarily through their promotion by Juster. He had initially treated two parkinsonian patients (one post-encephalitic, one idiopathic) in 1924 doses of up to 1½-2g stramonium daily in pills prepared from the leaves of the plant, and with a success he judged to be superior to atropine-class drugs; the rigor responded especially well, and movement became easier.

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224 Tschirch, 1923, III pp.302-304; Grieve, 1931, p.805; Trease and Evans, 1983, p.551. The last named authors indicate that in mature plants the hyoscyamine content is double that of hyoscine, but that the latter dominates in younger plants. Varying levels of a range of other alkaloids are also found in various parts of the plant.
225 Cosson et al., 1966.
227 For this reason, Indian D. metel has long been used as a commercial source of scopolamine, and commercial “Datura leaf” generally consists of the dried leaves and flowers of D. metel and the closely related D. innoxia. Tschirch, 1923, III pp.302-306; Grieve, 1931, p.807; Trease and Evans, 1983, p.551.
228 Evans, 1990. The same suggestion was made for D. innoxia, also employed as a hallucinogen in South America, in 1947: Gerlach, 1948. Further over traditional medical uses: Rätsch, 1998, pp.211-212.
229 A dissertation on the properties and the effects of the Datura stramonium and on its use in medicine, p.29, cited in Hoedemaker and Burns, 1930 (who give 1797 as date) and Witzleben, 1942, p.113 (who gives 1779).
the accompanying movements more natural. He also noted a significant improvement in the mood of the patients. It is interesting that Juster was not overly enthusiastic in his first paper on stramonium; he was concerned by the dose required to produce an effect (noting that the French Pharmacopoeia recommended a maximal daily dosage of one gram), so that he wondered whether the therapeutic effect was achieved only in a state approaching toxic delirium. Nevertheless, he was pleased with the symptomatic relief obtained, the only major side effect being the mydriasis which impeded reading. Concerned with the possibility of dependence and tolerance, he suggested alternating stramonium with arnica or scopolamine to avoid habitation. He was also aware that the effect disappeared on discontinuation of the drug, but, in the absence of appropriate causal therapies, he felt justified in reporting his case.231

The improvement in rigidity and psychology of the post-encephalitic parkinsonian were also the features Juster emphasized in subsequent papers on the subject, as well as the absence of side effects, which he attributed to the particular alkaloid combination of the plant. He regarded stramonium as ideally suited for becoming the “daily bread” of parkinsonian patients. Stramonium contained an alkaloid, he noted, ‘daturine’; it was unclear, however, whether this ‘alkaloid’ was a mixture of atropine and hyoscyamine, was identical with atropine, or was an isomer of atropine which crystallized in a different way.232 It was on the basis of its containing atropine-like substances which prompted Juster to try stramonium in parkinsonism, especially as Trousseau and Pidoux rated the stramonium extract as more potent than that of belladonna.233 The dose was distributed throughout the day at two hourly intervals. He subsequently found that the dose could be gradually reduced from the large amounts that he initially employed to about ½g/day, and that the application via suppository was practicable if preferred by the patient.234 Laignel-Lavastine and Valence claimed success with the therapy in 80% of their patients during a year-long study, sometimes to the extent that the patients classified themselves as “cured”. Tremor was abolished in many cases and mood greatly elevated. These authors, however, noted side effects all too reminiscent of belladonna alkaloids: mydriasis, dryness of mouth, nausea and so on. They attempted to circumvent this problem by alternating periods with and without treatment, but this was inevitably accompanied by the return of full rigidity during the “off” phases.235

Despite a number of further positive reports, it was noted that these experiments were for a long time largely unrecognized outside France. As the first adherent in Germany, Erich Sternberg (Neurological Ward of the Hufeland Hospital, Berlin) extolled the virtues of stramonium for both post-encephalitic (28 patients; 26 successes) and idiopathic parkinsonism (14 cases; 11 successes) in 1930 as the “absolute and relative best symptomatic weapon” available, especially for the tremor, akinesia, freedom of voluntary movement and speech, but less so for the rigor; all tasks of daily living were executed in a more fluid and coordinated manner. He was quite frank about his ignorance regarding the reason for this success:

231 Juster, 1925.
232 Curiously, von Planta had demonstrated as early as 1850 that daturine and atropine were identical. It should be noted, however, that Ladenburg reported in 1880 that pharmacologists still doubted the assertion by chemists of the identity of the two alkaloids. Ladenburg himself identified daturine with a mixture of hyoscyamine and atropine; commercial daturine (Merck) was almost pure hyoscyamine; Ladenburg and Meyer, 1880.
233 Cited in Juster, 1925.
234 Juster, 1925; 1927.
235 Laignel-Lavastine and Valence, 1926.
In the individual case, we are still thoroughly dependent on trying the drugs one after the other in order to find the most effective. We have repeatedly seen how different the effects of related agents can be in individual cases which are clinically very similar; it happens that when scopolamine fails, atropine works, and vice versa, and that . . . in the end, stramonium can be better than all the alternatives.\textsuperscript{236}

The dose had to be gradually increased in order to determine the optimal level for a given patient; Sternberg commented on his surprise that the range in optimal dose for his patients was so wide. At the same time, the doses employed in Germany were far lower than elsewhere, with most patients receiving less than 0.7g/day. Curiously, the different forms of administration (tablet, mixture, pessary) were also variably effective in different patients. The quality of the drug was of paramount importance; it was found that most stramonium sold in Berlin, principally for smoking by asthmatics, was unsuitable for use in parkinsonism. The onset of action of the therapy could occur immediately, or take months, especially in less severe cases of parkinsonism. In thirty-three cases, Sternberg classified the improvement as “great”, based purely on his observations of their movement and mood on the ward. Sternberg reported that tremor was improved to a greater extent than rigidity, but most other workers experienced the reverse; oculogyric crises and restlessness were also relieved. Thirty-two patients reported no side effects; those that did were mostly affected by dryness of the mouth and nausea, while accommodation disturbances were notably rare. Five patients, however, experienced serious psychotic states, usually involving nocturnal delirium and frightening visual hallucinations; withdrawal from the drug resolved the crises within twenty-four hours. Other patients reported altered perception which mostly concerned intensified or inappropriate color perception.\textsuperscript{237}

Sternberg appears to have been motivated to try stramonium by the outstanding successes reported by Sophie Shapiro (Oak Forest County Hospital, Illinois) in the United States. Shapiro, who had been inspired by Juster’s initial report to commence her own study in 1926, reported that stramonium (in the form of dried leaves), which addressed all symptoms of both paralysis agitans and post-encephalitic parkinsonism without eliciting untoward side effects, was without doubt the best agent available for both forms of parkinsonism; only those with exceptional tremor or suffering from arteriosclerotic parkinsonism failed to respond. Shapiro regarded her report as the first in either English or German on the subject.\textsuperscript{238}

Carmichael and Green (Medical Professorial Unit, St. Bartholomew’s Hospital, London) reviewed the literature regarding the treatment of post-encephalitic parkinsonism in the same year, and conducted a comparative investigation of the benefits of hyoscine and stramonium for such cases, using an ergographic device to measure the rigidity of their subjects’ arms. They found that tincture of stramonium was at least as effective as high doses of subcutaneous hyoscine, and superior to orally applied hyoscine; it could also be used for longer periods without presentation of intolerable side effects. Carmichael and Green were also impressed with the effects on rigidity and mental condition of the patient. The authors also investigated the effects of the alkaloids presumed to underlie the action of stramonium (atropine, D- and L-hyoscynamine; the procurement of the D-isomer was difficult (in this case supplied by the Burroughs Wellcome Laboratory), so that this was a rare example of the effects of the

\textsuperscript{236} Sternberg, 1930.

\textsuperscript{237} Ibid. See also Schuster, 1931b (Schuster was Sternberg’s director).

\textsuperscript{238} Shapiro, 1928. For a further American report on stramonium in parkinsonism, see Steen (1931).
two isomers of atropine being compared), and found that none was as effective as stramonium itself. There was, however, no effect on tremor.239

The year following Shapiro’s report, Jacobson and Epplen (King’s County Hospital, Seattle) described dramatic improvements in all symptoms of their post-encephalitic patients, except for paresis:

[Patients 1 and 2] were in bed 90 per cent of the time, practically leading a vegetative existence, staring at the ceiling and unable to attend to any of the functions of life without assistance. They are now highly self-reliant and get a certain enjoyment out of life in listening to the radio and playing cards and checkers, and have even become useful in helping with work about the wards.240

They also made the common experiences that the most severely affected cases often showed the most dramatic improvements, that large doses of stramonium (up to 4.3mL, 3-4 times per day) were required to elicit an effect, and that the effect of stramonium was enhanced when combined with scopolamine.

Stramonium was officially regarded in England in 1929 as being second only to hyoscine,241 and was regarded favorably by the Matheson Commission in New York.242 The English physician Hurst favored a low initial dose followed by gradual increases until quite a high level was achieved. Commencing with $3 \times 0.6$mL *tinctura Stramonii* in 14mL water, the dose was doubled over periods of 8 days until blurred vision or intolerable dryness of mouth developed; at this point 6.5mg pilocarpine nitrate would be added to the formula, and the stramonium concentration again increased until the appearance of the first toxic symptoms. The side effects were thus similar to atropine, but milder.243 Other authors found an effect also on the rigor or no effect at all. In Holland, Wiersma reported similar results to Sternberg.244 Hoedemaker and Burns reported encouraging results in America, although they noted that the effect on tremor and in paralysis agitans was negligible; there were also cases which, for unidentifiable reasons, did not respond.245 Harris (Maudsley Hospital, London), on the other hand, was disappointed by the effects of stramonium; this might be explained by the low doses which he administered ($3 \times 1.5$mL/day of the tincture);246 Worster-Drought and Hill (West End Hospital for Diseases of the Nervous System and Post-Encephalitic Unit, Metropolitan Asylums Board) determined in 1930 that the alkaloid content of the stramonium tincture of the British Pharmacopoeia was only about 5% that of the extract prescribed in the United States Pharmacopoeia.247

Worster-Drought and Hill compared the benefit achieved by the administration of tincture of stramonium, a dried extract and of dried leaves, and found that, adequately dosed, similar effects could be attained with all forms. More importantly, the mean dose of $3 \times 750$mg *extractum Stramonii* U.S.P. per day elicited improvements which equalled

239 Carmichael and Green, 1928.
240 Jacobson and Epplen, 1929; also 1930.
241 Hill, 1929a.
242 Darrach et al., 1929, pp.172-173: of fifteen reports, thirteen were favorable and none unfavorable.
243 Hurst, 1934b.
244 Wiersma, 1930.
245 Hoedemaker and Burns, 1930.
246 Harris, 1927.
247 Worster-Drought and Hill, 1930.
those produced by parenteral hyoscine.248 The aim of these workers had, in fact, been the identification of a more convenient alternative to what was regarded at the time as the most effective therapy for parkinsonism. The disadvantage of the dried leaves was their bulk, of the tincture its expense; the dry extract was therefore preferred purely on the grounds of utility. They recommended that the optimal dose be quickly established and then maintained for the life of the patient. Tolerance developed only slowly, and:

No deleterious effects result from the prolonged administration of stramonium nor, indeed, from any of the atropine group of alkaloids and there is no cumulative action. Owing to the exceptional tolerance of these alkaloids shown by parkinsonian cases, overdosage is not easy to produce and is rarely serious.249

That long-term administration of atropine drugs has no deleterious effect is doubtful, as will be discussed below, and this comment reflects the limited experience of these workers with such agents at this point.

These authors also discussed the central effects of the various belladonna alkaloids in an attempt to understand the superiority of stramonium over belladonna in the treatment of parkinsonism. Atropine exerted a marked central stimulation and slight depression, while the reverse was true for hyoscine; hyoscyamine, the major alkaloid in stramonium, had both moderate stimulatory and depressive effects. This did not explain the qualities of the extract, and the authors noted that other, unknown alkaloids might be significant.250 Jacobson and Epplen were similarly puzzled that stramonium was of remarkable benefit for most symptoms of post-encephalitic parkinsonism and could not be regarded, as stated in the then current textbooks, as merely an alternative to belladonna.251 The question thus remained open.

In general, stramonium enjoyed a good reputation, although its limited effect on tremor required supplementation with scopolamine. Severity of parkinsonian symptoms did not appear to determine response to the agent; although the most disabled cases were often resistant to the effects of stramonium, it was often the less severe patients who required an extended period of treatment before the benefit of the agent was manifested. Many physicians found that stramonium was more effective in post-encephalitic than paralysis agitans patients (although, in contrast to most solanaceous preparations, it was not without benefit for the latter); further, women were more liable to experience adverse responses, particularly during menstruation.252 Critchley noted in 1958 that tincture of stramonium had been popular in the past for the treatment of post-encephalitic parkinsonism, but that the dried extract of the drug (extractum Stramonium siccum, 3×250mg/day) was generally regarded as more effective. By this time, however, stramonium had largely been supplanted not only by derivatives of the Bulgarian treatment but by the range of synthetic anti-parkinsonian agents.

248 It was found that 1g dried leaves were equivalent to 0.25g extractum Stramonii or 3 drachm (~11mL) tinctura Stramonii B.P., all of which elicited the same benefit as 1/100 grain hyoscine; ibid.
249 Ibid.
250 Ibid.
251 Jacobson and Epplen, 1929.
Bulbocapnine

In Amsterdam, Hermann de Jong and various collaborators reported some positive results with the aporphine bulbocapnine on parkinsonian tremor in the mid-1920s. The wine extract of the larkspur (‘Hohlwurz’ or ‘gemeiner Lerchensporn’; Corydalis cava (L.) Schweigg. & Körte = Coryallis tuberosa; Fumariaceae)253 had been a popular remedy in the Middle Ages for headache, tremors and paralysis:

The bitter tasting root, simmered in wine, is used in diseases of the head and the nerves, and also for tremor, pains and paralysis of the joints.254

By the beginning of the 19th century, however, its therapeutic uses appear to have been forgotten.255 An alkaloid was first isolated from the root in 1826 by Wackenroder, and Ziegenbein and Gadamer had identified a total of eleven alkaloids by the turn of the century, all with effects on central nervous function.256 Bulbocapnine was first isolated from the larkspur root by Adermann in 1890 and given its current name by Freund and Josephi in 1892.257 The dried root consisted of up to 6% alkaloids, mostly bulbocapnine and corydaline.

It was known from the work of Peters that higher doses (10mg.kg⁻¹) induced a catalepsy-like state in rats, so that the limbs can be bent like “stiff lead pipes”;258 muscular tone and responsiveness to stimuli were preserved, but voluntary movement was impossible. He suggested that it might be of use in disorders of movement, and bulbocapnine found use as a treatment for muscular tremor and vestibular nystagmus.259 High doses, however, can also induce tremor and clonic convulsions in humans, even to the extent of fatal circulatory and respiratory damage.260

253 As is often the case with medicinal plants, confusion of different unrelated species is possible here: the larkspur is to be distinguished from the field larkspur, also known as lark’s heel or knight’s spur (‘Feld-Rittersporn’; Delphinium consolida or Consolida regalis) or the stavesacre (Delphinium staphisagria; both of the family Ranunculaceae). Both these alternative plants have also be known as ‘delphinium’; the ‘lark’s heel’ referred to by Gerard in his herbal may well have been the latter, as he identified it tentatively with the staphisagria of Dioskorides (IV, 156), which Gerard referred to as ‘delphinium’. To confuse matters further, the official designation for the corydalis rhizome was Tuber Aristolochiae cavum; Brandt and Wasicky, 1927-1929, pp.951-952.


255 John Gerard wrote in his Historie of plantes that “We find little extant of the vertues of Larks heele, either in the antient or later writers, worth the noting, or to be credited”; further, he did not believe that, thrown before a scorpion or other venomous beast, that they were fixed to the spot until its removal. Gerard, 1633, p.1083. Geiger noted in Pharmacopoea universalis (Heidelberg, 1835) that it was only used by veterinarians; in citing this remark, Peters (1904) noted that even this was no longer the case.

256 History reviewed briefly in Peters, 1904. Major papers: Ziegenbein, 1886, Gadamer, 1902; see also Gadamer, 1927. The major recognized alkaloids were the weak bases corydaline, corybulbin and isocorybulbin; the moderate bases corycavamin and corycavin; and the strong bases bulbocapnine, corydin and corytuberin. The nomenclature was somewhat confused; Adermann initially designated bulbocapnine ‘corydaline’, which name was retained by certain authors for some time: Ziegenbein, 1886.

257 Freund and Josephi, 1892.

258 The term, often used to describe the effect of bulbocapnine in animals, appears to have been first used by Mella in 1926.

259 Peters, 1904.

260 Wilson, 1954a, pp. 105-106.
This work was extended by Fröhlich and Meyer (Pharmacological Institute, Vienna University), de Jong and Hugo Mella (Harvard Medical School) in animal studies during the first half of the 1920s. They noted the similarity of bulbocapnine and apomorphine (figure 5-5), although bulbocapnine is optically dextrorotary, while apomorphine is levorotary. De Jong’s interest had been directed to the substance by Magnus (Utrecht), whom he had consulted regarding the production of experimental catatonia. De Jong did not regard the state induced by bulbocapnine as true catalepsy, as the manipulated limb of treated animals returned to its resting position if not supported. Together with Baruk, with whom he collaborated at the University Psychiatric Clinic in Paris and in his own Laboratory for the Clinical Physiology of the Nervous System (University Neurological Clinic, Amsterdam), de Jong published a comprehensive volume on the physiological and pharmacological effects of bulbocapnine in animals in man in 1930.

At the same time, Georg Schaltenbrand (University Neurological Clinic, Hamburg-Eppendorf) sought advice from Johannes Gadamer (1867-1928) at Marburg with regard to an effective alternative to scopolamine in parkinsonism. Gadamer had determined the structure of bulbocapnine in 1910, and suggested that it might be worth further investigation. Schaltenbrand examined the effects of bulbocapnine in a variety of animals, and found that all exhibited an apathetic immobility. The animals were capable of movement, but only when disturbed from a characteristic bent position (“flexion position”); muscle tone was increased. Apes and dogs also exhibited a resting tremor, so that he compared the syndrome produced by bulbocapnine in these animals

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262 De Jong, 1923.
263 La catatonie expérimentale par la bulbocapnine (Masson, Paris). See also de Jong, 1945.
264 Schaltenbrand (1897-1979), “the most prestigious German neurologist of his time” (Aird, 1988), achieved his doctorate with research into the effects of hyoscine on motor and cognitive performance in parkinsonian patients (1924a; 1925). He was later active at the Psychiatric Clinic in Würzburg he founded an autonomous neurological division within the Clinic for Internal Medicine in 1938), after his candidature for the chair of psychiatry in Hamburg was blocked by his perceived political unreliability (Nonne was instead succeeded by Pette). In 1940, he conducted experiments involving the administration of cerebrospinal fluid from multiple sclerosis patients (or from monkeys treated with cerebrospinal fluid from multiple sclerosis patients) to severely affected neurological patients in order to test the transferability of the pathogen. On the other hand, he opposed to the euthanasia program coordinated by the Würzburg Professor of Psychiatry, Werner Heyde. Biography: Hopf, 1980; Aird, 1988; Shevell and Evans, 1994.
to human parkinsonism. Schaltenbrand also administered himself 350mg bulbocapnine, and noted a reduction of all forms of cognitive ability together with a feeling of leaden tiredness, although he found that he was still fully capable of movement if he could summon the will to do so. His urine developed an olive-green color on standing.265

In June 1923, de Jong began administration of small doses of bulbocapnine to patients with diseases including tremor as a major symptom, and at the end of the year Schaltenbrand joined him to continue the investigation of the alkaloid. In four paralysis agitans cases, a patient with cerebellar tremor and another with essential tremor, 200mg bulbocapnine reduced the tremor amplitude by up to 75%, with a slight increase in muscle tonus. In light of the effects which Schaltenbrand had himself experienced, they did not dare to further increase the dose.266 De Jong pursued the question further in a paper with William Hermann (Boston) in 1926; it was found that bulbocapnine was of definite benefit with respect to tremor in two of four parkinsonian patients, and of some benefit in the other two. Neither atropine nor phenobarbital had shown any effect on tremor in any patient, whereas scopolamine had also achieved striking improvement in two patients (one of whom had shown a clear response to bulbocapnine). But de Jong noted that there were cases which appeared entirely refractory to the effects of bulbocapnine. Further, the doses at which the effect on tremor was achieved corresponded to those which induced sleep in animals; indeed, sleep was often also observed in humans at such levels, accompanied by cessation of tremor. He concluded that the effect on the latter was therefore connected in some way with the narcotic effect of the drug. De Jong had proposed a “discharge theory” of the catatonic effects of bulbocapnine in animals, in which the drug reduced the threshold level of stimulation required for the discharge of neurons in certain brain regions, leading to simultaneous activation of “agonist and antagonist muscles”. The low doses of the drug used in humans, however, were conceptualized as elevating the stimulation threshold of motor centres, thus explaining the production of sleep and the reduction of parkinsonian tremor.267 Mella also reported relief of tremor in paralysis agitans by 200mg bulbocapnine.268

Bulbocapnine, at the instigation of Gadamer, was made available for clinical use by Merck in 1924; apart from paralysis agitans and parkinsonism, disorders for which it was recommended included other forms of tremor, athetosis, chorea and multiple sclerosis.269 It could be administered orally or by hypodermic injection, and was excreted largely unchanged in the urine. Oral administration necessitated in many patients the addition of sodium bicarbonate and coating with stearic acid in order to avoid stomach-associated pain. When administered by injection, the duration of action could be doubled if applied in olive oil or gum arabicum to slow absorption. Lewy reported one of the most interesting results concerning bulbocapnine and its effect on tremor: he found that seven of ten genuine paralysis agitans patients responded well to the drug, as did one case of chorea, but all four post-encephalitic parkinsonian patients examined proved refractory to its influence. He explained the reduction in tremor as the result of increased rigidity, but this was not perceived as unpleasant by his patients. Lewy administered 100mg bulbocapnine intramuscularly or subcutaneously and found

265 Schaltenbrand, 1924.
266 De Jong and Schaltenbrand, 1924a, 1924b, 1925a, 1925b.
267 De Jong and Hermann, 1926; de Jong, 1927, 1931.
268 Mella, 1926.
269 Merck’s Jahresbericht for 1924, p.28.
that the full effect was maintained for about seven hours, although cases where the
duration extended to 3-5 days were also noted; in two cases, the tremor had disappeared
altogether after several months’ therapy.\footnote{Lewy, 1926. He did not indicate which patients responded best to the drug; but of the eleven who experienced relief while receiving the agent, seven were paralysis agitans patients (the others were three with tremor of unknown etiology and one chorea patient).} Von Witzleben reported that sublingual
administration was effective against tremor for about a day, whereas the effectiveness of
pills ended after about two hours. There appeared to be no danger associated with long
term use, and withdrawal symptoms were minimal.\footnote{Witzleben, 1942, p.95.} Commercial extraction of
bulbocapnine was not restricted to the larkspur; \textit{Dicentra canadensis} (turkey corn) was
also exploited for this purpose; both it and the larkspur are members of the family
\textit{Papaveraceae}.\footnote{Extra Pharmacopoeia, 1952, p.111. Other references for bulbocapnine in parkinsonism: \textit{Mercks Jahresbericht} for 1930, p.85-86; 1934, p.84.}

Kamil Henner (Prague) had administered 500mg to humans, inducing what he
termed a “\textit{paralysis agitans without tremor}”, by which he meant “\textit{a kind of psychic and}
corporeal viscosity}”. The major motor effect was the eliciting of a state of mental and
motor akinesia; the facial expression was fixed, it was difficult to shift attention from
one object to another. He further characterized the mental state induced by
bulbocapnine as involving:

\begin{quote}
\textit{a pleasurable state of calm (not of fatigue), a sentiment of harmony in relations with the external world without questions, problems or doubts.}\footnote{Henner, 1928.}
\end{quote}

De Jong regarded this as more closely resembling catatonia than paralysis agitans sine
agitatione. In France, Delmas-Marsalet found that the influence of bulbocapnine on
parkinsonian tremor was correlated with its relief of \textit{`réflexe de posture'} of the foot,
consistent with the findings of the same author with regard to the effects of scopolamine
(discussed above).\footnote{Delmas-Marsalet, 1930.}

In contrast to de Jong, Henner found that bulbocapnine accentuated parkinsonian
symptoms, and even brought latent symptoms to a florid state; this corresponded to
what he regarded as the parkinsonian states produced by the drug in apes and dogs. This
contrasted with its beneficial effects on tremors of cerebellar origin.\footnote{Fleischhacker, 1926. amongest others, also reported largely negative experiences with the use of bulbocapnine in post-encephalitic parkinsonism; the last named author, however, found that its effects on the tremor of true paralysis agitans was impressive. Interestingly, a discussant following the presentation of Mella’s paper remarked that he had read a detailed review of the bulbocapnine literature in the \textit{Psychiatrie en Neurologische Bladen}, and found that the “\textit{paralysis agitans results were not encouraging}”.\footnote{Ibid.}

Interest in bulbocapnine therapy for parkinsonism dwindled as it was recognized that
the mental symptoms of the disorder were often accentuated by the drug, especially the
loss of contact with reality, and that the difference between the therapeutic and

\begin{footnotesize}
\begin{footnotelist}
\item Lewy, 1926.
\item Witzleben, 1942, p.95.
\item Extra Pharmacopoeia, 1952, p.111. Other references for bulbocapnine in parkinsonism: \textit{Mercks Jahresbericht} for 1930, p.85-86; 1934, p.84.
\item Henner, 1928.
\item Delmas-Marsalet, 1930.
\item \textit{Ibid.}
\item Fleischhacker, 1926.
\item Mella, 1926.
\end{footnotelist}
\end{footnotesize}
cataleptic doses was not great; reduced blood pressure and vertigo were also reported. Added to this was the fact that it was very expensive to produce. A further problem was the lack of clarity regarding its site of action, although there was some evidence that bulbocapnine acted at the cortical level.278 It is significant that in 1932, Schaltenbrand recommended scopolamine and atropine as the most useful agents in the therapy of paralysis agitans and parkinsonism; harmine and bulbocapnine were mentioned only in passing.279 Interestingly, scopolamine was found to prolong bulbocapnine-induced catalepsy in the monkey as measured by the ‘hanging response’, in which the animal continues to grasp a horizontal bar for an abnormally extended period; on the other hand, scopolamine alone also elicited this response.280

Bulbocapnine was also tried as a therapy for the behavioural problems which were often more prominent than parkinsonian signs in children who had suffered encephalitis lethargica.281 These problems generally involved a loss of inhibition, leading to often violent and otherwise socially inappropriate responses to internal and external stimuli. Attempts to treat this syndrome, which in many ways resembles what is now described as “attention deficit disorder”, by psychotherapeutic means had proved futile, and attention had turned to chemical options. The usual narcotics, hypnotics and other central nervous system depressants had proved ineffective at doses which did not induce sleep in the patient. T.R. Hill (Post-Encephalitis Lethargica Unit, Metropolitan Asylums Board, London), however, had achieved some success by 1929 with bulbocapnine. Behavioural restlessness was controlled in six boys (total number treated was not given) by 3×0.1-0.2g/day (s.c. or p.o.) and continued as long as the drug was administered (at this point, up to 8 weeks). The major side effects were a slight drowsiness and lack of initiative, but Hill was pleased that some of the cases “became practically no more troublesome to look after than normal boys.” In a single case where the subject also presented mild general parkinsonism and dystrophia adipogenitalis, the parkinsonian rigidity was worsened by bulbocapnine and his behaviour not improved. Hill assumed that bulbocapnine was acting as a depressant at the thalamostriatal level, and discussed the similarities of schizophrenic catatonia, bulbocapnine-induced catatonia and the parkinsonian state.282 Clerici found that similar doses of the drug were particularly effective against impulsive rage and related changes in social behaviour.283 Bulbocapnine was also trialled in America in to treat the behavioural symptoms associated with chronic encephalitis in teenage boys, but without success.284 The drug does not appear to have been tried in girls.

The drug remained in limited use until the mid-1950s in post-encephalitic parkinsonism and chorea; the report of the Matheson Commission (1929) regarded bulbocapnine as worth further investigation,285 but Neal reported that it had been abandoned in New York as early as 1932 because of its toxic effects.286 Goodman and Gilman noted in 1955 that it was not official in America for any indication and difficult

278 De Jong, 1931; Krause and de Jong, 1931.
279 Schaltenbrand, 1932.
280 Paterson and Richter, 1933.
281 See, for example, Howe, 1930; von Economo, 1931, pp.128-131; and references therein. For psychiatric symptoms in adult patients, see Stern et al., 1930.
282 Hill, 1929b.
283 Clerici, 1929.
284 Jenkins and Rowley, 1936.
285 Darrach et al., pp.146-147.
286 Neal and Bentley, 1932.
to obtain. Hassler remarked in 1953 that it was especially useful for tremor, but had to be employed with caution because of the danger of inducingparkinsonian symptoms. In this respect, it is interesting that a number of substances known to stimulate higher cerebral centres antagonize bulbocapnine-induced catalepsy, including cocaine and benzedrine. Cocaine has apparently been used by some Australian physicians to manage rigidity but not tremor.

The pharmacology of bulbocapnine has proved to be a great deal more complicated than originally thought. While in some respects bulbocapnine acts as a dopamine receptor agonist, it also acts at some sites as an antagonist. Loewi’s pupil, Franz Brücke (Pharmacological Institute, Vienna), noted in 1935 that bulbocapnine blocked the ability of apomorphine to induce stereotypic behaviors in pigeons and rabbits, but did not inhibit its induction of emesis in dogs. He concluded that it was difficult to compare the effects of the drugs in different species, but also noted that the behavioral effects of apomorphine in pigeons and rabbits had been linked to the corpus striatum.

Sharman reported in 1966 that bulbocapnine elevated striatal concentrations of the dopamine metabolite homovanillic acid (HVA) without affecting dopamine levels, suggesting that it increased dopamine turnover, possibly by blocking autoreceptors. Interestingly, bulbocapnine was also reported to induce a fourfold increase in central histamine levels in the albino rat. The same group noted that bulbocapnine antagonized adrenergic and serotonergic effects. Finally, A.M. Ernst noted in 1962 the structural similarities of bulbocapnine, papaverine and a number of other drugs (including mescaline) which induce a “hypokinetic rigid syndrome with tremor” in animals, and proposed that O-methylation of the benzene ring underlay this phenomenon; he also suggested that O-methylation of dopamine in the para-position might cause rigidity in man. The positive effects of bulbocapnine on parkinsonism seem ultimately to have been more closely related to its potent sedative effects in humans than to a specific biochemical effect.

**Nicotine and curare**

It would be suggested in the 1950s that the effectiveness of antiparkinsonian agents was associated with their ability to antagonize the actions of nicotine. Many workers during the 1920s and 1930s also regarded the use of tobacco to be deleterious to the condition of their parkinsonian patients, although this appears to have been associated more with concepts of healthy lifestyle (alcohol and red meat were often also discouraged in debilitated patients) than a specific causal approach to the disorder. It is therefore somewhat curious that Henry Moll at the University of Leeds suggested in 1926 that nicotine (3×1/10 grain/day) was of “undoubted benefit” in the treatment of post-encephalitic parkinsonism. The rationale was that nicotine paralyzes the

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288 Hassler, 1953, p.831.
289 Buchman and Richter, 1933; Spiegel, 1938.
290 Maudsley and Macdonald, 1927.
291 Pendleton et al., 1975.
292 Brücke, 1935.
293 Sharman, 1966.
296 Ernst, 1962.
preganglionic sympathetic cells, and might thus block the sympathetic prespinal arc, thereby reducing plastic tone. Moll found that hypodermically applied nicotine (3×1/30-1/5 grain/day) elicited a marked, though temporary, reduction in rigidity, while leaving tremor and sialorrhea unaffected. It is, of course, interesting that smoking is associated with a reduced risk for Parkinson’s disease. Hyslop and colleagues, on the other hand, found that nicotine sulphate (1/30 grain ≈ 2mg s.c.) relieved rigidity for only a few minutes. Herrmann and Wotke administered 1-2mg nicotine tartrate to a patient who had reported that his tremor had been improved by heavy smoking; the pure alkaloid was ineffective, but a decoction of cigarette tobacco was found to be mildly beneficial in some cases. These reports, however, remained isolated.

Curare is the generic expression for any of a number of extracts employed as hunting poisons by South American natives; the first samples were brought to Europe by Walter Raleigh at the end of the 16th century. Alexander von Humboldt, amongst others, established in the early 19th century that curare in the eastern Amazon region derived from a number of Strychnos species, but it was not until the work of Gill in the 1930s that sufficient authentic drug was available to researchers for extensive scientific investigation. Given the limited role which the drug would play in antiparkinsonian therapy, the history and pharmacology of curare, fascinating though they are, cannot be discussed here in detail. It must suffice here to remark that the agent was prepared from a number of plant species, the exact choice depended on which plants were available in a particular tribal region. A variety of different forms of curare were distinguished:

- **Tube curare**: packed in bamboo tubes, derived principally from Brazil and Peru. It was prepared from menispermaceous species of the genus Chondrodendron. The first alkaloid (‘amorphous tubocurarine’) was isolated in 1895 by Boehm; it was crystallized in 1935 by King. Interestingly, tubocurarine is a dopamine derivative.
- **Calabash curare**: packed in gourds, derived principally from Guiana, Venezuela and Colombia. It was prepared from a number of Strychnos species. Its major alkaloid constituents are indole alkaloids, including the C-curarines and the toxiferines; the Strychnos alkaloids of South America, in contrast to those from the rest of the world, are mostly quaternary neuromuscular blocking agents. A total of nearly 200 alkaloids have been identified. Calash curare was formerly the usual form of commercial curare.
- **Pot curare**: packed in clay pots; it was also prepared from menispermaceous species.
- **Tin curare**: a viscous, dark brown extract which King showed to be equivalent to tube curare.

The term ‘curare’ (which, incidentally, is only one of several South American words for the preparation) was thus even less clearly defined than many of the traditional European plant preparations. This clearly rendered interpretation of its effects difficult,
especially as the type of curare was often not given or was, indeed, unknown to the physician.\textsuperscript{303}

The physiological action of curare was first described in 1846 by Claude Bernard, who proposed that it blocked nervous transmission at myoneural junctions. It was introduced almost immediately into the clinic, where it was employed to treat any form of convulsion, including epilepsy, rabies, tetanus, chorea, tics and strychnine poisoning; it was especially popular in France. By the 1870s, however, it had largely fallen out of use, although it remained listed in many pharmacopoeias.\textsuperscript{304} There were a number of reasons for this, including uncertainty about its action, improper dosing (the duration of the curare effect is quite short) and the poor quality of much of the curare used; more significant was the fact that its action was entirely inappropriate for the treatment of most diseases in which it was applied. This was largely due to ignorance of electrical aspects of nerve and muscle function, an ignorance which began to be relieved only in the first decade of the new century.\textsuperscript{305} The action of both curare and coniine was understood as paralysis of “\textit{the end-organs of the motor nerves}”, whereas gelsemine and methyl coniine paralyzed the motor centres in the brain.\textsuperscript{306}

But the thoughts of some physicians turned to the alkaloid towards the end of the 1920s as rigidity rose to become the most prominently regarded symptom of parkinsonism. Further, Bremer, Titeca and Van der Meiren had reported in a series of papers (1927-28) that curare relieved decerebrate rigidity and tetanus in the cat.\textsuperscript{307} Kairiukschtis and Kutorga (State Hospital, Kovno, Lithuania), who admitted in the opening of their paper that they were prepared to try just about anything in post-encephalitic parkinsonism, thus attempted in 1927 to reduce parkinsonian rigidity in six patients through application of 1.5-3mL ‘Curaril’ (Byk-Guldenwerke), a 0.5% curare solution; the solution was injected into muscles in which local rigidity was a problem. The injection itself was extremely painful, but four patients were afforded relief from rigidity in the treated muscle, without an effect on other symptoms; the effect was said to last for weeks. The authors recommended that curare be only used where local rigidity was a severe problem; otherwise, their standard therapy consisted of hyoscine, arsenic and tincture of cannabis.\textsuperscript{308} Royo Villanova and Pardo Canalis reported in 1933 that tremor of various origins – post-encephalitic, senile, hysterical, alcoholic, lead poisoning, hyperthyroidism – responded well to curare supplied by Merck (½% solution administered with novocaine as anesthetic), whereas less success was achieved in cases of paralysis agitans and multiple sclerosis.\textsuperscript{309} 

\textsuperscript{303} Tschirch, 1923, III, pp.463-471; West, 1935; McIntyre, 1972; Gilman et al., 1990, p.167; Bisset, 1995. Most of the classic papers related to curare were collected in the volume by Burnap and Little (1968), Burman noted in 1939 that there was generally only a limited amount of curare available for research; in 1938 there had been none.

\textsuperscript{304} According to Potter (1902), it had been reported to have effected cures in cases of tetanus, chorea and epilepsy, although the author does not exude his normal confidence in this respect except in the treatment of tetanus. It was not mentioned by Scoresby-Jackson in 1880.

\textsuperscript{305} West, 1935.

\textsuperscript{306} Potter, 1902.

\textsuperscript{307} References in West, 1932.

\textsuperscript{308} Kairiukschtis and Kutorga, 1927. Curare was used by veterinarians for relieving cramp, particularly in dogs.

\textsuperscript{309} Royo Villanova and Pardo Canalis, Revista Espanola de Medecina y Cirurgia Sept. 1933, cited in Mercks Jahresbericht for 1934, p.117.
Ranyard West is generally credited with having conducted the first major study of curare in man in the 20th century, publishing a comprehensive historical and pharmacological review on the subject in 1935. Three years earlier, West had administered 2-20mg curare from a thirty year old stock intramuscularly to thirty patients suffering from rigidity of various etiologies, including parkinsonism, epilepsy, multiple sclerosis and spastic hemiplegia. The agent, which he decried as a “resinous mass of the consistency of hard toffee” measurably reduced muscular rigidity of all origins without impairing voluntary muscular power; side effects included a drop in systolic blood pressure associated with giddiness; this effect, attributed to the alkaloid curine, could be counteracted by adrenaline. Bremer had noted this antagonism of curare and adrenaline, and also the fact that curare selectively reduced the rigidity associated with local tetanus; normal muscular tone could be spared by appropriate dosing. In 1939, Michael Burman (New York) administered up to 40mg curare intramuscularly or intravenously; the treatment effectively relieved spasm and muscular rigidity in patients with spastic paralysis. While tonus could not be completely abolished, it was possible to execute complex movements after treatment; certain forms of rigidity, however, were resistant to its effects, such as palmar flexion of the wrist. In 1949, Borgarello and Donegani reported their lack of success with curare in the treatment of parkinsonism.

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310 West, 1932. This paper contains the first employment of the word ‘lissive’ to describe the rigidity-relieving effect of curare.
311 Bremer, 1929; see also Burman, 1939.
312 Burman, 1939.
The scarcity of curare prompted Burman to try the alkaloid *erythroidine*, listed in the U.S. Pharmacopoeia as a powerful muscle relaxant, in a limited number of patients. The agent had been isolated by Altamirano in 1888 from *Erythrina coralloides* and in 1937 by Folkers and Major from *E. americana*. Of the two isomers, β-erythroidine proved to be the most convenient to isolate in a pure state, and also exhibited the most potent action as a powerful muscular paralyzant. Burman’s preliminary results indicated that it had to be administered in larger quantities (up to almost a gram) than curare, but exerted similar effects with a broader range of safety. It was also easier to prepare and standardize. Harvey reported similar results in 1942.

Despite some indications that curare and erythroidine might be useful in the treatment of rigidity, safety and convenience factors, as well as their brevity of action, prevented their widespread application. Berger reported in 1956 that intramuscular depot curare was a valuable adjunct to benzhexol/benztropine therapy in severely incapacitated paralysis agitans patients, but it remained an isolated report. A derivative of β-erythroidine, dihydro-β-erythroidine, would be re-examined in the 1950s (see below), and a number of synthetic curare analogs would be tried, but none succeeded in gaining a major role in the therapy of parkinsonism. It would later be discovered that the neuromuscular blocking effect of curare (which does not cross the blood-brain barrier) was inappropriate for the treatment of parkinsonian rigidity, which is determined centrally and not in the neuromuscular junction. Curare alkaloids found wider application as a muscle relaxant for use before general anesthesia or electroconvulsive therapy, although even here they were ultimately supplanted by synthetic analogs.

‘Striaphorin’ and ‘Neurosmon’

An organotherapeutic approach was introduced in the mid-1920s in Berlin by Professor H. Rosin. On the basis that the basal ganglia had been shown by several studies to be an important centre for automatic motor activity, Rosin had asked the firm Dr. Freund & Dr. Redlich to prepare an extract of the “large nervous nuclei which are designated in a broad sense as the striatal nuclei”; the source of the material was bovine. The extract, designated “Striaphorin”, was administered to patients as tablets three times a day. In 1927, Rosin reported that he had used this agent for two years, and announced that he would be making a more detailed report on his successes elsewhere; the purpose of the current report was to encourage further investigation. He had treated a total of eight advanced parkinsonian patients with ‘Striaphorin’ with great success; they exhibited “stabilization of their condition and even remission while using the agent, exacerbation when it was withdrawn.” Rosin presumed that the administration of ‘Striaphorin’ “supplemented or stimulated the [consequences of] the loss or, at least, reduced activity of the functional activity of those central ganglia”, which ganglia he presumed to be central to the symptoms of paralysis agitans. The theoretical basis of the therapy was extremely interesting. Rosin noted that the ‘Striaphorin’ therapy pursued...
different goals and was founded on an entirely different premise to scopolamine and harmine, the most popular antiparkinsonian agents at the time:

_It may be assumed that the functional failure or loss of the striatal ganglia is supplemented or stimulated through the administration of its own healthy substance; on the condition that the administered elements are not destroyed by digestion and can access the damaged region via the circulation and can there be somehow utilized. . . . it is possible that degenerating centres in the central nervous system can still be rescued or that such centres which are liable to degeneration can be preserved by administration of healthy nervous substance with the same function._ \(^{317}\)

Supplementation of reduced nervous function by administration of brain extracts was quite popular in the 1920s and 1930s;\(^{318}\) nevertheless, the conceptual link with later transmitter supplementation and neurotransplantation therapies cannot be overlooked. That certain brain regions were responsible for certain functions had been established in the 19th century, and it was assumed that substances contained within a region were of functional significance; in 1930, however, it was unknown which substances were important and how any of the candidates might be linked to a particular function. Administration of the entire organ was thus quite a logical approach – with the caveats noted by Rosin.

He was aware of all the objections which could be levelled at this purely empirical approach to the therapy of paralysis agitans:

_ but these reservations must be put to one side when, as appears to the case here, success can be achieved with a disorder, the resistance of which to any therapy and whose hopeless course is known._ \(^{319}\)

A similar plea could have been expressed 35 years later when L-DOPA was first introduced. It was an expensive therapy, costing about 50 Mark per month due to the preparation of the brains; Rosin recognized that its parenteral application might have been more effective, but more expensive and inconvenient. Professor Toby Cohn, also of Berlin, added his cautious recommendation of ‘Striaphorin’ on the same page as Rosin’s preliminary report; he had received the agent from Rosin, and treated thirteen paralysis agitans and five post-encephalitic parkinsonian patients for periods of weeks to months during the previous year. The post-encephalitic patients did not respond to the drug, with one exception; the paralysis agitans cases, all in an advanced stage of the disease, experienced considerable relief of their subjective symptoms with regard to rigor, tremor and freedom of movement. Cohn was not so certain that objective improvement had occurred, although the rigidity may have been reduced.\(^{320}\) Leibholz, who also received his material from Rosin, also reported positive results in a limited number of patients, with almost total abolition of tremor and improvement of speech and memory.\(^{321}\)

\(^{317}\) Ibid.

\(^{318}\) See the extensive list of brain extract preparations in Frerichs _et al._, 1927-29, pp.361-363.

\(^{319}\) Rosin, 1927.

\(^{320}\) Cohn, 1927.

\(^{321}\) Cited in Rosin, 1930, and _Mercks Jahresbericht_ for 1930 (English edition), p.284. Rosin noted that at this point only he and these two workers had employed the extract.
In early 1929, Rosin recommended the combination of ‘Striaphorin’ with the newly introduced banisterine (see below).322 In the following year, he claimed success in twelve of thirty-four treated patients, with possibility of a beneficial influence in nine others (he suspected that the cost of ‘Striaphorin’ had dissuaded some patients from using it as regularly as recommended), the use of scopolamine with the preparation, particularly at the beginning of therapy, was to be commended. Rosin also registered in this paper his claim to priority with regard to the use of nervous material as a stimulant in the treatment of a neurological disease.323 Apart from these few references, however, I have not located further discussions of the therapy in the literature. ‘Striaphorin’ (manufacturer: Schering-C.A.F. Kahlbaum, Berlin-Adlershof) was listed as a treatment for Parkinson’s disease in the 1929 edition of the Handbuch der praktischen und wissenschaftlichen Pharmazie324 and the 1948 Repertorium pharmaceutischer Spezialpräparate,325 but by 1936, E. Gamper (Prague) was dismissing the successes of Rosin and Cohn as the result of the exceptional suggestibility of parkinsonian patients; he himself had, however, also tried the therapy in his parkinsonian patients (without lasting success).326

A related philosophy was represented by ‘Neurosmon’, a preparation of cerebral and spinal lipid and protein developed by A. Gehrke (University Surgical Clinic, Berlin) and marketed by the Hamburg firm Promonta as a further development of its lipid-phosphatide extract “Promonta-Nerven-Nahrung” (= ‘nerve-food’).327 Herzog noted that it was important to avoid high temperatures in its preparation, as the preservation of naturally occurring enzymes and hormones was desired; this, in turn, demanded that stringent hygienic standards be observed.328 The original product possessed only low efficacy:

> Then – according to Bier – his colleague came to the “happy insight” that the nervous system should be stimulated with strychnine and so “rendered receptive to the organ extract which would otherwise be rejected by it”. Brilliant successes are now said to have been achieved with the preparation.329

The preparation was thus marketed in two forms: ‘Neurosmon’-stark’ (‘strong’; combined ‘Neurosmon’ with 0.5-1.0mg strychnine per tablet) and ‘Neurosmon’-schwach’ (‘weak’), the two to be employed alternatively. Similar preparations were planned for kidney and gastrointestinal disorders.

Gehrke saw a course of treatment with ‘Neurosmon’-stark as the ideal means for stimulating the central nervous system and increasing cerebral perfusion in degenerative disorders, such as tabes dorsalis, polyneuritis and multiple sclerosis.330 Pohl von Pollenburg (Ravenstein) reported in 1930 that the Gehrke treatment also relieved most of the symptoms of post-encephalitic parkinsonism, including rigidity and depression.

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322 Rosin, in discussion of Lewin and Schuster, 1929.
323 Rosin, 1930.
324 Thoms, 1927-29, VI, p.2076.
325 Ludwig et al., 1948, p.888. Curiously, Rosin (1930) commented that he had requested that Schering not list the preparation in their catalog.
326 Gamper, 1936, p.799. Witzleben dismissed the therapy in 1942 as being of “little importance”; p.35.
327 Ludwig et al., 1948, p.620.
328 Herzog, 1930.
329 Ibid.
330 Gehrke, 1929.
Citing the results of a number of workers (without, however, giving exact details) regarding the increased sensitivity of the brain for a number of alkaloids following administration of ‘Neurosmon’, he suggested that:

*through the administration of the unchanged brain lipoids contained in ‘Neurosmon’, the defensive capacity of the central nervous system is increased and existing damage to cells is repaired by the administered lipoids.*

Von Pollenburg thus regarded ‘Neurosmon’ therapy as playing an *“etiological role”* in the treatment of post-encephalitic parkinsonism which he complemented with symptomatic treatment with harmine (see below). Enge (Strecknitz Sanatorium, Lübeck) reported an almost complete cure of a patient who had developed parkinsonian symptoms following influenza-induced encephalitis; the ‘Neurosmon’ treatment lasted just over five weeks. Polstorff reported that the combination of ‘Neurosmon’ and high atropine therapy was useful. Despite such positive experiences, however, organotherapy of post-encephalitic parkinsonism was not extensively employed after the emergence of high atropine therapy, and was, in fact, regarded by most workers as worthless.

**The harmala alkaloids**

An interesting addition to therapy of parkinsonism was the introduction of the harmala alkaloids at the end of the 1920s. Harmine, or methoxyharman, is found in a number of plants, usually in association with a wide variety of other alkaloids, but the two names by which it was known in this period derived from plants found at opposite ends of the world:

- the seed-pods of the Asian or Syrian rue, *Peganum harmala* (family *Zygophyllaceae*), native to the Russian steppe (where it is known as ‘Zyserlik’; also found in northern India, north Africa and southern Europe).
- the liana *Banisteria caapi* (*Malpighiaceae*), native to the rainforests of northern South America.

The Syrian rue is a hairless bush up to one metre high; it is profusely branched and covered with short, spiky multifid leaves (c. 6-7 cm). The white flowers are enclosed in deep calices; the capsule is spherical (c. 1 cm across), deeply lobed, and contains three seeds, each in a separate chamber. The active alkaloids are found only in the seed husks, which Tschirch described as *“one of the most beautiful objects of microhistochemistry”*. The plant, however, is regarded as a noxious weed; it suppresses the growth of other plants but is itself not eaten by any animal. It has long been utilized for anesthetic and intoxicant purposes, the latter especially in the context...
of religious rituals. In Ayurvedic medicine, the Asian rue is listed as an anthelmintic, febrifuge (especially in chronic malaria), anodyne, antiseptic and abortifacient, as well as for inducing lactation and menses.\(^{338}\) Both Syrian rue and the common rue (\textit{Ruta graveolens}) were important to ancient Greek medicine;\(^{339}\) \textit{Peganon agaron} is one of the several plants which have been identified with \textit{μωλυ} (\textit{moly}), the plant which Hermes gave Odysseus to protect him against the potions of Circe. Dioskorides noted that this was due to its white flowers and black root, the only clues which Homer gave as to the identity of the magic plant. Dioskorides recorded a preparation of the bitter seeds which was good for "\textit{dullness of sight}".\(^{340}\) Avicenna also listed the plant in the second volume of his \textit{Canon}, where he added to Dioskorides’ commentary the observations that it was also a powerful emetic, and could be used to induce urine or menstruation; perhaps its most useful use was that it could render the drunken sober.\(^{341}\) A broad range of further disorders are reputed to have been treated with parts of the plant at one time or another. The Persians treated edema with extracts of the plant, while Turks used it both as a spice and in the preparation of the dye "Turkish" or "Harmala red", identified with harmalol.\(^{342}\)

This latter compound attracted the especial attention of western chemists, as most alkaloids are colorless, and the presence of the dye led to the first commercial exploitation of the plant in Europe.\(^{343}\) The keen competition between Goebel (Dorpat), who was the first to isolate the dye (which he named ‘harmala’), and Fritzsche (St Petersburg) regarding this compound was recorded by Goebel himself in 1841:

\textit{For the fact that I have not described here how one converts harmaline into harmala I beg the kind patience of the reader. . . . I had to publish the current preliminary report on the new pigment in order not to lose the priority on a discovery made by myself three years ago, for the government official Mr. Fritzsche in St. Petersburg, who is well acquainted with my scientific and technical occupation with harmala, has also begun investigations of the seeds of the harmala plant, without informing me.}\(^{344}\)

The Russian government bought the “secret” of harmala synthesis from Goebel (ostensibly with aim of publishing it),\(^{345}\) but Fritzsche had already elucidated the process independently, naming the compound ‘harmalol’.\(^{346}\) Harmaline is also anthelminthic. By the twentieth century, the plant had not been used therapeutically in Europe for some time, although Baillon noted in 1873 that the seeds had a stimulant effect.\(^{347}\) Pharmacists were thus surprised when harmine, itself having been known in the laboratory for nearly a century, came to use in the clinic in 1928.

\(^{339}\) Kroll, 1914, 296-300.
\(^{340}\) Dioskorides, III, 53. He described \textit{Ruta graveolens} in III, 52 (\textit{Peganon to kepaion}).
\(^{341}\) Avicenna, 1507, II, cccxl. Duke (1985) lists "insect repellant, pediculicide, and pesticide; . . . abortifacient, alterative, amebicidal, anodyne, aphrodisiac, diuretic, emetic, emmenagogue, intoxicant, lactagogue, narcotic, soporific, stimulant, sudorific, and vermifuge, . . . asthma, calculus, cancer, colic, dysmenorrhea, fever, gallstones, hiccups, hysteria, jaundice, laryngitis, malaria, neuralgia, parkinsonism, prolapse of the womb, rheumatism, and urogenital ailments." (p.352)

The Germans are said to have used it as a truth serum during World War II; Emboden, 1972, p.168.

\(^{342}\) Flury, 1911.

\(^{343}\) The descriptions by Flury of the metabolic products of harmine in the rabbit are correspondingly colorful. Harmine itself is colorless; harmaline salts are yellow; harmol is green; Flury, 1911.

\(^{344}\) Goebel, 1841.

\(^{345}\) Anonymus, 1848.

\(^{346}\) Fritzsche, 1848a; 1848b.

\(^{347}\) Cited in Neuner and Tappeiner, 1895.
Two active principles had been isolated from the husks of the seed in the first half of the 19th century, the bitter-tasting harmaline (dihydroharmine) by Goebel (1837) and harmine by Fritzche (1848). The first, constituting 4% of the seed mass, was found to be a febrifuge and thus aroused revived interest in the plant. But the first detailed pharmacological investigations were reported by the Munich pharmacologists Tappeiner and Neuner (1895) and the Würzburg pharmacologist Flury (1911); the latter found that both harmine and harmaline induced convulsions in animals and concluded that there was no indication that either would be useful additions to the clinic. The seed husk consists of about 4% alkaloid, two-thirds of which is harmaline. Harmine was found to induce cramps and paralysis in mammals, to increase blood pressure and salivary production and to elicit respiratory irregularities; the toxicity of the alkaloids results from paralysis of the respiratory organs. The seeds also contain harmalol and peganine (vasicine) and a red resin with an odor similar to that of Cannabis indica.

The trigger for introducing harmine into the modern pharmacopoeia was provided by the mescaline-like hallucinogenic and other psychological effects induced by yagé (or yaqué), prepared from Banisteria caapi by South American natives; the most commonly cited native name for the plant was Aya-Huasca, or “dead man’s wine”. The sacred drink also known by this name always contained ayahuasca, but usually in combination with DMT-containing leaves of plants such as chacruna (Psychotria viridis or similar species) and oco yagé (Diplopterys cabrerana). The rich visual hallucinations were the especial feature of the drug; they were notably absent from descriptions of the.

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348 Flury, 1911.
349 Neuner and Tappeiner, 1895; Flury, 1911; Tschirch, 1923, III, p.731.
350 Caapi is the name used by the Jibaro tribe. See especially Lewin, 1924, pp.140-144; McKenna et al., 1995. It is interesting to note that increased density of platelet 5-HT uptake sites has been found in ayahuasca drinkers: Callaway et al., 1994.
351 “The partaker ‘sees’ all the tribal divinities; the creation of the universe, of the first human beings, and of the animals; . . . jaguars, alligators, snakes, and turtles, in complex mythological scenes.” Ayensu, Medicinal plants of West Africa (Reference Publication, Algonac, Michigan, 1978), p.330, cited in Duke, 1985, p.75. Apart from harmala alkaloids, the liana includes a number of other psychoactive agents, including a variety of methylated tryptamine derivatives; ibid., p.76. See also Rivier and Lindgren, 1972.
effects of the alkaloid harmine which were to be reported in Europe. It may also have been used by the natives for senile paralysis. The plant is a climbing liana with zygomorphic flowers arranged in racemes; there are seventy varieties of Banisteria in South America (mostly in the forests of Brazil), and some doubt has been raised concerning the identity of at least some of the B. caapi which reached Europe; it has also been recently reported that yagé is, in fact, a generic term for a number of ritual and medicinal preparations derived by native Americans from a variety of plant sources.

Richard Spruce described and named Banisteria caapi in 1853, having become acquainted with the intoxicating drink prepared from the vine in November 1852, and the plant and drug were first presented in a work generally available in Europe by Manuel Villavicencio (Quito) in 1858. But the drug became well known in Europe only after an expedition by Zerda-Bayón in the first decade of the 20th century, whose reports were popularized in France by Warcollier. In 1905, Zerda-Bayón identified the presence in the drug of an alkaloid which he named ‘telepathin’, but Fischer-Cardenas was the first to isolate the substance, as described in the first scientific publication regarding yagé, his thesis published by the University of Bogota in 1923. He noted that the alkaloid possessed an action similar to but safer than hashish. Barriga-Villalba, also of Bogota, pursued the investigation of the alkaloid further, which he crystallized and named ‘yajéine’ in 1925, leading to broader interest being aroused in Europe. The Belgian Edouard Clinquart published a detailed examination of the macro- and microscopic structure of the source leaf and its chemical components in 1926; in France, Perrot and Raymond-Hamet confirmed the presence of an alkaloid identical with that described by his Colombian colleagues, for which they preferred the name ‘telepathin’. These workers, in turn, provided Hoffmann-La Roche (Basel) with 9kg of raw yagé, from which Elger isolated an alkaloid in 1927 which he demonstrated (with the assistance of Robert Robinson in Manchester) to be identical with harmine; it was, in fact, purer than that commercially available, which was normally contaminated with harmaline. Further, the Director of the Kew Botanical Gardens in London, A.W. Hill, had confirmed that the liana supplied to Elger was authentic B. caapi.

More recent investigations of the plant revealed that the vine contains 0.11-0.83% alkaloid, the branches up to 0.4% and the leaves 0.3-0.7%, while the alkaloid content of the root may be as high as 2%. Harmine constitutes between 40 and 96% of total alkaloid, harmaline 0-15%. A panoply of minor alkaloids is also present.
Merck, which had been investigating harmine since 1911, received a large quantity of yagé from Colombia in March 1926, and isolated an alkaloid from the plant in 1927. The company then decided to enlist the help of the prominent pharmacologist Louis Lewin (1850-1929) to further investigate the alkaloid. Lewin was an intriguing character who worked in partly self-imposed isolation from conventional academic circles in a “dingy apartment” in the Ziegelstrasse in Berlin. Born in West Prussia, he had spent most of his life in Berlin; he received his medical degree in 1875 and completed his habilitation in pharmacology in 1881. Despite his difficult temperament and his refusal to abandon his Jewish faith (for which reason a standard academic career was impossible), he was highly regarded by academic scientists and clinicians. Working from the private laboratory in his apartment, he was one of the first investigators of morphine addiction; his work on the Mezcal cactus (source of mescaline) resulted in its being named *Anhalonium lewinii*. His study also served as a lecture hall for pharmacology students, often illustrated by practical demonstrations of the drugs which formed the topic of instruction, and was reportedly always filled to capacity. Lewin’s range of academic interests was broad, his command of languages remarkable; Huebner attempted to encapsulate his field of intellectual activity thus:

*Every type of effect of chemical substances interested him, and every type of connection of these effects with other aspects of human activity: the criminal poisoning of historical persons of days long past or the use of medicinal plants by primitive peoples no less than the voluntary self-poisoning of the addict or the unwitting poisoning of the industrial worker of our time.*

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362 Wolfes and Rumpf, 1928.
363 Macht, 1931.
364 Heubner, 1930.
Lewin’s literary output was immense, and included several authoritative volumes on toxicology, the side effects of drugs, abortificants, as well as a book on the role of poisons in history. By the time Merck asked him to examine banisterine, appropriate in light of his authoritative text on psychotropic agents (Phantastica, die betäubenden und erregenden Genußmittel; 1924), he was in semi-retirement, having been professor at the Technical University of Berlin since 1919; the handful of publications dealing with the alkaloid of B. caapi were the only ones to appear after the publication of Phantastica.

Lewin initially dubbed the alkaloid isolated from the liana ‘yagéin’, and then ‘banisterine’, after the plant supplied to him had been identified. Lewin, having examined its effects both in dogs and monkeys, found that small doses (25-70mg s.c.) led to feelings of euphoria, warmth and lightness of the limbs in neurological patients in the Neukölln Hospital. Lewin then considered whether it might be useful in the treatment of paralysis agitans; according to his own report, he requested that Wilmanns and Beringer carry out the corresponding experiments in Heidelberg. At a presentation by Lewin and Paul Schuster (Neurological Ward, Hufeland Hospital, Berlin) before the Berlin Medical Society in February 1929, however, this suggestion was recorded as having been made by Wilmanns. Merck had already conclusively established the chemical identity of harmine and banisterine by this point, but Lewin remained unconvinced until his death a year later. Merck had determined that the two substances shared common empirical formulae, melting points, fluorescence properties and metabolism, but Lewin repeatedly insisted that there was no substitute for banisterine and that harmine did not have the same clinical efficacy.

Lewin regarded banisterine as being far superior to hyoscine in its effects on rigor. At the beginning of 1928 he reported in Paris that experiments by Wilmanns and Beringer had indicated that banisterine might be useful in the treatment of cardiac disease:

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Harman

Harmine

Harmaline

Harmalol

**Figure 5-10**: The major ‘harmala alkaloids’.

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366 Lewin, 1928a; this was also the opinion of Schuster in 1931. Lewin’s paper was submitted in October 1927; Wolfes and Ivers were also prepared to publish their results in 1927, but due to “outside circumstances” (Wolfes and Ivers), the paper was delayed until 1928, after the appearance of Elger’s paper (as they somewhat ruefully noted).

367 Lewin and Schuster, 1929.

368 Lewin had never fully recovered from a brain hemorrhage which he suffered in 1928.

369 Lewin, 1928a, 1928b; Lewin and Schuster, 1929. For the identification of the two compounds: Wolfes and Ivers, 1929; Kreitmair, 1929; Gunn, 1929; Beringer and Wilmanns, 1929; Dalmer, 1929.
But even more so, those suffering inflammation of the brain (encephalitis lethargica), so-called cerebral influenza, and treated with banisterine, felt better, perceived that their condition had improved. Muscular rigidity, the most apparent symptom of the disease, decreased. The gait became freer, and speech more accented. With 0.04g, the rigidity disappeared almost entirely. Remedies hitherto used are far from equaling banisterine.36

Schuster had treated eighteen patients with “paralysis agitans and similar striatal diseases”, with similar success; the side effects – light nausea, itching, paleness, occasional vomiting – were minimal. Most patients experienced relief of their rigor for several hours, in some cases for days; Schuster and Lewin were thus searching for a means to extend the effect, and were trying constriction of the jugular vein.371 In the discussion, Stern offered that he had treated four patients with a similar substance, harmine; Lewin replied that the two alkaloids were probably not pharmacologically identical. The editors of the journal felt obliged to append a footnote that Merck had indicated that the two were in fact the same substance, and that harmine was freely available in Germany in 0.02g ampoules. Shortly afterwards, the Senior Consultant in Schuster’s department, H. Pinéas, published a report comparing his experiences of the effects of banisterine and harmine in extrapyramidal patients. The trial reported by Schuster and Lewin had been his direct responsibility, while Merck had supplied him with harmine at about the same time. Harmine, like banisterine, was found to be of benefit for most patients suffering from post-encephalitic parkinsonism, and to a lesser extent for those with paralysis agitans; rejecting the need for standardized tests of performance, he noted the increased freedom of movement and liveliness of affect and face of the responding patients.372

Lewin approached government authorities in 1929 for the funding of an expedition to South America to acquire more banisterine. While the Asian rue was easy to procure, the required liana was found in almost inaccessible regions of Peru, Ecuador and Colombia. Further, the alkaloid yield from this plant was low (ca. 0.4%); at the beginning of 1929 he noted that the entire German supply of banisterine amounted to 1.2g, and 50kg of the liana were required to produce 200g of the drug. As a result, a mineralogical institute was commissioned with the closer analysis of harmine and banisterine: crystal analysis, polarization microscopy, X-ray examination and ultraviolet absorption all confirmed the identity of the two substances.373 The Health Department decided thereupon that the South American expedition was not required.374 Flury was also stimulated by the “sensational reports” in the newspapers to write to the Münchener medizinische Wochenschrift that harmine was not “an extremely precious, rare and newly discovered medication”, but rather a well researched agent from a broadly distributed plant available in virtually unlimited quantities.375 There was no shortage of emotion in the banisterine story.

Kurt Beringer (1893-1949; Psychiatric and Neurological Clinic, Heidelberg) was also consulted by Merck in 1927, and wrote in May 1928 of a “new alkaloid with effects on the extrapyramidal motor system (banisterine)”. Beringer, after serving on

370 Lewin, 1928b.
371 Lewin and Schuster, 1929.
372 Pinéas, 1929.
373 Brückl and Mußgnug, 1929. See also Chen and Chen, 1939.
374 Dalmer, 1929; Herzog, 1930.
375 Flury, 1929.
the Russian front in the First World War, had worked at the Heidelberg clinic under Wilmanns since 1921. Here he was exposed to the methodological ideas of the Karl Jaspers school which had been adopted enthusiastically by the Heidelberg psychiatry: the practice of psychopathology with the phenomenological spirit and clarity of definitions which allowed it to be simultaneously an instrument of investigation and of diagnosis.\textsuperscript{376} Beringer’s major research area in the 1920s had been idiopathic and drug-induced psychosis, in the course of which he prepared his important works on \textit{Schizophrenic thought disturbances} (1924, 1926) and the habilitation work which appeared in 1927 under the title \textit{Mescaline intoxication, its history and features}. The latter work described self-experiments which provoked him to take the utterances of schizophrenics seriously, but not as literally as was currently the case in German psychiatry.\textsuperscript{377}

Beringer had commenced his experiments with banisterine in December 1926. The dose recommended by Merck on the basis of animal experiments (30-50mg.kg\textsuperscript{-1}; this would have rendered it one of the least toxic alkaloids known) proved to be far too high when administered to one of the laboratory assistants, and elicited alarming toxic responses, amongst which Beringer emphasized the “uncontrollable tremor of the arms and legs, similar to that which we see in parkinsonian patients.”\textsuperscript{378} This prompted Beringer to consult the literature, where he discovered that banisterine intoxication was often accompanied by marked ease of movement, and he hypothesized that the drug might be of benefit for parkinsonian rigidity. Beringer also consulted Lewin, who supported his idea, and encouraged him to proceed in that direction.\textsuperscript{379} His first experiments (in fifteen patients) were successes:

\begin{quote}
I thus gave post-encephalitic patients 0.02[g] banisterine. It was now evident that this alkaloid actually exercised a surprising effect on some of the parkinsonian symptoms, and indeed on both rigor and hypokinesia. The tremor, on the other hand, was not significantly affected.\textsuperscript{380}
\end{quote}

In one case, the benefit appeared to last for more than a week following administration. Beringer found it paradoxical, on the other hand, that some patients felt subjectively better when taking hyoscine, although the objective effect of this drug was not as great. Banisterine was effective per os or subcutaneously applied, but the toxicity of the drug at doses slightly higher than that required for the therapeutic effect dictated that the accidental injection into a vein had to be avoided. Beringer made the acute observation that patients who responded well to banisterine did not necessarily make use of their new-found recovery of motor function; he interpreted this surprising circumstance as indicating that the psychic effects of the post-encephalitic syndrome – the lack of motivation, of responsiveness, the slowness of thought – were not directly related to the loss of motor function. He saw this insight as an example of the possibilities of using

\begin{footnotes}
\item Jaspers had transferred from psychology to become Professor of Philosophy at Heidelberg in 1921.
\item Obituaries: Jung, 1949; Zutt, 1949.
\item Beringer, 1928.
\item In his 1929a paper on the drug, Beringer commented that Lewin had not known in advance of this experiment; “\textit{he has therefore mistaken, when he claims that the experiment was undertaken at his request.}” Paul Schuster, Director of the Neurological Department of the Hufeland Hospital in Berlin, who had investigated harmine in parkinsonian patients with Lewin, concurred with Beringer’s view of the priority question: Schuster, 1929b.
\item Beringer, 1928.
\end{footnotes}
banisterine and similar agents for investigating the connections between the symptoms of this and other neurological disorders.\textsuperscript{381}

The variability of response, however, was a problem, and Beringer warned that the alkaloid should not be used arbitrarily, nor should “hopes be aroused in the sick that are not subsequently fulfilled and therefore elicit disappointment.”\textsuperscript{382} In a similar vein, Beringer commenced a short overview of the therapy in 1929 with the remark:

\begin{quote}
The writer wrote a year ago for the first time about the effectiveness of banisterine on the extrapyramidal motor system in post-encephalitic conditions as well as in paralysis agitans. Shortly afterwards, exaggerated and extravagant reports appeared in the newspapers about the miraculous effect of banisterine . . . which overstated the clinical findings in an irresponsible manner and aroused hopes in the ill which could not be fulfilled.\textsuperscript{383}
\end{quote}

Medical breakthroughs were clearly as liable to sensationalization in 1928 as they are now; further, the attention which banisterine attracted underlines the public significance at this time of a drug which promised to control the symptoms of parkinsonism. A number of German clinics had reported positive experiences with the alkaloid during 1929 and 1930,\textsuperscript{384} Merck devoted the first nineteen pages of the Jahresbericht über Neuerungen auf den Gebieten der Pharmakotherapie to harmine,\textsuperscript{385} and its fame had even extended to England, where the Oxford pharmacologist P. Gunn had published his initial positive impressions in the \textit{Lancet},\textsuperscript{386} and France,\textsuperscript{387} Beringer feared that the drug might fall into disfavour with respectable clinicians as a result of the irresponsible media coverage of the scientific findings. This was especially imaginable, as the mechanism of action of banisterine was still obscure; his investigations had led him to believe that its effects were not limited to the extrapyramidal system.\textsuperscript{388}

Progress, however, had also been made: the chemical and pharmacological identity of harmine and banisterine was now generally accepted; Lewin’s objections to this view, which he maintained until his death, no longer carried much weight, as harmine, in contrast to banisterine, was commercially available in usable quantities. Harmine proved to be of benefit in paralysis agitans, post-encephalitic parkinsonism, pallidal rigidity following carbon monoxide poisoning and arteriosclerotic rigidity. In each case, improvements in voluntary movement and, to a lesser extent, of the rigor were reported; the greatest obstacle to its acceptance, however, was the fact that some workers reported that the effect did not last much longer than an hour. Other clinicians, however, saw subjective and objective improvements which lasted for periods of days following administration.\textsuperscript{389} A further problem was that many clinicians saw no or little effect

\begin{footnotes}
381 Ibid.
382 Ibid.
383 Beringer, 1929a.
384 Amongst others: Rustige, 1929; Fischer, 1929; Beringer and Wilmanns, 1929; Schuster, 1929a; Frank and Schlesinger, 1930; von Pollenburg, 1930; Rosenberger, 1930.
385 With contributions from Wolfes and Ivers (chemistry), Kreitmair (pharmacology) and Beringer (therapeutics).
386 Gunn, 1929.
387 Decourt and Bocquentin, 1929; these workers, however, conceded that they could not recommend harmine with the same enthusiasm as their German colleagues, and were not convinced that it was superior to scopolamine or stramonium. See also Devic \textit{et al.}, 1930.
388 Beringer, 1929a; Beringer and Wilmanns, 1929.
389 Anonymus, 1930; Marinesco \textit{et al.}, 1930; see also references in footnote 384.
\end{footnotes}
following oral administration; it was, however, reported that keratinized gelatin capsules containing the drug were more effective than tablets, but the daily dose needed to be raised to 40-120mg. Harmine suppositories were also found to be effective in some cases. On the positive side, there were no lasting damaging effects associated with the alkaloid when the dose was controlled to avoid intoxication. Further, Beringer had treated some patients for more than a year with harmine (principally in the form of keratinized capsules distributed throughout the day) without indications that the effect had diminished; he had also commenced experimental infusion of *Peganum* extracts, and found that these had a remarkable effect on tremor. Beringer nonetheless recommended that patients continue to be treated concurrently with atropine and scopolamine, as the harmine effect was somewhat “moody”:

\[ \text{The brilliant successes are currently a minority, and are matched by an equal number of complete treatment failures. In between lie the bulk of the cases, where only a moderately significant improvement of varying practical and therapeutic degree can be achieved. The reason for this unreliability of the therapeutic effect, in total as well as with respect to specific symptoms, is currently as unknown as the mechanism by which the alkaloid acts.}^{391} \]

Beringer and Wilmanns were of the opinion, however, that failure of harmine alone to achieve satisfactory results should not be cause for its being immediately abandoned; combination with a solanaceous alkaloid could be more effective. Further, they were also examining the effects of total fluid extracts of *Peganum harmala*, as:

\[ \text{it is well known that total extracts of the plant are not infrequently superior to the administration of isolated components.}^{392} \]

Unlike belladonna, however, total plant extracts were never a popular means for the administration of harmine.

Ernst Rustige (Psychiatric and Neurological Clinic, University of Göttingen) received sufficient harmine from Merck for twenty-seven injections (5-50mg) in a total of eighteen patients and for oral administration (3×10mg/day for several days) in two patients. Rustige reached largely the same conclusions as Beringer; he noted principally, however, a general improvement of the overall motor function, demonstrated in objectively increased speed and variety of movement, and including a return of the so-called accompanying movements, which are lacking in parkinsonism. Oculogyric crises, however, were unresponsive. The improvement of both voluntary and automatic aspects of motor performance was accompanied by a psychological reaction (*Rückstoß auf die Psyche*) which was similarly absent from Beringer’s experiences:

\[ \text{These patients were pleased – unfortunately, overly pleased – with the new agent which would now help them: they repeatedly showed the other patients with pride everything of which they were now capable, and were disappointed over the rapid decline of the} \]

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390 Beringer, 1929b.
391 Beringer and Wilmanns, 1929. Beringer was appointed Director of the Psychiatric and Neurological Clinic in Freiburg in 1934, where he continued his research into a number of matters, including disturbances of motivation in the brain-damaged until his death in 1949. In 1929 he was co-founder of the *Nervenarzt*; he also edited a number of other journals.
Rustige cited the example of an academic who requested harmine injections before giving lectures or attending conferences, in order to be able to move more freely and be less aware of the disorder; another patient asked for harmine before undertaking a journey. But he also noted that in only in six of the patients could an objective reduction in rigidity be measured; further, tremor was reduced by harmine in six patients, but increased in three. More critically, the improvement in voluntary movement rarely lasted more than an hour. The effect of the drug was thus certainly remarkable, but also tinged with the psychological effects mentioned above by Hall (page 136). This was especially true in the case of harmine, lauded in the press as a wonder treatment.

By the end of 1930, the literature on the beneficial effects of harmine for the rigidity and hypokinesia of post-encephalitic parkinsonism (but not on tremor) had grown. In general, the cogwheel rigidity, the oculogyric crises and the réflexes de posture were decreased and the spirit elevated by harmine; the lack of accompanying movements, the vegetative symptoms, the mask face and the tremor generally remained, although there were reports that these symptoms were also resolved. In a brief report to the Berlin Medical Society, Erich Jacobi (Königsberg) reported that harmine was most effective when combined with scopolamine; with 10mg harmine and 0.5mg scopolamine he saw no side effects, but a lasting improvement of rigidity and freedom of movement in two thirds of 20 patients. The effect on tremor was less marked; but tremor was often reported to be increased at the commencement of treatment with harmine. Heinz and Schlesinger (Mannheim) reported similar results. P. Eichler (Provincial Sanatorium and Psychiatric Clinic of the Medical Academy, Düsseldorf) reported that objective improvement in 20 of 22 patients with regard to both strength and speed of repetitive movement as measured by ergographic techniques. Müller wrote in 1931 that harmine had been used in all extrapyramidal disease patients at Nonne’s clinic during the previous 1½ years, and with great success. The daily schedule consisted initially of a 20mg injection in the morning and a 20mg keratin-coated pill at midday; after 10-20 injections, this was changed to two pills per day (20-40mg, with meals) for a period of three to four weeks, followed by an up to a week’s intermission. Excellent improvement was achieved in 26% of patients, good improvement in 37%; no lasting side effects or habituation were experienced. Harmine was more effective in post-encephalitic parkinsonism than in paralysis agitans patients, with rigidity and mobility improved to a greater extent than oculogyria, tremor or psychological aspects of the disorder. Combination with scopolamine was recommended. Pohl von Pollenburg (Ravenstein) combined the alkaloid with ‘Neurosmon’ (see page 164) with satisfactory results. Fleck advocated administration as suppositories or as capsules soluble only in the small intestine.

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393 Rustige, 1929.
395 Jacobi, 1930.
396 Heinz and Schlesinger, 1930.
397 Eichler, 1929.
398 Müller, 1931.
399 Pollenburg, 1930.
Marinesco and his colleagues at the Neurological Clinic of the University of Bucharest even concluded that the effect of harmine was greater in paralysis agitans than in post-encephalitic cases. They also identified a number of effects of harmine on vegetative responses and parameters. Further, the autonomic responses of post-encephalitic patients defined them as “vagotonic”, or dominated by the parasympathetic side of the vegetative axis. Harmine reduced the excitability of the parasympathetic system and elevated that of the sympathetic system in post-encephalitic patients as measured by a number of parameters (sensitization of reflexes of the sinus caroticus and of vascular reflexes), restoring these parameters to closer to normal levels. For example, the rise in blood pressure elicited by challenge with adrenaline (1 mL of a 1:100 000 solution) was found to be blunted in parkinsonian patients (11-12 mm Hg rise; normal is 30-50 mm Hg); following a harmine injection, the response was increased to about 16 mm Hg.

The initial hypothesis that harmine, like hyoscine, acted on the extrapyramidal tracts, was questioned in some quarters. L. Halpern (Psychiatric and Neurological Clinic of the University of Königsberg) had proposed a “dual hypothesis” for the mechanism of parkinsonism:

1. The dominance of continuous stimulation of the muscles by the extrapyramidal system, resulting in involuntary rhythmic automatisms of a vegetative nature.
2. The loss of the normal cortical control of voluntary movement.

Halpern supported this hypothesis with electromyographic recordings made with and without drug application. Accordingly, he proposed that hyoscine acted by depressing overactive centres in the extrapyramidal system, and that harmine stimulated motor centres in the cortex, increasing spontaneity and facilitating transmission of voluntary action via the pyramidal tract. This was seen as explaining the feeling of muscular lightness produced by harmine without affecting tremor, whereas a combination of harmine and hyoscine appeared to address the complete spectrum of parkinsonian motor symptoms. This was probably the first explicit attempt to treat the disorder by pharmacological intervention at multiple levels. Indeed, Halpern was able to present electromyographs demonstrating that harmine, in contrast to scopolamine, had no effect on the rhythm of the action current, although eliciting objective and subjective changes in rigidity. Halpern regarded his theory that rigor and tremor are neurologically distinct entities, which contradicted conventional opinion at the time (especially in England), as being vindicated by these findings. The effect of harmine on the parkinsonian patient was thus primarily the relief of akinesia, and thereby of the rigidity of the disorder, a novel interpretation of the mechanism underlying the disease.

Halpern also maintained that depression and lack of motivation in the parkinsonian patient were organically determined, but not in the manner which one might expect; indeed, he contrasted the “organic psychic effects” of parkinsonism with those seen in psychosis. Instead, he suggested that the psychic response of the patient was the result of the “discrepancy between will and competence” which manifested itself in the contradiction between the voluntary nervous impulses to the nerves and the responses of the musculature, of an “organically produced motor disjunction”. That is, psychic

401 Marinesco et al., 1930; see also results from Decourt and colleagues cited in Mercks Jahresbericht for 1931, p.190.
402 Halpern, 1930a.
403 Ibid.; Halpern, 1931.
disturbances in parkinsonism resulted from discrepancies between the signals sent to and received from the muscles. He did not deny, however, that this organic problem might eventually have consequences for the “psyche itself”; that is, for the personality of the patient, which was seen as distinct from abnormal psychological expression.404

Halpern had subjected himself to a two week self experiment with harmine on the basis that the physician could only be therapeutically effective and be competent in the interpretation of the responses of his patient if he himself had experienced the effects of the agent; Halpern also believed that the issue of the identity of banisterine and harmine could be better settled in this manner than by any other method “of objective research, be it of chemical, pharmacological or clinical nature”.405 The self experiment with psychotropic drugs was, of course, as old as medicine itself and would remain a part the research approach of even the most respectable pharmacologist or clinician into the 1960s. Halpern opened his report with the programmatic assertion:

No amount of submersion or reflection [Versenkung], however profound, can convey so immediate an insight into the inner workings of a patient as the own experience. For this reason, the self administration of intoxicating drugs has frequently been employed to artificially elicit pathological psychiatric conditions in order to investigate their psychological content, as well as to investigate the special nature of toxic effects in the central nervous system.406

One of his findings would prove to be a limiting factor in the use of harmine: he determined that a “physiological dose” of the drug was 0.01 g s.c., a “limiting dose” 0.02 g and the “toxic dose” 0.03 g; this is clearly a somewhat narrow therapeutic range. It should be noted that other workers found that up to 40 mg was well tolerated by post-encephalitic patients.407 Halpern described the feelings elicited by the drug thus:

It was difficult for the subject to remain in his place and to attend to his intellectual work. An increased need for movement developed which resulted in a purposeless pacing up and down in the room. The subject felt best during physiological harmine intoxication if caught up in the crowds on the street. He felt as if every act could be carried out with subjectively physical ease. At the same time, the processes of consciousness were untouched by this intoxicating lightness.408

This supported Halpern’s view that harmine was acting at the cortical level, although with the restriction that it did not stimulate “psychic energies” which might be expected from an intoxicating drug; the restlessness was instead achieved by setting the entire musculature in a state of readiness without involving the conscious aspects which normally accompany this state. This was compared with the action of caffeine, which stimulated motor activity by arousing “the entire personality”. Unfortunately, harmine not only elicited a need for movement, it also increased his aggressiveness (he started an unnecessary fight with a passer-by on the street which he knew he must lose) and produced feelings of insecurity which expressed themselves in the unsettling impression that his consciousness was bereft of its basis. Despite these problems, Halpern saw the agent as being useful for the treatment of motor disorders, including parkinsonism; he reasoned that the untoward effects in normal persons were related to the inhibition of

404 Ibid.
405 Halpern, 1930b.
406 Ibid.
408 Halpern, 1930b.
cortical control of subcortical (extrapyramidal) motor systems by toxic levels, similar to the effects of alcohol, whereas the drug stimulated the cortex of parkinsonian patients. This difference between therapeutic and toxic effects required further investigation, including more self-experiments.\textsuperscript{409}

Eichler also regarded cortical stimulation as underlying the improvement of voluntary motion and oculogyria without an effect on vegetative signs.\textsuperscript{410} Later evidence, however, suggested that harmine was also acting at a subcortical site. A.G. Beer found that harmine elicited its typical motor and psychic effects (but not convulsions) following cortical excision in the cat;\textsuperscript{411} Sato found that a variety of harman derivatives, including harmine, excited the pons in mammals, resulting in compulsive motor activity and rigidity of the limbs.\textsuperscript{412}

Harmine and harmaline were known to produce convulsions in rodents, an effect also attributed to stimulation of the motor cortex; J.A. Gunn (Pharmacological Laboratory, University of Oxford), who had extensively investigated the biochemistry and pharmacology of the harmala alkaloids in the first half of the 1930s, therefore proposed the examination of the effects of the harmine derivatives harmol and harmalol in post-encephalitic parkinsonism, as they lacked this convulsive action. He found, however, that the alcohol derivatives produced the same effects as harmine in parkinsonian patients;\textsuperscript{413} the mechanism thus remained unclear, but a few new agents had perhaps been discovered. Gunn examined the effects of harmine in a number of animals and concluded that the major mechanism was "the paralysis of spinal reflexes"; as Halpern had also described, it seemed to elicit compulsive and often stereotyped movements in these animals, as well as hallucinations. He also noted that harmaline and quinine shared a number of pharmacological properties, including their effects on the central nervous system, heart rate and the viability of protozoa; at the same time, none of these properties had been converted into clinically useful approaches in the case of harmaline.\textsuperscript{414} Eichler had found that the effect of harmaline in six cases of post-encephalitic parkinsonism was similar to that of harmine; above a dose of 40mg, however, the side effects (strong feelings of intoxication, tiredness, nausea and vomiting) were quite severe.\textsuperscript{415} Interestingly, harmine was found to be "incomparably more effective" than any extract of \textit{Banisteria caapi},\textsuperscript{416} so that a plant extract therapy analogous to the Bulgarian treatment was never seriously considered.

There was much about the banisterine story which would be repeated decades later when the \textit{L}-DOPA therapy was first introduced: the new "wonder drug" which relieved parkinsonian symptoms to a degree not previously seen, it was a completely new direction in the therapy of the disorder, various workers and erstwhile collaborators clashed over priority issues, excitement in the press was followed by a more sober assessment of the value of the drug. The outcome of the story, however, was different.

\textsuperscript{409} Ibid.
\textsuperscript{410} Eichler, 1929.
\textsuperscript{411} Beer, 1939a; 1939b.
\textsuperscript{412} Sato, 1935.
\textsuperscript{413} Cooper and Gunn, 1931.
\textsuperscript{414} Gunn, 1935.
\textsuperscript{415} Eichler, 1929.
Sternberg commented that the “undoubted successes” associated with the introduction of banisterine had brought new hope and movement into the therapy of parkinsonism:

These experiments were also the motivation in our department to give up the therapeutic resignation which up till then had been the rule and to seek further agents with which an improvement of such disease states is possible.\(^{417}\)

Comparison of the effects of harmine with those of the then popular hyoscine were, however, contradictory. Some authors found harmine more effective than hyoscine, others the reverse or no difference; adherents often pleaded for an extended trial in patients before dismissing its effects.\(^{418}\) Halpern suggested that parkinsonian patients could be divided into harmine-responsive and hyoscine-responsive groups; the former consisted largely of patients who whose major symptoms were rigor and akinesia, but not tremor. Halpern argued that the physiological basis of parkinsonism was not identical in all patients (not even in all paralysis agitans or post-encephalitic parkinsonian patients), and that a differential approach to therapy was required: some cases would require harmine, some scopolamine, and many a combination of the two:

The nature of the situation is thus such that only in very small number of cases will harmine therapy alone be the medication of choice, while the alkaloids of the solanaceous group must continue to be accorded the leading role.\(^{419}\)

From the beginning, however, some clinicians had been totally unimpressed by the effects of harmine. Hill and Worster-Drought (Post-Encephalitis Unit, Metropolitan Asylums Board, England) treated nineteen patients in 1929 with both orally and intramuscular harmine and concluded that:

Harmine in doses of up to 0.04g given hypodermically has no perceptible objective or subjective effect in ameliorating any of the symptoms presented in the parkinsonian syndrome and is of no value in the treatment of this condition.\(^{420}\)

The authors criticized earlier positive reports because patients often received only one or two harmine injections each; with longer term administration, the English workers had found that the nausea and vomiting began to dominate the response. They were also suspicious that the continental authors had not been able to observe a dose-response relationship with regard to the beneficial effects of harmine. Gausebeck found that harmine alone was clearly inferior to scopolamine, although it appeared to facilitate the effects of the latter agent.\(^{421}\) Von Witzleben had also examined the drug in 1927, but without consistent success.\(^{422}\) Decourt and Bocquentin, although they saw harmine as a useful adjunct to the therapy of parkinsonism, particularly in those cases which did not respond adequately to solanaceous alkaloids, were concerned that its effects were very short-lived; further, in contrast to Beringer, they found that the degree of therapeutic benefit achieved was proportional to the degree of bradycardia and hypotension it induced. The French authors believed that the agent would be useful in the investigation of the physiopathology of parkinsonism and of muscle tone in general.\(^{423}\)

\(^{417}\) Sternberg, 1930.
\(^{418}\) Reviewed in Schuster, 1931a.
\(^{419}\) Halpern, 1931; see also Halpern, 1930a.
\(^{420}\) Hill and Worster-Drought, 1929.
\(^{421}\) Gausebeck, 1929.
\(^{422}\) Witzleben, 1942, p.113.
\(^{423}\) Decourt and Bocquentin, 1929.
The rapid rise of the agent following its success in Heidelberg was matched by its rapid decline in popularity. The 1932 report by Merck on its hitherto star performer was less optimistic than in previous years:

*Even if the effect of harmine . . . on the symptoms of post-encephalitic parkinsonism can only be rarely regarded as a lasting improvement, it cannot be denied that that even this temporary symptomatic relief, especially of rigidity, often restores inner peace and zest for life to the despairing patient, so that they find their fate more tolerable.*

There had been some negative reports, primarily from England; Marinesco and colleagues had offered, however, that at least some non-responsive patients were “*hyoscinomanic*”; that is, a dependence on hyoscine had developed as a result of its extended use, analogous to morphine addiction. In 1931, Schuster examined the question “*Has harmine proved to be of value in the treatment of parkinsonism?*” His conclusion was less enthusiastic than when he commenced his work with Lewin two years earlier:

*In certain forms of parkinsonism – particularly in predominantly akinetic parkinsonism – harmine achieves often good short-term results. For longer term treatment, combination with genoscopolamine is to be recommended, or, even better, with stramonium.*

The major problem with harmine had been mentioned by Rustige in 1929: its effects were so fleeting that, despite its interesting pharmacological properties, it would remain a curiosity until some means of prolonging its actions was found. Schuster was of the same opinion: although most workers agreed that harmine was of immediate benefit for the parkinsonian patients, reports of this benefit lasting more than a few hours at most were rare. Neither intensification of nor tolerance to its effect developed with chronic use; but Schuster also noted that there was no additional benefit to be gained by raising the dose beyond 20mg s.c. The limits of the benefits which could be achieved with harmine had already been reached; Schuster’s experiences over 2½ years led him to the conclusion that “*harmine is not suitable for continuous, chronic administration on its own.*” Beringer and Wilmanns’ experience that the harmine effect increased with length of treatment was not replicated in most clinics. Instead, the more usual practice was increasingly to combine harmine with scopolamine or genoscopolamine; Schuster preferred to combine stramonium with scopolamine, and to administer harmine 2-3 times per week as an adjunct therapy. The reason for this was that he, like most workers (but in contrast to Beringer) found that the subcutaneous administration of harmine was superior to the use of pills; it was thus somewhat less convenient than belladonna alkaloids.

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424 Mercks Jahresbericht for 1932, p.185.
425 Marinesco et al., 1930. This possibility had been suggested in 1905 by Higier, and in 1924(b) by Schaltenbrand. The latter author, however, interpreted as evidence of addiction the fact the parkinsonian symptoms of advanced patients deteriorated rapidly following withdrawal of scopolamine hitherto employed as monotherapy; this form of ‘dependence’, however, can hardly be compared with opiate addiction, despite Schaltenbrand’s opinion to the contrary.
426 Schuster, 1931.
427 Eichler (1929) reported a single injection improving a patient for days; in 1931, Müller even claimed an effect which lasted for a period of weeks (cited in Schuster, 1931a).
428 Schuster, 1931a,b.
Although a few positive reports concerning harmine in the therapy of parkinsonism and other motor disorders continued to appear in the early 1930s, Baldauf commented in 1938 that harmine was only rarely used in parkinsonism; by this stage, the use of belladonna alkaloids dominated the clinic to the exclusion of most other forms of treatment. By 1941, ‘Peganum’ was accorded only a brief note in the Martindale Extra Pharmacopoeia to the effect that it was used to treat parkinsonian symptoms, but was regarded as less effective than hyoscine; by 1952, the harmala alkaloids had generally dropped out of use in the treatment of parkinsonism, especially after the synthetic anti-parkinsonian agents had begun to dominate the clinic, and neither Peganum nor harmaline were listed in Martindale’s.

It was only in 1958 that Sidney Udenfriend’s group (National Institutes of Health, Bethesda) would report that harmine, harmaline and a number of related β-carbolines were potent reversible inhibitors of monoamine oxidase (MAO), and thus elevated central 5-HT levels; Holzer and Hornykiewicz reported a similar effect on central dopamine in 1959. All other MAO inhibitors known at this time were irreversible, and it was recognized that a reversible inhibitor might be more desirable in certain clinical situations. The authors noted that these alkaloids had earlier been used for a number of conditions now treated with iproniazid. Harmaline had been shown by the same group to inhibit MAO in man at doses which had been used in the therapy of parkinsonism.

The role of MAO inhibitors in the history of parkinsonian therapeutics will be taken up below. It was a completely new beginning which saw the re-emergence of this class of drugs in the therapy of parkinsonism; this time, they were adopted on the basis of biochemical models of the disorder which had developed during the 1950s. At this point, it suffices to note that Hornykiewicz and Birkmayer would later find that the inhibition of MAO alone is not capable of raising central dopamine levels to a degree which would compensate the loss in Parkinson’s disease. It is interesting, on the other hand, that Halpern found akinesia to be the symptom most influenced by harmine administration, which would also be the symptom most effectively addressed by L-DOPA; also similar is the fact that tremor was the symptom least responsive to either drug. It is, however, extremely difficult to compare the patient groups treated in the 1930s and 1960s; even comparison of the responses of post-encephalitic patients during the two periods is complicated by factors including the different age distribution of the groups, and the fact that it cannot now be clarified whether the neurological damage sustained by the two groups was comparable. As discussed above, it would appear that those who developed parkinsonian symptoms some years after exposure to encephalitis lethargica experienced a progredience of their disorder similar to that seen in idiopathic parkinsonism; this would mean that post-encephalitic patients treated in the 1930s may

430 For example: Baader, 1932; Petersen and Winter, 1932. The latter authors emphasized its capacity to relieve muscular stiffness.

431 But Hechler (City Hospital, Mannheim) wrote in 1939 that until recently the three standard medicaments had been atropine, scopolamine and harmine; the Bulgarian treatment was beginning, however, to supplant all three.

432 Martindale Extra Pharmacopoeia, p.894.

433 Udenfriend et al., 1958.

434 Ibid. See also Pletscher and Besendorf, 1959.

435 As noted above, harmine is, indeed, known to elicit tremor in mammals; further, harmala alkaloids have also been used in animal models of parkinsonism to enhance lesion-induced postural tremors: Poirier et al., 1966; Poirier, 1971. See also Iwata et al., 1993.
not yet have suffered the massive losses in the substantia nigra and other regions which Hornykiewicz and colleagues would report in post-encephalitic patients in the 1970s.\textsuperscript{436}

In their 1960 review of the MAO inhibitors, however, Pletscher and his associates at the Research Division of Hoffmann-La Roche in Basel noted that the benefit of harmalol, which is only a weak MAO inhibitor, for the rigor of parkinsonism casts doubt on the importance of MAO inhibition in the effects of harmala alkaloids in parkinsonian patients;\textsuperscript{437} further, it is now recognized that harmine is principally an inhibitor of MAO type A\textsuperscript{438} (as are most naturally occurring MAO inhibitors), whereas inhibition of type B would be more beneficial for parkinsonian patients. This in itself is interesting; the role of MAO inhibition in the anti-parkinsonian effects of deprenyl, which would represent the first permanent entry of MAO inhibitors into the therapy of parkinsonism, has also been questioned (see below). A number of authors reported from the first half of the 1960s that it was likely that some effects of the MAO inhibitors must be attributed to factors other than their inhibition of MAO.\textsuperscript{439} Harmine was reported in the early 1960s to release catecholamines under certain conditions, although this has not been reported with respect to dopamine.\textsuperscript{440} Green and Slotkin found in 1973 that harmine also exerted reserpine-like effects on isolated adrenal medullary vesicles ($EC_{50} \approx 10\mu M$), thus adding another possible facet to the action of the alkaloid. This was not surprising, given the structural similarities of the two molecules; indeed, the authors described reserpine as a “highly substituted harmine derivative” (figure 5-11). Unlike reserpine, however, the inhibition of amine uptake by harmine is reversible. Further, it had no effect on the activities of any of the enzymes involved in adrenaline synthesis.\textsuperscript{441} Effects on serotonergic parameters have also been suggested; harmaline increased brain 5-HT levels (while decreasing dopamine synthesis and turnover) in the cat, while 5-

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure5_11.png}
\caption{Comparison of the structures of (a) harmine and (b) reserpine.}
\end{figure}

HTP blocked the production of tremor by harmaline.\textsuperscript{442} The fact that harmine is mildly anti-protozoic and anti-malarial presumably played no role in its actions in parkinsonism; early attempts to exploit this feature of the harmala alkaloids produced, in any case, negative results.\textsuperscript{443}

\begin{itemize}
\item \textsuperscript{436} Bernheimer \textit{et al.}, 1973.
\item \textsuperscript{437} Pletscher \textit{et al.}, 1960.
\item \textsuperscript{438} Grosso and Gawienowski, 1976.
\item \textsuperscript{439} For example: Pletscher, 1959; Matthies and Popov, 1966.
\item \textsuperscript{440} Huković and Muscholl, 1962; Schmitt and Schmitt, 1964.
\item \textsuperscript{441} Green and Slotkin, 1973.
\item \textsuperscript{442} Zetler, 1957; see also Poirier \textit{et al.}, 1966; Kim \textit{et al.}, 1970.
\item \textsuperscript{443} Gunn, 1935.
\end{itemize}
VI. The 1930s and 1940s: The dominance of atropine and belladonna

As already mentioned, atropine was a part of the standard Pharmacopoeia of most countries since the middle of the 19th century. The signs of atropine toxicity were well known: dryness of the mouth and throat, dilatation of the pupils, nausea and excited delirium. At higher doses, paralysis follows these signs, and death is heralded by rapid pulse, coldness of the extremities and respiratory depression. The fatal dose of atropine for humans is estimated as lying in the vicinity of 100mg, although serious symptoms of toxicity are manifested from about 10mg; one case of survival following the consumption of 1000mg has been recorded; Goodman and Gilman wrote that of “all the potent alkaloids, atropine has one of the widest margins of safety.”\(^1\) The half-life of atropine in blood is about four hours and the greater part is excreted unchanged within 36 hours in the urine.\(^2\) In the first half of the 20th century, atropine was available principally in the following forms:

- **Extractum Belladonnae Siccum** (>1.3% alkaloids; black) and **Tinctura Belladonnae** (0.03% alkaloids; intense brown), both prepared from the leaf, and as **Extractum Belladonnae Liquidum** (0.75%; black), prepared from the root. The tincture was the most widely used form.
- **Extractum** (0.15%; black) and **Tinctura Hyoscyami** (0.004%; intense greenish-brown), prepared from leaves and tops: Hyoscyamus extracts were rarely employed by the 1930s.
- **Extractum** (0.3%; black) and **Tinctura Stramonii** (0.03%; light brown), prepared from leaves and tops.
- Salts of purified atropine, the most widely used being atropine sulphate.\(^3\)

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3. All figures according to the International Agreement of 1930, cited in the British Pharmacopoeia of 1932. Slight variations on these figures in different countries existed (the British Pharmacopoeia contains a table of variations of B.P. preparations from the International Agreement); for details on
As discussed above, Charcot and many other workers had mentioned trying atropine in parkinsonism in the 19th century, almost always without success. In 1936, Gamper noted that Eulenburg, Hansen and Verhoogen had recommended atropine, but most patients did not tolerate the side effects, including dryness, disturbance of appetite and blindness.\(^4\) A pamphlet published in the United States in 1905 (\textit{A Treatise on Belladonna}) listed a range of applications for belladonna root and leaf, but did not include paralysis agitans; interestingly, however, indications which were listed are “\textit{spasms of the body orifices},” “\textit{dull and expressionless countenance}” and “\textit{congestion of the brain and spinal cord}.”\(^5\) The use of atropine first found widespread use in the therapy of Parkinson’s disease during the middle of the 1920s. Its employment was promoted by Radovici and Nicolesco in Marinesco’s clinic in Bucharest (1921),\(^6\) by Jean Caro in Italy\(^7\) and by Pette in Nonne’s clinic in Hamburg-Eppendorf; the combination with scopolamine was also introduced by the latter clinic.\(^8\) In their original paper, Radovici and Nicolesco administered atropine by subcutaneous injection; the stimulus for this experiment was the successful employment of atropine in the control of visceral spasms. They were adherents of the model whereby the muscle was subject to innervation by both sympathetic elements, responsible for muscle tone, and parasympathetic elements, which elicited voluntary and clonic contractions; the control of tonus was distributed over several mesencephalic and cortical centres. They conceded that the current state of knowledge precluded any firm hypotheses as to the action of atropine on muscle; although the classic mechanism of atropine was to paralyze parasympathetic nerve terminals, it could not be excluded that it, and indeed other belladonna alkaloids, also have central effects. The toxic effects of atropine could not be attributed to a single effect of atropine on the brain, the cerebellum or the spinal cord. The authors, however, tended to the view that the administered doses of atropine exerted a sedative action on the tonic centres of the brain, particularly on the mesencephalon and striatum, seats of the principal lesions involved in involuntary, rhythmic movements of encephalitis lethargica.\(^9\)

W. Szyszka (Medical Clinic, Würzburg), who had adopted the therapy after hearing of the approach from Nonne at a meeting in Hamburg, also reported some success with oral atropine therapy in nine cases (4-6×0.5mg pills/day), with the patients able to dress themselves and write legibly after 2-3 days, the tremor usually abolished; no further improvement was usually seen after two weeks’ therapy. Szyszka saw atropine as the breakthrough in the therapy of parkinsonism:

\textit{After the failure of the therapy of parkinsonism up until now, a means has thus been discovered in atropine with which one can admittedly not heal the disease, but can influence it to the extent that it is possible to maintain the ability of the patient to work for a considerable period, or at least to completely relieve his subjective complaints or to ameliorate them to an extent that makes him forget the severity and the hopelessness of his situation and to make him more tolerable for his surroundings.}\(^10\)

\(^{4}\) Gamper, 1936, p.800.
\(^{5}\) Niederkorn \textit{et al.}, 1905.
\(^{6}\) Radovici and Nicolesco, 1921.
\(^{7}\) See Musella, 1936, who noted that Caro had employed small doses of atropine since 1922.
\(^{8}\) Pette, 1922.
\(^{9}\) Radovici and Nicolesco, 1921.
\(^{10}\) Szyska, 1923. See also Morawitz (also of Würzburg), 1922.
He thus noted that the patients’ relatives were especially grateful for the improvement; Szyszka claimed to have had not a single treatment failure. Despite the enthusiasm of Szyszka, however, the results were anything but spectacular, and it was not widely regarded as being more effective the other pharmacological remedies of the mid-1920s; some workers even reported that “high doses” of atropine exacerbated rigidity and worsened the general condition of the patient.\footnote{Kennedy et al., 1922; the doses used, however, were not defined.}

An interesting phenomenon noted at this time was that post-encephalitic parkinsonian patients responded better to the belladonna alkaloids than paralysis agitans cases, and were also able to tolerate relatively high doses of atropine. This was definitively demonstrated by Friedrich Bremer (I. Medical Clinic, University of Munich) in 1925, although the apparent subsensitivity of such patients to atropine (and pilocarpine) had been anecdotally noted previously by several workers. The potential for abuse in such patients was also recognized:

\emph{The second patient, especially, demanded increasing amounts of atropine. On one occasion he secretly took the atropine bottle and emptied it, after which he admittedly succumbed to a state of hallucinatory excitement.}\footnote{Bremer, 1925.}

Bremer saw the explanation for this reduced sensitivity as lying in the increased power of the serum to bind atropine, the nature of which binding power he admitted was a mystery, and perhaps in the putative detoxification capabilities of the liver. It was recognized that the plasma of certain animals – in particular, the rabbit – appeared capable of “detoxifying” atropine,\footnote{Fleischmann, 1910; see also van Leeuwen and van den Broeke, 1920; van Leeuwen and van den Made, 1920; van Leeuwen, 1924. Both groups found that the physiological effects of atropine were reduced by incubation with serum; rabbit serum was magnitudes more powerful than human serum in this respect.} but Bremer could not relate this to the situation in parkinsonism. Bremer’s methods were criticized by some workers, especially by pharmacologists,\footnote{Polkovnikova and Bouračeskij, 1929; Witzleben, 1942, p.100.} but his report simply confirmed an observation made in many clinics. Patients with traumatic injuries to the basal ganglia or who had suffered carbon monoxide poisoning were also hyposensitive to atropine, but paralysis agitans patients were not;\footnote{Čohn (1932) recorded the contrary.} the latter often exhibited, on the contrary, an extreme sensitivity which prohibited the employment of atropine or associated therapies.\footnote{Witzleben, 1942, p.100.} Meerloo would note later that in unilateral post-encephalitic parkinsonism, the side effects of the Hirsau high dose atropine therapy (see below) were most prominent on the unaffected side, so that he interpreted the elevated tolerance for atropine as a consequence of the disease process.\footnote{Meerloo, 1935.} Lewenstein noted, however, that healthy persons could also develop this tolerance if the dose was raised slowly.\footnote{Lewenstein, 1931.}

**High dose atropine: the “Römer” or “Hirsau therapy”**

Carl Römer (director of a sanatorium in Hirsau in the Black Forest) and his senior physician Anna Luise Kleemann are regarded as having introduced the high dose...
VI. The 1930s and 1940s: the dominance of atropine and belladonna

Atropine therapy for post-encephalitic parkinsonism at the meeting of the Southwest German Neurologists and Psychiatrists in Baden-Baden in 1929. As discussed above, high dose scopolamine and stramonium therapies were favoured by some workers, so that it was probably inevitable that the same approach would be taken at some time with atropine, although its greater notoriety for toxicity rendered it a less suitable indicate. But, as noted by Hurst in 1934, unusually high doses of atropine were also employed in the treatment of duodenal ulcers; large doses of other agents were also becoming accepted, such as of adrenaline in asthma and of morphine in chronic intractable pain.

It is not clear when the high atropine therapy was first used by Römer. Kleemann prefaced her report with the wish to relate therapeutic experiences “since we instituted a special encephalitis ward in the Sanatorium Hirsau 5 years ago.” Further, Römer wrote in 1933 that he had achieved “surprising and unprecedented improvements in the first cases treated with high dose atropine”, and specifically indicated that this occurred in 1924. On the other hand, both Römer and Kleemann stated that the idea for the therapy was provided by Bremer’s paper on the high tolerance of post-encephalitic patients for atropine, and this appeared only at the end of 1925. It would also have been remarkable if the Hirsau team had waited five years to present the new method at a congress or in a paper, which would have been the case if the therapy had been introduced in 1924.

In any case, the sanatorium had commenced using the therapy with the aim of ameliorating the changes in muscle tone which accompanied encephalitis lethargica. Commencing with $3 \times \frac{1}{4}$ mg/day (as drops of a $\frac{1}{2}$% solution; 1 drop = $\frac{1}{2}$ mg), the dose was raised slowly until no further improvement was seen; the dose was then gradually reduced until symptoms began to reappear, then raised again slightly to the ‘optimal level’ determined in this manner. With this method, it was possible to administer up to $3 \times 20$ mg atropine per day (the median dose was $3 \times 5$-10 mg/day), together with up to 150 mg scopolamine. This amount of atropine was an order of magnitude greater than the maximum dosage recommended in the pharmacopoeias; a toxic to lethal dose was usually given as 50-200 mg. Atropine-free days, which would now be termed “drug holidays”, were originally included as part of the therapy, but the resultant nausea, vomiting and other autonomic responses to the withdrawal were so severe as to necessitate the cessation of this practice. Kleemann recommended the use of atropine sulphate tablets as the most convenient mode of administration, but intravenous injection was also possible, whereby the dose could be reduced by about one third.

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19 Von Witzleben noted that a “charlatan” was reputed to have had success in Zürich in 1920 or 1921 in the treatment of parkinsonian patients with injections of what proved to be large doses of atropine; Witzleben, 1942, p.99.
20 Hurst, 1934a.
21 Kleemann, 1929.
22 Römer, 1933b.
23 Meerloo noted that he had adopted the ‘English version’, whereby the atropine sulphate solution was prepared so as to give $\frac{1}{4}$ mg per drop; he also added 120 mg salicylic acid per 100 mL in order to prevent the growth of mould (“which influences its effect”); Meerloo, 1935.
24 The highest allowable dose according to Hagers Handbuch was 1 mg per dose or 3 mg per day; Frerichs et al., 1925-1927, p.647.
25 Kleemann, 1929.
26 Witzleben, 1942, p.102.
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Once the maintenance dose had been achieved, there was generally no need to increase or otherwise alter the dose with time; nevertheless, Römer recognized that the drug did not affect the course of post-encephalitic parkinsonism, so that deterioration of the patient’s condition was inevitable should therapy be discontinued. Römer also conceded in 1933 that the condition of some of his patients had deteriorated somewhat in the previous three years; this he attributed partly to the progredience of the disorder, but also to a large extent to the patients reducing their own atropine intake. He also noted that, although “every symptom of the post-encephalitic syndrome can be resolved or at least ameliorated by atropine”, psychiatric symptoms, with the exception of bradyphrenia, were not affected by this approach. Finally, atropine therapy was regarded by its discoverers as superior to belladonna and other plant preparations because it “was the easiest to administer at a specific dose, applicable in all forms [of the disorder], stable for an unlimited period and, further, the least expensive preparation”. Römer also regarded scopolamine addiction as a real problem; ‘atropinism’, on the other hand, had not been observed.

It was soon recognized that one of the problems with high atropine therapy was the difficulty of again weaning the patient from the drug. On the other hand, the patients appeared to tolerate atropine well, and the drug improved the major symptoms in most cases after treatment for 3-4 months; most subsequent authors reported that improvement commenced within a few weeks if a patient were to derive benefit from the therapy. Dryness of mouth could be a problem initially, but often disappeared with time; otherwise chewing gum or some other means for stimulating salivation could be added to the treatment. Kleemann found that in her 35 treated patients, rigidity was improved in 95% (abolished in 35%) and tremor in 89% (abolished in 36%); sialorrhea was completely relieved in all patients, while the mask face, oculogyria, chewing and swallowing disturbances and problems with “propulsion” also responded well to the drug. Two thirds of her patients were able to return to work, while a further 28% were capable of limited work. Kleemann emphasized the requirement for simultaneous physical and psychological therapy, and was especially aware of the necessity to avoid psychological damage to the patient caused by intimations from the physician that their situation was incurable. Assistance with social readjustment was especially urgent in those cases where a return to the original profession was not possible. Although encouraged by her results, Kleemann felt that a treatment which rendered the patient reliant on a particular medication was “incomplete”; nevertheless:

Given the irreparable damage to the brain, it is doubtful whether a way will ever be found to improve the patients to such a degree that they could maintain a sufferable condition without drugs; any treatment method which resolves the symptoms of the disease, or at least ameliorates them, is thus an advance.

Römer hypothesized that lower doses of atropine primarily modulate peripheral responses, whereas higher doses were necessary to achieve effects at the level of the midbrain; scopolamine, on the other hand, acted primarily in the cortex, so that he regarded as essentially inferior to atropine in the treatment of parkinsonism. In response to a question in 1933, Römer replied that high levels of atropine posed no problems for such patients with respect to either the central nervous system or the circulatory system, as long as the dose was elevated slowly. Heart rate was increased immediately after

27 Romer, 1933b.
28 Ibid.
29 Kleemann, 1929.
atropine administration, the result of inhibition of vagal control, but returned to normal within a few hours; blood pressure was not affected at all. Römer had been advised by Palewka at Tübingen that most of the atropine administered was eliminated within eight hours, so that accumulation did not represent a problem if the spacing of the doses was correct. He advised that in those rare cases where signs of psychomotor restlessness, choreiform or athetoid movements or hallucinations indicated a toxic response, the problem could be easily resolved by reducing the dose.30 Both problem and solution are strongly reminiscent of the high dose L-DOPA therapy in the 1960s. By 1933, Römer had treated 350 patients in this manner (of which 25 were paralysis agitans cases), and reported that 60% were able to return to their previous occupations. In general, the most severe patients required the highest maintenance doses, but there was no predictive relationship between the degree of the patient’s disability and the amount of atropine required for a therapeutic effect. Römer also noted that paralysis agitans cases did not respond well to high doses of atropine, and proposed that this could be exploited as an instrument for differential diagnosis.31

The Römer method spread quickly within the German-speaking world; but, as noted by Hans Cohn (Neurological Institute, Frankfurt University), it had to compete with harmine and stramonium, which were introduced at about the same time.32 The detailed review of the therapy in the Mercks Jahresbericht for 1932 was generally positive, but included marked comments to the effect that not all symptoms were addressed by atropine, and that harmine, in certain respects, was to be preferred.33 Ulrich Fleck (Göttingen Encephalitis Station) wrote that the traditional therapies achieved improvement in only 6.6% of patients, whereas high dose atropine was beneficial in 52% of cases.34 Both he and von Witzleben also noted that patients who were overly sensitive to atropine could be treated with the more expensive ‘Bellafolin’ until tolerance was developed. The sensitivity to atropine was highly variable amongst parkinsonian patients; it was obscure why treatment with ‘Bellafolin’ could elevate tolerance to the alkaloid, but it was certainly a commonly employed tactic.35 At the meeting of the Oberlausitz Medical Society at the beginning of 1931, he therapy was eulogized in the following manner:

It is absolutely amazing how hitherto completely incapacitated patients, incapable of any movement and dependent on care by others, regain their lust for life and mobility, often only a few days after the commencement of treatment.36

Stemplinger reported that it was even possible to implement high atropine treatment on an ambulant basis, with improvements in performance of up to 100% recorded.37 This, however, was highly controversial; most physicians regarded the concurrent implementation of complementary physio- and psychotherapeutic programs as essential components of the therapy, and that the therapy must at least commence under supervision in an institution.

30 Römer, 1933a.
31 Römer, 1930; 1932a; 1932b; 1933a.
32 Cohn, 1932.
33 Mercks Jahresbericht for 1932, pp.89-90. It should be noted that the popularity of harmine, marketed by Merck, had reached its peak by 1931, and was actually in decline at this point. Further references in Mercks Jahresbericht for 1933, p.146; 1936, p.197.
34 Fleck, 1933.
36 Hess, 1931.
37 Stemplinger, 1930.
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This issue was the subject of a number of papers in Germany throughout the 1930s. Post-encephalitic patients were generally accommodated at this time in nursing homes or sanatoria (‘Heilanstalten’); in Prussia, they were, in fact, usually placed in asylums for the insane. Further, many general practitioners failed to correctly recognize the condition of such patients when they presented themselves:

Such patients, who could not be helped by any doctor and whose disorder had until this point not been diagnosed, are often recognized as post-encephalitics only by a specialist in an outpatients clinic, who can give them the cheery news that their suffering can probably be alleviated and that they can even perhaps return to work at some point. Many of these patients had to be supported by their community in some manner. But nobody knew what to do with them. Because of their helplessness and depressed mood, they were regarded as being mentally ill; the attempt was thus made to place them in an asylum, usually with success. This approach to the care of post-encephalitics has remained the same everywhere until today.38

Heinicke had remarked as early as 1926 that existing facilities for the care of post-encephalitic cases were inadequate and required alternative approaches. Lewenstein (Provincial Nursing Home and Neurological Clinic, Bonn), for example, argued that a two month visit to a sanatorium was imperative at the commencement of therapy, and pleaded for the establishment of specialist encephalitis wards in all major centres. If this were not possible, specialist post-encephalitic wards should at least be provided in the existing institutions in order to remove these patients from the odium attached by the public to ‘mental patients’.39 Braune (State Nursing Home Altscherbitz) stressed that the directors of asylums were often embarrassed by the perceived need to accept patients who were clearly not psychiatrically ill, and suggested that the interests of both patient and physician would be better served by admitting post-encephalitic patients to normal public hospitals for treatment. At the same time, both general practitioners and institutional physicians required urgent education in the recognition of post-encephalitic patients. Finally, many patients could be returned to their own homes, with the proviso that a reliable person undertake the responsibility administration of the patient’s atropine in the future; Braune cited instances where this role had been successfully assumed by the village teacher or the wife of the local priest.40 As will be discussed below, special institutions for post-encephalitic patients were established initially in Italy and, to limited extent, in other parts of Europe in the mid-1930s, many of which still exist today (Queen Elena clinics). The deterioration with time and gradual incapacitation of post-encephalitic parkinsonian patients, however, dictated that most were ultimately institutionalized in nursing homes, at least where this was financially possible.

Lewenstein regarded the high dose therapy as more effective than previous approaches, but did not achieve the dramatic successes reported by Römer: he found that 12% were able to resume their former occupations, while 72% were capable of some form of work; 16% were treatment failures.41 This would prove to be a recurring theme in anti-parkinsonian therapy: dramatic initial breakthroughs followed by a series of more sobering, moderate successes or even failures. Different observers also reported varying accounts of the course of the response to atropine: Lewenstein found that

38 Braune, 1931.
39 Lewenstein, 1931.
40 Braune, 1931.
41 Lewenstein, 1931.
involuntary movements, such as compulsive yawning and tics, were the first symptoms to be resolved, and that tremor was not affected at all.\textsuperscript{42} Von Witzleben reported the complete opposite, as did most workers: rigidity, tremor and salivation were inhibited from the beginning of therapy, while involuntary movements were improved only at a later stage. Like most workers, however, he recognized that atropine alone was not effective in abolishing tremor.\textsuperscript{43} Muntner (Charlottenburg) suggested that the addition of pilocarpine at doses which he regarded as being only peripherally effective (5-10mg/day) to the atropine therapy eliminated most of the unpleasant side effects,\textsuperscript{44} but Römer emphatically rejected the necessity for this addition.\textsuperscript{45} Cohn made the interesting observation that where the motor symptoms were not improved, sialorrhea was also unaffected by atropine therapy; these were generally very advanced cases.\textsuperscript{46} Nevertheless, the high atropine therapy (combined with scopolamine) had established itself in Germany as the therapy of choice for parkinsonism by the early 1930s. Gumper had observed in his 1936 manual that the combination of scopolamine and atropine appeared to be more beneficial than either alone, especially given the subjective unpleasantness of atropine.\textsuperscript{47}

The spread to other countries was slower; the method was first published in France, Holland and America in 1934;\textsuperscript{48} in Italy, according to Panegrossi, the method never achieved significance due to the serious side effects of the treatment.\textsuperscript{49} The Bulgarian treatment (see below) had also arrived in Italy at about the same time as the Römer therapy. High dosage therapies had also been tried in England. A.J. Hall (Professor of Medicine, Sheffield) had asked himself in 1926 whether his lack of success with tincture of belladonna in parkinsonism might be due to his not using enough, and began to raise the dose to up to 30 minims thrice daily. He found that often “astonishing” changes could be effected by such treatment in about two-thirds of his patients. He was certain, however, that the effect was to be attributed to the euphoric effects of the therapy, and not primarily to its motor effects. He had also excluded the power of suggestion as underlying the response; he stated that he replied frankly to patient enquiries about their prospects of recovery, which usually resulted in them becoming profoundly depressed. The effect of the belladonna therapy could therefore be somewhat temporary, as the energizing effect gradually faded as the patient recognized the reality of their condition. Hall assumed that the atropine-class drugs somehow depress an overstimulated part of the motor arc, allowing voluntary control of muscles to be re-asserted.\textsuperscript{50} Amongst the more disturbing side effects of high dose belladonna were the restlessness and agitation described by the term “belladonna jag”.\textsuperscript{51}

\begin{footnotes}
\item[42] Ibid.
\item[43] Witzleben, 1942, pp.104-105.
\item[44] Muntner, 1931; also Muntner, 1936.
\item[45] Römer, 1932a.
\item[46] Cohn, 1932.
\item[47] Gumper, 1936, p.800. See also Beringer, 1931; Schenk, 1931; Busse, 1932; Askgaard, 1935.
\item[48] Wuite, whose doctoral thesis examined the Römer method (Gröningen; 1934), suggested that the effectiveness of the approach might at least have been psychological; Wuite, 1935. For an American report, see Jewett et al., 1938.
\item[49] Bauer et al., 1935; Panegrossi, 1938.
\item[50] Hall, 1926. 30 minims is by no means a spectacular dose, corresponding to about 1.8mL of what would later be regarded as a weak tincture.
\item[51] Doshay, 1960, p.85.
\end{footnotes}
Hall later reported that “remarkable improvement” could be achieved in certain post-encephalitic cases with even higher doses of atropine, especially where the major symptoms were muscular rigor and excessive flow of saliva; tremor and oculogyric crises were affected to a lesser extent. He followed the Römer-Kleemann method in principle, although he noted that the dose could be raised more rapidly in patients who had previously received tincture of belladonna. He divided his 58 patients into three classes of physical disability (complete, partial or no independence of movement) and also into two classes of psychotic disability (primary or predominant v. secondary or negligible). In the patients where psychotic disability was not a major problem, the results of the high dose therapy were very impressive in the most cases, although Hall reserved the epithet “remarkable improvement” for cases of severe initial disability; it referred to patients who had been bedridden for years but were now restored to full independence, tremor in most cases no longer significant. The therapy was associated, however, with the risk of serious hyperpyrexia, and, as with all treatments, could not be terminated without a rapid decline in the condition of the patient, although, contrary to some reports, the omission of a single dose was not associated with serious consequences. Patients with severe psychotic problems, however, did not respond to the treatment. Hall noted that in cases where the psychiatric symptoms were secondary to the motor defect, the benefit achieved by atropine led in some cases to an improvement in the psychiatric state which made possible further amelioration of the motor symptoms; this appeared to support his previously expressed hypothesis of the involvement of psychological factors in the response to anti-parkinsonian therapy.

Doshay and Ford listed a number of other positive reports concerning the high atropine therapy in 1942. Doshay also remarked (in 1965) that the clinic at Columbia University (New York) had also employed a high atropine therapy (1½% solution) with some success at about this time; Doshay suggested that the tolerance of post-encephalitic patients for this therapy had less to do with the disease than with their relative youth. When he originally presented these results in 1939, his audience was somewhat skeptical, although Neal was amongst them and reported her first successes with use of the Bulgarian method. This was consistent with Lewenstein’s assertion that atropine tolerance was not unique to parkinsonian patients, but could also be achieved in normal persons through careful titration.

The side effects of atropine therapy were distressing for many patients, and often led to its rejection by those in the early stages of the disorder. The major side effect of the therapy which disturbed patients were the focal accommodation problems and pupil dilatation which rendered reading especially difficult. The only solution to this problem was the use of spectacles. Dryness of mouth, throat and conjunctiva were experienced by most patients, while urinary retention and constipation were also often reported. Increased libido was sometimes noted. Marinesco and Façon noted that anorexia was a common problem, but could be treated by the co-administration of insulin; diarrhea responded to the concomitant application of pepsin and hydrochloric acid. Many patients complained of mental confusion, loss of drive and nausea; this could occur even with a dose which had been long tolerated. Lewenstein and von Witzleben

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52 Van der Meulen, Nederlands Tijdschrift voor Geneeskunde 77 (1933), 5693ff., cited in Hall, 1937.
53 Hall, 1937; see also Hall, 1935.
54 Doshay, 1965b; compare with Doshay, 1939.
55 Lewenstein, 1931.
56 Marinesco and Façon, 1933; 1936a,b.
emphasized the mental changes which often occurred, including the development of feelings of anxiousness and suspicion, as well as the psychiatric picture associated with atropine toxicity, such as hallucinations.\textsuperscript{57} The Dutch worker Grewel found the psychotomimetic effects of atropine a particular problem in older patients.\textsuperscript{58} An increase in pulse rate following administration of atropine was often reported, but no increase in blood pressure. As an alternative to atropine itself, the \textit{N}-oxide derivative \textit{génatropine} (Amido Laboratories, Paris) was employed by some workers; Fleck found that this form was also of use in paralysis agitans.\textsuperscript{59}

A more disturbing side effect was reported by in 1935 by Siegmund and Fehsenmeier (Pathological Institute, St Catherine’s Hospital, Stuttgart). Römer had noted in 1932 that close attention had to be paid to gastrointestinal condition in atropine-treated patients; although the nutritional status of such patients was generally normal, X-ray investigations had revealed that reduced gastric and large intestinal motility was not uncommon, leading to severe constipation and, in some cases, to megacolon formation.\textsuperscript{60} In 1935, Siegmund and Fehsenmeier reported that six cases of post-encephalitic parkinsonism who had been treated for many years with large atropine doses had died suddenly; autopsy revealed that all had dramatic gastrointestinal changes, including megacolons with stercoral ulcers. Fluoroscopic examination of all post-encephalitic patients on the ward revealed that, with a single exception, all regions of the gastrointestinal tract in these patients were slack and air-filled, and peristaltic processes were much slower; stomach acidity was also much lower than normal persons.\textsuperscript{61} It was not immediately apparent whether these changes were characteristic for post-encephalitic parkinsonism or for those treated with atropine; similar changes in post-encephalitic patients not treated with atropine had also been identified by Hess and Faltischek.\textsuperscript{62} But Siegmund and Fehsenmeier assumed, correctly, that long term atropine use was associated with vegetative changes reflected in altered gastrointestinal function. Ceni’s earlier findings that similar changes were evident in animals exposed to the Bulgarian extract, which also includes atropine, were relatively unknown; significantly, however, they were elicited only by oral administration of the agent.\textsuperscript{63} Brednow demonstrated in the same year by X-ray examination that four weeks’ treatment with atropine was sufficient to elicit marked gastrointestinal changes: general tonus was reduced, the stomach enlarged and the pylorus spastically contracted, movements reduced in magnitude and frequency.\textsuperscript{64} It is now recognized that gastric secretion is markedly inhibited by atropine, especially the fasting secretion of hydrochloric acid. Further, because of the dominance of the parasympathetic tone in the control of gastrointestinal motility, atropine also tends to decrease the tone and slow the amplitude and frequency of peristaltic contractions. This effect had long been recognized; atropine was used in the early part of the century to reduce intestinal tonus in constipation. These effects have led to the use of antimuscarinic drugs in the control of gastrointestinal spasms and peptic ulcers. Given the high doses of atropine administered to post-

\textsuperscript{57} Lewenstein, 1931; Witzleben, 1942, p.104.  
\textsuperscript{58} Grewel, 1938.  
\textsuperscript{59} Fleck, 1933. Römer (1932a) regarded \textit{génatropine} as offering no advantage in comparison with atropine, and, more importantly, noted that it was too expensive for implementing a high dose cure in large numbers of patients.  
\textsuperscript{60} Römer, 1932a.  
\textsuperscript{61} Siegmund, 1935; Fehsenmeier, 1935.  
\textsuperscript{62} Hess and Faltischek, 1927.  
\textsuperscript{63} Ceni, 1935.  
\textsuperscript{64} Brednow, 1935.
encephalitic parkinsonian patients, it is thus not surprising that gastrointestinal problems of an unprecedented magnitude should arise.

Sahlgren also reported “peculiar changes” in the parkinsonian patient treated with atropine in 1937: gastrointestinal disturbances, vomiting and emaciation, and also speech problems and paresis of the facial and hypoglossal nerves.\(^{65}\) It is interesting to note that such dramatic problems were not encountered with the synthetic anticholinergic drugs employed after the War, but Schwab reported in 1961 that about 40% of his patients experienced difficulty with their gastrointestinal tract during therapy. This included an increased tendency to constipation and the development of ulcers, which he interpreted as an aggravation of an underlying condition in parkinsonism involving the sluggishness of the entire gastrointestinal system. Further, most of his patients experienced progressive weight loss and even a degree of malnutrition. Many patients receiving chemical therapy in Schwab’s clinic could not adapt to the effects of anticholinergic drugs and needed to be evacuated by means of enemas twice a week.\(^{66}\) Given that most if not all of his patients would have been receiving anticholinergic drugs for many years, it is difficult to apportion the relative involvement of disease and therapy in this situation. England and Schwab suggested the use of a cholinesterase inhibitor (neostigmine) to counter intestinal motility problems.\(^{67}\)

Fritz Polstorff (Rhineland Provincial Sanatorium, Johannistal by Süchteln) reported largely negative experiences in six female post-encephalitic patients; he justified the publication of such a small study on the basis that it was necessary to bring a problem to the attention of his colleagues which might otherwise be overlooked in the general enthusiasm for the Römer method. Five of Polstorff’s patients suffered from co-existent psychiatric problems; only in the sixth were satisfactory results even with respect to motor performance achieved. Polstorff concluded that:

\[\text{The presentation of psychic disturbances, especially feelings of paranoia or reduced control, reduce the effectiveness of the atropine treatment or, in certain circumstances, render its implementation impossible.}\]

Polstorff noted that both the co-operation of the patient and their belief in the efficacy of the treatment were essential to the success of the high atropine approach. He does not, however, appear to have noted that this therapy itself led to deterioration of psychiatric or cognitive performance, an issue which would later be discussed in connection with anticholinergic therapy of parkinsonism in general.

In one of his earliest contributions to the investigation of the therapy of parkinsonism, Lewis Doshay (Department of Neurology, Columbia University and Neurological Institute, New York) came to the conclusion that the atropine doses employed in the Römer-Kleemann therapy were excessive. As a result, he commenced a study in 112 parkinsonian patients (all but three were post-encephalitic cases) with a “moderate dosage” regimen, in which maximally 3×5-10 drops of a \(\frac{1}{2}\%\) solution (1 drop = \(\frac{1}{200}\) grain) was administered. Doshay found that a once or twice daily administration was also possible if the patient found that the blurring of version interfered with their work. He also noted that the patient could easily dispense his own

\(^{65}\) Sahlgren, 1937.
\(^{66}\) Schwab, 1961.
\(^{67}\) England and Schwab, 1959; 1961.
\(^{68}\) Polstorff, 1931.
medication at home, adding the appropriate number of drops to a glass of water, which also helped overcome the problem of dryness of mouth encountered by 93% of his patients; as the drug was inexpensive (~50 cents/month), they should also be advised to buy a new preparation each month, as some deterioration of the stock solution occurred. Using this moderate dosage, Doshay reported great improvement in 26% and slight improvement in 38% of cases, comparable with the results achieved by other authors with higher doses. It was also superior, in Doshay’s experience, to various forms of the Bulgarian treatment. Doshay therefore recommended the use of moderate doses of atropine as the primary therapy in post-encepha
ilitic parkinsonism, and scopolamine as an adjunct therapy for the management of tremor. He noted, as had Hall, that scopolamine was not able to replace atropine as a monotherapy, as it depressed higher centres (whereas atropine was stimulatory) and did little if anything to relieve muscular rigidity. In contrast, he recommended hyoscine as the drug of choice in true paralysis agitans.\textsuperscript{69}

One of the problems with atropine therapy which would repeatedly prove a bane to testing new therapies was the dependency which the high doses employed caused in parkinsonian patients. Baldauf described in 1938 the responses to atropine withdrawal which were manifested in the first few days:

\textit{At first, thoroughly individual deficits, both objective and subjective, are evident, an intensification of the dyskinetic and vegetative symptoms, but also a psychological decline, restlessness, depressive mood, tendency to complain, oversensitivity, suicidal ideas; signs which are known to appear as a result of the recognized atropine dependence of such patients following the rapid withdrawal of atropine.}\textsuperscript{70}

Although it was generally acknowledged that a true “atropinism” analogous to morphine dependence did not develop in post-encephalitic patients, sudden withdrawal was to be avoided. Amongst the physical signs of atropine withdrawal were vomiting, rapid decline with regard to both parkinsonian state and general condition and, in extreme cases, serious cardiopulmonary problems, even collapse. This was generally attributed to an adaptation of the vegetative nervous system to the effects of the drug. Further, the long term use of any atropine preparation led to the presentation of ‘atropine paranoia’ and auditory hallucinations in some patients.\textsuperscript{71} Goodman and Gilman advised against the use of any belladonna alkaloid agent until the severity of the symptoms rendered it imperative, especially in younger patients, precisely because it was difficult to interrupt therapy once it had begun.\textsuperscript{72}

The site of action of atropine in parkinsonism was controversial. It was long recognized that the belladonna alkaloids exerted both central and peripheral actions, but in the case of atropine it was not clear which site was most important for the antiparkinsonian effect. The central effects of atropine were divided into two types:

- Cerebral effects: initial excitation followed by depression (especially of psychic functions) at higher doses, manifested as restlessness, choreoid movements, incoherence, hallucinations and delirium, followed by drowsiness, coma and asphyxiation.

\textsuperscript{69} Doshay and Ford, 1942.
\textsuperscript{70} Baldauf, 1938.
\textsuperscript{71} Flinker, 1932; Kucher and Zutt, 1939; Hartmann-von Monakow, 1960a, p.86.
\textsuperscript{72} Goodman and Gilman, 1955, p.555.
Effects at the level of the medulla and spinal cord: weak strychnine-like effects, regarded as of little importance.73

Cushny recognized in 1905 that atropine could paralyze striated muscle; that this effect was not seen in the whole animal was attributed to the prior fatal paralysis of the heart muscle.74 Riesser and Neuschloß, investigating muscle contraction in the frog, also found in 1921 that atropine (as well as novocaine and curare) could block contractions induced by acetylcholine, which they tentatively hypothesized as reproducing those of the normal excitatory agent on the ‘receptive substance’ of the ‘neuromuscular substrate’.75 Haffner, on the other hand, noted that only doses which exceeded those which could be applied to a living animal inhibited muscle response to nervous stimulation in a curare-like manner.76 Masayama in 1932 also assumed that the action of atropine on smooth muscle and the mixed type muscle of the abdominalis rectus was also located in the muscle cell itself.77 This view led to many therapeutic trials with spasmolytic compounds in parkinsonism, usually without a great deal of success. Other anticholinergic parkinsonian agents, on the other hand (scopolamine and, later, apoatropine), were recognized to exert primarily central effects. Lewenstein wrote in 1931 that this was also true for atropine:

We know today that atropine affects firstly the motor centres of the large basal ganglia and also the vegetative centres of the brainstem, and thus exerts its effects in precisely those parts of the brain which are most severely altered by encephalitis. . . . We exploit this action of atropine in the treatment of encephalitis, while we avoid the eliciting of the effects of atropine on the cortex (hallucinations, delirium) by using the appropriate dosage.78

Worster-Drought and Hill discussed the effects of the various belladonna alkaloids in an attempt to understand the superiority of stramonium preparations to similar belladonna extracts. They noted that John Hunter’s model of the dual innervation of muscles79 explained the benefit of belladonna alkaloids as being a depressant action on the sympathetic nerve endings, but conceded that this model was not entirely unproblematic. In their view, the effects on bradyphrenia and tremor were “certainly central in origin”, while the suppression of sialorrhea, for example, was a peripheral action.80

In general, however, the peripheral effects of atropine were assumed to dominate in the therapy of parkinsonism. Walshe had found that novocaine rendered flaccid the rigid muscles of paralysis agitans (without any effect on tremor), and proposed that the integrity of the proprioceptive reflex arc from the muscle was requisite for the rigidity of paralysis agitans.81 Davis and Pollock consequently demonstrated that atropine was capable of inhibiting decerebrate rigidity in the cat by an action on this reflex arc, and proposed that this also explained its anti-rigidity action in parkinsonism;82 this opinion

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74 Cushny, 1905.
75 Riesser and Neuschloß, 1921.
77 Masayama, 1932.
78 Lewenstein, 1931.
79 See, for example, Hunter, 1924. (John Hunter was Professor of Anatomy at Sydney University).
80 Worster-Drought and Hill, 1930.
81 Walshe, 1924.
82 Davis and Pollock, 1930.
VI. The 1930s and 1940s: the dominance of atropine and belladonna

**Figure 6-1:** Atropine and two synthetic analogs introduced into the clinic as safer alternatives to the natural alkaloid. Novatropine was the methylbromide of homatropine, which had been first synthesized by Ladenburg in 1883 (Ann. 217, 82); ‘Syntropan’ was launched by Roche in 1934.

was cited with approval by Sollmann in 1943: “The action is probably on the proprioceptive reflex.” It is significant that in the 1906 edition of his handbook, Sollmann commenced his discussion of the effects of atropine with a discussion of its central effects; in the 1943 edition, only a small section on atropine toxicity at the end of the article handles this area.

This view would influence the future development of anti-parkinsonian therapy greatly. A number of synthetic atropine analogs had been developed in the 1920s and 1930s as less toxic alternatives to atropine itself in the treatment of spasmodic conditions (figure 6-1); it was hoped that similar analogs might be developed for parkinsonism which lacked the central effects believed to underlie the untoward responses to the alkaloid. It is certainly ironic that by the end of the 1950s, however, the view was expressed by some workers that these unpleasant side effects were essential to the success of the therapy.

In 1933, Ulrich Fleck (Göttingen Encephalitis Station) published an overview of the experiences in his ward since its opening in 1926; it provides a convenient means for assessing the situation at this point in time. 502 patients, mostly with parkinsonian symptoms, had been treated up until March 1931. Of 197 patients from before the introduction of the high atropine therapy, 11 had died of natural causes (6.1%); the most puzzling of these were four cases who suddenly collapsed and died without apparent reason. Fleck attributed these cases to a catastrophic failure of basic neural processes associated with essential functions, a “vegetative death.” 6.6% of these patients were significantly improved by treatment, another 6.8% were somewhat improved; 86.6% were treatment failures. Fleck noted that this improvement disappeared rapidly after release from the station, even where medication was maintained, so that he believed that

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83 Sollmann, 1943, p.374.
84 For example, homatropine, ‘Syntropan’ and novatropine: see Goodman and Gilman, 1941, pp.477-480. These drugs were sometimes used in place of atropine in the therapy of parkinsonism; for example, Meerloo (1935) wrote that he tripled the dose when using novatropine in place of atropine.
85 In 1963, Jacob and Schrappe reported two cases of patients with post-encephalitic parkinsonism who died suddenly after development of fever; as this sudden deterioration could not be explained on the basis of the pathological findings, the authors proposed that parkinsonian patients suffered a predisposition to autonomic problems of all types, rendering them liable to dramatic collapses of this type.
the beneficial effect was largely attributable to the pleasant milieu and social support provided by institutional care. Fleck criticized the results of other workers who reported only the status of patients on release from the hospital without regard for the lasting benefits of therapy, if any. Of the many drugs tried at this stage, only scopolamine and atropine were of any benefit; arsenic preparations and harmine were without effect. In February 1930, the Kleemann-Römer method was adopted. The symptoms most improved were the vegetative signs, especially the excessive salivation. The rigor was the most improved of the cardinal motor symptoms; the improvement often led to a markedly improved quality of life for the patient. In general, however, tremor was unresponsive even to this therapy, and continued to be treated with scopolamine. Oculogyric crises were reduced in frequency in some patients, but this was not consistent. While the motor restlessness of the patients was unaffected, an improved sense of initiative and reduced bradyphrenia was noted; this did not, however, exceed that observed with low doses of atropine. At this time the Italian preparation ‘Eustateina’ (see above; principal component: scopolamine) was also somewhat popular, but was not consistently found to be effective. But while atropine was the most effective agent in the treatment of post-encephalitic parkinsonism, Fleck did not consider it the ultimate answer; only in combination with hydrotherapeutic, gymnastic and psychotherapeutic measures did it achieve any lasting benefit.86

Combination therapies

One often encounters the comment in the contemporary literature that a particular therapeutic approach was “only” palliative in his nature; it is clear that many clinicians were disheartened by the fact that no causal, let alone curative, therapy appeared possible in the case of paralysis agitans, a feeling of frustration and impotence increased by the nature of the victims of post-encephalitic parkinsonism, mostly struck down in the prime of life. Otto Lampl (Prague) addressed these doubts at the beginning of a short therapeutic review in August 1929:

It is undoubtedly better to help relieve the symptoms than to not to intervene therapeutically at all; after all, we are accustomed to treat other diseases symptomatically: I remind you only of bromium therapy for epilepsy or insulin treatment in diabetes mellitus.87

Lampl asked the reason for the reluctance to aggressively pursue such therapy in parkinsonism, and suggested a number of reasons for the relative “passivity” of both doctors and relatives:

- The failure or short duration of efficacy of all available methods. Lampl noted that post-encephalitic patients were both capable of tolerating higher doses of solanaceous alkaloids and excreting them more rapidly.
- Agents which helped one patient were ineffective in another; further, the response of an individual patient to a particular drug could be inconsistent.

Lampl proposed a solution to this problem which has been employed by most physicians who have treated parkinsonism, both before and since: the simultaneous administration of a number of agents. It was recognized that such an approach, disparaged by many as “polypharmacology”, was not unproblematic:

86 Fleck, 1933.
87 Lampl, 1929.
We know from recent theoretical investigations that the central effects of scopolamine make it the antagonist of the centrally stimulating atropine; experience teaches us, however, that the situation is different in chronic encephalitis; indeed, the combination of the two alkaloids in a particular form even leads to a certain potentiation of the effects of each.  

Lampl had found that freshly prepared alkaloid extracts were usually superior to the purified substances. At the same time, he recognized the necessity of standardization of such preparations: he attributed many of the problems regarding negative reactions to a drug dose which had earlier benefited a patient to inconsistency of drug preparation; the varying potencies of plant extracts prepared by different pharmacists was especially troublesome. On the basis of his experiences, he had developed a mixture of extracts prepared from *Scopolia carniolica*, *Hyoscyamus niger*, *Datura stramonium*, *Atropa belladonna* and *Nicotiana rustica*; the combination – the exact composition was not revealed – was marketed under the names ‘Encephanyl’ and ‘Striasolan’. Lampl combined these tablets with the fever/calcium injection therapy which he had earlier recommended (see page 125), and also with arsenic, insulin (for malnutrition), strychnine (or genostrychnine; for oculogyria) and occipital diathermy (analogous to X-ray irradiation of the basal ganglia). Interestingly, Lampl excluded ‘duboisine’ from his tablets on the basis that he had never found this ‘alkaloid’ to be of benefit in parkinsonism. Lampl was pleased with the results achieved by this approach, but others were not as convinced; one authority wrote in 1941 that there was “little doubt that such polypharmacy has little or no value.” Neither Lampl preparation was listed in the 1946 *Repertorium pharmazeutischer Spezialpräparate*.

As an example of a prescription combining various elements of therapeutics which were thought to be of possible benefit in post-encephalitic parkinsonism, I cite the following from the Dutch clinician A.M. Meerloo (Zennwarts te ’s-Gravenhage):

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Pulveris folii Belladonnae</em></td>
<td>mgr. 5</td>
</tr>
<tr>
<td><em>Pulveris folii Strammonii</em></td>
<td>“ 15-30</td>
</tr>
<tr>
<td><em>Pulveris Glandulae Thyroidiae</em></td>
<td>“ 10-20</td>
</tr>
<tr>
<td><em>Sulphatis atropini</em></td>
<td>“ 0.05-1.000</td>
</tr>
<tr>
<td><em>Nitratis strychnini</em></td>
<td>“ 0.3</td>
</tr>
<tr>
<td><em>Glycerophosphatis calcii</em></td>
<td>“ 100</td>
</tr>
<tr>
<td><em>Pulveris radicis liquiritiae</em></td>
<td>quantum sufficit</td>
</tr>
</tbody>
</table>

Eighty pills were prepared from these components; three were to be administered thrice daily.  

The Bulgarian treatment

The high dose atropine therapy dominated the clinic in the first half of the 1930s; it achieved good results, but was nonetheless attended by serious side effects. An alternative but equally effective therapy was thus eagerly awaited. In 1926, the

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88 Ibid.  
89 Witzleben, 1942, p.110.  
90 Meerloo, 1935; ingredients have been presented here in full (standard pharmaceutical abbreviations were used by Meerloo).  
91 The Bulgarian Nikoloff, writing in 1937, gives 1924 as the year in which an unnamed “natural healer” (*Volksheilkundiger*; in French he was described as a *guérisseur*) first used the method. I have
VI. The 1930s and 1940s: the dominance of atropine and belladonna

Bulgarian apothecary and plant collector Ivan Raeff (or Raew, Raev, Raëv; 1876-1938) introduced to parkinsonian patients in the Bulgarian countryside the white wine extract of the belladonna root, together with a special diet and psychotherapy; this became known as the “Bulgarian treatment”. Raeff was born in Sopot in the Balkan Ranges (central Bulgaria); his father was one of the many traditional herbal therapists for which the town was renowned. Ivan Raeff left Sopot in 1900, studied medicinal plants under the Moslem cleric Hoxha in Istanbul, and returned to Sopot in 1905. In 1919, he married the daughter of a folk healer in Šipka (near Kazanlük; about 50km east of Sopot), where he settled for the rest of his life.

According to Apostolov and Ivanova (Medical Academy, Sofia), Raeff was moved to attempt to treat encephalitis lethargica with high doses of *Atropa belladonna* in 1922 by a number of factors. Folk healers had traditionally employed their plant for a number of indications; Alexander of Gabrovo was said to have employed doses which induced madness before the cure was achieved. Further, Raeff’s father had achieved some fame as a veterinary herbalist in his treatment of cattle with belladonna; the popular name for encephalitis lethargica in Bulgaria was, curiously, “buffalo sickness”. In any case, Raeff empirically determined the dose which was effective without being fatal, and was soon achieving great success.

The following account of the discovery, attributed to the herbalist Neitchev (1928), was related by the Bulgarian P. Dossev in 1972:

> During the years following the First World War, the shepherd Ivan Raëv in the Kazanlik region was known as a collector of medicinal plants. One day, while making his rounds to collect samples, he happened upon the hut of shepherd in which a woman was suffering from a severe post-encephalitic syndrome (Economo’s encephalitis). He agreed to look after her and prepared a decoction from the root of *Atropa belladonna*, which he had her drink. After having drunk the decoction, the patient felt ill at ease and, upset, and soon the convulsions made their appearance. Her relatives, anxious, sent for the shepherd, in order to demand an explanation. But oh: a miracle! The convulsions disappeared after having gradually decreased, and the patient calmed herself and was restored. Later her general condition improved and she started to move about. The peasants were very surprised and sought the shepherd Raëw with even greater urgency in order to thank him, but they could not find him. Having learned their intention, Ivan had gone into hiding.

Apparently Raeff was eventually located as news of the sensation spread. The response of the medical authorities in Bulgaria was initially negative, and Raeff was imprisoned for some time for practise medicine without a licence. Peter Nikoloff (Pharmacological Institute, University of Sofia), who also noted that belladonna had been used by Bulgarian folk healers to treat nervous diseases and rheumatism in

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92 Little has been published outside Bulgaria on the biography of Raeff. Z. Petrov published a biography in Sofia in 1978 and edited the proceedings of a conference concerning Raeff in 1976; a collection of papers in his honor was also published in 1972. I did not have access to any of these publications.

93 Apostolov and Ivanova, 1991. Raeff also took part in the uprising (“Officers’ Putsch”) of September 1923.

94 Dossev, 1974.

95 As folk healers were numerous at this time, it cannot be excluded that Raeff’s political activities were also involved in his arrest.
Bulgaria since ancient times, commenced investigating Raeff’s method in the laboratory and clinic in 1925, and concluded that the treatment was more effective than any alternative for the management of the sequelae of encephalitis lethargica. He also determined the components employed by Raeff in his cure (to be discussed below); the most important was the white wine decoct of belladonna, the chosen extraction method maximizing alkaloid recovery by formation of salts with the acetic acid in the wine.96

News of the new method reached the Royal Palace, which communicated the tidings to Queen Elena of Italy, who was also curious about Raeff and his technique following the successful treatment of an Italian colonel. Two professors were despatched to Bulgaria to investigate the cure, and they soon confirmed the efficacy of the method. A functionary of the Rumanian court inquired at the store of Neitchev the herbalist as to the identity of the root involved; he recognized it at once as belladonna. A short time later, the same official purchased a kilogram of the root from Neitchev, and shortly afterwards another, commenting that the Palace was awaiting a communication from Italy concerning the medical properties of the drug. The secretary of the Italian Queen soon requested further supplies of the drug for clinical investigations, and Raeff was persuaded to travel to Italy in 1934 to introduce the therapy personally; within a short period of time, he had registered ninety ‘cures’ in the Royal Hospital in Rome. Raeff’s method was introduced in commercial tablet form in Italy shortly thereafter as ‘Pantropa’ and in Bulgaria as ‘Curabulgarin’. In 1935, the Italian physician Panegrossi announced at an international congress in Berlin that 1346 patients had been successfully treated with the method.97

Raeff was recognized in Italy by the award of the Medallion of the Royal Crown, his inscription in the roll of foreigners who had rendered great service to Italy, and most significantly by the conferring of an honorary medical degree; a hospital in Rome was also named for him. He returned to Bulgaria, from where he despatched kits containing the components of his treatment throughout Europe, and also investigated phytotherapeutic approaches to the treatment of tuberculosis and epilepsy. Raeff died in 1938, just at the point when his method was achieving international recognition.98

‘Bellafolin’, a total alkaloid extract of belladonna leaves, had been used with some success in paralysis agitans in western Europe for a number of years, but the root had generally been neglected. The Bulgarian treatment was heralded by many on the continent as a cure for post-encephalitic parkinsonism; the Italian Queen Elena, who had previously studied medicine, was so impressed that she founded a trust to fund a string of state-funded clinics across Europe (which still operate today), primarily for the further investigation of the method.99 Giuseppe Panegrossi of the Encephalitis Clinic in

96 Nikoloff, 1937; Apostolov and Ivanova, 1991.
97 Dossev, 1974; Apostolov and Ivanova, 1991. Although Dossev introduced his account with the note “according to Neitchev, 1928”, his account extends at least as far as 1938; further, no sources are listed (although these may have been named at the conference at which the paper was presented). Apart from this anecdote, I have not been able to find further details about Raeff or how his method came to the attention of western medical authorities. Von Witzleben (1942) mentions only that rumours had spread throughout Europe in the mid-1930s of a miracle cure being employed in Bulgaria. There are no further details in Panegrossi’s book on the treatment (1940), nor in his other major publications on the treatment (Panegrossi, 1938a, 1938b, 1938c).
98 Apostolov and Ivanova, 1991.
99 Madaus (1938; p.677) recorded that the Queen had paid 4 million lira for the recipe of the treatment; it is not clear what he meant by this, unless this referred to her financing the initial importation of Raeff’s kits (see below).
Rome was the most enthusiastic proponent of the therapy, and he and Caccuri published and further investigated the procedure for its preparation during the 1930s. The Clinica Sanatrix in Turin (headed by Negro), amongst others, was also largely devoted to the new method, as were clinics in Bari, Milan, Bologna and Trieste. This association and the popularity of the therapy in Italy led to its also being known as the “Italian-Bulgarian treatment”.

The first publication on the treatment in an English-speaking country appeared in the *Lancet* in 1937. The authors noted that the treatment was being used in Italy “on a national scale” and that it was also popular in Germany (where the Queen Elena Clinic in Kassel-Harleshausen had opened on August 1, 1937 under the leadership of the “Great Officer of the Crown of Italy”, Walther Völler), Austria, France and Belgium. They also noted that the meeting of the Société Médicale des Hôpitaux in March 1934 had recommended the “Roemer or Kleeman high-atropine method” as the best treatment for post-encephalitic parkinsonism, whereas a year later Panegrossi had declared the superiority of the new method. Repeated visits to the Roman and other clinics had convinced them that there was something about the Bulgarian treatment which distinguished it from therapies using alkaloids isolated from the plant, provoking their own investigations.

The original instructions for the method as devised by Raeff are given in Box 6-1. The method was supplied by Raeff’s company as a package, initially brought to the attention of the West by advertisements in the Italian press. It was embellished with a portrait of Čipka, contained the following items:

- Root Nr I: well-dried pieces of *Radix Belladonnae* (266g); Ferrannini suggested that the belladonna root (which for most workers included the rhizome) was mixed with some *Radix Iris* for its camphor content.
- Powder Nr II: 10 packets of charcoal, each 100g. Von Witzleben spoke always of “Tierkohle”, which is prepared from animal bone; this was presumably based on the analyses of Di Mattei and Panegrossi, who determined its origin as being horn or a chitinous substance. Ferrannini, on the other hand, and Dutch investigators determined that the charcoal was of vegetable origin.
- Pills Nr III: a sack of 103 irregularly shaped pills (principally bread dough with traces of mint and nutmeg; average weight, 100mg).
- Root Nr IV: a few pieces of the root or rhizome of sweet calamus (*Acorus calamus*; also: ‘sweet flag’).

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100 See, for example, Mann and Gopcevich, 1936: this extensive report in the journal of the Trieste Medical Association reported extensively of the experiences with sixty-one post-encephalitic patients in the previous two years.

101 For example: Völler, 1941. According to the Royal decree of 29 October 1936, Italian sufferers of “acute post-encephalitic parkinsonism” were to be treated in special hospital departments dedicated to this cause, and the patients were to be accommodated in sanatoriums during their convalescence; the costs for those who were unable to pay for this care were to borne by the local authorities.


102 Neuwahl and Fenwick, 1937.

103 Völler, 1941.

104 Neuwahl and Fenwick, 1937.


106 Kuiper and van der Wielen, 1937; Panegrossi, 1940, p.24. Nikoloff (1937) also referred specifically to “carbo ligni”.

107 Price for the package was 100 Bulgarian leva, which corresponded at the time to 2.50 Dutch guilder; Kuiper and van der Wielen, 1937.
VI. The 1930s and 1940s: the dominance of atropine and belladonna

Box 6-1

The Bulgarian treatment as described by Ivan Raeff (1926)

Source: Kuiper and van der Wielen, 1937. Significant deviations in the German instructions prepared by Nikoloff (1937) are given in square brackets; sentences appearing in the original French instructions but lacking in the German are marked with an asterisk.

Take 30g from Root No. I and a powder from Powder No. II and boil both substances together with 600g of a natural white wine [in a closed pot]. The boiling is allowed to continue for 10 minutes after the mixture begins to simmer, and the pot then removed from the fire, the fluid sieved, and filled into a bottle which shall be well corked and stored in a cool place. Of this decoction one gives the patient the following amount as a single dose after the first few hours of sleep (the patient must be awoken):

½ spoonful of the soup for infants up to 5 years.
1 spoonful of the soup for infants 5-15 years.
2 spoonfuls of the soup for persons of 15-25 years.
3 spoonfuls of the soup for persons of 25 years or older.

[Up to the age of 5 years, a half soup-spoon must be taken daily; from 5-10 years, a full soup-spoon; from 10-20 years, 2 soup-spoons; and from 20 years, 3 soup-spoons per day.]

In the first [3-4] days after the commencement of therapy, a reaction [crisis], which can take any of several forms (delirium, incoherent language, . . . ), occurs, but this is only temporary and disappears after a few hours. It is then necessary to give the patient as much milk as possible for drinking, preferably unprocessed, and to not leave him unattended.* If the crisis is particularly severe, the amount is temporarily decreased by a spoonful. [Should the crisis not pass after 5-6 days, it will be necessary to temporarily reduce the dose by a few soup-spoons.] If weak, one can increase the dose.*

Every morning, a pill from the package Pills Nr 3 will be taken on an empty stomach, and fresh milk or hot tea must be drunk immediately after taking the pill. One can give these pills to children of all ages, but they are to be crushed before giving them.*

Every two hours, a piece of Root Nr 4 the size of a corn grain [bean] is to be cut and swallowed [chewed], a total of 6-7 pieces per day. One can chew them before swallowing,* after which the mouth is rinsed with water. This root is only given to children over 10 years of age; cod liver oil is also recommended during cold weather for those of a delicate nature.* A spoonful is taken 3 times a day with soup before meals.*

In the event of constipation, one takes ricine (castor oil) or English salt (Epsom salts; magnesium sulphate), or one generally washes the rectum with soap.* The patient is highly recommended to move as much as possible.* Other medicines and injections are strictly prohibited during the use of this medicine.*
Box 1 (continued)

Diet

No fish.* Only white meat is allowed: hen, chicken, turkey, calf. [No meat may be consumed, neither from warm-blooded nor cold-blooded animals.] Bouillons and soups are acceptable except when fatty.* The diet must be varied and substantial: eggs, milk, butter, cheese, vegetables, olives, rice, pastries, cakes, sweets, candies, raw or processed fruits, stewed fruits.* Spices are forbidden, as are spirituous drinks. [Food of any type spiced with pepper, sour foods (except for lemons and lemon juice), ripe beans, peas and all alcoholic drinks must also be avoided. All other food types and their combinations are acceptable.]

The patient should lie on his right side, as little as possible on the left and avoid lying on his back.* During hot weather, the patient should bathe for 10 minutes after dinner in water warmed by the sun.* All sources of excitation (spirits, sexual relations, . . .) are strictly forbidden.*

[The prescribed diet is to be maintained for the entire duration of the therapy.]

The accompanying letter indicated that ten boxes were required for the annual treatment of a patient. The identity of the items was not given in the original presentation; they were later identified in Italy by di Mattei (Pavia; 1935), Ferrannini (1935) and Tocco (Messina; 1936) and in the Netherlands by Kuiper and van der Wielen (1937). As von Witzleben commented, it sounded somewhat mystic, but even popular recipes were to be considered in the case of a disease whose prognosis was as dark as that of post-encephalitic parkinsonism. Further, Raeff’s fame in his own country must be presumed to have been based on at least partial success.

The alkaloid content of the extract was highly variable, but included varying amounts of hyoscyamine, atropine and, in lesser quantities, scopolamine and belladonnine; it was presumed that this alkaloid mixture was in some way responsible for the relative lack of side effects in comparison to treatment with atropine alone. The main problem, however, remained toxicity; the undefined alkaloid content of the dose (corresponding to 0-3-1.0g belladonna root) and the possibility of accidental poisoning was acknowledged by Raeff himself when he spoke of “crises” in his instructions.

It was originally claimed that the superior qualities of Bulgarian belladonna root (Radix belladonnae bulgaricae), which contained about 0.80% alkaloids (yielding a decoction of about 0.02%) and also exuded a pleasant mint-like odor, were essential to the quality of the treatment. Panegrossi, Nannizzi and other Italian workers examined

108 Subsequent investigations of the alkaloid content of the belladonna root included Bailey (1938a, b), Taylor and Hobart (1938), Kuhn and Schäfer (1938) and Küssner (1939). Comprehensive review of Italian literature is to be found in Panegrossi, 1940.

109 Witzleben, 1938a.
this as their first task, as the question was naturally of economic and practical importance. First indications were that the Bulgarian root was indeed superior to the Italian, but after growing conditions were taken into consideration, it was found that the origin of the belladonna used made no difference to its potency. Similar findings were subsequently reported for English, German and American belladonna. The alkaloid content of roots from various sources varied (table 6-1), but the content of the final preparation was titrated to give a desired concentration, so that this should have played no role in the effectiveness of the therapy. Great variations in the alkaloid content of belladonna root related to growing conditions, care of collection and storage and other factors have also been noted; cultivated belladonna, for example, generally contains a higher alkaloid content than the wild plant. None of these variations should have affected the quality of the final decoction, as it was titrated to give a specific alkaloid content (expressed in hyoscyamine equivalents). This required titration, however, does not appear to have always been conducted; the pharmacist Henriksen wrote to the Lancet in 1938 to warn against the use of preparations without controlling the alkaloid content, as he had found that the efficiency of the extraction varied from 40 to 80%. He emphasized that the use of unstandardized preparations was in any case unscientific; the potential toxicity of the Bulgarian extract rendered such slovenliness dangerous.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Alkaloid content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antolini-Frugoni</td>
<td>0.86%</td>
</tr>
<tr>
<td>Panegrossi</td>
<td>0.8%</td>
</tr>
<tr>
<td>Neuwahl</td>
<td>0.46%</td>
</tr>
<tr>
<td>Kauders</td>
<td>0.39%</td>
</tr>
<tr>
<td>Various English authors</td>
<td>0.24-0.42%</td>
</tr>
<tr>
<td>Antolini-Frugoni</td>
<td>0.3-0.7%</td>
</tr>
<tr>
<td>von Witzleben</td>
<td>0.526%</td>
</tr>
<tr>
<td>Kauders and</td>
<td>0.52%</td>
</tr>
<tr>
<td>Oesterreicher</td>
<td></td>
</tr>
<tr>
<td>von Witzleben</td>
<td>1.65%</td>
</tr>
<tr>
<td>Vollmer*</td>
<td>&gt;0.45%</td>
</tr>
<tr>
<td>Neuwahl</td>
<td>0.38%</td>
</tr>
<tr>
<td>Bailey</td>
<td>0.57%</td>
</tr>
</tbody>
</table>

110 See, for example, Ceni, 1935; Neuwahl and Fenwick, 1937.
111 Findings of Ferrannini and Nannizzi with respect to this question are reviewed in Witzleben, 1942, pp.119-120 and Panegrossi, 1940, pp.24-27.
112 Kauders and Oesterreicher, 1936; Hill, 1938; Baldauf, 1938; Bailey, 1938a, b; Henriksen, 1938a, b, c; Taylor and Hobart, 1938; Price and Merritt, 1941; Fabing and Zeligs, 1941.
113 For a recent examination of this question: Claire et al., 1976. See also Romeike, 1953.
114 Henriksen, 1938b; 1938c. Henriksen noted that one fluid ounce of the Raeff preparation corresponded to 250 minims stramonium (1932 standard), while the maximum recommended dose of the latter was 30 minims. He acknowledged, however, that it was normal to administer parkinsonian patients much larger drug doses as allowed by the Pharmacopoeia.
VI. The 1930s and 1940s: the dominance of atropine and belladonna

Box 6-2

The Bulgarian cure, as described by Antolini (1936/37)

(R esoconti del Reparto “Regina Elena”; taken from German translation by von Witzleben, 1938a)

Macerate in a percolator 20% v/v Radix belladonnae in 1% tartaric acid/0.1% salicylic acid solution for thirty hours, then percolate. Add the filtrate to a half-volume of the extraction solution, macerate again for twenty-four hours. This can be repeated a third time to maximize the drug yield. The three filtrates are then filtered together; the final filtrate must be fully clear. The solution is titrated and adjusted to a concentration of 0.02% with tartrate/salicylate solution.

Antolini had abandoned the use of alcohol for financial reasons; the acid solution acted as an alternative preservative medium.

After the Italian belladonna was accepted as the equal of its foreign competitor, various methods for the preparation of the decoction and the assay of its alkaloid content were designed and tested, primarily in Italy. The leader of the chemical laboratory at the encephalitis clinic in Rome, Antolini, devised the cold method of preparation which was ultimately accepted as the standard preparation method (Box 6-2). Most workers adopted the Antolini method because it was less expensive and simpler than alcohol extraction; Völler preferred it to alternative methods (vacuum or alcohol extraction) on the basis that the

"Paracelsus maceration process releases the most effective and for humans most tolerable healing factors."

Patients tended to prefer it because, in contrast to the original Raeff preparation, it was not of a dirty, cloudy appearance; for physicians it was preferable because it was more stable than the Raeff version and the dose thus easier to calibrate over time.

Although some workers continued to promote the superiority of the Bulgarian root, it had become generally accepted by the 1940s that the effectiveness of the therapy depended only on the alkaloid content of the final decoct, so that the national origin of the plant was irrelevant. The contingencies of the War no doubt also contributed to greater employment of local belladonna, especially in England and the United States. This acceptance of the chemical basis of the Bulgarian therapy also paved the way for the employment of standard preparations of the constituent alkaloids. Von Witzleben had already marketed a standardized form of the plant extract in the 1930s under the name ‘Bulgakur’ (Treupha, Switzerland) or ‘Homburg 680’ (Chem.-Pharm. AG, Bad Homburg), and was originally prepared from authentic Bulgarian root; a drop

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115 Völler, 1941.
116 See, for example, Scheiffarth, 1939.
corresponded to about 0.075mg total alkaloid (per mL: 2.3mg hyoscyamine, 0.6mg atropine, 0.08mg scopolamine). Total root alkaloid extracts were also available under the names ‘Belladonna “Blomberg”’ (Apotheek Dr. J. Blomberg, The Hague), ‘Bellafit’ (Gedeon Richter, Budapest) and ‘Bellapan’ (Bulgarian Pharmaceutical co-operative ‘Galenus’, Sofia); similar preparations were sold in English-speaking countries as ‘Bellabulgara’ (Lederle; 0.45mg tablets), ‘Vinobel’ (William S. Merck; wine extract) and ‘Bulgadonna’ (Lascoff; wine decoction: 0.16mg.mL⁻¹; 0.4 and 0.8mg tablets). Combinations of the extract with other components were also marketed; ‘Belladonorm’ (Dr. Degen & Kuth, Düren, Rhineland), for example, also included he alkaloid extract of baldrian.117

Response to the Bulgarian therapy

In general, the response of post-encephalitic parkinsonian patients to the Bulgarian therapy can be summarized as follows:

- **Muscular hypertonus** brilliantly influenced; one Italian group complained that a patient was so agile after treatment that he ended up in prison.118
- Involuntary movements were reduced, except for the oculogyric crises. Vollmer, on the other hand, noted that such crises were “definitely improved” by an alkaloid mixture which he designed to approximate that of the Bulgarian extract.119
- While Panegrossi noted that tremor was not markedly improved,120 Dillenberg et al. regarded tremor as being improved to a greater extent than rigidity.121 Kauders and Oesterreicher saw the main advantage of the method over the Römer treatment (apart from the lower alkaloid levels involved) as being its abolition of tremor.122 Von Witzleben made the paradoxical observation that tremor could, in fact, present for the first time during the early part of the therapy; he also noted that the there was a great deal of discrepancy in the reports concerning the response of tremor to the therapy.123
- Excessive sweating and sialorrhea were controlled; the vegetative improvements were often the most impressive responses apart from the control of rigidity.
- Some improvement in psychological aspects of the disorder, most notably in motivation, mental slowness, psychological rigidity and concentration, and even a tendency to euphoria in some patients.
- Significant improvements in mobility, speech and writing were reported by most authors; relief of bradykinesia was also often reported.
- Metabolic changes noted by Italian workers included reduced weather sensitivity and normalization of water balance parameters.124

117 This preparation, however, was principally intended for use as a spasmolytic and sedative.
118 Baldauf (1938) noted that the behavioural problems associated with post-encephalitic syndrome were often overlooked because of the motor symptoms: “We find patients who principally exhibit an egocentric attitude, unpredictability, moodiness and grumpiness, and others in whom the psychic abnormalities actually achieve a criminal level, even dominating the clinical picture, and who must therefore be institutionalized.” Behavioural problems were especially marked in boys who contracted encephalitis lethargica, as discussed above in connection with bulbocapnine.
119 Vollmer, 1940.
120 Panegrossi, 1938.
121 In discussion contained in Dillenberg et al., 1942.
122 Kauders and Oesterreicher, 1936.
123 Witzleben, 1938a; 1942, p.128.
124 Reviewed in Panegrossi, 1935a, 1935b, 1938; Witzleben, 1938a, 1942, pp.128-129; Vollmer, 1940. See also other reports cited in this chapter.
VI. The 1930s and 1940s: the dominance of atropine and belladonna

<table>
<thead>
<tr>
<th></th>
<th>Percentage of all cases *</th>
<th>Total improved</th>
<th>Marked or very markedly improved</th>
<th>Practically cured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Light cases</td>
<td>14.9%</td>
<td>100%</td>
<td>26%</td>
<td>60%</td>
</tr>
<tr>
<td>Moderate cases</td>
<td>43.3%</td>
<td>99.3%</td>
<td>36.1%</td>
<td>49.2%</td>
</tr>
<tr>
<td>Severe cases</td>
<td>24.4%</td>
<td>99.9%</td>
<td>48.1%</td>
<td>14.6%</td>
</tr>
</tbody>
</table>

Table 6-2: Success rate claimed by Panegrossi (1940) in the application of the Bulgarian treatment; total number of patients treated: 1968. Several comments should be made about these figures, which were the most spectacular reported. Firstly, the figures presented here are almost identical to those reported by Panegrossi in May 1938, at which time the number of patients treated was 1346; the figures for ‘severe cases’ are, in fact, the same in the two reports. This consistency to the first decimal place is certainly remarkable. Secondly, Panegrossi indicated that there was a fourth category of patient, the ‘most severe cases’; the results for this group (about 17% of all patients) were presented in neither report. * These figures are calculated from the 1938 report as they are not given in the 1940 table.

Improvement in patient condition was normally evident within two to three weeks of commencement of therapy, but it could take months to determine the optimal dosage. As with atropine, treatment commenced with a small dose and increased gradually. The standard practice was to distribute the total dose over three daily applications, but some physicians preferred more frequent administration of lower amounts. Many clinicians were surprised by the fact that the Bulgarian treatment could be suspended for weeks in some patients without any apparent detriment to their condition; further, the toxicity of the preparation was surprisingly low. Patients were receiving the equivalent of 2-4½g of root per day, whereas the recommended maximum dose of *Radix belladonnae* was 0.4g/day.\textsuperscript{125} Panegrossi noted the tolerability of the treatment varied according to a range of factors, including the attitude of the patients (a few of his treatment failures were attributed to “weakness of character”), the weather and time of year; the dose was usually reduced in summer because of this. Administration via enema was possible at the beginning of treatment in cases where gastrointestinal problems were too severe. He claimed, however, that “side effects were practically totally absent.” He also noted the wide variation in optimal dose required by his patients; although the average amount lay in the range 60-120mL for men and 60-90mL for women, he also had patients receiving as little as 6-7mL or as much as 300mL (~60mg total alkaloids) per day. In his experience, benefits were shown immediately if they were to be shown at all, and subsequent treatment maintained this initial level of improvement.\textsuperscript{126}

Influenced by the Römer atropine therapy and clinical experience, Panegrossi abandoned early the dosing schedule proposed by Raeff and substituted a scheme of gradually increased administration until an optimal symptomatic effects was achieved. This approach was also generally adopted by those who subsequently adopted the therapy. As with atropine, there appeared to be no direct relation between the severity of the disease and the dose required, although it was generally the most severe cases

\textsuperscript{125} Frerichs \textit{et al.}, 1925-27, p.643. The vegetarian diet employed by many therapists was sometimes justified by the observation that grazing animals tolerate high levels of belladonna.

\textsuperscript{126} Panegrossi, 1938.
who received the highest doses, perhaps in an effort to control what was often no longer controllable. Panegrossi found that it was generally the younger patients who responded best to the therapy. Völler wrote that most of his patients received between 15 and 60mL of the water extract per day (~3-12mg total alkaloid), although he had had one patients receiving 123mL/day. He also noted that paralysis agitans patients received a lower dose than post-encephalitic cases on the basis of their much higher age; of the 1300 patients treated at the Queen Elena Clinic between 1937 and 1941, 64 suffered from “Parkinsonism essentiale” (4.9%). The major advance in the Bulgarian treatment was for many workers the reduction in the atropine dose thereby administered; about 4mg atropine per day was received in this method, compared with 15-45mg in the Kleeman high dose therapy or 8mg in the “moderate dose therapy” employed by Doshay and Ford, which was still high when compared with the recommendations found in pharmacopoeias.

As with most therapies for parkinsonism, criticisms that the approach afforded nothing but symptomatic relief were often raised. Nikoloff replied to these complaints with the following observation:

Certainly, no one would actually assert that the belladonna alkaloids could actually replace destroyed nervous tissue. We can, however, ask the question: does digitalis restore the damaged cardiac valves to their former state, and are its effects also of a permanent nature?

Von Witzleben was not prepared to venture a guess as to whether the therapy achieved more than symptomatic relief, and was not especially bothered by the suspicion that it might not; he was, however, aware that the duration of the treatment could not be foreseen in advance, and was in all probability indefinite. He saw no problem in the patient administering the medication themselves following their discharge from hospital. Panegrossi saw it as the responsibility of the patient and the state to continue the therapy after discharge from hospital. But, despite insistence upon the fact that the benefit of the treatment was purely symptomatic, Panegrossi was clearly convinced that progression of the disorder could be achieved in a significant number of patients, in effect achieving a ‘cure’:

If the treatment is continued long enough, a permanent success is almost always to be expected. . . . It is thanks to this method that not only a human, but also an economic and a social problem have been solved, with which one had previously struggled for years.

**Mechanism of action of the Bulgarian therapy**

The pharmacological basis for the effectiveness of the therapy occupied the minds of many clinicians, more so than seems to have been applied to many of the other treatments employed at the time; perhaps the unlikelihood of a country doctor on the Balkans discovering the long sought for cure was too great. The Bulgarian treatment was initially received by many clinicians with reservation, partly owing to its irregular

127 Ibid.
128 Völler, 1941.
129 Nikoloff, 1937.
130 Witzleben, 1938a.
131 Panegrossi, 1940, p.103.
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origins. Hermann Vollmer (Neurological Service, Mount Sinai Hospital, New York) was dismayed by the credulous attitudes expressed by Italian and German workers such as Panegrossi, von Witzleben and Völler with respect to the therapy, and preferred a stable preparation of known composition to an extracted root. He knew, however, that there would be opposition to this; some believed in an as yet unidentified substance in the extract which was essential to its efficacy, while others were attracted by the mysticism which attached to the Bulgarian original and its claims to “natural healing”. This resistance had to:

be met with facts. The history of digitalis has illustrated how a valuable drug can be lost for a century because the varying efficacy of its natural source rendered its dosage an art of the individual physician.132

For von Witzleben, these issues appear to have been of secondary importance; he had convinced himself of the efficacy of the preparation, and needed no detailed explanation to justify his confidence. He described an Italian patient depicted in a film by Panegrossi:

It was a man who displayed not only by the usual, rather severe signs of parkinsonism, such as rigidity, sialorrhea, etc. The poor soul was also plagued day and night by a mixture of all possible movement disorders: torsion dystonia, hemiballism, athetosis and chorea Huntington. And after 5 months, it had all disappeared.133

Von Witzleben admitted he expected that negative experiences with the therapy would be reported; however:

To achieve success, it is not sufficient to “apply” the therapy. Also required is work which lasts years, is strenuous and demands enormous patience, which will only be successful if one has conscientious, untiring assistants, which I have over many years been lucky to find in different countries. When one thus makes the criticism that I work under ideal conditions, the criticism is justified but tolerable.134

In general, the therapy was regarded as a type of “atropine plus” therapy, a gentler form of the Römer-Kleemann method, but the reason for its effectiveness and tolerability were a puzzle. Panegrossi announced at a conference in Rome in 1935:

The mechanism of the treatment is not difficult to explain when one considers that epidemic encephalitis affects not only the extrapyramidal motor system but also the organic-vegetative system, and that the nightshade plants have a clearly regulative influence upon the latter.135

He noted that it was not the entire brain which was damaged in post-encephalitic parkinsonism, but rather small regions, “almost impossible to detect, even with a microscope”, in the midst of generally healthy tissue. As a result, he concluded, it was not surprising that a belladonna extract should be of such great benefit in these cases. As he conceded in 1940, however, this somewhat skeletal argument did not answer any of the significant questions which the therapy subsequently posed: the vegetative system was clearly affected by the agent; was there also a direct effect on the motor

132 Vollmer, 1940.
133 Witzleben, 1938a.
134 Witzleben, 1941a.
135 Cited in Panegrossi, 1940, p.83.
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system? If yes, was a central or peripheral effect, excitatory or inhibitory? And with respect to autonomic effects, were sympathetic as well as parasympathetic systems involved?\(^{136}\)

Friedrich Duensing (Encephalitis Ward, University of Göttingen) cited Alexieff as believing that:

> the beneficial effect of the wine and of the atropine were partly attributable to a hyperemia of blood vessels of the brain, which itself affected the damaged vegetative centres of the midbrain and was accompanied by a rise in temperature.\(^{137}\)

Kauders and Oesterreicher also regarded the alcohol as important in assisting resorption of the active alkaloids.\(^{138}\) Duensing noted that the wine probably assisted the patients to sleep, but was also aware that Panegrossi no longer prepared an alcohol extract of the root, and that the aqueous preparation appeared to be even more effective against the parkinsonian symptoms than the original version. Duensing himself had investigated the contributions of the various alkaloids in the belladonna root to the beneficial effect of the treatment. According to various authorities, the alkaloid content of the root consisted of the following substances:

- Hyoscyamine: 80-90%.
- Atropine: 2-7% (Küssner), 3-15% (Kuhn and Schäfer).
- Scopolamine: absent from most root preparations; maximally 1%.
- Apoalkaloids: 5-10% (belladonnine: maximally 5%).\(^{139}\)

Panegrossi also mentioned duboisine as a component of the decoction, but, as mentioned above, this had long been recognized to consist of hyoscyamine and scopolamine. The relatively low amount of atropine in the root was surprising at the time; Panegrossi was not alone in the assumption that the Bulgarian cure was in principal an “atropine wine”.\(^{140}\) The low amount of scopolamine indicated to Duensing that this alkaloid was not decisive in the Bulgarian treatment, despite the opinions of Nikoloff, Kauders and Oesterreicher.\(^{141}\) Similarly, although he had satisfied himself of the beneficial effects of apoatropine and, to a much more limited extent, of belladonnine (see below), he was convinced that the major contributors to the therapeutic effect must be hyoscyamine and atropine.\(^{142}\)

If the Bulgarian treatment was nothing more than a variant of the high atropine approach, however, the question arose as to why it was more effective, a point on which most European workers were agreed. One of the major arguments directed against those who criticized the Bulgarian treatment was that the root also contained two other alkaloids which had long been used in the treatment of parkinsonism (hyoscyamine and scopolamine). Di Mattei especially pointed to the possibility that synergism between the effects of the various components probably underlay the success of the therapy.\(^{143}\) An

\(^{136}\) Ibid., p.84.

\(^{137}\) Duensing, 1940.

\(^{138}\) Kauders and Oesterreicher, 1936.

\(^{139}\) Duensing, 1940. See also Küssner, 1938; Kuhn and Schäfer, 1938.

\(^{140}\) Panegrossi, 1938.

\(^{141}\) Nikoloff, 1937; Kauders and Oesterreicher, 1936.

\(^{142}\) Duensing, 1940.

\(^{143}\) Di Mattei, 1935.
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An interesting experiment was reported by Trabucchi in 1935: he examined the antagonism of the alkaloid solution of acetylcholine-stimulated responses in the isolated frog heart, and found that it was twice as effective in this capacity as atropine. He rejected the suggestion that the alkaloid preparation was perhaps rich in hyoscyamine, which is more active than atropine, in favor of the hypothesis:

> that there were further anti-vagus substances in the extract which facilitate the penetration of the alkaloids and their influence upon those organs which they are supposed to modulate, or that these other anti-vagus substances are not drawn off as alkaloid bases in the ether phase in the preparation of the extract, even if they are not detectable by chemical methods.\(^{144}\)

Most employers of the Bulgarian method, however, were satisfied with the explanation that the naturally occurring alkaloid combination in the wine was fortuitously the best available for the treatment of post-encephalitic parkinsonism:

> That the extract of this drug is more effective than the individual pure alkaloids is not surprising if one considers the totality of individual therapeutic energies which a purely natural product can offer. . . . One has noticed for some time, even in the area of purely pharmacological therapy, that a rational rapprochement with nature appears to be taking place.\(^{145}\)

Von Witzleben readily acknowledged that the mechanism of action of the Bulgarian treatment was an almost complete mystery. Völler described attempts to replicate the effect of the extract with artificial combinations as doomed to failure, attributing this to the undefined but essential influence of the “ballast material” of the plant, which he believed reduced the toxic effects and accentuated the therapeutic characteristics of the active components, as well as the “vital-electric forces” of the natural root.\(^{146}\) Kauders and Oesterreicher had attempted to replicate the percolate by adding the appropriate amount of atropine to white wine, but the patients had noticed the difference and were only again satisfied when small amounts of scopolamine were also added. These authors believed that the alcohol facilitated the absorption of the active components of the treatment. Bedridden patients were made mobile by the combination wine, but returned to immobility when the scopolamine was omitted.\(^{147}\) The wine itself, however, appeared not to be essential, as the Antolini method was conducted entirely in aqueous solution.

The significance of the non-belladonna components of the Bulgarian treatment was doubtful, although the chewing of the aromatic camphor-rich calamus root promoted salivation and may have worked against the mouth-drying effects of atropine; most workers assumed that calamus could thus be replaced with hardy candy or chewing gum. It is, however, interesting that *Acorus calamus* (Sanskrit: *Vacā*, the rhizome is referred to as *Ugra-gandhā*), which is also found wild and cultivated in India and Sri Lanka, was regarded in Ayurvedic medicine as useful in the treatment of neurosis, insomnia, depression and hysteria; it thus had a similar therapeutic spectrum to *Rauwolfia serpentina*. It was also used to improve memory, administration of a paste made from the rhizome and ghee to infants is believed to facilitate their intellectual

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\(^{144}\) Panegrossi, 1940, p.101.

\(^{145}\) Zalla, cited in *ibid.*, p.102.

\(^{146}\) Völler, 1941.

\(^{147}\) Kauders and Oesterreicher, 1936.
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The root consists to 1.5-3.5% of a yellow aromatic volatile oil; the chief component is α-asarone, but it contains a complex array of other substances, including choline and eugenol. Waller’s British Herbal noted that it was “of great service in all nervous complaints, headaches and hypochondrial affections”. An investigation in the mid-1950s found that an alcoholic extract of the root possessed potent analgesic and sedative properties and was mildly vasodepressive; the de-alcoholized extract induced relaxation of isolated rat intestine preparation. More recent work has found that a water-soluble dried powder of alcohol extract antagonized spontaneous motor activity and amphetamine-induced hyperactivity in mice; another group found that the alcohol extract exhibited a range of interesting pharmacological properties, not all of which could be attributed to α-asarone.

The charcoal could conceivably have assisted gastric absorption of the active principles of the extract. Holzman has noted that soot was employed by medieval and later witches in the intoxicating ointments prepared from various solanaceous plants. He noted that this mode of administration was pharmacologically sound: the oil of the unguent would assist the passage of the alkaloids across skin and mucous membranes, while the slightly alkaline soot would neutralize the positive charge, also assisting their passage. Peruvian coca chewers also mix cinders in their mouths with the plant to increase alkaloid absorption. It should, however, be also noted that powdered charcoal was long regarded as an antidote to atropine poisoning and safer to use than morphine, which was generally employed for this purpose in the 19th century. Even Raeff’s countryman Nikoloff regarded satchels II and III as contributing only to the “mystic” nature of the treatment. In any case, the treatment as implemented outside Bulgaria was usually reduced to use of the belladonna extract, usually in combination with more or less rigorous dietary restrictions, and as such met with great success. Idiosyncratic additions were made by some clinicians; in Sofia, the clinic director Alexieff added 30-40 daily injections of any lipoid preparation as a nervous irritant; others added liver extract injections (‘Campolon’; “Bayer” Igepha, Zürich) because of the association of the striatum and the liver in Wilson’s disease.

Belladonna extracts of various types proved relatively effective against all parkinsonian symptoms, especially those of post-encephalitic cases, and thus remained

\[\text{Figure 6-2: } \alpha\text{-Asarone}\]

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148 It was also used for a number of other purposes, including the improvement of gastrointestinal function; Kapoor, 1990, pp.18-19; Sivarajan and Balachandran, 1994, pp.494-495.
149 Cited in Grieve, 1931, p.728.
150 Agarwal et al., 1956.
151 Panchal et al., 1989.
152 Vohora et al., 1990. For further investigations, see Bose et al., 1960; Dandiya and Sharma, 1962; Das et al., 1962; Menon and Dandiya, 1967; also Motley, 1994, and references therein.
154 Other agents used in the case of belladonna poisoning included iodine, tannin, pilocarpine and physostigmine; Merck’s 1899 Manual, p.20; Extra Pharmacopoeia, 1952, p.157.
155 Nikoloff, 1937.
156 Alternatively, of sour milk, yoghurt or lactose; Nikoloff, 1937.
157 Witzleben, 1938a; Völler, 1941.
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In use until the 1960s. The popularity of the Bulgarian treatment was partly based on the recognition that the combination of alkaloids in the preparation, together with the fact that the decoction process did not racemize hyoscine to atropine, might be a more effective agent than atropine itself. The major arguments in favor of the special properties of the Bulgarian recipe included:

- The low toxicity of the belladonna preparation; whereas the pharmacopoeias specified a maximum dose of leaf powder of 0.2g/day, 1 minim of fluid root extract or 30 minims of the tincture, the equivalent of up to 4.5g root/day was ingested in the Bulgarian treatment.
- The absence of significant side effects; for example, the gastrointestinal problems associated with high atropine therapy were less marked or even absent.
- The treatment could be interrupted for weeks without reappearance of parkinsonian symptoms.
- The benefit was greater and manifested more quickly than with any other alkaloid preparation.

Apart from mystical interpretations, the most common explanations for the properties of the Bulgarian treatment were as follows:

- Presence of secondary or intermediate alkaloids which added to the effect of the preparation, either directly or by enhancing the effects of a known alkaloid.
- Presence of ballast or buffering substances which reduced toxicity, facilitated absorption or prolonged the effects of the alkaloids.
- “The potentially stronger action of the decoction of the whole root.”

By the 1940s, there were few workers outside of Italy and Germany who still accepted such arguments, which were flawed in a number of ways. For example, the comparison of leaf and root doses was clearly inadmissible, as it had long been recognized that the alkaloid content of the different parts of the belladonna plant were not the same. Nor was the superiority of the Bulgarian variety of belladonna still taken seriously, but the importance of the preparative process was recognized. Wine extracts produced qualitatively different pharmacologic effects to hydro-alcoholic extracts (tinctures); von Witzleben had noted in 1938 that the use of white wine, low in tannic acid, would prevent the rapid breakdown of alkaloids. Hill, one of the first to use the treatment in England, found that acute toxic symptoms were more common with the acid-alcohol decoct than with that prepared in white wine, presumably because of its higher alkaloid content. Further, the greater efficacy of the Bulgarian cure compared with alternative treatments, and the possibility of temporarily suspending treatment without loss of effect, was not widely accepted outside continental Europe, nor was the claims that side effects were lacking.

The anatomic localization of the effect of the Bulgarian treatment was obviously as obscure as that of atropine. Panegrossi presented results from a number of Italian workers which led him to the conclusion that both vegetative and motor systems were modulated by the Bulgarian wine, and that these effects were both central and peripheral. A more detailed analysis of its effects were not forthcoming, and, perhaps at

158 Neuwahl and Fenwick, 1937.
159 Witzleben, 1938a.
160 Hill, 1938.
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At this stage, not possible; it was principally clinicians, and not the physiologists who were in a position to provide some form of detailed answer to these questions, who were investigating the treatment at this time. The best suggestion was therefore speculative:

\[\text{one can theoretically assume that it paralyzes the centres which control muscle tone which are themselves no longer regulated, or stimulates elements of the higher extrapyramidal centres which have an inhibitory-regulatory function, and which have been attacked but not entirely destroyed by the disease. This means, then, that it exerts a regulating influence, with more or less disputed effectiveness, upon the extrapyramidal elements of the cortex, the substantia nigra Soemmeringi and other anatomical structures.}\]

Despite the claims that the Bulgarian treatment had been raised to the level of “scientific medicine” in Rome, then, any attempt to explain its effects were purely post hoc speculations based on uncertain knowledge of the physiology of the motor system.

Most of the direct evidence appeared to indicate a peripheral effect. Ceni found that it reduced both sympathetic and parasympathetic tone, the latter effect predominating; he had detected histological changes in the gastrointestinal tract, but not the brain or cord. Marinesco and Façon believed that the main effect of atropine, as evidenced by its prominent autonomic effects, was to depress the exaggerated vagal tone of paralysis agitans; they were, however, unconvinced that the Bulgarian extract was superior to the high doses of atropine which they had been employing since the early 1930s, and suggested that it was compromised by a number of (unidentified) problems. Von Witzleben noted that most workers believed that it both exerted central effects and acted directly at the muscle; he himself hypothesized that it might modulate the substantia nigra.

The ultimate benefit of the Bulgarian in post-encephalitic patients treatment probably consisted of its combination of the administration of a variety of alkaloids with comprehensive psycho- and physiotherapy programs, not to mention the enthusiasm of the doctors who believed in it. It was once said that an essential component of anti-parkinsonian therapy was that at least one of the partners – the doctor or the patient – had faith in it; this certainly played a significant role in the story of the Bulgarian treatment. One cannot help but notice that it never achieved the same prominence in countries where it was viewed with suspicion as in Germany and Italy, where it was enthusiastically taken up as part of the “new medicine”.

**Side effects and contraindications**

The side effects of the treatment were similar to those seen with atropine, but appeared later and were milder in nature; this is probably attributable to the smaller atropine levels administered. As with atropine and any of the other high dose therapies which would be developed for parkinsonism, the initial dose needed to be low, and then slowly increased according to the responses of the individual patient until the optimal dose was achieved. The gastrointestinal effects associated with long-term atropine treatment were also minimized in this manner. Kauders and Oesterreicher observed that

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161 Panegrossi, 1940, p.87.
162 Ceni, 1935.
163 Marinesco and Façon, 1936a.
164 Witzleben, 1938a.
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A number of patients experienced a subjective drunkenness which they compared with the effects of alcohol, and were relieved to return to pure atropine treatment. Two patients also experienced nocturnal hallucinations similar to those of an “atropine delirium”. They were, however, a minority. Physostigmine was employed to control the xerostomia, pilocarpine the blurring of vision; a prescription for spectacles was written once the optimal dose of the treatment was achieved. Further, withdrawal symptoms were generally quite mild in comparison to those of atropine, with nausea and emesis rare. Interestingly, parkinsonian patients tolerated higher doses of the Bulgarian extract than normal persons, but not to the same degree as with atropine.

Most practitioners maintained an absolute interdiction of the use of alcohol, nicotine and coffee; Panegrossi was especially strict in this regard:

_I regard it as appropriate, if one wants to administer a poison in high doses to someone, to first remove, as far as possible, all other poisons._

The consumption of meat was restricted to a maximum three portions of lamb for lunch per week; Hechler prescribed an almost vegan diet. Von Witzleben preferred a complete vegetarian schedule, but recognized that the patients’ resistance to such extreme measures was too strong to be worth imposing. He nevertheless restricted meat intake to calf once or twice a week; beef, smoked or pickled meat and fish and all forms of sausage were strictly forbidden, as were peppers, sour foods (with the exception of lemons), peas and ripened beans. By 1942, he had relaxed his views on meat and tobacco, but alcohol remained prohibited.

Scheiffarth noted that different opinions had been expressed regarding diet in parkinsonian patients; he preferred to be fairly tolerant, in order to avoid unnecessary disturbance of the patient, but regarded the acidic effects of meat and the effects of alcohol, nicotine, coffee and tea on the circulation as necessitating their restriction. He also mentioned that some workers favored a vegetarian diet because of its alkalinizing effects, while others administered ammonium chloride in order to promote acidosis.

Contraindications for the Bulgarian treatment were the same as for therapy with any belladonna alkaloid preparation:

- Cardiac disease: not an absolute contraindication if managed, but extreme care was required in cases of angina pectoris.
- Glaucoma: this was in any case usually being treated with large doses of pilocarpine, which would nullify the effects of belladonna therapy. Von Witzleben remarked that he had never encountered a case of glaucoma in a post-encephalitic patient.
- Ulcerative pulmonary tuberculosis.
- Liver insufficiency: a common problem in post-encephalitic parkinsonism, but rarely mentioned in reports on the Bulgarian treatment.
- Kidney insufficiency.

165 Kauders and Oesterreicher, 1936.
166 Vollmer, 1940.
167 Panegrossi, 1940, p.33.
168 Hechler, 1939.
169 Witzleben, 1938a.
170 Witzleben, 1942, p.32.
171 Scheiffarth, 1939.
172 Ibid., p.124.
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- Prostate enlargement.
- Syphilis: usually treated with large doses of arsenic.
- Gastrointestinal disease.
- Epilepsy.
- Psychopathic personalities.

Also excluded were encephalitis lethargica patients still experiencing the acute stage of the disease, and those who were physically debilitated; the last symptoms of the encephalitis had to have disappeared and the general health of the patient restored before the instigation of the Bulgarian therapy. Hypertension, age and pregnancy were not usually regarded as obstacles to initiation of treatment. Attention to the intestinal changes induced by large doses of atropine had also to be carefully followed; they could be controlled to a certain degree by stomach gavaging and injections of endopituitrin (extract of the posterior pituitary). Only about 1% of patients could not tolerate the Bulgarian mixture at all; von Witzleben attributed a proportion of these failures to disregard for the ban on tobacco and alcohol which the regimen required.\(^{173}\) An important absolute interdiction was the combination of belladonna alkaloid treatment with any fever or shock treatment, as the atropine class drugs exerted strong effects on thermoregulatory centres.

The Bulgarian treatment in Germany

After an initial period of scepticism, the Bulgarian method, seen by many as a refinement of the Römer method, was also enthusiastically adopted in Germany.

The treatment of the sequelae of encephalitis lethargica with the Bulgarian belladonna root is in some quarters completely unknown, in others rejected with a shrug of the shoulders as quackery and the enthusiasm in Italy regarded as unjustified. Until recently, you could find the same attitude, before the beneficial effect of the Bulgarian preparation, hitherto promoted in newspaper advertisements and by individual country doctors, was subjected to closer scientific examination.\(^{174}\)

The neurologist Heinrich D. von Witzleben (Sanatorium Kreischa, near Dresden)\(^ {175}\) claimed that he introduced the Bulgarian treatment to Germany at the end of 1936, and there was certainly no more enthusiastic German proponent of the therapy.\(^ {176}\) He described the philosophy of his approach to encephalitis lethargica in the following manner on the front page of the *Klinische Wochenschrift* of March 5, 1938:

The progressive disorder leads in many cases to the complete or almost complete inability to work, and the helpless victims become a burden for the public and must be accommodated in hospitals and other institutions. For this reason, encephalitis epidemica has a quite significant social importance, especially as the number of post-encephalitic patients is considerable. Neustadt estimated that there were 20,000 in the German Empire in 1932, Stern estimated 30,000 in 1936, which represents about half of the acute encephalitis patients. A question for the Public Service Insurance with its 4½ million members to decide is whether and to what extent these patients should be...

\(^{173}\) He noted in particular that many European patients did not classify beer as alcohol; Witzleben, 1942, p.32.

\(^{174}\) Selzer, 1937.

\(^{175}\) An institution of the Imperial Insurance Fund for Public Servants (*Angestellte*).

\(^{176}\) The two earliest German papers on the method in major journals, however, appear to have been those of von Rouques and Nikoloff in 1936.
treated. It is understandable that, according to the guidelines of the Public Service Insurance Act, that one can only rarely approve the granting of funds for therapy, in view of the fact that, ultimately, these chronic cases cannot be helped and that there is no question of these patients being able to work again. I, on the other hand, have always taken the view that one should always attempt therapy in all cases where the patient was not completely bedridden and unable to be transported. Even many years ago it had impressed me how much one can achieve with a goal-directed therapy and how incredibly willing to work these patients are. . . . It only rarely happens that such a patient wants to accept a pension; the majority, under all circumstances, want to work again.177

This viewpoint was presumably problematic; the order for the “destruction of unworthy life” would only be issued by the German government in the following year, but the question of euthanasia and the preservation of hopeless cases had nonetheless already come under serious discussion. When the act came into effect in October 1939, the ability to work was one of the major determining criteria.178 It is, however, interesting to note that Völler later commented that the Queen Elena Clinic in Kassel, despite the fact that 70% of the patients were financially disadvantaged, had never wanted for funds from the authorities; special funds for the treatment had been made available by Hitler, and these had been tripled in 1941 at the instigation of Hitler’s personal physician.179 It is not unlikely that this privileged treatment of parkinsonian patients was linked to the fact that Hitler himself suffered from the disorder.180

In any case, von Witzleben was more than willing to attempt to assist his patients, whom he saw as suffering from chronic encephalitis; he was one of the most ardent proponents of the view of the disorder which regarded parkinsonian symptoms and signs of amyotrophic lateral sclerosis as expressions of the chronic stage of the disease. Having quickly exhausted the small supply of Bulgarian root to which he initially had access, he had commenced using ‘Panatropa’, a dragée form of the cure produced in Milan. This version, however, was not tolerated by many of his patients, and was difficult to acquire. He found, however, that returning to the Römer high atropine therapy could only be achieved with some discomfort to his patients. He therefore asked the pharmaceutical firm AG Bad Homburg (Frankfurt am Main) to prepare the drug from German and Bulgarian belladonna. Amongst its features was the stabilization of the preparation to prevent the conversion of hyoscyamine to atropine.181 It proved once again that the origin of the root had no effect on the alkaloid content of the percolate. Interestingly, the inclusion of Raeff’s charcoal in the percolate reduced the alkaloid content by about 7% — but the substitution of this powder by charcoal produced by Merck (carbo medicinalis) adsorbed the entire alkaloid content, leaving none in the

177 Witzleben, 1938b. Von Witzleben’s two 1938 papers were also published in the same year as a monograph by Springer, Berlin.
178 The informal order is included in Hünten, 1995, pp.338-339.
179 Völler, 1941.
180 There is an extensive literature on Hitler’s parkinsonism; see Gibbels, 1988; Lieberman, 1997; Gerstenbrand and Karamat, 1999; Schenck, 2000, pp.426-440. Hitler’s final doctor, Theo Morell, was not competent in the treatment of neurological disease, and employed almost every possibility in this direction during the final months of Hitler’s life: nicotinamide, bromides, scopalamine, bulbocapnine, ‘Neurosmon’, placental extract, calcium, vitamin B1; in March 1945 he resorted to galvanization; in April he turned to a combination of the Bulgarian treatment and harmine.
181 The approach to this company is mentioned in his 1938 papers; in his 1942 book, published after his move to the United States, he wrote that the initial approach was to a Swiss pharmaceutical firm, presumably Treupha. He continued to refer to the preparation, however, as ‘Homburg 680’, its German designation. See also Hechler, 1939.
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final decoction. In general, the charcoal was omitted from further work, with no apparent loss of effectiveness of the final preparation. This is the product which was designated ‘Homburg 680’, and which von Witzleben promoted aggressively in the coming years:

We have today fortunately again learned that the most exact laboratory which isolates the active components and produces them in their purest form cannot compete with Nature’s laboratory.

Völler similarly appealed for the superiority of “lumen naturae” to the “lumen apothecariorum”. There indeed existed a tendency in the mid-1930s to turn from pharmacologically pure substances to their original plant sources. Kauders and Oesterreicher, citing Panegrossi and de Mattei, recorded that:

there is a similar movement for the preference of digitalis leaves to digitalis preparations, of opium to morphine, of ergot to ergotine, and . . . no doctor would protest against the use of these herbs.

This “movement” had begun in the mid-1920s. With respect to parkinsonism, Rapp and Stoll had developed the Sandoz product ‘Bellafolin’, consisting of a total belladonna leaf alkaloid extract in the form of the malate, as an alternative to purified atropine. In its annual report on developments in pharmacology, E. Merck noted:

[Atropine] has not completely supplanted the galenic preparations, such as belladonna extracts, as the latter, including all the alkaloids in the plant, exhibit different effects to those of atropine alone. As different preparative methods and source plant material mean that these galenic preparations are neither quantitatively or qualitatively consistent with respect to composition, the need for a clinically usable preparation including the total alkaloid content of the belladonna has been expressed.

Further, Lampl and Wiechowski had found that fresh extracts of particular parts of the appropriate plant were superior to purified atropine and scopolamine; they also noted, however, that the preparation had to be “biologically assessed in order to produce a standardized extract.” A number of authors attributed the apparent superiority of the Bulgarian treatment in comparison with other alkaloid-based approaches, with respect to both the effectiveness and safety, to the synergism of the various components of the total extract, including contributions by as yet unidentified components. This was a difficult hypothesis to test, and was in fact disputed by most English-speaking authorities (as will be discussed below), but many European workers were prepared to accept their empirical experience of the therapy, colored as this was by the expectations attached to the therapy.

It was in this spirit that von Witzleben introduced ‘Homburg 680’. He preferred to market the agent as a liquid in a calibrated bottle, as it was easier to dispense precisely

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182 Witzleben, 1938a.
183 Ibid.
184 Völler, 1942.
185 Kauders and Oesterreicher, 1936. Panegrossi argued similarly in his 1940 monograph (p.99); see similar comments in von Rouques, 1936.
186 Mercks Jahresbericht for 1924, p.70.
187 Lampl, 1929.
188 For example, Kreitmair, 1947.
than tablets; the ‘Panotropa’ tablets each contained 1.25mg total alkaloid, whereas a drop of ‘Homburg 680’ contained 0.075mg. Von Witzleben also argued that the absorption of a liquid extract was innately superior to that of a tablet. On the other hand, the patient was expected to prepare his own medicine once he was discharged from hospital; the dispensing of several dozen drops must have represented a considerable challenge for any person with severe tremor. Von Witzleben commenced treatment with a single drop on the first day and reached the mean dose of $3 \times 20-25$ drops per day only after 2 months (table 6-3). In order to compensate for dryness of mouth, von Witzleben used chewing gum and sour or menthol-eucalyptus bonbons. Von Witzleben published a review in 1941 of the results gained with therapy with 827 post-encephalitic patients whom he had personally treated over a number of years. His statistics are given in table 6-4; the success in light and moderate cases is without doubt impressive.

Von Witzleben’s philosophy on the therapy of parkinsonism was also interesting. He supported the idea of the institution of special units for post-encephalitic patients, as had been introduced in Italy in 1936 and proposed by Perkins in the United States. Parkinsonian patients were generally hospitalized with a mixture of neurological and psychiatric cases at this time, a situation which von Witzleben regarded as deleterious to their progress:

\[
\text{One should not forget that in spite of many mental disturbances and psychomotor deviations in personality, a large part of the psychic life of these patients functions normally. Even though they are unable to express what is going on within them, there is an inside and they have an emotional and effective (sic) life, often a very sensitive one.}^{191}
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In addition to the attention to the psychological and physiotherapeutic care of these patients, common to most discussions of the therapy of parkinsonism, von Witzleben emphasized that the stay of a parkinsonian patient in hospital must be treated as training them for coping with their disorder for the rest of their lives:

\[
\text{The patient suffering from post-encephalitic Parkinsonism should not be brought to the hospital merely to enjoy the efforts of others on his behalf, but he himself must be encouraged to cooperate and to learn a very strict discipline. The milieu of the hospital, therefore, may be considered a training milieu which, together with certain methods of medical and physical treatment, will improve the patient’s state.}^{192}
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Von Witzleben was one of the few authorities on the subject who devoted so much attention to the post-discharge therapy of the patient, which would, in any case, be of incommensurably longer duration than the period spent under the direct care of hospital staff.

Walther Völler at the Queen Elena Clinic in Kassel was also an ardent supporter of the “genuine” Bulgarian treatment (as opposed to treatment with purified alkaloids), his only variation being the use of multiple doses throughout the day instead of the

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189 Witzleben, 1938a; 1942, pp.121-123.
190 Witzleben, 1941a.
192 Ibid., p.33. Arthur Hurst (1934b) at Guy’s Hospital in London was of a similar opinion: “Vigorous psychotherapy in the form of explanation, persuasion, and re-education with the aid of a friendly, but strong-willed nurse or companion is essential, as lethargy of the body gives rise to lethargy of the mind.”
prescribed three. He described the "the unexpurgated composition of the [belladonna] plant as the most complete of medications". Völler had empirically determined that this procedure was more effective in keeping oculogyric crises to a minimum and also had a beneficial effect for the tremor, as determined by the "concentration test", in which the patient was required to balance a small celluloid object on the back of their hand. Völler, who like most therapists combined medical treatment with an extensive dietary, gymnastic and psychiatric schedule, regarded a program of about 11½ weeks for paralysis agitans cases and 15 weeks for post-encephalitic patients as sufficient; this varied according to the individual, so that a third of post-encephalitic cases required treatment for only 4-8 weeks, while 4.7% needed more than six months to show improvement which justified their release from the clinic. As depicted in table 6-5, Völler confidently claimed a high "success" rate; he rated 54% of cases as being capable of return to work at the end of their treatment (though not necessarily to their former occupation), while a further 26.6% of those "cured" were suited to work under certain conditions. Völler’s enthusiasm to demonstrate the success of his clinic was no doubt inspired as much by the need to justify the existence of such a clinic in the midst of a World War as by purely medical pride.

Scheiffarth (University Medical Clinic, Erlangen) adopted a more critical approach to the Bulgarian method in a 1940 paper, although he regarded it as the best available therapy for post-encephalitic parkinsonism. He commenced his discussion by noting that it was probable that only those symptoms which he classified as the "amyostatic symptom complex" were amenable to pharmacological therapy; he explained that he used this term to designate disturbances of muscle tone, which were invariably associated with characteristic vegetative dysfunctions. All other motor symptoms were to be regarded as secondary to this problem, which he believed to the result of a specific anatomical lesion, the site of which was yet to be conclusively determined. Secondly, he regarded the belladonna alkaloids as "vegetative poisons"; that is, whatever benefit the Bulgarian treatment might bring, the eventual presentation of undesirable side effects by all patients was inevitable, and supplementary drugs were required to manage these phenomena. Thirdly, he rejected the current treatment schema under which the extract was administered three times per day; he invoked instead the "principle of the depot effect", whereby he argued that the continuous administration of a drug was more effective than a series of large doses, and administered the drug at four-hourly intervals from 6 a.m. to 10 p.m. Finally, he restricted the treatment to patients with clinical

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193 Völler, 1942.
194 Völler, 1941.
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<table>
<thead>
<tr>
<th>Light cases</th>
<th>Percentage of all cases</th>
<th>Total improved</th>
<th>Marked or very markedly improved</th>
<th>Practically cured</th>
<th>Able to work</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>28.5%</td>
<td>99%</td>
<td>38%</td>
<td>58%</td>
<td>97.3%</td>
</tr>
<tr>
<td>Moderate cases</td>
<td>34.1%</td>
<td>96%</td>
<td>45%</td>
<td>45%</td>
<td>86.8%</td>
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<tr>
<td>Severe cases</td>
<td>37.4%</td>
<td>93%</td>
<td>71%</td>
<td>9%</td>
<td>37.6%</td>
</tr>
</tbody>
</table>

Table 6-4: Success rate claimed by von Witzleben (1941a) in the application of the Bulgarian treatment; total number of patients treated: 827 (671 males, 156 females).

pictures principally characterized by rigidity and akinesia; those with hyperkinetic syndromes, under which term he included genuine paralysis agitans and other forms in which tremor predominated, did not benefit from the therapy. The Bulgarian treatment also found application by the akinetic syndromes which followed brain trauma of various types.  

H. Hechler (City Hospital, Mannheim) noted that higher doses of ‘Homburg 680’ were required if a patient had been treated for long periods with scopolamine or atropine; further, those patients who failed to respond to the preparation had generally also proved resilient to the benefits of atropine. Hechler was particularly impressed by the psychological changes achieved in his patients; a general improvement in morale, in one case to the extent that suicidal ideas were abandoned, was one of the pleasing features of the approach.

F. Baldauf (Sanatorium Klingenmünster, the Pfalz) was also impressed by the success of the Bulgarian method, but was convinced from the outset that German belladonna was the equal of Raeff’s. He contracted the firm Madaus & Co. (Dresden-

<table>
<thead>
<tr>
<th>Light cases</th>
<th>Percentage of all cases</th>
<th>Total improved</th>
<th>Well or significantly improved</th>
<th>Functionally cured</th>
<th>Able to work</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>24.6%</td>
<td>100%</td>
<td>89.7%</td>
<td>35.7%</td>
<td>100%</td>
</tr>
<tr>
<td>Moderate cases</td>
<td>47.3%</td>
<td>100%</td>
<td>85.4%</td>
<td>14.6%</td>
<td>62.5%</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+37.5%*</td>
</tr>
<tr>
<td>Severe cases</td>
<td>24.2%</td>
<td>100%</td>
<td>64.7%</td>
<td>5.5%</td>
<td>5.5%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+31.5%*</td>
</tr>
<tr>
<td>Most severe cases</td>
<td>3.9%</td>
<td>100%</td>
<td>44.1%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Table 6-5: Success rate claimed by Völler (1941) in the application of the Bulgarian treatment at the Königin-Elena-Klinik, Kassel. * The second figure refers to those patients who were capable of limited work.

195 Scheiffarth, 1940.
196 Hechler, 1939.
Radebeul) to produce a whole root extract from shavings of the fresh root (‘Radix belladonnae Teep preparation’). Baldauf noted that this was, in fact, a slight departure from the Bulgarian treatment; he consciously chose to use fresh instead of dried material, and included the entire contents of the root (both alkaloids and ballast), without extensive purification or selection. The success in treating post-encephalitic patients with 2-9mg alkaloid/day was so remarkable that some patients reportedly threatened suicide should they be required to return to atropine therapy. The side effects were the same as those with the normal Bulgarian treatment. Baldauf was one of the few authors who retained the chewing of the calamus root as part of the therapy, in order to counter dryness of mouth; alternatively, jaborandi preparations (containing pilocarpine) could be used. Although the use of local plants instead of Bulgarian belladonna had quickly been accepted in most countries, as was necessitated by the outbreak of World War Two, the use of fresh root shavings as the basis of the treatment only achieved limited spread due to the practicalities of the approach.197

The Bulgarian treatment in England

Neuwahl and Fenwick (Law Nursing Home, Rochdale, Lancashire) were the first workers to report their experiences of the Bulgarian therapy in England. They were also convinced that the effects of the Bulgarian treatment was more than the sum of its alkaloid parts: in 1937, they noted that the effects of the treatment as implemented by Panegrossi in his Rome clinic with reports on treatment with those of atropine, hyoscine, stramonium and commercial belladonna alkaloids were qualitatively different. Further, Neuwahl and Fenwick rejected most emphatically the notion that atropine underlay the effect of the preparation. They justified this view by subjecting the Bulgarian decoction to a number of treatments which eliminated its mydriatic effect when tested in the cat, but preserved the clinical efficacy of the preparation in the parkinsonian patient; this included filtering the solution twelve hours after its preparation and producing a concentrated decoction by boiling away half the volume.198 Further, the effect of the preparation on the frog heart exceeded what would have been expected from the atropine content of the decoct; similarly, the atropine content of the dose of Bulgarian extract required to maintain patients previously receiving high dose atropine was only half that expected.199 Neuwahl found that despite adjustments for variations in alkaloid content, some of his patients were only satisfied with Bulgarian belladonna (which he was receiving from Raeff via Hill in early 1939). Neuwahl claimed a great deal of success with the Bulgarian treatment: of 118 patients for whom follow-up after 3-15 months was possible, 51 were “symptomatically cured”, 55 fit for work; even in the 56 severe cases, 10 were “cured”, a further 13 “greatly improved”; 12 were “fit for work”. Neuwahl and Fenwick also noted that the treatment was inexpensive; the annual cost for 100 patients was estimated to be no more than £7. This presumably, however, encompassed only the cost of the preparation and omitted the ancillary costs of the therapy.200

197 Baldauf, 1938. The preparation, however, was marketed at least as late as 1950: Ludwig et al., 1950, p.268. ‘Teep’, short for ‘Teepulver’ (‘tea powder’), was a special drug preparation introduced by the firm Madaus; shavings from the fresh plant were dried without heat, pulverized and combined with sugar or another substance to promote stability of the preparation. The aim was to avoid the loss of active principles – including alkaloids, glycosides, etheric oils and enzyme activity – associated with normal preparative purposes. See Radaus, 1938, pp.306-314.

198 Neuwahl and Fenwick, 1937. The authors noted that their work replicated that of Tocco (1936).

199 Ibid.; Neuwahl, 1939.

200 Neuwahl and Fenwick, 1937.
Alcock and Carmichael (Research Unit, National Hospital, Queen Square, London) were somewhat more skeptical regarding the new method. They quickly dismissed the non-belladonna components of the treatment as irrelevant, and also emphasized the need to compare equivalent doses of the Bulgarian wine and other alkaloid drugs in an objective manner; this they attempted by use of a modified ergograph to assess the speed and extent of rapidly alternating movements at the elbow. They concluded that English belladonna was as effective as the Bulgarian variety, and that the standard B.P. tincture achieved the same results as the decoction. More importantly, stramonium proved to be more effective in four of the five patients who took part in the trial. The case number was low, and the lack of enthusiasm in this investigation was unmistakable.201

At about the same time, P. Kuiper and P. van der Wielen (Laboratory for Pharmacology, University of Amsterdam) reported the most detailed analysis of the Raeff package which I have discovered, including the original instructions (in French). They had requested that Raeff send them a sample of the plant from which the root was collected, but he replied that it was not possible at that particular time of year, and forwarded instead a page from a Bulgarian herbal which depicted *Atropa belladonna*. They estimated the alkaloid content in both Bulgarian and Dutch belladonna root under two possible situations: firstly, assuming that the optical activity was due principally to hyoscyamine, and secondly to hyoscine. In both cases, the total alkaloid content was similar in roots of either origin (0.58%); the proportion represented by atropine, however, was higher in the Bulgarian root (0.28-0.34% v. 0.13-0.20% atropine).202 Both this and the papers by Neuwahl aroused great interest in the method in England, but a more skeptical approach in the evaluation of the therapy was generally adopted from the beginning in these countries than in other European clinics. Both the Dutch workers and their counterparts in England established that the root samples included in the kit were indistinguishable on both the macroscopic and microscopic levels from Dutch or English belladonna root of the national pharmacopoeias. Kuiper and van der Wielen calculated that the atropine dose received by a patients in this treatment was about 16.5mg/day, commenting that it was thus "no wonder that the treatment elicited different responses (delirium, incoherent language, . . . .)."203 The Dutch workers also concluded that the belladonna root alone was responsible for any beneficial effects of the treatment program, and that the medication could be prepared as effectively (and more cheaply) by adding the appropriate measure of *tinctura radicis Belladonnae* and of *sirup aurantiurum* to water. The price for Bulgarian belladonna was apparently not outrageous, as the authors regarded it as no impediment to using it for the preparation of the tincture.204

During 1938, reports on the pharmacognosy of the Bulgarian belladonna continued to appear in the pharmaceutical press in England. Arthur E. Bailey (Resident Chemist, Three Counties Hospital, Arlesley) noted in passing that the quality of even genuine “Bulgarian” root was variable, as crop failures in Bulgaria had led farmers to seek alternative means of income, and the popularity of the “Bulgarian treatment” meant that

201 Alcock and Carmichael, 1938.
202 Kuiper and van der Wielen, 1937. The calculated figure for atropine is quite high.
203 Ibid.
204 Syrup of orange peel was commonly employed both as a tonic and digestive, and as a vehicle for other medications. It includes a small amount of tannic acid; this is interesting, as tannic acid is used to precipitate alkaloids from plant extracts, and wines low in tannic acid were required for preparation of the Bulgarian treatment.
belladonna cultivation had become a widespread alternative. Bailey also listed the theoretical problems of the Bulgarian treatment:

- Up until this point, belladonna root had not been extensively used in English medicine as an internal agent; its use was limited to external application, so that there was little experience in this area.
- The preparation of the treatment, involving maceration followed by decoction, was “almost unheard of as a method for the extraction of the active principles of an alkaloidal drug.” Boiling in an acid medium would, in fact, be expected to hydrolyze many alkaloids; he also noted, however, that post hoc assays had indicated that this was not a great problem. It must be commented, however, that the Raeff method was actually similar to the older British Pharmacopoeia method for preparation of atropia from belladonna root (box 6-3).
- The use of white wine as the menstruum was also unusual, yielding an extract which represented a compromise between a weak tincture and an acetum.205
- The final preparation was largely undefined. Apart from the known alkaloids, one must also consider the minor alkaloids of the belladonna root and other components such as volatile pyridine bases, β-methylaesculetin, as well as components contributed by the wine itself. These latter compounds, the “minute constituents” discussed by Lampitt as contributing to taste, odor and other characteristics of foodstuffs, were generally unknown factors.206

Bailey criticized Neuwahl and Fenwick for not conducting quantitative assays of their material before using it in patients, especially as they themselves had recognized this as being “desirable”. He also failed to replicate their finding of a lack of a mydriatic effect in the final preparation. He then investigated six different methods for preparing the root wine, using either English and Bulgarian belladonna. The Raeff method (maceration 4 hours, boiling, filtration) extracted about 80% of the available alkaloids (as did boiling after filtration or omitting the boiling altogether), but the high starch content of the root resulted in the “production of a most inelegant preparation”; the preparation was consequently difficult to filter and assay. Further, a few starch granules inevitably reached the final decoction, and could only be removed by “careful and tedious” centrifugation; otherwise, they gave rise to chloroformic emulsions and also served as culture medium for bacteria and fungi, presumably the reason for which Neuwahl and Fenwick found it necessary to refrigerate their preparation. Bailey found an almost 100% alkaloid yield with maceration in white wine, 1% acetic acid or 15% alcohol for twenty-four hours followed by filtration. He concluded that acetic acid with some alcohol as preservative was probably the best menstruum for the preparation of the drug.207

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205 *Tinctura:* solution of the components of a crude drug in alcohol, whether by simple solution, maceration or maceration followed by percolation. The tincture of belladonna B.P. used diluted rectified spirit (final concentration: 62½% w/v). *Acetum:* acetic acid employed as menstruum. There were far fewer official aceta as tincturae. Extracts prepared in wine were also recognized by the B.P. (such as *Vinum cocae*, prepared with plain red wine); although a number of formulae for the extracting wine were official, most prescriptions used sherry-type wine (17-18% w/v alcohol). Such preparations were more pleasant to the taste than tinctura, but were not as stable over time. See Sollmann, 1906, pp.56-63.

206 Bailey, 1938a; 1938b.

VI. The 1930s and 1940s: the dominance of atropine and belladonna

Box 6-3

Atropia, prepared according to the British Pharmacopœia of 1864 (pages 187-188)

Take of Belladonna Root, recently dried, and in coarse powder, two pounds;
Rectified Spirit, ten pints;
Slaked lime, one ounce;
Water, half a fluid ounce;
Dilute Sulphuric acid, a sufficiency;
Carbonate of Potash, a sufficiency;
Chloroform, three fluid ounces;
Purified Animal Charcoal, a sufficiency;
Distilled Water, ten fluid ounces.

Macerate the root in two quarts of the Spirit, for twenty-four hours, with frequent stirring. Transfer to a displacement apparatus, and exhaust with the remainder of the Spirit by slow percolation. Add the Lime to the tincture placed in a bottle, and shake occasionally several times. Filter, add the Dilute Sulphuric Acid in very feeble excess, and filter again. Distil off three fourths of the spirit, add to the residue the Distilled Water, evaporate at a gentle heat, but as rapidly as possible, until the liquid is reduced to one third of its volume and no longer smells of alcohol; then let it cool. Add very cautiously, with constant stirring, a solution of the Carbonate of Potash so as nearly to neutralize the acid, care, however, being taken that an excess is not used. Set to rest for six hours, then filter, and add Carbonate of Potash in such quantity that the liquid shall acquire a decided alkaline reaction. Place it in a bottle with the Chloroform; mix well by frequently repeated brisk agitation, and pour the mixed liquids into a funnel furnished with a glass stopcock. When the chloroform has subsided, draw it off by the stopcock, and distil it on a water bath from a retort connected with a condenser. Dissolve the residue in warm Rectified Spirit; digest the solution with a little Animal Charcoal; filter, evaporate, and cool until colourless crystals are obtained.

S.A. Taylor and F.G. Hobart (Pharmaceutical Department, Westminster Hospital, London) also found that the boiling step was unnecessary for achieving the full therapeutic benefit of the treatment. These workers devised as the next stage of their investigation a defined menstruum to replace the wine they had used (detannated Spanish white wine), and derived the following formula: 2% lactic acid (to match the pH of the wine), 5% syrup and 16% alcohol (90% w/v). Maceration of the root for twenty-four hours followed by filtration resulted in an extraction efficiency of 94% (final pH: 3.0); the lower efficiency achieved by Henriksen using a similar method was attributed to his not acidifying the menstruum. Taylor and Hobart then prepared salts of the extracted alkaloids, and concluded that the major alkaloid in the preparation was hyoscyamine. The preparation was tried in three post-encephalitic patients and in one paralysis agitans case; considerable improvement of tremor and movement was noted in
the first three patients, as well as a general improvement in mood. Interestingly, the pharmacologists rated the effect achieved as better than that with hyoscine; in an appended note, the treating physician himself, however, indicated that he was not convinced of the superiority of the new method. He remarked that the preference of the patient was sometimes dictated by the individual response to untoward side effects; he was still of the opinion that hyoscine together with pilocarpine and strychnine was the best treatment for parkinsonism, which he rated more highly than stramonium.208

Richard Henriksen (Chief Pharmacist, West Park Hospital, Epsom) pursued similar investigations to his English pharmacological colleagues with regard to the extraction process, and concluded that maceration in 80% alcohol, boiling under reflux and filtration was most efficient. The effect on patients was assessed by administering first the Neuwahl-Fenwick preparation then the Henriksen preparation to seven parkinsonian patients (type not stated) over a period of six months. The two preparations were found to be equally effective as stramonium but not superior to it. He also commented upon the fact that the new-found popularity of belladonna cultivation in Bulgaria meant that the quality of the delivered root was highly variable; that supplied by Raeff was, in fact, the highest quality available.209

**The Bulgarian treatment in America**

The Bulgarian treatment also attracted attention across the Atlantic, but was generally regarded with greater scepticism than in Europe. Vollmer criticized the preparation method of Antolini as being subject to too many errors, and preferred the simpler version adopted by the Pharmacopoeia of the United States (U.S.P.), which involved extraction in an aqueous solvent containing 15% alcohol (95% w/v) and 1% tartaric acid. He also noted that commercially available belladonna roots were often of poor quality because of their growing conditions, transport, storage or other factors; the superiority of Raeff’s roots were probably to be ascribed to the care with which he collected his plants.210 Two American groups reported simultaneously their experiences with white wine extracts of U.S.P. belladonna in 1941, with the following results:

- In parkinsonian patients with moderate severity of disease, 90-100% showed clinical improvement of a moderate (objective improvement in rigidity and/or tremor, gait, speech, mobility; no need for nursing care) to maximal degree (complete or almost complete abolition of parkinsonian symptoms and complete or almost complete social/economic rehabilitation).
- In patients with severe disability, 60-91% showed moderate to maximal improvement.
- The dose required by patients varied widely; in one study the range was 3 to 50 tablets per day (each 0.4mg alkaloids), the average dose being 7-10 tablets per day.
- The drug was effective in post-encephalitic patients, but less so in “degenerative” or “arteriosclerotic” patients, who were unable to tolerate high doses. Incidentally, the authors appeared to regard these two forms as encompassing the spectrum of parkinsonism.211

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208 Taylor and Hobart, 1938.
209 Henriksen, 1938b; 1938c. Husa and colleagues (Pharmacology, Florida University) had also published a series of papers in 1935 regarding the most efficient means of belladonna alkaloid preparation (not in connection with antiparkinsonian therapy, but as a model for plant alkaloid extraction in general), including Husa and Huyek (1935) and Husa and Yates (1935).
210 Vollmer, 1940.
211 After the outbreak of post-encephalitic parkinsonism, many authors tended to divide patients into post-viral and arteriosclerotic parkinsonians. Macdonald Critchley, in particular, distinguished
VI. The 1930s and 1940s: the dominance of atropine and belladonna

- The most common toxic effects were those associated with atropine toxicity: dryness of mouth (88%), blurring of vision (68%). These symptoms could be counteracted in the short term with physostigmine or pilocarpine, but their own effects prohibit long term use (pilocarpine in particular, produced severe diarrhea, profound general weakness, profuse sweating and headaches).212

Vollmer reported in 1940 that the benefits of the Bulgarian treatment could be replicated with an empirically determined mixture of alkaloids in a 66% aqueous alcohol solution (3mg alkaloids.mL⁻¹) in the proportion 90.2% hyoscyamine hydrobromide, 7.4% atropine sulphate, 2.4% scopolamine hydrobromide. This became the composition of the American drug ‘Rabellon’.213 Post-encephalitic patients responded better than paralysis agitans cases; 50% of post-encephalitic patients were markedly improved and 32% moderately, compared with 17% and 33% for paralysis agitans patients. Vollmer spread the dose across the day as three separate administrations. The major problem he encountered was a decline in effect which paralleled the loss of morale which ensued when the patient realized that the drug, although “the best medicine they have ever had”, was not a cure, and had to be taken on a permanent basis. Vollmer paid a great deal of attention to the psychic state of parkinsonian patients, noting that it could be improved by belladonna alkaloids, but could also interfere with their effects. In general, he found parkinsonian patients to be trusting, helpful, willing to obey instructions and eager to get well; these characteristics of the parkinsonian personality needed to be considered to maximize the effectiveness of therapy. Vollmer presented diagrams in his report which illustrated the progress of eight patients treated with his alkaloid mixture (figure 6-3). The rigor could usually be abolished, and the tremor also disappeared in some cases; Vollmer preferred to assess this last symptom via the patient’s handwriting than by dynamographic recordings. Vollmer admitted his ignorance regarding the mechanism of the preparation, noting that rational considerations could not always be invoked to explain pharmacological phenomena. Atropine and (to a lesser extent) hyoscyamine were central nervous system stimulants, scopolamine a central nervous system depressant; further, atropine was supposed to possess half the pharmacological effectiveness of hyoscyamine, but a double dose of atropine did not produce the same effects as a single dose of hyoscyamine. Finally, the effects of the alkaloid combination were not simply the sum of the individual effects of its components.214 Other groups reported only moderate success with artificial combination preparations.215

Von Witzleben noted in 1941 that the Bulgarian therapy had now even be accepted by “the careful and very skeptical leader of the centre for encephalitis research at the Neurological Institute in New York, Josephine B. Neal”, who now championed it as the drug of choice.216 Neal had warmly recommended in 1939 the Bulgarian treatment (in the form of a white wine extract of the root, as Bellabulgara or as tablets supplied by

212 Price and Merritt, 1941; Fabing and Zeligs, 1941.
213 Introduced by Merck, Sharp & Dohme in 1939: tablets contained 0.45mg hyoscyamine, 0.04mg atropine and 0.01mg scopolamine. It also found limited application in the therapy of Huntington’s disease: Tomlinson, 1947.
214 Vollmer, 1940. See also Maybarduk, 1940.
215 Neal and Dillenberg, 1940; Simon and Morrow, 1941; also Kauders and Oesterreicher, 1936, Witzleben, 1942, p.120.
216 Witzleben, 1941a.
Lederle) in the first paper on the therapy to be published in the United States.\textsuperscript{217} At the 1940 meeting in New York of the Association for Research in Nervous and Mental Disease, the experiences of international investigators with the therapy had been presented as a joint paper by Stanley Dillenberg (Neurological Institute of New York, Lenox Hill Hospital, Welfare Island Hospital): different forms of the treatment (belladonna extracts, alkaloid combinations) were compared and found to be generally equivalent with respect to both clinical benefit and side effects. Von Witzleben’s results were greeted, however, as particularly spectacular, both with respect to number of patients treated at this point (500; the next largest study was that of Doshay and Ford, 112 patients) and the success achieved: 60% great and 23% moderate improvement (table 6-6). Similar success rates had been reported by Panegrossi for the Queen Elena Institute in Rome, who by 1938 had treated nearly 2000 patients. Von Witzleben was quick to emphasize that the Bulgarian treatment was not always appropriate; hemilateral parkinsonism, for instance, was better treated by surgery, and the use of benzedrine was indicated in some patients. But, in general:

\textsuperscript{217} See her initial assessment (Neal, 1939) and her subsequent report (Neal and Dillenberg, 1940).
It has rather been confirmed again and again that the therapy which I introduced, and which has been often described, is at the present time the best treatment and the one with the greatest prospects, even if there are other methods which, under circumstances, might be drawn upon in a support role.\textsuperscript{218}

He was also incensed that the Americans often used the term ‘Bulgarian treatment’ for the application of ‘Rabellon’; the less impressive results gained with the “\textit{laboratory mixture}” demeaned those gained with the natural extract. It is certainly true that the results gained with ‘Rabellon’ were far less impressive than those with ‘Homburg 680’, and this stimulated speculation about the significance of subsidiary alkaloids in the

<table>
<thead>
<tr>
<th>Degree of improvement</th>
<th>Total patients treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Great</td>
<td>Moderate</td>
</tr>
<tr>
<td>Fabing and Zelig, 1941</td>
<td>'Vinobel'</td>
</tr>
<tr>
<td>Moderate severity</td>
<td>70.5%</td>
</tr>
<tr>
<td>Marked severity</td>
<td>43.3%</td>
</tr>
<tr>
<td>Price and Merritt, 1941</td>
<td>'Vinobel'</td>
</tr>
<tr>
<td>'Rabellon'</td>
<td>20.6%</td>
</tr>
<tr>
<td>Bulgarian belladonna wine</td>
<td>6.6%</td>
</tr>
<tr>
<td>Vollmer, 1940</td>
<td>'Rabellon'</td>
</tr>
<tr>
<td>'Rabellon'</td>
<td>50%</td>
</tr>
<tr>
<td>Neal and Dillenberg, 1940</td>
<td>'Rabellon'</td>
</tr>
<tr>
<td>'Bellabulgara' (marked severity)</td>
<td>30.4%</td>
</tr>
<tr>
<td>Neal, 1940</td>
<td>'Bellabulgara'</td>
</tr>
<tr>
<td>Marked severity</td>
<td>46.4%</td>
</tr>
<tr>
<td>Moderate severity</td>
<td>31.6%</td>
</tr>
<tr>
<td>Von Witzleben, 1935-1940</td>
<td>'Homburg 680'</td>
</tr>
<tr>
<td></td>
<td>60%</td>
</tr>
<tr>
<td>Doshay and Ford, 1942</td>
<td>Moderate dose atropine sulphate</td>
</tr>
<tr>
<td></td>
<td>25%</td>
</tr>
</tbody>
</table>

\textit{Table 6-6}: Treatment of post-encephalitic parkinsonian patients with various forms of the Bulgarian treatment and with atropine, as presented at the meeting of the Association for Research in Nervous and Mental Disease in New York in December 1940. Based on material presented in Dillenberg et al., 1942.

\textsuperscript{218} Dillenberg \textit{et al.}, 1942. Von Witzleben appears to have moved from Dresden to Zürich sometime between 1939 and 1940, and from there to the Elgin Hospital in Illinois in 1941. From 1953, he was active at the Veterans Administration Hospital in Palo Alto as Professor of Psychiatry (letter to Anna Freud, 9 January 1956). I have not been able to determine when he died; his 75th birthday was noted in the \textit{Deutsche Medizinische Wochenschrift} in 1971, and he was in regular written contact with Anna Freud until at least the end of 1980.
belladonna extract. The latter was never precisely chemically characterized; for example, it was known that aporphine was found in the extract, but whether this was an original constituent or a product of the extraction process was not known.\(^{219}\)

In general, clinicians in the United States tended to favor standardized preparations of defined composition to any direct belladonna extract, and even then the enthusiasm was not great; many believed that the effects achieved were no greater than those with other alkaloid preparations, and certainly represented no major advance in the relief of parkinsonism. The first edition of Goodman and Gilman’s *Pharmacological basis of therapeutics* (1941) found that the belladonna alkaloids brought a measure of relief to parkinsonian patients, but was more skeptical concerning the Bulgarian treatment:

> While it is possible that the particular combination of alkaloids of belladonna found in the root of the plant may be more beneficial to some patients than other preparations, considerably more evidence is needed to establish this point.\(^{220}\)

By 1955 the authors had seen no reason to alter the wording of this assessment.\(^{221}\)

**The Bulgarian treatment: concluding remarks**

Belladonna preparations were of undoubted benefit for post-encephalitic parkinsonism, provided the patient could abide the side-effects. The search for less toxic alternatives was thus pursued with great zeal. The Bulgarian treatment can be seen as the culmination of solanaceous plant-based anti-parkinsonian therapy; it combined both efficacy and tolerability to a degree not achieved with alternatives up to this point. Von Witzleben noted in 1942:

> the Bulgarian treatment must now be considered the treatment of choice in post-encephalitic Parkinsonism. There are no longer any mixtures or “pure” alkaloids which are active competitors.\(^{222}\)

His American colleagues were not entirely unanimous on this point; preparations of pure alkaloids in fixed combinations were especially popular in the United States, and clearly found to be as effective and less complicated that only partially defined root extracts. That such combinations were even produced, however, is also evidence of the relative efficacy of the original Bulgarian method; never before had the pharmacological basis of an antiparkinsonian therapy been so eagerly and thoroughly investigated, even if the results of such inquiries were ultimately less than clear-cut. There was also the problem that, as noted in the above quotation, the therapy was primarily effective in the management of post-encephalitic parkinsonism; other forms, especially paralysis agitans, were less responsive to this approach. Von Witzleben suggested that tolerance of the cure could, in fact, be employed for the differential diagnosis of post-encephalitic and idiopathic parkinsonism.\(^{223}\) As late as the 1950s, however, this was not considered a great impediment, as the bulk of parkinsonian patients were of the post-encephalitic type; the challenges posed by a majority population of idiopathic parkinsonian patients would only become an issue in the 1960s.

\(^{219}\) Degkwitz, 1963.
\(^{220}\) Goodman and Gilman, 1941, p.473.
\(^{221}\) Goodman and Gilman, 1955, p.555.
\(^{222}\) Witzleben, 1942, p.131.
\(^{223}\) Witzleben, 1938a.
Belladonna alkaloid preparations of various compositions would continue to be extensively employed in the clinic until this time; the Bulgarian treatment itself would survive in the form of preparations such as ‘Homburg 680’ and ‘Rabellon’. Even today, two belladonna extracts are listed in the German *Rote Liste* of licensed medical preparations for the treatment of parkinsonism; interestingly, none of the purified alkaloids appear on this list, and most of the synthetic anticholinergic agents which succeeded the Bulgarian cure have also disappeared.\(^{224}\)

**Belladonnine and apoatropine**

A final variation on the belladonna alkaloid theme was the use of the “minor alkaloid” belladonnine, which was investigated by E. Merck, Darmstadt as an anti-parkinsonian agent from about 1938.\(^{225}\) The name ‘belladonnine’ had been applied to a variety of entities since the middle of the 19th century. Lübekind had given the name ‘belladonnine’ to an unpurified and uncharacterized alkaloid mixture isolated from belladonna.\(^{226}\) Belladonnine as a distinct alkaloid was first separated from raw atropine by Friedrich Hübschmann in 1858 as a yellow resin which rendered the crystallization of atropine isolated from henbane berries a difficult task.\(^{227}\) A Dresden firm (Gehe & Co.) had recognized early that this belladonnine, which was produced as an amorphous residue during the isolation of other alkaloids, exerted atropine-like properties, upon which basis it (unsuccessfully) attempted to market the agent.\(^{228}\) Gehe & Co. also supplied most of the belladonnine which was analyzed by various workers in the following years. ‘Raw belladonnine’ (*Rohbelladonnin*) from Merck, it should be noted, referred to a waste product of atropine extraction which was also supplied to chemists for investigation. The stability of belladonnine during heating in baryta water (120-130°C, several hours) compared with that of other belladonna alkaloids provided the means by which several workers prepared a reasonably pure alkaloid; Kraut was the first to successfully exploit this stability in its separation from commercial atropine in 1868.\(^{229}\) Buchheim appears to have been the first to prepare the alkaloid in large quantities, and described it as a resinous yellow powder which could be decomposed by treatment with alcoholic potassium hydroxide to tropine and an acid not identical with tropic acid.\(^{230}\) An alternative means for separating belladonnine from hyoscyamine and atropine was by treatment with concentrated sulphuric acid.\(^{231}\)

\(^{224}\) The two preparations are ‘Belladonnysat Bürger’ (Ysatfabrik Joh. Bürger, Bad Harzburg) and ‘Tremoforat’ (Klein, Zell-Hammersbach). ‘Belladonnysat’, a leaf extract available since the late 1920s, is currently available as a syrup (5mL = 0.5mg alkaloid, standardized with respect to hyoscyamine) and drops (100 drops = 50mg); it is primarily employed as a spasmolytic. ‘Tremoforat’ is available in tablets of 4mg extr. Rad. belladonnae sicc. (total alkaloid: 0.06mg); the recommended dose for parkinsonian tremor of 3 × ½-1 tablet/day is to be raised gradually if required. *Rote Liste* 1997, section 70.

\(^{225}\) *Isatropic acid ditropine ester; isatropyliditropeine. The experimental preparation was named C 45; the bisulphate was released as ‘Bellacristin’.*

\(^{226}\) Cited in Merck, 1892. Geiger and Hesse (1833a) had also noted the amorphous alkaloid during extraction of atropine, but had not named it.

\(^{227}\) Cited in Merck, 1892.

\(^{228}\) *Merck, 1892.*

\(^{229}\) *Kraut, 1868.*

\(^{230}\) *Buchheim, 1876.*

\(^{231}\) *Hesse, 1891.*
Ladenburg and Roth identified during the isolation of belladonnine traces of a base they named "oxytropin";\textsuperscript{232} Merling reported similar results,\textsuperscript{233} but most other workers regarded it as an artefact. The composition of raw belladonnine, and whether there in fact existed a distinct alkaloid 'belladonnine', was, in fact, controversially and sometimes heatedly discussed in the pages of German chemical journals throughout the last decades of the 19th century. Many argued that belladonnine was nothing more than a difficult to separate mixture of atropine, hyoscyamine and hyoscine; Dürkopf, for example, had found that the raw belladonnine from Gehe & Co. included 15-20% hyoscine, and argued that the base isolated by Ladenburg and Roth was none other than pseudotropine.\textsuperscript{234} Merck noted that 'belladonnine' was not found in the lye which remained from atropine isolation in his factory, and opined that the Gehe & Co. substance was the result of a mixture of residues from various sources.\textsuperscript{235}

Despite the efforts of a number of subsequent investigators, however, it was only in 1938 that W. Küßner of the Alkaloid Research Division of E. Merck reported the first successful crystallization and chemical characterization of belladonnine, leading to its recognition as a discrete alkaloid and not a mixture of various components. Küßner actually noted at the end of his report that he had found a vial in the alkaloid collection at Merck with the label "Crystallized from belladonnine, August 1912", and found that it contained about 40% crystalline belladonnine; this is perhaps the only instance in the story of the therapy of Parkinson’s disease where priority was unnecessarily ceded to another, and indeed to an unknown predecessor. Küßner had also examined the alkaloid content of belladonna root of varying geographical origin (Bulgarian, German, Italian, Indian) and found no major differences, phenomenon which he interpreted differently to most other workers. Küßner had heated another alkaloid, apoatropine, at 110°C to obtain belladonnine. He noted that the racemization of hyoscyamine to atropine also occurred at 110°C, and that this alkaloid was partially converted to apoatropine in the presence of water; it was this phenomenon which he believed underlay the efficacy of the Bulgarian treatment.\textsuperscript{236}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{belladonnine_and_apoatropine.png}
\caption{The belladonna alkaloids belladonnine and apoatropine. Note the inclusion of two tropane ester moieties in belladonnine.}
\end{figure}

\textsuperscript{232} Ladenburg and Roth, 1884.
\textsuperscript{233} Merling, 1884.
\textsuperscript{234} Dürkopf, 1889.
\textsuperscript{235} Merck, 1892.
\textsuperscript{236} Küßner, 1938.
Further investigations at Merck by E. Kreitmair revealed that that belladonnine was, in fact, the dimeric form of apoatropine, produced when atropine is heated, and is thus an extremely stable tropine-class alkaloid (figure 6-4). The Italian chemist Pesci had first synthesized apoatropine in 1881 by treating atropine with nitric acid; Ladenburg had produced it in 1883 by repeated evaporation of a solution of tropine atropate with dilute hydrochloric acid. Apoatropine lacked the mydriatic effects of the major belladonna alkaloids. In 1890, Oswald Hesse precipitated an alkaloid from crude atropine which he named “atropamine”; he found that this was converted to the amorphous belladonnine when treated with acid and left in the sun. Emmanuel Merck established in the early 1890s that atropamine was identical with the apoatropine, and demonstrated that acid treatment of apoatropine similarly leads to the formation of belladonnine. Hesse initially vehemently rejected but eventually accepted this identification. He noted in 1893 that apoatropine itself was generally rather amorphous, but could be brought to crystallization if seeded with a single crystal of the alkaloid, and that this state could be preserved by solution in ether. He also found that hyoscyamine could be converted under certain laboratory conditions successively to atropine, apoatropine and belladonnine, and that these possibilities probably led to a contamination of commercial preparations of both hyoscyamine and atropine.

Apoatropine was thus widely held responsible until the 1930s as a toxic contaminant in preparations of the Bulgarian treatment and other scopolamine and atropine preparations, explaining the occasional negative reactions of patients to such preparations, and thus largely shunned by the medical community. Kobert reported the first detailed investigations of apoatropine in 1906 as part of an investigation into the cause of side effects associated with scopolamine preparations, and noted that it stimulated both spinal and medullary elements of the frog and induced salivation in cats; other investigators found that dogs and rabbits were even more sensitive to its effects. Kobert himself observed that 10mg.kg$^{-1}$ were sufficient in dogs to elicit epileptiform cramps which culminated in the death of the animal. Meyer-Gottlieb (1933) regarded apoatropine as a dangerous contaminant of scopolamine preparations which acted centrally to oppose the actions of scopolamine itself, while Sasa reported in 1937 that it was also a contaminant of atropine produced from hyoscyamine; in fact, he attributed the greater part of atropine toxicity to the central effects of apoatropine.

Investigators at Merck were not certain in the 1930s whether apoatropine was actually a natural constituent of the belladonna root, or whether it was simply a by-product of the heating process involved in alkaloid extraction. The negative reputation of apoatropine was supported by the findings of Kreitmair that although the anticholinergic effects of apoatropine were weak in comparison with those of atropine

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237 Pesci, 1881; 1882.
238 He named it ‘Atropatropeïn’.
239 Kobert (1905), cited in Kreitmair and Wolfes, 1938.
240 Merck, 1892; 1893a. At the same time he identified a further alkaloid (pseudo-hyoscyamine) which was physically distinct from atropine, hyoscyamine, hyoscine and apoatropine; it did not include tropine or tropic acid, and may thus have been of the tigloidine-class alkaloids discovered in the 1930s in Barger’s laboratory.
241 Hesse, 1891; 1892; 1893.
242 Ibid. Cushny noted in 1903 that the hyoscyamine supplied by Merck (USA) often proved to be optically inert.
243 See, for example, Hirschlaff (1918)
244 Kobert, Meyer-Gottlieb and Sasa cited in Kreitmair and Wolfes, 1938.
when tested in a number of animal models, the lethal dose in both dogs and rodents was two orders of magnitude lower than that of atropine. The form of death, however, was completely different; instead of mydriasis, restlessness, nausea, vomiting and finally paralysis which characterized atropine and hyoscyamine poisoning, apoatropine induced spasms and fits of epileptic cramps without any indication of mydriasis. Kreitmair and Wolfes described apoatropine as a spasmodic (Krampfgift) which attacked the entire central nervous system from the cortex to spine; unlike the atropine-type drugs, however, its effects on smooth muscle were direct and not mediated by the parasympathetic system. Interestingly, they found that orally administered apoatropine was more effective than subcutaneous.

In co-operation with Merck, F. Duensing (Encephalitis Ward of the Göttingen University Neurological Clinic) demonstrated that at doses of up to 30mg it was, in fact, fairly innocuous in humans. Clinical experience also indicated that it was always the same patients who reacted negatively to a particular scopolamine preparation, even when a common solution was applied to the entire ward. This suggested that negative reactions were related to the sensitivity of individual patients to scopolamine, and not to any contaminant. Duensing therefore examined whether this "minor alkaloid" might be of use in post-encephalitic parkinsonism. The usual schedule was to commence with $3 \times 1\text{mg}$ apoatropine hydrochloride solution p.o., raising the dose by $3 \times 1\text{mg}$ per day for nine days, and by $3 \times \frac{1}{2}\text{mg}$ per day thereafter until side effects appeared. Once the optimal dose was reached, it was more convenient to administer the drug as pills. A beneficial effect of apoatropine was noted in less severe parkinsonian cases; rigidity and akinesia, in particular, responded well to doses of 15-30mg/day. Most patients could tolerate 30mg/day (some over 60mg/day) without side effects; it was found that similar tolerance was also exhibited by non-post-encephalitic patients, thus differentiating it from atropine. The therapeutic dose also showed a stimulating effect on general mood. The side effects characteristic of atropine were completely absent. This was associated with the observation that the agent did not appear to possess peripheral parasympatholytic properties, which pointed to a central site for its actions (probably in the basal ganglia) and perhaps also those of atropine itself. The major side effect at very high doses was nausea and "butterflies", occasionally leading to emesis, and tiredness. Duensing saw the drug as a valuable addition to therapy of early cases of parkinsonism; he commenced treatment with apoatropine alone, added scopolamine if tremor was a problem, and used atropine only as the disease progressed to the point where it became absolutely necessary.

Duensing was particularly impressed by the effect of apoatropine on akinesia, a symptom which had been largely neglected up to this point. He actually commented in 1938 that it was not the severity or duration of the parkinsonism which determined the response to therapy, but the symptoms which dominated in a particular patient:

> Extremely surprising improvements, even to a degree bordering on cure, can be achieved with alkaloid-based therapies in general in patients in whom pure akinesia, the "rigidity-free immobility" [rigofreie Starre] of Bostroem, is present or even dominates. The rigidity and adiadochokinesia can also be well managed; it is more difficult to calm the tremor.

245 Kreitmair and Wolfes, 1938; also Kreitmair, 1939.
246 Duensing, 1938; 1940.
247 Duensing, 1938.
Duensing spoke of “reversible” and “irreversible” elements of the symptomatology of parkinsonian patients; it was not always possible in advance, however, to predict which symptoms in which patients would respond to a given therapy. This recognition of patient heterogeneity with which the clinician was confronted under the umbrella term ‘parkinsonism’ was not always as clearly recognized in the literature of this period; particularly with respect to post-encephalitic parkinsonism, most spoke of rather stereotypic ‘stages’ of the disorder, as if the course was the same or at least similar in most patients. This was not the case, which made therapy and therapeutic investigations particularly difficult; it also led to a type of competition amongst the various therapeutic options which was not justified.

Duensing also addressed the question of the significance of apoatropine for the success of the Bulgarian treatment. He noted that doses of apoatropine required for the treatment of parkinsonism were far higher than those available in the Bulgarian cure (maximally 1-2mg; investigations at Merck indicated that apoalkaloids constituted maximally 10% of total alkaloids in the extract). Further, a potentiation of the effects of atropine or scopolamine by apoatropine could not be detected, so that the alkaloid mixture could not be invoked as an explanation of a heightened effect of the root extract in comparison with preparations of individual alkaloids. He concluded that whatever benefit apoatropine might offer the parkinsonian patient, it could not explain the effects of the Bulgarian treatment. Scheiffarth (Medical Clinic, Erlangen), on the other hand, regarded the central excitant effects of apoatropine as crucial to the value of the Bulgarian extract, although he conceded that the therapeutic range of the alkaloid was very narrow; a small increase in dose led to epileptic cramps rather than muscular relaxation. Scheiffarth, however, does not appear to have considered the amount of apoatropine available in the Bulgarian treatment, and to have based his opinion largely on the effects of apoatropine in animals, which, as noted by Duensing, differed markedly from those in man.

Kreitmair and Wolfes had also investigated the pharmacology of belladonnine itself. The anticholinergic effects of this agent were exceedingly small; its parasympatholytic capacity was only $\frac{1}{30000}$ of that of atropine and $\frac{1}{600}$ of that of apoatropine. When tested on isolated rabbit small intestine stimulated with barium chloride, it was not spasmolytic like atropine and apoatropine, but itself stimulating; this effect could be blocked with papaverine. Duensing found that four parkinsonian patients tolerated extremely high doses of the agent (up to $3 \times 120$mg/day) without signs of toxicity; on the other hand, however, it did not improve their condition.

Rudolf Hotovy (Pharmacological Institute, University of Heidelberg) continued investigations of the pharmacology of belladonnine (principally in the form of the bisulphate) during the early 1950s, publishing a comprehensive review of his findings in 1954. He essentially confirmed and extended the findings of Kreitmair and Wolfes: belladonnine had central excitatory effects which at higher doses shifted to central paralytic effects; it was anticonvulsive; and it possessed only weak parasympatholytic

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248 Duensing, 1940.  
249 Scheiffarth, 1939.  
250 Kreitmair and Wolfes, 1938.  
251 Duensing, 1940. Duensing remarked in passing that a case of unilateral parkinsonism (19 year old male) responded neither to belladonnine nor other alkaloids, and that “it is recognized that strictly unilateral cases of Parkinsonism frequently respond poorly to alkaloid treatment.”
properties. It failed to inhibit nicotine-induced cramps in the test for anti-parkinsonian drugs devised by Bovet and Longo. Hotovy’s group had attempted, however, to establish a second test for the assessment of anti-parkinsonian drugs. This measured the effect of an agent on the increased performance of the electrically stimulated rat chewing apparatus elicited by prostigmine, strophantine or potassium chloride. In this test, belladonnine proved to be “anti-parkinsonian” at doses of 5-20mg.kg\(^{-1}\)\(^{252}\).

Herbert Finke reported preliminary experiments in thirty-nine parkinsonian patients with belladonnine in 1952; he found that the effect of 12-55mg belladonnine on rigor and tremor was significant, but was not accompanied by the usual side effects associated with anticholinergic agents.\(^{253}\) This can be attributed to the fact that the alkaloid is weakly parasympatholytic, but totally lacking in anti-nicotinic activity; this also partly explains why it was not a great clinical success in the treatment of parkinsonian tremor. Further, animal experiments had found that the difference between the doses producing paralysis and death was alarmingly small. Walter Laux (Psychiatric and Neurology Clinic, University of Kiel) was also impressed in 1954 by the effectiveness of the drug, which he saw as “at least equal in our experience to the best treatments for the symptoms of parkinsonism”, and the absence of notable side effects (42 patients treated; 30-60mg/day as 3-8 doses). He found that the drug was less valuable in more advanced patients, but attributed these failures to the difficulties of weaning such cases from their former medication, especially in cases where high doses of atropine had been administered for over a decade. Laux convinced himself of the safety and convenience of the drug by self-administration of up to 80mg/day, noting only a slight feeling of increased warmth on the second day.\(^{254}\)

R.C. Behrend (University Neurological Clinic, Hamburg-Eppendorf) undertook a small trial in 1951/52 involving 22 patients, and was so impressed with the results in comparison with the effects of other anti-parkinsonian agents that he immediately sought larger quantities of the agent in order to further examine its potential. During this larger trial of ‘C 45’ (October 1952-March 1953; 50mg/day administered as 3-6 tablets per day), he saw a significant improvement in the rigidity of 34 of 71 patients (excellent improvement in fifteen) in the absence of any vegetative effects (such as inhibition of salivary flow) and accompanied by a vague “sensation of liberation”. Unfortunately, this benefit was bought only at the price of increased tremor. Further, even the positive aspects of the alkaloid’s action were not as impressive as in the preliminary trial. Behrend saw this as a psychological difference between the two groups. The first consisted of patients who had attended his clinic for many years and were well known to him, and they had also taken part in several other experimental studies; they exhibited only minimal withdrawal symptoms during the reduction in dose of their normal medication. The second series utilized patients from nursing homes whose attitude to new agents, medication and life in general was anything but positive (“nursing home atmosphere”). The long-term administration of belladonna alkaloids to some of these patients also appeared to produce stronger withdrawal reactions, which in the confines of the home were conveyed psychologically to their fellow patients. Nonetheless, Behrend saw in belladonnine a component of the “combination therapy of the future” of parkinsonism; his philosophy was that only a combination of agents with different pharmacological actions would be capable of managing the total clinical


\(^{253}\) Finke, 1952.

\(^{254}\) Laux, 1954.
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picture of parkinsonism. Further, subsets of patients, who could not be identified in advance, responded to a different degree or even in a different manner to the various available therapeutic alternatives. As neither tremor nor sialorrhea were significantly inhibited by C 45, the addition of at least scopolamine was, for example, indicated.255

It was also reported about this time that apoatropine hydrochloride (Merck) was as effective as ‘Homburg 680’ and caramiphen in the treatment of mild cases of akinetic parkinsonism. The oral dose was raised from 3×1mg/day to 3×10mg/day over ten days, and then by ½mg/day until the optimal dose (∼3×30mg/day) was achieved.256

Belladonnine was released commercially by Merck in 1953 as ‘Bellacristin’ and was still available in the 1960s, but any interest in a new belladonna alkaloid was largely overwhelmed by the synchronous advent of the synthetic anticholinergic drugs, particularly benzhexol.257 Hartmann-von Monakow noted in 1960 that he had employed the agent since 1954, and had found that it was particularly effective in the control of akinesia and rigidity. While its effects on tremor were less reliable, it was found that it often showed its greatest influence in this regard on tremor which could not be reduced by other pharmacological agents; in particular, arteriosclerotic patients, who often demonstrated a supersensitivity to the usual anti-tremor agents, benefited markedly from belladonnine.258 More recently, β-belladonnine dichloroethylate was listed by the French company Latoxan as a short-acting muscle relaxant, twice as active as d-tubocurarine, but not intended for human use. According to this company, β-belladonnine selectively blocks cardiac muscarinic receptors (ED50: 13µg.kg−1); blockade of muscarinic receptors in smooth muscles and secretory organs requires a 10 to 20 times higher concentration. β-Belladonnine blocks skeletal muscle nicotinic receptors only at very high doses (ED50: 50-60mg kg−1), but also presents some antihistaminic activity.259

Other alkaloids of the belladonna root

The success of the Bulgarian treatment motivated the search for further alkaloids in the root of the belladonna as a possible explanation of its efficacy. In 1941, King and Ware, using a novel separation method, isolated from nearly 10kg of root 750mg of a new alkaloid which they named ‘bellaradine’. They doubted that such a low concentration would contribute markedly to the efficacy of the Bulgarian treatment.260 Reinouts van Haga isolated ‘cuskygrin’261 from the belladonna seed in 1954, an alkaloid first identified by Liebermann in coca leaves in 1898; in 1955, the Swiss

255 Behrend, 1952; 1954.
256 Mercks Jahresbericht for 1951, p.140.
257 Barlen reported in 1955, however, that he found belladonnine to be more effective than the then increasingly popular synthetic antiparkinsonian agents, although he found combination with ethopropazine to be useful. He also insisted on a strict lactovegetarian diet.
258 Hartmann-von Monakow, 1960, pp.87-88. See also Barlen, 1955.
259 β-1,3-Bis(1-methyl-2-pyrrolidinyl)-2-propanone; cuscohygrine.
260 King and Ware, 1941.
workers Steinegger and Phokas (Bern) demonstrated the identity of this alkaloid with bellaradine. The same group also identified a new alkaloid, ‘hellaradin’, which occurred at levels of 0.002% and exhibited atropine-like spasmolytic qualities. None of these constituents have been pursued clinically. More recently, N-oxides of hyoscyamine and scopolamine have been identified as normal constituents of belladonna.

Mood altering drugs in the treatment of parkinsonism: stimulants and sedatives

L-Ephedrine was first isolated by Nagayoshi Nagai (1844-1929) in 1887 from the Chinese plant Ma-Huang, and was recognized in the first quarter of the 20th century to be pharmacologically similar to adrenaline. Merck first isolated the alkaloid in Europe in 1888. Ephedrine, in the form of extracts of the plant Ephedra vulgaris var. helvetica, had been used as a nerve tonic, circulatory stimulant and sedative in cough in China for millennia under the name of the plant from which it was prepared, Ma Huang; it was first mentioned in the pharmacopoeia (Pentsao) of the Emperor Shen Nung (supposed to have lived ca 2700 B.C.); it certainly appeared in the revised Pentsao of Li Shih Cheng (A.D. 1596). It had enjoyed a meteoric rise in popularity in the European clinic in the second half of the 1920s, in large part due to the research of K.K. Chen and Carl Schmidt at the Peking Union Medical College. The major indications for the use of ephedrine were hay fever and asthma, as a mydriatic, and as a respiratory stimulant, particularly in cases of barbiturate poisoning; it was also used to counter acute scopolamine toxicity and had been shown to be of some benefit in myasthenia gravis. Ephedrine was also employed in the treatment of narcolepsy. Post-encephalitic patients often experienced disturbances of their sleep patterns, and ephedrine proved to be useful in relieving daytime sleepiness in these patients; if the drug was administered before noon, it did not disturb nocturnal sleep, and thus produced some normalization of the sleep-wake cycle, allowing the patient to undertake normal work.

Amphetamine (β-phenylisopropylamine; Smith, Kline & French) sulphate, an ephedrine derivative, had been first synthesized in 1887 and investigated by Barger and Dale early in the century. It was introduced into the therapy of narcolepsy as ‘benzedrine sulphate’ in 1933 by Myron Prinzmetal’s group in America; they had noted that not only was the core symptom resolved, but that the drug had a more general
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Figure 6-6: The two psychostimulants ephedrine and amphetamine, with the transmitter adrenaline shown for comparison. In methamphetamine, the terminal amine group of amphetamine is methylated.

energizing effect. Hypothesizing that it might thus play a role in other diseases involving asthenia, the same group investigated the effects of benzedrine (10-160mg/day per os; slowly increased) in twenty-eight post-encephalitic parkinsonian patients for periods of between one and sixteen months, alone and in combination with scopolamine or stramonium; twelve patients also received ephedrine, alone or together with a solanaceous agent (no doses indicated). This was probably the first time that a group had taken the subjective nature of their patients’ responses into account in a detailed manner while testing a new antiparkinsonian agent:

Since the evaluation of the results depended largely on the subjective accounts of the patients, efforts were made to reduce the effects of suggestion to a minimum. The patients were told that they were to try a new medicine which might not help them but could do them no harm. They were not told in what direction improvement might be expected; they were told, in addition, that some of the medicine might have no effect; finally they were urged to be very critical of any change, since, if the medicine had no effect, there were other medicines and combinations that we then wished to try.

In nineteen cases, the unannounced substitution of “blank pills” was also used to control the experiment. The authors found that benzedrine alone was useful in cases where the major complaint was drowsiness and anergia, but that it was more effective in combination with scopolamine or stramonium, which in turn were less effective alone than in combination with benzedrine. Subjective improvement of rigor and muscular strength were reported by 70% of subjects, but could not be objectively substantiated; the major effect was the increased feeling of energy which allowed many to resume tasks of normal living which they had previously found too demanding (such as housework and driving). The effects disappeared during the administration of the placebo, and the effects of benzedrine were not replicated by ephedrine (24-48mg). Benzedrine had no beneficial effect in ten arteriosclerotic parkinsonian patients or in twenty of twenty-two psychoneurosis cases in which the major complaint was asthenia; further, both these groups exhibited a higher incidence of untoward side-effects than the post-encephalitic group, mostly insomnia and vertigo. Further positive results were reported in a number of small group studies; its application in parkinsonism was also supported by the finding that benzedrine was especially useful in managing

272 Solomon et al., 1937.
273 Ibid. See also Solomon and Prinzmetal, 1936a; 1936b.
gastrointestinal spasm (spasmolytics were still regarded at this stage as potential antiparkinsonian agents).274

Myerson and associates (Tufts College Medical School, Harvard Medical School; Boston City, Boston State and Beth Israel Hospitals) hypothesized that the effects of amphetamine were due to improved cerebral circulation and possibly to an additional direct chemical effect. They noted that it had a synergistic effect with atropine-based drugs in the treatment of parkinsonism, and that the latter potentiated the vasopressive effects of amphetamine. The interesting interpretation of these results was the hypothesis of a “pharmacological autonomic balance” between the sympathetic and parasympathetic systems; a balanced lever or see-saw used to illustrate the concept was especially reminiscent of models proposed in the 1960s and 1970s regarding functional balances between neurotransmitter systems.275 This was supported by Hughes’ finding that a combination of ephedrine and hyoscine was more effective than either drug alone in treating paralysis agitans.276 Davis and Stewart reported in 1938 that the most impressive results of therapy with amphetamine in a study involving seventy-four patients were in the subjective sphere; most patients reported a decline in fatigability and increase in alertness which allowed them to perform tasks which many had not performed for some time. Blood pressure was increased in forty-one of fifty-eight patients with control levels of less than 130mm Hg; paradoxically, ten of sixteen patients with higher blood pressure responded with a change in the opposite direction. There were no untoward side effects, except for those patients “who failed to follow instructions and took the drug late in the afternoon”, resulting in insomnia.277 Stanley Cobb reported in 1940 that it was effective in some patients against tremor and akinesia (dose: 5-20mg), but increased nervousness in other patients led to exacerbation of tremor.278

Amphetamine was popular for a time in the therapy of Parkinson’s disease, and was briefly seen as second only to atropine and scopolamine in the control of rigidity. Amphetamine was chiefly useful as a general psychic energizer in parkinsonian and other patients suffering from secondary depression. Its use in patients with a genuine primary endogenous depression, however, was fraught with danger; the resultant euphoria and suppression of inhibition could, paradoxically, facilitate the realization of suicidal ideas.279 Despite the confidence of Myerson,280 habituation and addiction could also be problematic; as Cobb warned, benzedrine was freely available over the counter, and there was “no telling where this will lead us for a drug that will keep one awake is enticing and may be quite harmful.”281 But like other non-cholinergic-based drugs fell out of favour as a specific antiparkinsonian agent after the War. It was, however, long

274 Discussion in Myerson, 1936; Council on Pharmacy and Chemistry, 1937; Finkelman and Shapiro, 1937; Davis and Stewart, 1938; Matthews, 1938; Dressler, 1938; E. Mercks Jahresbericht for 1939, p.254; Davidson, 1940.
275 Myerson, 1936; Myerson et al., 1936.
276 Discussion in Myerson, 1936.
277 Davis and Stewart, 1938.
278 Cobb, 1942.
279 Witzleben, 1942, pp.85-86.
280 Discussion in Myerson, 1936.
281 Ibid. In its review of current pharmacological agents, Merck commented in 1939: “Even if the substance has quickly been accepted in America as means for elevating performance in healthy persons, a warning against uncontrolled use of the agent would appear to be urgently required”; E. Merck, 1939, p.253.
regarded by some as useful in reducing the incidence of oculogyric crises, a symptom which was both characteristic for post-encephalitic parkinsonism and notoriously difficult to treat, and the psychic abnormalities associated with the disorder. It would be recognized at the end of the 1960s that amphetamine acts to increase motor activity by releasing dopamine from striatal nerve endings and by inhibiting the re-uptake of dopamine after release. Its energizing effects are, however, attributable to its releasing noradrenaline from central neurons, particularly in the reticular activation apparatus. Both sets of effects can be blocked by α-methyl-p-tyrosine, an inhibitor of catecholamine synthesis.282

A number of sedative agents were also tried to specifically address the problem of oculogyric disturbances, including benzyl benzoate, bromide and phenobarbital (‘Luminal’).283 The Ziskinds, however, had warned against the use of the latter in parkinsonism; even moderate therapeutic doses (3×100mg/day) were found to exacerbate the rigidity of the disorder to the point where the “body could be moved as if made of one block.” There had been isolated reports of barbital- and phenobarbital-induced parkinsonism, as well as parkinsonism in advanced epilepsy treated with phenobarbital.285 It was not known at this point which central nuclei were attacked by the drug, although isolated reports of a concentration in the basal ganglia had been made.286 Theoretical objections to the use of such agents in parkinsonian patients were also raised; Stern argued that sedatives could not be expected to exert effects on nuclei which had been destroyed, while Claude and Baruk questioned their application in a disorder where the cortex-brainstem interaction was already severely disturbed.287

Miscellaneous therapy attempts

Quinine as a treatment for paralysis agitans had often been tried and abandoned, partly on the basis that it calmed malarial trembling. The last reference to its use in parkinsonism which I have found is that by Milhorat in 1941. Quinine sulphate (2-3×0.3g/day p.o.) had only a moderate effect on rigidity and tremor, but potentiated the effects of scopolamine. The benefit of quinine declined after a few days, but could be restored by temporarily withdrawing the patient from the medication.288 Quinine (200-300mg) is still used today to relieve “night cramps” which occur in the legs while the patient is recumbent.

Antispasmodic agents had been tried without great success in parkinsonism since the previous century, but new candidates were nevertheless investigated for their ability to

283 For example: Kutuzinski, 1925 (who recommended in particular the combination of phenobarbital with atropine); Cooper, 1932.
284 Ziskind and Sommerfeld-Ziskind, 1937.
285 Hodskins and Yakovlev, 1930; Fournier et al., 1932; Meerlo, 1933; Stone, 1936.
286 Keeser and Keeser, 1927; 1935; but see Koppanyi et al., 1934; Koppanyi and Dille, 1935.
287 Cited in Witzleben, 1942, p.83.
288 Milhorat, 1941.
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relieve parkinsonian rigidity. As an example, the combination preparation ‘Eupaco’ might be mentioned; it consisted of the antispasmodic moxaverine, the antipyretic/analgesic aminopyrine, phenobarbital and atropine methylbromate.

As a curiosity, I add the review which appeared in the *Lancet* in 1932 of the use of trypan blue injections by a number of French groups; it was first proposed by Chevallier and colleagues in 1929. The course consisted of intravenous application of a 1% solution in water (2×1mL, 3-4×2mL; 3 to 4 days between injections, one month between courses). The injections were stopped when the physicians observed “a bluish tinge of the conjunctiva and integument”; this did not always correspond with the onset of the rather unreliable symptomatic improvement, mostly of rigor. Laignal-Lavastine and Sterne believed the effect to be more than symptomatic; they reported a permanent abolition of rigidity following a full course of injections, and some amelioration of tremor. Larger doses of genoscopolamine (almost a gram per day) than sanctioned by his physician were required by the patient to abolish tremor to the patient’s own satisfaction; following a renewed course of trypan blue injections, this dose could be reduced by one-third. The trypan blue therapy did not spread far beyond its country of origin; it was marketed under the name ‘Parkibleu’ (later: ‘Parkipan’) from 1930 by Laboratoires Aron (Suresnes, Seine). The theoretical basis of the therapy was obscure; Chevallier’s group noted that large doses had been employed in the treatment of certain animal diseases (it had been used, for example, in the control of trypanosome-caused diseases in dogs and cattle, such as malignant jaundice), but even this was unusual by the end of the 1920s, and the connection with encephalitis lethargica or post-encephalitic parkinsonism is not obvious. McCartan commented that Lubin Popoff had surmised in a paper published in a French dermatologic journal in 1933 that trypan blue exerted its effect by blocking the reticulo-endothelium; the English physician found the possibility of such an action more alarming than explanatory, and also noted that such dyes had recently been found to be immunosuppressant.

Gayle and Williams (Neuropsychiatry, Medical College of Virginia, Richmond) tried cobra venom in the treatment of parkinsonism in 1938 on the basis that it had been found to reduce chronic pain in a variety of diseases; it was also noted that rattlesnake had earlier been used in the treatment of epilepsy. Eighteen patients at various stages of post-encephalitic parkinsonism received an initial dose of 0.5mL venom intramuscularly, followed by 1mL/day on alternate days over a period of three weeks. Twelve of the patients experienced relief of their muscular pain after four or five injections. One of the treatment failures proved to be suffering from multiple sclerosis. The patients also noted a reduction in rigidity, but this was not objectively measurable; nevertheless, the authors repeated that it was possible to rapidly withdraw other chemical treatment following venom therapy.

289 3-Ethyl-6,7-dimethoxy-1-(phenyl-methyl)isoquinoline. Marketed as ‘Eupaverin’ (Merck).
290 4-(Dimethylamino)-1,2-dihydro-1,5-dimethyl-2-phenyl-3H-pyrazol-3-one = dimethylaminophenazone. Marketed as ‘Pyramidon’ (Bayer Igepha, Zürich; later: Winthrop).
291 *Mercks Jahresbericht* for 1933, p.166-168. The constituents of ‘Eupaco’ were later altered: see Ludwig *et al*., 1948, p.334.
292 Anonymus, 1932b.
293 Laignel-Lavastine and Sterne, 1932.
294 See negative report by McCartan, 1932. The assessment of therapeutic progress by blueness of the gums is reminiscent of the use of silver nitrate in the 19th century.
295 McCartan, 1934.
296 Gayle and Williams, 1938. The major component of cobra toxin is cobrotoxin, a peptide chain consisting of 62 amino acids and containing four disulphide bridges; see Tu, 1977, pp.174-189.
VI. The 1930s and 1940s: the dominance of atropine and belladonna

The Sauerbruch-Hermannsdorfer diet was mentioned by one author as being of benefit in parkinsonism. This diet was originally conceived by Max B. Gerson (1881-1959) in 1919 in Bielefeld as a treatment for his own migraine; it was essentially a high potassium/low sodium vegetarian diet. As described in his 1930 book, he also found it to be effective in lupus vulgaris (tuberculosis of the skin, then considered incurable). In 1924, he was invited by the noted surgeon, Ferdinand Sauerbruch, to test his diet in a lupus clinic being established by the Bavarian government at the University of Munich. As Sauerbruch recounted it in his autobiography, 446 of 450 patients recovered – once he had discovered and put an end to the smuggling of sausages, cream and beer to the patients in the late afternoon. Later extended to pulmonary tuberculosis as well, this Gerson-Sauerbruch-Hermannsdorfer diet was widely used in Germany for a number of conditions, including parkinsonism, but it became more famous as a “macrobiotic therapy” for cancer, in which role it still retains adherents today. Fuchs reported in 1930 that after a few weeks the diet achieved reduction of tremor and rigidity and increases in mobility and body mass, occasionally even in advanced cases. While his name disappeared from the title of the diet in Germany during the 1930s (Gerson was Jewish), it is now generally known as the “Gerson diet”.

Anecdotal and curious was the finding of Bucy that parkinsonian symptoms could be relieved with large doses of alcohol. This is especially interesting, as abstinence was often considered a part of the parkinsonian “rigid personality”. He reported the case of a 31 year old male referred to him in 1939 with parkinsonian tremor and facies and some rigidity; he had been treated for syphilis since 1928. The effect of alcohol on the tremor was tested on December 30; between 11\(^{10}\) and 11\(^{35}\) he drank 240mL whiskey (45% v/v), followed by 120mL ethanol between 12\(^{20}\) and 12\(^{30}\). His blood alcohol reading had reached 222mg% and “the effect of alcohol upon his entire behaviour was obvious”, but his tremor had disappeared. Having refused lunch, he slept through the afternoon; at 16\(^{45}\) he was sitting in a chair, and his tremor had returned to 75% of its normal severity. By 17\(^{45}\) (blood alcohol: 104mg%), his condition had returned to its normal state. Following a series of other examinations, he was finally subjected to neurosurgery.

In early 1949, Buell and Biehl reported that tremor was abolished in four patients during hypnosis. As the lesion in Parkinson’s disease was assumed to be subcortical, and the electroencephalogram corresponded to that of the waking and not of the sleeping state, the authors had no explanation for this effect. Nor did they see the experiment as pointing to a practical therapeutic approach. Marshall reported in 1936 that a program combining psychotherapy, relaxation, exercises in physiotherapy and occupational therapy “apparently” improved the lot of some of his post-encephalitic parkinsonian patients; while conceding that the disorder ultimately had an organic basis, he believed that the “mental catharsis” was responsible for the improvement achieved. The exact consideration of his case reports renders his optimism somewhat puzzling; of nine patients, one improved markedly, one showed improvement “to some degree”, three showed improvement until their “entrance into a public institution”, two showed “some improvement” during the two or four weeks before they left the hospital, and two required chemical therapy.

298 Cited in Stemplinger, 1930.
299 Gerson, 1930; 1990.
300 Bucy, 1942.
301 Buell and Biehl, 1949.
302 Marshall, 1936.
The situation in 1945

By the end of the Second World War, it thus seemed that only the belladonna alkaloids offered much hope of relief for the parkinsonian patient. Völler wrote in 1941 that of the patients treated by him at the Queen Elena Clinic in Kassel, 89.7% had already been treated with other drugs; he listed the most common methods as being:

- atropine and scopolamine 51.8%
- ‘Homburg 680’ 10.9%
- ‘Parkinsan’ 3.9%
- Syntropan, belladonna tablets, belladonna wine, ‘Eustateina’, ‘Bellafulin’, harmine 10.5%
- preliminary treatment with the genuine Bulgarian treatment 1.9%
- phenobarbital, ‘Lubrokal’, arsenic “a vanishingly small percentage”
- “did not know” (presumed in most cases to have received atropine and scopolamine) 10.7%

The vast majority were thus receiving belladonna alkaloids in some form. Macdonald Critchley reviewed the “modern therapy of Parkinsonism” in 1941, and recommended only solanaceous alkaloids (which he called the “datura group of drugs”). Critchley was concerned chiefly with the relief of rigidity:

There is no remedy for [tremor], and much heart-burning will be avoided if this is gently explained to the patient at the outset.305

This was a curious position, given that subcutaneous would later be used specifically for the treatment of tremor where synthetic alternatives failed. Rigidity, on the other hand, was quite amenable to pharmacological intervention. Hyoscine hydrobromide (which Critchley combined with potassium bromide and tinctura Nucis vomicae), stramonium, high dose atropine (the latter two were particularly useful in post-encephalitic patients) and tincture of belladonna could be recommended; he saw no real evidence, however, that the Bulgarian treatment was superior to the usual belladonna tincture. Apart from these agents, only benzedrine (to relieve oculogyria) and glycerine suppositories and an occasional enema (to “satisfy the traditional beliefs as to alimentary hygiene”) might be required in order to manage the total spectrum of complaint in parkinsonism.307 The second edition of Wilson’s Neurology, published in 1954 but apparently reproducing much of the first edition, also listed the solanaceous alkaloids as the most reliable agents for the treatment of post-encephalitic parkinsonism, although the preference here was for genoscopolamine; alternatives were dismissed in a few words:

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303 Atropine sulphate tablets (Calwalaboratorium, Calw, Baden-Württemberg); not to be confused with the tradename for budipine, introduced by Byk-Gulden in the 1970s.
304 Ionogenic bound bromine (0.6g), sodium phenylethylbarbiturate 0.04g; Chemische Werke Albert, Wiesbaden-Biebrich. Indications: excitement, sleeplessness, epilepsy.
305 Critchley, 1941.
306 ½75-½50 grain hyoscine hydrobromide, 10 grains potassium bromide, 10 minims tr. Nucis vomicae, made up with ½ ounce infusum Gentianae compositum (a bitter tonic, used as vehicle); ibid.
307 Ibid.
VI. The 1930s and 1940s: the dominance of atropine and belladonna

Curare, tried about 1927 has been abandoned. . . . of the vaunted bulbocapnine less is now heard than at first. . . Harmine and banisterine barely touch the symptom [tremor].

Otherwise, hyoscine/codeine combinations could be recommended; excessive salivation might be managed with X-ray irradiation of the salivary glands.

The effectiveness of the solanaceous agents was ascribed to their anticholinergic characteristics, although how this property was actually translated into symptomatic relief was still unknown. The were also opinions to the effect that chronic parkinsonism involved a mixture of both sympathetic and parasympathetic disturbances, thus eliminating the possibility of classifying the entirety of the syndrome on a single "sympathetic-vagotonic" axis of nervous function – and thereby rendering effective therapy all the more difficult. The treatment of parkinsonism was ultimately entirely empirical, despite the protestations of promoters of one or other approach, and relied on experience and analogies with the effects of drugs in other disorders. The Matheson commissioner Neal commented in 1932 that effective remedies would not necessarily emerge from an understanding of the etiology of the disorder:

This is certainly true in the therapy of infantile paralysis, which is known through experimental transmission to be due to a specific filtrable virus. Moreover, the finding of a specific method of treatment need not wait on the determination of the cause. It was known that quinine was specific in malaria and mercury in syphilis long before the plasmodium of malaria or Spirochaeta pallida was discovered.

But at least by this stage, the plethora of handling methods which had been employed at the turn of the century had been whittled down. A quick glance at the pharmacopoeias and supplementary handbooks of the period might appear to indicate otherwise, but closer analysis reveals that most of the listed agents were either variations on a few basic themes or rarely employed leftovers from earlier hopes. Taking Germany as an example, the following items were listed in the Repertorium pharmazeutischer Spezialpräparate (1948) and the supplements of 1948 and 1950 (items in the latter supplement are marked with an asterisk):

- Combination of belladonna extract with barbiturate compound: ‘Bellatropin’, ‘Jacksonal’, ‘Donnatal’*.
- Parathyroid preparations: produced by Byla, Fournier, Custodis, Henning, Nyco, Parke-Davis.

Ibid.
For example: Langfeldt, 1930.
Neal and Bentley, 1932.
VI. The 1930s and 1940s: the dominance of atropine and belladonna

- **Vitamin B6:** ‘Benadon’, ‘Vidoxina’.
- **Antispasmodic:** ‘Propivane’.

The dominance of belladonna extracts and solanaceous alkaloids was even clearer in contemporary reviews of antiparkinsonian therapy, even if national differences existed with the form in which therapy was applied: Bulgarian treatment in most of continental Europe, stramonium in France and England, high dose atropine in France, belladonna tinctures in England, defined alkaloid combinations in the United States. It had thus become somewhat clearer what direction future developments might take (table 6-7).

And future developments were sorely needed; it was clear that the agent or agents which could restore a parkinsonian patient to acceptable functionality had not yet been discovered, and certainly none that had any influence on the inexorable course of the disease, of whatever etiology.

### Table 6-7 (next page): Recommended agents for the treatment of parkinsonism according to the Extra Pharmacopoeia of Martindale (and Westcott), 1884-1954.

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<th>Edition</th>
<th>Indications</th>
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<td>‘Paralysis agitans’ listed in catalog of indications.</td>
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<td>18th</td>
<td>No specific agent recommended for post-encephalitic parkinsonism.</td>
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<td>‘Paralysis agitans’ not listed.</td>
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<td>20th</td>
<td>‘Paralysis agitans’ not listed.</td>
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<td>21st</td>
<td>Recommended for the sequelae of encephalitis lethargica.</td>
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<td>22nd</td>
<td>Recommended for both paralysis agitans and post-encephalitic parkinsonism.</td>
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<td>23rd</td>
<td>Separate listing for post-encephalitic parkinsonism omitted. Note that ‘harmine’ never entered this list; the ‘Bulgarian treatment’ was only mentioned indirectly, in that from the 21st edition ‘belladonna’ was recommended in the treatment of ‘encephalitis lethargica’, while in the 22nd edition ‘folia’ and ‘radix belladonnae’ were listed; this became ‘belladonna preparations in the 23rd edition. The table does not include the synthetic preparations introduced after 1948; these will be treated separately in the next chapter. The 24th edition of the Extra Pharmacopoeia appeared in 1958.</td>
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312 Also included in 1948 was ‘Parpanit’, and in 1950 ‘Diparcol’; these were the first of the synthetic antiparkinsonian drugs, to be discussed in the next chapter.
VI. The 1930s and 1940s: the dominance of atropine and belladonna

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Part II

The synthetic antiparkinsonian preparations

För die Beurteilung der Wirkung von Arzneimitteln ist die Kenntnis ihrer chemischen Constitution unumgänglich notwendig.

*Louis Lewin,*
*Untersuchungen über die Wirkung des Aconitin auf das Herz*
*(Dissertation, 1875)*
VII. The 1950s: The synthetic anticholinergic and antihistaminergic preparations

The fifteen years following the war saw the introduction of a plethora of synthetic preparations aimed at controlling the symptoms of parkinsonism; only a few proved to be successful, and even fewer survived the L-DOPA revolution of the late 1960s. In many cases, however, they were perceived as an improvement on the old plant-derived substances in that they were specifically defined with respect to composition; they were the results of the first attempts to rationally design new products for the disorder, rather than implementing entirely empirical choices. A few were even reputed to manage parkinsonian symptoms better than the older choices. Doshay noted in 1965 that this shift in focus was necessary for a number of reasons, amongst them the fact that atropine was not safe for many parkinsonian patients due to the danger of glaucoma. There was also the fact that the availability of many traditional agents was restricted by the contingencies of World War Two. From a theoretical point of view, however, the problem lay in the fact that:

\[\text{the only two active ingredients of all natural products consist of nothing more than hyoscine and atropine;}\]
\[\text{if we were to extract the solanaceous plants for another hundred years, we could not possibly derive anything else of therapeutic value.}\]^{1}

This was the view of someone who was convinced of the superiority of the synthetic benzhexol (see below) over the Bulgarian treatment, and who thus regarded the further exploration of potentially effective ‘minor alkaloids’ as unnecessary. Nonetheless, there was certainly a great deal of truth in what he said. This was quite apart from the fact that the available drugs were less than completely satisfactory in treating the symptoms of parkinsonism. Some workers had noted a general decline in the tolerance by patients

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1 Doshay, 1965b.
of belladonna alkaloids, and indeed of many plant-derived drugs (such as digitalis and strophanthine) which had previously been the mainstays of pharmacological therapies. The development of novel pharmacological antiparkinsonian substances by the directed employment of applied chemistry was thus accepted by the growing pharmaceutical industry as a challenge and pursued with vigor. That is not to say that the new drugs were accepted with unconditional enthusiasm; Behrend expressed his cautious skepticism regarding the potential benefits of new “wonder drugs” in his 1952 review of the status quo thus:

Max Bürger recently wrote that anybody who leafs through the volumes of proceedings of the professional conferences through the years will note with resignation how many therapeutic innovations were once taken up with enthusiasm and have now been forgotten. If one examines . . . the variety of ways and means which have been employed during recent decades in the treatment of extrapyramidal disorders, and especially parkinsonism, . . . one must unfortunately realize that only the fewest therapies have survived and that in no case has success ever really been satisfactory.

Behrend also welcomed the new possibilities offered by synthetic agents, but wished to calm in advance any exaggerated hopes of a cure for parkinsonism.

**Introductory remarks: Theoretical considerations at the commencement of the 1950s**

The New York Centre for the Study of Nervous and Mental Disease held a major conference in 1940 on diseases of the basal ganglia. One of the participants, Clemens Benda, found it noteworthy that the meeting regarded paralysis agitans as the major disease of the basal ganglia. He contrasted this clear emphasis with a meeting of the New York Neurological Society in 1903; here the major topic of discussion had been the differentiation of paralysis agitans from multiple sclerosis, and it had been agreed that the localization of the lesion for the latter in the brain, and not the spinal cord, was probably the best indicator. By 1940, the cord was no longer a candidate for the site of the lesion in parkinsonism, but controversies still raged over the significance of the various lesions which had been identified in the brain. The lesion in the substantia nigra was recognized as a relatively constant finding, but its role in paralysis agitans, if not in postencephalitic parkinsonism, was still controversial. But of most interest for the present discussion is the fact that of nineteen presentations, fourteen concerned the anatomy and physiology of the disorder. Of the five papers dealing with therapy, four discussed the surgery of parkinsonism, while only one was devoted to pharmacological therapy; this was the co-operative paper on the Bulgarian treatment to which reference has already been made. The neurosurgeon Russell Meyers introduced his paper on the surgery of the basal ganglia with a brief survey of the disappointment which had accompanied chemical, psychotherapeutic and physiotherapeutic approaches; there was

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2 Brandt and Brandt, 1955. With respect to differential sensitivity to solanaceous alkaloids: Benjamin Boshes mentioned in passing at a 1963 conference that his preceptor (Pollock) had remarked that fair-skinned patients were especially sensitive to these drugs; Sem-Jacobsen replied that he was not aware of any differences between the responses to these drugs in America and Scandinavia; Forster et al., 1963.
3 Behrend, 1952.
4 Putnam, 1942.
5 In discussion of Alexander, 1942 (pp.481-482).
6 Dillenberg et al., 1942.
The paper which is generally mentioned as having definitively established the central role of the nigral lesion in the substantia nigra was published by the eminent British neuropathologist, J. Godwin Greenfield (1884-1958) in 1953. In 1921, he had published Pathology of the Nervous System with Sir Farquhar Buzzard; between 1923 and 1946 he had been Dean of the Institute of Neurology at Queen Square National Hospital in London. He made a number of significant contributions to neuropathology, including descriptions of the lesions in encephalitis epidemicam, which were encapsulated in the work which appeared shortly after his death, Neuropathology. In 1953, he published with Bosanquet the definitive paper on “the brainstem lesions in parkinsonism”. They were able to distinguish the postencephalitic (ten cases) and idiopathic forms (nineteen cases) on the basis of histopathology, but the differences were more quantitative than qualitative; they were satisfied, however, that the postencephalitic and idiopathic disorders were distinct entities. Further, they noted the significance of the nigral lesion and the Lewy hyaline inclusions for the disorder: the occurrence of such features in the substantia nigra, combined with cellular loss, was specific for parkinsonism, and was not seen in twenty-two cases of normal ageing. Not all workers, however, were convinced even by this paper; Denny-Brown still favored disruption of corticostriatal tracts as the basis of the disorder in 1962, while the pallidal site was still mentioned as late as the mid-1960s. Nevertheless, Kenneth Earle noted at the Second International Symposium on Parkinson’s disease in 1963 that neuropathologists were generally agreed upon the following five points:

- Severe lesion of all parts of substantia nigra in postencephalitic parkinsonism, lesser lesion in paralysis agitans;
- Marked nigral neurofibrillary tangles in postencephalitic parkinsonism;
- Lewy bodies common in paralysis agitans;
- Involvement of locus ceruleus, third nerve nucleus and dorsal motor nucleus in postencephalitic parkinsonism;
- Gliosis more marked in postencephalitic than idiopathic parkinsonism.

There were nevertheless still significant authorities who, despite differences in the clinic of the two syndromes which became clearer as the age of the postencephalitic cases reached that of the idiopathic patients, regarded any subdivision of parkinsonism as artificial, regarding idiopathic parkinsonism as similar to post-encephalitic parkinsonism, but consisting of fewer symptoms, occurring sporadically exclusively in older persons and less aggressively progressive in its nature.

The impact of these discussions on the therapy of parkinsonism was negligible. One of the few essays combining neurological findings and therapy was published in 1951 by G. Heilig (Queen Elena Clinic, Kassel) under the title “Treatment of parkinsonism in

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7 Meyers, 1942.
8 Greenfield and Bosanquet, 1953.
11 See Merritt, 1956.
its relationship to brain pathology”. The bulk of the article was concerned with discussion of central nervous system organization, with two aspects particularly accentuated: the ideas that the organization of the brain reflects its evolutionary history, and that brain function and processes in the brain substance are parallel rather causally related processes. There is no room here to discuss these issues, which were not infrequently presented in the German literature until the 1960s as background to the discussion of neurological dysfunction; there significance here lies in the justification of the then current antiparkinsonian therapy. Heilig argued that pallidal degeneration, which he saw as the critical lesion in parkinsonism, released phylogenetically lower motor reflexes, located in the brainstem, from appropriate control; as the damaged tissue cannot be repaired, control had to be re-asserted by invoking the activity of the higher psychomotor centres. In other words, by the use of psycho- and physiotherapy, the patient must learn, like a child, to once more control his movements with his will, until once more they are executed automatically. The role of the belladonna alkaloids was to support this program by suppressing parasympathetic tone and thereby granting the will the greatest freedom of action. Pharmacological therapy was thus only an adjunct in this view of antiparkinsonian therapy, which Heilig claimed was blessed with great success. He also admitted that the therapeutic approach had been devised empirically and theoretically underpinned only in retrospect. Nevertheless, he saw the consistency of theory and practice as confirming the correctness of both.13

There was thus no significant attempt made to devise more effective therapeutic approaches on the basis of neuropathologic findings, nor could the worth of current therapy be related to such findings. A telling comment on the situation was made by Greenfield in 1955:

Anatomical and histological studies seem unlikely to reveal much more of the pathogenesis of the disease. The cause of the neuronal degeneration remains a problem whose solution may be found in enzyme chemistry, or some other new field of investigation.14

The advent of L-DOPA therapy and the mapping of the nigrostriatal pathway led by the end of the 1960s to views of the following tone:

In the brain with idiopathic Parkinsonism the only naked-eye abnormality is loss of pigmentation of the substantia nigra and locus caeruleus pontis. . . . Changes in the globus pallidus and putamen are less constant and usually less severe than those in the substantia nigra, and it has been suggested that they are merely the result of loss of nigral neurons.15

The consensus described in 1963 had thus been accepted in detail. In retrospect, it is remarkable that the bleaching of the substantia nigra, which, as stated by Lewis, is often apparent without resort to microscope analysis, should have been overlooked for so long.

Developments which would have a major impact on the therapy of parkinsonism were also being to become apparent in another field of investigation. It was also at the

13 Heilig, 1951. Similar thoughts were expressed by Bostroem in 1922.
14 Greenfield, 1955. See also Spiegel, 1965 (“Is pathological study the ultimate solution in Parkinson’s disease?”).
15 Lewis, 1971.
end of the 1940s that Wilhelm Feldberg (Physiological Laboratory, Cambridge) provided at least a partial chemical basis for the relative effectiveness of the solanaceous alkaloids in the therapy of parkinsonism. That acetylcholine functioned as a transmitter in the brain was itself little more than a hypothesis, but a hypothesis for which Feldberg believed there existed a great deal of evidence. Henry Dale (1875-1968) had asked himself in 1934 whether acetylcholine or an acetylcholine-like substance might be concerned with normal transmission at central synapses,\(^\text{16}\) and evidence supporting this hypothesis had accumulated from studies of the effects of various acetylcholine-related substances on the electroencephalogram, although negative results had also been reported.\(^\text{17}\) This did not mean, however, that chemical transmission at these synapses was necessarily invoked, as the following explanation demonstrates:

*In this connection we would offer the hypothesis that, in consequence of the stimulation or facilitation of synapses by eserine and acetylcholine, streams of repetitive electrical impulses are initiated or accelerated across the synaptic junctions; these impulses lead to the discharge of the effector neurones.*\(^\text{18}\)

It must also be remembered that at this point, atropine and its analogs were not defined as essentially ‘anticholinergic’ agents; the introduction of this concept was, in large part, the service of Feldberg. Previously, it had been recognized that, in general, atropine antagonized the effects of acetylcholine, but the expression of this antagonism appeared to be different in isolated tissue preparations and in the whole animal. Further, and rather puzzlingly, atropine was recognized to exert effects even in the presumed absence of acetylcholine. In his comprehensive 1945 review of “*present views on the mode of action of acetylcholine in the central nervous system*”, Feldberg presented evidence that atropine and acetylcholine produced opposite effects when applied to the central nervous system. In considering the effects of atropine when given alone, Feldberg commented:

*There is another well known action of atropine, its sedative effect on the rigidity and tremor of parkinsonism. It is tempting to regard this effect as a central atropine-acetylcholine antagonism, similar to that observed when both drugs are applied artificially to the central nervous system.*\(^\text{19}\)

The problem still persisted that atropine had only a minor effect on spontaneous and reflex activity in the central nervous system; further, not all workers noted an antagonism between acetylcholine and atropine on the EEG. Feldberg assumed that this would be explained by the release of acetylcholine inside or at least very close to its target tissue, so that it was difficult to block its activity by the application of an antagonist. This solution had also been suggested by Dale and Gaddum to explain the same problem in the peripheral nervous system.\(^\text{20}\) Feldberg noted that scopolamine also antagonized the effects of acetylcholine in the periphery; it had, however, not yet been extensively examined with respect to its actions in the central nervous system. Despite this comment, it should be noted that many Parkinson therapists had expressed the opinion that scopolamine acted primarily by dampening cortical activity, which effect

\(^{16}\) But: “*With no direct experience of central nervous physiology, I cannot properly allow myself merely to speculate.*” Dale, 1934a. See also Bronk, 1939. For review of ideas on transmission in the 1930s: Eccles, 1936; de Nô, 139.

\(^{17}\) Miller *et al.*, 1940; Chatfield and Dempsey, 1942; Brenner *et al.*, 1942; Forster, 1945; Bornstein, 1946.

\(^{18}\) Miller *et al.*, 1940.

\(^{19}\) Feldberg, 1945.

\(^{20}\) Dale and Gaddum, 1930; Dale *et al.*, 1930; Dale, 1934a.
was linked to its potent sedative properties.\textsuperscript{21} For Feldberg, a role for acetylcholine in the central nervous system was highly probable; he was not, however, opposed to the idea that it might not be the universal central transmitter, and that electrical transmission might be important at some synapses:

\textit{Must we assume different transmitter substances in the central nervous system or must we assume that, in some, excitation is effected by the circulating currents from the presynaptic terminations? In that case both transmission processes might be involved in the transmission across a single synapse, the relative importance of one or the other varying at different synapses.}\textsuperscript{22}

Attempts to demonstrate the presence of acetylcholine in the brain commenced at the end of the 19th century, but the first reliable report of its presence in brain tissue was published in 1931.\textsuperscript{23} Although the broad regional distribution of acetylcholine in the cat and dog brain had been reported by MacIntosh in 1941, and its relative concentration in a number of specific nerves had been reported from as early as 1925,\textsuperscript{24} it would not be until the 1960s that methods would be developed which allowed the precise quantification of acetylcholine (ACh) levels in nervous tissue:

\textit{The data from brain samples do not, in general, permit the deduction that ACh. occurs, or does not occur, in individual tracts and nuclei. Such information could possibly be obtained only by study of a larger brain, since the assay of ACh. in samples weighing less than a few mg. is impossible with available methods.}\textsuperscript{25}

MacIntosh found the highest levels in the brain in the basal ganglia (7.0µg/g), frontal lobe (4.5µg/g), superficial medial pons (3.2-5.0µg/g) and striatum (2.7µg/g).\textsuperscript{26} The Indian pharmacologist Dikshit used bioassay techniques to demonstrate the presence of an acetylcholine-like substance in the cat basal ganglia of about 0.5µg/g in 1933, and lower levels in that of the rabbit; he suggested that the release of acetylcholine in the central nervous system by sensory elements of the vagus might be involved in central transmission.\textsuperscript{27}

In place of the direct measurement of acetylcholine, measurement of the enzymatic activity involved in acetylcholine metabolism was employed to “map” the transmitter. The catabolic enzyme choline esterase\textsuperscript{28} was thus first mapped in the central nervous system by Nachmansohn in 1939 and by Birkhäuser in 1940. The enzyme content was relatively high in the putamen and caudate nucleus, moderate in the pallidum, relatively low in the thalamus opticus and cortex and lowest in the white matter of the brain. This suggested to G. Weber (Neurosurgical Clinic of the Zürich District Hospital) in 1952 that the enzyme might be involved in \textit{“the function of these regions as transfer stations for incoming impulses”}. He therefore measured brain choline esterase levels in brain slices from six deceased patients, of which two were cases of postencephalitic

\begin{itemize}
  \item Doshay expressed the opinion in 1939 that high atropine therapy was superior to scopolamine therapy, the mainstay of antiparkinsonian therapy in America at this point, as scopolamine did not have the cerebral stimulating properties of atropine.
  \item Feldberg, 1945.
  \item Chang and Gaddum, 1931.
  \item Wilanowski, 1925; for further references, see MacIntosh, 1941.
  \item MacIntosh, 1941. MacIntosh was examining the cat brain.
  \item Ib\textit{id}.
  \item Dikshit, 1934. See also Plattner, 1934; Kwiatkowski, 1935.
  \item The distinction between the various choline esterases was not made until a later timepoint.
\end{itemize}
parkinsonism. Choline esterase activity was not detectable in the three regions investigated (putamen, pallidum, nucleus ruber) in these parkinsonian cases. The author did not reach any rash conclusions, but the finding suggested that reduced catabolism of acetylcholine in the parkinsonian basal ganglia might explain the efficacy of antiparkinsonian drugs.29

Feldberg and Marthe Vogt examined the “enzyme or enzyme system” choline acetyltransferase in forty distinct regions of the dog brain in 1947.30 As expected, the highest relative values were found in the anterior horns and motor nuclei of the cranial nerves; this was consistent with the known cholinergic nature of the lower motor neuron. Apart from these regions, the highest levels were found in the caudate nucleus, the significance of which was cautiously remarked upon by the authors:

the caudate nucleus . . . belongs to a group of basal ganglia which inhibit voluntary impulses to the skeletal muscles. . . . The fact that administration of atropine in Parkinsonism can partly compensate for the loss of these centres is interesting in this respect, although it is not possible at the moment to offer any explanation, since the mechanism of the inhibitory action of these centres is anything but understood.31

And that is where the matter remained for some time. Although it was recognized that the most effective antiparkinsonian drugs were parasympatholytic agents, there was no firm concept of how this correlation should be interpreted. Despite the opinion of workers such as Ken Kuré that sympathetic innervation also played a part in the regulation of muscle tone, it was generally accepted that most clinical experience pointed to the predominance of parasympathetic mechanisms in this function. Frank, for example, had shown in animal experiments that physostigmine induced rigidity of the limbs and, at sufficiently high doses, rhythmic tremor reminiscent of that seen in paralysis agitans. This was interpreted as a chemical alteration of the muscular sarcoplasm leading to changes in viscosity and, at the functional level, increased muscle tone.32 In 1960, Haas (Knoll, Ludwigshafen) noted that the selection of the few agents which were effective in the therapy of parkinsonism was purely empirical, “without any detailed knowledge of their sites or modes of action in the CNS”; he also noted that the extent to which central cholinergic mechanisms were involved in the pathology of parkinsonism was still unclear.33 The belladonna alkaloids had not been introduced into therapy on the basis of their anticholinergic nature, nor did the synthetic drugs introduced in the 1950s owe much to theoretical considerations; they were the results of empirical testing and experimentation, and the fact that the role of acetylcholine in the central nervous system would not be clarified for many years was of minor importance.

The introduction of synthetic drugs for parkinsonism

In 1939, the Bulgarian treatment, atropine, hyoscine and stramonium were the major options for the treatment of parkinsonism; by the beginning of the 1960s, England and Schwab could remark that the belladonna drugs have “a limited place in therapy”, stramonium “may be effective”, hyoscine was rarely tolerated but might be beneficial,

30 Reported in 1948.
31 Feldberg and Vogt, 1948.
32 Cited in Scheiffarth, 1939.
33 Haas, 1960.
while the Bulgarian derivatives “have no special virtue”. The 1950s experienced a revolution in the therapy of parkinsonism which saw the almost total displacement of plant-derived agents by compounds designed by chemical companies. The relative success of the natural anticholinergic compounds dictated that the new synthetic compounds would be based on the assumptions made regarding the mode of action of the older agents. It must also be remembered that at this time a great deal more information regarding the role of cholinergic mechanisms in neural and muscular function was available than for the involvement of sympathetic mechanisms, the major hypothetical alternative; as will be discussed in the next chapter, the very presence of catecholamines in the mammalian brain was first demonstrated in 1946.

The first synthetic drug for parkinsonism was actually tried before the war. ‘Syntropan’ (= amprotopine; figure 6-1), developed primarily as a less toxic alternative to atropine for use in ophthalmology, was tried in several American clinics in the 1930s with mixed results. The drug was one of the first synthetic antispasmodics and was also used for the management of sea-sickness and the abbreviation of labour. It appears to have been first employed in parkinsonism by Ratschow in 1934 in two patients; tremor and rigidity were abolished in one case by 800mg ‘Syntropan’ daily. Chiabov achieved some success with the drug (300mg daily) as an adjunct to atropine in three patients and as a monotherapy in one. Schlezinger and Alpers reported mild to moderate symptomatic relief in fourteen of sixteen patients with doses of up to 2400mg daily. Tremor, rigidity and salivation were generally reduced to the same degree as by atropine, but without the toxic side effects noted with atropine or stramonium. One of the problems which impeded the success of the drug was the high price associated with one of the first patented agents to be used in parkinsonism.

The first synthetic anticholinergics introduced expressly for the treatment of parkinsonism were essentially modifications of the atropine or scopolamine molecules, which are themselves examples of the general “spasmolytic structure” (figure 7-1). Both natural drugs are esters which can be hydrolytically cleaved to yield a secondary alcohol (tropine or scopine) and tropic acid. Both the alcohol and the acid can be modified to some extent without losing the anticholinergic character of the total molecule; an amino alcohol can replace the alkamine, other acids can be substituted for tropate. Such variations also occur in nature; belladonnine, for example, is the ester of tropine and β-isooatropic acid.

The first synthetic drug to be introduced into the therapy of parkinsonism after the War (in 1946) was produced in this manner: caramiphen hydrochloride39 (‘Parpanit’; Geigy, Basel), described by three co-operating Swiss groups in a set of papers which appeared in the Schweizerische Medizinische Wochenschrift at the end of 1946. R. Domenjoz (J.R. Geigy, Basel) had been investigating a series of analogs of the

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36 Cited in Schlezinger and Alpers, 1941.
37 Schlezinger and Alpers, 1940; 1941.
39 1-Phenylcyclopenteneacarboxylic acid 2-(diethylamino)ethyl ester HCl. Also marketed as ‘Panparnit’ (in the U.S.A.), ‘Toryn’ (the ethanesulfonate; Smith, Kline & French) and ‘Pentafin’. Swiss patent granted to Geigy in 1945.
spasmolytic adiphenine (‘Trasentin’), and had found that caramiphen, first synthesized by Henry Martin and Franz Häfliger in the Basel laboratories of Geiger, had a weaker spasmolytic and anticholinergic effect than atropine and was relatively non-toxic with respect to its effect on vegetative functions (mydriasis, salivation). The conceptual basis which underlay Domenjoz’ inquiry was the question:

*Is the paralyzing effect of a substance on the parasympathetic system related to its effect on the extrapyramidal motor system?*

The question was of immense practical importance. Domenjoz noted that it was either tacitly or explicitly understood by most workers that this question was to be answered in the affirmative. This had the consequence that the unwanted autonomic side effects of solanaceous alkaloid therapy were unavoidable: if suppression of sympathetic tone underlay both its desired and the undesirable effects, there seemed no possibility for inducing one without the other. For example, Scheiffarth (Medical Clinic, Erlangen) wrote in 1939:

*When one considers that the belladonna alkaloids are vegetative toxins, it is pointless discussing whether it is actually possible for a preparation to have a selective effect on regulation of muscle tone, as was for some time suggested in the case of apoatropine. . . . One must . . . settle for those agents which exhibit the greatest therapeutic range; that is, have the least toxic effect.*

For Scheiffarth, the alkaloids of the belladonna root met this condition best. The only exception to this position of which Domenjoz was aware was Duensing, who had reported that the effects of apoatropine on parkinsonian symptoms were noticeable at doses which did not affect peripheral parameters. This view was also supported by the relative effectiveness of the alkaloid series which resulted from the heating of hyoscyamine, as reported by Kreitmair in 1938 (table 7-1). After examining a number

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40 Diphenylacetyldiethylamino ethanol ester, Ciba; developed as an atropine analog, its antispasmodic action was similar to that of atropine, but its side effects were less marked. Swiss patent to Ciba, 1937.

41 Domenjoz, 1946.

42 Scheiffarth, 1939.

43 Duensing, 1938.
VII. The 1950s: The synthetic anticholinergic and antihistaminergic preparations

Caramiphen ('Parpanit')

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{CH}_2\text{CH}_3 \\
\text{CH}_2\text{CH}_3 & \quad \text{C} \\
\end{align*}
\]

Adiphenine ('Trasentin')

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{CH}_2\text{CH}_3 \\
\text{CH}_2\text{CH}_3 & \quad \text{C} \\
\end{align*}
\]

Propivane ('Prospasmine')

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{CH}_2\text{CH}_3 \\
\text{CH}_2\text{CH}_3 & \quad \text{CH}_3 \\
\end{align*}
\]

Oxyphenonium bromide ('Antrenyl')

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{CH}_2\text{CH}_3 \\
\text{CH}_2\text{CH}_3 & \quad \text{CH}_3 \cdot \text{Br}^- \\
\end{align*}
\]

Figure 7-2: The first of the synthetic agents designed for the therapy of parkinsonism, caramiphen, and three related amino esters employed as spasmolytics. Commercial caramiphen was supplied as the hydrochloride (for use as an anticholinergic) or as the ethane disulfonate (for use as an antitussive). Adiphenine was patented in 1937 (Ciba), propivane in 1941 (Rhône-Poulenc) and oxyphenonium in 1949 (Ciba).

<table>
<thead>
<tr>
<th>Neural effect</th>
<th>Muscular effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcholine-induced contraction</td>
<td>BaCl₂-induced contraction</td>
</tr>
</tbody>
</table>

| L-Hyoscyamine | 2 | 1 |
| Atropine | 1 | 1 |
| Apoatropine | 1/60 | 5 |
| Belladonnine | 1/50,000 | cramp-inducing |

Table 7-1: ‘Neural’ and ‘muscular’ effects of the alkaloids resulting from the heating of hyoscyamine, as assessed by their effects on two standard models of muscular contraction (Kreitmair, 1938). The inverse nature of the two effects indicated by these results suggested that the benefit of belladonna alkaloids for parkinsonian patients was probably not attributable to classic parasympatholytic mechanisms.

of candidate substances, Domenjoz confidently concluded that the two panels of effects could be pharmacologically separated, offering the prospect of an antiparkinsonian medication without side effects. Caramiphen was the most promising in this respect of the compound examined.

E. Grünthal (Brain Anatomy Laboratory, University Psychiatric Clinic, Waldau-Bern) reported in the second paper of the series that the effect of caramiphen on the proprioceptive responses of striped muscle was sufficiently strong to completely abolish the sense of muscular tension (Kraftsinn):
in the majority of cases, the sense of tiredness in the muscles of the hand and lower arm employed in [the ergographic assessment of muscular strength] which was always clearly present in the absence of the drug, was experienced during the effect of the drug with greatly reduced intensity, or, if it still presented itself, it subsided more quickly than usual.\textsuperscript{44}

This prompted Grünthal to examine the effect of caramiphen on parkinsonian patients and in patients suffering other extrapyramidal disorders. This corresponded to the idea that parkinsonian tremor was the result of simultaneous activation of antagonistic muscles, encapsulated in the axiom that “tremor is diluted rigidity”, and could thus be modulated both centrally and peripherally. This derived from the observation that, while tremor and rigidity tend to coexist in parkinsonism, the degree of presentation of the two symptoms is often inversely proportional.\textsuperscript{45} Nevertheless, several workers had previously reported strong evidence for the etiological independence of the two symptoms, even if, as would be expected, the presentation of one symptom by a patient affected the expression of the other.\textsuperscript{46} In any case, Grünthal reported some success with the agent, although psychic alterations which manifested themselves before the motor effects of the drug, including disturbances of self-perception, were also noted. Intravenous administration could even lead to short psychotic episodes.\textsuperscript{47}

Caramiphen was found to partly atropine-like in its actions, in that it not only reduced rigidity but also inhibited to some extent the excessive sweating and sialorrhea which often irritate the parkinsonian patient; partly spasmolytic, dampening cramps in smooth muscle; and partly curare-like, reducing the excitability of striated muscle.\textsuperscript{48} In 1947, Hartmann (University Neurological and Medical Polyclinics, Zürich) and Habermann (Encephalitis Ward, Göttingen) confirmed the positive experiences reported by Grünthal concerning caramiphen as antiparkinsonian agent. In the same year, Geigy (New York) made the drug available to Robert Schwab at the Massachusetts Hospital, where a clinical investigation in a total of sixty-seven patients commenced. Schwab set himself a quite strict set of conditions for the evaluation of the drug, being acutely aware of the psychological factors involved in the therapy of parkinsonism; specifically, the pharmacological effect of the drug had to be:

- specific and independent of the effects of co-administered agents.
- clearly distinguishable from that of an appropriately chosen placebo.
- independent of the regional and cultural attributes of the patient.
- objective, recordable and, if possible, quantifiable; the effect had to be clear enough to be demonstrable to a disinterested observer.\textsuperscript{49}

\textsuperscript{44} Grünthal, 1946.\textsuperscript{45} Becker, 1956. Similar statements are to be found in the works of various authorities, including Wilson; the idea stems ultimately from Hughlings Jackson (1835-1911), who is often quoted as stating that “tremor differs from rigidity, not fundamentally, but by degree” or regarding “tremors as rigidity spread out thin and rigidity as tremors run together”. See Jackson, 1884; 1899. Interestingly, this idea is not as common in the German literature. Incidentally, Jackson (1896) is usually cited as the source of the second quote; although the article discuss theoretical points related to this issue (as does Jackson, 1895), the axiom is not to be found in this paper.\textsuperscript{46} Walshe, 1924; reviewed in Walshe, 1929. Wachs \textit{et al.} (1960) came to the conclusion that the two symptoms had separate origins, but that a “mutual interaction and modification in a direct qualitative relationship” occurred when a patient presented both symptoms.\textsuperscript{47} Grünthal, 1946. See also Simma,1947; Habermann, 1948.\textsuperscript{48} Heymans and de Vleeschhouwer, 1948 (and references therein); Heymans and van den Heuvel, 1949.\textsuperscript{49} Schwab and Leigh, 1949.
He therefore used a ten item checklist to assess the response of the patient to the drug: the patient was evaluated on a three-point scale (‘better’, ‘no change’ or ‘worse’) with regard to: 1) subjective patient report, 2) report of relative, 3) appearance and posture, 4) performance in daily life, 5) neurologic examination, 6) electromyogram, 7) speed of movement and gait, 8) handwriting, 9) placebo and substitution effect and 10) opinion of an outside medical observer. The assessment within each of these categories was, in the most instances, subjective; it was, however, a good example of an early attempt to avoid simply classifying patients into broad categories of ‘improved’ or ‘not improved’.

Schwab found that of fifty patients who been treated on an ambulatory basis with caramiphen for at least three months (mean: 5×50mg/day; range: 90-600mg/day), the drug was superior to scopolamine or stramonium in 62% of cases, and was of equal benefit in 22%. The major benefit was reduced rigidity, but even here the improvement achieved by caramiphen was only of the order of 25% (as assessed by electromyograph). The figure itself, however, was interesting, as it was one of the earliest concessions that the effect of even a preferred agent fell somewhat short of miraculous. The response in the postencephalitic (n = 38) and paralysis agitans patients (n = 5) was similar, but none of the arteriosclerotic patients (n = 7) derived benefit from the drug. The main side-effects were dose-related bouts of giddiness. Four bedridden patients were also found to be unresponsive the drug. Schwab saw the future of caramiphen as being an adjunct to belladonna preparations.50

This, however, proved ultimately to be one of only a handful of papers which endorsed caramiphen with any degree of assurance.51 Doshay’s group was not at all impressed by caramiphen,52 but it must be noted that they were already ardent champions of the alternative synthetic agent benzhexol. Merritt’s group (various New York institutions), however, were equally unimpressed; only four of seventeen postencephalitic parkinsonism patients and one of eleven idiopathic cases showed subjective improvement; none exhibited objective improvement, while eleven in all showed a decline in condition.53 Most of the subsequent reports on caramiphen derived from Germany or Switzerland, and produced mixed results; Behrend, for example, reported that better results in more patients could be achieved with the various belladonna alkaloids.55

After 1951, the drug was no longer reported in journals, but continued to be used, if without enthusiasm, until the 1960s. Nevertheless, many patients were satisfied with caramiphen to an extent which could not be achieved with any other medication; for arteriosclerotic and advanced post-encephalitic patients, however, the side effects negated the value of any benefit achieved.56 In mild cases, rigor could be almost completely abolished; the akinesia was unaffected but voluntary movement was facilitated by the effects of the drug on the mood of the patient. Quite unpleasant side effects even at normal doses were often observed, including nausea, loss of balance, epigastric burning and cardiopulmonary irregularities. In general, however, the objective benefits (if any) lasted only a few hours and did not justify the side effects

50 Ibid. See similar report by Dunham and Edwards, 1948.
51 See also Daeninck and Libbrecht, 1948; Joachimoglu and Klissuinis, 1948.
52 Doshay and Constable, 1951.
53 Sciarra et al., 1949.
54 See references in Behrend, 1951.
55 Ibid.
56 Hartmann-von Monakow, 1960, p.98.
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The related amino ester spasmylytics propivane (‘Prospasmine’; Rhône-Poulenc) and oxyphenonium bromide (‘Antrenyl’; Ciba) (figure 7-2) found only limited use as antiparkinsonian agents, having been quickly superseded by more effective alternatives.

Phenothiazine derivatives

Also introduced in the late 1940s were the first phenothiazines to be employed in the clinic. Phenothiazines were first synthesized towards the end of the 19th century as byproducts in the production of aniline dyes. Promethazine was fortuitously discovered to have exceptional antihistaminergic and sedative effects during the 1930s; as a result, it was introduced as a sedative for psychiatric patients in the 1940s, but met with only limited success. It was then discovered that it prolonged barbiturate-induced sleeping time in rodents, leading to the search for related compounds which might be used to potentiate surgical anesthesia. This resulted in the synthesis of chlorpromazine by Charpentier in 1949, the first neuroleptic; it did not of itself induce sleep, but increased the tendency through decreased arousal. This became the prototype of a broad series of highly successful drugs for the treatment of psychotic disorders.

A sedative which did not reduce its user to total inertia seemed an appropriate candidate for the treatment of parkinsonism. One feature of the phenothiazines which appeared to be associated with this effect was their marked antihistaminergic action. This activity appears to be determined by the length of the carbon chain between the ring nitrogen and the amino nitrogen; the N-C-C-N configuration of promethazine is the ideal length. Increasing the length of the chain or the addition of a propyl group increases the sedative action of the compound. The amino group is also of importance; the replacement of the two methyl groups of promethazine with ethyl groups (as in diethazine and ethopropazine) decreased the antihistaminergic effect but increased the antiparkinsonian effect of the molecule, by virtue of increased antinicotinic activity. The second feature which appears central to the antiparkinsonian effect of the phenothiazines appeared, in fact, to be this parasympatholytic effect. A specific effect on the parkinsonian syndrome was thus not achieved with these agents, but rather a general suppression of both nicotinic and histaminergic mechanisms.

The first of the phenothiazines specifically applied to the therapy of parkinsonism was diethazine HCl (‘Diparcol’; Spezia, Paris, May & Baker), developed originally by Rhône in their search for a novel novocaine-type product. The other major member of this class to be employed in parkinsonism was the more active but less toxic

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57 See Schaepdrijver, 1948. Marketed by Geigy as ‘Taoryl’. See Hardman et al., 1996, p.552. An extensive literature list for the pharmacology of caramiphen, much of it concerned with its effects on bronchial function, is given in Hartmann-von Monakow, 1960 (pp.139-143).

58 For the history of the phenothiazines see Issekutz, 1971, pp.142-146; Deniker, 1983. This topic will be examined in greater detail in chapter X.

59 10-(2-Diethylaminoethyl)phenothiazine. Also marketed under a variety of other names, including ‘Antipar’ (Farmitalia), ‘Casantin’ (Curta), ‘Latibon’ (Bayer), ‘Aparkazin’ and ‘Thiontan’ (VEB Deutsche Hydrierwerke); the simple compound was also marketed as an antiparkinsonian agent. U.S. patents granted to Rhône-Poulenc: 1950, 1952.
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Figure 7-3: The major phenothiazines employed in the therapy of parkinsonism.

ethopropazine HCl (= isothiazine HCl; ‘Parsidol’; Spezia, Paris),<sup>60</sup> but mepazine (‘Pacatal’; Prolonta),<sup>61</sup> promethazine HCl (‘Phenergan’; Spezia, Austria, May & Baker),<sup>62</sup> promazine HCl (‘Sparine’; Wyeth)<sup>63</sup> and novazine (‘Transergan’; Sweden)<sup>64</sup> have also been employed. Most (but not all) workers agreed that the non-halogenated phenothiazines were most valuable in the treatment of rigidity.<sup>65</sup> Phenothiazines were generally used in combination with benzhexol and an antihistaminergic agent, although some of the phenothiazines themselves possessed antihistaminergic properties. The dose was gradually raised, and the final level could be quite high; in the case of diethazine, up to 3g per day could be applied. The major side effects were dryness of mouth, problems with urination and mental confusion.<sup>66</sup>

Diethazine was especially intensively investigated in France and England from 1946.<sup>67</sup> It was generally found to be equally effective in all classes of parkinsonism, with the major effect being reduction of rigidity and, to a lesser extent, of tremor and akinesia; improvements in gait, posture and speech articulation were also reported. It was particularly useful in the management of oculogyria, whereby intramuscular

<sup>60</sup> 10-(2-Diethylaminopropyl)phenothiazine. Also marketed as ‘Dibutil’ (Farben Bayer), ‘Lysivane’ (May & Baker) and ‘Parisitan’ (Poulenc-Canada). U.S. patent granted to Rhône-Poulenc: 1952.

<sup>61</sup> (N-Methyl-3-piperidyl)methylphenothiazine. Antipsychotic also used as a veterinary tranquilizer. U.S. patent granted to Promonta: 1952. See Schulz, 1957.


<sup>64</sup> β-Diethylaminohexyl phenothiazine-N-carboxylate hydrochloride. ‘Transergan’ was little use outside Scandinavia; see Dahlbom et al., 1953; Johnson, 1955; Eliasson and Tejning, 1956.

<sup>65</sup> See, for example, Doshay et al., 1956; England and Schwab, 1959; in both cases tremor was reported to respond better than rigidity.

<sup>66</sup> England and Schwab, 1959; Doshay, 1956.

<sup>67</sup> See the extensive reference list in Hartmann-von Monakow, 1960, pp.143-145; also Behrend, 1952.
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administration of up to 250mg brought rapid relief. The largest examination reported was that of Sigwald involving 106 cases (40 paralysis agitans and 66 post-encephalitic patients); he had been the first physician to employ the drug (in 1946). Both rigor and tremor were ameliorated by diethazine; in 9.5% of cases the improvements were classified as “excellent”, in 33% as “good”. Sigwald was satisfied that diethazine was more effective than the belladonna alkaloids, and proposed that it acted in medullary centres responsible for muscle tone. Heymans and colleagues wrote, in contrast, that diethazine had effects on cortical, motor and medullary centres.

A number of other mildly positive reports concerning diethazine in small group studies were published between 1949 and 1951, but the side effects, including nausea, gastrointestinal unrest and occasional increase in tremor, tended to limit the usefulness of the agent and to overshadow any benefit. Doshay’s group saw it as being useful only in those post-encephalitic patients who could tolerate high doses of other anticholinergic agents. But it was another reason which eventually led to the withdrawal of diethazine from the market in most counties by 1954. Agranulocytosis and leukopenia, which had also been anecdotally linked to the use of caramiphen, were much more widely reported in connection with diethazine, often with a fatal outcome; the toxic effect on the kidney was a further unacceptable side effect, particularly in light of the safer alternatives which had been released in the meantime.

Ethopropazine (‘Parsidol’, ‘Lysivane’) proved to be a more useful antiparkinsonian drug. As a spasmolytic, it was comparable with diethazine; it was more effective, on the other hand, as a parasympatholytic, while also exhibiting nicotinolytic, anticonvulsive and antihistaminergic properties. All parkinsonian symptoms were reported to be improved by ethopropazine, but rigidity (and, to a much lesser extent) akinesia were those symptoms most consistently reported as being responsive to this therapy, although Doshay recommended it particularly for the treatment of major tremor. Palmer and Gallagher found that tremor responded especially well primarily in those patients for whom rigor was not a major problem. Together with stramonium, ethopropazine was also found to be especially effective against oculogyric crises. Ethopropazine could be used in large doses as a monotherapy, but was generally employed as an adjuvant; the average daily dose ranged between 50 and 600mg, although daily doses of up to a gram were occasionally reported. The drug was well tolerated by most patients; the major side-effects, as to be expected with a drug with significant anticholinergic qualities, were drowsiness and dizziness; this was alleviated,

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68 Sigwald, 1947.
69 Sigwald, 1949.
70 Heymans et al., 1949; see also Bovet et al., 1950.
72 Doshay and Constable, 1951.
73 Booij, 1948; Anonymus, 1949; Pilcher, 1950; De Haas, 1952; Gulcher and Kampfs, 1953. Diethazine is now listed only in the French pharmacopoeia.
74 Bovet et al., 1950; Ziegler and Torres, 1955; Burke, 1986. The latter author found that ethopropazine was not especially selective for either m1 or m2 muscarinic receptors.
75 Wilson (1954a; p.161) and Doshay et al. (1956), however, regarded the effect on tremor as more prominent.
76 Doshay, 1960, p.108.
77 Palmer and Gallagher, 1950a, b.
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when it did not spontaneously resolve itself, by lowering the dose or adding amphetamine or caffeine to the therapy. The blurring of close vision was also a problem in about one in six patients, but was generally not regarded as a major difficulty. Nevertheless, some authorities, including Hassler, rejected its long term use because of these side effects, especially after more effective, safer agents became available.79

Sigwald reported that ten of one hundred and six patients treated with ethopropazine for up to eighteen months were restored to near normal motor function; only eight patients showed no improvement at all. A comparison with other synthetic agents (caramiphen, diethazine, promethazine, diphenhydramine) indicated to Sigwald that ethopropazine was superior to all hitherto employed antiparkinsonian agents.80 Doshay’s group regarded ethopropazine as the most effective treatment for severe tremor in a large group of patients selected for their failure to respond to other agents.81 Garai (Neurology, King’s Hospital, London) found that its major effect was on rigidity, eliciting improvements in 72% of forty-three cases (compared with 74.5% of fifty-one patients with benzhexol); more idiopathic patients responded positively (fourteen of seventeen) than in the postencephalitic group (fifteen of twenty-four). Garai noted, however, benzhexol was as effective an antiparkinsonian agent but less toxic.82 Gillhespy (Parkinson Clinic, Dudley Hill Hospital) reported in 1953 that sixty-eight of one hundred patients showed sufficient improvement to allow a return to "normal activities".83 Palmer and Gallagher (Public Hospital, Dunedin, New Zealand) were particularly impressed by the psychic effects of the agent:

The sense of being “rooted to the spot,” which is perhaps the most important symptom of parkinsonism, invades the mental aspects of the self as well as the motor, and we often find that our patients treated with lysivane “lighten up” in their emotional life in a manner which does not seem to be satisfactorily explained simply in terms of the disappearance of rigidity and tremor.84

This comment would appear to indicate both an effect of the drug on akinesia, and also the prevailing conceptual view of akinesia as primarily a psychological problem.85 A number of other generally positive reports for published in the first half of the 1950s,86 and Hartmann-von Monakow wrote in 1960 that he still prescribed it frequently (in combination with benzhexol and stramonium); he found that paralysis agitans patients in whom rigidity dominated the clinical picture and post-encephalitic paralysis agitans without major vegetative symptoms responded best to the drug, but also that arteriosclerotic patients, otherwise difficult to treat, also derived some benefit.87 By the mid-1960s, however, ethopropazine had been superseded by newer agents and was dismissed by most reviewers as being of little value in the treatment of parkinsonism.88

A two month double-blind trial in sixty hospitalized parkinsonian patients (thirty-seven

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79 Hassler, 1953, p.832.
80 Sigwald, 1949.
81 Doshay et al., 1956.
82 Garai, 1951a.
83 Gillhespy, 1953; see also Gillhespy, 1951.
84 Palmer and Gallagher, 1950.
85 Being “rooted to the spot” could also refer to so-called ‘freezing’, but this could not be described as “the most important symptom” of parkinsonism.
87 Hartmann-von Monakow, 1960, p.100.
88 For example: Strang, 1966a.
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paralysis agitans, thirteen presumptive arteriosclerotic, ten post-encephalitic) reported in 1966 found, in any case, that it was not a particularly effective antiparkinsonian drug; the availability of better alternatives eliminated the necessity for its use. Ethopropazine remains available in some countries, although it is no longer prescribed for parkinsonism in the United States or the major European countries.

Promethazine (‘Phenergan’), a potent antihistaminergic agent, met with similar success in the clinic of parkinsonism; Sigwald regarded its effectiveness as comparable with that of diethazine. The doses employed in parkinsonism (200-400mg/day) exceeded those required for its general application as an antihistamine (up to 75mg in severe cases). With the emergence of diphenhydramine as an effective antihistaminergic antiparkinsonian agent, however, promethazine was relegated to a relatively minor role in the therapy of parkinsonism.

Related to the phenothiazines was the thioxanthene derivative methixene HCl (‘Tremaril’; Wander, Bern), which became commercially available in 1960, and was unusual in that it was more effective in the relief of parkinsonian tremor than of rigidity. Restlessness and depression were also ameliorated, and it also reduced the tremor of a number of other extrapyramidal and cerebellar hyperkinesias. The side chain of methixene was similar to that of the antipsychotic thioridazine HCl (‘Melleril’; Sandoz); this agent was also employed in the management of parkinsonian tremor, having proved to be only moderately active as a neuroleptic. Methixene resembled atropine in its pharmacological activity, but was more active centrally than the belladonna alkaloid and also has antihistaminergic and direct spasmyloytic properties. Vas and colleagues (General Infirmary Leeds) found in a double-blind study that intravenous injection of 10mg methixene effected the abolition or significant reduction of tremor in thirteen parkinsonian patients; a later trial indicated, however, that this effect could not be achieved with oral methixene. Higher doses of the drug were subsequently recommended when administered orally; commencing with 3-6×2.5mg/day, the dose was gradually raised according to the patient’s requirements, with the final dose of 60mg/day not unusual. Most remarkable for many clinicians was the beneficial effect of methixene for arteriosclerotic tremor, which had hitherto been regarded as largely untreatable. Side effects were regarded as negligible, and the agent was still widely employed in Germany after the introduction of L-DOPA.

In the 1960s, further thioxanthene derivatives were introduced, including chlorprothixene (‘Taractan’, Hoffmann-La Roche, Grenzach; ‘Truxal’, Tropon-Werke,
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Methixene ('Tremaril')

Thioridazine ('Mellaril')

Chlorprothixene ('Taractan')

Prothipendyl ('Dominal forte')

Figure 7-4: Thioxanthene derivatives which have been employed in the therapy of parkinsonism.

Köln-Mülheim).\(^98\) Another neuroleptic phenothiazine reported to benefit tremor in parkinsonism was prothipendyl ('Dominal forte', Homburg).\(^99\) Both neuroleptics are employed today as sedatives in patients for whom benzodiazepines are unsuitable, but were largely rendered superfluous in the treatment of parkinsonism by the arrival of L-DOPA shortly after their release; prothipendyl is, however, employed to treat psychiatric conditions in patients receiving L-DOPA.

The employment of phenothiazine derivatives in the therapy of parkinsonism, however, was regarded as problematic by many workers. This was because it had become well recognized during the second half of the 1950s that many members of this class, particularly those with longer chains between the two nitrogen atoms, were found to induce parkinsonian symptoms in certain patients (figure 7-5). This was particularly a difficulty in the 1950s when chlorpromazine was frequently used to sedate psychiatric patients; phenothiazines were also used in patients suffering from a range of other disorders, including chronic pain, nausea and emotional distress. It was no consolation to find that an effective alternative introduced in the mid-1950s, reserpine, was equally capable of eliciting a parkinsonoid syndrome. In most cases, the syndrome resolved itself after reduction of the dose or total removal of the agent in question; otherwise, treatment with certain synthetic antiparkinsonian agents, including benzhexol, benztropine or diphenhydramine, was generally effective.\(^100\)

\(^98\) 3-(2-Chloro-9H-thioxanthen-9-ylidene)-N, N-dimethyl-1-propanamine. British and U.S. patents to Merck: 1960. It was reported in Selecta in 1964 that a clinician had rejected chlorprothixene as a neuroleptic for his patients because it did not induce parkinsonian symptoms; Steinbrecher, 1964.


\(^100\) See Ayd, 1961; McGeer et al., 1961.
In many cases, neuroleptic-induced parkinsonian syndromes could not be distinguished from the natural disorder: akinesia and rigidity were especially prominent, but problems of gait, mask face and excessive salivation were also seen. It was later established that despite the similar appearance of these drug-induced syndromes to idiopathic or post-encephalitic parkinsonian states, they were only indirectly related to the underlying pathology of naturally occurring parkinsonism. Neuroleptic-induced parkinsonism will be discussed in greater detail in chapter X, as it would play a major role in the development of non-cholinergic therapy of parkinsonism. It suffices here to not that the use of L-DOPA in such cases was not to be recommended, as there existed the risk of exacerbating the psychosis for which the patient was receiving neuroleptics. In any case, the effect of L-DOPA in such patients is often minimal, as the phenothiazines are potent dopamine receptor blockers.101

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101 Degkwitz et al., 1960; McGeer et al., 1961.
Benzhexol HCl (‘Artane’) and congeners

Critchley noted in 1958 that physicians differed in their opinions on the relative efficacy of the various antiparkinsonian agents which had become available, but that “one preparation stands out as the drug of choice in the experience of most practitioners”: benzhexol (USA: trihexyphenidyl; ‘Artane’; Lederle, New York). It would indeed become the most used antiparkinsonian agent of any type during the 1950s and is still employed today as an adjunct to L-DOPA therapy. It was one of a series of more than one hundred piperidine compounds investigated by Denton and co-workers at Lederle in the 1940s as potential spasmolytics; structurally, it is distantly related to the alkaloid coniine. Cunningham and associates (also at Lederle) established by 1949 that the compound possessed significant anticholinergic activity (about half as potent as atropine) and was potently spasmolytic; it was also nicotinolytic and, to a lesser degree, muscle relaxing (table 7-2). Its other attractive features included the absence of toxic effects on cardiopulmonary parameters. It was released by Lederle for clinical trials in Parkinson’s disease during 1947. Kendall Corbin (Department of Neurology and Psychiatry, Mayo Clinic) and Lewis J. Doshay and Kate Constable (Department of Neurology, Columbia University and the Neurological Institute, New York) published the first clinical results almost simultaneously in the Journal of the American Medical Association in mid-1949.

Both groups reported extremely positive results in interesting papers. Corbin commenced with a general discussion of what the physician could achieve for the parkinsonian patient, and emphasized the utility of physical and psychotherapy, not only as means for maintenance of the patient’s morale, but also as effective therapy for a disorder which, in any case, was unlikely ever to be cured. As the etiology of the

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Table 7-2: Comparison of the pharmacological properties of adiphenine (Trasentin), atropine sulphate and benzhexol (compound 275C) as reported by Cunningham et al., 1949. The drugs were administered intravenously to dogs and intraperitoneally to cats; doses were 0.5mg.kg⁻¹ for testing salivation and cardio-vagal inhibition, and 2.0mg.kg⁻¹ for mydriasis. The response to atropine was arbitrarily set at 100.
disease remained unknown, the physician should direct his attention to treating those symptoms which are most distressing for the patient and which are indeed relatively responsive to therapy; Corbin defined these as being muscular rigidity and cramp, tremor, the feelings of weakness and fatigue, and the general inability to handle the normal tasks of daily living. By managing these specific problems, the morale of the patient is fortified, and this “probably postpones the time when these patients become hopelessly crippled and bedridden.” The outlook for parkinsonian patients in 1949 was clearly less than rosy. He then discussed the difficulties of evaluating new parkinsonian therapies, and concluded that anything which improved a patient’s ability to cope with daily life had to be accepted as “improvement”. Corbin therefore explicitly rejected the necessity for objective measures of drug effects:

The type of evidence which has seemed to me to be of greatest value is that presented by the intelligent and cooperative patient who has had parkinsonism for many years and who has tried all of the standard remedies. If this patient experiments with trihexyphenidyl . . ., diphenhydramine hydrochloride . . ., amphetamine . . ., mixed atropine alkaloids . . ., and other remedies, and finally, after a year’s trial, tells me that trihexyphenidyl gives him equal or greater relief with fewer disagreeable side effects than does any of the other preparations, I accept this as evidence favoring this compound for this particular patient.

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105 Corbin, 1949a.
106 Ibid.
He admitted that in such cases he himself rarely noted any indications of improvement, or, if improvement was evident, it lasted only a few weeks, as was often the case with new spasmyotics used in the treatment of parkinsonism. At the time of his paper, Corbin had treated seventeen cases of postencephalitic parkinsonism, sixty-nine of “idiopathic parkinsonism”, and eighteen other disorder movement cases with benzhexol for periods of one to more than twelve months (more than half for greater than six months); most had previously received belladonna alkaloids. 77% of the idiopathic and 71% of the postencephalitic parkinsonian patients felt that their condition had improved; most spoke of reduced rigidity, while 50% also reported reduced tremor. The usual anticholinergic drug side effects were experienced by around 40% of the group, but could be controlled by cautiously adjusting the dosage. In general, Corbin judged benzhexol to be superior to belladonna preparations with respect to both its antiparkinsonian benefit and its reduced toxicity; the dose required for subjective improvement did not elicit marked side effects, in contrast to his experience with belladonna alkaloids.107

‘Artane’, however, is generally associated with the name of Lewis J. Doshay, who investigated and promoted it extensively throughout the 1950s. Doshay was born in Poland at the end of the last century, and came to America as a child. After receiving his medical degree from the University of Maryland in 1922, he specialized in neurology and neuropsychiatry. He commenced his association with the College of Physicians and Surgeons at Columbia University (New York) in 1936; at the Neurological Institute of the Columbia-Presbyterian Medical Center, he also directed from this time research into the causes and symptoms of parkinsonism and into methods of assessing response to therapy. Doshay practised as a neurologist both at the Columbia-Presbyterian and his Park Avenue practice; he was also chairman of the board of the National Parkinson Foundation. Doshay has already been mentioned in the previous chapter concerning his early papers on antiparkinsonian therapy; he research and publishing in this area continued until his death following a heart attack in late 1965 at the age of 68. Apart from his many papers, his guides for physicians and patients (Parkinson’s disease: Its meaning and management and The Parkinson patient at home (with Robert Schwab) continue to be recommended by American Parkinson’s disease support groups today.108

Doshay and Constable, who had decided to try benzhexol after discussions with Cunningham’s group regarding their animal experiments, also commenced their report philosophically, including a brief account of the history of parkinsonism and its treatment up to that point. It was stated in passing that the majority of cases prior to the encephalitis lethargica epidemics were “arteriosclerotic parkinsonian patients”. This was a view which would be debated during the coming decade, and put Doshay decidedly at odds with the viewpoint of Macdonald Critchley (amongst others). Curiously, Doshay and Constable distinguished between arteriosclerotic and idiopathic parkinsonism when discussing the subjects of the investigation described in the paper, which included forty-seven postencephalitic, thirty-three idiopathic and thirty-seven arteriosclerotic patients. By the time the paper was published, the authors had treated a further 150 patients, but did not include them in the report. Similar doses were

107 Ibid.
employed to those in the Corbin study (average dose: 6-10mg/day; up to 50mg/day tolerated).

Doshay and Constable also chose on methodological grounds to classify patient responses as “improved” or “not improved”, although the means for allocating the patients to the two categories was not explicitly defined. The condition of none of the patients deteriorated during the course of the study; Doshay, however, had allowed the concurrent use of alternative antiparkinsonian agents and other medications where required, especially at the commencement of benzhexol therapy. The percentage of patients who improved was remarkably similar to that reported by Corbin: 76.1% showed improvement, particularly of rigidity. Idiopathic and arteriosclerotic patients responded better than postencephalitic cases, who required larger doses to receive any benefit. The authors presented charts demonstrating that the percentage of patients showing improvement was slightly better than patients treated with atropine and much better than those receiving caramiphen, but with a much lower incidence of disturbing side effects than with either of the alternatives (figure 7-7). The motor effects were accompanied by a marked “cerebral stimulation” which effectively reduced the depression and inertia common to these patients. Doshay and Constable concluded that benzhexol recommended itself as the drug of choice in arteriosclerotic and idiopathic parkinsonism, and should be further examined in postencephalitic parkinsonism.109

A number of other clinics soon reported equally encouraging results, with success rates of between 66 and 80%.110 Garai reported that by combining trihexyphenidyl with amphetamine, that parkinsonian patients who had been confined to bed for years could again move independently:

Most of the severe postencephalitic cases treated with artane and amphetamine sulphate were in a distressing state of almost total immobility. . . . Since the introduction of artane and amphetamine sulphate treatment there has been a striking

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110 Canelis et al., 1949; Schwab and Tillmann, 1949; Effron and Denker, 1950; Ellenbogen, 1950; Goebel, 1951; Harris and Torrens, 1950; Salzer, 1950; Garai, 1951a; Wright, 1952. See further references in Mercks Jahresbericht for 1951, p.143.
change in the atmosphere of the ward. Most patients can now feed themselves, and many can dress and attend to their own toilet.\footnote{Garai, 1951a.}

Phillips and colleagues (Highlands Hospital, London) were impressed by the effect on “the emotional hebetude so characteristic of the disease”, by which the authors designated parkinsonian akinesia, and commented that the only the only obstacle to benzhexol becoming the drug of choice in post-encephalitic parkinsonism was its “prohibitive cost”.\footnote{Phillips et al., 1950.}

Doshay’s clinic, however, pursued the benzhexol therapy with especial vigor. By 1954, he was able to publish a five year follow-up study which included his experience with 411 cases of parkinsonism. The conclusion was clear:

Judged solely by the initial response of the patients, trihexyphenidyl indisputably qualifies as an excellent treatment for paralysis agitans. The result of our study indicate that is efficacy continues undiminished over extended periods. . . . No other agent now available produces equal results in the treatment of paralysis agitans.\footnote{Doshay et al., 1954.}

Amongst the remarkable findings were that facts that 73% of parkinsonian patients of all types showed improvement, and that 63% had continued treatment for between two and five years.\footnote{Doshay et al., 1954.} Parkinsonian patients were notorious for seeking to change their medication at short intervals:

the length of the illness leads patients to shift and experiment with various drugs, until they find those that provide the greatest comfort and release from symptoms. Thus it follows that drugs which possess some positive value to the patients never fail to find their true level of use in accordance with their merits.\footnote{Doshay et al., 1952.}

Without producing serious side effects, the authors claimed that the “acclaim that has been given this drug since its original use [was] not accidental”, but attributable to its effectiveness against rigidity, tremor, akinesia, oculogyria, lethargy, sialorrhea and depression – in short, against every major symptom of parkinsonism.\footnote{Doshay et al., 1954.} Rigidity was generally controlled to a greater degree than tremor; benzhexol also exerted positive effects on the psyche of the patient. On the basis of objective tests of mobility, tremor and strength of grip, a Canadian group concluded in 1963 that there was “no doubt that the average patient with typical signs of Parkinson’s disease is helped by Artane treatment.”\footnote{Burns et al., 1964.} Nevertheless, even Doshay did not apply the drug alone in most cases; the leading adjuncts were ‘Bellabulgara’ (35%), diphenhydramine (25%), benztropine
(24%) and scopolamine (23%). Most other workers applied benzhexol in combination with an antihistaminergic agent.

The acceptance of benzhexol, however, was not unanimous, with the occasional dissent being recorded. The New York physicians Berkowitz and Alvermann found no significant differences between the effects of stramonium and benzhexol; Kaplan and associates reported in 1954 that benzhexol, caramiphen and scopolamine were all clearly superior to placebo in eliciting subjective improvement, but their effects could not be distinguished from one another, nor from that of placebo when objective measures were employed. Gillhespy reported that “benzhexol has been found to be one of the least effective of the drugs used in attempting to control the symptoms of all forms of Parkinsonism”; less than 20% of the 240 patients attending his clinic received the drug, and then only in combination with “more effective” drugs. He recommended orphenadrine and ethopropazine as the drugs of choice in parkinsonism. Garai and Wright were concerned about the side effects of benzhexol, particularly hallucinations and other psychiatric phenomena; Zerbini and Schulinger were not convinced that its effects, particularly on tremor, were superior to those of atropine. Vollmer regarded benzhexol as inferior to ‘Rabellon’, the prevailing form of the Bulgarian treatment in the United States, and attributed the effects of the synthetic agent to a placebo effect.

Nevertheless, benzhexol became the most successful of the synthetic anticholinergic drugs for parkinsonism. In reviewing the recent history of parkinsonian therapy in 1956, two Swiss workers noted that therapy had been dominated until 1946 by the Bulgarian treatment in all its variations; from this year onwards, however, new preparations had entered the market in rapid succession, only to disappear with equal celerity. That benzhexol should still be highly regarded seven years after its introduction was “significant, given the constant flood of new preparations.” This was not only attributable to its direct benefits, but also to the absence of significant side effects, at least in comparison with those which parkinsonian patients had previously been forced to endure. Normal precautions taken with atropine had to be observed and the side effects associated with benzhexol were similar to those of other anticholinergic drugs, but were milder in nature and easily reversed by withdrawal of the drug. The most disturbing were mental changes, including confusion, agitation and hallucinations but ranging as to psychotic states resembling those of atropine intoxication. Porteous and Ross reported such symptoms in ten of fifty-two treated patients, and Doshay noted that 19-30% of patients treated with anticholinergic drugs experienced mental changes including confusion, depression and delusions. The general incidence of serious mental problems, however, was estimated as being less than 2%, although the need

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118 Doshay et al., 1954.
120 Berkowitz and Alvermann, 1952.
121 Kaplan et al., 1954.
122 Gillhespy, 1956. He made the same recommendation in 1958.
123 Garai, 1951a; Wright, 1952. It should be noted, however, that Garai tended to use higher benzhexol doses than other authors (up to 100mg/day) with no increase in symptomatic benefit.
125 Vollmer, 1951.
126 Harder and Prelicz, 1956.
127 Porteous and Ross, 1956.
128 In Brock et al., 1956.
129 For example, Onuaguluchi, 1964, p.120.
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for physician and relatives to be alert to their presentation was often emphasized.\footnote{130} It was reported in 1972 that three patients with closed angle glaucoma suffered partial blindness after receiving 15mg benzhexol per day for up to two years.\footnote{131} This had not always been recognized; in 1956, Constable explicitly stated that glaucoma, whether pre-existing or developed during therapy, was no contraindication for the full use of benzhexol.\footnote{132} It was recognized much later that even low doses of benzhexol (2mg/day) (or other antimuscarinic drugs) may have a detrimental effect on memory in older persons; this effect, however, may be reversible.\footnote{133}

Benzhexol was available throughout the 1950s in the form of 2mg and 5mg scored tablets, as well as an elixir (2mg/5mL). The initial dose was usually 3×1-2mg/day, and then gradually raised until the optimal level was determined; this could lie in the range of 50mg/day for severe post-encephalitic parkinsonian patients. In 1957, Lederle produced (at the suggestion of Hartmann-von Monakow)\footnote{134} 6mg (later: 10mg) slow release capsules of the drug (‘Artane Sequels’ or ‘Sustets’). It originally consisted of a capsule containing benzhexol pellets enclosed in different layers of “enteric material”. This preparation allowed the patient to receive his entire day’s medication in a single dose taken in the morning; the first third of the drug was released immediately after the capsule had been swallowed, the other two portions at approximately four-hourly intervals (later: 1½-2-hourly). Schwab and Doshay found this form to be a practicable choice in parkinsonism, but suggested that it also be available in a 5mg form, as older patients did not tolerate the higher dose; this suggestion was adopted by the firm.\footnote{135} Despite the convenience of the approach, other workers regarded the occasionally unpredictable response of patients to the slow release format to reduce its attractiveness.\footnote{136}

Interestingly, benzhexol was the subject of one of the first double-blind, placebo-controlled examinations of an anticholinergic antiparkinsonian drug. In 1964, Brumlik and colleagues (Neurology and Psychiatry, Northwestern University Medical School, Chicago) found no evidence in a study involving thirty-two patients that the agent was superior to placebo; parameters examined included tremor (assessed by variable reluctance accelerometer), muscle tone (strain gauge), poverty of movement, speech, respiration and psychological state.\footnote{137} This study confirmed the desultory attitude of Boshes towards the pharmacological therapy of parkinsonism (see below). Koller, on the other hand, reported in 1986 that in a small double-blind crossover study (nine patients), accelerometer spectral analysis indicated that 8mg benzhexol per day produced an almost 60% reduction in tremor, making it superior in this respect to amantadine and about equally effective as L-DOPA/carbidopa.\footnote{138} This was particularly interesting, as the influence of benzhexol on parkinsonian tremor had been a controversial point in the 1950s.

\footnotemark[132] In Brock et al., 1956.
\footnotemark[133] Sadeh et al., 1982.
\footnotemark[137] Brumlik et al., 1964.
Although it was true that even at its zenith "Artane [had] by no means emerged from this competition as the victor", benzhexol was nevertheless the most popular antiparkinsonian agent in all forms of the disorder, including neuroleptic-induced parkinsonism, until the L-DOPA revolution. In the wake of this success, a number of other piperidine derivatives were examined by various investigators for their effect in Parkinson's disease; of these, the following found reasonable acceptance in the clinic:

- **cycrimine** (= compound 08958; 'Pagitane'; Lilly, Indianapolis): similar pharmacological profile to benzhexol (compare structures in figure 7-6), with benefits for rigidity, oculogyria and mild tremor; perhaps a little more intensive, especially in postencephalitic parkinsonism. Its central stimulating effects were also useful in the management of akinesia, lethargy and tiredness, but were not as well tolerated in older patients; the maximal dose in younger patients of 10-50mg/day, in older cases (especially those with arteriosclerotic parkinsonism) considerably less. Doshay found it to be of advantage in patients whose response to benzhexol had diminished. The side effects, apart from those also seen with benzhexol, included anorexia and gastric discomfort; confusion and hallucinations were occasionally reported.

- **biperiden(e)** ('Akineton'; Knoll, Ludwigshafen): more potently anticholinergic than atropine, also strongly antinicotinic. It possessed little intrinsic antihistaminergic activity, and was therefore often combined with an antihistamine (such as bamipine). The dose was gradually increased from 3×1mg/day to a daily dose of maximally 20mg. There was a lower tendency than benzhexol to elicit side effects; Haas and Klavehn predicted on the basis of its structure that its effect on secretion and accommodation should be weak. W. and G. Brandt (Queen Elena Clinic, Kassel) reported their positive experiences in 350 patients in 1955; rigidity, which they saw as the major symptom of parkinsonism, was markedly reduced, as was akinesia, but tremor was unaffected, so that they recommended a combination of biperiden with bamipine and belladonna alkaloids. Biperiden had been used in Europe for about five years before it began to attract widespread interest in England. Biperiden remained a popular antiparkinsonian agent even after the introduction of L-DOPA.

- **triperiden** ('Norakin'; Fahlberg-List Salutas/Hexal, Barleben-Magdeburg): predominantly centrally active anticholinergic employed in the German Democratic Republic and the Soviet Union. Like benzhexol, ethylbenzhydramine and biperiden, it

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139 Behrend, 1954.
141 Magee and DeJong, 1953; Mulder, 1953; Sigwald and Payot, 1955.
142 Zier and Doshay, 1954.
143 Dow and Smith, 1954; Pierik, 1954. Cycrimine is no longer listed amongst the antimuscarinic agents in the Martindale drug manual.
144 1-Phenyl-1-bicycloheptenyl-3-piperidino-1-propanol. U.S. patent to Knoll: 1957 (German application and priority: 1953).
145 N-Phenyl-N-benzyl-4-amino-1-methylpiperidine; 'Soventol', Knoll, Ludwigshafen. The 'Akineton'-'Soventol' combination was especially popular in Germany; Hartmann-von Monakow, 1960a, p.109.
146 Haas and Klavehn, 1955.
147 Brandt and Brandt, 1955; 1956.
150 Kline et al., 1974; Magnus, 1980.
151 β-Phenyl-β-tricyclo(2.2.1.0²⁶)hept-3-yl-1-piperidinepropanol hydrochloride.
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Inhibits replication of ortho- and paramyxoviruses in vitro, and, like amantadine, it inhibited influenza A virus replication. Note that the currently available product ‘Norakin N’ (Hexal) is biperiden.

- pridinol (‘ParKS 12’; Hommel, Zürich) and pridinol mesylate (HH 212, ‘Lyseen’; Hommel, Hamburg): reported to elicit less side effects than benzhexol, but otherwise similar to its prototype. Harder and Prelicz found it to be also effective against chlorpromazine- and reserpine-induced parkinsonism.

Related to the piperidine-class antiparkinsonian agents was another compound introduced at the end of the 1950s, procyclidine or tricyclamol (‘Kemadrin’; Burroughs Wellcome, London). It exhibited an almost identical pharmacological profile to benzhexol (from which it differed only in the substitution of a pyrrolidine ring for the terminal piperidine moiety), but was also compared with ethopropazine. The optimal daily dose usually lay in the range 20-30mg, although doses as high as 60mg/day were tolerated. Increased sense of well-being was reported by most patients, and rigidity was more effectively addressed than tremor, while oculogyric crises and sialorrhrea were also responsive. Schwab’s group found it about as effective as benzhexol and cycrimine; Doshay valued its role in the management of arteriosclerotic parkinsonism, which was generally resistant to benzhexol; Strang reported a significant improvement of akinesia in eight of nineteen patients (from a total group of fifty parkinsonian patients) presenting this symptom. A double-blind trial in 1970 using bulb ergograph indicated a mean 27% improvement was achieved. Procyclidine has also been used in epilepsy.

These agents were all structurally similar to trihexyphenidyl and consequently similar in action, with only the minor variations noted above; the availability of equipotent alternatives, however, was welcomed by clinicians who recognized the tendency of parkinsonian patients to fail to respond to any given medication after a period of time which ranged from weeks to years. Although not explicable in biochemical terms, the same phenomenon would later be noted with the combination of L-DOPA with different decarboxylase inhibitors.

Benztropine mesylate (‘Cogentin’) and congeners

Developed directly as an atropine analog was the agent benztropine methane sulfonate (‘Cogentin’; Merck, Sharp & Dohme, Philadelphia). It was the most potent of the synthetic anticholinergics; its structure essentially combined the tropine moiety of

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152 Presber et al., 1984; Schroeder et al., 1985.
153 1,1-Diphenyl-3-piperidino-1-propanol. British patent to Wellcome Foundation: 1949; German application by Hoechst: 1941.
154 1,1-Diphenyl-3-piperidino-1-propanol methane sulphonate.
157 Schwab and Chafetz, 1955; Zier and Doshay, 1957; Strang, 1965. For other reports, see Hartmann-von Monakow, 1960a, p.149.
158 Timberlake, 1970.
159 Millichap et al., 1968.
160 Tropine benzhydryl ether, 3-(diphenylmethoxy)-8-methyl-8azabicyclo[3.2.1]octane methanesulfonate; also written benztropine and benzatropine. U.S. patent to Merck: 1952 (priority: 1949). Also marketed as ‘Cobrentin’ (Argentina) and ‘MK-02’ (Merck, USA).
VII. The 1950s: The synthetic anticholinergic and antihistaminergic preparations

Atropine and the benzhydryl component of diphenhydramine (figure 7-8). As a result, it was also associated with the same side effects as atropine. Its parasympatholytic effect was about half that of atropine, and its antihistaminergic, antinicotinic and muscle-relaxing capacities about equal to those of its prototype. Its apparent link with gastric ulcers almost led to its being abandoned in the first months of its clinical trials, but Doshay persuaded Merck that its antiparkinsonian effect was sufficient to justify its further study. He had examined the drug for a period of five years before Merck released it commercially.\textsuperscript{161} Doshay found it to be highly safe and effective against rigidity, spasm, cramps, sialorrhea and severe tremor in thirteen of twenty patients examined; in a five year follow-up in 300 patients, it was found to be beneficial in 52\% of subjects. As it was particularly effective against these symptoms in postencephalitic patients, he recommended its use especially in this patient group; as it was devoid of cerebral effects, he recommended administration together with benzhexol. He also found the side effects to be less disturbing than for any other agent apart from benzhexol.\textsuperscript{162} Other workers found that its lack of central stimulatory effects meant that it was well tolerated by elderly patients, many of whom preferred its sedative effects to

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{images/figure7-8.png}
\caption{Synthetic tropane derivatives employed in the therapy of parkinsonism.}
\end{figure}

the action of benzhexol.\textsuperscript{163} Critchley regarded benztropine as the second best synthetic antiparkinsonian agent in 1958, despite the fact that it was less well-known than its chief competitor, benzhexol; according to his experience, it controlled tremor better than any other preparation.\textsuperscript{164} Benztropine was usually employed together with another

\begin{itemize}
\item \textsuperscript{161} Doshay, 1965b.
\item \textsuperscript{162} Doshay, 1956.
\item \textsuperscript{163} Extra Pharmacopoeia, 1972, p.232.
\item \textsuperscript{164} Critchley, 1958.
\end{itemize}
antiparkinsonian agent; Hartmann-von Monakow suggested that it could replace belladonna alkaloids as adjunct to the synthetic therapy of parkinsonism.¹⁶⁵

Benztropine was, indeed, unusual amongst the synthetic antiparkinsonian drugs in that it was specifically indicated in cases where tremor, rather than rigidity, predominated. It was also useful in otherwise drug-resistant cases, especially arteriosclerotic parkinsonian patients. A small initial dose (~1mg) could be cautiously increased until the side-effects (dryness of the mouth, nausea, rashes) become irritating; cumulative effects determined that this maximum dose did not exceed 6mg daily. Its slow-acting and cumulative effects, however, also represented an advantage, as a single morning dose could suffice for the entire day. The agent could alternatively be administered in the evening; this had the additional advantage of reducing nocturnal restlessness and stiffness, allowing better rest and improved performance on the following day.¹⁶⁶ More recently, benztropine was reported to protect mice against the neurotoxic effects of MPTP;¹⁶⁷ it was also found to be an appropriate adjunct to L-DOPA therapy.¹⁶⁸

Two compounds structurally related to benztropine also attained some recognition in the treatment of parkinsonism:

• *tropacine* or *tropazine*¹⁶⁹ was used primarily in the Soviet Union in the same capacity as benztropine; it was reported to possess cholinolytic, nicotinolytic, spasmyloytic and local anesthetic properties, but the peripheral side effects of the agent were less intense than those of atropine.¹⁷⁰ Despite originally being a Swiss product, the agent never achieved prominence in the West.

• *ethylenbenztropine* or *tropethydrylin* (UK 738; ‘Ponalid’; Sandoz, Basel)¹⁷¹: a mild atropine-like anticholinergic with antihistamine properties. It was reported in 1961 to be particularly effective against rigor in any type of parkinsonism; some effect on tremor and akinesia, although Onuaguluchi regarded it as inferior to orphenadrine.¹⁷²

**Antihistaminergic agents**

Apart from the anticholinergic agents, the other drug group which played a major role in the therapy of parkinsonism until the 1960s was that of the antihistamines. Drugs which blocked the effects of histamine and thus protected against allergic and anaphylactic reactions had been sought since the discovery of histaminase (later: diamine oxidase) in 1930.¹⁷³ Inhibition of the enzyme proved to be an unsuccessful

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¹⁶⁵ Hartmann-von Monakow, 1960a, p.105.
¹⁶⁹ Diphenylacetic acid 3α-tropinyl ester hydrochloride. Swiss patent to Ciba: 1939.
¹⁷⁰ Mashkovskij, *Farmakolija i Toxikolija* 16: 3-10 (1953); see *Chemical Abstracts* 48: 5373f (1954). See also Fries et al., 1960.
¹⁷¹ N-Ethylnortropine benzhydryl ether. British patents to Sandoz (1958) and Boehringer Ingelheim (1959).
¹⁷³ See Zeller, 1938.
strategy, and attention turned to histamine analogs which competed with the natural amine at its site of action. A systematic search in France for such substances, particularly in Halpern’s laboratory at Rhône-Poulenc, resulted in the identification of a number of candidates; phenbenzamine (‘Antergan’; Rhône-Poulenc) was the least toxic and found some clinical application, and served as prototype for a series of antihistamines containing an ethylenediamine group synthesized by a number of groups between 1943 and 1947.174 A major breakthrough was achieved in 1945 with the synthesis at the laboratories of Parke, Davis & Co. (Detroit) of diphenhydramine (‘Benadryl’),175 the first member of a new class of antihistamines, the benzhydryl group. Loew, Kaiser and associates reported in a series of papers that a number of benzhydryl ethers (figure 7-9) protected guinea-pigs against histamine-induced anaphylactic shock with an effectiveness almost three times as great as the alkaloid papaverine.176 In the years immediately following the War, a number of antihistaminergic drugs were released commercially, amongst the most popular were initially pyrilamine or mepyramine (‘Anthisan’; May & Baker), methapyriline (‘Thenylene’; Abbott; ‘Histadyl’, Lilly) and antazoline (‘Antistin’; Ciba).177

The range of effects associated with antihistaminergic drugs extended far beyond their amelioration of allergic reactions, and included inhibition of the contraction of smooth muscle and of vascular dilatation, features which recommended them for trials in parkinsonism and other disorders associated with muscular spasm. This application was, then, purely empirical, and did not represent any form of theoretical re-orientation with respect to the physiological basis of parkinsonism; indeed, their adoption might be compared with the readiness of doctors in the 19th century to try any new antispasmodic agent in their parkinsonian patients. Partly as a result of their success in the treatment of parkinsonism, it was assumed for many years that antihistaminergic agents were by nature also anticholinergic; it was, in fact, often not clear whether the ‘antihistaminergic’ actions of an agent were at least in part consequences of its ‘anticholinergic’ activity.178 It is now recognized that the early antihistamines are H1 histamine receptor antagonists, many of which also possess antimuscarinic activity.179

176 Loew et al., 1945; 1946a, b, c. Issekutz (1971; p.243) notes that the synthesis was achieved by Rieveschl, but I have not been able to obtain a copy of the paper to which he referred. Papaverine is the most important isoquinoline alkaloid of the opium poppy (Papaver somniferum); its actions of which are quite distinct from those of morphine. It relaxed smooth muscle without affecting normal contractions, and had thus been tried in the treatment of spastic colic, but without success. Until 1930, it was the most effective known blocker of the actions of histamine. See Dewick, 1997, pp.307-309.
177 See detailed listing in Extra Pharmacopoeia, 1952, pp.715-730 (under ‘Mepyramine maleas (and other ANTIHISTAMINE SUBSTANCES)’.
178 See review of pharmacology of antihistaminergic agents in Bovet, 1950. Antihistamines also exhibited less consistent anti-adrenaline and anti-serotonin effects.
179 Hardman et al., 1996, pp.586-600.
Diphenhydramine was the first drug specifically classified as a antihistamine to be employed in parkinsonism, and undoubtedly the most popular in the long term. As discussed above, ethopropazine, which also has antihistaminic properties (as does promethazine), was employed in parkinsonian patients as early as the mid-1940s; its particularly strong anticholinergic effect, however, was the immediate reason for its employment. Diphenhydramine had been quickly recognized to be of value in a range of respiratory and skin conditions with allergic components, despite the fact that its precise mechanism of action was unknown. But Loew’s group (and a number of others) had also noted early that it exhibited certain atropine-like characteristics; for example, its mydriatic effects were recognized from the beginning. Flexner is reported by Hartmann-von Monakow to have first suggested the use of antihistamines in the therapy of parkinsonism on precisely this basis; unfortunately, he did not give any further information as to where Flexner made this suggestion. Bovet and Longo were the first to demonstrate that diphenhydramine also possesses antinicotinic activity in the central nervous system, thus legitimizing post hoc its application in parkinsonism.

Joseph Budnitz (Albany Medical College, Albany and House of Mercy and St Luke’s Hospitals, New York) first used diphenhydramine on a “purely empirical basis” in a single patient in September 1946. He was so impressed by the results achieved that he decided to determine whether this was an especially suggestive parkinsonian patient, or whether he had discovered a real effect. He therefore treated eight “arteriosclerotic” parkinsonian patients with the drug; four of them continued to also use belladonna-type drugs. Budnitz noted a remarkable increase in the ease of movement of the patients, reduced sweating and decreased restlessness and anxiety after a few days of treatment; the effect was maintained by a daily oral dose of between 200 and 300mg for periods of up to fourteen months. The drug appeared to act synergistically with drugs of the atropine series, and the author suggested that such a combination therapy might be useful in the treatment of parkinsonism. There had been some reports that diphenhydramine exerted atropine-like actions; further, it appeared to cause “congestion of the choroid plexus”, leading Budnitz to suggest that it might enhance perfusion of the striatum.

In the course of examining the effects of diphenhydramine in normal persons and in a range of (mostly allergic) disorders, McGavack, Elias and Boyd (New York Medical College and Fifth Avenue Hospital) reported in 1947 similarly gratifying results in three of four arteriosclerotic parkinsonian patients treated for five to fifteen months, at least as assessed by the patients themselves; two also exhibited reduced tremor and improved work performance as assessed by the investigators. The stated rationale for treating these and a number of other neurodegenerative disorders involving regions around the thalamus and basal ganglia (multiple sclerosis, progressive muscular dystrophy, spinal muscular atrophy, inactive tabes dorsalis) was the observation that the drug often induced drowsiness, vertigo and lack of coordination. None of the other neurodegenerative disorders responded to diphenhydramine. The authors noted the atropine-like effect of diphenhydramine on the eye when applied topically; further, the altered sensorium (drowsiness, lightheadedness, blurred vision, slight lack of

181 Code, 1945; Harris et al., 1946.
182 Hartmann-von Monakow, 1960a, p.102.
183 Bovet and Longo, 1951.
184 Budnitz, 1948.
coordination in movement and speech) which sometimes accompanied its use reminded
them of the effects of hyoscine.\textsuperscript{185} Two English physicians reported at about the same
time that they had also been inspired by the response of a test patient to undertake
further investigations, and had thus far treated forty patients with success.\textsuperscript{186}

Other clinics reported similar successes,\textsuperscript{187} and diphenhydramine quickly became a
standard agent in the treatment of parkinsonism. By itself, the normal dose (3-4×50mg
capsules/day; maximum: 500mg/24hr) was usually of little benefit, but combined with
belladonna drugs or scopolamine was found to improve the condition of at least 50% of
patients to a "surprising degree".\textsuperscript{188} The cardiologist Edwards (Washington, St. Louis).
However, found in a comparative study that diphenhydramine was the most effective
single antiparkinsonian agent, its benefits exceeding those of benzhexol alone.\textsuperscript{189}

Diphenhydramine could also be applied intravenously, which could be required in the
case of neuroleptic-induced parkinsonian states;\textsuperscript{190} this relieved tremor and rigor for 3-6
hours. Rigidity and muscular cramp was consistently and often dramatically improved,
sometimes allowing confined patients at least temporary release from their beds.
Tremor was only improved in mild cases, akinesia and oculogyric crises never; in fact,
akinesia was exacerbated in patients where this was the major symptom. The only major
common side effect was mild somnolence which could easily be overcome with 5mg
amphetamine. Recently, however, there have been scattered reports of diphenhydramine
inducing dystonic extrapyramidal reactions.\textsuperscript{191} The mode of action of diphenhydramine
was unknown; it was hypothesized that at least some parkinsonian symptoms were the
result of a "denervation-sensitization phenomenon in the nervous system", others saw
its only effect as sedation, thus reducing the tremor in the same manner as sleep.\textsuperscript{192}

Derivatives of diphenhydramine were also prepared in the search for more effective
agents, including:

- \textit{chlorphenoxamine} ("Phenoxene"; Pittman-Moore, USA)\textsuperscript{193}: the addition of the chlorine
and methyl group reduced the antihistamine effect but increased the anticholinergic
character of the molecule. Side effects were minimal. A double-blind trial in 1961
appeared to indicate that it was of benefit for neither parkinsonian rigidity or tremor,\textsuperscript{194}
but could still be recommended for its mild anti-tremor and euphoriant effects.\textsuperscript{195}

\textsuperscript{185} McGavack \textit{et al.}, 1947. The euphoric properties of diphenhydramine led to sporadic abuse; in
Australia, abuse of Benadryl elixir, freely available for the symptomatic treatment of coughs and
containing 250mg/100mL diphenhydramine, was long recognized as a problem, particularly among
\textsuperscript{186} Ryan and Wood, 1949.
\textsuperscript{187} See: Gates, 1949; Montuschi, 1949; Effron and Denker, 1950; Denker and Effron, 1950; Bercel, 1951.
\textsuperscript{188} Hartmann-von Monakow, 1960a, p.102; see also Effron and Denker, 1950; Moore, 1951. Effron and
Denker found that the percentage of unselected parkinsonian patients who benefited from hyoscine
and diphenhydramine was similar (about 72%); hyoscine achieved, however, marked improvements
in no patients and moderate improvement in less than 10% of patients, compared with figures of 7%
and 35% for diphenhydramine. Administered together, marked improvement was achieved in 5%,
moderate in about 55% and slight improvement in 35% of parkinsonian patients.
\textsuperscript{189} Edwards, 1954.
\textsuperscript{190} Smith and Miller, 1961.
\textsuperscript{191} Santora \textit{et al.}, 1989; Roila \textit{et al.}, 1989.
\textsuperscript{192} Comment by Doshay in Brock \textit{et al.}, 1956.
\textsuperscript{193} \(\beta\)-Dimethylaminoethyl-\((p\text{-chloro-}\alpha\text{-methylbenzhydryl})\)ether. U.S. patent to Asta-Werke: 1957
(German priority: 1952). Also marketed as ‘Systral’ (Asta, Hamburg) and ‘Clorevan’ (Evans).
\textsuperscript{194} Uldall \textit{et al.}, 1961.
\textsuperscript{195} Friend, 1963. See also: Doshay and Constable, 1959.
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Diphenhydramine ('Benadryl')

Chlorphenoxamine ('Phenoxene')

Ethylbenzhydramine = etanautine ('PKM', 'Rigidyl')

Orphenadrine ('Disipal')

Phenindamine ('Thephorin')

Bamipine ('Soventol')

Pyrilamine = mepyramine ('Anthisan')

Clofenetamine ('Keithon')

Figure 7-10: Antihistaminergic agents which have been employed in the therapy of parkinsonism.

- clofenetamine ('Keithon', ASTA-Werke): Steger and Hufschmidt reported a relief of rigidity in forty-one parkinsonian patients, with little benefit for tremor; sleep was also

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196 (2-(p-Chloro-α-methyl-α-phenylbenzyloxy)triethylamine.
VII. The 1950s: The synthetic anticholinergic and antihistaminergic preparations

facilitated. Interestingly, drug-naive post-encephalitic cases responded best, but arteriosclerotic patients also showed improvement. The drug possessed some nicotinolytic capacity in addition to its antihistaminergic and anticholinergic features.197

- ethylbenzhydramine or etanautine (‘PKM’; Montavit, Absam, Austria)198: weakly antihistaminergic; anticholinergic effect equal to that of benzhexol. Minimal side effects with the usual dose (50-300mg/day). ‘Rigidyl’, as the name suggests, was found to be particularly effective in the treatment of rigidity without being of major benefit for tremor.199

An agent which acquired a degree of popularity in the 1960s was orphenadrine or mephenamine (BS 5930, ‘Disipal’; Brocades-Sttheeman, Amsterdam).200 In comparison with diphenhydramine, it was found to be five times weaker as an antihistamine but twice as potent as an anticholinergic.201 The initial dose of 3×50mg/day was gradually raised to as high as 400mg/day; intramuscular administration of up to 120mg in divided doses could also be employed for the rapid control of drug-induced extrapyramidal responses. Rigidity was improved in about two thirds of patients by orphenadrine; tremor, even where minor, was less responsive. Most workers emphasized the euphoric and energizing effects of the drug, to which its benefits for akinnesia and anergia were attributed, as well as its positive effects on oculogyria and blepharospasm; Doshay and Constable recommended it on this basis, as these disturbing symptoms were not helped by most other agents.202 Hartmann-von Monakow saw the mood-elevating effects of orphenadrine as its most valuable, allowing its substitution for amphetamine preparations, associated with addiction and psychic changes in the patient.203 Its atropine-like qualities also rendered it useful in the effective management of sialorrhea and excessive sweating. Its effects, however, tended to decline after a few months, and doubt has been cast on the significance of its stimulant properties.204 Interestingly, it was reported that some of its effects opposed, others synergized with those of reserpine; in animals, orphenadrine did not exert atropine-like excitant effects.205 Because of its lack of serious side effects – dizziness, nausea, urine retention, transient dyskinesia were rare, xerostomia and visual problems somewhat more common, but much less so than with scopolamine – it remained a popular adjunct to antiparkinsonian therapy even after the introduction of L-DOPA.206 It was later discovered that orphenadrine is a non-competitive NMDA receptor antagonist, a property it shares with amantadine,

197 Steger and Hufschmidt, 1958. See also Anonymus, 1957; Finke, 1959.
198 β-Diethylamino-ethyl-benzhydryl ether. U.S. patents to Geigy (1946) and Parke-Davis (1947). Also marketed as ‘Rigidyl’ (Medicinalco, Copenhagen) and ‘Antiparkin’ (in the German Democratic Republic).
199 Demel et al., 1952; Corbin, 1959; Hartmann-von Monakow, 1960a, p.104; further references in Degkwitz, 1963.
200 β-Dimethylamino-ethyl-2-methyl-benzhydryl ether. U.S. patents to Parke-Davis (1951; priority: 1946) and Brocades-Sttheeman (1961; Dutch priority: 1952). Also marketed as ‘Broca-Disipal’ (Denmark) and ‘Mephenamin’ (Boehringer, Mannheim).
201 Bijlsma et al., 1956. Orphenadrine was listed by Martindale’s Extra Pharmacopoeia as an anticholinergic agent (later as an antimuscarinic), not an antihistamine.
203 Hartmann-von Monakow, 1960a, p.104.
204 Strang, 1965b.
205 Valdecasas et al., 1960.
206 Whyte et al., 1971; Bassi et al., 1986. For side effects, see Extra Pharmacopoeia, 1972, pp.244-245.
memantine and budipine; it has been proposed that this antagonism might play a neuroprotective role in antiparkinsonian therapy.\footnote{Kornhuber et al., 1995; Lange et al., 1997.}

A number of other antihistaminergic drugs also found application in the clinic of parkinsonism, the most important being the following:

- **phenindamine** ('Thephorin'; Hoffmann-La Roche, Basel)\footnote{2-Methyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene; as the tartrate. U.S. patent to Hoffmann-La Roche: 1949 (application: 1947).} possessed an energizing effect, which could result in insomnia and even convulsions. An effective muscle relaxant, its benefit for tremor was minimal. Despite possessing only mild anticholinergic properties, it also elicited xerostomia, nausea and gastrointestinal discomfort. It was often administered in combination with benzhexol or procyclidine, a popular method involved the administration of 100-200mg phenindamine and 8-10mg benzhexol in four doses throughout the day.\footnote{Berger, 1949; Denker and Effron, 1950; Effron and Denker, 1950; Cohen and Criep, 1952; Tomarkin, 1952; Höhnke, 1953. Schwab and Prichard (1951) and Ottesen (1951; cited in Hartmann-von Monakow, 1960a, pp.102-103) were not impressed with the effects of phenindamine.}

- **bamipine** ('Soventol'; Knoll, Ludwigshafen)\footnote{N-Phenyl-N-benzyl-4-amino-1-methylpiperidine. U.S. patent to Knoll: 1954 (German priority: 1949).} often combined with biperiden in Europe for the treatment of tremor, this was one of the most popular antihistamines in Germany. Possesses pronounced sedative effects.\footnote{König, 1959; Hartmann-von Monakow, 1960a, p.102.}

- **pyrilamine** or **mepyramine maleate** ('Anthisan'; May and Baker)\footnote{2-[(2-Dimethylaminoethyl)(p-methoxybenzyl)amino]pyridine. U.S. patent to Rhône-Poulenc: 1950 (French priority: 1943).} antihistamine with duration of action longer than that of diphenhydramine but shorter than that of promethazine. Only occasionally recommended for use in parkinsonism.

Numerous other antihistamines were also tried in parkinsonism, but none with the success of the named agents. Gair and Ducey reported in a placebo-controlled comparison of ten antihistamines which aimed to determine the structural requirements of an effective antiparkinsonian agent that diphenhydramine was "successful" in 64% of trials; **pheniramine** ('Trimeton'; Schering)\footnote{N,N-Dimethyl-γ-phenyl-2-pyridinepropanamine, = prophenpyridamine. U.S. patent to Schering: 1954.} and **doxylamine succinate** ('Decapryn'; Merrill)\footnote{N,N-Dimethyl-2-[1-phenyl-1-(2-pyridinyl)ethoxy]ethanamine. No patent found.} were also reasonably effective (60% and 51% successful), while phenindamine was associated with severe side effects and **tripelenamine** ('Pyribenazine'; Ciba),\footnote{N,N-Dimethyl-1-(2-thienyl)-1-(2-pyridyl)ethylenediamine hydrochloride. U.S. patent to Monsanto: 1952.} **methapyriline** ('Histadyl'; Lilly)\footnote{2-N-Benzylanalinomethyl)-2-imidazoline. U.S. patent to Ciba: 1948.} and **antazoline** ('Antitistin'; Ciba)\footnote{2-(N-Benzylanalinomethyl)-2-imidazoline. U.S. patent to Ciba: 1948.} were ineffective.\footnote{Gair and Ducey, 1950; see also Effron and Denker, 1950.} None of these substances, apart from diphenhydramine and phenindamine, achieved widespread application in parkinsonism. Considering the synthetic anticholinergic and antihistaminergic drugs which palliated parkinsonian symptoms, the authors arrived at a "skeleton formula" for antiparkinsonian agents; as they noted, it corresponded closely to the novel analgesic, methadone (figure 7-11).\footnote{1,1-Diphenyl-1-(2-dimethylaminopropyl)-2-butanol. German patent applications to Farbwerke Hoechst: 1941, 1942, 1944; U.S. patents to Merck (1953; appl. 1947) and Abbott (1961; appl. 1959).}
VII. The 1950s: The synthetic anticholinergic and antihistaminergic preparations

Figure 7.11: (a) Skeleton formula for substances with parkinsonism-alleviating effect, as proposed by Gair and Ducey (1950). At the time, the major exceptions to this formula were the solanaceous alkaloids, amphetamine and myanesin (discussed below); even phenindamine could theoretically be redrawn to conform to this scheme. * Methyl groups could be substituted in these terminal positions. (b) Methadone, described as one of the most potent central analgesics then known. It should be recognized that three dimensional molecular models were somewhat speculative at the time; as noted by the authors themselves, their attempts to determine structural similarities shared by atropine and the synthetic antiparkinsonian agents, which they envisioned as being necessary for the rational design of more effective medications, were thus of a preliminary nature.

Miscellaneous synthetic anticholinergic agents

A variety of different synthetic anticholinergic preparations were also examined for their effects on parkinsonian symptoms during the 1950s, but their employment never achieved the broad support of those described thus far in this chapter. They included:

- *mephenesin* (‘Myanesin’; British Drug House): Animal experiments had indicated that at low doses this glycerine ether relaxed muscles by inhibition of multisynaptic reflex pathways involving the reticulospinal system; only at higher doses did it manifest a curare-like effect on the motor endplate. It was employed on this basis as a curare substitute in gas anesthesia.

- *Hotovy and Erdniss*, 1950. The agent employed by these authors was designated at the time ‘Curaril’, emphasizing its derivation as a curare substitute, and was said to correspond to English ‘myanesin’; it was later renamed ‘Byk M1’, but had been withdrawn from sale by the 1960s; Degkwitz, 1963. Although all authorities writing in the 1950s agreed that ‘Curaril’ was myanesin, it should be noted that Byk marketed an agent under this name before the War which was described by Thoms as “high quality, precisely calibrated aqueous extract of calabash curare” (1927-29, p.561). See also Hunter and Waterfall, 1948.
it actually exacerbated extrapyramidal symptoms; further, it had be administered in gram doses.\textsuperscript{224} There were reports of its being associated with agranulocytosis; interestingly, one report of hair depigmentation following its application was also published.\textsuperscript{225} Even as an adjuvant it was regarded as inferior to scopolamine. As a theoretical tool, however, it attracted some interest before the discovery of the dopamine deficiency in parkinsonism.

**Benactyzine** HCl (‘Suavitil’; Medicinalco, Copenhagen and Merck, Sharp & Dohme)\textsuperscript{226}: a tranquilizer with weak anticholinergic, anesthetic and spasmolytic effects. Doses of 2-3×2mg/day inhibit cognitive and volitional processes, reduces sensitivity for unpleasant experiences, and relaxes the musculature of the extremities. For this reason, it found application as an adjunct in antiparkinsonian therapy, although its effects on rigidity and spasm were minimal; it was, however, valued by many physicians as a mood elevator (‘happy pills’).\textsuperscript{227}

- **N-butylscopolammonium bromide** or **hyoscine butylbromide** (‘Buscopan’; Boehringer, Mannheim)\textsuperscript{228}: curare-like effect; its effects were compared to those of atropine, but were milder and of shorter duration. The few reports concerning its employment in parkinsonism are conflicting.\textsuperscript{229} Most commonly used currently for the relief of visceral spasm. **Methscopolamine bromide** (U-0382, ‘Pamine bromide’; Upjohn)\textsuperscript{230} was also examined in parkinsonism but found greater application in therapy of duodenal ulcer.\textsuperscript{231}

- **Febarbamate** (‘G-Tril’; Sapos, Geneva)\textsuperscript{232}: a glycerine ether recommended by Hartmann-von Monakow for tremor.\textsuperscript{233} Febarbamate has also been used in preparations for minor anxiety and alcohol withdrawal, but recent reports of significant hepatotoxicity and pulmonary eosinophilia sharply reduced its employment.\textsuperscript{234}

- **Phenglutarimide** (‘Aturban’ or ‘Aturbal’; Ciba, Basel)\textsuperscript{235}: another distant relative of conine, phenglutarimide was strongly anticholinergic, both peripherally and centrally, and was also anti-nicotinic and anti-adrenergic. Unlike most synthetic atropine-like drugs, it is not an ester. Its central effects resemble those of scopolamine, and was found by some to particularly good against tremor; it was supposed to have a special affinity for the brainstem. Keller reported that it improved rigidity, tremor and akinesia, especially in postencephalitic patients, and was also impressed by its effects on vegetative signs.\textsuperscript{236} Hartmann-von Monakow reported similar results, but noted that it had little effect on...
VII. The 1950s: The synthetic anticholinergic and antihistaminergic preparations

![Mephenesin](image1)

**Mephenesin** ('Myanesin', 'Tolserol')

![Benactyzine](image2)

**Benactyzine** ('Suavitil')

![Butylscopolammonium bromide](image3)

**Butylscopolammonium bromide** ('Buscopan')

![Febarbamate](image4)

**Febarbamate** ('G-Tril')

![Phenglutarimide](image5)

**Phenglutarimide** ('Aturban')

Figure 7.12: Miscellaneous anticholinergic agents employed in the therapy of parkinsonism.

coarse tremor or in arteriosclerotic patients. Side effects were rare (less than 10% of patients), and were the familiar effects of anticholinergic agents.

Novel anticholinergic agents for the treatment of parkinsonism continued to be developed and tried into the 1980s; the following are cited only as examples:

- **Elantrine**: found to be somewhat more effective in management of tremor than benzhexol. Development reported to have ceased at clinical phase II.

- **Minepentate** (UCB 1549; U.C.B. Pharmaceutical Division, Brussels): Strang reported benefit in 44 of 100 patients observed during an eight month period in 1966, particularly with respect to rigidity.

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237 Hartmann-von Monakow, 1960a, p.111.

238 Further positive reports (in about 50% of patients): Battegay, 1958; Bein and Tripod, 1958; Gerstenbrand and Pateisky, 1958; Hartmann, 1958; Hughes et al., 1958; Balestrieri and Signorato, 1958a, b.

239 Blonsky et al., 1974; Blonsky, 1976; Rix, 1977.
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**Figure 7-13:** Anticholinergic agents developed for antiparkinsonian therapy since the 1960s.

- **Benapryzine:** Lamid and Jenkins found that it was as effective as benzhexol, but with fewer side effects; the major drawback was that it did not control sialorrhea. Development reported to have ceased at clinical phase II.

- **Bornaprine or Kr 339 (‘Sormodren’; Knoll):** this quarternary ammonium antispasmodic was an analog of biperiden examined by Haas (Knoll) in 1960 as part of his investigation of the mechanism of action of the latter. Kr 339 blocked nicotine- and tremorine-induced tremor (see chapter IX), and reduced central acetylcholine levels without a significant effect on peripheral cholinergic systems. It was found in 1969 and 1974 to be beneficial for parkinsonian tremor, for which property it has found limited employment in Europe, but required combination with further agents to treat other

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240 2-(2-Dimethylaminoethoxy)ethyl-1-phenylcyclopentane carboxylate.
241 α-Hydroxy-α-phenylbenzeneacetic acid 2-(ethylpropylamino)ethyl ester; AP 1288, BRL 1288. Dutch patent application (1963) and U.S. patent (1973) to Beecham.
242 Lamid and Jenkins, 1975.
243 2-Phenyl-bicyclo-(2,2,1)-heptane-2-carboxonic acid-(3-diethylamino-propyl)ester HCl.
244 Haas, 1960.
VII. The 1950s: The synthetic anticholinergic and antihistaminergic preparations

symptoms. According to Vernier, development ceased at clinical phase II; in Italy, however, it was still investigated in parkinsonian patients as late as the mid-1980s, and it is currently available in Germany.245

- **Dexetimide** (‘Tremblex’; Janssen):246 long-acting piperidine derivative particularly useful in the treatment of drug-induced parkinsonism, with benefits for all three cardinal symptoms. It did not achieve widespread popularity outside western Europe.247

- **Mazaticol** (‘Pentona’; Tanabe):248 tropane derivative investigated in Japan. It has been reported that it binds m₃ receptors with higher affinity than atropine, whereas trihexyphenidyl and biperiden selectively bound m₁ receptors with high affinity. The effect of mazaticol on EEG was found to be similar to that of other anticholinergic antiparkinsonian drugs, but induced mild delirium with visual and auditory hallucinations at a dose of 8mg in five of six subjects.249

- **Tropatepine** (‘Lepticur’; Diamant):250 structurally interesting, as it combines tropane and benzodiazepine elements, it was initially examined by French authors in the treatment of neuroleptic-induced parkinsonism, it was reported to be particularly effective against akinesia. It has, however, found little application outside France.251

**Tigloidine (Tiglyl-ψ-tropine)**

In the 1950s, the potential of yet another naturally occurring solanaceous alkaloid was investigated in the treatment of parkinsonism. Tigloidine252 is an alkaloid of *Duboisia myoporoides*, from which it was first isolated by Barger and colleagues in 1937 as a “thin colourless syrup”,253 and *D. leichhardtii*; it is usually described as a close homologue of atropine, with tropate moiety replaced by tiglic acid and tropine by its isomer pseudotropine.

Tigloidine hydrobromide (‘Tiglyssin’; T. & H. Smith, Edinburgh) was reported in widely spaced reports by two Australian groups to produce improvements in a small number of parkinsonian, Huntington’s disease and spastic paraplegic patients.254 As predicted by animal studies, it reproduced all the desired effects of atropine, without its side effects; for example, 10mg.kg⁻¹ tigloidine reduced

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245 Avenarius and Gerstenbrand, 1968; Iivanainen, 1974; Sancesario et al., 1984; Bergamasco et al., 1985; Piccirilli et al., 1985; Cantello et al., 1986; Vernier, 1996.

246 3-Phenyl-1´-(phenylmethyl)-[3,4´-bipiperidine]-2,6-dione.


248 2-Thiophenacetic acid-α-hydroxy-α-2-thienyl-6,6,9-trimethyl-9-azabicyclo[3.3.1]non-3-yl ester.

249 Saito et al., 1982; Katayama et al., 1990; see also Suitsu, 1992.

250 3-Dibenzo(b,e)thiepin-11(6H)-ylidene-1αH,5αH-tropine; 3-dibenzo[b,e]thiepin-11(6H)-ylidene-8-methyl-8-azabicyclo[3.2.1]octane.

251 Vauterin and Veillon, 1975; Delaunay and Guibert, 1976; Lambert et al., 1976; Brion, 1982; Celsis et al., 1989; Devoize et al., 1989.

252 Pseudotropine 2,3-dimethylacrylate, 2-methyl-2-butoenoic acid [1α,3α(E),5α]-8-methyl-8-azabicyclo[3.2.1]oct-3-yl ester; tiglyl-ψ-tropine.

253 Barger et al., 1937.

254 Trautner and Noack, 1951; Trautner and Gershon, 1958; see also O’Rourke et al., 1960.
motor overactivity elicited by 1mg.kg⁻¹ methedrine in dogs. Interestingly, tigloidine has only limited antinicotinic effects, marking it off from all other antiparkinsonian agents before l-DOPA. Trautner’s group noted the similarities in the structures of atropine and its analogs and of tigloidine, but remarked that most of the pharmacological effects of atropine and its analogs appeared to require the esterification of the basic portion of the molecule with an aromatic acid, a feature lacking in tigloidine. The effect of delayed recovery (whereby atropine and similar drugs induce rapid fatigue in a repeatedly stimulated muscle) in the isolated toad sartorius, on the other hand, required an unsaturated carboxylic acid attached to the tropine moiety: tigloidine thus produced the effects on muscle which were believed to underlie the benefits of atropine in Parkinson’s disease, while lacking its central vegetative effects.²⁵⁵ Sanghvi and colleagues later reported that tigloidine reversed the effects of both physostigmine and tremorine, but not those of reserpine.²⁵⁶

Trautner’s group assumed that tigloidine did not act directly on the root problem in extrapyramidal disease, as it was noted that the lowest effective dose (for Huntington’s disease: 100-400mg/day) also produced almost the maximum benefit for a patient. They were also impressed by the fact that only involuntary movements were affected by the agent; even at higher doses, voluntary movements were unimpeded. Some patients also experienced euphoria during treatment with the drug, but there did not appear to be a direct association of this effect with motor benefits. The limitation of its peripheral effects was naturally an advantage, but its excessive cost prohibited extensive use; only 0.5% of the alkaloid content of D. myoporoides consists of tigloidine, and even Trautner and Noack conceded that the continuation of clinical trials was precluded by this fact. Like atropine, tigloidine did not reverse reserpine-induced sedation; in cats and dogs it facilitated the behavioural actions of amphetamine at doses at which it itself exerted no discernible behavioural effects.²⁵⁷

**Sympathomimetic agents**

The search for an effective treatment of parkinsonism was not restricted to the anticholinergic and antihistaminic drugs, despite their relative success thus far. Indeed, as it was recognized that the hitherto effective agents had been largely anticholinergic – that is, parasympatholytic – drugs, it had been reasoned as early as the 1930s that sympathomimetic agents might be of use in parkinsonism, as discussed above. Hassler saw this as an attempt to restore normal vegetative balance.²⁵⁸ Early experiments with L-amphetamine (commonly referred to simply as ‘amphetamine’; = benzedrine) and methamphetamine (= ‘Pervitin’) in combination with atropine-class drugs showed positive effects for mood and motivation, but the danger of addiction mitigated against their long term application for many physicians. Hanson reported in 1967 that the central actions of amphetamine are mediated by catecholamines; it is interesting to note that amphetamine was later reported to also act via tyrosine hydroxylase activity.²⁵⁹

²⁵⁶ Sanghvi *et al.*, 1968.
²⁵⁸ Hassler, 1953, p.831.
²⁵⁹ Hanson, 1967; Mandell and Morgan, 1970.
Amphetamine was most recently re-examined as an antiparkinsonian agent in 1975. Parkes and colleagues reported that both l- and d-amphetamine (the latter at lower doses) produced a reduction in total disability, tremor, akinesia, and rigidity scores of about 20%. The d-amphetamine required for this improvement was lower than that of l-amphetamine. The side effects observed were distinct from those of L-DOPA therapy.260

Kennedy and colleagues had noted as long ago as 1922 that adrenaline (20 minim of a 1: 1000 solution) increased the pulse rate of postencephalitic patients by 50% (15% in normal controls) and exacerbated rigidity for two hours. The same group had also found that subcutaneous administration of the hormone led to increased rigidity in non-postencephalitic parkinsonism.261 In a remarkable study, Loman and associates at the Division of Psychiatric Research of the Boston State Hospital examined the effects of a wide range of agents in a 25 year old unilaterally parkinsonian patient in 1941, including sympathomimetics. Adrenaline (1-10µg i.v. or 300µg i.m.) markedly exacerbated the tremor on the affected side, without eliciting changes in the contralateral limbs. This and its less dramatic exacerbation of rigidity could be relieved by scopolamine. Most other sympathomimetics tested (hydroxy-, methoxy- and 3,4-methylendioxoamphetamine, ephedrine, norephedrine) elicited no remarkable changes; amphetamine itself decreased rigidity when administered intravenously (5-30mg), the effect lasting for two hours or more. When administered intramuscularly in a gelatin vehicle, the benefit could be extended to 24 hours. D-amphetamine was found to produce better results than the L-isomer, although neither isomer moderated tremor. The combination of amphetamine with scopolamine or atropine did not increase the motor effects of the anticholinergic drugs, but did overcome their tendency to induce drowsiness in the patient. The authors concluded that the combination of scopolamine and amphetamine in gelatin, both intramuscularly, was the best approach to the therapy of parkinsonism:

*Although the pathologic process in Parkinson’s syndrome resides mainly in the basal ganglia, the rigidity and tremor are finally the expression of a functional dysbalance between these structures and the cortex, the latter becoming relatively overactive. Scopolamine may be assumed to produce its favorable results by depressing the cortex, while amphetamine sulfate decreases rigidity by stimulating the basal ganglia.*262

Hassler reported the findings of Lindenberg that the thrice daily administration of the weaker sympathomimetic racemic ephedrine (‘Ephetonin’; Merck, Darmstadt) together with intravenous ascorbic acid had positive effects on rigor.263 In general, however, the use of sympathomimetics was restricted to roles as adjunct therapies which could alleviate some side-effects of anticholinergic drugs, but did overcome their tendency to induce drowsiness in the patient. The authors concluded that the combination of scopolamine and amphetamine in gelatin, both intramuscularly, was the best approach to the therapy of parkinsonism:

The effects of natural sympathetic agents on the parkinsonian tremor were directly examined by the English physician Henry Barcroft in Schwab’s laboratory in 1952. They noted that the degree of tremor often increased with emotional excitement, and posed the question as to whether this might be related to sympathetic activity. The infusion of either adrenaline or noradrenaline (10µg in 4mL saline/minute) elicited

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260 Parkes et al., 1975.
261 Hyslop, 1922; Kennedy et al., 1922.
262 Loman et al., 1942.
263 Hassler, 1953, pp.831-832; see also Kreitmair, 1927.
increases in blood pressure and an increase (adrenaline) or decrease (noradrenaline) in heart rate of patients who had been withdrawn from their normal antiparkinsonian medication (diphenhydramine, caramiphen, benzhexol). But only adrenaline caused an increase in resting tremor from an average 12 integrator signals per minute to a mean of 45 per minute, an increase seen in eight of fourteen patients examined. In eight patients still receiving their medication, adrenaline had no effect on tremor, although it still exerted its normal hypertensive effects. The authors were unable to explain their results; tremor was clearly not directly related to blood pressure changes alone, as evidenced by the facts that the motor and circulatory effects of norepinephrine were not correlated, and that the reduction of pressure by amyl nitrate or near syncope did not reduce parkinsonian tremor. The divergent effects of the two catecholamines were also puzzling at the time, although not unprecedented. The authors, however, suggested that the effect of adrenaline was probably central rather than peripheral, as tremor could be elicited in some normal subjects by administration of the catecholamines. It should be noted that to suggest that adrenaline exerted central effects on nervous function was an unusual suggestion at this time. Further, of the three antiparkinsonian medications employed by the patients, only diphenhydramine had previously been reported to possess adrenolytic effects.264

**Apomorphine**

Schwab was also part of a group which reported in 1951 the effects of apomorphine265 in parkinsonism. Apomorphine, a synthetic alkaloid produced by the dehydration of morphine by concentrated mineral acids, was synthesized by Matthiessen and Wright (St Bartholomew’s Hospital, London) in 1869 as part of a chemical investigation of the opium alkaloids; as indicated in figure 7-15, it is closely related to codeine.266 Apomorphine was known to medical practitioners since the 19th century, chiefly as an injected emeticum. This action seemed to be related to stimulation of the vomiting centre on the floor of the IV ventricle identified by Thumas in 1891. In the same year as its synthesis, the physician Samuel Jones Gee (St Bartholomew’s Hospital, London) identified the fact that apomorphine elicited stereotyped motor behaviours in dogs,267 which was later found to be also true in rats and other animals incapable of vomiting.268 Gee also reported the sedative effects exerted by apomorphine in a 9 year old boy suffering mania, which led to its being tried clinically in a number of states associated with excitement.269 Siebert, a student of Schmiedeberg’s (Dorpat University) and Quehl (Halle University) published detailed investigations of the pharmacological effects of apomorphine in 1871 and 1872;270 in 1874, Erich Harnack (Experimental Pharmacology, Strassburg University) published the first of his papers on the pharmacology of apomorphine, lamenting the fact that it had been hitherto regarded primarily as an emetic, whereas it exhibited a range of further interesting

264 Barcroft *et al.*., 1952.
265 10,11-Dihydroxyaporphine.
266 The structure was first described in 1902 (Pschorr *et al.*), its absolute configuration only in 1955 (Corrodi and Hardegger); the total synthesis was achieved only in 1970 (Neumeyer *et al.*; U.S. patent to A.D. Little, 1973).
267 Cited by Hughlings Jackson, who seemed more impressed by the accompanying emetic response than by the stereotypy. Gee himself was skeptical about this response in humans, as a result of which he became one of the first to test the drug on himself; see Pearce, 1995.
268 Harnack, 1874.
270 Inaugural dissertations summarized and discussed in Harnack, 1874.
pharmacological properties.\textsuperscript{271} Gee, Siebert, Quehl and Harnack all noted the central excitatory effect on motor activity in mammals. Amsler (Pharmacological Institute, University of Latvia, Riga), however, appears to have been the first to explicitly associate this action of apomorphine with the striatum, this insight being achieved by the selective extirpation of brain regions of dogs, rodents and pigeons in a series of experiments elegant in the conception but somewhat gruesome in the execution.\textsuperscript{272}

![Figure 7.15: Apomorphine, codeine and dopamine depicted in order to allow structural comparison. Morphine differs from codeine in that the marked methyl group is replaced by a hydrogen atom; in apocodeine, a methyl group is substituted for the marked hydrogen in apomorphine.](image)

Apomorphine had been immediately trialled in clinics following the publication of Gee’s initial results. Apart from its use as an emetic, it was also combined with scopolamine for the induction of obstetric and surgical anesthesia.\textsuperscript{273} Pierce, for example, reported in 1870 that it benefited patients with chorea associated with rheumatic fever. The use of apomorphine chlorhydrate (6mg s.c.) in Parkinson’s disease was suggested as early as 1884 by Weill (Medical Clinic, Lyon University), who examined its effect in a range of other motor disturbances (chorea, epilepsy, hiccough), and noted that motor effects could be achieved at doses which did not induce nausea.\textsuperscript{274} But the idea seems to have been subsequently forgotten, largely because apomorphine was regarded purely as an emetic. Gee had noted in 1869 the reduction in muscular power induced by apomorphine and its antagonism of tetanus in frogs, but it was subsequently recognized that apomorphine reduced the responsiveness of striated muscle in amphibians but not in mammals.\textsuperscript{275} The observed reduction in muscular strength in mammals by earlier workers was now believed to be secondary to stimulation of emesis, although it was still noted that it “produces direct depression of excised cardiac and skeletal muscle”.\textsuperscript{276} Interest in apomorphine as an agent for the management of motor disorders, apart from its role as a general sedative, had waned by the 1920s. Even this application had become less common by the 1940s, as barbiturate compounds assumed their role as standard sedatives; these latter agents, however, were not unproblematic, and there had been some experimentation with alternatives, including apomorphine.\textsuperscript{277}

\textsuperscript{271} Harnack, 1874.
\textsuperscript{272} Amsler, 1923.
\textsuperscript{273} See references in Extra Pharmacopoeia, 1952, p.196; Neumeyer et al., 1981.
\textsuperscript{274} Weill, 1884.
\textsuperscript{275} Sollmann, 1943, pp.574-576; Neumeyer et al., 1981.
\textsuperscript{276} Sollmann, 1943, pp.573.
\textsuperscript{277} For example, Lehmann (1949; Montréal) recommended a barbiturate-scopolamine-apomorphine combination in organic brain disease and for the sedation of geriatric patients.
Dordoni had found in 1948 that certain drugs which modulate the activity of the reticular substance, pontine region and basal ganglia were capable of relieving surgically induced rigidity in animals, an observation confirmed and extended by McCulloch and Lettvin. Its usefulness in Parkinson’s disease was therefore tested by Jerome Lettvin in Chicago, work which was continued by Luis Amador (also Chicago) and Robert Schwab (Boston). The major anticipated side effect being the stimulation of the emetic centre, but 0.6-0.9mg apomorphine s.c. was found to produce only mild and transient nausea (lasting about three minutes) in some patients, while a period of up to three hours followed in which tremor, rigor and muscular weakness were reduced and the patient experienced feelings of well-being. A severe drop in blood pressure accompanied the feelings of nausea and could lead to near syncope if the patient was not lying down. Objective and subjective improvement of parkinsonian symptoms lasted between one and six hours; in no case, however, was “there anything like a restoration of a normal condition.” It was found that the patients could be treated at home, receiving the injections up to four times a day from a district nurse or relative; one patient had been receiving daily injections on this basis for a year without evidence of accumulation, side effects or addiction developing. Patients treated for longer than three months continued to exhibit increasing improvement.

The authors recognized the difficulties associated with an injected medication in Parkinson’s disease, and had attempted to produce a slow release formulation. This having failed, they prepared a stable mixture which could be taken orally in fruit juice: 0.375mg apomorphine HCl, 50ml tincture belladonna, 10g citrate, 2g sodium bisulfite made up to a litre in isoalcoholic elixir. The administration with juice is interesting, as it is now recognized that ascorbate blocks the action of apomorphine. The dose was slowly increased from 1ml to 4ml per day (~1.5mg apomorphine HCl and 10 drops belladonna tincture). The effects were not as dramatic as with the injection, but more sustained; the patient was more relaxed and able to sleep at night.

Schwab and England interpreted the apomorphine effect as being similar to that of amphetamine in post-encephalitic parkinsonian patients; that is, it acted as an analeptic, presumably at the level of the mid-brain reticular formation, but did not produce the insomnia associated with the high amphetamine dosage tolerated by these patients. The authors soon found that belladonna, initially included to calm gastrointestinal reactions, could be safely omitted. It was reported during 1952 and 1953 that subconvulsive doses of pentylenetetrazole (‘Metrazol’; 3-5×100mg/day) reduced mental confusion and facilitated alertness and motor capacity in geriatric patients; paradoxically, it also appeared to aid sleep. As a result, Schwab and England changed their formula in 1954 to a combination of amphetamine (5mg), apomorphine (1.5mg), strychnine (1mg) and pentylenetetrazole (50mg) in 4mL vehicle; from 1956, the strychnine was omitted. Doses of 2-8mL was found to be “of considerable benefit” in forty of sixty-three parkinsonian patients. A newer analeptic, ‘PM 1090’ (Parke-Davis), could be substituted for pentylenetetrazole and was generally found to be less toxic and of a longer duration of action. Where a particular patient proved overly sensitive to the analeptic, phenytoin (‘Dilantin’; Parke-Davis) could be administered to forestall the presentation of convulsions.

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278 Cited in Schwab et al., 1951b.
279 Schwab et al., 1951b.
280 Ibid.
281 2,2,3,3-Tetramethyl-succinimide.
Concurrent with these developments, there were isolated investigations of apomorphine in animal models of parkinsonism. Vernier and Unna reported in 1951 that apomorphine alleviated the experimental tremor induced in monkeys by lesions of the ventral medial tegmentum. Struppler and Uexküll (Second Medical Clinic, Munich University) reported in 1953 an investigation into the mechanism whereby apomorphine exerts its effects on tremor; they found that it stimulated the vagus, exerted a sympathomimetic effect on the stomach and circulatory system, as well as acting as a psychic energizer. The main site of action of apomorphine, they concluded, was in the brain itself, but attempts to localize the effect more precisely were made impossible by “our inadequate knowledge of the site and mechanism involved in the production of tremor.” Small doses of apomorphine induced indifference, higher doses apathy.

Another interesting observation, and even more interesting interpretation was recorded:

Patients, whose tremor had been quickly and impressively improved by oral apomorphine, exhibited after a time the same effect when they received distilled water instead of apomorphine (same bottle, same volume, etc.). This effect could be reproduced as often as desired even after the effect of distilled water had diminished, by treating the patient again with apomorphine.\(^{283}\)

Most authors would have seen a type of placebo effect in this phenomenon; Struppler and Uexküll, in contrast, saw this as evidence of subliminal nausea being elicited by the distilled water as a Pavlovian conditioned reflex to the previous administration of apomorphine. In any case, they did not see it as undermining the effectiveness of apomorphine, and they concluded that the actual chemical stimulation of the emetic centre was not required for either its emetic or motor effects. Instead, the authors understood the tremor of parkinsonism as an intentional tremor produced by a shift to the ergotropic side of the vegetative reaction spectrum; the correction of this change relieved parkinsonian tremor only incidentally as part of the nausea reaction.\(^{284}\)

Although Struppler and Uexküll agreed with Schwab that parkinsonian tremor was suppressed by apomorphine, the drug does not appear in any of the major reviews of potential agents for parkinsonism before it is listed as a curiosity by Degkwitz in 1963. The successes reported by England and Schwab do not appear to have been further pursued to any significant extent, although they themselves recommended in their 1959 review on the management of parkinsonism their apomorphine/D-amphetamine/pentylenetetrazole combination as the most effective approach for overcoming the typical lethargy of parkinsonism.\(^{285}\) A reason for this was cited by the authors themselves in 1956:

Analeptics like amphetamine have their use in the treatment of Parkinson’s disease but seem to be decreasing in their usefulness, possibly due to the aging of the group.\(^{286}\)

Older patients, whether post-encephalitic or idiopathic, were not as tolerant of amphetamine or apomorphine as when they were younger, and these agents were thus no longer as appropriate as earlier.

That apomorphine should be so thoroughly ignored is also probably a tribute to the power of the anticholinergic paradigm which dominated the therapy of parkinsonism at

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\(^{283}\) Struppler and Uexküll, 1953.

\(^{284}\) Ibid.


\(^{286}\) Schwab and England, 1956.
this time, although the transience of the symptomatic improvement elicited by apomorphine was also a serious hindrance to its establishing a niche in antiparkinsonian therapy. Further, Brücke and associates at the Pharmacological Institute in Vienna reported in 1957 that the arousal effected by apomorphine in the rabbit was opposed by atropine and scopolamine (as well as by chlorpromazine, hexobarbital (‘Evipan’), mephenesin and the muscle relaxant guaifenesin (‘Myoscain’). Although it was known that atropine acted to inhibit arousal reactions in many models, the authors were puzzled by its antagonism of the effects of apomorphine, as it had been reported that there existed no such antagonism between atropine and amphetamine with respect to arousal. In any case, their results provided no compelling motivation for re-examining apomorphine in the treatment of parkinsonism at this time.

Interestingly, the antagonism which existed between certain effects of apomorphine and those of the phenothiazines – particularly those known to be capable of inducing a parkinsonian syndrome – was noted as early as 1957. In 1965, the Dutch pharmacologist Anton Marie Ernst drew attention to the structural similarities of dopamine and apomorphine. Interest in the alkaloid was re-ignited shortly afterwards by the introduction of L-DOPA therapy; this will be discussed at the appropriate point below.

**Energizers and sedatives**

Therapy for parkinsonian patients also required management of the psychological effects of a chronic, incurable disorder and the often uncomfortable side effects of the major chemical therapy of the motor symptoms. A panel of stimulant drugs, mostly amphetamine derivatives, had been used since the 1930s in patients in whom the effect of the anticholinergic therapy produced excessive drowsiness or lethargy. Methylphenidate hydrochloride (‘Ritalin’; Ciba, Basel), a mild central nervous system stimulant structurally related to amphetamine (and sharing its abuse potential) was introduced in America for the treatment of chronic schizophrenia associated with motivational deficits. It was found in the mid-1950s to temporarily relieve reserpine-induced parkinsonism and surgically induced tremor in monkeys; Glow reported in 1959 that it also reversed the rigid syndrome accompanied by tremor which reserpine elicited in rats. It was suggested at the time that reserpine either stimulated parasympathetic or, more probably, inhibited sympathetic centres in the hypothalamus, and that methyl phenidate somehow blocked this effect, restoring the balance in hypothalamic function. It was thus trialled in parkinsonian patients in 1960/1, and both intravenous and oral application were found to increase freedom of movement and decrease rigidity in about half the patients; tremor was barely affected. The major effect, however, was on mood, and its effect on motor symptoms were ascribed to this effect; its euphoric actions also led to restlessness and insomnia in some patients. The authors noted that the dose employed was maximally one twentieth of that used in animal models (on a per weight basis), but that it was impractical to elevate the dose

287 Brücke et al., 1957. Brücke had also found in 1935 that bulbocapnine antagonized the production of stereotypic behavior by apomorphine.


290 Cole and Glees, 1956.
any further.\textsuperscript{291} Methyl phenidate was thus unsuccessful as an antiparkinsonian agent, but later became well known in the therapy of so-called attention deficit disorder; it is also currently used to treat narcolepsy.

Other agents used as “energizers” included pent(ameth)ylene tetrazole (‘Cardiazol’, ‘Metrazol’, Knoll)\textsuperscript{292} and \(D\)-amphetamine (which was also effective against oculogyric crises);\textsuperscript{293} Doshay found that the latter was better tolerated by older patients than \(L\)-amphetamine. England and Schwab, as just discussed, employed cocktails of apomorphine, strychnine and \(D\)-amphetamine for analeptic purposes; they had also tried the MAO inhibitor iproniazid; the latter, however, was discontinued by 1959 for fear of toxic side effects.\textsuperscript{294} The \(\beta\)-adrenergic antagonist pronethalol\textsuperscript{295} was reported in 1964 to reduce parkinsonian tremor in a controlled study,\textsuperscript{296} but was later withdrawn because of its carcinogenicity in mice; the much more potent antagonist propranolol\textsuperscript{297} was subsequently tested in ten patients in a controlled double blind study, but found to be ineffective.\textsuperscript{298} By the 1980s, however, it was suggested that propranolol and the related nadolol (‘Anabet’/’Corgard’, Squibb)\textsuperscript{299} be considered as an adjunct therapy for refractory tremor, particularly where its presentation was associated with emotional stress.\textsuperscript{300} The \(\alpha_2\)-adrenergic agonist clonidine (‘Catapres’; Boehringer Ingelheim)\textsuperscript{301} was also without effect in parkinsonism.\textsuperscript{302} Carlsson’s group, however, described a remarkable synergism between clonidine and atropine in monoamine-depleted mice;\textsuperscript{303} this has, however, not been converted into a practical therapy.

\textit{Imipramine} HCl (‘Tofranil’; Geigy)\textsuperscript{304} was examined at the end of the 1950s as an “energizer” in the treatment of parkinsonism. This compound, the prototype tricyclic antidepressant, was another example of serendipity in pharmacology. Häfliger and Schindler had synthesized a range of iminodibenzyl derivatives in the late 1940s with the aim of finding novel antihistaminergic, antiparkinsonian, sedative and analgesic agents.\textsuperscript{305} Amongst them was imipramine, in which the sulphur of the phenothiazine

\begin{footnotesize}
\textsuperscript{291} Halliday and Nathan, 1961.
\textsuperscript{292} U.S. patents granted in 1925 and 1926.
\textsuperscript{293} British patent granted: 1939; U.S. patent granted to Smith, Kline & French: 1942. Marketed by SK&F as ‘Dexedrine’.
\textsuperscript{294} Schwab and England, 1956; England and Schwab, 1959; 1961. See also Doshay in Brock \textit{et al.}, 1956.
\textsuperscript{296} Herring, 1964; see also Sekiya and Vaughan Williams, 1965.
\textsuperscript{297} 1-((tert-Butylamino)-3-[(6-Chloro-3-m-tolyloxy]-2-propanol. German (1973, 1974) and U.S. patents (1976) to Squibb.
\textsuperscript{298} 1-((tert-Butylamino)-3-[(5,6,7,8-tetrahydro-\textit{cis}-6,7-dihydroxy-1-naphthalenyl)oxy]-2-propanol. German (1973, 1974) and U.S. patents (1976) to Squibb.
\textsuperscript{300} Tarsy \textit{et al.}, 1975.
\textsuperscript{301} Tarsy \textit{et al.}, 1975.
\textsuperscript{302} Carlsson and Carlsson, 1989.
\textsuperscript{304} Schindler and Häfliger, 1954.
\end{footnotesize}
molecule is replaced by an ethylene bridge to produce the typical seven member central ring (figure 7-16). Imipramine proved to be a poor sedative but an excellent “energizer” and antidepressant. It rapidly became one of the most widely employed psychoactive agents throughout the world; many see its introduction as marking the birth of modern psychopharmacology. It had been noticed that, despite its similarity to the phenothiazines, imipramine did not induce chemical parkinsonism even at high doses, and could be safely used in the treatment of depression in parkinsonian patients without fear of exacerbating their extrapyramidal symptoms.306

Several small studies had yielded encouraging results with respect to a role for imipramine in Parkinson’s disease, particularly for akinesia; its benefit for the often coexistent depression was also not insignificant.307 In 1963, the results of a larger study involving 66 patients were published by Gillhespy and Mustard (Parkinson’s Disease Research Unit, Birmingham). They found that imipramine (3×25-50mg/day) produced objective and subjective improvement in 65% of patients; thirty-two of forty-six patients who had previously shown inadequate response to antiparkinsonian drugs benefited from the adjunct therapy.308 The authors ascribed the effect to the

306 History of imipramine reviewed in: Kuhn, 1970; Maxwell and Eckhardt, 1990, pp.133-141.
307 For example, Denmark et al., 1961.
308 Gillhespy and Mustard, 1963b.
anticholinergic quality of imipramine, as reported by Domenjoz and Theobold in 1959, although they also regarded the sedative action of imipramine in elderly and agitated parkinsonian patients as significant. Birkmayer favoured the “energizing” and mood-elevating hypothesis as the basis of its benefit in parkinsonism, as did England and Schwab, who described in 1961 a patient who used imipramine just before business conferences; the tranquilizer meprobamate could be used for similar purposes.

Shortly after it was introduced into the clinic, it was demonstrated that imipramine inhibited the re-uptake of noradrenaline into the cell, thus increasing its extracellular concentration. Later it would prove that it also inhibited the re-uptake of dopamine and 5-HT. This occurred just after Hornykiewicz and Birkmayer had published their results regarding the reduced concentrations of certain biogenic amines in particular brain regions in parkinsonism. Norbert Matussek and Hermann Pohlmeier (Max Planck Institute for Psychiatry, Munich) thus tried the use of an imipramine derivative, desmethylimipramine (‘Pertofran’; Geigy), which lacked the anticholinergic capacity of imipramine. Both agents had already been found to reverse reserpine-induced “parkinsonism” in animals. The two Munich workers found that imipramine and desmethylimipramine (25-100mg/day) were of similar benefit for all three main symptoms (rigor, tremor, akinesia) in seven postencephalitic and three arteriosclerotic parkinsonian patients; the authors attributed the benefit to a compensation of the dopamine deficiency which had recently been identified. Duvoisin, on the other hand, reported that in a double-blind study the effects of desmethylimipramine could not be distinguished from placebo. Nevertheless, small doses of tricyclic antidepressants were favoured by many physicians until the 1970s as therapy for tremor.

The use of analeptics in parkinsonism was accepted only begrudgingly by many workers, as they had no direct effect on the major symptoms of the disorder (tremor and rigidity), and problems of addiction and even abuse could not be overlooked. Nevertheless:

\[
\text{we need these analeptic substances. They are a definite help to many of the afflicted. I use them in combination with the antihistamine drugs. They help the mood of some who are discouraged by the handicaps produced by this disease. They facilitate getting these folks started in the morning, to help them develop a will to get into motion.}
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Pragmatism overcame the reservations of the physician: a different attitude to the European adherents of the Bulgarian treatment and the attempt to implement a Spartan lifestyle devoid of caffeine, alcohol and even chocolate.

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312 Axelrod et al., 1961; Glowinski and Axelrod, 1964.
313 Carlsson et al., 1968.
315 See McKearney, 1982.
316 Matussek and Pohlmeier, 1965; Pohlmeier and Matussek, 1965; see also Matussek et al., 1964.
318 Strang, 1965c.
Schwab also noted that many clinicians interpreted akinesia, bradyphrenia and loss of affect as indicative of hypothyroidism and consequently administered thyroid extract to their parkinsonian patients. He found that this was inadvisable except where clinical hypothyroidism had been ascertained, as it indeed is in normal persons; suppression of thyroid activity with radioactive iodine, on the other hand, appeared to be of some benefit for the tremor and restlessness of some patients exhibiting marked weight loss.320

Stimulation was not always the required approach in parkinsonian patients. The converse was also often necessary: anxious or restless patients required treatment with tranquilizers and sedatives. The use of phenothiazines and reserpine in parkinsonism, however, was somewhat problematic, as will be discussed below. Schwab noted that it was frequently necessary to employ a hypnotic cocktail which assisted sleep but allowed the patient to function normally the following day; he suggested the addition of 50mg sodium pentobarbital (‘Nembutal’; Abbott)321 to meprobamate or diphenhydramine or the employment of small doses of chloral hydrate.322

\[
\text{Sodium pentobarbital ('Nembutal')}\quad \text{Phenobarbital}\quad \text{Amobarbital ('Amytal')}
\]

\[
\text{Chloral hydrate} \quad \text{Meprobamate}
\]

Figure 7-17: Tranquilizers commonly employed in the therapy of parkinsonism in the 1950s/1960s.

(‘Luminal’; Winthrop)323 or amobarbital (‘Amytal’, Somnal; Lilly),324 on the other hand, tended to exacerbate the diurnal sluggishness of the patient.

The need to manage both the motor and psychic effects of parkinsonism itself, the side effects of antiparkinsonian therapy and the concomitant disorders in what by the end of the 1950s were generally elderly patients, led to the administration of a confusing smorgasbord of medication on a daily basis. As a result, it was also common

321 Sodium 5-ethyl-5-(1-methylbutyl)barbiturate; Schwab, 1961.
322 Schwab, 1961. Monnier and Krupp reported that meprobamate also has a slight relaxant effect on muscular tone.
323 5-Ethyl-5-phenybarbituric acid.
324 5-Ethyl-5-isopentylbarbituric acid.
to combine several agents into a single pill or capsule; for instance, belladonna extracts were not only available in a pure form, but also in a range of composite preparations, including a selection of belladonna-phenobarbital combinations.\footnote{The American Drug Index for 1965 listed twenty-nine separate belladonna-phenobarbital combinations, and nine including other barbiturates: Wilson and Jones, 1965, pp.91-95.} Although forms of this latter mixture had been commercially available since the beginning of the century,\footnote{For example: ‘Belladenal’ (Sandoz; introduced in 1927) consisted of 0.25/0.5mg ‘Bellafolin’ and 50/100mg phenobarbital; used for a range of neurological diseases, including paralysis agitans, as well as for muscular spasm, various neuroses and sea-sickness.} many workers regarded this combination as contraindicated as it rendered the patient dull and listless.\footnote{England and Schwab, 1959.}

**Pyridoxine (Vitamin B₆)**

Vitamin B₆ was distinguished from the vitamin B₂ complex in 1934 by Paul György (Babies’ and Children’s Hospital and Department of Pediatrics, Western Reserve University School of Medicine, Cleveland), who named it ‘pyridoxine’;\footnote{György, 1934, 1935; György crystallized the vitamin in 1938, as did groups in Germany, the United States and Japan; see Issekutz, 1971, p.352.} it was first synthesized by Harris and Folkers four years later.\footnote{Harris and Folkers, 1939.} What György called ‘pyridoxine’ actually consists of three related molecules, pyridoxol (also designated pyridoxine), pyridoxal and pyridoxamine (figure 7-18).\footnote{Baker, 1941.} All three water-soluble molecules share common pharmacological characteristics, and may be referred to as ‘vitamin B₆’, but the A.M.A. Council on Pharmacy and Chemistry has determined that the vitamin is officially the form designated ‘pyridoxine’. Commercial preparations contain the hydrochloride of pyridoxine.\footnote{3-Hydroxy-4,5-di(hydroxymethyl)-2-methylpyridine; see Hardman et al., 1996, pp.1561-1562. The commercial preparations used in the papers described here (‘Benadon’, Hoffmann-La Roche, introduced in 1945; ‘Becitan’, Spécia; ‘Hexobion’; Merck) consist of the hydrochloride.}

![Figure 7-18: The different molecular forms of Vitamin B₆.](image)

Clinical studies into the role of the vitamin in human nutrition had already begun in 1938, and indicated that symptoms responsive to pyridoxine supplementation included nervousness, cramps, muscular rigidity and difficulty in walking.\footnote{See Spies et al., 1939; 1940.} Antopol and Schotland successfully applied pyridoxine in 1940 in patients suffering pseudohypertrophic muscular dystrophy, on the basis that pyridoxine-deficient rats exhibit muscle atrophy and the fact that high doses of the substance induce convulsions.
and tremor in rats. Norman Jolliffe (New York University College of Medicine) was the first to treat paralysis agitans patients with pyridoxine, in the belief that muscle metabolism was abnormal in the disorder; Spies and associates conveyed Jolliffe’s initial results to the 1940 meeting of the American Medical Association in November 1940 as a personal communication. In thirty patients, none of the postencephalitic cases responded, nor any of those hospitalized for more than three years; six patients with nonencephalitic parkinsonism who had been helpless for under a year, however, showed dramatic improvement, leading to the suggestion that a pyridoxine deficiency might be involved in the earlier stages of parkinsonism. Spies’ own collaborative study found that all three vitamin-treated postencephalitic patients (duration of disease: minimum of four years) responded within minutes to pyridoxine with a marked reduction in rigidity; only two of eight arteriosclerotic patients exhibited similar responses. In none of these studies was the route of administration indicated.

Jolliffe presented a paper to the meeting of the American Medical Association in June 1941 on the role of vitamin therapy in a number of “neuropsychiatric disorders”. In this study, fifteen parkinsonian patients received daily intravenous injections of 50-100mg pyridoxine, often supplemented by oral administration of brewers’ yeast, for a period of two to three weeks. Four of nine idiopathic or arteriosclerotic patients showed improvement to some degree, with benefits for rigidity, tremor and sialorrhea; one of three postencephalitic patients also improved, as did a post-syphilitic parkinsonian case and one of two cases of parkinsonism of unknown origin. It was often reported that paralysis agitans cases were more amenable to pyridoxine therapy than postencephalitic cases. Oral administration of the vitamin, however, to four idiopathic patients did not elicit such promising responses. The paper as a whole and its claimed successes in parkinsonism were received by the conference with mixed responses. Meyer Zeligs reported that his contact with Jolliffe had encouraged him to attempt to replicate the study – with entirely negative results. Jolliffe objected that Zeligs had treated his patients for only a short period of time; further, paralysis agitans was probably a group of disorders, not all of which were amenable to pyridoxine therapy. Several positive reports with similar doses of pyridoxine (and several negative reports) appeared in the American journals during the following two years. By 1951, the American Medical Associations Council on Pharmacy and Chemistry had concluded that there was no evidence which supported the use of pyridoxine in the therapy of parkinsonism.

In the 1950s, however, a number of European workers, particularly in Germany and Austria, recommended a high dose therapy in which the daily dose was set in the region

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333 Antopol and Schotland, 1940.
334 Spies et al., 1940. According to this paper, Jolliffe had also presented at least some of these results in April 1940 at a symposium on vitamins at the Mount Sinai Hospital, and also at a meeting of the Minnesota State Medical Association.
335 Spies et al., 1940.
336 Jolliffe, 1940; 1941.
337 Examples of positive reports: Baker, 1941 (nineteen cases, 100g i.v. or 50mg p.o. daily); Meller, 1942 four post-encephalitic cases (who did not respond) and six paralysis agitans patients, commenced with 50mg s.c. or i.m, further treatment (19 das-15 months) depended on initial response); negative reports: Barker et al., 1941 (seven patients, 100mg/day i.v., two weeks); Zeligs, 1941 (fifteen patients; repeated injections of 50-100mg). Further references are listed in Duvoisin, 1973. It is interesting that most positive report reports appeared in local state journals in America, whereas the positive appeared in more respected publications.
of 600-1400mg; up to 750mg/day was administered intravenously, while higher doses were required if taken orally. The major benefit was seen in the relief from rigidity and the reduction of tremor, accompanied by a general increase in physical strength and improvement in mood; Sigwald’s group also found an effect on akinesia. Marked improvements in specific tasks, such as the co-ordination of movement and speech, were also noted with some surprise. The therapy was most effective for patients in the early stages of the disease and after a long period of treatment with the vitamin, as summarized by Finke (Neurological Clinic Neuemühle, Kassel-Niederzwehren):

The vitamin B₆ therapy must be seen as the preparation of choice for the treatment of parkinsonism (especially of early identified cases). Significant objective improvement in cases which are 4 or 5 years old, however, cannot be expected even with high doses of pyridoxine because of the severity of damage to the globus pallidus and substantia nigra.

Finke believed that the progression of the disorder could be slowed by pyridoxine therapy, so that it was not merely another symptomatic treatment. Some authors (for instance, Hartmann-von Monakow, who had employed the vitamin in the treatment of parkinsonism since 1945) found that pyridoxine could even be used alone in early cases; it was, however, worthwhile at any stage of the disease, as it could be combined with any other antiparkinsonian medication, produced no side effects, improved the temper of the patient and increased his general physical fitness and resistance to infection. Hartmann-von Monakow also saw administration of pyridoxine as an absolute requirement following stereotactic operations to correct parkinsonism symptoms; he found it highly efficient in managing the psychic disturbances (loss of motivation and memory) and speech impairment which were often the unwanted sequelae of pallidal coagulation.

There were, however, many skeptics regarding even the high dose pyridoxine therapy. The major problem with this approach, however, was that pyridoxine production was very expensive at this time; Finke, for example, thanked Hoffmann-La Roche for enabling him to conduct his trial in twenty patients.

Why pyridoxine might benefit the parkinsonian patient was unknown. Jolliffe and Spies believed that the vitamin was acting on the muscle itself. Glanzmann proposed that it was involved in the construction of the myelin sheath of the nerve fibres. Antopol, Schotland and Birkmayer saw its site of action inside the cell. As the vitamin appeared to exert a fairly specific effect on the extrapyramidal system, it was also discussed in connection with the high iron content of these nuclei. By 1961, it was generally assumed that pyridoxine therapy, which involved doses which exceeded those which would be required to overcome a simple dietary deficiency, must have a

340 Sigwald et al., 1956.
341 Finke, 1952; 1954.
343 For example, Alleva, 1960; see also Duvoisin, 1973.
344 Finke, 1952; 1954.
345 Spies et al., 1939, 1940; Jolliffe, 1941.
346 Cited in Finke, 1952.
347 Antopol and Schotland, 1940; Birkmayer and Schmid, 1949.
348 Finke, 1954.
pharmacodynamic effect on high turnover metabolic processes such as decarboxylation and transamination, explaining its benefit in neurological disorders which potentially involved these processes, including parkinsonism, but also chorea, essential tremor and childhood brain damage.349

At the beginning of the 1960s, Hartmann-von Monakow (amongst others) began to emphasize the fact that pyridoxine played an essential role as cofactor in a number of decarboxylation reactions, including those leading to the synthesis of tryptophan, histamine and GABA, as well as of the catecholamines. Although its role in a wide variety of metabolic reactions was noted (including glycogenolysis, nicotinic acid synthesis and transamination), the crucial role of the vitamin in biogenic amine synthesis attracted the most attention; at this point, serotonin was especially considered in this respect, as its role in psychiatric changes was currently the focus of intense investigation (see chapter X).350 There was also some revival in interest in pyridoxine therapy with the advent of the L-DOPA therapy; as the vitamin was the cofactor for the decarboxylase which converts L-DOPA to dopamine, it was considered by Birkmayer and Hornykiewicz as a possible adjunct therapy.351 Such an approach also received some support from the work of Sourkes and colleagues concerning the metabolism of L-DOPA by normal and pyridoxine-deficient rats.352 These hopes were disappointed; if anything, the co-administration of pyridoxine reduced the benefits of L-DOPA. Duvoisin and colleagues (amongst many others) attempted to increase the response to oral L-DOPA and to control the involuntary movements associated with its use by the addition of pyridoxine to the therapy of twenty-five patients, but the initial dose of 750-1000mg/day partially abolished the effect of L-DOPA within twenty-four hours and completely within ninety-six hours. The authors therefore withdrew the vitamin before trying increasingly smaller doses, but as much as 5-10mg/day were sufficient to significantly reduce the benefit of L-DOPA in most patients.353 This finding was of both practical and theoretical importance; many parkinsonian patients used vitamin supplements to control nausea or for other reasons.

The reduced effectiveness of L-DOPA following pyridoxine administration was initially puzzling, and remained so until the introduction of the peripheral decarboxylase inhibitors into antiparkinsonian therapy. Duvoisin’s group had noted that the rise in plasma L-DOPA levels was reduced in patients receiving the vitamin, but that homovanillic acid levels were about the same as in patients receiving L-DOPA alone. As hypothesized by the authors, it was later found that DOPA decarboxylase is indeed sensitive to pyridoxine levels; so much so, that the pyridoxine supplementation led to sharply increased peripheral decarboxylation of L-DOPA, thus nullifying the central benefits of L-DOPA therapy.354 After L-DOPA was regularly combined with peripheral decarboxylase inhibitors, the clinical response to L-DOPA was enhanced.

349 Birkmayer and Schmid, 1949; Hartmann-von Monakow, 1961. The normal daily requirement in humans is about 3mg, easily supplied by a normal diet.
351 See also Holtz and Palm, 1964; Lévy and Michel-Ber, 1965.
352 Sourkes et al., 1964a. The effect of pyridoxine deficiency on the metabolism of D,L-DOPA in these experiments was more marked than on that of L-DOPA.
353 Duvoisin et al., 1969b. Birkmayer and Hornykiewicz, as will be discussed below, did not find in general that pyridoxine administration blocked the L-DOPA effect in parkinsonian patients, only that it did not augment the effect achieved by the amino acid alone; in contrast to later workers, however, they administered L-DOPA intravenously, not orally, allowing more rapid access to the central nervous system.
VII. The 1950s: The synthetic anticholinergic and antihistaminergic preparations

decarboxylase inhibitors, pyridoxine supplementation was again possible. As a
mainstay of therapy, however, it was obsolete. Duvoisin reported in 1973 that it had no
measurable effect in parkinsonism, either alone or in combination with a traditional
antiparkinsonian medication. Further, an augmentation of the central effects of
endogenous L-DOPA when pyridoxine was administered together with a decarboxylase
inhibitor was discernible, but the effect did “not appear to be useful for routine
therapeutic purposes.” Interestingly, the vitamin appeared to exacerbate the negative
effects of the 5-HT precursors L-tryptophan and 5-HTP on parkinsonian
symptomatology; this did not occur, however, in patients treated with L-DOPA.355

Miscellaneous agents

It should not be thought that the dominance of anticholinergic and antihistaminergic
agents put a complete stop to the seemingly unrestrained experimentation with novel
therapies in the treatment of parkinsonism. As most would not play a significant role in
the future development of therapy and received only limited recognition even at the
time they were proposed, they are listed briefly here:

- **Curare** and **d-tubocurarine** continued to be examined spasmodically as antiparkinsonian
agents, but their short duration of action reduced the value of any benefit.356

- **Dihydro-β-erythroidine**, a derivative of the curare-like alkaloid isolated from *Erythrina
americana* Mill (figure 5-6), was found to be ineffective in twenty-four paralysis agitans
cases when used alone (200mg/day p.o.); together with a belladonna product (‘Rabellon’
or Vinobel), it had a striking effect on rigor, while not affecting tremor or oculogyria.357 It
enjoyed more success as a curare substitute in surgical anesthesia.

- **Sulphonylurea compounds** (*tolbutamide*358 and *chlorpropamide*359): used in the treatment
of type II diabetes, Gates and Hyman noted that the tremor of one of his older diabetic
patients was relieved while taking 3g tolbutamide/day.360 Gillhespy treated eighty-eight
parkinsonian patients with chlorpropamide (either alone or together with antiparkinsonian
agents), and noted improvement in fifty subjects.361 An association between diabetes
mellitus and hypothalamic dysfunction had been proposed in the mid-1950s,362 and there
had been anecdotal reports of diabetes being improved in parkinsonian patients who had
undergone surgery for their motor symptoms.363 Sulphonylurea drugs were thus
recommended by a few authors at the beginning of the 1960s but dismissed by as many as
being nothing other than placebos. The major side effect was, not unexpectedly,
hypoglycemia in some patients.364 Disturbed glucose metabolism in post-encephalitic
patients had been reported as early as the 1920s.365

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355 Ibid.
356 Examples: Borgarello and Donegani, 1949; Berger, 1956.
357 Shapiro and Baker, 1950.
358 N-[(Butylamino)carbonyl]-4-methylbenzenesulfonamide; British and German patents to Hoechst
359 4-Chloro-N-[(propylamino)carbonyl]benzenesulfonamide; British patent to Pfizer (1960). Pfizer
tradename: ‘Diabinese’.
363 Gillingham et al., 1960.
365 McCowan et al., 1926b; see also Birkmayer and Weiler, 1956.
VII. The 1950s: The synthetic anticholinergic and antihistaminergic preparations

• Zoxazolamine (‘Flexin’, McNeil, Philadelphia): a muscle relaxant; its synaptic blocking activity more intense and of longer duration that of mephenesin. It was useful in the treatment of spastic conditions of spinal origin, but was tried by two groups in the mid-1950s in parkinsonism without significant success, and was dismissed by 1958 as being “of little or no value in basal ganglion disturbances, such as Parkinson’s disease”.

• Testosterone with heparin: this was a rare attempt to specifically treat arteriosclerotic parkinsonism, suggested by Weinberg in 1954. He hoped by this means to increase the vascular supply of the extrapyramidal system-hypothalamic region; sialorrhea was improved, but no other symptom was consistently responsive.

• Garai reported in 1951 that inhaled amyl nitrite temporarily reduced the amplitude of tremor in a number of patients with idiopathic or postencephalitic parkinsonism. The rationale for the experiment was the recognition since the middle of the 19th century that amyl nitrite is a potent vasodilator; Brunton first used it in 1857 to treat angina. Further, the cortical theta rhythm (6Hz) was believed to be ‘paced’ by basal ganglia mechanisms and to be depressed by amyl nitrite. Garai reported no untoward side effects and proposed that other members of the alkyl nitrite class be investigated as antiparkinsonian agents; there was, however, a recognized risk of postural hypotension and even collapse. The drug is now used only as an acute agent in various cardiac complaints, particularly angina and congestive heart failure, as well as a recreational stimulant.

• In the case of arteriosclerotic parkinsonism, there were suggestions from some authors to treat the circulatory problems of the patient, in order to improve cerebral perfusion. Both Degkwitz and Birkmayer had concerned themselves with the nutritional consequences of reduced cerebral circulation in older patients before their investigations of the pharmacology of parkinsonism.

There were also, as often has occurred in the history of antiparkinsonian therapy, surprising reports; Keller, for instance, found that low doses (0.5-1.5mg/day) of reserpine – as will be discussed in chapter X, this sedative was often associated with the production of a parkinsonian syndrome – achieved a small but objectively verifiable improvement in four of seventeen patients also receiving phenglutarimide. The other patients exhibited sharp declines after 0.75mg reserpine. Keller noted that the patients who responded positively were “affectively labile, overanxious, insecure patients whose motor disturbances appeared more or less psychogenic, but with clear extrapyramidal symptoms.” Constable and Doshay also tried reserpine in various forms in a total of ninety-eight parkinsonian patients (10% postencephalitic parkinsonism, 45% each arteriosclerotic and idiopathic) in which symptoms such as hypertension, agitation, restlessness, depression, hallucinations and other psychiatric complaints were prominent. Used alone for up to twenty days, reserpine caused deterioration of symptoms in six of thirteen patients, and improvement in none; used together with an antispasmodic agent (not identified), improvement was noted in 35% of cases, deterioration in only 12% (total number of trials: 113). The improvement, however, was

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366 5-Chloro-2-benzoxazolamine; U.S. patents to McNeil Laboratories and Dow (both 1961).
367 Amols, 1956; Rodriguez-Gomez et al., 1956.
368 Extra Pharmacopoeia, 1958, p.663.
369 Weinberg, 1954.
370 Garai, 1951b.
371 Degkwitz: see chapter XI; Birkmayer: see Birkmayer, 1965, pp.95-145.
372 Keller, 1959.
373 ‘Rau-sed’, ‘Raudixin’ (E.R. Squibb & Sons), ‘Sandril’ (Eli Lilly & Co.), ‘Serpasil’ (Ciba), ‘Serpiroid’ and ‘Rauwiloid’ (Riker Laboratories). ‘Serpasil’ was the most commonly employed agent (65 cases).
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largely of a non-specific nature (increased calmness, reduced blood pressure); in only three cases was minor tremor improved, in one an improvement in gait was recorded. The doses employed were lower than those used in psychiatric practice (for example: for ‘Serpasil’, the maximum dose was 1.5mg/day), but one Huntington’s disease patient developed parkinsonian symptoms while receiving similar doses. The most disagreeable side effects were gastrointestinal responses.374

Problems associated with the anticholinergic therapy of parkinsonism

The long term use of potent anticholinergics revealed serious side effects which had, in fact, been noted earlier, but had been accepted as the price for symptomatic relief (table 7-4). Many physicians interpreted this phenomenon as indicative of the fact that not all parkinsonian patients were suitable candidates for drug therapy; they argued that both rigor and tremor could be abolished by simply increasing the dosage of the appropriate medication, if only the side-effects could be tolerated:

if not for disturbing side reactions, we would have enough drugs at present to control every symptom of Parkinson’s disease. If patients could tolerate 2,000 or 3,000 mg of Parsidol a day, there would not be a trace of tremor left in any Parkinson patient.375

(The normal dose of Parsidol (ethopropazine) was 50-600mg/day). Degkwitz voiced the opinion of an opposing camp when he argued that the side effects were the necessary biochemical consequences of the agents used.376 Russell DeJong argued similarly; he found that drugs with fewer side effects were generally also less potent, and that when used at doses which increased their symptomatic effect, the side effects were also increased.377 Baldauf had acted similarly before the War; he noted that he did not treat the mydriasis caused by his version of the Bulgarian treatment for fear of reducing the motor effect of the therapy;378 Arthur Hall had argued in 1929 that the solanaceous drugs were most effective when dosage is gradually increased to the point where toxic responses appeared.379 Clinical experience also indicated that rigidity was reasonably responsive to therapy; tremor, in contrast, was more resistant to such intervention, and was, in fact, usually exacerbated if the dosage was increased beyond a certain point.

Another serious drawback of anticholinergic therapy was the realization that these agents are also potent psychotomimetics. The amnesic effects of scopolamine had been exploited in “twilight sleep” narcosis; the hallucinogenic effects of accidental or deliberate belladonna and stramonium ingestion were also well known. It was also long recognized that anticholinergic medication frequently impaired recall and short term memory performance.380 The introduction of the “atropine toxicity” and “atropine coma” therapies into psychiatry and the increasing investigation of agents such as atropine in normal persons also underscored the psychotomimetic aspect of the antiparkinsonian drugs.381 By 1965, Duvoisin was estimating that up to one-third of

374 Constable and Doshay, 1956.
375 Doshay, 1961a; see also Doshay, 1961b.
376 Degkwitz, 1963.
377 DeJong, 1966a.
378 Baldauf, 1938.
379 See also Garland, 1952.
380 Duvoisin, 1965; see also Pondal et al., 1996.
381 For example, Forrer (1951) reported that the intramuscular (deltoid) injection of 32mg atropine was of benefit in schizophrenics; see also Miller et al., 1958.
### Antiparkinsonian agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication (where not antiparkinsonian)</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphenhydramine</td>
<td></td>
<td>19</td>
</tr>
<tr>
<td>Benzhexol</td>
<td></td>
<td>19</td>
</tr>
<tr>
<td>Procyclidine</td>
<td></td>
<td>7</td>
</tr>
<tr>
<td>Cycrimine</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Chlorphenoxamine</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Atropine</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Biperiden</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Benztropine</td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

### Supplementary antiparkinsonian agents

- D-Amphetamine: 3
- Meprobamate: 2
- Promethazine: 2

### Others

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrochlorothiazide</td>
<td>Diuretic</td>
<td>3</td>
</tr>
<tr>
<td>Chlortal hydrate</td>
<td>Hypnotic</td>
<td>2</td>
</tr>
<tr>
<td>Chlordiazepoxide</td>
<td>Anxiolytic</td>
<td>2</td>
</tr>
<tr>
<td>Ethinamate</td>
<td>Sedative/hypnotic</td>
<td>1</td>
</tr>
<tr>
<td>Rauwolfia, hydralazine</td>
<td>Antihypertensive</td>
<td>1 each</td>
</tr>
<tr>
<td>Desipramine, imipramine, nortriptyline</td>
<td>Antidepressant</td>
<td>1 each</td>
</tr>
<tr>
<td>Tolbutamide</td>
<td>Antidiabetic/antiparkinsonian</td>
<td>1</td>
</tr>
<tr>
<td>Chlorthalidone</td>
<td>Diuretic/antihypertensive</td>
<td>1</td>
</tr>
<tr>
<td>Griseofulvin</td>
<td>Antifungal</td>
<td>1</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>Antibacterial</td>
<td>1</td>
</tr>
<tr>
<td>Phenylbutazone</td>
<td>Anti-inflammatory</td>
<td>1</td>
</tr>
<tr>
<td>Estrogens</td>
<td>Hormones</td>
<td>1</td>
</tr>
</tbody>
</table>

**Table 7.3:** Drugs received in the previous three months by thirty-two parkinsonian patients studied by Weil-Malherbe and van Buren (Washington/Bethesda) in 1969. Twenty-two of the patients were diagnosed as idiopathic Parkinson’s disease, four as post-encephalitic parkinsonism, four as post-influenzal parkinsonism, one as head trauma-linked parkinsonism, and one as either trauma- or influenza-linked parkinsonism. Sixteen of the patients had undergone unilateral thalamectomy, six bilateral thalamectomy. Two patients (uncertain etiology/unilateral operation; idiopathic/bilateral operation) were not currently receiving any medication.

**Table 7.4 (next page):** The most common side effects associated with antiparkinsonian agents. The table is intended to give only a broad overview of the major problems associated with these agents and should not be seen as comprehensive, in that less common reactions and responses not seen as impeding the application of the agent in parkinsonian patients are not included. Based on information in contemporary editions of Martindale’s Extra Pharmacopoeia, Doshay (1961a), Degkwitz (1963) and Franck (1965). The seven drugs printed in bold were regarded by Doshay (1960) as the ‘standard antiparkinsonian medications’, with those underlined useful in the treatment of all symptoms.
### Basic antiparkinsonian medications

<table>
<thead>
<tr>
<th>Agent</th>
<th>Indication</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzhexol</td>
<td>All symptoms</td>
<td>Xerostomia, blurred vision, nausea, agitation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Overdose: confusion, delirium</td>
</tr>
<tr>
<td>Benztropine</td>
<td>Spasms, cramps, severe rigidity, freezing</td>
<td>Xerostomia, nausea, confusion, constipation, blurred vision, skin reactions</td>
</tr>
<tr>
<td>Biperiden</td>
<td>Akinesia, rigidity</td>
<td>Similar to benzhexol, but less marked</td>
</tr>
<tr>
<td>Caramiphen</td>
<td>Rigidity</td>
<td>Dizziness, disturbed peripheral proprioception</td>
</tr>
<tr>
<td>Chlorphenoxamine</td>
<td>Rigidity, akinesia, fatigue, weakness, sialorrhea, depression</td>
<td>Some xerostomia</td>
</tr>
<tr>
<td>Cycrimine</td>
<td>All symptoms</td>
<td>Similar to benzhexol, but less marked, psychic disturbances in older patients</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>Tremor, insomnia, agitation</td>
<td>Sleepiness, dizziness</td>
</tr>
<tr>
<td>Ethopropazine</td>
<td>Tremor, rigidity</td>
<td>Sleepiness, dizziness, muscular cramp</td>
</tr>
<tr>
<td>Methixene</td>
<td>Tremor</td>
<td>Sleepiness, dizziness, nausea, confusion, blurred vision</td>
</tr>
<tr>
<td>Orphenadrine</td>
<td>Rigidity, akinesia, fatigue, weakness, sialorrhea, depression</td>
<td>Some xerostomia, nausea</td>
</tr>
<tr>
<td>Phenglutarimide</td>
<td>All symptoms</td>
<td>Nausea, constipation, xerostomia, blurred vision, tachycardia, urinary retention</td>
</tr>
<tr>
<td>Pridinol</td>
<td>All symptoms</td>
<td>Similar to benzhexol, but less marked</td>
</tr>
<tr>
<td>Procyclidine</td>
<td>All symptoms</td>
<td>Similar to benzhexol, but less marked, excitement, muscular cramp, gastric disturbances</td>
</tr>
</tbody>
</table>

### Supplementary medications

<table>
<thead>
<tr>
<th>Agent</th>
<th>Indication</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamines</td>
<td>Akinesia, lethargy</td>
<td>Agitation, restlessness, tremor, hypertension</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>Agitation, restlessness, insomnia</td>
<td>Sleepiness, habituation, motor function retarded</td>
</tr>
<tr>
<td>Meprobamate</td>
<td>Agitation, restlessness, insomnia</td>
<td>Sleepiness, dizziness, mental functions retarded</td>
</tr>
<tr>
<td>Phenindamine</td>
<td>Hypersensitivity</td>
<td>None reported</td>
</tr>
<tr>
<td>Promethazine</td>
<td>Muscle cramp</td>
<td>Xerostomia, some indigestion</td>
</tr>
<tr>
<td>Zoxazolamine</td>
<td>Muscle cramp</td>
<td>Muscular weakness, bradykinesia</td>
</tr>
</tbody>
</table>

### Non-synthetic agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Indication</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyoscine</td>
<td>Tremor</td>
<td>Severe xerostomia, blurred vision</td>
</tr>
<tr>
<td>Reserpinoe</td>
<td>Agitation, restlessness, insomnia, hypertension</td>
<td>Sleepiness, bowel looseness, parkinsonian symptoms</td>
</tr>
<tr>
<td>Belladonna alkaloids</td>
<td>Muscle cramp</td>
<td>Xerostomia, blurred vision</td>
</tr>
</tbody>
</table>
patients receiving normal doses of antiparkinsonian medication experienced mental confusion, restlessness, disorientation or hallucinations; larger doses brought vertigo, slurred speech, ataxia, hyperreflexia and extensor plantar responses. High doses of atropine-class drugs also led to disturbances of homothermia which were not seldom fatal. As noted by Duvoisin, both the somatic and psychic side effects were often attributed to the disease rather than to the treatment.\textsuperscript{382} Solanaceous plants achieved a certain degree of popularity as hallucinogenic agents during the 1960s, although their unpleasant side effects prevented their achieving the popularity of the indole alkaloids. The abuse of antiparkinsonian agents by psychiatric patients, especially schizophrenics, has also been reported.\textsuperscript{383} It is probably significant that the same hallucinations can be elicited in patients by either anticholinergic or L-DOPA therapy, suggesting a common neurological substrate, possibly at the level of the limbic cortex.\textsuperscript{384}

After the introduction of L-DOPA and the withdrawal of many patients from anticholinergic agents, it was found that the anticholinergic drugs had had specific but reversible negative effects on both long and short term memory. It was also recognized that they also exacerbated pre-existing mentation deficiencies, so that there use in patients with such deficits was contraindicated.\textsuperscript{385} Significantly, even non-demented parkinsonian patients appear to be more sensitive than non-parkinsonian controls to scopolamine-induced memory impairment; a similarly increased sensitivity to the effects of benzhexol on cognition has also been detected.\textsuperscript{386}

The withdrawal of anticholinergic medication from parkinsonian patients was also often attended by difficulties. Such withdrawal was almost always marked by the sharp re-emergence of parkinsonian symptoms (within two or three days), often to a degree worse than that before the commencement of therapy; improvement might be manifested within a half hour of the re-institution of therapy, but could also require a period of days to achieve the status ante quo.\textsuperscript{387} Some workers reported in the early 1970s that the complete withdrawal of anticholinergic therapy was in fact impossible in a large subset of patients, even where large L-DOPA doses were employed.\textsuperscript{388} This problem contrasts with the effects of L-DOPA withdrawal, where the deterioration of motor performance is generally more gradual. The rapid deterioration in condition following discontinuation of anticholinergic therapy was later explained in terms of central cholinergic supersensitivity which had developed as a result of chronic anticholinergic therapy; Ruberg and colleagues, for instance, found elevated muscarinic receptor levels in the cortex of parkinsonian patients treated with such agents.\textsuperscript{389} MacIntosh also found that atropine actually increases the rate of acetylcholine release by brain tissue;\textsuperscript{390} this explained the long unexplained phenomenon that atropine causes a massive depletion of acetylcholine in the brain. It is now assumed that this effect is mediated by the action of atropine at muscarinic autoreceptors; further, the synthetic anticholinergic agents are more potent antagonists of these receptors than atropine.
VII. The 1950s: The synthetic anticholinergic and antihistaminergic preparations

The anticholinergic approach to the therapy of parkinsonism thus had fundamental limitations which could scarcely be overcome; a new direction was required, and this seemingly necessitated a better understanding of the function of central acetylcholine.

**Outlook for antiparkinsonian therapy at the beginning of the 1960s**

Whatever the results being achieved by the medical treatment of parkinsonism, greater hope for a long term solution was being placed by the early 1960s in the possibilities of neurosurgery. Many regarded the improvement in the specificity and effectiveness of neurosurgical techniques as the only means by which the progression of the disease could be halted. Chemical management was seen by the neurologist as capable only of alleviation of the worst symptoms of the disease; in the end, however, pharmacological therapies only postponed the necessity for surgical intervention:

> As long as a patient continues to be comfortable, productive, and independent in his activities of daily living, and maintains his ability to carry out gainful employment, then one may choose to continue drug therapy even though the disease is progressing. . . . Drug therapy, at best, can produce a 15 to 20 per cent objective reduction in tremor, rigidity and incapacitation of parkinsonism. Basal ganglia surgery is capable of producing a complete and lasting relief of tremor, rigidity and incapacitation.

Frøvig was almost apologetic in introducing his discussion chemical therapy at the Sixteenth Congress of Scandinavian Neurologists in Oslo in 1962; he recognized that physicians were “fighting a losing battle against a steadily progressive pathological process”, but argued nonetheless that drug therapy could “lighten our patients’ burdens and make their lives easier to live”. Boshes felt that surgery was a more systematic approach to the problem, in that patients were carefully assessed before treatment with respect to both their parkinsonism and other problems, and the intervention was correspondingly tailored to their individual situation. He did not want to appear a “therapeutic nihilist”, but drug therapy was something of a lottery; individual responses to a drug varied too much in order to be able to predict the outcome:

> Now it is just like lining up 3 or 4 men at a bar and giving them each 5 drinks out of the same bottle. One wants to fight everyone in the room. The second one wants to make love to the barmaid. The third one wants to sing. And the fourth one passes out and falls asleep. Now this is with the same medicine out of the same bottle under the same conditions.

He questioned whether the anticholinergic drugs were still appropriate, or whether psychic energizers might be the better choice in light of recent findings concerning the catecholamines; whatever the choice, “when we are using a drug, we ought to know what we are doing.” Other members at the same conference commented on the expense of modern antiparkinsonian therapy (“one no longer speaks of the price of a pill, but of the price per milligram”).

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391 Collier, cited by Sourkes, 1999; see also Hulme et al., 1978.
392 Cooper, 1961, p.10.
393 Frøvig, 1963.
394 Forster et al., 1966.
395 Ibid.
396 Ibid.
Despite the surgical emphasis of neurology at this time, however, not all authorities were as optimistic concerning the possibilities of neurosurgery as Cooper. Parkinsonism was nonetheless generally regarded as being the direct result of aberrant neural circuits in the brain caused by a definable (if not yet defined) physical lesion, such as the compression or degeneration of specific brainstem regions, or a focal lesion in the pallidum, or by a general metabolic dysfunction. There remained a great degree of uncertainty at the physiological level; while an anatomic lesion in the substantia nigra was generally regarded as being associated with the disease, it was observed in histopathological studies that this lesion was often negligible or even totally absent, especially in idiopathic Parkinson’s disease. Further, the relationship between this lesion and the frequently observed abnormalities in the pallidum awaited a satisfactory explanation. Nevertheless, physical abnormalities had been identified in the parkinsonian brain, so that surgical intervention appeared to be at least feasible.

What little was known about the specific neurochemistry of the central nervous system at the time, on the other hand, was not regarded as being directly relevant to the treatment of the disorder. Most handbooks of this era gave only brief coverage to the chemical therapy of the disorder, while devoting large sections to surgery; Hartmann-von Monakow’s monograph (1960) was an exception in this regard. As late as 1967, the English neurologist Oliver published a handbook on parkinsonism in which the section devoted to surgical treatment was almost six times longer than that describing pharmacological treatment; even here there was, however, no mention of ‘neurotransmitters’.  

Table 7-5 (next page): Chronological listing of the major synthetic antiparkinsonian agents discussed in this chapter. Agents are listing primarily according to year of introduction as given by Hartmann-von Monakow (1960a), supplemented by information in Frøvig, 1963. The dates in square brackets are those for year of introduction in the United States, as listed in A.M.A. Council on Drugs (1960-1964); these, however, are given only where the year is different to that listed by Hartmann-von Monakow, or where the latter author has not listed a date of introduction. In general, the earlier date corresponds to the first use of the agent in the clinic; the later date indicates when the agent became commercially available in the United States.

397 Hartmann-von Monakow devoted 32 pages to the clinic of the disorder, 45 pages to the chemical therapy and only 7 pages to surgical therapy.

398 Oliver, 1967.
<table>
<thead>
<tr>
<th>Year</th>
<th>Amino esters</th>
<th>Phenothiazine derivatives</th>
<th>Amino ethers</th>
<th>Propanol derivatives</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>1946</td>
<td>Caramiphen ('Parpanit')</td>
<td>Diethazine ('Diparcol')</td>
<td>Diphenhydramine ('Benadryl')</td>
<td>[Pyrilamine] ('Anthisan')</td>
<td></td>
</tr>
<tr>
<td>1947</td>
<td></td>
<td></td>
<td></td>
<td>Mephenesin ('Myanesin')</td>
<td></td>
</tr>
<tr>
<td>1948</td>
<td></td>
<td></td>
<td></td>
<td>Phenindamine ('Thephorin') [Mephenesin]</td>
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</tr>
<tr>
<td>1949</td>
<td>[Caramiphen]</td>
<td>Ethopropazine ('Parsidol', 'Lysivane')</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1950</td>
<td></td>
<td></td>
<td>卞酚甲胺 ('Artane')</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1951</td>
<td></td>
<td>Etanautine ('Rigidyl')</td>
<td></td>
<td>Bamipine ('Soventol')</td>
<td></td>
</tr>
<tr>
<td>1952</td>
<td></td>
<td></td>
<td>Procyclidine ('Kemadrin')</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1953</td>
<td></td>
<td></td>
<td></td>
<td>Benztropine ('Cogentin')</td>
<td></td>
</tr>
<tr>
<td>1954</td>
<td>[Ethopropazine]</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>1955</td>
<td></td>
<td>Orphenadrine ('Disipal')</td>
<td></td>
<td>Benztropine ('Cogentin')</td>
<td></td>
</tr>
<tr>
<td>1956</td>
<td></td>
<td>Benactyzine ('Suavitil')</td>
<td></td>
<td></td>
<td>[Methyl phenidate] [Zoxazolamine]</td>
</tr>
<tr>
<td>1957</td>
<td></td>
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<tr>
<td>1960</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

VII. The 1950s: The synthetic anticholinergic and antihistaminergic preparations
VIII. Assessment of the pharmacological therapy of parkinsonism

There were thus a wider variety of drugs to choose from at the end of this era of the therapy of Parkinson’s disease than in 1945, even if in the most cases the principle of action was essentially the same as that in the previous period: anticholinergic mechanisms. A casual perusal of the many short reviews and summary articles of this period, however, reveals that the various “experts” were not totally unanimous in their personal selections as to the “best” antiparkinsonian agents. As has been mentioned several times, parkinsonian patients, particularly those of postencephalitic etiology, were infamous for their apparent need to switch medications on a regular basis. The question of the development of tolerance to antiparkinsonian drugs was also problematic; England and Schwab were of the opinion that patients merely became frustrated with the lack of improvement of their condition after treatment with a particular agent for some time, and thus reported that the drug had lost its effectiveness in order to gain access to an alternative.\(^1\) Others accepted the tolerance claims as real:

> Because tolerance to most agents develops in varying degrees and at varying rates, the physician must continually be aware of this and adjust the dose or shift to another agent as needed.\(^2\)

Whether the acquired tolerance was real or not, it was clear that the clinician would be always pleased to have an array of drugs of fundamentally similar character which could be substituted for one another as any particular agent began to lose favor with an individual patient. Allied to this issue are the finicky habits of some patients; Boshes mentioned one trial in which the red capsules normally used for benzhexol met with the

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1 England and Schwab, 1959.
2 Friend, 1963 and references therein.
disapproval of many patients, purely on the basis of their color; the same medication in white capsules was tolerated without comment.\(^3\) There was also the question of individual response; patients do not always respond to a given medication in the manner prescribed by textbooks or pharmaceutical firms. This is, of course, hardly surprising in a disorder with a neurological basis which even today has not been completely elucidated; these varying responses have often led, in fact, to further speculation and insights concerning the underlying cause of the disease and how it might be better attacked.

There was another problem, however, which could not always be corrected by changing medication. A commonly encountered phenomenon was the presentation of a patient with mild parkinsonism in his fifth decade, whose symptoms were adequately controlled by low levels of anticholinergic medication for a number of years, maybe even decades. Eventually, his condition would suddenly deteriorate, and it would prove that not only did elevation of the doses employed not improve his situation, it actually exacerbated it, a frustrating experience for both patient and physician. Precisely at the point when the patient required reliable pharmacological assistance, even small improvements were now difficult to obtain. This was the natural consequence of a progressive disease and a nervous system treated for many years with anticholinergic medication. It was sometimes possible to overcome this difficulty by switching agents, but by 1960 the frequency of this phenomenon had emerged as a disturbing problem.\(^4\)

**Which were the “drugs of choice”?**

Behrend (University Neurological clinic, Hamburg-Eppendorf) commented rather cynically in 1954 that there was an incredible literature on the excellent effects of a seemingly endless range of new antiparkinsonian agents, but:

*one cannot escape the impression that the value of the results is inversely proportional to the amount of criticism to which they have been subjected.*\(^5\)

A major problem, as Behrend saw it, was that optimism and the lack of standardized testing was a hindrance to progress in the therapy of parkinsonism. He criticized the small numbers of patients involved in most reports, and also the overly positive interpretation of dubious results:

*The literature on the therapy of parkinsonism is full of “good impressions” which lack any basis when judged soberly.*\(^6\)

Behrend was especially irritated by clinicians who reported that a drug had achieved only moderate benefits – for example, excellent results in three of twenty-three patients – but still concluded their essay with the comment that *“the drug had made a positive impression on the therapist.”* Behrend saw part of the problem as being the rise of modern pharmaceutical firms as arbiters of medical therapy; doctors no longer considered their patients as individuals but as end-receivers of the latest products. He argued that the clinician must be prepared to patiently try a series of drugs, new and old,

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\(^3\) Forster \textit{et al.}, 1966.

\(^4\) England and Schwab, 1959; Porteous and Ross, 1956.

\(^5\) Behrend, 1954.

\(^6\) \textit{Ibid.}
with each patient over months or even years; he himself had been surprised by seemingly intractable cases which suddenly registered improvement. The doctor must be aware that there still existed a choice of agents, and that he must make the choice on the basis of the individual patient. There was thus, per definitionem, no “drug of choice”, only alternatives, which in the most cases must be used in combination with one another to achieve anything approaching a satisfactory result.\textsuperscript{7}

Despite these caveats, certain drugs were prescribed more often than others, presumably because treating physicians found them more useful. Indeed, as noted by Frøvig in 1963, medical treatment of the disorder had become more stable since 1946; “\textit{no fundamentally new departures}” had been introduced to the clinic since that time.\textsuperscript{8} Most authorities agreed that benzhexol was the breakthrough in parkinsonian therapy of the post-War period. Apart from this, the only constant in the review literature was that the synthetic antiparkinsonian agents quickly displaced the belladonna alkaloids in the favor of most physicians after their introduction. To cite a few examples:

- An early list by Gillhespy nominated ethopropazine ahead of benzhexol as the most useful agent, followed by phenindamine, promethazine and pyrilamine.\textsuperscript{9} He later promoted the combination of ethopropazine and orphenadrine as the most effective in the greatest number of patients.\textsuperscript{10}

- From Doshay’s point of view in 1958, only six new agents had survived the test of “\textit{large-series and long-term study}”: benzhexol, procyclidine, ethopropazine, orphenadrine, benztrpine and cynamine. The surprising omission from this list was the otherwise universally praised diphenhydramine, which was the only major deviation from the list published by Critchley in the same year.\textsuperscript{11}

- By 1964, Onuaguluchi (Pharmacology and Therapeutics, Ibadan; formerly Materia medica and Therapeutics, Glasgow) regarded only the first four of Doshay’s list as being of “\textit{outstanding value}”.\textsuperscript{12}

- Becker’s 1956 list (University Neurological Clinic, Würzburg) was somewhat divergent, in that he still valued the belladonna alkaloids more highly than the synthetic alternatives; he advised against atropine and scopolamine, preferring to begin with ‘Homburg 680’, whereas many physicians regarded the use of the Bulgarian treatment in the elderly as somewhat perilous.\textsuperscript{13}

There was thus some difference of opinion with respect to preferred agents, with the exception that benzhexol appeared on most recommendation lists. But all authorities recognized that no single agent represented a “therapy” in itself:

- Bruce, as editor of Wilson’s \textit{Neurology} (1954), noted that the value of pharmacological therapy in the treatment of paralysis agitans was variable. Rigidity could be alleviated to some degree by the belladonna class drugs, with the specific

\textsuperscript{7} Ibid.
\textsuperscript{8} Frøvig, 1963.
\textsuperscript{9} Gillhespy, 1953.
\textsuperscript{10} Gillhespy, 1956, 1958.
\textsuperscript{11} Critchley, 1958.
\textsuperscript{12} Onuaguluchi, 1964, p.124.
\textsuperscript{13} Becker, 1956.
choice depending on the individual patient. The synthetic preparations had also started to prove their value; he adopted Gillhespy’s preferences with regard to these agents.\textsuperscript{14}

- Edwards (1954) recommended diphenhydramine alone (4×50-100mg/day) in mild cases, to be supplemented with ‘Rabellon’ or ‘Bellabulgara’ as necessary. In more advanced cases, therapy commenced with benztpoline alone, to be supplemented with benzhexol and diphenhydramine as necessary. Cycrimine at higher doses could be useful in post-encephalitic cases.\textsuperscript{15}

- Doshay (1958, 1961a,b) prescribed as the basis of therapy a combination of benzhexol, cycrimine and procyclidine; benztropine should be added in cases of strong rigidity, akinesia or spasms, isothiazine in the case of strong tremor, and orphenadrine and chlorphenoxyamine in cases of troublesome fatigue or depression.

- Keller (1959) began with physiotherapy in cases of severe rigor and hypokinesia. With younger patients, chemical therapy began with belladonna alkaloids and an energizer (phenmetrazine, methamphetamine or ephedrine), together with scopolamine in cases of strong tremor; in middle-aged patients, with biperiden, benzhexol or caramiphen, and the addition of an energizer after the motor symptoms were controlled, together with an antihistamine for strong tremor. Older patients received a slowly increased dose of tinctura stramonii and an antihistamine.

- England and Schwab (1959) began with a synthetic anticholinergic in cases with rigidity as the main symptom, gradually increasing the dose until side effects appeared. In cases where tremor dominated, a phenothiazine was administered at the lowest possible dose and then slowly increased. Where both symptoms were significant, therapy began with either a phenothiazine or a propanol derivative, a member of the other drug group being added later, as was an antihistaminergic followed by an energizer as necessary.

- Hartmann-von Monakow (1960a, 1961) began with pyridoxine in light cases and added stramonium as the disease progressed; advanced cases of postencephalitic parkinsonism with minimal vegetative symptoms received phenglutarimide (and, if required, bamipine), while those with more severe vegetative complaints received belladonna alkaloids followed by phenglutarimide, benzhexol, biperiden or cycrimine, although other choices could also be considered. Paralysis agitans cases were treated with phenglutarimide, benzhexol, orphenadrine or benztpoline together with stramonium, ‘Bulgakur’ or pyridoxine, while arteriosclerotic cases started with pyridoxine and belladonna, and received only later, if at all, phnglutarimide, benzhexol, biperiden or orphenadrine. Hartmann-von Monakow was one of the few review authors at this point who specifically approached the three forms of parkinsonism as distinct therapeutic entities.

- In 1962, Birkmayer recommended ‘Artane’ for rigidity and ‘Homburg 680’ for the tremor, testament to the enduring popularity of the Bulgarian treatment. Amitriptyline and scopolamine were used for oculogyric crises. For akinesia, none of the existing therapies provided satisfactory results.

Apart from the observation that the most effective therapies for Parkinson’s disease combined anticholinergic with antihistaminergic elements, the biochemical action and

\textsuperscript{14}Wilson, 1954b, pp. 938-940. His recommendations regarding post-encephalitic parkinsonism were similar, but also retained measures which aimed to control the presumptive viral or bacterial cause of the disorder; Wilson, 1954a, pp.159-162.

\textsuperscript{15}Edwards, 1954.
specific sites of action of these agents was largely unknown, and progress in the chemical therapy of Parkinson’s disease was a matter of trial and error. Onuaguluchi, however, commented that a 30% improvement was the average expectation when objective measures were used, and then only if the clinician had determined the optimal combination of agents.\(^{16}\) The new drugs were not necessarily more effective than the belladonna alkaloids, and many authorities saw the continued application of the solanaceous agents as justified; but, as several authors noted, approximately 60-70% of patients responded positively to any given drug for at least a period of time, so that the cheapest alternative was naturally to be preferred (cf. table 8-1).

There were also certain preferred and contraindicated combinations of antiparkinsonian drugs. This also arose from the realization that no single agent was capable of treating all symptoms in a single patient. Hartmann-von Monakow wrote that synthetic agents and alkaloids should never be combined. Nor should etybenzatropine be used with benztrpine, nor benzhexol with biperiden, procyclidine or cycrimine; that is, related synthetic compounds should not be combined, presumably because of the possibility of cumulative toxicity.\(^{17}\) It should be noted, however, that Doshay (for example) did not heed this advice;\(^{18}\) Onuaguluchi saw the remaining value of belladonna alkaloids precisely in their role as adjuvants to synthetic therapy.\(^{19}\) General contraindications for the use of any anticholinergic agent, natural or synthetic, continued to be co-existent glaucoma, heart disease or prostate hypertrophy – all problems which were increasingly encountered in the aging parkinsonian population. Although glaucoma was a constant problem with any of the anticholinergic drugs,

\(^{16}\) Onuaguluchi, 1964, p.124.

\(^{17}\) Hartmann-von Monakow, 1969.

\(^{18}\) Doshay, 1958; 1961b.

\(^{19}\) Onuaguluchi, 1964, pp.119, 124.
Russell de Jong was of the opinion that if controlled, it did not constitute a contraindication for normal use of antiparkinsonian drugs, but conceded that the measurement of intraocular tension can be a problem in some Parkinson’s disease patients.\(^ {20} \)

**Comparing different antiparkinsonian agents**

Detailed comparisons of the effectiveness of several agents was rarely reported in the literature; at best, the use of a new agent was often recommended by a particular author because available agents were less well tolerated by a specific group of patients. In 1952, Behrend appended his own experiences with a range of synthetic agents to a review of those of other workers, but this was no more than a survey of the literature, even if it was useful in assisting clinicians to maintain an overview of the current pharmaceutical options. As was typical of this form of report, individual agents were either recommended or rejected, but direct comparisons of their effects and effectiveness were not undertaken.\(^ {21} \)

One of the earliest exceptions was a rather surprising report by Loman and associates (Division of Psychiatric Research, Boston State Hospital) in 1942. These authors compared the effects of a variety of drugs on the rigidity and tremor of postencephalitic parkinsonism: sympathomimetics, parasympathomimetics and anticholinergics, central stimulants and various combinations of these classes. The astounding feature of the study, apart from the ambitious pharmacological scope, was that it was conducted in two patients: a 25 year old woman whose unilateral symptoms had begun developing at the age of 17 (with no definite history of encephalitis), and a 42 year old woman who had experienced encephalitis for six months in 1919 and had begun to develop bilateral rigidity and tremor in 1937; she had been institutionalized since 1938. Further, the discussion of the results was restricted almost entirely to those of the first patient. The authors concluded that the agent with the most consistent benefit for the patient was scopolamine administered parenterally; atropine was also good, but its sedative effects were not as marked. Amphetamine was of use in controlling rigidity, but not tremor; none of the central stimulants (caffeine, strychnine, ethylenediamine, theophylline, pentylenetetrazole, nikethamide\(^ {22} \)) had any effect on parkinsonian symptoms. Surprisingly, acetylcholine was found to be mildly beneficial for the rigidity, as was neostigmine. The best drug combination appeared, in fact, to be scopolamine together with neostigmine, caffeine or amphetamine, all of which greatly reduced rigidity and tremor, often abolishing the latter; these effects, however, were also seen to a large extent with scopolamine alone.\(^ {23} \)

**Table 8-2 (next page):** Recommended agents for the treatment of parkinsonism according to the Extra Pharmacopoeia of Martindale, 1952-1972. Notes: \( \bullet \) Listed as ‘and other parasympatholytics’ or ‘anticholinergic agents’ from 1958. \( \oplus \) ‘Amphetamine and other CNS stimulants’. \( \ominus \) Benzhexol (and many other synthetic antiparkinsonian agents) were discussed under ‘atropine’ from this time; with the increase in the number of current pharmaceutical agents, the Extra Pharmacopoeia gradually moved from listing individual items to a classification system based on major pharmacological action.

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20 DeJong, 1966b.
21 Behrend, 1952.
22 Pyridine-3-carboxylic acid diethylamide; ‘Coramin’ (Ciba). U.S. patent: 1922.
23 Loman et al., 1942.
### VIII. Assessment of the pharmacological therapy of parkinsonism

<table>
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<tr>
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<tbody>
<tr>
<td>Hyoscyamus</td>
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<tr>
<td>Hyoscine</td>
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<tr>
<td>Belladonna preparations</td>
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<tr>
<td>Stramonium</td>
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<tr>
<td>Bulbocapnine</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Atropine and other parasympatholytics</td>
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<td>1</td>
<td>1</td>
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<tr>
<td>Pyridoxine</td>
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<td>Cobra venom</td>
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<tr>
<td>Amphetamine</td>
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<tr>
<td>Datura leaves</td>
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<tr>
<td>Tigloidine</td>
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<tr>
<td>Mephenesin</td>
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<td>Ethopropazine</td>
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<tr>
<td>Benzhexol</td>
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<tr>
<td>Diethazine</td>
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<tr>
<td>Caramiphen</td>
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<tr>
<td>‘Antihistamines’</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>‘Other CNS stimulants’</td>
<td>2</td>
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<tr>
<td>Quinine</td>
<td></td>
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<td></td>
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<tr>
<td>Methamphetamine/Dexamphetamine</td>
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<tr>
<td>Promethazine</td>
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<tr>
<td>Alcohol paste injections</td>
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<tr>
<td>Tropaine</td>
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<tr>
<td>Levodopa</td>
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<tr>
<td>Amantadine</td>
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</tbody>
</table>
Doshay and associates published in 1947 a comparison of the effects of various belladonna alkaloid treatments in fifty-five of their patients. Interestingly, they also examined the effect of the atropine analog homatropine (‘Novatrine’; Ayerst/Campbell Products), a drug expected to have no effect and thus included as a control medication. The study is difficult to interpret, in that the etiology of the parkinsonism in each case, its duration and severity, and the age of the patients varied; further, the number of patients receiving a particular drug ranged from fifteen (atropine) to thirty-one (hyoscine), while a number of patients had tried a number of different agents in the course of the study. Nor were the relationships between these variables explained (in particular, reason for treating any single patient with a particular agent). Nevertheless, the attempt to compare medicaments and the classification of patients according to various factors (for example, this is the first paper of which I am aware in which the investigators gave statistics on the numbers of patients whose disease was of “rapid” or “slow” progression or stationary). The results of his sample were as follows:

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Patients showing improvement</th>
<th>Patients showing deterioration</th>
</tr>
</thead>
<tbody>
<tr>
<td>hyoscine</td>
<td>31</td>
<td>74%</td>
</tr>
<tr>
<td>‘Bellabulgara’</td>
<td>18</td>
<td>61%</td>
</tr>
<tr>
<td>‘Vinobel’</td>
<td>24</td>
<td>54%</td>
</tr>
<tr>
<td>atropine</td>
<td>15</td>
<td>53%</td>
</tr>
<tr>
<td>‘Rabellon’</td>
<td>18</td>
<td>50%</td>
</tr>
<tr>
<td>stramonium</td>
<td>22</td>
<td>50%</td>
</tr>
<tr>
<td>homatropine (control)</td>
<td>17</td>
<td>6%</td>
</tr>
</tbody>
</table>

The authors concluded that atropine together with hyoscine was perhaps to be preferred in postencephalitic parkinsonism, stramonium in idiopathic and arteriosclerotic cases, while the other agents were suitable for any form of the disorder; overall, the drugs are all fairly well equally effective, and the choice is largely a matter for the patient. They were, however somewhat resigned to the fact that none of the agents offered much long-term hope; at best, they were “entirely harmless and the reactions minimal”, and without them the patients would be “far more miserable and disabled”; real hope, in the eyes of the authors, lay only in the development of effective neurosurgical procedures.25

William Tillmann (Psychiatry, Massachusetts General Hospital) devised a method by which the effects and side effects of serially administered agents were rated and compared with each other, resulting in a quotient for each drug (“therapeutic index”); it was calculated as follows:

\[
\frac{(4 \times \text{Number of patients for whom drug as monotherapy was best treatment} \\
+ 2 \times \text{Number in whom it achieved good results} \\
+ 1 \times \text{Number in whom the drug in combination with another agent achieved the best results})}{(4 \times \text{Number who reported toxic side effects} \\
+ 2 \times \text{Number in whom it had no effect})}.
\]

24 The mandelic acid atropate of tropine; it was preferred to atropine as a mydriatic because of its shorter duration of action.

25 Doshay et al., 1947.
Using this formula in August 1949; Tillmann concluded that benzhexol, caramiphen and diphenhydramine should be the drugs of choice (125 patients assessed).\textsuperscript{26} Schwab and Prichard reapplied this technique in May 1950, at which point it emerged that benzhexol was easily the best agent available, while caramiphen, diphenhydramine, stramonium and scopolamine were also highly useful (100 patients; table 8-3). The values calculated deviated somewhat from the earlier assessment, reflecting the subjectivity of the index. Nevertheless, the relative positions on the table were similar, but this would be expected given the short time difference and its application by the same group. The authors noted that no treatment for parkinsonism achieved more than temporary symptomatic amelioration; this they compared with the reduced options but greater successes in diseases such as diabetes, myasthenia gravis, epilepsy and heart disease.\textsuperscript{27}

<table>
<thead>
<tr>
<th>Drug</th>
<th>Number of patients</th>
<th>% Favorable effects</th>
<th>Therapeutic index</th>
<th>Therapeutic index (Tillmann, 1949)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzhexol</td>
<td>75</td>
<td>78</td>
<td>8.4</td>
<td>3.1</td>
</tr>
<tr>
<td>Caramiphen</td>
<td>87</td>
<td>64</td>
<td>3.5</td>
<td>2.8</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>72</td>
<td>61</td>
<td>2.1</td>
<td>2.0</td>
</tr>
<tr>
<td>Stramonium</td>
<td>38</td>
<td>52</td>
<td>2.2</td>
<td>0.8</td>
</tr>
<tr>
<td>Scopolamine</td>
<td>92</td>
<td>46</td>
<td>1.9</td>
<td>0.3\textsuperscript{1}</td>
</tr>
<tr>
<td>Promethazine</td>
<td>14</td>
<td>43</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>Belladonna alkaloid</td>
<td>27</td>
<td>37</td>
<td>1.3</td>
<td>—</td>
</tr>
<tr>
<td>Phenindamine</td>
<td>41</td>
<td>32</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>36</td>
<td>31</td>
<td>0.5</td>
<td>0.4</td>
</tr>
<tr>
<td>Dimethazine\textsuperscript{2}</td>
<td>25</td>
<td>24</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Mephenesin</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Table 8.3: ‘Therapeutic index’ for antiparkinsonian drugs as reported in Schwab and Prichard in 1951. The results gained in 1949 by Tillmann, who devised the technique, are also given for comparison. \textsuperscript{1} Figure given for ‘scopolamine or belladonna’; \textsuperscript{2} Dramamine (Searle): a compound anti-emetic which included a component with the classic spasmolytic structure (2-(diphenylmethoxy)-N,N-dimethylethanamine).

Degkwitz listed without exact source the results of an assessment of a range of antiparkinsonian medications by the Dutch Advisory Committee for Applied Scientific Research which had been published in 1955 (table 8-4); the responses of individual patients to a particular drug, however, could not be predicted by this table. Orphenadrine appeared to emerge from this comparison as by far the best agent; but it was noted that this was not the case for all patients.\textsuperscript{28}

There thus existed no consensus regarding the choice of medication in the therapy of disease, nor indeed with regard to the course that therapy should take as the disorder progressed. A direct comparison of the effects of individual agents assumes that these effects can be clearly defined and delineated both in advance and during the course of therapy. But some clinicians attempted to withdraw their patients from their previous

\textsuperscript{26} Cited in Schwab and Prichard, 1951.

\textsuperscript{27} Schwab and Prichard, 1951.

\textsuperscript{28} Degkwitz, 1963.
medication before trying a new drug, whereas others saw this as impractical, and attempted the withdrawal process only after the new drug had shown signs of promise. Still others specifically tested new agents as additions or adjuncts to the therapy of particular patients, with the aim of better control of a particular symptom. Most clinicians finally found that a combination therapy was necessary; Schwab and Prichard would begin with a single drug, serially adding new agents as the existing combination revealed the inadequacy of therapy hitherto.29

**Problems in the assessment of antiparkinsonian medication**

As one peruses the older literature regarding the therapy of parkinsonism, the reader cannot help but be struck by the fact that each new medication was greeted with optimistic enthusiasm, enthusiasm supported by the generally positive results initially reported. Before the Second World War, such optimism generally expected that the new therapy would benefit the bulk of the parkinsonian population, with the forewarning that ‘arteriosclerotic’ parkinsonian patients were largely untreatable. After the War, new therapeutic approaches were initiated by chemical or pharmaceutical firms rather than by individual physicians, and expectations were scaled down; if 50-70% of patients were helped by an agent, it could be regarded as a valuable new addition. Nonetheless, the optimistic results reported in the literature for these agents do not harmonize with descriptions from the early 1960s of geriatric wards filled with miserable patients eking out a wretched existence until death granted merciful release.

It is clear that a deterioration in the general condition of the hospitalized parkinsonian population was to be expected as the post-encephalitic cases aged, gradually raising the mean age of parkinsonian patients to that of what are now designated ‘idiopathic’ parkinsonian patients. There was also the phenomenon noted by Schulz in 1961:

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29 Schwab and Prichard, 1951.
Figure 8-1: Size of the Martindale Extra Pharmacopoeia, 1888-1992, based on total page area (page number was not an appropriate indicator of size, as the page size was altered dramatically throughout this period). The figure is presented to demonstrate the increasing difficulty with which the physician has been confronted regarding available medicaments; note especially the steep climb since the 1950s.

The Parkinson patient, however, who recognized with great joy not only the greater effectiveness of the new compounds, but quite clearly in most cases also the much reduced and less disturbing side effects, now appraised these medicaments . . . more critically, which is quite understandable, but with the result that therapeutic benefits, for which perhaps 10 or 15 years ago no patient would have dared to hope, would now be regarded by the patient as unsatisfactory.  

But until the 1960s, the assessment of the effectiveness of a new therapy was largely the prerogative of the individual physician. There were no multicentre trials, no standard protocols for the implementation or assessment of a new agent, no statistical analysis of results (the appropriateness of which, in any case, would have been questionable in light of the small sample numbers involved), often no objective means utilized for judging the benefit of a drug. In short, there existed a range of methodological problems regarding the scientific investigation of antiparkinsonian medications. This is not necessarily a major problem: the circumspect physician, assisted by vigilant nursing staff, should be capable of assessing whether his patients benefit from a particular drug. It was, however, difficult to judge whether the newest ‘miracle drug’ should be tried immediately, allowed to prove itself in other clinics before examining it, or dismissed as a nine day wonder. Further, no physician can be expected to be acquainted with the entire current pharmacopoeia; as a result, each doctor tends to develop a preference for a limited range of medications, which becomes the basis of choice in the clinic over years. In this situation, it is imperative that the physician’s choices are guided by reliable data derived from validly executed investigations.

In 1963, Degkwitz analyzed sixty-five published reports on a total of twenty-five antiparkinsonian drugs examined in trials which included at least seven patients – this figure itself speaks volumes about the style of therapeutic trial undertaken at this time – and found that in most cases the investigators reported improvement in about two-thirds

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30 Schulz, 1961a.
of patients; a similar result was found whether he included all studies, only those with over 100 cases,\textsuperscript{31} or any of a number of subdivisions based on case number.\textsuperscript{32} It thus seemed that "all drugs work equally well, as long as they are administered under the same conditions."\textsuperscript{33} As he noted, this was, in fact, not the case; the responses to any particular drug depended on a number of variables:

- Administration of the drug on an ambulant or stationary basis; the response was, not surprisingly, usually better under the former conditions.

- Severity of the disorder: this was partly correlated with the previous consideration. In general, severe cases were, not unexpectedly, less responsive to therapy. Using the large Bulgarian treatment series of Völler and Panegrossi as examples, Degkwitz showed that the "mild cases" accounted for most of the "significantly improved" patients; their overall success rates, however, were also about 66%\textsuperscript{34} Duvoisin noted that less severely affected cases were often unwilling to tolerate the side effects of anticholinergic therapy, while more advanced cases experienced any benefit afforded as significant relief.\textsuperscript{35}

- Related to this issue was the fact that even significant objective relief of tremor and rigidity was often insufficient to produce a noticeable improvement in motor function if the disease was too advanced. In such cases, the drug might objectively be judged as effective, even though the patient remained incapacitated.

- The psychological state of the patient was usually neglected in the analysis of results. Schwab and colleagues followed a group of sixty-five parkinsonism patients (various types) for three to five years and arrived at the astonishing conclusion that, regardless of medication, 67% of "difficult patients" (those who were depressed, anxious, complaining or similar) showed symptom progression compared with 25% of patients with a more optimistic and cooperative attitude.\textsuperscript{36}

- The type of parkinsonism: postencephalitic patients were able to tolerate higher doses of the belladonna alkaloids, and in many cases seemed to respond better to any form of therapy. This would also be found by Birkmayer with L-DOPA,\textsuperscript{37} but later workers found that these patients did not tolerate the high L-DOPA doses introduced by Cotzias;\textsuperscript{38} the reasons for this discrepancy have not been entirely clarified. In many reports, the type of parkinsonism was not indicated; there were also differences in classification, so that ‘paralysis agitans’ and ‘arteriosclerotic parkinsonism’ were often collated as one group, and entities such as ‘post-syphilitic’ parkinsonism were employed by a few groups.\textsuperscript{39} In general, however, arteriosclerotic patients were the least responsive patients to any form of therapy.

\textsuperscript{31} There were twelve studies with over 100 patients, eight of them conducted by Doshay.
\textsuperscript{32} Degkwitz, 1963. The Matheson Commission made the following comment in 1929 on the effectiveness of drugs for treating the various stages of encephalitis lethargica: "In summarizing the favorable and unfavorable results of or comments upon, many therapeutic measures, it is a striking fact that very often approximately two-thirds have been favorable, and one-third unfavorable" (pp.136-137). They had attributed this to the fact that the mortality rate of the epidemic was about 33%.
\textsuperscript{33} Degkwitz, 1963.
\textsuperscript{34} See Panegrossi, 1938; Völler, 1941.
\textsuperscript{35} Duvoisin, 1965.
\textsuperscript{36} Prichard et al., 1951.
\textsuperscript{37} Birkmayer and Hornykiewicz, 1964.
\textsuperscript{38} Calne et al., 1969; Hunter et al., 1970; Krasner and Cornelius, 1970; Sacks et al., 1970.
\textsuperscript{39} Schwab and England (1968) had found 59 cases of syphilis-related parkinsonism in the literature (the first in 1898).
A classic dose-response effect was rarely observed; more usual was the achievement of a certain degree of relief after increasing the dose to a particular point, beyond which only side effects increased. This optimal dose varied widely even between apparently similar patients.

In short, there were certain difficulties in assessing the effects of agents possessing pharmacological activity which had only been broadly defined in a disorder for which the etiology in many cases and the neurological basis in most cases was unknown. More importantly, consideration of these confounding factors was not indicated in the majority of papers published during this period.

These methodological problems were further complicated by the psychological aspects of parkinsonism:

> So great are the spontaneous day-to-day variations in the degree of dysfunction in parkinsonian patients that there was a time when parkinsonism was considered to be a functional disorder.\(^{40}\)

Most clinicians agreed that parkinsonian patients were highly susceptible to suggestion: (although a few were of the opinion that parkinsonism patients had experienced so many false dawns and disappointments that psychosomatic influences of therapy could be disregarded):

> it is well to bear in mind that chronically ill patients, no matter how critical or objective they try to be, are biased in favor of new medicines. If the drug produces any euphoria or alteration in mental state, it is well-nigh impossible to rely on subjective impressions. An if the physician is convinced of the new drug’s effectiveness, his enthusiasm alone may produce a transient benefit all too often ascribed to the medication which he is unconsciously “selling.”\(^{41}\)

Indeed, most saw medical treatment as useful only when administered as part of a comprehensive therapeutic program which included both psycho- and physiotherapeutic components. Nevertheless, this provoked a problem when assessing the effectiveness of chemical therapy, as noted by Schwab and Prichard:

> In the case of Parkinson’s disease excessive scientific detachment in a therapeutic regimen will build up enough disappointment and resentment in the patient to produce exacerbations and symptoms that may well neutralize any benefit that the therapy can achieve. It is essential, in assessing the effects of therapy in this disease, to maintain the usual level of friendly, supportive patient-doctor relationship.\(^{42}\)

The parkinsonian patient was exposed to enough stress and disappointment without being handled as if he were an experimental animal; the impact of the physician on the progress of the patient could thus not be eliminated from the analysis. As von Witzleben noted earlier, it is not enough to compare the results of two clinics on the basis of the drug used; the technique and attitude of the treating physician was of decisive importance.\(^{43}\)

\(^{40}\) Gianvito et al., 1956.
\(^{41}\) Corbin, 1949b; compare with Budnitz, 1948.
\(^{42}\) Schwab and Prichard, 1951.
\(^{43}\) Witzleben, 1941a.
Literature regarding the psychology/psychiatry of parkinsonism extends back to the 19th century, but most workers assumed that the primary role was played by an anatomic lesion. Transient parkinsonism as a form of combat neurosis (for example) has occasionally been reported, but such cases were regarded as exceptional. In an attempt to determine the impact of personality on response to antiparkinsonian therapy, Prichard and colleagues divided one hundred patients treated consecutively at the Massachusetts General Hospital into three broad personality groups, and found that those patients who were determined to set themselves very high standards and who possessed a low tolerance for frustration and failure derived the least benefit from drug therapy (a range of natural and synthetic drugs were used); this group was also most susceptible to stress. This, however, would appear to be anything but surprising. The importance of this type of work was undoubtedly that it highlighted the role of psychological factors in response to therapy without denying the essential neurological roots of the disorder. Schwab and his associates opposed most emphatically the view proposed by, for example, by the psychoanalyst Gotthard Booth:

In response to difficult childhood experiences, a powerful constitutional aggression and libido have been projected desperately onto his environment, while the own personality, fearful of the ideal self as it once was as a child, remains neglected. Egoistic wishes and emotions have thus always had only a clearly limited area of influence. . . . Under external pressures and the exhaustion of the own vitality, the aggression and libido ultimately withdraw to the own body, although the strict demands of the conscience remain the same.

Parkinsonian symptoms were supposed to be the result of this conflict, but were also reinforced by the sympathy – and thus the attention long needed by the patient’s ego – which these symptoms awoke in others. Further:

1. Parkinsonism, postencephalitic as well as senile, is a syndrome which is characteristic of a specific personality type.
2. The Parkinsonian personality is characterized by urge towards action, . . . striving for independence, authority, and success within a rigid, usually moralistic, behavior pattern.
3. . . . .
4. The disease symptoms . . . satisfy the dominant needs of the Parkinsonian on a symbolic level: compulsive activity of the motor system and rigidity of behavior. . . . Aggression is also expressed through increased salivation.

Irving Sands (Neurology, Columbia University) had also noted that parkinsonian patients possessed a so-called “masked personality” in the preclinical stage: they were of normal or superior intelligence, were aggressive but socially conforming, and tended to be the strong and stable centre of support in their family and social environment. Internally, however, they were in a state of constant emotional tension which they felt obliged to conceal; the confrontation with a trauma which no longer permitted this strategy led to the emergence of clinical parkinsonism. Sands had known four people

44 Grinker and Spiegel, 1943.
45 Prichard et al., 1951.
46 Cohen-Booth, 1935.
47 Booth, 1948; Booth traced the origins of such models to Camp’s dissertation on paralysis agitans in the 1913 edition of White and Jelliffe’s *Modern treatment of nervous and mental disease*. See also Guggenheim and Cohen, 1959.
for more than a quarter century with this personality; all four had developed parkinsonism. His conclusion was that preventative psychotherapy could prevent the development of parkinsonism if the personality was recognized sufficiently early.48

It had also been suggested that akinesia, in particular, and which was regarded by some workers as related to catalepsy, represented a psychological defence mechanism. Smith Ely Jelliffe and Bürger-Meyer and Gross regarded the akinesia of parkinsonism as a strategy for containing aggressive and other ‘motoric’ impulses.49 Stengel pointed to the psychiatric symptoms often developed in lieu of motor impairment by younger victims of epidemic encephalitis, which he attributed to a failure of the superego to manage the destructive impulses unleashed by the disease process; the more developed adult superego utilizes parkinsonism as a means of controlling these urges ("instinctual defusion").50 Such ideas were further fostered by the development by Papez during the 1930s of his model of a limbic circuit which traversed basal ganglia nuclei traditionally associated with motor control.51

Bostroem (Psychiatric and Neurological Clinic, Leipzig), on the other hand, had regarded the psychic changes in parkinsonism as secondary to the motor disability. The loss of normal motor coordination and automatic movements led to an increased requirement for voluntary control of motor activity. The outcome was reduced variety of movement, bradykinesia and lack of smooth coordination. The immense concentration required for this level of conscious motor control necessarily reduced attention to environmental stimuli, with consequences for both emotional and cognitive performance (‘psychomotorische Einengung’).52

It had also been long noted that there appeared to be a degree of antagonism between parkinsonism and the schizophrenic process.53 This would today be interpreted neurochemically, but had earlier been seen as yielding clues to the psychogenic nature of parkinsonism; it was suggested that, given the “despair” experienced by neurologists attempting to explain the disorder in their own terms, parkinsonism should be viewed as “a complex reaction pattern in which both neurologic and characterologic factors play interdigitating roles”.54 Guggenheim and Cohen extended this idea to neuroleptic-induced parkinsonism. Here they saw individuals being restored to psychiatric health, but not yet psychologically equipped to deal with their new situation; “the apparent defensive usefulness of parkinsonism as a form of armoring” was once again invoked to explain the presentation of extrapyramidal symptoms “in service of ego-homeostasis”.55

Even if these somewhat overstated views of the relationship between psychological factors and motor dysfunction are discounted, the response of the patient to their disorder certainly played a major role in determining the response to therapy. Doshay distinguished between several patient types that he had encountered:

48 Sands, 1942.
50 Stengel, 1935.
51 Papez, 1937; see also Papez, 1942.
52 Boestroem, 1922.
53 Staehelin, 1954. Doshay (1954) remarked upon the reduced liability of parkinsonian patients to develop cancer, hypertension and tuberculosis. He also made the interesting comment that about 2% of all paralysis agitans patients had syphilis, although he saw no causal connection.
54 Guggenheim and Cohen, 1959.
55 Ibid.
the “overzealous type” whose constant search for novel remedies meant that he often seemed “to know more about some new drugs than physicians”. Tact was required here in order to avoid dampening the patient’s spirits or conveying the impression that the physician was not up to date with developments.

• the “neurotic person”, depressed by thoughts of impending deterioration and invalidity, who “more or less challenges the physician to prove he can help him”. Family support, psychotherapy and possibly shock therapy were indicated in these cases.

• the “self-conscious type” is embarrassed by the perception that the world is as preoccupied with his abnormality, particularly the tremor, as he is, and requires reassurance and to be usefully occupied.

• the “attention-seeking type”, seeking to please the physician, will respond to every new drug with enthusiasm for a week or two, rendering assessment of therapeutic benefit impossible. Such patients require an audience for their litany of ailments more than actual therapy and need to be handled tactfully.

• the “vain and stubborn type” who accepts the realities of the disease, but will not adjust to it. Doshay described an extreme case of a patient with moderate parkinsonism who could not be dissuaded from fulfilling his long stated intention of suicide on the day that he could no longer mount his horse.

• the “drug-sensitive type” were generally elderly patients who valued their intact mental faculties despite their physical handicaps. These persons were quick to reject any drug which induced ‘fogginess’ or otherwise compromised clarity of consciousness and thought.

These real world problems were, of course, not only of concern for the investigator attempting to assess the value of a new drug, but also for the physician attempting to assist the individual patient. The existence of this heterogenous parkinsonian patient population was, however, a major hindrance to the collection of reliable data on the value of particular medications, especially as most trials involved the patients of a single physician or those housed in a single institution; this meant that the patients in any study had, in effect, been ‘selected’ in advance, and could not be regarded as representative of all parkinsonian patients.

Objective measures in the assessment of antiparkinsonian agents

As mentioned, one problem in the testing of new antiparkinsonian agents was the sensitivity of patients to suggestion. Some workers regarded suggestibility as itself a hallmark of the disorder, and it was certainly clear to many that it impeded objective assessment of therapy. Many authors differentiated between “objective” and “subjective” responses to a drug, and were forced to note with disappointment that the first percentage was usually a small fraction of the second. In many cases, the definition of what constituted “improvement” or how the “degree of improvement” was ascertained cannot be clearly gleaned from an author’s publication. Doshay was particularly critical of investigators who reported simple percentages of improvement or work capability following treatment with a particular agent; in 1942 he commented:

*It is probable that the claims of massive-dosage [atropine] proponents ten years ago, that 60–70 per cent of their treated cases were returned to effective work (but have never since been heard from), possessed no greater substance than the more recent reports of 60% of cases rendered self-supporting through Bulgarian belladonna root treatment.*

56 Doshay, 1954.

57 Doshay, 1942.
He noted that “useful work” was often actually nothing more than “simple chores, such as gardening or peddling, arranged by the benevolence of relatives and friends.” Hall noted similarly that:

zealous enthusiasts, carried away by the real but temporary improvements characteristic of this chronic disease, deceive themselves and raise false hopes in others.\(^58\)

This problem became particularly pertinent in the 1940s. Until the encephalitis lethargica epidemic, the number of parkinsonian cases did not merit a great deal of attention and physicians were content to accept that hyoscine/scopolamine afforded the little relief which was possible in the disorder. During the height of the encephalitis lethargica epidemic, a crisis mood dictated that almost anything could be tried, and whatever showed any benefit was gratefully accepted into the clinic; such judgements were largely based on the opinions of the treated patients, and, despite critical comments from some of the leaders in the field, there existed no widely perceived need to establish objectively the effects of a drug. Further, although a seemingly endless list of therapeutic possibilities existed, few of the choices were actually employed by more than a restricted circle of adherents; the exceptions were the various forms of belladonna alkaloid therapy which dominated therapy at this point. With the advent of synthetic antiparkinsonian agents, however, the situation changed; the potential for producing new compounds by the chemical industry was, in fact, boundless, and there was clearly a need to devise means by which appropriate candidates could be detected early in their development, and less useful compounds discarded. The new compounds were also (in general) more expensive than alkaloid extracts, so that the choice of new agents also needed to be justified on an economic basis, particularly as parkinsonian patients could be expected to require such medication over a period of decades. Finally, the move to synthetic agents created a closer association between experimental or basic scientist and the clinic than had previously existed; attempts were made to rationally design new agents, and this attitude to experimental pharmacology brought with it the desire for more rigorous assessment of the new products.

That this problem was widely recognized is evidenced by the attempts to ‘objectivize’ the investigation of agents after the War. Many papers published between 1946 and 1960 commence with a discussion of the phenomenon that patient expectations and the enthusiasm of the clinician often led to hopes for a new agent which could not be sustained in the longer term. The multilevel instrument for the investigation of caramiphen devised by Schwab and Leigh, whereby patient impressions formed only a small component, has already been discussed above (page 262). In his investigation of diphenhydramine, Moore considered patient reports only if they were consistent with those of the physician and of family members:

Relatives and friends of patients who have been through successive periods of disillusionment and discouragement have a tendency to assess gains conservatively.\(^59\)

But even such approaches, while eminently practical, did not deliver ‘objective’ data. This deficit had also been recognized since the late 1920s, as reflected by the evident growing need to establish objective tools of assessment. Various mechanical devices for

\(^{58}\) Hall, 1935.

\(^{59}\) Moore, 1951.
the measurement of tremor, rigidity and even bradykinesia were described;60 there were also attempts to define basic units of movement, the assessment of which could be used both in the diagnosis of a patient and the assessment of his condition through the course of a therapy.61 Graphic recording of parkinsonian tremor, in particular, had been undertaken since the 19th century, but it was now increasingly employed to “objectivize” the effects of medical intervention. Attempts to quantify rigidity and akinesia were even more difficult, allowing the conclusion by some physicians that they represented no great advance on “subjective” assessment of these parameters.62 These techniques, however, did not find widespread acceptance outside their laboratories of origin, and were generally applied only by those with an interest in experimental physiology; most clinicians, including those reporting in the major journals, were content until the late 1940s to rely upon their skills as an observant physician, with many openly disdaining such devices. A generally recognized means for the assessment of antiparkinsonian drugs would long remain a problem. The use of competence in specific tasks, such as handwriting or strength of grip, was also employed as an indication of drug effectiveness; such an approach was simple and inexpensive to execute and reflected the benefit for the patient of a drug in a more direct manner than measures of tremor or rigidity.63 Related to such techniques was the method for assessing akinesia described by Birkmayer, whereby the speed and acceleration curves of three defined ‘basic’ movements (linear movement, swinging motion, thrust; recorded on film) were evaluated mathematically. This yielded a statistical complex which enabled comparison of the patient’s performance with that of normal controls.64

It would require an even longer period of experience before it would be clearly recognized that even “objective” assessment methods did not yield unequivocal results. Parkinsonism is marked by frequent variations in symptomatic intensity; further, the very suggestibility which has been discussed can lead to “objective” improvements which cannot be properly attributed to the therapy employed. In any therapeutic trial, the patient is aware of their status as an object of special attention, of the hopes of their caretaker, and of the potential for release from the torture of their symptoms; such knowledge cannot fail to influence the response to any new therapy, particularly when the patient is as sensitive to such influences as the parkinsonian patient. Most workers have, in fact, emphasized the importance of the clinical setting and the associated support mechanisms for extracting the maximum benefit from any therapy; in Europe, this underlay the belief expressed by many clinicians that therapy should commence in an institution dedicated to the care of parkinsonian patients.

The English pharmacologist John Henry Gaddum (1900-1965) expressed a similar view when he noted that the exclusion of the impressions of both patient and physician in favour of purely objective assessment was not always satisfactory; it was preferable to include all forms of data, but to conduct the trial so that neither party was aware of which agent or placebo was being administered: “This is known in America as a double blind test.”65 The growing application of the double-blind trial in the 1950s66 and the

60 See chapter VI.
61 See, for example, Birkmayer, 1938.
62 Agate et al., 1956; Wachs et al., 1960; Webster, 1960; Onuaguluchi, 1963.
63 For example: Schwab and Prichard, 1951; Onuaguluchi, 1964, pp.134-164.
64 Birkmayer, 1938; 1965, pp.178-182.
65 Gaddum, 1954.
66 Strong (1999) noted in a brief review that the first double-blind test may have been that by Gold and colleagues (1937) in the investigation of relief of cardiac pain. He identified seven other papers until
use of “blank” or placebo preparations was a partial response to this challenge in the assessment of drug response; but, as will be seen below, even such measures are far from perfect in a disorder such as parkinsonism. For the fact remained that, if a particular drug elicited even a minor change, the patient was quickly alert to this effect; should the effect be more dramatic, it was simply not possible to maintain the “blindness” of the test, particularly if subjects receiving drug and placebo were in contact with one another. There was also the ethical problem of withholding medication from patients suffering a distressing disorder; worse still was the notion of withdrawing reasonably effective medication from a patient in order to test a new drug or even to administer a placebo. Further, parkinsonian patients had long been exposed to a variety of medications, their effects and their side-effects; this “training” rendered it inevitable that over time they developed into veritable “drug-tasting experts” who were eminently equipped to distinguish between agents on the basis of their own responses. Gillhespy and Ratcliffe, for example, noted that a double-blind test was, for this reason, only possible in de novo patients. Gillhespy and Ratcliffe, for example, noted that a double-blind test was, for this reason, only possible in de novo patients. 67 Doshay commented that he was not convinced that “blind” or “double blind” studies were appropriate in testing anti-parkinsonian medications; in his opinion, the investigator was usually “blinder” than the patient, as the latter can detect

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a \text{placebo within 15 minutes after ingestion, by the total absence of the usual anticholinergic reactions of dryness of the throat, taste in the mouth and blurring of vision.}^{68}
\]

These responses could involve matters as banal as the taste of the test substance; one current worker has advised me that he allows his test subjects to open the capsule before a trial and taste it, as he is aware that professional trial participants will in any case endeavour to determine at the earliest possible moment what they have received. There is also the understandable reluctance of patients in the early period of the disorder, where the symptoms have not yet become severe, to tolerate the unpleasant side effects of anticholinergic therapy, and of the more advanced patients, who have become accustomed to their therapy, to try a new agent if they fear deterioration of their condition. Pohlmeier and Matussek wrote in 1965 that it was difficult to wean patients from their current medication in order to test the effect of tricyclic antidepressants:

\[
\text{We had quite similar experiences in 1955 with other patients. At that time, it was extremely difficult, for the same reasons, to change the therapy from scopolamine drops and atropine derivatives to the newly developed Akineton.}^{69}
\]

It was thus necessary in 1965 to introduce the antidepressant gradually while reducing the standard medication (Akineton!) quite slowly. But even under these conditions, it was unavoidable that “signs of vegetative adjustment manifested themselves and became unpleasantly apparent for the patients.” Vollmer similarly noted in 1940 that it was difficult to persuade patients to change from drops to tablets, even if the composition was identical; they often raised the objection that they had previously received tablets, but they had been of no help. 71

1954 which used the technique, principally in cardiology. The double blind approach did not achieve widespread use until the second half of the 1950s. See also Kaptchuk, 1998.

68 Doshay, 1965a.
69 Pohlmeier and Matussek, 1965.
70 Ibid.
71 Vollmer, 1940.
Investigations which examined the effectiveness of antiparkinsonian drugs (or of most drugs) during this period were certainly conducted in a manner which would not be deemed acceptable today, and there existed a growing awareness of the theoretical problems concerning the methods employed. Trials were generally open, uncontrolled and, at best, single blind, although it appears that in many cases the treating physician advised the patient that he would be receiving a drug which might improve his condition. Standardized protocols, even with respect to the withdrawal or maintenance of existing therapy in trial subjects, were not adopted; nor was there agreement on the criteria by which the effectiveness of a medication could be judged, with many workers openly disdainful of objective measurements of performance and preferring subjective assessment of general motor competence as the basis for assessment. This was no great advance on the method by which Parkinson had identified the existence of the disorder in the first place. Others regarded objective assessment as desirable but impractical:

*It has been found impossible to devise tests which are both practical and sufficiently objective to allow measurement of the amount of improvement as regards spasticity and tremor. The simple tests which have been experimented . . . all fail for the same reason, i.e., as soon as the person was instructed to perform these tests, there was an immediate increased disturbance of the emotional state, the tremors and rigidity were intensified, and the subsequent attempt to carry out these tests gave worthless results.*

Montuschi and colleagues noted that performance of such tests was modulated by:

*suggestion, training, degree of mental concentration, interest in the task, the patient’s mood, and his attitude to the investigator. . . . Repetition of the same task improves performance; hence, if several drugs are tested in succession, the results are likely to be better with the last drug tested than with the first.*

The emotional factor in parkinsonism rendered the interpretation of such tests difficult; the same authors noted that the skill with which a relaxed parkinsonian patient played billiards had "to be seen to be believed." Finally, most investigations were initiated by single clinics, often at the behest of a pharmaceutical firm which believed that it had developed a valuable new agent. This led to a situation where the vast majority of published reports were based on quite small patient numbers, who were quite heterogenous with respect to age, coexistent illness and degree of impairment; indeed, in many cases, drugs were assessed in groups of patients who presented a variety of distinct motor disorders. While this freedom of investigation no doubt expedited the identification of novel agents, it also undermined the credibility of the drug examination process, as teams of competing physicians examined a plethora of candidate therapies in an often haphazard manner.

**Target symptoms in the therapy of parkinsonism**

It should also be noted here that not only was the objective measurement of improvement a problem, but also the definition of the target symptoms in parkinsonism. It was generally agreed by the 1960s that rigidity responded better than tremor to treatment. But all aspects of poverty of movement or inability to execute smooth movement appear at times to have been subsumed under the term ‘rigidity’; akinesia as

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72 Gillhespy, 1953.
73 Montuschi et al., 1952.
74 Ibid.
such, for example, was rarely discussed as a major symptom of the disease, despite its
now being regarded as one of the "classic triad". Schwab for example, listed akinesia at
ninth place on a list of the major symptoms of parkinsonism, behind sialorrhea (3),
constipation (6) and bradykinesia (8). Denny-Brown stated bluntly in the Croonian
lectures for 1960 that "The symptomatology of paralysis agitans consists of the well-
known tremor and rigidity". This neglect of akinesia was perhaps partially due to the
attempt to objectivize drug effects by use of devices which quantified tremor and
rigidity; this was more difficult for akinesia. Duvoisin noted this in 1965:

Careful observation suggests that the benefits derived from anti-Parkinson drug therapy
depend not only on a reduction of tremor and rigidity but reflect a more general effect,
including an amelioration of akinesia and gait disturbances.77

Akinesia was often seen as being secondary to rigidity and tremor, although it was
explicitly recognized that there were akinetic parkinsonian patients in whom these two
symptoms were comparatively minor problems. Others regarded akinesia as the
psychological response to chronic disease, and suggested that physiotherapy, an ordered
daily life and counselling, not pharmacology, were the answers. Nevertheless, akinesia
was increasingly recognized as an extremely disabling aspect of the disease, even in
patients where tremor and rigidity could be reasonably well managed, and received
increasing attention from the late 1950s. Further, parkinsonism was clearly a
heterogenous disorder with regard to presentation of symptoms, even if most patients
shared a similar neurological substrate; for example, tremor and rigidity were not
always prominent in patients of non-postencephalitic etiology (table 8-5). But even
within parkinsonian types there was a great deal of symptomatic heterogeneity.

There was also a shift at the beginning of the 1960s in the direction of lending
greater weight to these so-called "negative symptoms" (gait and balance disturbances,
bradykinesia), which necessarily resulted in the change of the assessment of
antiparkinsonian therapy. While the concept of positive and negative symptoms had
existed since the 19th century and was often referred to in the 1950s, they had tended
to be disregarded as secondary to the major positive symptoms of rigidity and tremor.
England and Schwab had described three classes of symptom (X, Y and Z) in 1959; the
core symptoms of parkinsonism constituted the reasonably easy to treat "X" symptoms;
akinesia, however, belonged to the more difficult "Y" group, which consisted largely of
negative symptoms. Martin and colleagues (Highlands Hospital, Winchmore Hill;
National Hospital, Queen Square, London) drew further attention to these symptoms
and their significance for the post-encephalitic parkinsonian patient in 1962, attributing
them to central lesions of pathways involved in postural reactions, possibly involving
the pallidum. On the other hand, Duvoisin had concluded by 1965 that there was
really no hard evidence that the various antiparkinsonian drugs available, plant-derived
and synthetic, differed in their mechanism of action, and that the specific treatment of
individual symptoms with particular agents was futile. This aspect of parkinsonism

75 Schwab, 1965b. The full list was: 1. Tremor, 2. Rigidity, 3. Sialorrhea, 4. Retropulsion, 5. Oculogyria,
76 Denny-Brown, 1960.
77 Duvoisin, 1965.
78 For example, Constable in Brock et al., 1956.
79 See, for example, Jackson, 1896.
81 Martin et al., 1962.
82 Duvoisin, 1965.
VIII. Assessment of the pharmacological therapy of parkinsonism

<table>
<thead>
<tr>
<th></th>
<th>Post-encephalitic (n = 100)</th>
<th>Morbus Parkinson (n = 41)</th>
<th>Arteriosclerotic (n = 50)</th>
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<tr>
<td><strong>Age of onset: range</strong></td>
<td>2nd-7th decade 39.6 years</td>
<td>5th-8th decade 61.5 years</td>
<td>6th-9th decade 71.2 years</td>
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<td><strong>Age of onset: peak</strong></td>
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<td>50</td>
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<tr>
<td>Tremor</td>
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<td>Seborrhea</td>
<td>23</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sialorrhea</td>
<td>47</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Sweating crises</td>
<td>38</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Heat crises</td>
<td>35</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Depression</td>
<td>25</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Asymmetric symptoms</td>
<td>49</td>
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<td>7</td>
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<tr>
<td>Dementia</td>
<td>0</td>
<td>0</td>
<td>29</td>
</tr>
<tr>
<td>Confusion</td>
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<td>5</td>
<td>21</td>
</tr>
<tr>
<td>Bradyphrenia</td>
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</tr>
<tr>
<td>Other neurological deficits</td>
<td>0</td>
<td>0</td>
<td>34</td>
</tr>
</tbody>
</table>

Table 8-5: Major parkinsonian symptoms as reported by Birkmayer, 1965 (pages 164-166). The data is presented as an example of one clinician’s experiences in the differential diagnosis of parkinsonism, and is not intended to be a definitive classification scheme. For example, the absence of dementia and depression in idiopathic Parkinson’s disease is no longer accepted (nor was it by Birkmayer in later publications). It is interesting that 28% of ‘post-encephalitic parkinsonian’ patients had no history of encephalitis, and were classified thus on the basis of their clinical features; further, fourteen of the patients with a history of encephalitis experienced it in the period 1932-1945, so that only 58% of the post-encephalitic patients can trace their disorder to the major encephalitis lethargica epidemic.83

would, however, become particularly important with the development of L-DOPA therapy, as the major effect observed here was initially relief from akinesia; this was not the classic effect sought in a new antiparkinsonian agent, and would have failed most animal models which existed at the time.84

Other problems in the comparison of antiparkinsonian medications

A further complicating factor is that parkinsonian patients rarely received a single agent for their disorder. For instance, Onuaguluchi listed the following in 1964 as the major complications in parkinsonism requiring pharmacological or other intervention:

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83 Amsel reported in 1931 that 16% of his ‘post-encephalitic parkinsonian’ patients had no history of encephalitis, while in a further 42% the course of the disorder was ‘atypical’.

84 To be discussed in the next chapter.
Oculogyric crises: characteristic of post-encephalitic parkinsonism. Suggested therapies were the use of oral or intramuscular barbiturates in mild to moderately severe crises, intravenous hyoscine in severe cases; atropine sulphate was not as effective as either of these measures. Phenytoin had been suggested as a prophylactic measure, but had not been consistently effective.

Sweating crises: barbiturates were also preferred here, as intravenous atropine, while more effective, produced side effects which overshadowed its benefits.

Depression: orphenadrine had some euphoric benefits, and was thus worth trying; methylphenidate was also useful, but could produce agitation. Otherwise, imipramine, phenelzine or electroconvulsive therapy could be applied.

Constipation: purgatives were to be avoided in favour of suppositories and olive oil or soap and water enema. Constipation could be exacerbated by anticholinergic drugs, resulting in bowel dilatation and considerable pain.\(^85\)

Seborrhoea: cleaning of the skin with sulphur-containing compounds was recommended; the need to clean the ears of wax was also stressed.\(^86\)

Doshay commented that most patients required “three, four – or even five drugs at the same time for maximum control of all symptoms of the disease”.\(^87\) But these are not the only medications which the parkinsonian patient requires. Even today, a confusing cocktail of drugs might be administered to manage the multifarious motor and psychic symptoms of the disorder, as well as the other problems with which the elderly person contends (antidepressants, analeptics, nutritional supplements, sedatives, tranquilizers, cardiovascular medication, gastrointestinal agents, antibiotics, etc.). These combinations can themselves produce additional problems, especially as geriatric patients do not always respond to a given drug in the same manner as a younger person; reduced tolerance for anticholinergic drugs was a particular problem in this regard.\(^88\)

The final problem was that of the ‘significance’ of the drug trials which were conducted. The aim was to determine whether a new agent was superior to those already available. Today this can only be established to the satisfaction of the scientific community by presenting statistical analyses of the results of the study. This did not, however, become normal practice in the assessment of antiparkinsonian drugs until the late 1960s. This does not mean, however, that earlier workers were totally unaware of statistical methods. For example, Gillhespy and Ratcliffe remarked:

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\(^85\) See Howard and Markus, 1992.

\(^86\) Onuaguluchi, 1964, pp.75-81.

\(^87\) Doshay, 1961a.

\(^88\) See Doshay, 1954; Friend, 1961.
When the number of patients in the trial is small this comparison is, of necessity, a matter for the experienced clinician. Methods of statistical control, although highly desirable, should not interfere with the clinician’s freedom of action.\textsuperscript{89}

They also noted that for antiparkinsonian drugs, which were generally effective only in a subset of patients, the number of subjects required in order to achieve statistical significance was quite high (in comparison with the number of patients at the disposal of a single clinician):

\textit{In conditions of high incidence and distressing symptoms, such as the Parkinson syndrome, a drug which is genuinely effective in only 10\% of cases is still of value. The results of the present trial suggest that there will be an apparent response to treatment with inert material in about 10\% of cases also. Under these circumstances a “double-blind” trial would require not less than 100 patients in both the treated and untreated groups to reach the }p = 0.05\textit{ level of significance.}\textsuperscript{90}

These numbers were not simply available to most clinicians. Further, the clinician of the 1950s would have found the withholding of treatment from so many patients for a period of months to be abhorrent. It is easy to mock such attitudes, but the absence of multicentre trials rendered the statistical approach somewhat impractical. Further, one must question the value of material obtained today which is not infrequently analyzed with inappropriate statistical methods, or in which the focus on the ‘statistical significance’ of differences overrides consideration of their practical significance. It should also be noted that Gillhespy argued vehemently for the careful and rigorous assessment of any new therapy, an attitude which he missed in the work of some of his colleagues; in 1958, for example, he wrote a short but vigorous letter to the \textit{British Medical Journal} which criticized the recent positive report by Hughes and colleagues concerning the new agent phenglutarimide:

\textit{The total number of patients treated was only 16 and these are insufficient to prevent the favourable results represented being due to pure chance. Furthermore, this figure was further diluted by three patients being rejected from the trial due to symptoms from the withdrawal therapy.}\textsuperscript{91}

Gillhespy also criticized the conclusion of the authors that phenglutarimide was superior to \textit{“any therapy in current use”} on the grounds that they had not actually taken all possible alternatives into consideration. A survey in his clinic had recently revealed that the 398 patients attending the clinic regularly were receiving a total of twenty-five different drug combinations: the most common was orphenadrine alone (86 patients), but the most effective was orphenadrine plus ethopropazine (46 patients).\textsuperscript{92}

There have thus existed (and still exist) a complex of problems in assessing the effectiveness of drugs employed in parkinsonism (amongst other disorders), and at least some medical investigators were aware of these problems at the time. These problems

\textsuperscript{89} Gillhespy and Ratcliffe, 1955.
\textsuperscript{90} Ibid. It should also be noted that the variety of statistical methods now employed by investigators were unfamiliar to most workers at this point. Waud and Sheps (Pharmacology and Preventative Medicine, Harvard Medical school, Boston) published an article in \textit{Naunyns Archiv} at the end of 1959 which explained the mechanics and value of ‘analysis of variance’ (‘F-test’); they noted that it was widely used in England and America, but that what they regarded as an inferior variant was more common in Europe.
\textsuperscript{91} Gillhespy, 1958.
\textsuperscript{92} Ibid.
explain the initially puzzling fact that a number of clinicians could report success with a preparation which other clinics found to be useless or even harmful. These contradictions are by no means evidence of lack of scientific rigor or integrity in these earlier investigations; differences in patient populations, the quality of ancillary care, and numerous other factors certainly contributed to such discrepancies. In most cases, the investigators were also unaided and unburdened by the theoretical expectations which accompany the greatly increased biochemical knowledge which more recent workers enjoy. It must also be remarked that parkinsonian patients were never treated with pharmacological agents alone; most clinicians emphasized the necessity for concurrent physio- and psychotherapy – the nature and quality of which certainly varied from institution to institution, not to forget those patients treated on an ambulant basis. Finally, from the 1940s, increasing numbers of patients had also experienced neurosurgical intervention, thus creating yet another patient type with regard to potential benefit of pharmacological therapy.

An interesting facet of the benzhexol story were the circumstances of its development as related by Doshay years later:

> fortunately, in those days, we had none of the restrictions that currently hamstring and discourage clinical drug investigation. All that we required from the pharmaceutical manufacturer was the submission of preclinical studies with evidence of nontoxicity and some indication of anticholinergic activity in the new drug. From thereon we took over all the responsibility for required clinical evaluation, until the drug was placed on the market.93

Laws regulating the testing and licensing of new drugs were tightened around the world in the 1960s; in America, this commenced with the Kefauver-Harris Amendment to the Food, Drug & Cosmetic Act in 1962 and the enactment of the new Food and Drug Authority (FDA) regulations at the start of 1963. Amongst the regulations were requirements for the advance notification of the names of investigators and their qualifications, the structure and justification of the planned investigation, the obtaining of written informed consent from all patients and other subjects involved in trials and the furnishing of the FDA with written reports at all stages of the investigation. Philip Boyer (Hoffmann-La Roche, USA) lamented that this had not only increased the costs of pharmaceutical research (the new regulations had been intended to curb the spiralling costs of new medications) and time required for drug development, but could conceivably even lead to the loss of drugs which might be of use in parkinsonism. He concluded, however, that:

> The evaluation of new therapeutic agents now, more than ever, requires well trained, motivated clinicians who will develop and apply objective measures to their research and follow carefully planned protocols with adequate provision for controls. These physicians must be backed by administrative, nursing, laboratory, and other services.94

The question of bureaucratic bottlenecks would later become an issue in the licensing of L-DOPA. The new regulations certainly ended the autonomous investigations of isolated physicians; this development may have been inconvenient, but was certainly to be welcomed in light of the flood of new agents which advances in pharmaceutical technology had made possible. Prior to this, clinical investigations were much less formal. As described by Doshay, investigators commenced with selected cases

93 Doshay, 1965a.
exhibiting severe rigidity, akinesia and tremor, and established the optimal and maximum tolerable levels by carefully observing responses as the dose was gradually increased. In the "second phase", the pool of subjects was progressively broadened as the safety of the drug became more certain. A year was spent analyzing the individual responses of patients, the best route and dosage of administration and the responsive symptoms were determined. Finally, a report was submitted to the pharmaceutical firm, and the drug, if appropriate, placed on the market.95

Doshay and the Parkinson Laboratory had developed a few simple measuring devices for the objectivization of drug effects, but were not reliant upon such means. In his opinion, a "competent and careful investigator" could achieve evaluations which were at least as informative as objective measuring devices by careful long-term, large scale clinical investigations. Further:

\[\ldots\text{in those days, we had none of the current problems of obtaining written consent from the patients and their families, in order to test a new drug. Nor were we required to explain to them that it was a new and unknown drug containing many potentially dangerous side reactions. Our patients \ldots trusted us and were entirely confident that we would not give them anything to harm them. As a matter of fact, in the course of 30 years we had tested over 300 new drugs without a single instance of a serious toxic effect in thousands of patients.}\]

Doshay was dismayed by the regulations which in his opinion had begun to hamper research in the early 1960s; he felt that "freedom of investigation no longer exists and the patients wait in vain for new and better remedies."97 Similar feelings had already been expressed in 1959 by Saunders and Kline:

*The history of science is not simply the history of discoveries and new ideas that tend to approach closer to reality. It is also the history of the defense of these findings against errors due to propaganda, politics, and bureaucracy.*98

These authors were frustrated by the slow acceptance of iproniazid, an agent they regarded as indispensable in the clinic of affective disorders, because of its suspected hepatotoxicity. Their impatience, however, was undoubtedly experienced by many of their colleagues with respect to new drugs.

**Outlook for antiparkinsonian therapy at the beginning of the 1960s**

In their 1955 discussion of the relative benefits of procyclidine, benzhexol and cynamine, a telling comment relevant to this discussion was registered by Schwab and Chafetz:

*In our extensive experience with the treatment of patients with parkinsonism over the past ten years, we have been disappointed in not being able to show objective differences between two similar drugs that are reasonably effective. As we stated, we have always been able to show objective changes between no treatment and an effective one.*99

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95 Doshay, 1965a.
96 Ibid.
97 Ibid.
98 Saunders and Kline, 1959.
As examples, they noted that the supplementation of ethopropazine by diphenhydramine was welcomed by most patients as controlling their dizziness, but the clinicians could establish no objective benefit of the adjunct; similarly, the benefits of amphetamine, administered to control drowsiness, were not measurable. Further, their investigation of procyclidine had shown it to be no better – but also no worse – than either benzhexol or cyclazine. The fact was that some symptoms in most patients responded at least temporarily to any of a number of antiparkinsonian drugs, a frustrating experience for the physician and a hindrance for the development of novel strategies.

An interesting experiment reported by Benjamin Boshes (Neurology and Psychiatry, Northwestern University Medical School, Chicago) at the Second International Symposium on Parkinson’s Disease in 1963 should also be mentioned here. Boshes had compared the effects of placebo and benzhexol in the same parkinsonian patients; during the first week, placebo was administered, during the second and third placebo was either continued or replaced by medication, and in the fourth and fifth weeks this was reversed. If side effects were noted, the dose was adjusted until they disappeared. The experiment was conducted in a clinical laboratory instead of a clinic, so as to be kept “as cold-blooded as possible”. Boshes described the investigation as being “double-blind”, but how this could have been achieved with the described design is difficult to conceive. Thirty two patients commenced the experiment, but a number dropped out due to unpleasant side effects, including two patients receiving placebo at the time. Ten patients receiving benzhexol reported side effects, of which confusion (four patients) was the most common. Thirteen persons reported severe mental confusion while receiving placebo, of whom two had to be hospitalized. Other complaints included the typical side effects of anticholinergic drugs. Comparing the objective and subjective effects of benzhexol and placebo, it was found that benzhexol was only marginally better, and certainly much less impressive than previously reported; the only real improvement was noted in intensity and speed of speech.

Boshes concluded that “motivational and psychological factors” appeared to determine the response to therapy in Parkinson’s disease. Sem-Jacobsen commented at the same conference:

Medical therapy therefore appears to have very slight, if any, effect on the main symptoms of parkinsonism, but definitely comes into its own in tests concerned with reliability and more complicated movements.

The increased ability to perform tasks of daily living, combined with the stimulating effect of therapy, was seen by these authors as the major benefits of pharmacological intervention. Albert England supported this morose view in the discussion with his comment that “It seems to me that we get further away from solid scientific ground when we talk about drug therapy than in any other part of this symposium.” This comment, however, should be balanced against the fact that the proceedings of this symposium were published in the Journal of Neurosurgery. Nevertheless, England noted that there were a range of pharmacological alternatives available, and some patients seemed unable to do without some sort of medication, even if he personally thought the actual benefit was in many cases quite doubtful.

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100 Boshes, 1966.
101 Citation in Boshes, 1966.
103 Ibid.
A decade earlier, Berkowitz and Alvermann had found that after sixteen weeks of chemotherapy (benzhexol or stramonium) together with a program of physical and psychotherapy, positive changes were produced in a range of objectively measured parameters of performance; however, these changes were not significantly smaller in a small group receiving only physical and psychotherapy. Further, there was no strong correlation between subjective and objective measures of improvement; contrary to the views of those who preferred subjective assessment of patient performance to somewhat abstract objective measuring devices, poor performance on objective tests was correlated with a similar inability to perform tasks of daily living, so that these tests were a therapeutically valid instrument for assessing the effectiveness of therapy. Berkowitz and Alvermann gave an example of what they called the halo effect, whereby a patient extrapolated improvement in one task to the perceived improvement in a range of associated tasks: one patient was told by nurses that he had reached a level where he could dress himself, which he subsequently attempted, with success. He then subjectively extended this improvement to a number of other tasks, despite the fact that this was objectively inappropriate. The authors concluded that it must be doubted whether “the improvements noted can be ascribed to the chemotherapy.” 104 Kaplan and associates had similarly recorded in 1954 that antiparkinsonian drugs (hyoscine, benzhexol, caramiphen) were clearly superior to placebo in “eliciting . . . subjective reports of improved sense of well being”, but could hardly be distinguished from placebo when assessed by objective techniques. Most telling was the finding that tremor did not respond to any of the three agents, but deteriorated on their withdrawal. 105

It is interesting in this connection that it was recently reported that by Goetz and colleagues, who specifically investigated the role of the ‘placebo effect’ in trials of antiparkinsonian medication, that:

All domains of parkinsonian disability were subject to placebo-associated improvement, with a trend toward more response in bradykinesia and rigidity than in tremor or gait/balance/midline function. 106

The authors concluded that this phenomenon needed to be carefully borne in mind, and that clinical trials should be executed over a minimum of six months in order to unequivocally discern the effect of the test drug.

But in 1963, Boshes’ melancholy conclusion to his presentation was:

I fear that we have not gone far in the treatment of parkinsonism by drugs. 107

The pessimistic view expressed by the participants at this conference was nonetheless perhaps a little exaggerated; the experiment conducted by Boshes was not described well enough to be completely certain of what happened, but it could be objected that withdrawing patients from their medication and then reinstating it at short intervals was not appropriate for examining the effects of two therapeutic approaches. This is especially true in parkinsonism, where it has often been noted that longer term

104 Berkowitz and Alvermann, 1952. Further, the patients were switched after sixteen weeks to the alternative pharmacological agent; there was no apparent difference between the effectiveness of the two drugs.
105 Kaplan et al., 1954.
106 Goetz et al., 2000.
107 Boshes, 1966.
administration of an agent may be required to elicit a stable response. The experiment probably gives a better impression of the morale of those treating parkinsonism at this stage than it does of the effectiveness (or lack of it) of benzhexol.

That the psychology of the patients should play a role in response to therapy was, in any case, neither surprising nor particularly disturbing; but there seems to have existed a certain degree of frustration regarding the possibility that pharmacological therapy did not rest on a firm causal basis, which inevitably restricted its future development. The rosy expectations and brilliant results which appear to be reported in so many studies must certainly be balanced against the depressing reality which prevailed in the wards accommodating parkinsonian patients until the late 1960s. The situation with regard to the treatment of parkinsonism could hardly have been expressed more bluntly than it was by the great British neurologist Kinnier Wilson in his textbook of neurology:

*Paralysis agitans seems at present an incurable malady par excellence; the antidote to the local death of cell-fibre systems would be the equally elusive elixir of life. Amelioration can seldom, if ever, be regarded as lengthy or good.*  

This history of temporary hope and renewed failure engendered a certain degree of skepticism amongst researchers and clinicians as each new “breakthrough” was announced. The British physician Montuschi wrote similarly in 1949 that the “history of the treatment of parkinsonism is strewn with the corpses of remedies which have fallen into disuse after a period of popularity.”  

The comment made by Goodman and Gilman in 1955 was only slightly more encouraging than that of Wilson, and this after the introduction of a range of new antiparkinsonian products:

*The very best that one can expect from drug therapy is about 20 to 30 per cent improvement in about 60 to 80 per cent of patients.*  

In 1956, Gianvito and associates (Metropolitan Medical Center Research Unit, Bird S. Coler Hospital, Welfare Island, New York) related the following anecdote:

*At a meeting of the New York Neurological Society some years ago, the late Dr. Foster Kennedy, after hearing great claims made for the effectiveness of a new drug in the treatment of Parkinson’s disease, rose to state that he had heard such claims before, but that a clinic full of parkinsonian patients still looked essentially the same as a clinic full of parkinsonian patients in prior decades.*  

The authors noted that the situation had not changed much in the meantime, although the discouraged physician could regain his confidence by “*withdrawing medication and observing the devastating effects*” that this had upon the patient.  

Ten years later, another commentator was even more pessimistic:

*Any drug which can maintain a significant degree of clinical improvement in at least 30% of patients for a minimum period of three to four months is a worth-while addition to the overall therapeutic armamentarium of Parkinsonism.*

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108 Wilson, 1954b, p.938.
111 Gianvito et al., 1956.
112 Ibid.
113 Strang, 1966b.
VIII. Assessment of the pharmacological therapy of parkinsonism

Not everyone shared this pessimism. Doshay, in particular, actively promoted the message that “the future is bright” in a number of books and articles, while remaining well aware of existing problems. He regarded the parkinsonian patient as the “forgotten man” of the 20th century; while there were specific medical foundations for cancer, poliomyelitis, tuberculosis and other diseases, there were none for Parkinson’s disease of any type. This he saw as a problem demanding urgent rectification. Further, Doshay regarded the parkinsonian patient at an early stage as easy to treat; it was the advanced patient with their limb deformities, unsteady gait and speech and chronic psychological problems who posed the real difficulty. This was a problem not just for the patient, but for all concerned. The families of such patients sought relief from the doctor, but, as Doshay conceded, little solace could currently be expected from this source. Patients required long term treatment in rehabilitation centres – and the expense of such a solution rendered it unrealistic for the majority of patients.

Doshay’s reasons for optimism were nonetheless various. Firstly, he believed that the establishment of organizations such as the Parkinson’s Disease Foundation and the National Parkinson Foundation in America were an excellent means of coordinating basic and clinical research and delivering the benefits of their findings to the patient. During the 1950s, he had taken the first step in this direction with the establishment of the specialist Parkinson Clinic within the Department of Neurology at Columbia-Presbyterian Medical Center. Doshay spoke often of the rapidly expanding research

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114 Doshay, 1960, pp.190-205; 1961b; 1965a. Doshay was aware of the Queen Elena Clinics for (primarily) post-encephalitic parkinsonism in Europe, but was not impressed by the outcomes of their treatment; Schwab, on the other hand, regarded them favorably, although he doubted whether the improvement which they achieved was fully maintained after the patient returned home; England and Schwab, 1959; Schwab, 1965a.

115 This clinic has enjoyed consistently high calibre leadership: on Doshay’s death in 1965, Melvin Yahr assumed the directorship until he became Chairman of Neurology at Mount Sinai Medical Center in 1973. Yahr was in turn succeeded by Stanley Fahn as scientific director; during his time, the unit was renamed the “Center for Parkinson’s Disease and Other Movement Disorders” in order to reflect its broader scope.
into neurosurgical and medical means for alleviating the symptoms of Parkinson’s disease; one of the first “brain banks” had been established at this time at the Neurological Institute in New York, and was expected to facilitate the study of the pathology of the disorder. A number of research institutes dedicated in whole or partly to the investigation of Parkinson’s disease were also being built in America at this time.

Finally, Doshay believed that the world was standing “at the cross-roads for a breakthrough to the cause, means of prevention and possible cure of Parkinson’s disease”.116 Drug-induced parkinsonism had convinced him that it was only a matter of time before a toxin would be identified which would explain the occurrence of parkinsonism; the most likely candidates for him were accumulated waste products which “an impoverished circulation fails to remove from the cells of the basal ganglia, so that they are slowly and progressively damaged or destroyed” (figure 8-2).117

As it would turn out, the new direction of hope would be completely different to the solution which Doshay had envisioned. It would emerge on the other side of the Atlantic in a series of laboratories working independently on basic questions of chemical transmission and the clinical problem of parkinsonism. In the end, however, it would indeed prove to be the might of American clinical science which helped the solution to its triumph.

116 Doshay, 1961a; see also Doshay, 1960, pp.190-205.
117 Doshay, 1961a.
IX. Why was the anticholinergic therapy of parkinsonism successful?

Unless one is willing to ascribe the subjective and objective benefits of anticholinergic therapy for parkinsonian patients entirely to the caring nature of the physicians and nurses who treated these patients for so long or to the suggestibility of the patients themselves, there is little doubt that a measure of success was achieved in the treatment of parkinsonism with anticholinergic drugs. Doshay’s evaluation of the effectiveness of medication in Parkinson’s disease (table 9-1) seems a little optimistic in light of comments made by other clinicians, especially during the 1960s, but there is little doubt that the anticholinergic therapies afforded most parkinsonian patients some degree of relief. It might be difficult to estimate with any precision the degree of success, but the fact remains that certain agents achieved prominence in the battle against parkinsonism, while others were discarded after brief periods of popularity. I have already discussed the fact that neither clinicians nor researchers were clear about the mechanism of action of the drugs they were using; is there any greater clarity on this issue from our current standpoint?

Rudolf Degkwitz reviewed the chemical therapy of parkinsonism in 1963, and sought to classify those available, initially according to their chemical nature:

- Alkaloids
  a) Alkaloids of the solanaceous plants (belladonna alkaloids)
  b) Curare and erythroidine
- Synthetic agents
  a) Amino esters: caramiphen
  b) Aminoethyl esters: diphenhydramine, orphenadrine, diphenylhydramine
  c) Aminopropyl ethers: benactyzine
  d) Propylamines: biperiden, benzhexol, cycrimine, pridinol hydrochloride and methanesulfonate.
IX. Why was the anticholinergic therapy of parkinsonism successful?

Having recognized, however, that chemical structure was related to the effectiveness of these drugs only to a limited extent, he divided them again according to their chief pharmacological action:

- Parasympatholytic
- Anticholinergic
- Nicotinolytic
- Curare effect
- Spasmolytic
- Antihistaminergic
- Central effect

This classification scheme has a number of features worthy of comment. The antihistaminergic properties of antiparkinsonian drugs were judged by Degkwitz and most workers at this time as relatively unimportant for their correction of parkinsonian symptoms. It was more the coincidental anticholinergic and anti-nicotinic effects which rendered drugs of this class interesting. Went and colleagues reported in 1952 that histamine exerted “sympathomimetic” effects on the isolated guinea-pig and rat heart.

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**Table 9-1**

**Effectiveness of medication in Parkinson’s disease**

*(Doshay, 1961a; Table III)*

1. **Rigidity**

   Can be controlled in 50-75% of cases:
   
   a. If uncomplicated by severe contractures and deformities.
   b. If patient is not neurotic or hypersensitive to drugs.
   c. If patient is not in severe depression and resistant to therapeutic measures.
   d. Best results if:
      
      Treatment is started early and intensively.
      
      Patient is interested and cooperative.
      
      Physician shows interest and exercises close supervision of patient.
      
      Medication is combined with physiotherapy, exercises, activity, work.
      
      Rigidity is unilateral and uncomplicated by involvement of trunk and neck.

2. **Tremor, % Control**

   Mild and unilateral types – in 75% of cases.
   
   Mild and bilateral types – in 50% of cases.
   
   Severe and bilateral types – in 30% of cases (or more, if patient tolerates drug).

3. **Other symptoms, % Control**

   a. Sialorrhea – 75-100% of cases.
   b. Oculogyria – 75-100% of cases.
   c. Akinesia – 50-75% of cases. [Doshay treated akinesia with orphenadrine and other psychic stimulants, such as amphetamine].
   d. Diaphoresis [excessive sweating] – 75-100% of cases.
   e. Insomnia – 80% of cases.
   f. Dysarthria – 75% of cases (if combined with special exercises).
IX. Why was the anticholinergic therapy of parkinsonism successful?

preparations, in that at higher doses it led to catecholamine liberation;¹ the involvement of this phenomenon in the antiparkinsonian effect of these drugs, however, is unlikely. The spasmolytic effects of antiparkinsonian drugs could also be related to the inhibition of cholinergic effects, and, like curare-like effects, were no longer believed to play a major direct role in antiparkinsonian therapy. “Central effects”, concluded Degkwitz, was used by various workers to vaguely describe a range of effects, including the effects of high dose atropine; what was usually meant, however, was the energizing effects of certain sympathomimetics and the sedative effects of the antihistaminergics, and it was generally agreed that these played only a support role in the therapy of parkinsonism.

Degkwitz also pointed out that ‘parasympatholytic’ (which he equated with ‘atropine-like’) and ‘anticholinergic’ are not exact synonyms, despite the fact that this often seems to be assumed by some authors; there are, in fact, a few sympathetic fibres which utilize acetylcholine (ACh) as their transmitter. Further, it should be noted that ‘anticholinergic’ still generally indicated at this time what would now be termed ‘antimuscarinic’. Hunt and Taveau (U.S. Public Health and Marine Hospital Service, Washington) had noted in 1906 the intense vasodepressive action of synthetic ACh, and also that it was only partially blocked by atropine; a similar pattern of action was associated with certain ergot extracts² and compared with that of the active principle of Amanita muscaria.³ Dale noted in 1914 that the action of choline and certain of its ethers and esters included two distinct types of action: “a ‘muscarine’ action, paralysed by atropine, and a ‘nicotine’ action, paralysed by excess of nicotine.” One such compound was ‘acetyl-choline’; although it occurred in ergot, its instability rendered it “improbable that its occurrence has any therapeutic significance.” Dale noted that muscarine itself lacked nicotinic activity, and that certain quarternary ammonium bases were more or less devoid of muscarinic action while potently nicotinic.⁴ The two types of action exerted by ACh had thus been long recognized. Nevertheless, ‘muscarinic’ is only encountered rarely in the literature concerning pharmaceutical preparations until the 1960s; until this time, the term ‘cholinergic’ was more usual, and ‘nicotinic’ or ‘nicotine-curare’ was employed to specifically denote an additional character of an anticholinergic agent. This was partly explained by Dale’s comment in the same paper:

*Its [ACh] “muscarine” action can be shown to be an extremely powerful one when the observation is made on isolated organs. When it is injected intravenously the action on most organs is cut short and weakened; the reason for this, as I have suggested, being its extreme liability to hydrolytic decomposition. This makes it impossible to form any accurate idea of its “nicotine” action, since this cannot be studied satisfactorily outside the body.*⁵

The muscarinic action of ACh thus became its defining character, the nicotinic a specific secondary feature, despite the fact that Dale and others emphasized that the two could not be separated with clinical precision.

¹ Went et al., 1952.
² Acetylcholine was isolated from ergot by A.J. Ewins in 1914.
³ Hunt and Taveau, 1906.
⁴ Dale, 1914.
Evidence for the involvement of cholinergic systems in parkinsonism

Degkwitz’ next comment summarized the then current views of the anticholinergic effect in parkinsonism:

_In smaller doses, atropine stimulates certain parts of the central nervous system, in larger doses it is inhibitory, above all on the brainstem. The reticular apparatus is particularly affected by this action, which explains the antiparkinsonian effect of the substance._

If the dose were further elevated, “inhibition of inhibitions” was induced, and thus excitation and toxic psychosis, the “central effects” of the drug. At about the same time, Duvoisin noted that the synthetic antiparkinsonian drugs “_were by-products of the search for a peripheral anticholinergic drug that would not have the central effects of atropine._” In light of the above information, however, it was suggested that the future of antiparkinsonian therapy might lie in quite the opposite direction: drugs which were antiparkinsonian because of their central effects but which lacked the peripheral side effects of current alternatives.

Evidence for the involvement of cholinergic mechanisms in parkinsonism had been first provided, unwittingly, by Zucker in 1925, who reported that the administration of physostigmine to five post-encephalitic parkinsonian patients exacerbated existing symptoms to an alarming degree, an effect which could be reversed with scopolamine; this effect was, however, not seen in four paralysis agitans patients. Marinesco and Bourguignon reported a few years later that physostigmine increased the equinovarus foot turning in a pair of post-encephalitic children, while scopolamine achieved the opposite. The fact that physostigmine is a cholinesterase inhibitor was, however, unknown at this time. In 1941, Milhorat (New York Hospital; Cornell University Medical College) administered prostigmine (= neostigmine) to two patients with paralysis agitans, as he had noted some benefit from this drug in myasthenia gravis. He described the disturbing deterioration which Zucker had also noted:

_Within fifteen minutes after prostigmine methyl sulfate was administered [subcutaneously] the clinical picture was changed from one of paralysis agitans of moderate severity to one almost of the extreme state of the disease. There was marked cogwheel rigidity of all the extremities. The jaw moved in constant violent tremor. The tremor of the extremities was so severe that the patient had difficulty sitting in a chair. The gait was slow and shuffling with a tendency to trip; the entire body was held rigid and bent forward._

This rigidity and tremor were reduced within four minutes by the administration of 0.6mg atropine; a second dose resolved the crisis in a further three. The author interpreted his results as indicating that atropine and scopolamine were acting antagonistically at the level of the muscle; this was consistent with his view that excess muscular ACh was responsible for parkinsonian symptomatology, and with the fact that neostigmine has only limited access to the brain (its quarternary structure renders it

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6 Degkwitz, 1963.
7 Duvoisin, 1965.
8 Zucker, 1925.
9 Marinesco and Bourguignon, 1927.
10 Milhorat, 1941.
relatively lipid-insoluble). It was contrary, however, to the generally accepted view that scopolamine acted centrally (at the cortical level), which Milhorat recognized; his interpretation was inconsistent with the known pharmacology of the muscle.

Animal models for the testing of antiparkinsonian agents

In the mid-1940s, as already discussed, Feldberg suggested that atropine might act in parkinsonism by opposing the effects of endogenous central ACh. But attention gradually shifted from attempting to explain effects of the belladonna alkaloids to addressing the modes of action of synthetic agents, provoked by the hope that it would be possible to predict which structural modifications should be incorporated into the design of the “ideal” antiparkinsonian medication. This was thus an eminently rational approach to the therapy of the disorder, based on the assumption that chemical structure determines the activity of a molecule in a predictable manner. This approach, however, required animal models of the disease for convenient testing of candidate compounds, and the production of such models of parkinsonism had long been recognized to be a surprisingly difficult task. Kinnier Wilson had noted that parkinsonism-like tremor in animals had only been seen by a few workers, most commonly in decerebrate cats or following lesions to the cerebellar peduncle. There thus existed no reliable method for screening antiparkinsonian drugs before testing their effects directly in patients.

It was at this point that events took an unexpected turn: research suggested that it was not the anticholinergic (= antimuscarinic) effects of synthetic antiparkinsonian drugs which rendered them useful, but rather their anti-nicotinic character. C. Heymans and associates (Institute of Pharmacology, Ghent University) were in 1948/49 the first workers to suggest that the effectiveness of antiparkinsonian medication was correlated with its ability to block the effects of nicotine. Bovet and Longo (Chemical Therapeutics Laboratory, Institute of Health, Rome) exploited this fact in 1951 as the basis for the first widely recognized means by which antiparkinsonian drugs could be tested in animals. Bovet and Longo had been puzzled by the 1946 clinical reports on the effectiveness of diethazine and caramiphen in parkinsonism; they exhibited divergent pharmacodynamic properties “which in no way suggested their clinical applicability for the relief of symptoms caused by diseases of the basal ganglia.” They had noted, however, that both drugs were anti-nicotinic, and decided to test whether this was true of the other synthetic agents then being introduced. This they did by examining the ability of each drug to inhibit the twitching elicited by intravenous administration of nicotine in the hind leg of the rabbit. Their results indicated that the efficacy of synthetic anticholinergic agents in parkinsonism was, indeed, associated solely with their anti-nicotinic activity, and was independent of their anti-histaminergic, spasmolytic and sympathomimetic properties. Further, the peripheral nicotinic antagonists, tetraethylammonium bromide (TEA) and pentamethonium iodide (C5) did not block nicotine-induced tremor, supporting the hypothesis that the antiparkinsonian medications were acting centrally; this was consistent with the fact that prostigmine did not counteract the effects of antiparkinsonian agents. Bovet and Longo concluded:

11 Feldberg, 1945.
12 Wilson, 1925.
13 Heymans and Estable, 1949; Heymans and van den Heuvel, 1949; see also Heymans and de Vleeschhouwer, 1948. These authors coined the term “nicotinolytic”.
14 Bovet and Longo, 1951.
15 Pilcher, 1950.
It is possible to propose that the antagonism observed at the ganglia between acetylcholine and nicotine-like products on the one hand, and anti-nicotine preparations on the other, exists also at the central level. It does not seem unreasonable, on this basis, to think that the drugs effective against Parkinson’s disease block, at the level of the mesencephalic and bulbo-pontine centers, the effects of a cholinergic transmission no longer harmonically controlled by the superior center, destroyed or deeply injured by disease.16

There were, however, certain problems with the anti-nicotinic hypothesis of antiparkinsonian action. The first, and perhaps most obvious, was that atropine itself, long the mainstay of antiparkinsonian therapy, and scopolamine were only anti-nicotinic at very high doses.17 In a sense, this was unimportant, as it was recognized that the greatest effects of atropine were, in fact, achieved with high dose therapies; the fact that it was completely ineffective in the Bovet and Longo test, however, was reason enough for doubt about the validity of the model. Further, Cahen’s group (Maltbie Laboratories, New Jersey) reported that some central depressants and neuromuscular blockers, as well as certain anti-adrenaline agents, such as dibenamine18 also inhibited nicotine-induced tremor in the rabbit, suggesting that the test was not as specific as originally assumed. These authors found that anti-adrenergic and anti-nicotinic agents constituted overlapping but not identical classes; further, they supposed that agents drawn from the two classes blocked tremors induced by nicotine or other ganglionic stimulants by acting at different loci.19 Another objection to the Bovet model reflected more the shortcomings of neurochemical information at this time than those of the Bovet-Longo model:

There is, however, great difficulty in explaining the beneficial effect of an anti-nicotinic drug if one assumes that acetylcholine is the chemical transmitter, both at the synapses which inhibit mid-brain centres as well as those which transmit excitation towards the lower motoneurons. The higher inhibition is reduced in Parkinsonism, whereas the excitatory apparatus in the brain is not.20

Gillhespy thus argued that a “dose of anti-acetylcholine” should abolish the last vestiges of higher inhibition, while only reducing to a smaller degree midbrain activity, and thus exacerbate the symptoms of parkinsonism. He assumed that the model required expansion by allowing for varying sensitivity of the different centres for the effects of “anti-nicotines”.21 It was not possible at this point to suggest that the conundrum could be resolved by positing the existence of multiple central transmitters.

The Bovet and Longo method, however, became the most employed model for testing antiparkinsonian drugs in the 1950s. This had the further consequence that the effect of any new agent was evaluated with respect to its effect on experimental tremor, thus selecting a single symptom from the parkinsonian syndrome for the assessment of novel antiparkinsonian therapies. This symptom was regarded by many workers as most

16 Bovet and Longo, 1951. See also Bovet et al., 1950.
17 Interestingly, Kimura et al. (1948) demonstrated that amyl bis-atropine molecules, whether joined via the tropic acid hydroxyl groups or across the tertiary nitrogens, exhibited both anti-nicotinic and curare-like activity.
18 An irreversible α1/α2 receptor antagonist.
19 Cahen et al., 1953.
20 Gillhespy, 1953.
21 Ibid.
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urgently requiring new approaches; on the other hand, there was no evidence linking nicotine-induced tremor and that seen in parkinsonian patients.

Rudolf Hotovy and Helga Erdniss (Pharmacological Institute, University of Heidelberg) described in 1950 experiments using an alternative but similar method for assessing the direct effects of drugs on striated muscle.22 The effects of more than fifty agents, including a wide variety of antiparkinsonian drugs, was tested on the rhythmically stimulated musculus masseter of the rat; in some cases, prostigmine was also used to induce a state of tetany in the muscle. With respect to the effects of drugs used in the therapy of Parkinson’s disease, their results may be summarized as follows (all drugs applied i.v. or i.p.):

• Atropine paralyzed the muscle in the absence or presence of prostigmine. This capacity, to which Hotovy and Erdniss ascribed the effectiveness of atropine as a local anesthetic, had been recognized since at least Cushny.23

• Scopolamine had no effect on muscle, indicating that its effect in parkinsonian patients was primarily central; scopolamine-\( N \)-butyl bromide had a rapid but transient effect.

• Apoatropine showed a weak antagonism of prostigmine-induced tetany.

• Bulbocapnine, harmine, caramiphen, mephenesin, diethazine and adiphene HCl all opposed the prostigmine effect; the effects of harmine and diethazine were of particularly long duration.

• The two antihistaminergic drugs promethazine and antazoline also effectively blocked the actions of prostigmine.

The authors saw their model as a means for assessing to what degree a drug possessed a particular desired action – for example, the control of oral spasms in parkinsonism – but also emphasized that the model “did not say anything about what other characteristics a good anti-Parkinson agent should possess.”24

The most detailed comparison of the somatic effects of a range of antiparkinsonian agents in laboratory animals was published by Haas and Klavehn (Knoll AG, Ludwigshafen am Rhein) in 1955. They noted that the side effects of atropine therapy were long tolerated by clinicians as a “necessary evil”, assuming that a strong anticholinergic effect was necessary to obtain therapeutic relief. By the mid-1950s, this thesis appeared questionable; the pharmacology of the new synthetics diverged from that of atropine in that anticholinergic effects (and thus side effects) were not so prominent, while anti-nicotinic effects had assumed greater prominence. This stimulated the hope that it might be possible to manipulate individual cholinergic systems in the parkinsonian patients, and thus to elicit a symptomatic improvement without side effects. They therefore examined the effects of a range of antiparkinsonian drugs in a number of animal model systems:

• antagonism of ACh- or barium chloride-induced cramps in isolated guinea pig intestine;

• antagonism of blood pressure response in cat to ACh or vagal stimulation;

• antagonism of response of cat nictitating membrane to preganglionic stimulation, nicotine or adrenaline;

22 The method had been described the previous year by Hotovy and Eichholtz (Archives Internationales de Pharmacodynamie et de Therapie 80: 62; 1949).

23 Cushny, 1905.

24 Hotovy and Erdniss, 1950.
antagonism of pilocarpine-induced salivation in rabbit;
mydriasis in the mouse.

The authors concluded that of the nine substances examined, biperiden and oxy-
cyclohexylphenylacetic acid diethylaminoethyl ester\textsuperscript{25} possessed the best characteristics for an antiparkinsonian agent, in that they combined a relatively potent anti-nicotinic effect with a wide therapeutic range (difference between the effective and lethal doses); further, biperiden inhibited salivation and induced mydriasis only at relatively high doses, leading to the prediction that its side effects would be minor in comparison to available alternatives. Their recommendation was thus that biperiden would be an excellent agent in the treatment of parkinsonism.\textsuperscript{26} It should be remembered that ‘Akineton’ (biperiden) was, in fact, a Knoll product; nevertheless, the drug did prove to be a useful addition to antiparkinsonian therapy. Analysis of the biochemistry of biperiden was further pursued by Haas, who reported a number of interesting findings in a series of papers in 1960. In particular, biperiden reduced central ACh levels in the rat brain at much lower doses than other parasympatholytic and nicotinolytic substances; further, it reduced the elevated levels which were produced by treatment with reserpine, an agent which could elicit parkinsonian symptoms in man. Biperiden did not, however, reverse the reserpine-induced fall in central 5-HT levels; catecholamine levels were not examined.\textsuperscript{27}

That harmine can elicit tremor had long been recognized (since at least 1895),\textsuperscript{28} and its involvement of the extrapyramidal system proposed,\textsuperscript{29} but the effect of pharmacological agents on this tremor had been neglected until the mid-1950s. The tremor elicited by harmine in mice was described by Gerhard Zetler (Pharmacological Institute, University of Kiel) as “impressive”, and he demonstrated in 1956 that it could be inhibited with substance P.\textsuperscript{30} In 1957, he reported that he had tested the effects of a range of pharmacological agents on harmine-induced tremor, including more than twenty which had been employed in the treatment of parkinsonism; the most effective antagonists of the tremor were LSD, 5-HT, chlorpromazine, promethazine and apomorphine. The synthetic antiparkinsonian drugs examined also inhibited harmine-induced tremor to a degree, but usually at doses higher than those required to suppress nicotine-induced tremor. Harmine tremor, however, was also responsive to the belladonna alkaloids; in this respect it was certainly superior to the nicotine tremor model, as was the fact that it selected apomorphine as an effective agent, consistent with the recent work of several other others concerning this aporphine.\textsuperscript{31} The author thus believed that it might have a place in the testing of antiparkinsonian agents.\textsuperscript{32} The model was interesting, but its value in screening new antiparkinsonian agents was overshadowed shortly afterwards by the discovery of tremorine.

\textsuperscript{25} Oxyphenonium; the methyl bromide of this spasmolytic compound received brief attention as an antiparkinsonian agent. Also examined by Ehrenberg \textit{et al.}, 1952.
\textsuperscript{26} Haas and Klavehn, 1955.
\textsuperscript{27} Haas, 1960.
\textsuperscript{28} Neuner and Tappeiner, 1895.
\textsuperscript{29} Beer, 1939a, 1939b. Some investigators of the harmine/banisterine therapy of parkinsonism had earlier suggested that the site of action of the alkaloid may have been at some point in central control of motor activity, but Beer was the first to pursue the question systematically in animal experiments.
\textsuperscript{30} Zetler, 1956.
\textsuperscript{31} Vernier and Unna, 1951; Struppler and von Uexküll, 1953.
\textsuperscript{32} Zetler, 1957.
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Lesion models of parkinsonism

A number of lesions of the basal ganglia had been employed since the start of the century in an effort to produce experimental tremor, all without success. Mella had induced experimental tremor in monkeys through manganese poisoning in 1924, but this did not produce a specific, identifiable central lesion. The development of an appropriate animal model of parkinsonism was also naturally hampered by the ignorance of precise knowledge regarding the location of the lesion responsible for tremor in parkinsonism, without which it could not be rationally replicated in experimental animals.

The investigation of extrapyramidal function via lesioning of the primate brain received renewed interest in the 1940s; a number of other lesions producing extrapyramidal dysfunction were reported, but none produced the typical parkinsonian resting tremor, which by this time was being regarded as the central hallmark of the disorder. In the course of an investigation of an unrelated question, a group at the Department of Psychiatry, University of Illinois and the Department of Anatomy, Northwestern University Medical School stumbled in 1948 upon a bilateral lesion at the base of the tegmentum, extending from the nucleus ruber to the tail of the pons, which elicited a syndrome involving static tremor, mask face and poverty of movement in monkeys. It was assumed by this group that tremor was the result of uncontrolled activity in an unknown nucleus, probably located in the reticular formation; the area affected by the lesion which they had produced was therefore excluded from considerations regarding the seat of tremor. It does not appear to have occurred to the authors that they may, however, have thereby removed the pathway which controlled the tremor-producing centre. Folkerts and Spiegel, for example, suggested that tremor was the result of the reticular substance being released from inhibition by the substantia nigra.

The monkey model which gained widest acceptance involved lesions in the reticular formation and the posterior subthalamic region of macaque monkeys; this technique, first described by Vernier and Unna in 1953, elicited chronic postural tremor. The rank order of potency of antiparkinsonian drugs in the Vernier-Unna monkeys corresponded approximately to the relative oral doses of these drugs for the control of tremor in parkinsonism: scopolamine > atropine > benzhexol > caramiphen > diphenhydramine. Interestingly, apomorphine also diminished tremor in this test; it was more potent than atropine but shorter acting, so that the authors compared its effect with that of diphenhydramine. The authors saw their results as substantiating the involvement of enhanced central cholinergic activity in parkinsonism; physostigmine, but not neostigmine, increased tremor (as did amphetamine).

There were, however, several problems with the Vernier-Unna model, despite the fact that it represented a useful objective instrument. Firstly, it was not clear how these

33 Mella, 1924. For other early work on experimental lesions of the basal ganglia, see Schüller, 1902; Wilson, 1914; Edwards and Bagg, 1923; Morgan, 1927.
34 See, for example, Mettler, 1942, 1945; Richter, 1945. For further references, see Jenkner and Ward, 1953.
35 Ward et al., 1948; Peterson et al., 1949.
36 Folkerts and Spiegel, 1953.
37 Vernier and Unna, 1953; 1956.
lesions related to the natural neuropathology of parkinsonism, a fact underscored by the fact that several drugs which allayed the tremor in this model were not effective in the human disorder, including amyl nitrite and quaternary nitrogen derivatives of the phenothiazines.\textsuperscript{38} Further, the model yielded no information on the effect of drugs on rigidity. Many of the drugs employed also induced sleep or depression in monkeys, further confounding interpretation of results, although sedation had long been regarded as the most opportune means to reduce tremor. Further, the relative clinical efficacy of antiparkinsonian agents was not completely consistent with the Vernier-Unna model; for example, their monkeys predicted that scopolamine should be about ten times as effective as atropine, which was clearly not the case. Finally, the success rate in producing tremor in monkeys by this method was not excessive, so that the technique was extremely expensive. Ethical considerations, on the other hand, were not yet a problem with respect to this kind of experiment.

Fritz Jenkner (Surgical Clinic, Graz University) and Arthur Ward (Neurosurgery, University of Washington School of Medicine) suggested in 1953 that denervation supersensitivity to ACh of neurons in the medial reticular formation explained the value of anticholinergic agents in parkinsonism. This was based on their finding that electrical stimulation of this region produced a “rhythmically alternating peripheral movement analogous to tremor” which could be suppressed by antiparkinsonian drugs, most effectively by scopolamine and diethazine.\textsuperscript{39} Franco Rinaldi and Harold Himwich (Thudichum Psychiatric Research Laboratory, Galesburg State Research Hospital, Illinois) reported similarly that all antiparkinsonian drugs were potent inhibitors of the reticular activating system, with atropine the most potent in this regard; reserpine, diisopropyl fluorophosphate (DFP), nicotine and amphetamine were, in contrast, potent activators of this centre, and had at least anecdotally been associated with evocation of parkinsonian signs.\textsuperscript{40} Further, while low doses of chlorpromazine depressed reticular activity, higher doses stimulated it, consistent with the fact that chlorpromazine had also been associated with the production of parkinsonian symptoms.\textsuperscript{41}

All these models sought to induce a parkinsonian-type tremor in the test animals, at least partially with the aim of providing a useful screening test for antiparkinsonian drugs. Other workers placed lesions in various components of the basal ganglia in order to determine the likely site of the critical lesion in man. Denny-Brown (neurology, Harvard Medical School, Boston), for example, placed experimental lesions in three of the major candidate regions:

- Bilateral destruction of the caudate nucleus resulted in hyperactivity and restlessness, and exhibited a range of visual (but not tactile) compulsions. This he saw as the “release of a profusion of cortical automatisms (chorea)”.
- Electrolytic lesioning of the putamen (4mm in the rostral portion, 2mm in the medial portion) produced a soft, yielding rigidity in all limbs, but no postural abnormalities. It was concluded that the putamen was “concerned with contactual reactions, and that when these are impaired more general labyrinthine and body contact relations are released”. This release of primitive movements from cortical control was linked to athetosis and dystonia.

\textsuperscript{38} Garai (1951b), however, found that amyl nitrite was effective against parkinsonian tremor, which effect he attributed to dilation of blood vessels and elevated central perfusion.
\textsuperscript{39} Jenkner and Ward, 1953.
\textsuperscript{40} Rinaldi and Himwich, 1955. See also Frommel, 1958.
\textsuperscript{41} Review: Ayd, 1961.
Electrolytic lesioning of the pallidum resulted in a loss of placing and righting reactions, accompanied by intensification of tactual reactions. Richter\(^4\) had seen similar responses in monkeys with pallida damaged by exposure to carbon disulfide, but his animals also exhibited marked intention tremor and plastic rigidity.\(^4\)

In reviewing the literature concerning lesions of the substantia nigra, Denny-Brown noted that such damage had never been associated with tremor or rigidity.\(^4\) Denny-Brown saw the pallidum as the “head ganglion of the motor system”, and the disturbances of motor function observed after lesions to this region as analogous to the akinesia and bradykinesia of parkinsonism. Tremor and rigidity might relate to concomitant damage to other basal ganglia, but the central lesion for Denny-Brown was definitely pallidal.\(^4\)

**Tremorine**

Whatever the value of lesion models of parkinsonism, their greatest disadvantage lay in their expense, especially as it could not be guaranteed that every operated animal would receive the intended lesion. The introduction by Everett’s group of tremorine (figure 9-1)\(^4\) as an analytic agent at about the same time as Zetler’s work (1956) was thus greeted warmly. The agent produced parkinsonian-like tremor of head and limbs in a range of mammals ranging from mice to monkeys which could be suppressed with great effect by all current antiparkinsonian agents. Hypnotics, anticonvulsants and ganglion blockers were, in contrast, without effect. Further, the tremor was more sustained than that elicited by nicotine (lasting 3-4 hours in mice after 20mg.kg\(^{-1}\) by any route), and was demonstrated to be of central but subcortical origin. Treated animals were relatively akinetic and exhibited signs of rigidity; a profound drop in body temperature and a range of parasympathetic signs (increased salivation, miosis, diarrhea, bradycardia) were also evident. In monkeys, the tremor was less marked (lasting about 24 hours), but the parkinsonian-like facial changes were especially striking. A number of tremorine analogs were investigated by Everett’s group, but none produced the same effects as the parent compound.\(^4\) It was found a few years later that tremorine must first be converted to oxotremorine to elicit its effects;\(^4\) oxotremorine produces its effects much more quickly than tremorine itself, and is now known to be a cholinergic (muscarinic) agonist.

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\(^4\) Richter, 1945.
\(^4\) Denny-Brown, 1960.
\(^4\) He cited, for example, work by von Economo, 1902; Cannon *et al.*, 1944; Carrea and Mettler, 1955.
\(^4\) Denny-Brown, 1960. Derek Denny-Brown (1901-1981), a New Zealander, was at one time nominated for the Nobel Prize for his work on dyskinesias; Aird, 1988.
\(^4\) 1,4-Dipyrrolidin-1-yl-2-butyne. German patent to BASF: 1953.
\(^4\) Everett, 1956; Everett *et al.*, 1956.
\(^4\) Kocsis and Welch, 1960; Cho *et al.*, 1961.
The major problem with tremorine was that its site of action was unknown. An
action in the basal ganglia or the brainstem was sought in order to link it more closely to
human parkinsonism; but, apart from some evidence that it might be a cortical
stimulant, most evidence suggested that it acted in the hypothalamus.49

Farquharson and Johnston screened a number of compounds synthesized at the
Duncan, Flockhart Research Laboratories in Edinburgh for high anti-tremorine activity
coupled with low peripheral anticholinergic activity, the hope being that such drugs
might reproduce the central effects of atropine on parkinsonian symptoms without the
disturbing peripheral side effects. The interesting aspect of their results was that
diethazine and adiphenine proved much more effective in this test than the recognized
favorites benzhexol, orphenadrine and caramiphen.50 It could thus be suggested that
tremorine was more a screening tool for centrally acting spasmyotics, and this implied
that the search for a rational means of identifying antiparkinsonian agents in animal
models was hardly more advanced than in 1949; adiphenine was, after all, the parent
compound of benzhexol which had been modified to produce a more effective
antiparkinsonian agent. There were also significant exceptions to the anti-tremorine
capacity of antiparkinsonian agents, including tigloidine, the only atropine-class drug
lacking peripheral side effects. Trautner and Gershon (Departments of Physiology and
Pharmacology, University of Melbourne) objected in 1959 that many of the peripheral
effects elicited by tremorine were not seen in parkinsonism, and that the tremor was not,
as in Parkinson’s disease, a resting tremor, but was seen primarily when the animal was
disturbed. They surmised, correctly, that tremorine should be reckoned to those
parasympathomimetic agents which elicit increased glandular secretion, gastrointestinal
motility and muscular overactivity ranging from tremor to convulsions.51 Sanghvi and
colleagues, however, reported that tigloidine, although devoid of anti-nicotinic activity
in animals, did antagonize the effects of tremorine.52

Despite these reservations, tremorine long remained the best animal model of
parkinsonian tremor, although its relationship to the natural disorder was dubious. The
Dundee doctoral student Ahmed had found that there was a statistically significant
correlation between the anticholinergic potency of antiparkinsonian drugs and their
ability to inhibit tremors induced by tremorine, but not with their capacity for inhibiting
tremor produced by other agents.53 Stern and Gašparović (Pharmacology, Faculty of
Medicine, Sarajevo University) reported in 1961 that tremorine reproduced the
parkinsonian tremor better than any alternative, which at this time included veratrine
and harmine, as well as 3-amino-1,1,3-triphenylpropane-1-ol and \(N,N\)-diethyl
cysteptmine, and several aromatic amino acid decarboxylase inhibitors.54 These authors
had also responded quickly to Ehringer and Hornykiewicz’ 1960 report of reduced
dopamine levels in the striatum by examining the effects of drugs which modulate
central catecholamine levels on tremorine-induced tremor. Treatment with MAO
inhibitors (iproniazid or phenyl isopropyl hydrazide) twenty hours prior to the
administration of tremorine delayed the onset of tremor by a few minutes; 200mg.kg\(^{-1}\)
5-HTP had a similar, but less marked effect, while 200mg.kg\(^{-1}\) DOPA was without

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49 Baker et al., 1960 and references therein.
50 Farquharson and Johnston, 1959.
51 Trautner and Gershon, 1959.
52 Sanghvi et al., 1968.
54 Stern and Gašparović, 1961; Stern et al., 1961.
effect (both amino acids were administered two hours before tremorine). When the
animals were treated with both iproniazid and DOPA, there was no effect on the latency
of the tremor; but iproniazid and 5-HTP delayed the onset of tremor by at least half an
hour. Together with the findings by others that the “5-HT antagonists” harmine and
LSD and the 5-HT-depleting reserpine and chlorpromazine could also elicit tremor in
animals, the authors concluded that a central 5-HT deficiency was the underlying cause
of tremor in parkinsonism; the reduced activity of amino acid decarboxylase was seen
as the cause of both this and of reduced dopamine levels, this latter deficiency being
seen as underlying the akinesia of the disorder.55

Tremorine was a reasonable model of tremor, but did not yield information regarding
akinesia or rigidity. By the mid-1960s, however, there was even growing doubt about its
value as a model of parkinsonian tremor. There was, indeed, some danger of returning
to the situation which prevailed at some points of the 19th century where all tremors
were regarded as equivalent. Cotzias’ group published a paper in Nature in 1964 which
criticized the tremorine model of parkinsonian tremor on a number of grounds. They
had noted that the tremor (but not the autonomic effects) induced by tremorine in mice
were abolished if the mice were covered by a towel, sheet or even a hand; they ascribed
this effect to a reduction in the agitation which they believed was necessary for the
production of tremor, as had Trautner and Gershon in 1959. Similarly, reserpine
reduced the tremor in both mice and rats without affecting the autonomic effects of
tremorine. This contrasted with parkinsonism, where the vegetative symptoms were
easier to treat than tremor and rigidity. The authors concluded that tremorine did not act
in the basal ganglia, presumed to be the seat of Parkinson’s disease, but in the
hypothalamus; its usefulness for the assessment of antiparkinsonian agents was thus
questionable.56 Duvoisin noted further that tremorine-induced tremor was more like that
seen in acute cholinergic intoxication than in parkinsonism.57

As a result both of these questions and of the emergence of the significance of
catecholamines in parkinsonism, interest shifted increasingly to the neurochemical
effects of (oxo)tremorine. Tremorine was reported in the first half of the 1960s to
elevate brain levels of noradrenaline and histamine in the rat, mouse and guinea pig, and
of ACh in the rat; dopamine concentrations were elevated by the drug after an initial
decline, primarily in the caudate nucleus, in rat, guinea pig and rabbit.58 This seemed to
contrast with the changes in dopamine recently reported by Ehringer and
Hornykiewicz,59 but by this stage the site of action of tremorine was regarded as more
likely to be in the hypothalamus than the basal ganglia. This contrasted with the
demonstration by J.M. Gybels that experimental lesions producing parkinsonian-like
tremor in monkeys invariably involved the substantia nigra.60 A number of authors
found that tremorine induced a decline in brainstem noradrenaline which coincided with
the onset of tremor, followed by a reduction in 5-HT levels in this region; Friedman’s
group commented in this regard that knowledge of the neurochemistry of parkinsonism
was limited, hampering efforts to develop more effective therapies.61 Changes in brain

56 Patten et al., 1964.
57 Duvoisin, 1967.
58 Friedman et al., 1963; Holmstedt et al., 1963.
59 Ehringer and Hornykiewicz, 1960.
60 Gybels, 1962.
61 Friedman et al., 1963.
dopamine levels were not usually found.\textsuperscript{62} Spencer noted, on the other hand, that the reduction of tremorine-induced hypothermia in mice appeared to better predict the effectiveness of an agent in parkinsonism than its effect on murine tremor; interestingly, amongst the sympathomimetics which he applied, DOPA was effective against the hypothermia, but not the tremor, induced by tremorine.\textsuperscript{63} At the same time, Laverty and Sharman examined the effects of a range of drugs on the metabolism of dopamine, noradrenaline and 5-HT in the brains (caudate, thalamus, hypothalamus) of dog, cat and rabbit, and could establish no clear links between pharmacological and behavioural effects; the only drug to elevate caudate dopamine was DOPA, with atropine, caramiphen and diethazine without any effect on brain monoamine levels. Oxotremorine, which had recently been identified as being a muscarinic agonist, elicited an increased HVA concentration in the cat caudatus and the “rage response” which cats exhibit instead of tremor; the authors did not see this change as worthy of comment.\textsuperscript{64}

As would be expected with the recognition that oxotremorine was a muscarinic agent, the biochemical profile of tremorine-induced tremor became more complicated with time. Reserpine was found to reduce tremorine tremor in mice, principally by inducing catatonia; pargyline was also found to reduce tremor (but increased that elicited by harmaline), but only at doses which were lethal.\textsuperscript{65} In 1967, Corrodi’s group found that oxotremorine itself did not influence central catecholamine levels in the rat, but accelerated the depletion caused by a tyrosine hydroxylase inhibitor (H44/68),\textsuperscript{66} leading to the conclusion that the muscarinic agent activated noradrenaline and dopamine-containing neurons via a cholinergic link.\textsuperscript{67} This was thus an early step towards the involvement of a specific dopamine-ACh interaction in the brain in the action of antiparkinsonian drugs. By 1970, it had been recognized that the actions of (oxo)tremorine were blocked by a range of pharmacological agents, including spasmolytics and β-receptor blockers; it thus seemed that catecholamines were not directly involved in the production of tremor in the tremorine model, but might play a permissive role.\textsuperscript{68} Further, there were reports of drugs which blocked the action of tremorine in animals but were completely ineffective in parkinsonian patients, such as the barbiturate derivative AGN 511.\textsuperscript{69} Jurna and colleagues found that DOPA, verapamil and procaine relieved the rigidity elicited by tremorine by depressing α reflex hyperactivity, but only reduced the magnitude of the tremor; atropine and biperiden were able to abolish both signs, possibly by concurrent suppression of γ motor activity.\textsuperscript{70}

In the course of their investigation of the role of MAO inhibitors in antiparkinsonian therapy, Dandiya and Bhargava tested standard antiparkinsonian preparations with respect to their resolution of perphenazine-, tremorine-, physostigmine- and nicotine-induced tremor in the rat. It was found that different levels of protection were afforded

\textsuperscript{62} Cox and Potkonjak, 1967; but see Friedman and Anton, 1967, who found a transient fall followed by a significant rise.
\textsuperscript{63} Spencer, 1965.
\textsuperscript{64} Laverty and Sharman, 1965.
\textsuperscript{65} Agarwal and Bose, 1967.
\textsuperscript{66} Metyrosine (α-methyl-L-tyrosine) methyl ester; Netherlands patent to Merck (for metyrosine): 1966.
\textsuperscript{67} Corrodi \textit{et al.}, 1967.
\textsuperscript{68} Jacobi, 1967; Jurna \textit{et al.}, 1970.
\textsuperscript{69} Mattila \textit{et al.}, 1970.
\textsuperscript{70} Jurna \textit{et al.}, 1970.
by the different agents according to the etiology of the tremor; for instance, scopolamine and benzhexol provided full protection in most cases, but none against nicotine tremor, while diphenylhydramine was effective against all except tremorine-induced tremors. MAO inhibitors, incidentally, were of very limited effect in these tests. It was thus clear by this point that no single test in an animal model was adequate for the unequivocal assessment of putative agents for the treatment of parkinsonism.71

The gradual rise in popularity of the catecholamine hypothesis of Parkinson’s disease, even before the acceptance of L-DOPA therapy, led to a reduction of the significance of the role of tremorine in parkinsonism research. Newer therapies were namely designed to overcome the dopamine deficiency which was believed to underlie at least some of the symptoms of parkinsonism, and thus required a new appraisal of the role of cholinergic mechanisms in the disorder.

New directions in understanding anticholinergic therapy

Frommel (Institute of experimental Therapeutics, Faculty of Medicine, Geneva) had noted at the end of the 1950s that antiparkinsonian substances (belladonna alkaloids and synthetic agents) were generally inhibitory in man, a phenomenon which contrasted with their stimulatory effects in mice. He concluded that the antiparkinsonian actions of such agents could not be correlated in a simple manner with their anticholinergic actions in animal models (and not at all with their anti-histaminergic or anti-papaverinergic properties); rather, he proposed that those drugs effects which were often classed as “secondary” constituted a critical aspect of these agents, and were manifested either at the level of the reticular substance or the extrapyramidal system.72 In other words, Frommel argued that it was not the primary anticholinergic effects of antiparkinsonian agents which were directly responsible for their benefits in antiparkinsonian therapy, but instead the secondary effects dictated by the pathophysiological substrate upon which they were acting. It was also known that cholinomimetics exacerbated parkinsonian symptoms, but did not normally elicit them in healthy persons.73 The problem in parkinsonism was thus not simply one of cholinergic hyperactivity.

At the beginning of the 1960s, the role of the catecholamines in parkinsonism began to attract broader attention, as will be discussed in the following chapters. Haas (Knoll, Ludwigshafen) noted in 1960 that even if the assumption that antiparkinsonian agents acted in the reticular system were correct, it could no longer be assumed that their effects were entirely attributable to their modulation of cholinergic communication; it had been recognized since 1956 that there existed elements of the reticular system which were responsive to catecholaminergic agents.

One may therefore assume that blockade of cholinergic synapses in subcortical structures . . . is involved in the effectiveness of atropine and other antiparkinsonian agents in extrapyramidal disorders. This does not, however, mean that this mechanism alone is the most important for the effectiveness of therapy.74

71 Dandiya and Bhargava, 1968.
72 Frommel, 1958.
73 Ahmed and Taylor, 1959. Even more impressive was the report by Zucker (1925) that, in unilateral parkinsonism, physostigmine exacerbated parkinsonian symptoms only on the afflicted side.
74 Haas, 1960.
Haas’ investigation concerned the anticholinergic biperiden, but he noted in a detailed foreword to his paper the effects of reserpine on central neural function. Interestingly, he discussed the possibilities of altering central neurosubstance concentrations by pharmacological intervention, including the use of reserpine, MAO inhibitors and amine precursors; even more interesting, he restricted this discussion to 5-HT. Haas found that the effect of biperiden was increased by prior treatment with 5-HTP, serotonin, or iproniazid together with reserpine; he could offer no explanation for these observations.75

It emerged that the anticholinergic properties of antiparkinsonian agents could even be irrelevant to their therapeutic success. In 1969, the laboratory of Solomon Snyder (Departments of Pharmacology and Experimental Therapeutics and Psychiatry and the Behavioural Sciences, Johns Hopkins University School of Medicine, Baltimore) reported that a number of the synthetic agents used in antiparkinsonian therapy, including benzhexol, diphenhydramine and diethazine, were potent non-competitive inhibitors of [³H]dopamine uptake into rat striatal synaptosomes (and, less potently, competitive inhibitors of [³H]norepinephrine uptake into hypothalamic synaptosomes).76 Farnebo and associates reported a similar inhibition by anticholinergic agents of dopamine uptake into central neurons in 1970.77 Snyder’s group noted that, while it had been postulated in the late 1950s that antiparkinsonian agents might correct an overactivity of cholinergic elements in the striatal region, only a limited correlation between anticholinergic activity and efficacy in parkinsonism had been demonstrated. Further, the value of amphetamine in correcting akinesia and rigidity was generally recognized, but it possessed no anticholinergic activity. Coyle and Snyder therefore proposed that it was inhibition of dopamine uptake which was the important feature of these agents, not their anticholinergic action. There was no suggestion of a direct link between the uptake-inhibiting effects of these agents and their anticholinergic nature. Amphetamine would thus be expected to be the antiparkinsonian drug par excellence, but its central stimulating qualities were too potent to allow it to be useful in this regard. Coyle and Snyder had, however, also observed that in the striatum, unlike other brain regions, L-amphetamine was as potent an inhibitor of catecholamine uptake as the D-isomer, generally regarded as the more potent of the two isomers; it might thus prove useful as an antiparkinsonian agent.78 This finding is of interest as it would later be found that one of the metabolites of the antiparkinsonian agent deprenyl is L-amphetamine. It is usual to dismiss “amphetamine-like” effects of deprenyl treatment on the basis that it is less active than the D-isomer; if it exerted effects on striatal dopamine uptake, however, this metabolite might well contribute to its overall benefit.

At the end of the 1970s, Van der Zee and colleagues (Gist-Brocades, Haarlem) further examined the potent amine uptake inhibition in striatum and hypothalamus by benztpine and other aromatic substituted benzhydryl ethers. Benztpine was of particular interest, as it had been found to be a central nervous system stimulant in animals. Halogenation at the 4-(para-)position reduced the required dose for inhibition of striatal uptake of dopamine or 5-HT by an order of magnitude. Diphenhydramine and orphenadrine were found to be equipotent with imipramine and desipramine with regard to inhibition of striatal amine uptake, although much less effective in the inhibition of

75 Ibid.
76 Coyle and Snyder, 1969.
77 Farnebo et al., 1970.
78 Coyle and Snyder, 1969.
uptake in the hypothalamus; the authors, however, dismissed these antihistamines as “weak” uptake inhibitors. Once again, halogenation of the 4-position increased the potency of these agents by an order of magnitude. The differential effects of the agents led these workers to classify them as “striatal”, “hypothalamic” or “mixed” amine uptake inhibitors. Further, on the basis of work by Sourkes and Poirier and by Sano’s group,\textsuperscript{79} they hypothesized that it

\begin{quote}
may be favorable for an antiparkinsonian drug to have an inhibitory effect on the 5-HT uptake in the corpus striatum and on the NA uptake in the hypothalamus in addition to inhibition of DA uptake in the striatum.\textsuperscript{80}
\end{quote}

They proposed that flunamine, which also exhibited dopamine agonist activity, might be such a useful compound. This agent was briefly examined both as an antiparkinsonian agent and as an antidepressant, but never proceeded to the clinical phase.\textsuperscript{81}

Tropane analogs which inhibit dopamine uptake have also been investigated in the laboratory, the prototype for such compounds being cocaine. One aim has been to produce an efficient dopamine releaser which did not elicit the typical cocaine behavioral profile. Newman and colleagues reported on a candidate compound in 1994 (figure 9-2). The use of such agents in parkinsonism has, however, not been suggested.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure9-2.png}
\caption{Dopamine uptake inhibitors discussed in text.}
\end{figure}

**Problems concerning the development of a model for the testing of antiparkinsonian drugs**

All these attempts to develop an instrument for the identification of antiparkinsonian drugs were ultimately based on a number of doubtful premises. The first was the assumption was that antiparkinsonian drugs share a common mechanism of action, an assumption which was rarely explicitly questioned. Further, it seemed to be assumed by at least some workers that parkinsonism was a unitary disorder; that is, the major symptoms could ultimately be explained by a single lesion or other cause, so that the

\textsuperscript{79} Sourkes and Poirier, 1965, 1966a, b; Sano, 1972; see also Fahn et al., 1971.
\textsuperscript{80} Van der Zee and Hespe, 1978.
\textsuperscript{81} Van Beek and Timmerman, 1974.
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The total clinical picture should be amenable to control if not cure by a single agent or class of agents. This assumption ignored the fact that the three major forms of parkinsonism shared many features, but were also very different from one another in many regards, including probable etiology, presentation of signs and symptoms, and response to chemical agents. Further, neuropathological studies had led to the association of specific symptoms with particular anatomical lesions since at least the close of the 19th century, and certainly since the work of the Vogts and others in the first third of the 20th century. It had also long been recognized that the rigidity of parkinsonism was comparatively simple to treat, and that most antiparkinsonian drugs were efficient in this regard. Tremor was more resistant to therapy, and the number of drugs which addressed this aspect of the disorder were fewer in number. Akinesia was regarded at the beginning of the 1960s as almost totally unresponsive to anticholinergic therapy, although the literature of the 1950s often conveys the opposite impression; this was principally because it was long regarded as secondary to the primary symptoms of the disorder, if not as a purely psychiatric or motivational problem which could be divorced from basal ganglia mechanisms. Assessment of antiparkinsonian drugs thus often disregarded it entirely, describing control of at least one of the tremor and rigidity as success. The third factor which determined this approach to the therapy of parkinsonism was not an assumption, but ignorance: armed only with the knowledge that a brainstem lesion appeared associated with the disease, and unaware of the neurochemical changes in the parkinsonian brain, let alone their significance, it was simply not possible to devise a more complete model of antiparkinsonian drug action.

Doshay was thus justified when he observed in 1961 that, despite the massive strides taken in the therapy of parkinsonism since the introduction of synthetic agents, the pharmaceutical chemist was still handicapped:

> He has no criteria for predicting the actions of the new drugs against the symptoms of Parkinson’s disease, and he has no Parkinson patients for direct determinations of their value, uses and reactions. Up to now, it has been almost impossible to produce the symptoms of Parkinson’s disease in animals and the drug tremorine has proved ineffective as an indication of what a new compound will do against the tremor of Parkinson patients.\(^{82}\)

The interdependence of clinician and chemist was underscored by this observation, and Doshay was appalled that there existed no framework in America to promote such cooperation. It was partly out of this need to avoid missing valuable new compounds that the Parkinson Foundation of America had been founded by Doshay shortly before.

Broader models could only emerge in the early 1960s when the localization of neuroactive substances in the central nervous system had been mapped and their alterations in Parkinson’s disease measured. Even then they were restricted to rather abstract notions of “balances” between different neurosubstances. McGeer’s group proposed in 1961 that a balance between 5-HT and the catecholamines on the one hand and ACh and histamine on the other in favour of the latter group of substances was responsible for the symptoms of parkinsonism.\(^{83}\) Barbeau divided this into two separate disequilibria: the dominance of dopamine by ACh led to rigidity and akinesia, that by histamine of 5-HT to tremor and akathisia. Barbeau appears to have conceptualized these imbalances as involving excessive levels of one or the other substance, but more...

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\(^{82}\) Doshay, 1961a.

\(^{83}\) McGeer et al., 1961.
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Specific explanations than this were still not possible. These models were based purely on the empirical evidence provided by the responses of patients and normal persons to drug administration, and the developing awareness of “pools” of neuroactive substances in defined regions of the brain. This hypothesis was based on a number of independent observations:

- The ability of anticholinergic agents to relieve some parkinsonian symptoms
- High concentrations of histamine in striatum and hypothalamus
- Histamine and 5-HT occur together in mast cells
- Phenothiazines with marked antihistaminergic properties were less likely to induce extrapyramidal reactions
- Reduced urinary dopamine concentrations.

Anecdotal experiences gained in the surgery of parkinsonian patients also suggested the crucial role of cholinergic mechanisms in the disease; Velasco-Suarez found that implanted atropine crystals in the ventromedial thalamus provided symptomatic relief, while Nashold increased tremor in the contralateral limbs by injecting ACh into the pallidum, and suppressed it with an anticholinergic agent.

During the 1960s, it became accepted that ACh was acting as a central neurotransmitter; Bernheim remarked at the Second International Symposium on Parkinson’s disease in 1963:

*The brain has all the machinery for cholinergic transmission, and if there is none in the brain, it is carrying a lot of excess baggage.*

The direct detection of central ACh was still not a simple task, and some doubt had been cast on the methods employed for measuring it in the brain. There was also the problem that atropine did not appear to block responses to cholinergic stimulation in all cells; even more perplexing, atropine:

*does not show typical central anticholinergic activity when given to the normal individual, and yet it has a very definite effect when given to a patient with Parkinson’s disease.*

It was hypothesized on the basis of animal studies that atropine primarily antagonized the effects of excess ACh which resulted from an as yet unidentified pathological process. Another explanation was provided by the observation that tremorine increased central ACh levels, apparently without affecting esterase activity. But Bernheim concluded that more refined techniques would be required to map cholinergic tracts, and that such methods might allow an explanation of why “atropine is so ineffective under what may be called normal and apparently effective in abnormal conditions.”

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84 Barbeau, 1962.
85 Kopera and Lazarini, 1953; Parratt and West, 1956; White, 1959; Kahlson, 1960; McGeer et al., 1961.
86 Velasco-Suarez, 1964.
87 Nashold, 1961.
88 Bernheim, 1966.
89 Ibid.
90 Ibid.
At the same time, Duvoisin noted that the evidence linking antiparkinsonian medication with central anticholinergic effects was entirely circumstantial. He therefore examined whether cholinergic agents directly exacerbated parkinsonian symptoms in patients and antagonized the effects of antiparkinsonian medication. Earlier evidence in this direction has already been summarized above; but these results were often achieved in ignorance of the connections between the drugs employed and cholinergic systems. Duvoisin employed two cholinesterase inhibitors, the centrally acting physostigmine and the peripherally acting quaternary inhibitor edrophonium (figure 9-3). The subcutaneous administration of 1mg physostigmine salicylate to twenty parkinsonian patients who had been withdrawn from medication resulted in the exacerbation of parkinsonian symptomatology in seventeen; the extent of the effect appeared to be related to the responsiveness of the individual patient to anticholinergic therapy. It was also demonstrated in five patients that physostigmine antagonized the therapeutic benefit of scopolamine and benztropine, and that these drugs countered the effects of physostigmine. Edrophonium did not replicate the effects of physostigmine, nor did methylscopolamine, for which does the blood-brain barrier is also impermeable, modify the response to cholinesterase inhibition. Duvoisin noted that only existing symptoms were affected by the drug treatments; for example, unilateral parkinsonism remained unilateral, as also observed by Zucker in 1925. It thus seemed clear that excessive central (and not peripheral) ACh levels were involved in the motor symptoms of parkinsonism and the response to antiparkinsonian therapy, but the question of where remained open; he favoured, however, the view that the striatum was the most probable site.91

Although Duvoisin did not explicitly state it, it was also clear that these increased levels were in themselves insufficient to produce parkinsonian symptoms. It had indeed been tentatively suggested earlier that increased cholinergic receptor sensitivity consequent to reduced central ACh levels (“denervation hypersensitivity”) which might underlie the disorder, a proposal entirely consistent with the clinical data at the time of the proposal. But by this time, the Ehringer and Hornykiewicz results regarding striatal dopamine depletion in parkinsonism were well-known, and it was hypothesized that the release from the inhibitory influence of dopamine might lead to increased ACh release in the striatum. The effect of anticholinergic therapy would be to reduce this activity

91 Duvoisin, 1967.
and thus to remove the inhibitory influence of the striatum on motor activity; Duvoisin compared this to surgical interruption of some striatofugal fibres by pallidotomy or the lesioning of one of their major targets, the ventromedial thalamus.\textsuperscript{92}

Hornykiewicz reviewed the biochemical basis of the rational pharmacological therapy of Parkinson’s disease in 1970. His hypothesis that the two “\textit{neurohumors}” ACh and dopamine influenced the activity of some of the neuronal units in the striatum in an antagonistic way was essentially a reiteration of the equilibrium hypotheses which had circulated throughout the 1960s. Hornykiewicz, however, interpreted the model in a slightly different manner; while the anticholinergic drugs suppressed cholinergic tone and thus restored the equilibrium with dopamine, this produced a neurochemical situation in which the level of neither humor was at anything approaching its normal level. L-DOPA therapy, on the other hand, restored dopamine levels and thus re-established the balance in a positive fashion. While both anticholinergic agents and L-DOPA might be expected to relieve the symptoms of parkinsonism, only L-DOPA had the capacity to restore normal function of the striatum. Further, he saw the effects of the anticholinergic agents on dopamine re-uptake (discussed above) as being of minor importance, as there was very little dopamine in the parkinsonian striatum in the first place.\textsuperscript{93} In any case, the precise nature of the interaction of the two transmitters remained to be defined.

At about the same time, Kaeser and colleagues reviewed evidence gained from stimulation experiments during stereotactic operations that the $\alpha$-tonus was increased in parkinsonism, leading to rigidity, and the $\gamma$-tonus reduced, leading to akinesia. It was hypothesized that striatal ACh and dopamine played roles in regulating respectively the $\alpha$- and $\gamma$-systems, explaining the effects of antiparkinsonian agents (figure 9-4).\textsuperscript{94} The details of this model, however, remained to be elucidated.

Important advances were made during the 1970s and 1980s regarding the cytoarchitecture of the striatum and the distribution of various putative neuroactive substances within its structures. There was an interesting shift in emphasis from cholinergic and monoaminergic aspects to the definition of neuron populations on the basis of their peptide content, but transmitter distribution within these populations was naturally also of great concern. One of the most important aspects was the recognition that the striatum is not a homogenous tissue, but is actually composed of irregular “islands” interspersed in a distinct matrix. Further biochemical and pharmacological evidence was collated which supported the hypothesis of a broad “dopamine/ACh balance” in striatal function.\textsuperscript{95} In particular, dopamine receptor agonists reduced striatal ACh turnover as measured by a number of indices, whereas cholinergic substances, such as oxotremorine and physostigmine, increased dopaminergic turnover as indicated by striatal HVA levels; the dopamine release was also directly measured with push-pull cannula technique.\textsuperscript{96} These and other phenomena were interpreted as indicating that the targets of dopaminergic nigrostriatal neurons were the cholinergic elements of the

\begin{footnotes}
\item[92] Ibid.
\item[93] Hornykiewicz, 1970a, b; 1971b.
\item[94] Kaeser \textit{et al}., 1970.
\item[95] Reviewed in Pletscher, 1975.
\item[96] Bartholini, 1976; Bartholini \textit{et al}. , 1976. The push-pull technique had been developed in the late 1950s, and had been employed as early as 1964 to investigate caudate transmitter release: Sulman, 1958; McLennan, 1964.
\end{footnotes}
IX. Why was the anticholinergic therapy of parkinsonism successful?

Figure 9-4: Hypothetical scheme for the effect of anticholinergic drugs on rigidity and akinesia, as presented by Kaeser et al., 1970. (a) Balance between ACh and inhibitory dopamine, and thus between α and γ motor systems; (b) Reduced inhibition by dopamine = Parkinson’s disease; (c) Parkinsonism treated with anticholinergic drugs leads to equilibrium “at a lower level”, reducing rigidity but leaving akinesia unresolved; (d) Parkinsonism treated with L-DOPA, leading to re-establishment of natural equilibrium.

striatum; loss of this direct inhibitory control led to syndromes such as Parkinson’s disease and neuroleptic-induced tardive dyskinesia, while the dominance of dopaminergic tone in the degenerating striatum led to the symptoms of Huntington’s disease. Pletscher proposed a “feedback”-type association between the two elements as the basis of striatal transmitter balance (figure 9-5); the cholinergic element stimulated the inhibitory dopaminergic system, while dopamine inhibited the activity of the cholinergic neuron. Such a model left open the question of other inputs and that of the final output pathways, but provided a model of the dopamine-ACh balance which explained the relative effects of agents acting on these two systems in the therapy of parkinsonism. Pletscher also adopted the notion of inhibitory presynaptic dopamine receptors on the dopaminergic neuron, explaining increased dopamine turnover following dopamine receptor blockade with neuroleptic substances; at low doses of such agents (chlorpromazine, clozapine), ACh release was normal in cats, but with increasing doses was also increased.

Figure 9-5: Simplified depiction of a proposed cholinergic-dopaminergic feedback loop in the striatum; Pletscher, 1975.

97 Pletscher, 1975.
98 Ibid.
As might be expected in a brain region lying at the crossroads of motor and affective function and apparently involved in a range of different neurological disorders of various character, this initial model proved to be too simplistic. It was challenged in a classic paper by Lehmann (Department of Neuroscience, Johns Hopkins University School of Medicine, Baltimore) and Langer (Department of Biology, Laboratoires d’Etudes et de Recherches Synthélabo, Paris) in 1983. In a comprehensive review of the anatomic and pharmacological relationship of striatal ACh and dopamine, they came to the conclusion that dopaminergic terminals did not have synaptic contact with cholinergic interneurons in the striatum. Instead, they proposed that the cholinergic and dopaminergic terminals provided parallel inputs to a third neuronal type, which they believed was probably the medium spiny (GABAergic) neuron; ACh- and dopamine-releasing neurons interacted extrasynaptically, possibly by axo-axonic neuromodulation. Pharmacological evidence supported the identity of the dopamine D₂ receptors which modulated dopamine release (autoreceptors) and ACh release; it was thus argued that it could not be a post-synaptic dopamine receptor which regulated ACh release in the striatum.

**Figure 9-6:** The parallel dopamine/ACh input model for striatal dopamine and ACh interactions, as proposed by Lehmann and Langer, 1983.

The Lehmann and Langer model has since been modified and expanded, but the essential features of their hypothesis have since been substantiated. Current knowledge of ACh and its relationship with striatal dopamine function can only be briefly summarized here, as this relationship would ultimately play only a minor role in the further development of antiparkinsonian therapy; further, its discussion involves a leap forward in time with respect to the story of antiparkinsonian as presented thus far in this work. The neostriatum contains the highest concentrations in the central nervous system of all the cholinergic markers (ACh; the synthesizing enzyme choline acetyl transferase; high affinity choline uptake; muscarinic receptors). Dopaminergic fibres projecting from the brainstem interact both synaptically and extrasynaptically with the large (20-60mm) aspiny cholinergic neurons, which represent one of three classes of intrinsic striatal interneurons (the others are the GABA-parvalbumin and somatostatin-}

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neuropeptide Y-NO synthase neurons).\textsuperscript{101} These cells comprise only 1-2\% of striatal neurons, but appear to play an important role in the transfer of information between striatal inputs from the cortex and the substantia nigra and striatal output systems.\textsuperscript{102} Striatal D\textsubscript{2} receptor localization largely corresponds to that of these cholinergic neurons.\textsuperscript{103} The degree of striatal dopamine/ACh interaction is greatest in the shell of the accumbens and in the olfactory tubercle; in the core of the accumbens and in the caudate-putamen, the interaction is strongest in the “matrix” compartment (the “islands” in the striatal matrix are by definition poor in cholinergic markers).\textsuperscript{104} The extensive dendritic tree of the cholinergic neurons also receives GABAergic input from thalamic projections and from intrinsic neurons, particularly in the ventral striatum, with little (glutamatergic) cortical input.\textsuperscript{105} The cholinergic neurons have extensive intrastral projections (~ 0.5mm), and synapse in turn on GABAergic efferents to the substantia nigra, thus modulating the same fibres as dopaminergic input.\textsuperscript{106} There is also some evidence for extrastriatal cholinergic projections to the cortex.\textsuperscript{107}

Dopaminergic agonists acting at D\textsubscript{2} receptors on the cholinergic interneurons inhibit tonically the depolarization-induced release of ACh from these neurons.\textsuperscript{108} Serotonergic agonists also inhibit the release of striatal ACh,\textsuperscript{109} but the significance of serotonergic innervation of the striatum remains relatively unexplored. Dopamine release itself is predominantly modulated by cortical glutamatergic afferents.\textsuperscript{110} ACh regulates dopamine release in a complex manner (inhibition/stimulation), depending on striatal compartment.\textsuperscript{111} Muscarinic m\textsubscript{1} (high affinity) receptors distinct from ACh autoreceptors stimulate dopamine efflux (possibly by inhibiting presynaptic dopamine autoreceptors located in their close proximity), as do presynaptic nicotinic receptors, which also inhibit dopamine reuptake, both of which effects vary with age, unlike autoreception.\textsuperscript{112} Most anticholinergic drugs used in parkinsonism have a higher affinity for the m\textsubscript{1} than for m\textsubscript{2} (low affinity) receptors; the former is the dominant type in the rat forebrain.\textsuperscript{113} Interestingly, chronic nicotine reduces striatal dopamine turnover, and has positive effects on receptor binding, while acute nicotine potentiates the behavioural effects of haloperidol.\textsuperscript{114} With respect to the substantia nigra, it has been proposed that a direct cholinergic innervation of the dopaminergic cells of the pars compacta by the pendunculopontine tegmental nucleus acts via nicotinic receptors.\textsuperscript{115}

\textsuperscript{101} Cuello, 1987; Emson et al., 1993; Woolf, 1991; Kawaguchi, 1993.  
\textsuperscript{102} Phelps et al., 1985.  
\textsuperscript{103} Joyce and Marshall, 1985.  
\textsuperscript{104} Gerfen, 1992.  
\textsuperscript{105} Woolf, 1991; Emson et al., 1993; DeBoer and Westerink, 1994.  
\textsuperscript{106} Lehmann and Langer, 1983.  
\textsuperscript{107} Parent, 1990.  
\textsuperscript{108} Wedzony et al., 1988; Stoof et al., 1992a.  
\textsuperscript{109} Jackson et al., 1988a,b.  
\textsuperscript{110} Glowinski et al., 1988.  
\textsuperscript{111} Bernard et al., 1992.  
\textsuperscript{112} Raiteri et al., 1984; Barochovsky and Bradford, 1987; Joseph and Roth, 1988; Joseph et al., 1988; Dawson et al., 1990; Joseph et al., 1990; Rapier et al., 1990; Izenwasser et al., 1991; Sandor et al., 1991; Yamagami et al., 1991; Grady et al., 1992; Yu and Wecker, 1994; Clarke, 1995.  
\textsuperscript{113} Hammer and Giachetti, 1982; Burke, 1986.  
\textsuperscript{114} Emerich et al., 1991; Li et al., 1992.  
\textsuperscript{115} Clarke, 1995.
The interaction between ACh and dopamine is thus a great deal more complicated than originally envisaged by the simple equilibrium models of the 1960s. It is interesting and not a little ironic, however, that striatal cholinergic mechanisms are now largely disregarded in models of motor function; the interaction of dopaminergic, GABAergic and glutamatergic elements now dominates discussions. This in itself motivates the question of the function of the striatal cholinergic interneurons; they are presumably involved in modulation of the function of other neuronal types, but the precise significance of this role is yet to be elucidated. Nevertheless, as recently reviewed by myself and others, current models of the “motor loop” do not adequately account for all the clinical and pharmacological data to which we now have access; it may well be relatively neglected aspects such as the cholinergic interneuron which eventually resolve such problems.\textsuperscript{116}

In recent years, changes in ACh receptor density in the parkinsonian brain has also been assessed. In the striatum, Joyce found that the greatest loss of m\textsubscript{2} receptors was in the dorsolateral striatum, while m\textsubscript{1} receptors were reduced in most regions; these changes were coordinated to some extent with loss of D\textsubscript{2} receptor and dopamine uptake sites.\textsuperscript{117} Asahina and colleagues have reported increased muscarinic binding (that is, increased receptor sensitivity) in the cortex of parkinsonian patients in positron emission tomography (PET) studies.\textsuperscript{118} This was consistent with post mortem examinations which found that muscarinic receptor binding was increased in frontal cortex and normal in hippocampus, caudate nucleus and putamen; with respect to receptor subtypes, m\textsubscript{1} binding was increased in frontal cortex, normal in hippocampus and reduced in caudatus and putamen, while m\textsubscript{2} binding was reduced in cortex and normal elsewhere. Nicotine receptor binding was reduced in cortex and hippocampus.\textsuperscript{119} Griffiths and colleagues found reduced muscarinic binding in the medial pallidal segment in 1990. None of this has thus far been related to the mechanism of action of anticholinergic antiparkinsonian drugs. It is known that most of these agents bind with high affinity to m\textsubscript{1} and with moderate affinity to m\textsubscript{2β}-type muscarinic receptors.\textsuperscript{120} Significantly, m\textsubscript{1} receptors (α and β-types) are found in various central nervous centres, including the striatum and m\textsubscript{2β} receptors in externally and internally secreting glands, smooth muscle, striatum, cortex and hippocampus; cardiac muscarinic receptors, on the other hand, are of the m\textsubscript{2β} type.\textsuperscript{121} Further, PET studies have indicated that a single dose of benzhexol (4mg) suppressed cortical muscarinic binding by about 28% (while 400mg 1-L-DOPA together with 57mg benserazide had no effect on this parameter).\textsuperscript{122} Izurieta-Sanchez and associates recently reported that locally applied benzhexol had no effect on 1-L-DOPA-induced dopamine release in the rat striatum, suggesting a site of action distal to this locus.\textsuperscript{123}

\textsuperscript{116} Parent and Cicchetti, 1998; Foley and Riederer, 2000a.
\textsuperscript{117} Joyce, 1993.
\textsuperscript{118} Asahina et al., 1995, 1998.
\textsuperscript{119} Lange et al., 1993.
\textsuperscript{120} Burke, 1986; Syvaelahti et al., 1988; Larson et al., 1991.
\textsuperscript{121} Reviewed in Müller et al., 1999.
\textsuperscript{122} Shinotoh et al., 1994.
\textsuperscript{123} Izurieta-Sanchez et al., 1998.
Pharmacokinetics of the anticholinergic antiparkinsonian drugs

The pharmacokinetics of the anticholinergic drugs remain comparatively unexplored, partly because they were largely superseded by the time the techniques required for an accurate assessment became available. Clearly, the majority of the agents employed were readily absorbed from the gastrointestinal tract; the belladonna alkaloids in particular were also absorbed from the eye and mucous membranes, and to some extent across the skin.124 In the older literature, one rarely reads more than the fact that the peak therapeutic effect for most drugs was usually observed two to four hours after administration.

A study of the kinetics of the effects of atropine in three healthy volunteers after intravenous administration (1.35 or 2.15 mg) was reported in 1985; the pharmacokinetic data for atropine and its primary metabolite, tropine, were also determined using a sensitive gas chromatographic-mass spectrometric assay, and fitted to an integrated kinetic-dynamic model. The kinetics of elimination of atropine was first order. Two phases with apparent half-lives of one and 140 min were detected, corresponding to a linear two-compartment disposition model for atropine. 57% of the administered dose was excreted unchanged in the urine; 29% was detected as urinary tropine. Steady-state distribution volume was 210L, indicative of extensive tissue binding and/or partitioning. Renal plasma clearance was 660 mL.min⁻¹, suggesting significant tubular secretion. Maximum heart rate (∼100% increase) and minimum saliva flow (95% reduction) occurred 7-8 minutes after drug administration. Duration of the chronotropic effect of the drug was 3-4 hours, of the anti-sialogogue effect, 4-5½ hours.125

One of the few pharmacodynamic studies of benzhexol was that of Burke and Fahn in 1982. They found that the plasma half life of benzhexol in normal persons following an acute dose was 1.7±0.2h, in chronically treated dystonia patients, 3.7±0.3h.126 This suggested that a more continuous dosage scheme than the usual three times a day might have been advisable in parkinsonian patients; this had also been recommended by some workers during the 1930s for the belladonna preparations.127 Garbarg and colleagues estimated a somewhat longer half-life for benzhexol,128 but both papers were criticized on technical grounds by a recent investigation which identified a two phase elimination pattern, with half-lives of 5.3 and 32.7 hours.129

The pharmacokinetic data for other synthetic antiparkinsonian agents even less abundant: the bioavailability of biperiden was estimated at approximately 30%, suggesting extensive first pass metabolism (elimination half-life: 18 hours);130 orphenadrine was found to be almost entirely metabolized to eight derivatives which were identified in the urine (half-life in healthy volunteers: 15.5 hours; in two long-term patients: greater than 30 hours);131 procyclidine was found to be rapidly cleared from all tissues, although autonomic effects were still detectable after twelve hours.132 The

124 Scopolamine is particularly well absorbed across the skin: Ebert et al., 1998.
125 Hinderling et al., 1985a, 1985b.
126 Burke and Fahn, 1982.
127 For example, Scheiffarth, 1940.
128 Garbarg et al., 1983a.
129 He et al., 1995a. See He et al., 1995b for pharmacodynamics of benztropine in rats.
130 Hollmann et al., 1984; Grimaldi et al., 1986.
131 Labout et al., 1982; Rutigliano and Labout, 1982.
132 Whiteman et al., 1985.
metabolism of diphenhydramine, the application of which is not restricted to the therapy of parkinsonism, has been more extensively investigated. Readily absorbed in the intestines, first pass metabolism and extensive binding to plasma proteins modulate the bioavailability of the drug; diphenhydramine has access to all regions of the body, including the brain, and readily crosses the placenta and into breast milk. Little unmetabolized drug is found in the urine.\textsuperscript{133} It was found that elimination half-life and increased with age: $13.5 \pm 4.2$ hours in the elderly (mean age: 69 years), $9.2 \pm 2.5$ hours in adults (mean age : 31 years), and $5.4 \pm 1.8$ hours in children (mean age: 9 years). Conversely, sensitivity to the agent, as assessed by suppression of histamine-induced wheals declined with age, although the difference between younger and older adults was minimal.\textsuperscript{134}

**Summation: why were the anticholinergic antiparkinsonian agents successful?**

In conclusion, it must be said that the reason the anticholinergic agents worked as well as they did is largely unknown, and will probably remain so, as there is no longer sufficient interest to conduct further investigations into the question. For all the success of benzhexol, the Bulgarian treatment and other pharmacological interventions, there was no identified chemical abnormality with which to explain their effects, nor even a clear idea of what it was that the drugs might be doing. As already mentioned, parkinsonian patients have shown an idiosyncratic and variable preference for different members of the class over the years, and individual physicians have shown marked preferences for one or other of the alternatives. The reasons for these choices will to some extent remain obscure, although the effect of psychological factors in these choices is not to be overlooked. In light of more recent knowledge regarding the degeneration of the nigrostriatal pathway in parkinsonism, it is ultimately not surprising that the effectiveness of the anticholinergic agents declined as the disease progressed; if the symptomatic effect of these drugs did involve modulation of striatal dopamine release, this benefit could only be achieved while there still existed dopamine-releasing neurons to modulate.

The success of the anticholinergic agents was seen by Hornykiewicz as an impediment to research, as it deluded workers into believing that parkinsonism was a cholinergic disease.\textsuperscript{135} This is only partly true: Even had a European plant rich in L-DOPA been fortuitously discovered at some stage to have been useful for the management of parkinsonian symptoms, and chemists had determined that the active principle of this plant was L-DOPA itself, the neurochemical significance of these discoveries could not have been recognized before the end of the 1950s. A great deal of basic biochemical and neurochemical research was prerequisite to the insight that dopamine could function as a neurotransmitter, and that its deficit could lead to the presentation of parkinsonian symptoms. Further, even after this knowledge had been assembled, there persisted a great deal of resistance among some workers that any catecholamine, let alone dopamine, played a significant direct role in central neurotransmission. Marks wrote in a similar vein that the pathological anatomy of parkinsonism had been elucidated by the 1920s.\textsuperscript{136} This is also only partly true: although

\textsuperscript{133} Paton and Webster, 1985; Scavone et al., 1998.
\textsuperscript{134} Simons et al., 1990.
\textsuperscript{135} Hornykiewicz, 1976.
\textsuperscript{136} Marks, 1974, pp.2-3.
IX. Why was the anticholinergic therapy of parkinsonism successful?

the changes which are now regarded as the hallmarks of parkinsonian neuropathology had indeed been identified, only in the 1960s would a firm consensus emerge with respect to the security and the significance of these changes for the disorder. In short, the discovery of the basal ganglia dopamine deficit in parkinsonism could not have been discovered more than a couple of years earlier than it was. In order to enter the era of neurochemically buttressed therapy of neurological disease, the substructure provided by basic research needed to have been established; the laying of this foundation is the subject of the next chapter.
When the chemical constituents of the body are first understood, only then will the chemistry of the diseases arising therefrom become a clear science. For this purpose not only must methods be originated, but a combination of all developed methods must be used. In this regard the investigator is like a commander-in-chief; he must know not only the whole battlefield, but all agents which can be directed to prevail upon it.

Johann Ludwig Wilhelm Thudichum,
Grundzüge der anatomischen und klinischen Chemie (1886)*
DUVOISIN CONCLUDED HIS PAPER on cholinergic aspects of Parkinson’s disease in 1967 with a plea for “renewed interest in the pharmacology of parkinsonism”. At the time he wrote this, there had long been no new widely recognized development in the therapy of parkinsonism, so that the call was somewhat justified. But there had been a shift in the investigation of parkinsonism from direct pharmacology to neurochemistry, and dramatic changes were occurring in the therapy of parkinsonism even as Duvoisin’s paper was printed, and involved a completely new approach to the disorder. Kinnier Wilson had noted that:

*It is worse than useless to administer to the Parkinsonian any kind of nerve tonic to revive his dying cells; rather must some form of pabulum be sought, in the hope of supplying from without what the cell cannot obtain from within.*

This pabulum had not been provided by anticholinergic therapy; supplied instead were antagonists which blocked in an unknown manner a process or processes involved in the presentation of parkinsonian symptoms. It was not neurochemically rational in that its target was unknown; a long series of careful observations and analogies had revealed that the approach was of some benefit, without ever revealing precisely why.

There was a good reason for this: “neurochemistry” as we now know it, with its localized pools of transmitters, chemically defined pathways and multiple levels of interaction, did not exist before the middle of the 1950s. Up until this point, “neurochemistry” referred principally to the measurement of lipid, mineral and elemental levels in nerve and brain, without any clear idea of how this could be integrated into a model of central nervous function. Until this stage had been reached, not only was it impossible to devise a rational neurochemical approach to parkinsonism, it was not even possible to define the problem required attention. This would change from about 1957 onwards, and the pabulum sought by Wilson would be found; ironically, the required agent already had a reasonably long history, like many others which had become involved in the therapy of parkinsonism.\(^2\)

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¹ Wilson, 1954b.
² The first department dedicated solely to neurochemistry was established in 1928 in the Kaiser Wilhelm Institute in Munich by the American Irvine Page, at the invitation of Richard Willstätter; Page, 1957.
Dopamine and L-DOPA: the beginnings

It is not my intention to discuss here the entire history of catecholamine research, let alone the history of the development of the chemical transmission hypothesis of neural communication. Nevertheless, a detailed discussion of the emergence of dopamine as a central transmitter is appropriate, given that my aim is to present L-DOPA as the first neurochemically rational therapy of a neurological disease.

Dopamine was synthesized in 1909/10 in the course of independent investigations of substances related to “adrenine” (the active substance of the adrenal medulla) by Mannich and Jacobsohn at the Pharmaceutical Institute in Berlin (from the vanillin precursor eugenol) and by Barger and Ewins at the Wellcome Physiological Research Laboratories in London (from vanillin). Mannich and Jacobsohn commented that in the few years since its synthesis, adrenaline had advanced to become “one of the most important medicinal agents”; hence their interest in the synthesis of further phenolic organic bases. Barger and Ewins at the Wellcome Physiological Research Laboratories in London (from vanillin). Barger and Dale, having noted that the motor and pressor effects of the various catechol-based sympathomimetics were not closely correlated, classified dopamine (‘amino-ethyl-catechol’) as a weak vasopressor agent in the cat (this was later also reported in the dog). After this, dopamine sank into relative obscurity until the revival of interest in its role as precursor of adrenaline by Holtz in the 1930s; in the meantime, attention was directed to the roles of the “major catecholamines” (adrenaline and noradrenaline under various names).

In 1904, adrenaline had become the first hormone to be synthesized in the laboratory, specifically by the chemist Friedrich Stolz (1860-1936) in the Hoechst dyestuff laboratories near Frankfurt, who dubbed the compound “suprarenin”. It was in the same year that the doctoral student T.R. Elliott (Physiology, Cambridge) suggested that nervous transmission at sympathetic terminals might be mediated by adrenaline. Investigators were reminded by the dark oxidative products of adrenaline of similar reactions in cut plant tissues; this prompted the examination of a number of plants for similar pyrocatechol substances. L-3,4-dihydroxyphenylalanine (L-DOPA), the biochemical precursor of the catecholamines, was thus first isolated not from animal tissue, but from the pods and seeds of the broad bean (also: Windsor bean, navy bean; Vicia faba) by the Italian pharmacologist Torquato Torquati (Institute for Experimental Pharmacology, University of Sassari) in 1911, who also confirmed that tyrosine was present in the pods. This bean grows in various regions of the world, and was long a staple dietary component in the Nile valley and China.

3 Mannich and Jacobsohn, 1910. These authors commented that in the few years since its synthesis, adrenaline had advanced to become “one of the most important medicinal agents”; hence their interest in the synthesis of further phenolic organic bases.
4 Barger and Ewins, 1910.
5 However: “The optimum carbon-skeleton for sympathomimetic activity consists of a benzene ring with a side-chain of two carbon-atoms, the terminal one bearing the amino-group. Another optimum condition is the presence of two phenolic hydroxyls in the 3:4 position relative to the side-chain.” Barger and Dale, 1910.
6 The few papers from this period concerning dopamine include Tainter (1930), Raymond-Hamet (1931) and Gurd (1937); the latter, incidentally, received his dopamine from Barger. For review of early history of the catecholamines in general, especially for the development of nomenclature, see von Euler (1950).
7 Stolz, 1904. Stolz was honoured on his 70th birthday by Marburg University with the award of an honorary medical degree.
8 Elliott, 1904. He was quite specific in his presentation to the Physiological Society on May 21 1904 concerning the response of muscle to applied adrenaline: “Adrenalin might then be the chemical stimulant liberated on each occasion when the impulse arrives at the periphery.” In November 1933, Dale suggested the terms ‘adrenergic’ and ‘cholinergic’ “to avoid elaborate periphrasis, and to promote clear ideas” regarding the description of peripheral nerves with reference to their chemical action as distinct from their anatomic origin (sympathetic v. parasympathetic) (Dale, 1934b).
9 Torquati, 1913a, 1913b.
In the same year that Torquati isolated L-DOPA from the bean, the Polish expatriate Casimir Funk (Lister Institute of Preventative Medicine, Chelsea) described the synthesis of racemic DOPA from 3,4-carbonyl dioxybenzaldehyde and hippuric acid. Funk, along with many chemists at this time, was attempting to elucidate the synthesis of adrenaline, and the structural similarities of DOPA and adrenaline suggested to him that the former might be a precursor of the latter. The two obvious candidate substrates for catecholamine synthesis, tyrosine and phenylalanine, were regarded by Funk as unlikely to serve in this capacity, as their conversion to adrenaline would have required the hitherto unknown decarboxylation of an aromatic amino acid. Further, Ewins and Laidlaw had reported that adrenal tissue was incapable of forming adrenaline from tyrosine.\(^{10}\) As Funk noted, this did not necessarily eliminate tyrosine as a precursor; as had been proposed earlier by Halle, it was conceivable that adrenaline synthesis was a multistep process, perhaps involving several body tissues.\(^{11}\) Funk noted that DOPA was readily oxidized to a black product, and announced his intention to prepare the active \(\text{-L-}\) compound and to report on its physiological action. Funk, however, moved shortly afterwards into the investigation of beri-beri, a somewhat more urgent task, and did not return to DOPA research.\(^{12}\)

\(^{10}\) Ewins and Laidlaw, 1910.

\(^{11}\) Halle, 1906; Funk, 1911a.

\(^{12}\) See, for example, Funk, 1911b. Funk coined the term ‘vitamin’; Griminger, 1972.
It was thus Markus Guggenheim (1885-1970), of the chemical firm Hoffmann-La Roche in Grenzach (in Germany, directly across the border from Basel, Switzerland), who in 1913 published the first major paper on the physiological properties of L-DOPA, which he had isolated from Vicia faba beans according to the method of Torquati. Guggenheim had brought Torquati’s experiments to the attention of the German-reading public through his summaries of the Italian’s papers in German journals. Guggenheim had been awarded his doctorate in chemistry in 1907 by the philosophy faculty of the University of Basel, after which he studied physiological chemistry in Berlin; he joined Hoffmann-La Roche in 1909. Guggenheim’s interest in L-DOPA stemmed from his conviction that it was one of many unrecognized amino acids involved in protein synthesis, which he termed collectively the “proteinogenic amines”, in which class he also included adrenaline. In 1920, he coined the more inclusive term which replaced it, “biogenic amines”, having recognized that not all amino acids are involved in protein synthesis. The elemental composition calculated by Guggenheim for L-DOPA (C9H11NO4) differed from that of Torquati (C11H15NO5); he advanced convincing arguments for his interpretation, which was consistent with the structure of a hypothesized “mother compound” for adrenaline. The process employed to isolate L-DOPA is given here both for its historical interest and as an example of the biochemical techniques of the time:

Figure 10-2: Synthesis of adrenaline, as proposed by Halle, 1906.
10kg of pods, freed of seed, was treated with a dilute sulphuric acid solution, then finely chopped in a meat grinder. Pretreatment with sulphuric acid prevents oxidation which otherwise occurs quickly on contact with iron parts of the meat grinder. The chopped mass is thoroughly acidified with acetic acid and extracted with about 30L water. The cloudy, pale green filtrate is treated with 2½L 20% lead acetate solution. The large, dense precipitate is separated by filtration and washed. It contains no or very little dioxyphenylalanine. The filtrate is rendered thoroughly litmus-alkaline with ammoniac, which produces a large, yellowish-white precipitate. This is drawn up and washed several times with water. It is finally resuspended in about 5L water and decomposed with hydrogen sulphide. The pale yellowish filtrate, separated from the lead sulphide, is strongly concentrated in a stream of hydrogen or carbonic acid under about 15mm pressure. Dioxyphenylalanine separates as a yellowish-white crystalline powder. The yield is quite impressive: from 10kg fresh pods one gains about 25g raw product.

Guggenheim noted no unusual symptoms following his oral administration of 1g L-DOPA to a rabbit (2.2kg), nor did an intravenous injection (20mg) affect its blood pressure or respiration. The presence of an adrenaline-like substance in the urine of the animal following oral ingestion was indicated by a number of characteristic precipitation and color reactions (for example, a positive catechol reaction and the production of a green salt following treatment with a ferric chloride solution). The “indifference” (lack of physiological action) of L-DOPA was also demonstrated in tests on uterine and intestinal preparations.

Guggenheim then undertook the first self-experiment with L-DOPA by ingesting 2½g of the substance:

It became apparent that the substance is not completely innocuous. Ca. 10 minutes after ingestion I was overcome by extreme nausea; I had to vomit twice, so that the substance was not fully resorbed.

He nevertheless calmly noted the presence after two hours of the same reactive urinary substances as found in the rabbit; after five hours, however, different reactions were observed:

The urine showed in neutral and lightly acidic solution only a gradual darkening, while in ammoniacal solution a wonderful blue color developed which gradually faded to violet.

Hoffmann-La Roche was awarded a patent in 1914 for the L-DOPA isolation process described by Guggenheim; this, however, had already expired by the beginning of 1916.

Guggenheim had revived the research activities at Hoffmann-La Roche at a time when they were somewhat neglected, and continued to shape this aspect of the firm as leader of the research department until his retirement in 1948, despite the fact that he was blinded in 1916 as the result of an explosion in the Roche factory. He continued to search for a physiological role for L-DOPA, including its involvement in the synthesis of melanin. In 1920, his standard work *Die biogenen Amine* appeared and was subsequently translated into most major languages, the title encapsulating his

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16 Guggenheim, 1913. It should be noted that German authors frequently used the prefix ‘oxy-’ where English-speaking workers would use ‘hydroxy-’; hence “Dioxyphenylalanin”.
17 Ibid.
18 Ibid.
recognition that the role of these substances was not directly related to protein synthesis. His major research interest switched, however, to barbiturate derivatives as sedatives and pain-relieving medicaments. It is ironic Guggenheim died in the same year that L-DOPA was launched onto the market as a medication for parkinsonism.19

L-DOPA was subsequently identified in a number of plant species; Emerson Miller (Alabama Agricultural Experiment Station), using Guggenheim’s methodology, isolated the amino acid from a number of beans of the genus *Stizolobium*, including the velvet bean (*Stizolobium deeringianum* Bort). Miller did not describe any further pharmacological investigations, but noted that eating a small amount of Lyon beans (*Stizolobium niveum* (Roxburgh) Kuntze) led to both “vomiting and purging”.20

A synthetic method for producing racemic DOPA was described in 1914 by two Manchester chemists, Stephen and Weizmann, but they conceded that it was not appropriate for producing a pure preparation.21 Konrad Fromherz and Leo Hermanns (University Polyclinic, Freiburg) described a method for the synthesis of the mixture from vanillin in the same year. The Freiburg chemists were chiefly interested in DOPA as a possible intermediary in the catabolism of benzol-ring structures to aliphatic (chain) compounds. They viewed the oxidation of tyrosine as an alternative catabolic pathway in alkaptonuria, a disorder in which the metabolism of tyrosine is impaired at the level of homogentisic oxidase; this leads to the accumulation of homogentisic acid (2,5-dihydroxyphenylacetic acid) and consequently to darkening of the urine and, more importantly, arthritis. The pair made some important observations on the physiological effects of their preparation; these they attributed initially to contaminating substances, on the basis that Guggenheim had not observed them:

. . . the pharmacological effects of the amino acid were disturbingly apparent. . . . r-3,4-dioxyphenalanine, whether applied per os or subcutaneously, causes a severe emesis in dogs which makes any metabolic experiment impossible. Stimulation of the hair muscles on the entire body was also noted in the animals. Rabbits, who do not possess a vomiting reflex, exhibited a state of excitement similar to that of apomorphine toxicity, which manifests itself in restless wandering and continuous gnawing. The effect on the coat is the same. In larger intravenous doses, the substance lowers blood pressure.22

Waser and Lewandowski, two chemists in the Chemical Laboratory of the University of Zürich, published the first synthesis of optically pure l-DOPA in 1921. The method, the basis of which was the introduction of a second hydroxyl group onto the tyrosine ring, was derived from that of Erlenmeyer and Lipp for the synthesis of tyrosine from phenylalanine.23 Specifically, it involved the nitration of L-tyrosine, reduction of the nitrotyrosine, diazotation of the aminotyrosine, and finally the boiling of the diazo-compound (figure 10-4). The identity of the compound was confirmed by comparison with l-DOPA isolated from *Vicia faba* by Hoffmann-La Roche (and provided by Bloch).24 Their method, however, does not appear to have been well publicized;

19 For a brief autobiography, see Guggenheim, 1961; biography: Fischer, 1971. Guggenheim also instituted the “Markus-Guggenheim-Schnurr Foundation for the History of Medicine and the Sciences” in order to support work which “concerned the intellectual development and practical significance of a discovery or invention for the past and present.”
20 Miller, 1920.
21 Stephen and Weizmann, 1914.
22 Fromherz and Hermanns, 1914.
23 Erlenmeyer and Lipp, 1883.
24 Waser and Lewandowski, 1921.
Harington and Randle (Department of Pathological Chemistry, University College Hospital Medical School, London) declared in 1931 that “the optically active forms of this amino acid have not so far been artificially obtained”, and proceeded to describe their method, whereby they produced each of the isomers from β-3,4-diacetoxyphenyl-α-acetaminopropionic acid and brucine. Two Indian biochemists then reported the isolation of L-DOPA in large quantities from the seeds of a native plant Mucuna pruriens, as this is a story in itself, it will be discussed below.
Bruno Bloch (Department of Dermatology, Medical Clinic of the Basel District Hospital), Guggenheim’s uncle, reported in 1917 that l-DOPA was involved in the synthesis of melanin from tyrosine in pigmented cells. He continued his investigations into skin pigmentation until 1927 with a number of colleagues in the so-called “Asyl” (‘asylum’, ‘refuge’) at the Medicinal Chemistry Laboratory in Basel, as well as in his own department. Bloch also identified the fact that l-DOPA was the substrate for an enzyme-mediated oxidative reaction; the “dopaoxydase” or “dopase” which he had found would later prove to be tyrosinase. The role of melanin would be continually raised in the investigation of Parkinson’s disease, but it was only much later that differences between epithelial melanin and ‘neuromelanin’ were recognized. The role of melanin in the disorder is still unclear, largely due to the inscrutable nature of the molecule, as clearly noted by Bloch in his first paper on the subject. Related to Bloch’s work was that of Hans Schmalfuss and Alfred Heider (State Chemical Institute, Hamburg University), who were interested in the pigmentation of plants and insects. They had noted that the green pods of the broom (Sarthamnus scoparius Wimm.) darken more rapidly than those of Vicia faba, despite the fact that the latter contain l-DOPA; further, French workers had founded that the broom pods contained a substance which elevated blood pressure. The result of their investigation was the first isolation of dopamine from a natural source in 1931.

In 1926, Henry Stanley Raper (Physiology Department, Manchester) demonstrated for the first time that l-DOPA is formed when tyrosine is oxidized by tyrosinase, although it represented only 3% of the products formed. Raper also showed that l-DOPA was a better substrate for tyrosinase than tyrosine itself; he proposed that l-DOPA was the first product of the tyrosine-tyrosinase reaction, and that its further oxidation was responsible for the characteristic red color produced by the reaction. It was proposed that this red substance was ortho- or para-quinone, the precursor of a colorless substance which was itself the precursor of melanin. Finally, he found that in the presence of low concentrations of l-DOPA, the rate of tyrosine conversion by the enzyme was increased.

**l-DOPA and dopamine as precursors of adrenaline: Holtz and DOPA decarboxylase**

The relative neglect of dopamine until this point might be explained by its apparently innocuous pharmacological profile. Anticholinergic substances had been traditionally assessed according to their ability to induce mydriasis; catecholamines were similarly judged according to their effects on blood pressure. This focus on a single action of an entire class of chemical substances restrained the progress of neurochemical research to a certain degree, but must be understood in terms of contemporary knowledge. The catecholamines were not viewed as transmitters acting at multiple receptors in defined neural pathways, but rather as humoral messengers interacting in an undefined manner with the tissues with which they came into contact. Effects on the central nervous system, however, were regarded as unlikely except in pathologic or toxic situations.

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27 The presence of tyrosinase had previously been suggested by analogy with pigment formation in plants; Bloch doubted this; Bloch, 1917.

28 Ibid.

29 Schmalfuss and Heider, 1931.

30 Raper, 1926.
That L-DOPA was the precursor for adrenaline was presumed by many workers in the 1930s, especially as the related dopamine was by this time recognized as being adrenaline-like in its pharmacological activity; but in the absence of a physiological means for converting the amino acid to an amine, the question remained open, especially as there was no direct evidence at this stage for the natural occurrence of L-DOPA in animals. What was required was the decisive demonstration of the presence of a sequence of enzymes in animal tissue which could convert L-DOPA to adrenaline.

Much of this work was achieved and published in a series of landmark papers over a period of only a few years by Peter Holtz (Physiological-Chemical Institute of the University of Rostock). Holtz (1902-1970) was unusual in Germany at that time: although he had studied medicine, he came to pharmacology more through his interest in chemistry than applied therapeutics, and to this has been attributed the thoroughly biochemical direction of his approach. He had spent some time with Dale in London, where he investigated aspects of humoral communication in the vegetative nervous system; this was followed by his habilitation work in pharmacology (with Wels in Greifswald) concerning the production of histamine from histidine, introducing him to decarboxylase research.³¹ His biochemical reputation was acknowledged in his appointment to the Chair of Physiological Chemistry in Rostock in 1938. From 1953 until his death he was head of the Pharmacological Institute in Frankfurt am Main.³²

In 1936, it had been reported that the injections of large amounts of histidine led to increased histamine concentrations in the lung.³³ Holtz immediately suggested the existence of a decarboxylase which catalyzed the reaction, and by 1937 he had demonstrated the presence of histidine decarboxylase in mammalian kidney and liver.³⁴ This was the first of the decarboxylases to be identified; catalysts for the conversion of tyrosine and tryptophan quickly followed. The most active of these enzymes was also identified in 1937: Holtz was able to demonstrate in this year that kidney preparations rapidly decarboxylated L-DOPA to “oxytyramine” (= dopamine). He named what proved to be one of his most important discoveries “DOPA decarboxylase”. In the following years he demonstrated similar activity in the liver, intestine and pancreas.³⁵

Three methods were employed to demonstrate this activity:

1. the oxytyramine produced by the enzyme elevated blood pressure in cats.
2. carbon dioxide production could be assessed manometrically with the Warburg manometric apparatus; this was possible only due to the high activity of DOPA decarboxylase.
3. in experiments with kidney extracts, the oxytyramine could be isolated and chemically identified.

Dopamine actually causes a drop in blood pressure in guinea-pigs and rabbits; this was one of the reasons for its long being regarded only as a precursor for the pressor

³¹ ‘Habilitation’: the ‘second doctoral thesis’ required for professorial positions in German universities.
³³ Bloch and Pinösch, 1936. The investigation had been prompted in part by Guggenheim.
³⁴ Holtz and Heise, 1937a, 1937b. Werle and Herrmann (1937) also succeeded in demonstrating histidine decarboxylase in 1937, as acknowledged by Holtz (1941).
³⁵ Holtz et al., 1938; Holtz, 1939; Holtz et al., 1939; Holtz and Credner, 1941; further references in Holtz, 1959.
Holtz demonstrated that the oxidative metabolism of \( L \)-DOPA proceeded only via oxytyramine, and that the enzyme was absolutely specific for the \( L \)-isomer of DOPA; \( D \)-DOPA was not metabolized by the enzyme, nor is it identical with the histidine or tyrosine decarboxylases which he had previously described. The specificity of the enzyme for the \( L \)-isomer was later confirmed in vivo in rabbits. Further, the manometric assessment of its activity in kidney extracts showed that the reaction proceeded more slowly in the presence of racemic DOPA than with \( L \)-DOPA alone. Holtz’ conclusion was simple:

*DOPA decarboxylase could thus be of importance as an accessory enzyme in adrenaline synthesis by the organism.*

At the end of 1939, Holtz proposed the multistage synthesis of adrenaline which is now accepted:

- decarboxylation of \( L \)-DOPA to oxytyramine; this he regarded as the “pacemaker” step in the synthetic pathway.
- oxidation of the primary carbon of the side chain to arterenol (sympathin E; noradrenaline)
- methylation of the amino group to form adrenaline (sympathin I).

They recognized that if their theory was correct, the organism must have access to natural \( L \)-DOPA; but this amino acid had been found in no protein, and had only been isolated from the broom plant and cockchafer. Especially in the light of Raper’s work, however, they saw no problem in the concept that \( L \)-DOPA could be synthesized in vivo from tyrosine by any of a number of pathways, so that this was seen as no objection to their model of catecholamine synthesis.

Holtz proposed further that oxytyramine was oxidized by the cyanide-insensitive amine oxidase identified by Bernheim and investigated by Blaschko and colleagues. Apart from its role as adrenaline precursor, he regarded oxytyramine as a metabolic intermediate in the catabolism of \( L \)-DOPA, leading him to the suggestion that the decarboxylase and oxidase together constituted an enzymatic system, the “\( L \)-amino acid oxidase”. This hypothesis was supported by the finding that decarboxylase and amine oxidase activity in the kidneys of various species were found to be correlated.

The proof that amino acid decarboxylation actually occurred in vivo was published by Holtz and Karl Credner in 1941. The authors administered \( L \)-DOPA or \( L \)-histidine to guinea pigs and showed that detectable quantities of a blood pressure elevating (oxytyramine) or depressing substance (histamine) could be isolated from the urine of the animals. The following year, they published a more detailed paper which extended this result and also reported that oxytyramine was a normal component of human urine. Further, Holtz and Credner injected their assistant Wolfgang Koepp with 50mg \( L \)-
DOPA (in 6mL saline), and found that almost 40% of the dose could be demonstrated as dopamine in their urine, half of which was excreted in the half-hour following administration. L-DOPA produced no notable effects on Herr Koepp, except:

> for a somewhat considerable increased pulse, which, however, was probably at least partly a psychological phenomenon, caused by the expectation of a more or less marked circulatory effect – an expectation which had a certain justification, in light of the greater effect of larger intravenous Dopa doses on cats, which were at this time already known to us and will be described in the following section.\(^{44}\)

\(^{44}\) Holtz and Credner, 1942.
Only 12% of a larger dose of L-DOPA (150mg) was converted to dopamine, mostly excreted in the second and third hours following administration; this figure was increased, however, to 34% if the urine was heated in acidic solution. Holtz correctly interpreted this as indicating that dopamine is normally excreted bound to some inactivating substance, probably sulphuric acid. Holtz and Credner also surveyed previous work on the urinary pressor substance (‘Urohypertensin’) which had been first identified by Abelous and Bardier in 1909; they postulated that this substance consisted at least in part of dopamine. As they showed soon after, however, the more important pressor substance was another catecholamine, noradrenaline.45

The administration of intravenous L-DOPA to cats was found to elevate blood pressure, an effect which Holtz later found to be enhanced by co-administration of vitamin B₆ or iproniazid.46 Holtz and Credner established that the sensitivity to the pressor effects of dopamine were different in the cat, dog, guinea pig and rabbit; while the “adrenaline equivalent dose” of dopamine for dogs and cats was about 30-40×, that for the rodents was about 800-1000×. They attributed this partly to the varying MAO activity which they had assayed in the different species; they assumed that the rapid conversion of dopamine to the blood pressure lowering metabolite dioxypyhenylacetaldehyde was responsible for this phenomenon. Lower intravenous doses of L-DOPA thus elicited a drop in blood pressure in these species. The guinea pig and rabbit were the animals with the highest levels of DOPA decarboxylase, yet they were the least responsive to the effects of dopamine; Holtz and Credner interpreted this finding in the following manner:

The physiological significance of oxytyramine would thus not lie in its circulatory or general sympathomimetic capacity, but rather in its character as the precursor for adrenaline. The responsibility of producing physiological effects would belong to adrenaline as the finished hormone alone . . . The physiological significance of DOPA decarboxylase would correspondingly lie not in the production of a pharmacologically active substance in the organs in which it is found, such as the kidneys and liver, the intestines and pancreas, but in its production of what is perhaps the most important base substance (Muttersubstanz) for the medullary hormone produced in the kidneys.47

This view of a restricted role for dopamine as precursor would persist for the next two decades, even after it was recognized that the adrenal medulla possesses the entire synthetic pathway for adrenaline synthesis. The Holtz hypothesis of the intermediate role of dopamine was further bolstered when H. Langemann (Department of Pharmacology, University of Oxford) reported in 1951 that chromaffin tissue was rich in DOPA decarboxylase. Funk’s hypothesis that L-DOPA was the precursor for adrenaline had thus at last been vindicated. In 1952, Holtz reported that pyridoxal-5-phosphate activates adrenal cortex DOPA decarboxylase, and that a heat-stable activator could be isolated from the cortex which resembled pyridoxal-5-phosphate; this was the first identification of the co-factor for the dopamine-synthesizing compound.48

DOPA also attracted attention at this point for a related but slightly different reason. The physiologists Richard Bing and Marjorie Zucker (New York University) had found in 1938 that the injection of DOPA into the renal artery produced acute hypertension in

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46 Balzer and Holtz, 1956.
47 Holtz and Credner, 1941.
48 Holtz and Bachmann, 1952.
cats. In light of the work being reported by Holtz and their own investigation of renal
decarboxylation, they hypothesized that the formation of dopamine by the kidney,
together with the failure to deaminate this product under anaerobic conditions, was
responsible for renal or essential hypertension in man. Such an anaerobic state could
result, for instance, from chronic renal ischemia.49 Oster and Sorkin (Department of
Chemistry, Mount Sinai Hospital) reported shortly afterwards that the magnitude and
duration of the rise in blood pressure induced by intravenous injections of L-DOPA in
humans were markedly greater in hypertensive patients than in normal controls; the
other autonomic effects produced by the amino acid (nausea, emesis) were also more
marked in hypertensive subjects. In fact, most normotensive subjects could tolerate
120mg L-DOPA without a change in blood pressure, and up to 200mg without
experiencing nausea; the highest dose employed (450mg!), however, induced vomiting
even in a control subject.50 These early experiments in the administration of L-DOPA to
humans were largely overlooked by investigators of Parkinson’s disease, as the fields of
neurology and cardiology separated from “physiology” after the War. It is now
recognized that dopamine is a weak agonist at β2-adrenergic receptors. The L-DOPA
doses administered in the therapy of parkinsonism (since the introduction of peripheral
decarboxylase inhibitors) do not normally raise blood pressure, but such a response can
be controlled with β-antagonists if necessary. Barbeau would later report that L-DOPA
together with a decarboxylase inhibitor was of benefit in essential, but not malignant,
hypertension.51

Holtz had achieved a remarkable series of insights into the nature of DOPA
decarboxylase, all the more amazing because his techniques, including employment of
the Warburg manometric apparatus, were relatively insensitive. This explains many of
the negative results which he reported, leading him to overestimate the specificity of
adrenal decarboxylase. Circumstances, however, prevented the timely publication of the
findings which would have crowned this phase of his research. In 1944, Holtz, Credner
and Günther Kronenberg submitted a paper to Naunyn-Schmiedebergs Archiv für
experimentelle Pathologie und Pharmakologie in which they proposed that
urosympathin consisted of a mixture of the three catecholamines noradrenaline,
adrenaline and dopamine; further, sympathin E was identified as noradrenaline and
sympathin I as adrenaline. This paper indicated that the Rostock researchers were well
on the way to identification of noradrenaline as the sympathetic transmitter. Due to the
exigencies of the War and its aftermath, this paper did not appear until 1947.52 These
conditions also prevented him from immediately resuming his research, and it was thus
his friend Ulf von Euler who published the crucial papers on the identification of
noradrenaline in sympathetic nerve endings in 1946.

Ulf von Euler (1905-1983) seemed predestined to a career in science: his father, the
German Hans von Euler-Chelpin (1873-1964) was awarded the 1929 Nobel Prize for
Chemistry for his work in enzymology and fermentation; his mother was a Professor of
Botany; her mother, Per Cleve (1840-1905) had discovered the elements erbium,
holmium and thulium. Von Euler’s family had relocated to Stockholm in 1900. He was
awarded his doctorate in medicine by the Karolinska Institute in 1930. As a Rockefeller
Fellow, he isolated substance P in Dale’s laboratory in the same year; in 1935, having

49 Bing and Zucker, 1941.
50 Oster and Sorkin, 1942.
51 Udenfriend et al., 1971.
52 Holtz et al., 1947.
returned to the Karolinska Institute, he isolated prostaglandin from semen for the first time. He became Professor and Chairman of the Department of Physiology in 1939, which position he retained until his retirement in 1971. Von Euler shared the Nobel Prize for Medicine of 1970 with Julius Axelrod (*1912) and Sir Bernard Katz (*1911) for their contributions to understanding the electrical transmission of impulses along the nerve fibre.\(^{53}\)

Although active in many research areas of physiology, von Euler was especially interested in the hormones insulin, thyroxine and adrenaline. Thus it was that he reported in 1946 that noradrenaline, which he had first isolated during the Second World War, was the principle substance released from sympathetic nerves.\(^{54}\) In his various reviews of adrenergic function throughout the 1950s, noradrenaline would play the starring role, while dopamine was seen at best as an intermediate. His discussion of the composition of “urosympathin”, the name given by Holtz to the pressor substance found in the urine,\(^{55}\) did not consider dopamine, although Euler cited a great deal of Holtz’ work in his analysis of catecholamine metabolism. In the period immediately following the War, however, both workers were agreed: dopamine’s physiological significance lay solely in its position as precursor of the major catecholamines.

**The localization of brain catecholamines**

The history of neurochemistry is, like the history of brain function since the middle of the eighteenth century, a history of the localization of particular functional elements. It was therefore necessary, before any specific function could be ascribed to catecholamines in the central nervous system, to establish not only that they occurred in the brain, but also that they could be localized to specific regions of the brain. In the 1950s, this was not the same, for example, as defining a noradrenergic pathway; neural tracts were defined on the basis of the histological techniques with which they were visualized, not with respect to their possible transmitter content. Many of the leaders in the field would still be convinced as late as 1960 that chemical transmission played no significant role in central nervous function; a participant in a discussion at the Second Symposium on Parkinson’s Disease in 1963 could still suggest that “the evidence for such a function for the catecholamines is still indirect and unconvincing.”\(^{56}\)

One of the skeptics was Marthe Vogt (*1903), daughter of the great neuroanatomist couple Cécile and Oskar Vogt, and herself a leading investigator of the central nervous system. She had originally planned a career in neuroanatomy, following her parents, but had switched early to pharmacological chemistry. From June 1931 to April 1935 she headed the pharmacological chemistry division of the Kaiser Wilhelm Institute for Brain Research in Berlin, founded by her father in 1925; he and his wife were driven by the National Socialists to resign their positions at the Institute in 1936 after a three year campaign against the pair. In 1935, Marthe Vogt moved to Cambridge, financed by a Rockefeller scholarship; in 1947, she acquired British citizenship. From 1947 to 1960, she was based at the University of Edinburgh, after which she returned to Cambridge and the Institute of Animal Physiology. In 1983, she became the first woman to receive an honorary doctorate from the University of Cambridge.\(^{57}\)

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\(^{54}\) Von Euler, 1946; von Euler, 1956.

\(^{55}\) Holtz *et al.*, 1947.

\(^{56}\) Catherine Hebb, in Hebb *et al.*, 1966.

In 1954 Vogt published a landmark paper which would serve as an example for those who followed her: “The concentration of sympathin in different parts of the central nervous system under normal conditions and after the administration of drugs”. Sympathin was the term used to describe “noradrenaline with an admixture of adrenaline”;58 the presence of both catecholamines in the brain had been demonstrated by von Euler and Holtz.59 The aim of Vogt was simple and radical:

*The present work is concerned with the question whether these sympathomimetic amines, besides their role as transmitters at vasomotor endings, play a part in the function of the central nervous tissue itself.*60

Together with Feldberg, Vogt had already demonstrated the localization of acetylcholine (ACh) in the central nervous system, suggesting that only certain neurons employed ACh as a transmitter.61 Vogt had reported briefly in 1952 (in German) that sympathin also exhibited a distinct distribution pattern:

*This very fact suggests, though it does not prove, that these amines play a part in the specialized function of those regions of the brain in which their concentration is high.*62

She now undertook the detailed analysis of the localization of the two catecholamines in dog brain. Aware of the low concentrations of substance involved, Vogt carried out her assays “as speedily as possible”; the catecholamines were generally extracted from the brains and applied to chromatography paper on the day of dissection, the chromatograms developed overnight, the catecholamines eluted on the following morning and assayed in the afternoon. Biological assays were used: measuring the effect of noradrenaline on rat blood pressure and adrenaline on the rat uterus, detection limits of about 10ng (noradrenaline) and 5ng (adrenaline) per gram wet tissue could be achieved.63

The highest sympathin concentrations were found in the regions containing “the diencephalic, mesencephalic and bulbar representations of sympathetic activities”, as well as in the area postrema. She found that drugs which depleted peripheral catecholamines via central stimulation – ether, morphine, apomorphine – could sometimes also deplete central catecholamines if applied for prolonged periods. Of the other substances whose distribution in the central nervous system had been investigated – ACh, histamine, substance P, 5-HT –, that of 5-HT most closely mimicked that of sympathin. The distribution of the latter was not closely correlated with that of (mono)amine oxidase.64

Vogt concluded that nothing could be concluded about the function of brain sympathin on the basis of her report; while it was “tempting” to assign it a transmitter role corresponding to its function in the periphery, she felt that there were many reasons to be cautious; amongst others:

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60 Vogt, 1954a.
61 Feldberg and Vogt, 1948.
64 *Ibid.*
sympathin was also secreted in large quantities by gliomas;
• it was found to occur in high concentrations in the area postrema, a region devoid of ganglion cells;
• depletion of hypothalamic sympathin by electrical stimulation of the diencephalic representation of adrenomedullary secretion had no counterpart in the periphery.

Further, the administration of adrenaline did not seem to stimulate those centres in the brain which might be expected to use it as a transmitter, and the responses observed could be largely explained by its vasomotor effects; the response to noradrenaline was even less remarkable. Vogt entertained the idea that this might be explained by “assuming that parenterally injected sympathomimetic amines do not penetrate to the sites at which they are normally produced”.65 Indeed, Leimdorfer’s group had reported that intrathecal administration of adrenaline produced surgical anesthesia and rises in blood sugar.66 Vogt cited evidence that sympathin might modulate cholinergic actions; but the evidence for this hypothesis related to adrenaline, in which case one must assume that noradrenaline served only as the precursor for its methylated derivative. The third hypothesis, which Vogt regarded as unlikely, was that sympathin functioned as a humoral transmitter between the hypothalamus and the anterior pituitary; this, however, would not explain the large concentrations in the midbrain.67

Three years later, she noted that the sympathin concentration was particularly high in regions belonging to the newly described “ascending activating system of the reticular formation”, and that adrenaline was reportedly a potent stimulator of this system. But in the absence of clarity about the anatomical relations of the sympathetic centres and the reticular system, she was not prepared to speculate on the significance of these observations. Vogt concluded her discussion with the remark:

It will be clear from the foregoing discussion that our ignorance as regards the function of brain sympathin could not be more complete.68

In the subsequent discussion she remarked that a “central action of [circulating] adrenaline is likely”; however, its ability to cross the blood-brain barrier was, in her opinion, restricted.69

Speaking at the same Symposium, John Crossland (Department of Physiology, Bute Medical Buildings, The University, St. Andrews), discussing the evidence that certain substances other than ACh might have transmitter properties in the central nervous system, relegated sympathin to a small section at the end of the paper, concluding that:

While there is ample evidence that adrenaline and noradrenaline can modify the processes of synaptic transmission, and while this may well be a function of the circulating amines, there is little to suggest that they have any direct transmitter function in areas of low acetylcholine content.

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65 Ibid.
66 Leimdorfer and Metzner, 1949.
68 Vogt, 1957.
69 Ibid.
70 Crossland, 1957. He also commented: “It is remarkable that, although noradrenaline is known to be one of the non-cholinergic effector agents in the autonomic nervous system, it appears to have no such function at central synapses.”
This conclusion was particularly interesting as Crossland had noted in his introduction that the consensus had switched since 1953 to the view that chemical transmission was of significance in the central nervous system, but that ACh could not be the transmitter at all synapses; histamine, 5-HT and substance P were regarded as more likely candidates than the catecholamines in this regard. He defined the essential properties of a transmitter substance were defined as follows:

- Stored in the synthesizing neuron and identifiable in extracts
- Release under conditions of physiological stimulation; mimics effects of physiological stimulation
- Proximity of receptive (post-synaptic) elements to releasing element
- Rapid inactivation after activation of post-synaptic elements
- Protection from inactivation before release (assuming that inactivation is enzymatic)
- Inhibition or potentiation of inactivating enzyme extends or curtails duration of response
- Action on post-synaptic element is a direct action and can be blocked by same agents which block normal transmission

It was conceded by Crossland that conditions based on the definition of cholinergic transmission in the periphery might not be transferable to novel neurosubstances in the central nervous system, but the criteria were rigidly applied by most senior workers at this stage, leading to the exclusion of catecholaminergic transmission even as a working hypothesis.

The situation until the end of the 1950s was that even sympathin was not seriously considered as a locally synthesized or released transmitter in the brain; whatever central effects it might exert were attributed to its role as a circulating neurohumor; many saw even this role restricted to its modulation of central perfusion. Under these circumstances, it was understandable that an independent function for dopamine was not discussed.

**Dopamine as precursor of adrenaline: Blaschko**

At the Symposium on Neurohumoral Transmission held in Philadelphia in September 1953, the major workers in experimental pharmacology and physiology gathered to discuss the current situation. A consensus had finally been reached, following the conversion of John Eccles, that transmission at autonomic effector junctions was chemical, although an electrical component was still required to explain certain observations. The nature of this transmission, however, was still to be elucidated; it should be borne in mind that no direct neural effect upon a ‘receptor’ had yet been demonstrated. The major neurosubstance discussed remained ACh, but the respective contributions of adrenaline and noradrenaline to sympathetic transmission were also examined; single papers were also devoted to the place of other choline esters, histamine and “Darmstoff” (substance P) in transmission. An interesting comment from several notable investigators, including von Euler and Blaschko, was that the accumulation of a particular substance could not be interpreted as definitive proof of its physiological significance, and could, indeed, indicate its lack of activity.

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71 See also Paton, 1958; Gaddum, 1962.
72 Proceedings published in first issue (March) of the Pharmacological Reviews for 1954.
73 Blaschko, 1954; Von Euler, 1954.
Both Loewi in his opening address\textsuperscript{74} and Gerard (the sole American speaker at the conference) in his closing remarks\textsuperscript{75} noted that progress was currently limited by the tools for investigation which were available. It is also interesting to note that at this conference so many pharmacologists could discuss their work, but not draw conclusions regarding the consequences for therapy and disease: the available data at this point was insufficient to build concrete connections between the laboratory and the clinic.

Dopamine received little attention at the conference, still being regarded as simply a metabolic intermediate, and even this role was not universally accepted, as noted by Blaschko:

\textit{Last year at Paris, Professor von Euler considered it difficult to regard dopamine as a serious candidate for an intermediary rôle in the synthesis of noradrenaline.}\textsuperscript{76}

The major problem in the pathway from L-DOPA to adrenaline remained the mechanism by which the $\beta$-hydroxyl group was introduced (to convert dopamine to noradrenaline), although Blaschko did not regard this as a great objection.\textsuperscript{77} Although Gurin and Delluva (Department of Physiological Chemistry, School of Medicine, University of Pennsylvania, Philadelphia) had demonstrated in 1947 that adrenaline could be synthesized from radioactive phenylalanine in the rat,\textsuperscript{78} as late as 1955, Werle and Jüngten-Sell could suggest that \textit{threo}-3,4-dioxyphenylserine (DOPS), and not DOPA, was the natural precursor for noradrenaline in kidney and nerve (figure 10-6).

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure10-6.png}
\caption{L-threo-3-(3,4-dihydroxyphenyl)serine, or threo-$\beta$,3-dihydroxy-L-tyrosine; L-threo-DOPS. It was argued that noradrenaline could be formed by the decarboxylation of this amino acid, thereby avoiding the involvement of tyrosine and L-DOPA (tyrosine hydroxylase would not be isolated until 1964).}
\end{figure}

Holtz and Westermann replied to this suggestion with a good summary of the evidence which existed for the central role of the DOPA decarboxylase in adrenaline synthesis:

[Dopa decarboxylase] is found at high activity in those parts of the organism where the synthesis of the sympathetic substance occurs: in the adrenal medulla of cattle and pigs, as well as in nervous tissue, with the highest activity in the postganglionic sympathetic nerves, the sympathetic ganglia and trunk, with lower activity in the spinal cord and brainstem, and the lowest activity in the cerebral cortex. . . . Oxytyramine can be detected in the adrenal medulla as well as in sympathetic nerves and ganglia.\textsuperscript{79}

\textsuperscript{74} Loewi, 1954.
\textsuperscript{75} Gerard, 1954.
\textsuperscript{76} Blaschko, 1954; see von Euler, 1952.
\textsuperscript{77} The solution to this problem was reported by Demis, Blaschko and Welch in 1956 (see also Hagen and Welch, 1956), and soon thereafter confirmed to occur in vivo (Udenfriend and Wyngaarden, 1956) and in nervous tissue (Goodall and Kirshner, 1957, 1958). The enzyme responsible for the reaction, dopamine-$\beta$-hydroxylase, was first isolated by Levin \textit{et al.} (1960).
\textsuperscript{78} Gurin and Delluva, 1947. It had long been known that phenylalanine could be oxidized by the liver to tyrosine: Embden and Baldes, 1913.
\textsuperscript{79} Holtz and Westermann, 1956.
That dopamine was a normal constituent in some mammalian tissues was no longer debated. Dopamine was first detected in the adrenal medulla (in sheep) in 1951 by Goodall, a finding confirmed and extended by Shepherd and West in 1953; the latter group identified the amine in the adrenal medulla of sheep, ox and cow but not in medullary extracts from adult pig, dog, cat, rabbit or man. As the levels of dopamine measured were not correlated with the total catecholamine content of the gland, the authors concluded that dopamine might not be the immediate precursor of noradrenaline in all species; that dopamine might be the end product, however, was not discussed.\textsuperscript{80}

Views regarding dopamine began to change towards the middle of the 1950s, and to a great extent through the efforts of Hermann (“Hugh”) Blaschko (1900-1993).\textsuperscript{81} Born in Berlin, he was the son of the prominent dermatologist Alfred Blaschko, physician to many of Berlin’s leading citizens, including Einstein, Fermi and Born. He commenced his scientific training towards the end of the First World War at the Animal Physiology Institute in the Berlin Agricultural Academy, before studying medicine between 1917 and 1922 in Freiburg, where he befriended Hans Krebs, then also a medical student. In 1925, he commenced work with the Nobel laureate Otto Meyerhof (1884-1951)\textsuperscript{82} at the Kaiser Wilhelm Institute for Biology in Dahlem (Berlin), having expressed the desire to conduct research at the interface between physiology and medicine. It was at this time he also suffered his first bout of tuberculosis, a disease which would dog his steps for many years. He then spent time with A.V. Hill in London (1929-30), before finally leaving for England permanently in 1933 following the National-Socialist seizure of power.

In 1934, he transferred to the Department of Physiology at Cambridge, a move which initiated his rise to fame. In 1937, he discovered the enzyme “amine oxidase” (now monoamine oxidase), reportedly as a result of being challenged by the head of his department (Joseph Barcroft) with the question: “How is adrenaline destroyed?”\textsuperscript{83} Together with Derek Richter he then discovered that it also metabolized noradrenaline and dopamine.\textsuperscript{84} He admitted in a 1972 lecture that he was unaware of the broader significance of this work at the time; he had simply been set a biochemical problem for which he was determined to find the solution.\textsuperscript{85} Monoamine oxidase had already been investigated in the 1920s by Mary Hare-Bernheim, but her assay technique precluded discovering its metabolism of catecholamines, so that the full significance of her discovery was not recognized.\textsuperscript{86} Blaschko’s advantage with respect to Bernheim was that his earliest work in Meyerhof’s laboratory had involved the investigation of auto-oxidation; he was thus equipped to deal with the challenges posed by the investigation of adrenaline metabolism. In 1939, Blaschko proposed the same synthetic sequence for adrenaline as that suggested by Holtz in the same year. Parallel to Holtz’ work, he bolstered this assertion with his demonstration of the specificity of the DOPA decarboxylase for L-DOPA and its presence in all species he had examined.\textsuperscript{87}

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\textsuperscript{80} Shepherd and West, 1953.
\textsuperscript{81} Obituary: Smith, 1993.
\textsuperscript{82} Nobel Prize for Medicine or Physiology, 1922: “For his discovery of the fixed relationship between the consumption of oxygen and the metabolism of lactic acid in muscle.” The Prize was shared with the Englishman Archibald Vivian Hill, who was also acknowledged for his work on muscle metabolism.
\textsuperscript{83} Blaschko, 1972.
\textsuperscript{84} Blaschko \textit{et al.}, 1937.
\textsuperscript{85} Blaschko, 1972.
\textsuperscript{86} Bernheim’s work will be discussed in chapter XVI.
\textsuperscript{87} Blaschko, 1939, 1942.
In 1944, he joined the Pharmacology Department at Oxford, then headed by J.H. Burn, where he continued his work with the catecholamines after the War. Here he and the American Arnold Welch discovered in 1952 that most adrenaline in adrenal cells is bound to or within ‘particles’, a crucial discovery which would prove to be valid for most messenger substances throughout the body, including the central nervous system.\textsuperscript{88} They also reported in 1956 that DOPA labelled in the $\alpha$-position was not only converted to dopamine when incubated with adrenal medullary extracts, but also, albeit to a smaller degree, to labelled noradrenaline. This reaction was subsequently confirmed by a number of laboratories in a number of species, so that the second reaction in the synthesis of adrenaline was now provisionally accounted for, although the enzyme for the reaction had not yet been isolated.\textsuperscript{89}

By 1956, the presence of dopamine in a number of tissues had been demonstrated, but its active accumulation had not yet been demonstrated. Most significantly, Hans-Joachim Schümann, who worked in Holtz’ laboratory, had been the first to identify dopamine in nervous tissue (in sympathetic nerves and ganglia); he also suggested that what had hitherto been believed to be adrenaline in these tissues was probably at least 50% dopamine. In the same paper he had also produced compelling evidence that L-DOPA was the precursor of noradrenaline, and not dioxyphenylserine, still regarded at the time as a plausible alternative route to the major catecholamines.\textsuperscript{90}

In 1954, Blaschko was still uncertain about whether dopamine might be something more than an intermediate in catecholamine synthesis. Nevertheless, he was shortly afterwards among the first to place on record his opinion that dopamine might have a role not related to its being a precursor for adrenaline. At the meeting of the Swiss Society of Physiology, Biochemistry and Pharmacology in 1956, Blaschko posed the question of the functional significance of dopamine:

\textit{Its presence in human urine has been known for some time, and its occurrence in the adrenal medulla has also been demonstrated. In chromaffine tissue, only very small quantities of dopamine occur; this suggests that in this tissue, like a true metabolic intermediate, it is not stored. Schümann has recently shown that in adrenergic nerves this appears to be different; here the amounts of dopamine found are comparable with those of adrenaline present. This suggests the possibility that dopamine has some regulating functions of its own which are not yet known.}\textsuperscript{91}

Blaschko instilled this curiosity about dopamine in the young Austrian who came to work in his laboratory in 1956, Oleh Hornykiewicz; the consequences of this encounter will be discussed at length below. But the impetus which would lead to the recognition of an independent role for dopamine came at this point from a scientist working in Sweden: Arvid Carlsson.

\textbf{Reserpine and chlorpromazine: drug-induced syndromes as human models of parkinsonism}

Before the next stage in the dopamine story can be discussed, however, a clinical development which would have far-reaching consequences must be discussed. The

\textsuperscript{88} Blaschko and Welch, 1953.
\textsuperscript{89} Demis \textit{et al.}, 1956; Blaschko, 1957a,b.
\textsuperscript{90} Schümann, 1956. See also Dengler, 1957.
\textsuperscript{91} Blaschko, 1957a.
introduction of pharmacological management of psychosis in the 1950s was hailed as a major breakthrough; not only was the need for the formerly common methods of shock therapy considerably reduced, but the rate of release from institutions was increased considerably. It seemed that Freud’s dream was soon to be fulfilled:

Here we are concerned only with therapy only with respect to its use of psychological means – at the moment we have no alternatives. The future may teach us how to directly influence energy resources and their distribution in the psychic apparatus by means of particular chemical substances.\(^{92}\)

Nevertheless, it was recognized almost from the beginning that the medications which achieved this effect also dampened the initiative of patients, and in any some cases led to the presentation of extrapyramidal disturbances, including the development of a parkinsonoid state. Although reversible – the extrapyramidal problems disappeared with withdrawal of the drug – these side effects complicated therapy, but also led to new directions in thinking on the etiology of “natural” parkinsonism.

*Rauwolfia serpentina* (L.) Benth. ex Kurz.,\(^93\) native to the sub-Himalayan regions of the northern part Indian subcontinent but also found in Sri Lanka, Burma and Malaya, owes its name to its long, wandering roots; the plant itself grows to a height of about a metre and bears white or pink flowers. *Sarpa\(\)g\(\)an\(\)dh\(\)a*, as the drug is known in Sanskrit, was prescribed by the Ayurveda, the ancient Indian medical system, for a number of conditions, including fever, snake-bite and dysentery; Chopra and colleagues reported that preparations of its root reduced blood pressure, reduced bowel pain, and was used in a concoction to increase uterine contractions during labour.\(^{94}\) Because it was especially recommended in more recent times for the sedation of those with psychiatric illness, one of its popular appellations was *Pagal-Ka-Dawa* (”madness plant”).\(^{95}\) The first detailed European report of its medicinal properties was probably that of the Portuguese doctor Garcia da Orta in 1563.\(^{96}\) It was rediscovered by scientific Indian medicine in the 1930s, when it was demonstrated that it reduced the heart rate of frogs, cats and rabbits.\(^{97}\) Unspecific extracts of the root were used in India and elsewhere during the War and afterwards for its blood pressure-sinking effect. Indian doctors recognized that the powdered form of the dried root was not only useful in the treatment of psychiatric patients, particularly those suffering from anxiousness or restlessness, but in large doses effectively reduced blood pressure;\(^{98}\) it was introduced to the West largely through the efforts of Rustom Jal Vakil (Cardiology Department, King Edward

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\(^{92}\) *Abriß der Psychoanalyse*, in Freud, 1975, pp.420-421.

\(^{93}\) The genus *Rauwolfia* is named after the German physician and botanist Leonard Rauwolf, who published a work in 1582 on his expedition to investigate the medicinal plants of Asia and Africa. It is doubtful, however, that he knew *R. serpentina*. For review of history of the plant, see Dikshit, 1980.

\(^{94}\) Chopra et al., 1933; 1956, p.211; Schlittler et al., 1954; Kapoor, 1990, pp.284-286; Sivarajan and Balachandran, 1994, p.441.

\(^{95}\) R.N. Chopra, *Indigenous drugs of India* (Calcutta, 1933), cited in Weber, 1954. This name is used in Bihar and Uttar Pradesh, where it is also used to cause children to sleep. Chopra emphasized that the classical Indian medical literature does not describe the use of *Rauwolfia* in psychiatric disease (for example: Chopra et al., 1933).

\(^{96}\) *Coloquios dos simples e drogas he cousas medicinais da India*; Goa. For the early history of the plant, see Rieppel, 1956; Gicklhorn, 1960. For detailed review of history, botany and pharmacology of *Rauwolfia* and its alkaloids, see Kähler, 1970.

\(^{97}\) Chopra et al., 1933.

\(^{98}\) Sen and Bose, 1931; further references in Bein et al., 1953.
Interestingly, various parts of the *Rauwolfia vomitoria* Afzelius, a widely distributed plant in tropical Africa, are similarly used for a number of medical purposes (and as a hunting poison), amongst them as a sedative, particularly for cases of insanity. Reserpine is particularly rich in the root bark of this plant, but the pharmacology of its effects is complex: *R. vomitoria* includes an incredible range of alkaloids in its various tissues, including no less than twenty-two identified species in the root bark alone.\(^{102}\)

Alkaloid extracts of *Rauwolfia serpentina* were prepared at the end of the 19th century, but it was only in 1931 that the Delhi chemists Salimumuzzaman and Rafat...
Hussain Siddiqui prepared the first crystallized alkaloids (the ajmaline and serpentine group).\textsuperscript{103} Investigators at Merck in Germany commenced their own chemical and pharmacological investigations soon afterwards.\textsuperscript{104} By 1954, a total of fourteen alkaloids had been isolated from the plant and its relatives \textit{R. canescens} and \textit{R. trifoliata}, and by 1971 over fifty, of which ajmaline\textsuperscript{105} (= rauwolfine, pseudobrucine) occurred at the greatest concentration. Ajmaline, which modulates ion flow across cell membranes (it is commonly labelled a ‘Na\textsuperscript{+} antagonist’), has proved valuable in the treatment of tachyarhythmia and other cardiac irregularities; its pharmacological profile is quite distinct from that of reserpine, and it exhibits no sedative or catecholamine releasing effects. Throughout the 1940s, Indian workers had identified that the plant contained a sedative component which was distinct from ajmaline, but had not isolated it in pure form.\textsuperscript{106} In 1952, this sedative substance of the \textit{Rauwolfia} extract was isolated by Müller, Schlittler and Bein in the Pharmaceutical Division of Ciba in Basel, and dubbed

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure10-8}
\caption{The two major \textit{Rauwolfia} alkaloids discussed in the text.}
\end{figure}

‘reserpine’; it was marketed under the name ‘Serpasil’.\textsuperscript{107} Its mechanism of action was initially unknown; it exhibited a complex, species-specific pharmacological profile, which, however, generally included the striking effect which made it popular in the psychiatric clinic:

\begin{quote}
\ldots a unique sedation and inactivation that is characteristic for Serpasil and cannot be imitated by any of the currently available sedatives and hypnotics: the animals become peaceful, assume a natural resting or sleeping posture, but even after relatively high doses are not unresponsive (as is the case following treatment with narcotics), but can be roused by external stimuli; in monkeys, aggressiveness is significantly reduced.\textsuperscript{108}
\end{quote}

Reserpine also reduced blood pressure and, to a lesser extent, respiration and body temperature. The lack of effect on EEG, its antagonism of psychomotor stimulants

\textsuperscript{103} Siddiqui and Siddiqui, 1931, 1932. For earlier references, see Chopra \textit{et al.}, 1933.
\textsuperscript{104} Van Itallie and Steenhauer, 1932.
\textsuperscript{105} Named for the clinician who pioneered scientific application of Ayurvedic medicine and who suggested the investigation of rauwolfia, Hakim Ajmal Khan.
\textsuperscript{106} References in Chopra \textit{et al.}, 1956, p.210. Lieutenant-Colonel (later Sir) Ram Nath Chopra (1898-1973) was a leading figure in the investigation of the pharmacological properties of traditional Indian medicinal plants. He and his colleagues reported as early as 1933 that the \textit{Rauwolfia} root included \textit{an} alkaloid with \textit{potent} sedative properties.
\textsuperscript{107} Müller \textit{et al.}, 1952; Bein \textit{et al.}, 1953.
\textsuperscript{108} Weber, 1954.
(such as caffeine and cocaine), and the lack of effect on the primary motor and sensory pathways suggested a subcortical site of action. As the effects of reserpine reproduced in many respects the vagotonic syndrome which Hess observed after electrical stimulation of certain diencephalic structures, but could not be blocked by parasympatholytic agents, the Swiss workers proposed that reserpine dampened central sympathetic activity. The total synthesis of reserpine was first reported by Woodward and associates in 1956.

Reserpine was the first clinically useful drug identified which reduced sympathetic function, and also the first to be used in the chemical control of hypertension. The extent of the excitement which it aroused is perhaps indicated by the fact that the New York Academy of Sciences devoted two major symposia to the drug within two years of one another (1954 and 1955). Indian researchers had identified as early as 1945 in self experiments that excessive doses led to a parkinsonian-like impairment of motor performance. Reserpine and related Rauwolfia extracts had been introduced into Western clinics in 1953; by 1955, reports were mounting concerning the fact that between 5 and 60% of patients developed parkinsonian signs during reserpine therapy. It is also interesting that Steck reported in this connection the case of a patient whose schizophrenia was relieved by the contraction of encephalitis and the subsequent development of parkinsonism.

Reserpine differed in its pharmacological profile from those of the traditional hypnotics (barbiturates and bromide); it did, however, share some characteristics with chlorpromazine, the first synthetic neuroleptic. Chlorpromazine, a phenothiazine derivative, was one of the many antihistaminergic compounds developed by the Rhône-Poulenc (Specia) company after Henri Laborit, a French physiologist and naval surgeon, had noted that patients receiving antihistamines (in particular, promethazine) were less likely to experience shock following surgery; he also identified the fact that the tranquilizing effects of the drug, which had been noted by others but regarded as an unwanted side effect, were essential to its character as an antihistamine and could in fact be exploited in the clinic. Pierre Deniker and colleagues then described in 1952 the “miraculous” effect which chlorpromazine had produced on their psychiatric ward through its suppression of hallucinations and its general sedative effects. Its antipsychotic character was soon its most valued, and the agent was marketed with great success under the names ‘Largactil’ (Smith, Kline & French) and ‘Megaphen’ (Bayer). The introduction of chemical therapy for the psychoses was a major

109 Bein et al., 1953.
110 Miner, 1954, 1955. Other early reports on reserpine include Kline, 1954; Noce et al., 1954.
111 De (1944/45) reported the first clear cases of reserpine-induced parkinsonism, noting that they could be treated with tincture of belladonna. Further references in Weber, 1954; Bein, 1980.
112 Reviewed in May and Voegele, 1956.
113 Steck, 1955.
114 Promethazine and diethazine were synthesized by Charpentier in 1944 (the antihistamine properties of the former were reported in 1947); chlorpromazine in 1950 (report published 1952). The later belonged to a group of phenothiazine derivatives which the U.S. patent (2,645,640; granted to Rhône-Poulenc: 1953) described as being potentially useful as pharmaceuticals or as ‘potentiators’ of other pharmaceuticals.
115 Laborit et al., 1952.
116 Delay et al., 1952. This was the first in a series of papers by this group; a complete list of publications on the use of chlorpromazine in psychiatry appears in Deniker, 1983. See also Bennett (1998) for a review of the history of neuroleptics.
117 See Ernst, 1954.
The dopamine and L-DOPA story

Diethazine \( \text{CH}_2\text{CH}_3 \) \( \text{CH}_2\text{CH}_3 \) \( \text{S} \)

Promethazine \( \text{CH}_3 \) \( \text{CH}_3 \) \( \text{N} \)

Chlorpromazine \( \text{Cl} \) \( \text{N} \) \( \text{CH}_3 \)

Figure 10-9: The major phenothiazine compounds synthesized by Charpentier in the period 1946-50.

achievement; six of those involved in the breakthrough shared the Albert Lasker Award in 1957 for the introduction of the first drugs which could be used as monotherapies in psychosis.\(^{118}\)

Similar to reserpine, overdosage with chlorpromazine did not lead to narcosis, but to parkinsonian signs in about 10% of patients; the exhibition of some extrapyramidal response was regarded by many physicians as indicative of the success of the therapy.\(^{119}\)

Many interpreted the co-presentation of psychiatric improvement and parkinsonian symptoms during neuroleptic therapy as causally related; for example, Sainz believed that extrapyramidal reactions “far from being complications, are closely related to the drug’s effectiveness”; specifically, by acting on “glio-pallidal centers”, chlorpromazine was thought to elicit a “variable reduction in psychomotility” which could proceed to such a degree as to manifest itself in extrapyramidal symptomatology.\(^{120}\)

England and Schwab noted that in some hospitals chlorpromazine-treated patients were referred to as “the shakers”.\(^{121}\) It is thus somewhat curious that in 1956 Doshay remarked that what he described as a “synthetic motion-sickness drug” found application in parkinsonism; although he noted that it could aggravate parkinsonian symptoms, his reasons for restricting the dosage employed were the risks of agranulocytosis and hepatitis.\(^{122}\)

The association of extrapyramidal responses with chlorpromazine (in particular), Deniker and Delay introduced the term ‘neuroleptic’ for this type of drug (from the

\(^{118}\) For the priority dispute regarding the discovery of chlorpromazine, see Deniker, 1983. Full text of Lasker Award: “Joint award. To Dr. Jal Vakil for his brilliant and systematic studies on Rauwolfia in hypertension. To Dr. Kline for his demonstrations of the value of Rauwolfia derivatives, especially reserpine, in the treatment of mental and nervous disorders. To Dr. Noce for his studies of reserpine and its uses among the mentally ill and among mental defectives. To Dr. Laborit for his extensive studies of surgical shock and post-operative illness which resulted in the first application of chlorpromazine as a therapeutic agent. To Dr. Deniker for his introduction of chlorpromazine into psychiatry and for his demonstration that a medication can influence the clinical course of the major psychoses. To Dr. Lehmann for his demonstrations of the clinical uses of chlorpromazine in the treatment of mental disorders.” Cited from www.laskerfoundation.org/library/prev2.html (accessed 6.01.01).

\(^{119}\) Reviews: Ayd, 1961; see also Brooks, 1956; May and Voegele, 1956; Flügel et al., 1958; Guggenheim and Cohen, 1959; Delay and Deniker, 1968. Hall et al. (1956) were amongst the earliest critics to object that phenothiazine-induced extrapyramidal syndromes were “not really Parkinson’s disease”.


\(^{121}\) England and Schwab, 1959.

\(^{122}\) Brock et al., 1956.
Greek for ‘seizing the neuron’) at a French conference in 1955. The question as to which of reserpine and chlorpromazine represented the better neuroleptic was also widely discussed, often at symposia or similar gatherings devoted to one or other of the two agents. A comparison in the treatment of thirty-three psychiatric patients (including twenty-one schizophrenics) led E. Weber (University Psychiatric Clinic Burghölzli, Zürich) to the conclusion that the advantage of reserpine lay in the fact that the injection of chlorpromazine was more painful, and its employment often led to dependence. The major problem with reserpine was the extrapyramidal response of some patients:

In individual cases, the classic clinical picture of the parkinsonian syndrome developed with the typical posture, mask face, rigidity, coarse tremor, unclear articulation, poverty of movement and, in a third of cases, salivary flow. The symptoms disappeared after a few hours or, at latest, a few days after withdrawal of Serpasil. The salivation could be controlled by a few drops of atropine.

Weber viewed this reaction as temporary, and recommended that chlorpromazine be preferred to reserpine only when a disturbing extrapyramidal reaction to reserpine should appear before the desired sedative effect. Other workers were of the opinion that chlorpromazine should be used at high doses for a short period of time, while reserpine was more effective administered chronically at low doses. Delay and Deniker regarded the psychic and motor effects of these drugs to be inseparable; that is, just as the autonomic and antiparkinsonian effects of atropine were seen as inextricably linked, so too were the antipsychotic and akinesia-inducing effects of the neuroleptics. This view was promoted as a rule at a symposium held in Montréal in September 1960 on neuroleptics and Parkinson’s disease.

In contrast, two American physicians reported that some patients who developed parkinsonian symptoms during neuroleptic treatment required only temporary treatment with an antiparkinsonian agent (benztropine or benzhexol); after a few months, the drug could be withdrawn without the return of parkinsonian symptoms. This curious report remained isolated, but it is possible that the withdrawal of antiparkinsonian medication from such patients was a rarity, thus precluding more frequent observation of this phenomenon. As such, it is difficult to assess either its reliability or its significance, but it certainly seems to suggest at least a limited ability of monoaminergic systems to adapt to the effects of reserpine and chlorpromazine. On the other hand, Schwab and England reviewed several cases of phenothiazine-induced parkinsonism which persisted even after withdrawal of antipsychotics; all cases discussed, however, involved the long term administration of high neuroleptic doses.

Kinross-Wright noted that there existed differences between the panel of side effects associated with the two agents, but also in the parkinsonian state which they elicited. At normal therapeutic doses, reserpine produced tremor and other parkinsonian signs in some patients, but not rigidity; only at higher doses (60mg/day) did cogwheel rigidity develop in about 15% of patients, accompanied by hypersalivation and a coarser tremor. Chlorpromazine-induced parkinsonism was similar to this latter picture, but approached

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123 Deniker, 1983.
125 Kinross-Wright, 1955.
126 Cited in Deniker, 1983.
127 Cahan and Parrish, 1960.
the clinical state of natural parkinsonism more closely, including the presentation of
till-rolling movements. The author noted that he and a colleague had recently produced
such a state in other primates, but did not comment further on these experiments. Ayd
noted that the onset of parkinsonism in drug-induced cases was qualitatively different to
that in true parkinsonism: the first symptoms in 65% of cases were rigidity, loss of
associated movements and cogwheel phenomenon (compared with 30% in idiopathic
parkinsonism), while tremor appeared early in only 35% of cases (50%) and did not
appear at all in 40% of such patients. Steck, on the other hand, regarded
phenothiazine-induced parkinsonism as more reminiscent of post-encephalitic disorder
than of paralysis agitans. England and Schwab also noted that reserpine-induced
parkinsonism was quite mild in comparison with the natural disorder.

Of considerable practical significance, in any case, was the fact that benzhexol
afforded some protection against the effects of drug-induced parkinsonism; drug-
induced parkinsonism was, in fact, comparatively easy to manage with the normal
antiparkinsonian agents. England and Schwab reported that mental hospitals were the
largest market for one benzhexol manufacturer. It would later also prove to be
significant in the further development of antiparkinsonian therapy. The Austrian
pharmacologist Oleh Hornykiewicz would comment in 1964 that the fact he had been
invited to speak on the biochemical pharmacology of parkinsonism was a direct result
of the best model of the disorder available: that is, reserpine-induced parkinsonism.

May and Voegele had noted early that it appeared to be specific subsets of patients
who exhibited extrapyramidal responses to reserpine or chlorpromazine, and that the
two groups were largely congruent; that is, it seemed that there were particular patients
who were predisposed to developing extrapyramidal responses to both drugs. Frank J.
Ayd (Franklin Square Hospital, Baltimore) reported in 1961 a survey of 3775 patients
treated with various phenothiazine tranquilizers for a period of between three months
and six years, about half of them with chlorpromazine. Nearly 40% developed
extrapyramidal reactions during therapy: 21.2% akathisia, 2.3% dyskinesia and 15.4%
frank parkinsonism. Ayd identified a number of factors related to the frequency of such
responses: compounds with a trifluoromethyl group or high potency were more likely to
provoke extrapyramidal responses; women were twice as likely to exhibit akathisia or
parkinsonism; most instances of dyskinesia occurred within a week of commencing

treatment, while parkinsonism was slower to appear (90% within 72 days). In general,
however, Ayd concluded that his most important finding was that extrapyramidal
responses were seen only in neurologically predisposed patients; some patients had
received 1000mg chlorpromazine per day for four years without showing indications of
parkinsonism. Christensen and colleagues would later report that patients with
phenothiazine-induced oral dyskinesia usually exhibited reduced nigral cell number and
gliosis of the midbrain. Other groups also reported that the presentation of drug-

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129 Kinross-Wright, 1955.
131 Steck, 1955.
132 Schwab and England, 1968; they noted the same for α-methyl-dopa-induced parkinsonism.
133 England and Schwab, 1959. Rashkis and Smarr (1957) noted that they systematically added
benzhexol to the reserpine therapy of schizophrenics.
134 Hornykiewicz, 1966a.
135 May and Voegele, 1956.
137 Christensen et al., 1970.
induced extrapyramidal side effects and the occurrence of parkinsonism in blood relatives exhibited a certain correlation.138

The biochemical effects of reserpine

In the years following its introduction into the clinic, the biochemical effects of reserpine were gradually elucidated. This proved, however, to be a long process marked by controversy between two broad camps; this debate cannot be discussed here in detail, but an outline is necessary in order to clarify its relevance to future developments in the therapy of Parkinson’s disease. In 1955, Bernard Brodie139 and Parkhurst Shore, together with Alfred Pletscher, who was then working in their laboratories (Clinical Pharmacology, National Heart Institute, National Institutes of Health, Bethesda), proposed “serotonin release as a possible mechanism of reserpine action”.140 These authors saw the primary effect of reserpine as being the inhibition of 5-HT binding by those binding sites which normally protect it from metabolism by MAO; but its pharmacological effects are due not to 5-HT depletion, but rather to “the presence of persistent low concentration of free serotonin”.141 This interpretation was supported by the fact that lysergic acid diethylamide (LSD), then regarded as the major serotonergic antagonist, blocked some of reserpine effects; further, there was no reason to believe that reserpine affected 5-HT synthesis. Brodie was quickly convinced that 5-HT release explained all the actions of reserpine and would defend this view vehemently until the mid-1960s.142 In the year following the first publication on this proposal, Holzbauer and Vogt (Pharmacology, University of Edinburgh) reported that reserpine also depleted noradrenaline stores,143 and in 1958 Carlsson and colleagues reported the same for dopamine.144 Finally, Holtz’ group reported that reserpine also depleted central γ-amino butyric acid (GABA).145 Malhotra and Pundlik (Pharmacology and Therapeutics, Lady Hardinge Medical College, New Delhi), on the other hand, found that reserpine caused an increase in ACh levels in most regions of the dog brain, but a decrease in the hippocampus.146 It is interesting that Chaterjee and Hausler reported in 1955 that reserpine also exhibited anticholinergic and antihistaminergic properties. Specificity was clearly not one of the hallmarks of reserpine.

The debate during the following years centred on the question of whether the behavioural effects of reserpine should be attributed to its depletion of 5-HT or of catecholamines.147 The problem appears to have been that sedation was selected as the hallmark effect of reserpine, and Brodie’s group were able to present a series of results implicating serotonergic systems in this response. But the pharmacological effect of

138 Kurland and Darrell, 1961; Myrianthopoulos et al., 1962; 1967. The latter group also found that the susceptibility for drug-induced parkinsonism was greater in white than black Americans.
139 Brodie (1907-1989) and the research “dynasty” he established are the subject of a monograph by R. Kanigel (1993).
140 Pletscher et al., 1955.
141 Shore et al., 1957.
142 For example, see Brodie et al., 1960, 1966.
143 Holzbauer and Vogt, 1956.
144 Carlsson et al., 1958. Kuntzman and Spector reported in 1960 that it was the storage and not the synthesis of dopamine which was impaired.
145 Balzer et al., 1961; Palm et al., 1961.
146 Malhotra and Pundlik, 1959.
147 Joszef Knoll (1961) reviewed the literature and doubted if transmitter depletion actually underlay its depressive effects at all.
reserpine was more complex than simple sedation, and these other aspects were often the focus of attention in different laboratories. It thus came to pass that investigators discussing reserpine were often talking at cross-purposes; it was ultimately not possible (nor was it necessary) to explain all of the effects of reserpine in terms of depletion of a single substance, but the discussants often appeared to believe that this was necessary. Further, as noted by Everett (Pharmacology, Abbott Laboratories, North Chicago), there existed at this point a certain vagueness with regard to the behavioural parameters assessed; often the talk was restricted to the poles of “excitation” and “sedation”, or at best an assessment of the degree of either on a limited, often subjective scale. This overlooked the variety of behaviours which could be evoked by many drugs and consequently also limited the potential for extrapolation of the results gained to the human condition.

There were also technical questions which obfuscated interpretation of results from different laboratories. When the Finns Kärki and Paasonen reported what they regarded as definitive evidence that reserpine and another Rauwolfia alkaloid, raunescine, induced sedation at doses which did not affect central 5-HT levels, Brodie responded that sensitive fluorometric assessment of brain amines indicated that noradrenaline and 5-HT were reduced to the same extent. Similarly, Pletscher’s group Medical Research Division, Hoffmann-La Roche, Basel) reported that the potent tranquilizer Ro 4-1284 released more central noradrenaline than the weaker agent Ro 4-1398, while both were equally effective in releasing 5-HT; Brodie found that the rate of 5-HT release by Ro 4-1284 did exceed that of Ro 4-1398 during the first few minutes after administration; it was only after an hour that both agents appeared equally effective in this respect. On the other hand, Sheppard and Zimmerman (Ciba Pharmaceuticals, New Jersey) objected to the “toxic doses” employed by many workers in the investigation of reserpine, and reported that lower doses led to increased central catecholamine levels a few hours after administration. Brodie rejected the assertion that only high doses had been employed in the investigation of the alkaloid, and reported that their more sensitive method had failed to detect a rise in catecholamine levels following reserpine treatment. The Ciba

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148 Everett and Wiegand, 1962.
149 Differs from reserpine only in the substitution of -OH for -OCH₃ at the 17-position.
150 Kärki and Paasonen, 1959. See also Paasonen and Dews, 1958. Shore et al. (1957) had compared the effects of a range of Rauwolfia reserpine-related alkaloids on both sedation and central 5-HT levels.
151 Brodie et al., 1960; Brodie, 1960.
152 Pletscher et al., 1959.
154 Sheppard and Zimmerman, 1960.
155 Orlans and Brodie, 1960.
workers conceded in reply that they, too, had been unable to replicate their own results, but, like Everett, emphasized that their major point had been that the response to large doses had been entirely attributed to 5-HT, and described in toto as “sedation”; for instance, they regarded the “loss of righting reflex, enhanced salivation and active closure of the eyelids” noted by Brodie’s group as undesirable toxic side effects, not components of a clinically useful sedative effect. These issues were simply not resolvable with the techniques available in 1960.

Brodie and Shore were not only impressed by the similarities in the pharmacological effects of reserpine and chlorpromazine, but also by the differences. In contrast to reserpine, the effects of chlorpromazine were unrelated to the release of 5-HT, were not blocked by LSD and were correlated with central levels of the neuroleptic; further, in animals pretreated with the MAO inhibitor iproniazid, chlorpromazine elicited sedation, whereas reserpine produced excitement. This led these workers to extrapolate the sympathetic and parasympathetic nervous systems into the central nervous system (at least in the brainstem and hypothalamus), and to propose that 5-HT acted here as the parasympathetic neurotransmitter, and also tentatively suggested that noradrenaline might act as the central sympathetic mediator. The effect of reserpine would thus be parasympathomimetic, while chlorpromazine, in blocking sympathetic transmission, was sympatholytic; in effect, they would thus elicit the same responses in many model systems. Although the details of this proposal would undergo revision in the next decade, this proposal, presented at a symposium on psychotomimetic agents in New York, was one of the earliest detailed proposals for a multi-transmitter chemical transmission system in the central nervous system. As such, it was a major advance in the development of concepts regarding brain neurochemistry, and provided a platform for further investigation and controversy.

As a neuroleptic, reserpine was gradually abandoned by neurologists, largely because of the slow onset of effect in psychotic patients, but also because of the possibility of inducing psychotic depression and the exacerbation of peptic ulcer disease. There was also the ‘problem’ that reserpine, as a natural compound, could not be patented; being freely available from more than twenty companies, there was little financial profit in promoting its use. Although extensive attempts to synthesize derivatives which might be useful in psychiatry were undertaken, reserpine remained something of an oddity, in that such derivatives were never identified. Particularly sought by basic researchers attempting to elucidate the precise mechanism of the reserpine effect were more specific amine releasers. Pletscher’s group at Hoffmann-La Roche developed a series of benzoquinolizine derivatives which similarly depleted central noradrenaline and 5-HT stores and produced similar behavioral responses in animals without eliciting peripheral effects; the most important was tetrabenazine (Ro 1-9569), which had a shorter duration of action than reserpine and would later prove to also block dopamine receptors. Brodie’s group found that it antagonized the effects of subsequently administered reserpine, leading them to the conclusion that both acted at the same site. In contrast, the Ciba product syrosingopine was found to release

156 Published reply to Orlans and Brodie, 1960.
157 Brodie and Shore, 1957.
158 Karim et al., 1960a, 1960b; the first paper includes no less than twenty-nine references concerning reserpine analogs synthesized during the 1950s.
159 U.S. patent to Hoffmann-La Roche: 1958. See Pletscher, 1957a; Pletscher et al., 1958a; Leusen et al., 1959; Reches et al., 1982.
160 Quinn et al., 1959.
Brodie also reported that another Ciba product, Su 5171, selectively released central noradrenaline; he noted that only at higher doses, which also induced 5-HT depletion, was sedation elicited by this agent. A collaboration between Brücke’s and Lindner’s groups in Vienna and the Central Research Laboratory at N.V. Philips-Duphar in the Netherlands also produced a series of β-indolylethylamine and β-phenylethylamine derivatives with reserpine-like properties, but none achieved clinical significance.

Chlorpromazine and its derivatives, in contrast, were soon joined by a range of neuroleptics of other chemical classes, including the butyrophenones (haloperidol) and benzamides (sulpiride). It would not be until the mid-1960s that Carlsson and others would demonstrate that the efficacy of the classical neuroleptics was correlated with the antagonism of dopamine receptors, haloperidol, initially regarded as an antihistamine but later recognized as a potent dopamine receptor antagonist, was found to induce parkinsonian symptoms in 90% of patients. Pletscher and Gey also presented evidence that chlorpromazine inhibited the penetration by monoamines to and from their storage sites and through the blood-brain barrier; they found that treatment of cats with chlorpromazine for four days (7.5mg.kg⁻¹/day) led to a 50% reduction in dopamine levels in the striatum, but there was no association between the degree of reduction and the presentation of extrapyramidal signs. They later reported, however, that the changes detected were more likely due to enhanced inactivation of newly synthesized transmitter secondary to an effect on their storage.

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161 Orlans et al., 1960.
162 Brodie et al., 1960.
163 Kral et al., 1960.
166 Pletscher and Gey, 1962.
167 Gey and Pletscher, 1964b.
Carlsson, reserpine and L-DOPA

Arvid Carlsson (*1923), born in Uppsala, was the son of a Professor of History and an intellectual mother; following the death of her husband, her work on the legal status of women in the Middle Ages was recognized with an honorary doctorate from the University of Uppsala. Carlsson studied medicine at the University of Lund between 1941 and 1951, where he came into contact with, amongst others, Torsten Thunberg, the professor of physiology who had discovered tissue respiration and the dehydrogenases at about the same time as Warburg in Berlin. His first involvement in research was as assistant in the pharmacology department of the university, where he and another student were set the task of investigating the duration of action of the convulsant pentylenetetrazole. After completing a doctoral project investigating calcium absorption, he was appointed assistant professor in pharmacology. Initially planning to continue research in calcium metabolism in nervous tissue, he was advised by the committee which declined his declination for a post as associate professor that there was no future in this direction. Unclear about his future, Carlsson worked for a year as an internist, but his thoughts returned to the experimental pharmacology, whereupon he sought the assistance of the professor of chemistry, Sune Bergström, in finding a research position in the United States. The outcome was that in 1955, he commenced work as a visiting scientist in Brodie’s laboratory of Chemical Pharmacology at the National Heart Institute in Bethesda. Carlsson investigated with Brodie and Shore the action of reserpine on serotonin storage by platelets; this work resulted in the first unequivocal demonstration that reserpine blocked 5-HT storage in these cells.168

After five valuable months in Bethesda, during which he could not convince Brodie to examine the effect of reserpine on the catecholamines, Carlsson was barely returned to Lund (as associate professor of pharmacology) when events began to lead him in a different direction. Together with the associate professor of histology Nils-Åke Hillarp, who had recently made several important discoveries regarding the storage of adrenal medullary hormones, he reported that reserpine also depleted these catecholamines; shortly afterwards, Carlsson and his research students Åke Bertler and Evald Rosengren demonstrated that it also had this effect in heart and brain tissue. Further, they demonstrated that stimulation of sympathetic nerves after reserpine treatment did not elicit catecholamine release, and he hypothesized that this phenomenon might explain the central hypotensive effect of reserpine. Similar views with respect to the impact of reserpine on peripheral sympathetic function were published at about the same time by Vogt’s group. As Carlsson remarked in his most recent autobiographic sketch, these views on the mechanism of reserpine placed him at odds with his respected mentors Brodie and Shore on two grounds: firstly, he was proposing that depletion of catecholamines also played a significant part in the action of reserpine; secondly, Carlsson’s results suggested that it not was the release of transmitter triggered by reserpine which was primarily responsible for its effects, but rather the depletion of transmitter stores. This question led to quite heated discussions between the two groups for quite some time, both in print and at conferences.

168 Carlsson et al., 1957c.
169 Carlsson and Hillarp, 1956.
170 Carlsson et al., 1957b.
Carlsson sought to resolve the issue of whether catecholaminergic or serotonergic deficiencies underlay the behavioural effects of reserpine by replenishing the central stores of individual monoamines. There was, however, a problem: evidence had begun to emerge that exogenously applied serotonin\textsuperscript{173} and, probably, catecholamines did not readily penetrate the blood-brain barrier, and thus could not access the central nervous system.\textsuperscript{174} Carlsson’s consequential solution was to administer their amino acid precursors, which were not hindered by the blood-brain barrier from entering the brain. 5-hydroxytryptophan (5-HTP) had already been shown to increase central 5-HT levels and to induce central excitation in mice;\textsuperscript{175} preliminary results in Carlsson’s laboratory suggested that administration of DOPA had a similar effect on central catecholamine content. In the study which would prove to one of the most important in the history of the catecholamines, mice received an intraperitoneal dose of reserpine (20-40mg.kg\textsuperscript{-1}); after 16 hours, at which point marked sedation and eyelid ptosis were evident, D,L-DOPA, D,L-5-HTP or a combination of both was administered intraperitoneally. 5-HTP alone (up to 1000mg.kg\textsuperscript{-1}) did not relieve reserpine-induced sedation; 500-1000mg.kg\textsuperscript{-1} DOPA, on the other hand, completely reversed tranquilization within 15 to 30 minutes. This effect, however, lasted only an hour, after which the inactivity produced by reserpine was again evident.\textsuperscript{176}

Carlsson also described the dramatic effect of 200mg.kg\textsuperscript{-1} DOPA i.v. in rabbits treated with 5mg.kg\textsuperscript{-1} reserpine i.v.: within 10 to 15 minutes, all reserpine effects had been reversed, an effect recorded in a film with which he astounded many conference participants in the following years. The DOPA dose required could be reduced by pre-treating the animals with 100mg.kg\textsuperscript{-1} iproniazid, a MAO inhibitor; iproniazid, whose major reported effect in brain at this stage was to elevate 5-HT levels, including in reserpinized animals,\textsuperscript{177} did not produce this effect when administered alone. Central stimulation was also produced by DOPA in rabbits not treated with reserpine.\textsuperscript{178}

This report occupied about two-thirds of a page in the letters to the editor section of the 30 November 1957 issue of *Nature*; nevertheless, it would be nominated by most significant workers in the further development of the L-DOPA story as the paper which excited them with the possibilities of an effective, rational biochemical therapy for Parkinson’s disease. Together with the contribution of the group to the book *Psychotropic Drugs*, which further described the effect of reserpine on brain catecholamines,\textsuperscript{179} and subsequent papers from Carlsson’s group describing the localization of dopamine in the brain, the pathway to neurochemical analysis of central nervous function had been entered.

One curious aspect of this report was that the combination of DOPA and 5-HTP (each 250mg.kg\textsuperscript{-1}) produced a greater and longer lasting anti-reserpine effect than DOPA alone. This was a difficult result to explain; Carlsson himself did not pursue this question further. It is, however, interesting that both Birkmayer and Sano would later report that the combination of the two amino acids was also beneficial in Parkinson’s

\textsuperscript{173} Udenfriend et al., 1957.
\textsuperscript{174} First reports on the relative impermeability of the blood-brain barrier to (nor)adrenaline: Weil-Malherbe et al., 1959; Weil-Malherbe, 1960a.
\textsuperscript{175} Ibid.
\textsuperscript{176} Carlsson et al., 1957a.
\textsuperscript{177} Pletscher, 1956, 1957a.
\textsuperscript{178} Carlsson et al., 1957a.
\textsuperscript{179} Carlsson et al., 1957b.
disease; Sano especially believed that the two agents, most effectively in their L-forms, acted at different sites affected by the disorder. Roos and Steg, also of Göteborg University, investigated the effects of L-DOPA and D,L-5-HTP on reserpine-induced rigidity using electromyographic recordings of the calf muscle of the rat, and found that either amino acid was able to abolish the tremor and rigidity measured in this system, and to reverse the reserpine-induced changes in α- and γ-motoneuron excitability. As the authors noted, this did not contradict Carlsson’s 1957 results, which principally concerned reserpine-induced akinesia.

In the same year as Carlsson’s report, Holtz’ group reported that the administration of either DOPA or 5-HTP to rabbits pretreated with iproniazid led to central excitation (and depletion of adrenal medulla adrenaline), and in mice could block hexobarbital-induced narcosis (an effect not reproduced by the direct noradrenaline precursor threo-DOPS). Interestingly, this group appeared to attribute this effect of DOPA to the “amines” which were produced from the amino acid, although the final discussion considers only the involvement of noradrenaline in this effect. The same group demonstrated that the precursor amino acids were not acting in their own right by blocking their effects with the decarboxylase inhibitor α-methyl-DOPA. Other laboratories also reported results which supported the Carlsson interpretation of the behavioural effects of reserpine.

A few years later, Blaschko and T.L. Chruściciel essentially followed the lead of Carlsson’s 1957 paper; they found that 500 or 1000mg.kg⁻¹ L-DOPA increased motor activity in mice, and that this effect was increased if they were pretreated with iproniazid. Further, despite the fact that not only L-DOPA and m-tyrosine, but also 2,3- and 2,5-DOPA were rapidly decarboxylated by liver, kidney and brain extracts, only the first two compounds relieved the sedative effects of reserpine; D-DOPA did not have this effect (if anything, it decreased motor activity), nor was it metabolized by DOPA decarboxylase. This suggested a certain degree of specificity, although the precise mechanism of the m-tyrosine effect (presumably converted to m-tyramine; its further metabolism to dopamine was doubtful) was puzzling, although Mitoma and colleagues had demonstrated its conversion to m-tyramine, the authors suggested that m-tyramine might itself possess pharmacological activity, despite its not being found in the normal animal.

By this time, Blaschko was now fairly convinced that dopamine must be active in the central nervous system: the authors doubted that MAO determined the time-course of noradrenaline or adrenaline activity, but opined that there could “be little doubt that it is an important factor in the inactivation of dopamine.” Further:

*Its effects [that is, those of L-DOPA] upon the reserpinized animal are so profound that it is tempting to assume that the catechol amines are in some way essential for the maintenance of wakefulness in the normal animal.*

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181 Roos and Steg, 1964.
182 Holtz et al., 1957b; see also Holtz et al., 1957a. A curious aspect of Holtz’ work was the fact that administration of 5-HT itself was as effective as 5-HTP, despite the blood-brain barrier.
183 Westermann et al., 1958; see also Holtz, 1958.
184 For example: Everett and Toman, 1959.
185 Mitoma et al., 1957.
186 Blaschko and Chruściciel, 1960.
187 Ibid.
This comment also applied to noradrenaline, but Blaschko appeared to lean towards dopamine as the active product in his study; the noradrenaline precursor threo-DOPS, for instance, did not relieve reserpine-induced sedation, so that he and Chruściciel did not even bother to test its decarboxylation by test extracts (despite the fact that they conceded its lack of effect might also have been due to the relatively slow decarboxylation of this molecule in vivo). Before this role could be confidently asserted, however, the existence of localized dopamine pools in the central nervous system needed to be established.

Identification of dopamine in the brain

Dopamine had not initially been sought in brain; as it was only a precursor for adrenaline, its accumulation in tissue was not to be expected. It is possible that the first detection of central dopamine was by the cardiologist Wilhelm Raab’s group (Division of Experimental Medicine, College of Medicine, University of Vermont) in 1947. Raab was an expatriate Austrian who moved to Vermont at the commencement of the Second World War; here he had contact with, amongst others, Otto Loewi in New York (who supplied the dialysis equipment for his experiments) and Ulf von Euler in Stockholm. In 1948, he reported the presence in the brains of animals (Raab omitted to mention in this paper which animals were dissected) of an adrenaline-like substance which he named “encephalin”. Its pharmacological effects were similar to those of adrenaline and noradrenaline (arterenol), from which he distinguished it on the basis of various chromogenic reactions:

- encephalin produced a yellow color in acidified KIO₃, whereas adrenaline gave a deep purple reaction;
- with FeCl₃, adrenaline produced a green color which turned to orange, encephalin elicited no color change;
- the fluorescence reaction of Gaddum and Schild for sympathin was negative when applied to encephalin;
- further, it was impervious to destruction by iodine and ultraviolet light.

Further, encephalin could be distinguished from tyramine in that it induced an elevation of blood pressure when injected into the cat, and this effect was neither facilitated nor blocked by cocaine. Von Euler had reported in 1946 that he had been unable to isolate any sympathomimetic compound from the calf brain; Raab attributed this failure to the alcoholic extraction procedure employed by von Euler, a method which Raab had identified as inefficient in the extraction of encephalin. Finally, encephalin was found in relatively large amounts in all parts of the central nervous system, including the cerebrospinal fluid. Raab concluded on the basis of his results that he had isolated a catecholamine which more closely resembled noradrenaline than adrenaline.

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188 Ibid.
189 This new name for 3-hydroxytyramine had been suggested by Dale in 1952; he thought it appropriate to avoid confusion with ‘5-hydroxytryptamine’, and also to emphasize the connection between the amino acid (DOPA) and the amine. The name did not, however, become the standard designation until the mid-1960s. See Blaschko, 1952, and Shepherd and West, 1953.
190 Tainter (1930) had reported that the vasopressor response to dopamine was facilitated by cocaine (this was also true for the vasopressor effect of sympathin).
191 Raab, 1948; compare with Raab, 1943.
Raab continued to investigate encephalin during the following years, and in 1951 he published the results of his investigation of its distribution in the brains of humans and animals. In all mammalian species examined (table 10-1), the highest encephalin concentrations were found in the caudate nucleus, except in man, where the concentration was higher in the pituitary. This result was consistent with Raab’s earlier observation that the highest concentrations of the vasodepressants identified by many workers in the brain were always found in the basal ganglia. The response of rat brain encephalin to a range of drugs was then tested in vivo in a manner which would probably not win the approval of a present-day ethics committee: adrenaline, noradrenaline, 5-HT, desoxycorticosterone, thyroxine, insulin, adrenalectomy, hypophysectomy, pentobarbital, morphine, benzedrine, pentylenetetrazole, strychnine, DC or AC current through the head, stress (tied on back), exercise (swimming, 30-60 minutes), reduced air pressure (252mm Hg, 4hr), ACh injected into the carotid, alcohol in the drinking water, a nitrogen-free diet: none of these treatments affected central concentrations of encephalin. On the other hand, a single intraperitoneal injection of DOPA (300mg.kg−1) led to a 120% rise within 30 minutes, 134% in 60 minutes and 66% after two hours. Compared with the results reported in 1957 by the Carlsson laboratory, it is difficult not to suspect that encephalin consisted at least in part of dopamine, despite the problematic distribution pattern. This might be attributed to the fact that Raab was reportedly full of energy, to which the mammoth scale of the experiments reported in his papers attests, but his organizational skills were reportedly somewhat deficient for the accurate execution of biochemical investigations.192 His use of Shaw’s rather unspecific colorimetric method for the quantification of catecholamines also rendered his task very difficult.193 Raab also undertook something else which was remarkable for 1951: he compared the encephalin concentrations in sixteen normal human brains with those in eleven patients who had suffered psychosis. No differences were found, and Raab noted that the arbitrary choice of “psychotic” cases may have clouded the issue.194 It was, however, significant that the attempt to link
central biochemical changes with psychiatric disease was not yet regarded by most workers as feasible. As Hornykiewicz noted, it would have been interesting if Raab had examined a few parkinsonian brains in his study, especially given the high concentration of encephalin in the caudatus.195

Raab’s work was not completely overlooked and certainly not forgotten, despite remarks to the contrary by Mark and Duvoisin,196 even if himself did not pursue this area further. Von Euler cited both the methodology employed by Raab for determining catecholamine levels and his results;197 Vogt remarked that the distribution of sympathin was different to that described by Raab for encephalin,198 as did John Crossland in his discussion of “the problem of non-cholinergic transmission in the central nervous system.”199 The 1951 paper by Raab and Gigee was also cited by Blaschko in 1960 as evidence that peripheral administration of DOPA leads to increased central catecholamine levels.200

Katharine Montagu (Research Department, Runwell Hospital, Wickford, Essex) also referred to Raab’s work in her 1957 paper on the detection of an unknown catechol substance in brain, noting that her compound “X” was readily extracted in alcoholic solution, and was therefore not identical with encephalin.201 Montagu had previously used the ethylenediamine fluorescence method to demonstrate a seasonal variability in the concentration of noradrenaline and adrenaline in rat tissues.202 “Substance X” exhibited a similar variation in rat brain, and also in brains from rabbit, guinea pig, chick, frog and man (single sample). The method she employed had been developed by Weil-Malherbe (Research Department, Runwell Hospital, Wickford, Essex; based on a technique used by von Euler), who, together with A.D. Bone, published a paper in 1957 describing the intracellular localization of the catecholamines as determined by the same method.203 The method involved the condensation of catecholamines with ethylenediamine dihydrochloride to form fluorescent derivatives; that part of the fluorescence which was not explained by noradrenaline and adrenaline, as assayed by a parallel fluorescent trihydroxyindole method, was attributed to “X”, which was then assumed to be hydroxytyramine (dopamine). The concentration of DOPA and DOPAC were also estimated in human brain (table 10-2).204

Montagu’s paper has sometimes been cited as the first demonstration of dopamine in brain. Carlsson has justifiably questioned this interpretation on a number of grounds.205 Firstly, the subtraction method employed by Weil-Malherbe and Montagu did not demonstrate the presence of any particular compound, only that the total fluorescent product could not be accounted for by the two major identified catecholamines. This explains the caution with which Montagu discussed her results, including her designation of the unknown compound simply as “X”. The Weil-Malherbe-Bone

196 Mark and Duvoisin, 1995.
197 Von Euler, 1950.
199 Crossland, 1957.
201 Montagu, 1957.
202 Montagu, 1956a, 1956b.
203 Weil-Malherbe and Bone, 1957.
204 A detailed description of the method is found in Weil-Malherbe, 1961.
The dopamine and L-DOPA story

<table>
<thead>
<tr>
<th>Animal</th>
<th>Total ED-fluorescence in terms of A (ng. A/g brain)</th>
<th>N</th>
<th>A</th>
<th>X</th>
<th>Dopa</th>
<th>Dopac</th>
</tr>
</thead>
<tbody>
<tr>
<td>Man</td>
<td>110 21.2 4.38 94.2 200 90</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rabbit</td>
<td>229 126 20.2 288 ––– –––</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guinea pig</td>
<td>173 106 37.6 177 ––– –––</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rat</td>
<td>299 110 43.3 410 ––– –––</td>
<td>447</td>
<td>65.1</td>
<td>219</td>
<td>69.3</td>
<td>642</td>
</tr>
<tr>
<td>Chick</td>
<td>151 66.3 36.8 130 ––– –––</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frog</td>
<td>1,175 ––– ––– ––– ––– –––</td>
<td>1,140</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 10-2: Table I from Montagu, 1957: “Concentrations of catechol compounds in whole brains of different animals. *5 estimations”. ED = ethylenediamine dihydrochloride; N = noradrenaline, A = adrenaline.

method had also been subject to criticism by, amongst others, Holzbauer and Vogt on these and other grounds. At the 1958 Symposium on Catecholamines, William Manger (College of Physicians and Surgeons, Columbia University, New York) presented a paper defending the method and his modification of it for the assay of noradrenaline and adrenaline; the implication of his defence, however, was that substances other than the two target catecholamines (including, presumably, dopamine) did not interfere with the assay, thus rendering the Montagu approach questionable. Secondly, the major evidence for identifying “X” with dopamine was the similarity of their chromatographic Rf values; unfortunately, she did not document her chromatographic method, nor did she record the Rf values of either dopamine or “X”. This is not as serious a problem as the first, as Montagu presumably adopted without alteration the methods employed by Partridge in the 1948 paper which she cited with respect to the Rf value for dopamine. Finally, the relative regional concentrations described in the 1957 Weil-Malherbe and Bone paper are not entirely consistent with those of dopamine; for instance, they reported much higher values for dopamine than noradrenaline in the brainstem.

This is not to criticize Montagu; not the for the first or last time were methods being pushed to the limits of their performance, and the development of new approaches were necessary to reach unequivocal results. Further, neither Montagu nor Weil-Malherbe themselves, according to Carlsson, had ever claimed priority in the discovery of central dopamine, although the statement at the head of the 1957 paper by Weil-Malherbe and Bone was more definite than that of Montagu herself:

206 Holzbauer and Vogt, 1956.
207 Manger, 1959.
208 Weil-Malherbe and Bone, 1957.
A survey of animal tissues carried out in this Laboratory has shown that 3-hydroxytyramine is found more consistently and in higher concentrations in the brain than in a number of other tissues.\textsuperscript{209}

It is also curious that Montagu measured such large quantities of DOPA in the human brain, an anomaly which does not appear to have drawn any attention in the critical literature.

Montagu expressed no surprise in her paper at finding ‘dopamine’ in the brain, nor did she appear to recognize the significance of such a finding; this can not be said for the publication by Carlsson’s group the following year on “the presence of 3-hydroxytyramine in brain”. The Swedes, as discussed above, had discovered that L-DOPA, but not L-5-HTP, relieved reserpine-induced sedation in animals; this clearly indicated the involvement of catecholamine depletion, and not that of 5-HT, in the effect of reserpine. The most obvious candidate was noradrenaline, and so the levels of this catecholamine were measured in the reserpinized animals treated with L-DOPA:

\textit{When we analyzed the brains of these animals, we expected to see the norepinephrine stores filled up again because it was norepinephrine that we had found to be depleted in the brain. But the level of norepinephrine was still very low. To save face, we looked for the intermediate between L-dopa and norepinephrine, that is, dopamine, to see whether we could at least explain the action of L-dopa in terms of dopamine being formed.}\textsuperscript{210}

But this required an improvement in assay techniques if the measurements were to be unequivocal. The authors commenced their paper by noting that the lack of specificity of the Weil-Malherbe technique could be overcome by preparing the samples at pH 5; the fluorescence of the dopamine derivative was not only markedly increased, but the activation and fluorescence peaks were shifted to much shorter wavelengths, thus allowing the reliable assay of dopamine even in the presence of large concentrations of the other catecholamines. The major finding of the group was expressed in two pregnant sentences:

\textit{We have thus found that 3-hydroxytyramine is present in rabbit brain in an amount of about 0.4\ µg/g, which is roughly equal to the amount of noradrenaline in this tissue. This may indicate that the function of 3-hydroxytyramine is not that merely of a precursor.}\textsuperscript{211}

They also reported that reserpine (5mg.kg\textsuperscript{-1} i.v.) caused 3-hydroxytyramine to disappear from the tissue; the injection of 150mg.kg\textsuperscript{-1} D,L-DOPA caused the levels to rise to 2\ µg.g\textsuperscript{-1} tissue within an hour, accompanied by central excitation. Both responses were increased by pretreatment with the MAO inhibitor iproniazid. Finally, the changes in noradrenaline levels induced by DOPA or iproniazid treatment were \textit{“much less pronounced if present at all.”}\textsuperscript{212} It thus seemed that dopamine synthesis might be regulated independently of that of the other two major catecholamines.

\textsuperscript{209} Ibid.
\textsuperscript{210} Carlsson, 1998b.
\textsuperscript{211} Carlsson \textit{et al.}, 1958.
\textsuperscript{212} Ibid. Noradrenaline and adrenaline were measured using a modification of a method also developed by Carlsson’s group: Bertler \textit{et al.}, 1958.
The Carlsson group thus provided definitive evidence that dopamine was not only present in brain, but also that it could serve a function there independent of its role as noradrenaline precursor. The key to this function would be the identification of its exact location in the brain, and two of Carlsson’s doctoral students, Åke Bertler and Evald Rosengren, had already commenced this work. A brief paper at the beginning of 1959 in *Experientia* (submitted August 1958) announced that dopamine (as the compound was now generally known) had been identified at varying concentrations in the brains of eight mammalian species. Equally important was the finding that:

> the amine is predominantly localized in the corpus striatum of the hemispheres. For example the caudate nucleus of the dog contains about 6.5µg dopamine/g tissue, representing more than 80% of the total brain dopamine.\(^{213}\)

The distribution of dopamine was distinctly different from that of noradrenaline, which was also examined using the fluorescent techniques then being introduced in Carlsson’s laboratory. With few exceptions, the concentrations of dopamine in peripheral tissue in these species were very low; interestingly, these exceptions led to the identification of a new type of chromaffin cell in ruminants by Carlsson’s colleagues Falck and Hillarp. On the basis of the distribution of dopamine in the brain, and the fact that drugs which modulated its levels also affected motor performance, the authors concluded that “dopamine is concerned with the function of the corpus striatum and thus with the control of motor function.”\(^{214}\) It was also noted that reserpine, which depleted the striatum of dopamine, could elicit parkinsonian symptoms in humans.

Carlsson himself pursued this aspect further in his presentation to First International Catecholamine Symposium at the end of 1958, where the detailed results of the experiments described in the Bertler and Rosengren paper were presented. In his summation, Carlsson presented the following arguments for the involvement of dopamine in the control of motor function:

1) The presence of large amounts of dopamine in the corpus striatum, which forms an important part of the extrapyramidal system.
2) The extrapyramidal actions of reserpine, which depletes the dopamine from the corpus striatum.
3) The ability of dopa to counteract the hypokinetic action of reserpine.\(^{215}\)

Carlsson also explicitly stated that it was the absence of catecholamines following reserpine treatment, and not their release, which was responsible for the effects of the alkaloid; these could thus be logically compensated either by the administration of

\begin{table}
\centering
\begin{tabular}{|c|c|}
\hline
Species & Dopamine concentration (µg.g\(^{-1}\) tissue) \\
\hline
Rat & 0.60 \\
Sheep & 0.30 \\
Pig & 0.22 \\
Dog & 0.19 \\
Cat & 0.24 \\
Rabbit & 0.31 \\
Guinea pig & 0.34 \\
\hline
\end{tabular}
\caption{Dopamine concentrations in brains of various mammals as reported by Bertler and Rosengren, 1959.}
\end{table}

\(^{213}\) Bertler and Rosengren, 1959a.
\(^{214}\) Ibid.
\(^{215}\) Carlsson, 1959.
either the precursors of the lacking transmitter or of a sympathomimetic amine, what would today be termed an agonist.216

The next paper by Bertler and Rosengren extended their previous findings to the human brain. The highest concentrations of dopamine were found in the neostriatum (2.0-6.5µg.g⁻¹ tissue), while those of noradrenaline were found in the rostral and intermediate hypothalamus (0.8-1.9µg.g⁻¹ tissue). Dopamine synthesis in various regions of the rabbit brain was also measured over time; maximum levels were reached 15-30 minutes after injection of the precursor (100mg.kg⁻¹ D,L-DOPA, i.v.), with the amounts formed in individual regions corresponding to those measured in the normal animal; that is, mostly in the caudatus, with a smaller rise in the hypothalamus. Similarly, injection of 5-HTP led to increased 5-HT levels in the same regions. The identity of the DOPA and 5-HTP decarboxylases had not yet been definitively established in 1959; Bertler and Rosengren, however, demonstrated that there was an almost perfect correlation between the amounts of transmitter formed from the corresponding amino acid in each brain region, and that each amino acid inhibited the formation of the alternative transmitter when the two amino acids were administered together.217 This represented very strong evidence for the identity of the converting enzyme involved; it offered no explanation, however, for the synergistic effect in the relief of reserpine-induced sedation described in the 1957 paper. It was also a forewarning of a future problem: exogenous DOPA was converted to dopamine wherever DOPA decarboxylase was present, even in those regions where dopamine was not normally present.

The First International Symposium on Catecholamines at the National Institutes for Health, Bethesda, October 16-18, 1958218

In light of the results reported by the Carlsson laboratory, it might be expected that dopamine would have played an important role at the First International Symposium on Catecholamines at the end of 1958. This was not the case. In fact, the general tone gained from reading the proceedings is that of an attempt by the meeting to establish precisely where research in the field stood at this point in time. Methodological questions stood high on the agenda. The section with the most papers was actually concerned with “measurement of epinephrine, norepinephrine and related compounds”. Here the various alternatives were presented (and defended) by Gaddum (bioassay), chromatography (Vogt), trihydroxyindole-based fluorescence (von Euler, Cohen, Price), ethylenediamine-based fluorescence (Weil-Malherbe, Manger) and various other fluorescence methods (Shore, Carlsson). Competition between the various methods was clear from the presentations themselves; unfortunately, the discussion for this section was not included in the proceedings.

Catecholamine synthesis and metabolism was then discussed (including two largely historical reviews by Blaschko and Holtz), and the action of the catecholamines in various model systems described, including a discussion of the nature of catecholamine ‘receptors’. Blaschko noted that it was unclear whether dopamine, like noradrenaline,
played a dual role as precursor and hormone, but there was evidence that it did.\textsuperscript{219} Holtz discussed at length the possible metabolic pathways leading to dopamine synthesis, but a consensus regarding the synthetic route from tyrosine to adrenaline appeared finally to have been reached.\textsuperscript{220} A major methodological problem at this time with regard to this issue was the fact that the adrenal medulla served as the major model system for investigating the question; in this tissue, however, dopamine serves principally as the precursor for noradrenaline, and could thus be expected to yield few insights into the situation in the central nervous system. The rapid turnover of DOPA in this process also meant that it was not possible to measure this substance in the synthesizing tissues, so that the question of the origin of endogenous DOPA remained open, as it had since Guggenheim recognized that DOPA is not available via dietary protein. Whether dopamine was synthesized only from DOPA was also still unclear; it was conceivable that dopamine could arise through the direct hydroxylation of tyramine, despite inconclusive evidence to the contrary presented by Udenfriend’s laboratory.\textsuperscript{221} Holtz remarked that DOPA decarboxylase activity in the brain was greatest in the hypothalamus, thalamus and caudate nucleus, low in the cortex and absent from the white matter, and discussed possible explanations for this lack of correlation between DOPA decarboxylase activity and noradrenaline levels in the brain. (Udenfriend’s laboratory had reported the previous year that 5-HTP decarboxylase activity exhibited a similar distribution in the dog brain, the level being eight times as high as in the caudatus in the thalamus and forty times as high as in the cortex; the assessed region with the next highest activity was the “midbrain”, two and a half times the level in the thalamus.)\textsuperscript{222} Holtz recognized that there were a number of potential experimental artifacts, and also noted the probable identity of the DOPA and 5-HTP decarboxylases.\textsuperscript{223} He observed (without emphasis) that dopamine had recently been identified by Carlsson in the rabbit brain. But his conclusion tended to emphasize the possibility that dopamine was active in its own right:

\begin{quote}
The central excitation seen in animals pretreated with iproniazid after the injection of dopa sets in very promptly. It must therefore be attributed at least in part to the dopamine which is quickly formed by decarboxylation, and not to noradrenaline which is probably formed only slowly from dopamine. In fact, during the central excitation caused by an injection of L-dopa in rabbits Carlsson et al. found an increase in the dopamine, but not in the adrenaline content of the brain.\textsuperscript{224}
\end{quote}

He proposed, in fact, that the ‘sympathin’ described by Vogt and others was not a mixture of noradrenaline and adrenaline, but rather a mixture of noradrenaline and dopamine; he pointed out that neither Schümann nor Carlsson had identified even a trace of adrenaline in the brain, a finding confirmed early in 1959 by the Japanese investigator Sano. Holtz was also of the opinion that in certain non-nervous tissue, such as lung, intestine and liver, where dopamine accounted for more than 97% of catecholamine content, dopamine might also function as a local modulator in its own right.\textsuperscript{225}

\textsuperscript{219} Blaschko, 1959.
\textsuperscript{220} Holtz, 1959.
\textsuperscript{221} Udenfriend and Wyngaarden, 1956.
\textsuperscript{222} Bogdanski et al., 1957.
\textsuperscript{223} See Westermann et al., 1958; Fellmann, 1959.
\textsuperscript{224} Holtz, 1959.
\textsuperscript{225} Ibid.
Section V of the meeting was then devoted to the “central actions of catecholamines”, opening with a presentation by Vogt. Notwithstanding Carlsson’s and Schümann’s findings regarding high dopamine concentrations in nervous tissue, she believed that brain noradrenaline was mixed with a small proportion of adrenaline; the significance of Carlsson’s finding of dopamine in the brain was, she said, uncertain. Vogt had investigated the effects of reserpine on various brain substances, and aimed to determine which of these were important to its sedative effects by supplying the precursors. She found that 35mg.kg⁻¹ DOPA caused no significant changes in hypothalamic or ganglionic noradrenaline in the cat, despite occasional excitement; nor was hypothalamic noradrenaline (in contrast to ganglionic noradrenaline) affected by the co-administration of DOPA and iproniazid, although the behavioral excitement was much more pronounced. These results were difficult to compare with those of other workers, in that she reported that iproniazid alone caused a decrease in hypothalamic noradrenaline. In contrast to Carlsson’s findings, iproniazid did not protect cats against the effects of subsequently administered reserpine, leading to the conclusion that “the miosis cannot be related to low cerebral catecholamines”, by which she clearly meant sympathin. Curiously, she did not test the effect of DOPA in the reserpinized cat.²²⁶

The difference between the behaviour of hypothalamic and ganglionic noradrenaline clearly puzzled Vogt, as did Carlsson’s results, inexplicable in terms of her model of central nervous function. The next report was that by Carlsson, in which he presented the detailed results of the Bertler and Rosengren work, and explicitly advanced his views of its significance for Parkinson’s disease and other extrapyramidal disorders.²²⁷ Once again, the discussion of his presentation is not recorded, but, in the summary of the session by Seymour Kety (Laboratory of Clinical Health, National Institute of Mental Health, NIH, Bethesda), it is significant that dopamine is not mentioned, except as possibly being the rate-limiting point in noradrenaline synthesis. In the following presentation by Brodie’s group, one of the topics discussed was the action of reserpine, and the question of whether the depletion of noradrenaline or 5-HT underlay its actions; once again, dopamine was not mentioned, although Carlsson’s 1957 paper was referred to at the end of the paper:

> Whatever the reason for the excitatory effects of large doses of 5-HTP its mechanism of action differs from DOPA and other ergotropic agents, since it fails to reverse the actions of reserpine.”²²⁸

Brodie’s group were currently integrating the available neurochemical information into a bipolar schema which extended the divisions of the peripheral autonomic system into the central nervous system. In this model, noradrenaline was the neurohormone of the Hessian ergotropic system and serotonin, the most investigated neurosubstance at the end of the 1950s, that of the trophotropic system. It was unclear which role a third neurohormone, such as dopamine, could play in this design. Moreover, the effects of DOPA on the brain could not be properly classified under either of the then dominant principles of catecholamine action, ‘sympathomimetic’ or ‘sympatholytic’. Brodie’s group, in fact, ascribed the effects of DOPA in animals to its role as the precursor of noradrenaline in the reticular activating system. He interpreted Carlsson’s 1957 paper as indicating that dopamine exerted a “physiological antagonism” of the effects of

²²⁷ Carlsson, 1959b.
²²⁸ Brodie et al., 1959.
The view that the effects of DOPA in Parkinson’s disease patients were also essentially attributable to the psychostimulant effects of the catecholamines for which it is the precursor was a popular one throughout the 1960s. Any DOPA effect, whether in animal models or on parkinsonian symptomatology, could thus be dismissed as being indirect and ultimately unreliable.

The telling observation on the status quo stood at the head of Kety’s summary of the symposium:

> It is quite apparent . . . that definitive knowledge [on the central action of catecholamines] has not kept pace with our comprehension of the metabolism and action of these important substances elsewhere in the body.\(^{230}\)

The limitations of models based on observations made in the periphery for explaining the operation of the central nervous system were beginning to become evident; the specific investigation of brain neurochemistry was starting to emerge. The importance of methodological questions and of the need for “provocative and ingenious hypotheses, such as those which Dr. Brodie has developed” was emphasized, even if “many of the theories have to be developed far in advance of the data which may support them.”\(^{231}\) This last comment might explain the peculiar observation by Kety that DOPA had the ability to increase central noradrenaline concentrations, in direct contradiction to the evidence reported by both Carlsson and Vogt at the meeting. The conceptual shifts required by the new evidence were clearly difficult.\(^{232}\)

An alternative explanation for the presence of biogenic amines in the central nervous system was that they modulated central metabolic processes. The role of cellular metabolism and possible cerebral nutritional deficits in neurological disease was a much discussed question throughout the 1950s, and the role of neurohormones was widely discussed in this context. This focus on general metabolic processes points to another conceptual difficulty of the time; in the words of Brodie and colleagues:

> The pharmacologist has long sought biochemical reasons for the action of drugs on various organs. Similarly the physiologist has striven to explain the function of organs in terms of biochemical processes. However, the gulf separating physiology and pharmacology on one side from biochemistry on the other is still precariously bridged. Perhaps the reason for this has been the rather common conviction that the specific organ function can be explained in terms of the “universal” reactions of intermediary metabolism . . .\(^{233}\)

It was only emerging at this stage that specialized functions in different parts of the body – and, in particular, of the brain – were associated with unique enzyme systems and substrates. The metabolic approach to neurological disorders, despite the fact that at the time it competed to a certain degree with the central neurotransmitter concept, was

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\(^{229}\) Ibid.

\(^{230}\) Kety, 1959.

\(^{231}\) Ibid.

\(^{232}\) An interesting paper was published by the sociologist Baernard Barber in *Science* in 1961 regarding the “resistance by scientists to scientific discovery”. Amongst the factors discussed which might be pertinent here were problems caused by new methodologies, professional specialization within a particular field, the existence of scientific “schools” of thought and the relative seniority of the investigators involved.

\(^{233}\) Brodie *et al.*, 1959.
nonetheless not an aberrant one; the role of dysfunctions of cellular energy economy in certain modes of neurodegeneration is today receiving increasing attention.

Even the proponents of chemical transmission in the central nervous system were unclear about the precise role of brain dopamine. Receptors for dopamine had, of course not been sought at this stage, let alone identified; it should also be remembered that the utility of the ‘receptor’ concept itself was still being debated in 1960. The English pharmacologist Schild posed the rhetorical question at the CIBA Foundation Symposium on Adrenergic Mechanisms (1960): “Why then talk of receptors at all if they are not necessarily related to innervation?” It had also been only a few years since Werner Loewenstein (Zoology, University of California, Los Angeles) had commented:

That modulation of activity occurs at higher levels of the central nervous system, i.e. in cell bodies, is established. But apparently the only case in which a direct neural effect upon receptor elements has heretofore been established is that of inhibition occurring in the dendritic processes of a crustacean stretch receptor nerve cell.234

Although most biochemists assumed the existence of receptors for biogenic amines in the central nervous system, at least as a working hypothesis, it was still not clear whether the pharmacological response was the result of chemical modification of the amine, as by an enzyme, or of an electrostatic interaction between agonist and receptor. The precise mechanism by which DOPA or dopamine might influence nervous function (and, later, the symptoms of Parkinson’s disease) thus required more precise explanation.

**Isamu Sano and the first Japanese contribution to the L-DOPA story**

Interest in the role of catecholamines in central nervous function had also been excited in Japan. On January 26, 1959, a group headed by the neurologist Isamu Sano (Department of Neuropsychiatry, Medical School, Osaka University) submitted a paper to *Biochemica et Biophysica Acta* which extended the findings of Carlsson’s group concerning the distribution of dopamine to the human brain. Sano (1924-1975) graduated from the Osaka University Medical School in 1949, spent the period 1952-53 in Germany (Munich and Freiburg), and was awarded his doctorate by Osaka University in 1954. In 1955 he was appointed Associate Professor in the Department of Neuropsychiatry in the Osaka University Medical School, in 1967 Professor and Chairman of the Department of Neuropharmacology and Neurochemistry at the Institute of Higher Nervous Function at the Osaka Medical School. Sano was a respected figure in biogenic amine research in the 1950s. Patrick McGeer (University of British Columbia) remembers inviting him to a meeting on the Biochemistry of Mental Illness in June 1957;235 Hornykiewicz listed him amongst the small band who constituted the international “dopamine community” in the early 1960s.236 Sano’s group published a number of articles (in English and German) in the second half of the 1950s concerning uptake and release mechanisms for biogenic amines and their modulation by pharmacological agents (including reserpine); two of these papers were still being cited on a regular basis in the 1970s.237

234 Loewenstein, 1956, referring to Kuffler and Eyzaguirre, 1955.
235 Personal communication.
237 Sano et al., 1958, 1959b.
In 1959, Sano and his co-workers described for the first time the distribution of the catecholamines dopamine and noradrenaline and of the dopamine precursor DOPA in the human brain. Three brains were examined, and no less than forty distinct regions individually analyzed. Commencing with the statement “It is probable that norepinephrine and dopamine have some important function in the brain”, the paper confirmed that the distribution of noradrenaline reported by Marthe Vogt in the dog also applied in the human brain. Even more interesting was the finding that dopamine was especially concentrated in the human extrapyramidal system, consistent with the findings of Carlsson’s laboratory in other mammals. The paper ended with the comment that dopamine was regarded as important for motor function; “how this amine is related to this system remains unsettled, however, and is now under investigation.”

The significance of this paper was recognized immediately by the “catecholamine community”. Hornykiewicz, who had been investigating the biochemistry of dopamine since the early 1950s, cited Sano in his 1960 report concerning the crucial discovery of the basal ganglia dopamine deficiency in Parkinson’s disease; Barbeau and Sourkes also cited the paper several times in 1961/62.

In the meantime, Sano’s group published a more detailed report of their work in the Klinische Wochenschrift (15 January 1960), the printed, German version of a presentation to the Japanese Medical Association on April 5, 1959. The individual regional measurements for each of the three brains described in their previous paper were presented and the development of the methodology employed by their laboratory was discussed in detail. The von Euler trihydroxyindole and Weil-Malherbe ethylenediamine fluorescence methods for the estimation of catecholamines were discussed and criticized. K. Sano had developed in the period 1958-59 an alternative

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Table 10-4: Selected data from table I in Sano et al., 1959: “Concentration of dopamine, noradrenaline and Dopa in different parts of the human brain (µg/g wet weight). The value is the mean in the brains of three humans who died by strangulation, HF intoxication and brain softening.”

<table>
<thead>
<tr>
<th></th>
<th>Dopamine</th>
<th>Noradrenaline</th>
<th>DOPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>G. frontalis sup.</td>
<td>0.11</td>
<td>0.01</td>
<td>0.00</td>
</tr>
<tr>
<td>Medulla oblongata</td>
<td>0.17 ± 0.06</td>
<td>0.14 ± 0.03</td>
<td>0.02 ± 0.01</td>
</tr>
<tr>
<td>Nucl. caudatus</td>
<td>5.74 ± 0.41</td>
<td>0.04 ± 0.01</td>
<td>0.02 ± 0.01</td>
</tr>
<tr>
<td>Putamen</td>
<td>8.25 ± 0.82</td>
<td>0.07 ± 0.01</td>
<td>0.03 ± 0.01</td>
</tr>
<tr>
<td>Pallidium</td>
<td>1.01 ± 0.17</td>
<td>0.02 ± 0.01</td>
<td>0.02 ± 0.02</td>
</tr>
<tr>
<td>Substantia nigra</td>
<td>0.38 ± 0.16</td>
<td>0.07 ± 0.02</td>
<td>0.04 ± 0.01</td>
</tr>
<tr>
<td>Nucl. Ruber</td>
<td>1.17 ± 0.16</td>
<td>0.23 ± 0.05</td>
<td>0.08 ± 0.00</td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>1.12 ± 0.45</td>
<td>1.11 ± 0.22</td>
<td>0.06 ± 0.01</td>
</tr>
<tr>
<td>Nucl. amygdalae</td>
<td>0.13 ± 0.04</td>
<td>0.06 ± 0.02</td>
<td>0.01 ± 0.01</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>0.00 ± 0.00</td>
<td>0.01 ± 0.01</td>
<td>0.02 ± 0.00</td>
</tr>
<tr>
<td>Gl. pineale</td>
<td>0.50</td>
<td>0.10</td>
<td>0.04</td>
</tr>
<tr>
<td>Plexus chorioideus</td>
<td>0.11 ±0.02</td>
<td>0.04 ± 0.02</td>
<td>0.07 ± 0.02</td>
</tr>
</tbody>
</table>

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238 Sano et al., 1959a.
239 Sano et al., 1960b.
separation method which allowed a more precise estimation of the individual catecholamines, described in a series of papers in Japanese journals;240 this method was adopted with minor modifications by Isamu Sano’s laboratory. Its advantage lay not so much in improved detection limits, which were quite high in comparison with what would be acceptable today – Sano, in fact utilized the fluorescence methods employed by Weil-Malherbe – but in the more secure separation of the component catecholamines, thus allowing their more accurate quantification.

Sano’s group reported that they had detected the presence of dopamine and noradrenaline, but not of adrenaline, in the brains of a number of species (ranging from the eel to the cat). They then outlined the results of pharmacological experiments in the guinea pig, in which they had explored the possibilities of manipulating central catecholamine levels. Reserpine was found to reduce total brain levels of both noradrenaline and dopamine, and they confirmed the behavioural effects of biogenic amine depletion reported by Carlsson’s group in 1957. It was also established that the administration of the MAO inhibitors (iproniazid or JB-516241) or of DOPA elevated brain dopamine levels (and, to a lesser extent, those of noradrenaline); the effect of DOPA was even more dramatic following reserpine treatment or when administered together with a MAO inhibitor. The peripheral administration of neither dopamine nor noradrenaline affected brain catecholamine levels; this was not unexpected, although the relative impermeability of the blood-brain barrier to these substances was still uncertain at this time.242

At the end of this comprehensive paper, the authors also proposed a model of catecholamine release in which the active transport of catecholamines into the “mitochondrial” or “membrane-bound fraction” of the cell played the central role, rather than protein-bound neurotransmitter, as had been proposed by Brodie’s group with respect to serotonin release.243 Sano’s group had published a paper in the previous issue of the *Klinische Wochenschrift* in which they had described in detail the biochemical investigations of noradrenaline and 5-HT uptake into platelets which had led them to reject the Brodie model of passive release.244

This second paper from the Sano group on brain catecholamines did not attract the same international attention as their 1959 report, perhaps because it appeared in German, although the Canadian biochemist Sourkes cited it more frequently than the earlier paper. Sano’s group had commented that the depletion of dopamine, and not of 5-HT, was more likely to be responsible for reserpine-induced parkinsonism, a view which concorded with that of Carlsson’s group. In contrast, most workers at this time, including Brodie and Shore at the National Institutes for Health in Bethesda, still attributed the effects of reserpine solely to serotonergic mechanisms. Sano’s group had also observed the effects of DOPA administration on dopamine levels in reserpine-treated guinea pigs, but did not discuss the practical significance of these findings for human disease in this paper. As with Carlsson, however, he was aware of their consequences, as will be discussed below.

240 References in Sano *et al.*, 1960b.
244 Sano *et al.*, 1960a.
Metabolism of L-DOPA/dopamine in the brain

The metabolism of DOPA and dopamine continued to be pursued. Perhaps most significantly, Toshiharu Nagatsu and colleagues (Laboratory of Clinical Biochemistry, National Heart Institute, Bethesda) provided the final essential link in the tyrosine to adrenaline pathway in 1964 when they reported that L-tyrosine could be converted to L-DOPA by cell-free brain preparations, the first direct evidence for the presence of tyrosine hydroxylase in the brain; they also demonstrated that the enzyme was not identical with tyrosinase.245

Kenneth Shaw (Laboratory for the Study of Hereditary and Metabolic Disorders, Utah College of Medicine, Salt Lake City) and his group had established in 1957 that homovanillic acid (HVA)246 was present in normal human urine, and that its levels seemed unaffected by diet, except that it was increased by administration of L-DOPA (but not of D-DOPA). The authors concluded that HVA was the end-product of endogenous L-DOPA metabolism, thus providing the first direct evidence that L-DOPA was normally synthesized in man; nevertheless, they regarded its significance solely in its role as precursor for noradrenaline, adrenaline and the melanins. The results of their experiments led them to proposing a metabolic pathway for dopamine which was correct (figure 10-12); they also believed to have evidence that L-DOPA itself could be converted to DOPAC (via transamination to 3,4-dihydroxyphenylpyruvate). Finally, they suggested that the “protocatechuic acid” detected by Guggenheim in rabbit urine was probably, in fact, DOPAC.247


The issues which had been developed over the previous half decade appeared to come to a head at the symposium held at the Wellcome Building and the Ciba Foundation in London in the spring of 1960. Eighteen months had elapsed since the Catecholamine Symposium in Bethesda, and a great deal more evidence for an active role for the catecholamines in central nervous function had been reported, but many of the doyens of the field remained unconvinced. It is fortunate that the proceedings of this symposium have been preserved in a 600 page volume which also includes most of the discussions which took place after the various presentations; especially valuable is the debate which ensued at the end of the conference, captured in forty pages of invaluable transcript.248 Most of the “names” who would be expected at such a conference, with the exception of Holtz, were present. Eight sessions on specific topics, each with discussions, were held following the opening address by Sir Henry Dale:

1. Formation and inactivation of adrenergic transmitters (Chairman: Sir Henry Dale; five papers)
2. Storage of catechol amines (Chairman: H. Blaschko; four papers)
3. The adrenergic neurone (Chairman: J.H. Gaddum; five papers)
4. Adrenergic mechanisms in man (Chairman: W.D.M. Paton; 4 papers)

245 Nagatsu et al., 1964a, 1964b.
246 3-Methoxy-4-hydroxyphenylacetic acid.
247 Shaw et al., 1957.
248 Vane et al., 1960.
5. Actions of adrenaline and noradrenaline on the effector cell (Chairman: H.O. Schild; eight papers)
6. Mechanisms of action of other sympathomimetic amines (Chairman: U.S. von Euler; four papers)
7. Central adrenergic mechanisms (Chairman: Marthe Vogt; nine papers)
8. General (Chairman: J.H. Burn; three papers)

There were also two special sessions which occupy about a quarter of the proceedings:

Ciba Foundation sessions on peripheral adrenergic mechanisms (Chairman: H. Blaschko; 2 short communications with discussion)
Ciba Foundation sessions on central adrenergic mechanisms (Chairman: J.H. Gaddum; 2 short communications with discussion)
Two things are notable regarding this program: firstly, separate sessions devoted to methodology were omitted in favour of functional theme-based divisions; secondly, the need to separate central from peripheral mechanisms was accorded clearer recognition than at previous conferences. It is also noteworthy that immediately prior to the symposium, John Crossland (Lecturer in Physiology, University of St. Andrews) had published a review of “chemical transmission in the central nervous system” which examined a range of candidate substances, including acetylcholine, sympathin, serotonin, substance P, histamine and ATP – but not dopamine. This was the first paper in which Sano’s report concerning the differential distribution of catecholamines in the brain had been cited; it was cited, however, regarding the distribution of noradrenaline in the human brain, while his dopamine results were not mentioned. Nor, indeed, was dopamine mentioned in the entire review. Crossland had long supported the hypothesis of chemical transmission in the central nervous system, but:

Enthusiasm for chemical transmission has not always been combined with a critical assessment of the results being offered and there has been a tendency to lose sight of the essential qualities of a transmitter substance.

At this point, Crossland made clear one of the conceptual difficulties which impeded the acceptance of alternative chemical neurotransmitters:

It is an essential feature of the definition that the transmitter substance initiates the action potential of the effector cell and does not merely potentiate or modify a process which could occur, in a different form, in its absence.

Not only does this definition undervalue the role of signal summation in central neurotransmission, it relegates the concept of an ‘inhibitory transmitter’ to the rank of an oxymoron. On the other hand, while correctly noting that none of the central catecholamines satisfied the normal requirements of a neurotransmitter at this stage – indeed, it had not yet been established whether they were located in nervous or glial tissue – Crossland made an observation which of great importance:

many of the substances considered in this review are active on smooth muscle preparations but behave in a much less impressive fashion when they are tested on nerve cells. The use of the central nervous system itself, or of isolated nervous elements might be more satisfactory for the initial detection of central nervous transmitters.

There were certain practical difficulties associated with this proposal, but the recognition that the old model systems might not be appropriate for the investigation of central nervous activities was vital, and it would be the development of new techniques during the following years which would allow investigations which provided indisputable evidence for the new concepts.

For the present discussion, the Ciba Symposium of 1960 became most interesting towards its end. Significantly, the session on the “action of other sympathomimetic amines” (i.e., other than (nor)adrenaline) included presentations on tyramine but not dopamine. Marthe Vogt opened the seventh session, dealing with central effects of catecholamines, most provocatively:

249 Crossland, 1960.
250 Ibid.
251 Ibid.
252 Ibid.
The most extreme view taken about the rôle played by [central noradrenaline] stores is that their size is directly correlated with behaviour, such as excitement or motor activity, and that the clinical benefit derived from the treatment of depressive patients with amine oxidase inhibitors is due to raising the cerebral concentration of catechol amines. I wish only to state here that there is no evidence whatsoever for this attractive hypothesis, and the animal experiments, as far as they give any lead at all, do not support it.\(^{253}\)

Vogt conceded that sympathomimetic agents, including amphetamine and dopamine, might have central effects, but that this was not evidence that the level of endogenous noradrenaline determined the activity of the centres which these drugs modulated. She tended rather to the view that their influence could be attributed either to their general hypertensive effects or at least a change in local circulation. At the same time, she acknowledged the problems posed by experiments designed to investigate this supposition, and hoped that results presented at the current meeting might “solve the riddle posed by these contradictory findings.”\(^{254}\)

The first of the nine papers in this session was read by Carlsson, who, together with Margit Lindqvist and Tor Magnusson (all of whom had recently transferred to the Department of Pharmacology at the University of Göteborg), continued the direction which he had pursued in London with a talk programmatically entitled “On the biochemistry and possible functions of dopamine and noradrenaline in brain”. The speaker presaged new data to be published by Bertler concerning the central distribution of noradrenaline, dopamine and 5-HT, as a result of which his group had concluded that: “dopamine and noradrenaline seem to belong to different functional systems of the brain.” They then presented evidence for high turnover rates of both catecholamines in the mouse brain, and that this turnover was accelerated by treatment with MAO inhibitors to a greater extent than indicated by the absolute rise in catecholamine levels. The fact that MAO treatment of the reserpinized mouse and rabbit did not lead to catecholamine accumulation was explained in terms of synthesis inhibition following the exceeding of maximal catecholamine storage capacity, which had been reduced by reserpine to practically nil. Finally, further evidence for the crucial role of the catecholamines, rather than 5-HT, in the reserpine effect was presented.\(^{255}\)

This talk was followed by the Polish pharmacologist Chruściciel, who recapitulated the results he and Blaschko had recently published concerning the awakening effects of phenylalanine derivatives in the reserpinized mouse, confirming Carlsson’s results.\(^{256}\) In the short ensuing discussion, Spinks reported that the administration of an adrenergic antagonist an hour before DOPA could block the activation effects of the latter, while having no effect on the motor effect, suggesting a functional separation of the two responses. Weil-Malherbe noted that he had conducted similar experiments, and found that while neither DOPA nor JB-516 alone had a significant effect, their combined administration induced massive increases in both central dopamine and noradrenaline. The English pharmacologist Eleanor Zaimis objected that the reserpine doses employed by Carlsson were more suited to toxicology than pharmacology; Carlsson replied that he

\(^{253}\) Vogt, 1960.
\(^{254}\) Ibid.
\(^{255}\) Carlsson et al., 1960.
\(^{256}\) Chruściciel, 1960.
had also repeated his experiments with much lower doses (1mg.kg\(^{-1}\); nevertheless, Zaimis noted that the usual dose in man was 10µg.kg\(^{-1}\)).\(^{257}\)

The major discussion, however, did not take place until after the final presentation at the Ciba Foundation Sessions on Central Adrenergic Mechanisms. Weil-Malherbe spoke in detail on the results he had mentioned during the discussion of Chruściel’s paper. Rabbits had been treated with 1mg.kg\(^{-1}\) reserpine, which almost completely depleted brain catecholamines, and treated three days later, as catecholamines levels again began to rise, with 30-50mg.kg\(^{-1}\) DOPA (i.v.), 10mg.kg\(^{-1}\) JB-516 or a combination of the two. Noradrenaline and adrenaline were restored to normal levels within an hour of receiving intravenous DOPA in animals which had been pre-treated with the MAO inhibitor, while dopamine concentrations far exceeded those in untreated animals. Despite the 1957 papers of Carlsson and of his associate Montagu, Weil-Malherbe saw the parallel but unequal increases in noradrenaline and dopamine concentrations as evidence that the latter was simply precursor for the former; that noradrenaline levels did not rise as dramatically as those of dopamine was attributed to the fact that a large portion of the newly synthesized dopamine was found in the soluble, not the particulate, fraction of the cell preparation, and therefore unavailable for further processing. The final observation made by Weil-Malherbe regarding this study was also interesting:

> Five out of six animals which had received dopa, together with intravenous JB-516, died two to two and a half hours after the injection of dopa; almost immediately after the injection they showed symptoms of paralysis, convulsions, laboured breathing and opisthotonus. At the time of death noradrenaline levels were still only about 30 to 50 per cent of the normal level. The dopamine concentrations were at about their normal level or perhaps increased by up to 100 per cent.\(^{258}\)

Weil-Malherbe also noted that the increase was only transient, interpreting this as indicative of an inability to store the newly synthesized amines. On this point he was in agreement with Carlsson, who also argued that the alkaloid interfered in storage rather than release processes.

At the conclusion of his presentation, a wide-ranging discussion of central catecholamines then began. In reference to Weil-Malherbe’s results, Dale posed the question: “It is rather extraordinary that there should be a poisonous amino acid, isn’t it?”\(^{259}\) While Vogt observed that a MAO inhibitor together with reserpine is toxic, Weil-Malherbe objected that JB-516 together with DOPA was toxic whether the animals were reserpinized or not. Bacq commented that surprisingly low doses of tryptophan and tyrosine, if injected, could also be toxic.\(^{260}\) Von Euler remarked that a self experiment had demonstrated to him that a half gram of DOPA taken orally disturbed sleep; he later commented that it also caused “a disagreeable feeling of apprehensiveness and uneasiness.”\(^{261}\) Carlsson then presented further results from his laboratory which supported Weil-Malherbe’s contention that reserpine disturbed amine storage mechanisms; the data also underlined the non-specificity of the adrenal medulla

257 Carlsson also welcomed the question because “I now know one person who can tell me the difference between pharmacology and toxicology”; Vane et al., p.445.


259 Vane et al., p.550.

260 See also Freter et al., 1957 and Mitoma et al., 1957 for the toxic effects of transmitter precursor amino acids in animals.

261 Vane et al., p.551.
“DOPA decarboxylase”, in that it also synthesized 5-HT when supplied with 5-HP. Following a discussion of O-methylation, and speculation on the significance of the recently identified melatonin\textsuperscript{262} by Axelrod (who would concern himself with it further during the 1960s) before a skeptical audience, the talk turned again to MAO. Carlsson postulated that MAO was located close to the site of catecholamine synthesis, while catechol-O-methyl transferase was closer to the effector site; further, that MAO was essential to life, so that total inhibition was possible only at lethal doses. Vogt pointed out, however, that it was not known whether central noradrenaline was neural or glial; “so far neither tissue culture nor histochemistry has helped us at all.”\textsuperscript{263}

As the discussion resumed after an adjournment, Chruściel advised that he had also noted the lethality of L-DOPA in reserpinized mice, albeit at doses of 1000mg.kg\textsuperscript{-1}. The discussion then circled around the question of whether it was DOPA or one of its derivatives which was responsible for the observed responses. Carlsson ruled out L-DOPA itself as the directly acting agent, as its effect was increased by MAO inhibition. If, on the other hand, a derivative was responsible for the awakening effects of L-DOPA, it was not obvious which metabolite was the most significant, given the similar effectiveness of \textit{m}-tyrosine reported by Blaschko and Chruściel. Schild objected that the behavioural responses to the various drugs under discussion were clearly interesting, but was dubious as to whether these results could be extrapolated to man. Carlsson referred to the increased alertness recently observed by Degkwitz following the administration of L-DOPA to humans (see below), but the point was not further pursued.\textsuperscript{264}

Some time later, Vogt expressed the desire

\textit{to take up battle with Dr. Carlsson again and try to summarize the evidence for and against the view that brain levels of catechol amines on the one side, and of 5-HT on the other, are in any consistent way correlated with behaviour.}\textsuperscript{265}

Carlsson was by no means the only participant proposing such a correlation, but by virtue of the key papers emerging from his laboratory on the subject, he had become the figurehead of the “movement”. Vogt objected, quite validly, that

\[\text{[u]sing the amine oxidase inhibitors, and working on cats rather than on rabbits, we have not been able to convince ourselves that there was any correlation between alertness and high levels of catechol amines.}\textsuperscript{266}\]

The choice of species was indeed significant, the responses of the cat being different to those of most mammalian species; Carlsson and Schümman had also applied iproniazid in cats, but stopped as soon as it was recognized that this drug induced severe methemoglobinemia. Vogt also argued that a number of drugs stimulated sympathetic centres and depleted catecholamine stores, but do not share a common modus of action, including tetrahydronaphthylamine,\textsuperscript{267} insulin, ether and reserpine. Significant here was the fact that these drugs also elicited diverse behavioral responses, so that the latter

\begin{itemize}
\item \textsuperscript{262} Lerner et al., 1958.
\item \textsuperscript{263} Vane et al., p.561.
\item \textsuperscript{264} Ibid., pp.564-568.
\item \textsuperscript{265} Ibid., p.574.
\item \textsuperscript{266} Ibid., p.575.
\item \textsuperscript{267} 2-Aminotetralin, β-tetra.
\end{itemize}
could not be directly related to central catecholamine levels, further evidence against
the Carlsson position. Carlsson responded with a succinct table summarizing his
findings (table 10-5), and concluded that, despite certain puzzling inter-species
differences, “there is indeed a correlation between catechol amine levels and
alertness.”268 He added that the correlation was not perfect, but this was probably due to
the fact that catecholamine stores were assayed; it would be more informative if it were
possible “to determine the free and active monoamines in the brain.”269 Vogt rejoined
that she had recently elevated catecholamine levels in the rabbit without an increase in
alertness; further, the effects of dopamine should not necessarily be “lumped together”
with those of the other catecholamines, as it was possible that dopamine had an
amphetamine-like effect upon the reticular system. Vogt dismissed Brodie’s correlation
of 5-HT levels and behaviour on similar grounds; she showed thereby the conceptual
problem regarding reserpine which led to her scepticism:

The difficulty, as with the catechol amines, is that whenever the results do not fit the
theory that the low stores are decisive, there is always the alternative explanation that
reserpine-like drugs prevent the tissues from binding the amines, thereby leading to an
“excess of free amines”!270

Brodie had, indeed, suggested that the release of transmitter by reserpine might play a
role in its actions, whereas Carlsson emphasized the subsequent depletion of
catecholamine stores; it was recognized shortly afterwards, however, that it was the
binding of transmitter in the presynaptic terminal which was disrupted by reserpine
treatment, and this had also been suggested previously.271 Dell (Neurophysiology
Laboratory, Henri-Rousselle Hospital, Paris) objected that Vogt appeared to regard the
reticular formation and hypothalamus as the only brain regions involved in alertness;
this “heresy from the neurophysiological point of view” disregarded both the cortex and
the inhibitory influence of the bulbar nucleus.272 Vogt replied that that she was aware of
this, but:

\[\text{Table 10-5: Carlsson’s summary of the effects of manipulation of brain monoamines on}
\text{behaviour, as presented in the final discussion at the 1960 Ciba Foundation sessions on}
\text{central adrenergic mechanisms. Vane et al., 1960, p.576.}\]

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Brain</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>5-HT</td>
</tr>
<tr>
<td>Dopa</td>
<td>0</td>
</tr>
<tr>
<td>5-HTP</td>
<td>+</td>
</tr>
<tr>
<td>Reserpine</td>
<td>–</td>
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<tr>
<td>Dopa after reserpine</td>
<td>0</td>
</tr>
<tr>
<td>5-HTP after reserpine</td>
<td>+</td>
</tr>
<tr>
<td>Nialamide</td>
<td>+</td>
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<tr>
<td>Nialamide after reserpine (mice)</td>
<td>+</td>
</tr>
<tr>
<td>Nialamide after reserpine (rabbits)</td>
<td>+</td>
</tr>
</tbody>
</table>

268 Ibid., p.577.
269 Ibid.
270 Ibid., p.578.
272 Vane et al., 1960, p.578.
I am only trying to bring forward the evidence which is incompatible with the view that the level of catechol amines has some consistent correlation with behaviour, and the evidence that the level of 5-HT in the brain may determine certain aspects of behaviour. My personal view is that neither of these theories will have a long life.

She then added, however, that if the data spoke for the involvement of any of these substances in behaviour, it was for 5-HT; sedation following reserpine was more closely related in Brodie’s experiments to 5-HT than to catecholamine levels. Nevertheless, she believed that “any of these theories was a construction which some day will be amended.” Carlsson apologized for perhaps emphasizing the catecholamines at the expense of 5-HT, but noted that Brodie had been guilty of the opposite. Pratt (Maida Vale Hospital for Nervous Diseases, London) made the interesting observation that the clinician was, in fact, more interested in ‘mood’ than in ‘alertness’, so that the effect of an \( O \)-methyl transferase inhibitor in man would be interesting.

The discussion then moved to the actions of amphetamine, commencing with the observation that, despite being a sympathomimetic agent, it was no longer regarded as a MAO inhibitor, nor did its effects seem related to noradrenaline release, as it retained its effects in animal models and in man even after chronic reserpine treatment. The suggestion that amphetamine might act on tryptamine (5-HT) receptors was not universally approved, but allowed as a possibility. John Vane cautioned that the peripheral effects of a drug could not necessarily be transferred to the central nervous system, an observation which disturbed Dale. The discussion concluded with comments related to the role of MAO in the central nervous system; Blaschko repeated an earlier suggestion that it may act to regulate the dopamine levels, and thereby those of the major catecholamines. An independent role for dopamine was not to be discerned in his views, although he was more open on the question than Vogt.

The summary of the symposium by Sir John Gaddum (1900-1965; Institute of Animal Physiology, Cambridge), which had largely been prepared before the final discussion, confirmed the impression that the “old guard” was yet to be convinced of a transmitter role for central catecholamines, or of an active role for dopamine anywhere. Gaddum was without doubt one of the greats of British physiology and pharmacology; with Schild he had devised the first fluorometric assay for adrenaline, with von Euler had discovered substance P, and with Feldberg had demonstrated the transmitter role of ACh at ganglionic synapses. His investigations throughout the 1950s had examined adrenergic transmission, histamine, 5-HT and substance P; few people were as respected in the field at this time as Gaddum. He had introduced the sessions on central adrenergic mechanisms with the comment that a lot had been discovered since the Bethesda meeting at the end of 1958, as evidenced by the presentations at the current meeting:

During the last three days we have been asked to swallow a large number of facts, and I have been surprised what a lot of those facts were new to me. . . . These facts have mostly been told to us so fast that we have had to swallow them whole. We have been

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273 Ibid.
274 Ibid., p.579.
275 Ibid., p.580.
276 Ibid., p.582-587.
277 Between 1942 and 1958 he had been Professor of Pharmacology at the University of Edinburgh. For a recent appreciation of “the man who knew doses”, see Flower, 2000.
too polite to reject them immediately and we must now start to digest, absorb and assimilate them, and metabolize them. Some of them will fit into receptors in our brains and we will be able to remember them. Some of them won’t fit, however much we metabolize them, and perhaps we will excrete them.²⁷⁸

In his summation of the sessions, he presented a model of DOPA action in which dopamine was only an intermediate (figure 10-13). It is interesting that at this stage Gaddum felt obliged to justify his employment of the term ‘receptor’, defining it as “the chemical group in the tissue with which a single molecule of drug combines”;²⁷⁹ Dale insisted that this combination must be accompanied by a pharmacological response if the term were to be properly applied. Gaddum also defined the two “catecholamine receptors”, which he designated α and β,²⁸⁰ defined according to their respective inhibitors ergotoxin and dichloroisopropyl-noradrenaline (DCI)²⁸¹ and the responses which they mediated in various peripheral tissues. It was also noted that noradrenaline was particularly active at the α-receptor, isoproterenol²⁸² at the β-receptor. An interesting résumé of current concepts of drug-receptor interactions was then presented. In particular, the effects mediated by β-receptors were classified as “metabolic”, and were regarded as possibly being secondary to the accumulation of 3’,5’-adenosine

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²⁷⁸ Gaddum, 1960a.
²⁷⁹ Gaddum, 1960b.
²⁸⁰ “These were discovered by Sir Henry Dale, but they have got a new name.” The names were first proposed by Ahlquist in 1948 (who also believed that there was only one ‘sympathin’), and soon received the approval of Gaddum (1950), although he initially preferred to speak of “α-” and “β-effects”.
²⁸² N-Isopropynoradrenaline, isoprenaline. German patent to Boehringer Ingelheim, 1942; U.S. patent for resolution of isomers to Delmar Chemicals: 1955.
monophosphate (cAMP). The problem of "receptor supersensitivity" was also discussed without coming to a satisfactory conclusion. Finally, Gaddum ended his overview with a comment which seemed neither related to his foregoing discussion nor accurate given the presentations by Carlsson, Blaschko and others:

The meeting was in a critical mood, and no-one ventured to speculate on the relation between catechol amines and the function of the brain.\textsuperscript{283}

This peculiar remark can only be interpreted as meaning that Gaddum and the other senior workers had decided that the catecholamines could not play the central role which the younger members of the neurochemistry community were suggesting; this final word, however, was spoken in precisely the year when the trickle of evidence for the new view would turn into a torrent.

The Bel-Air Symposium on Monoamines and the Central Nervous System, September 1961

It was a different audience with different views who attended the Bel-Air Symposium "Monoamines et Système Nerveux Centrale" in Geneva in the fall of 1961. This meeting, as indicated by its title, was more accepting of a central role for the catecholamines, if not yet for dopamine itself. The opening presentation from Brodie and Costa was entitled "Some current views on monoamines". The paper published in the proceedings was a comprehensive (thirty-seven pages) discussion of the state of knowledge on the subject at the time of the conference. It opened with a broad discussion of issues related to the synthesis, storage and release of monoamines, before moving to reserpinized animal models. It was conceded that not only Carlsson,\textsuperscript{284} but also Everett and Toman,\textsuperscript{285} Kärki and Paasonen\textsuperscript{286} and Pletscher\textsuperscript{287} had presented convincing evidence that catecholamine depletion followed reserpine treatment: "Despite the lack of direct proof, the very logicality of the catecholamine deficiency theory made it an attractive one."\textsuperscript{288} This alternative theory was then demolished on the basis that if "reserpine acts through a deficiency of brain NE, then it should affect central adrenergic mechanisms."\textsuperscript{289} Correlations of 5-HT on the one hand and noradrenaline on the other with the various responses elicited by reserpine appeared to support the case for the central role of 5-HT depletion; but at no point was the role of dopamine even considered, the central point of Carlsson’s argument. Garattini and Valzelli (Department of Pharmacology, University of Milan) advanced similar arguments to support the Brodie and Costa standpoint, although aware not only of Carlsson’s results but also of the Degkwitz trial of L-DOPA in humans.\textsuperscript{290}

Carlsson (with Lindqvist as co-author) followed with his presentation "DOPA analogues as tools for the study of dopamine and noradrenaline in brain", opening with:

\textsuperscript{283} Gaddum, 1960b.
\textsuperscript{284} Carlsson et al., 1957.
\textsuperscript{285} Everett and Toman, 1959.
\textsuperscript{286} Kärki and Paasonen, 1959.
\textsuperscript{287} Pletscher et al., 1959.
\textsuperscript{288} Brodie and Costa, 1962. Brodie commented that the "seed of a rôle of 5-HT, based on reserpine action, seemed to have fallen on unfertile soil."
\textsuperscript{289} Ibid.
\textsuperscript{290} Garattini and Valzelli, 1962.
When listening to the previous most elegant presentations this morning, one might perhaps get the impression that the present field is one of perfect agreement. This is true to a certain extent. I think that everybody here agrees that the brain monoamines are important and that some of the psychotropic drugs act by interfering with their function.\textsuperscript{291}

But he then attacked the Brodie camp in no uncertain terms for their disregard of results gained with the monoamine precursors DOPA and 5-HTP. Carlsson observed, as he had in London, that experiments utilizing such agents, the catabolism of which to specific products was recognized, must be easier to interpret than those which employed, for example, imipramine or amphetamine, whose modi operandi were still not completely clear:

\textit{I do not think that one can use a drug as a tool to clarify physiological mechanisms until one has at least a faint idea of its mode of action.}\textsuperscript{292}

Precursor amines were clearly more specific tools than enzyme inhibitors and other indirect agents, the spectrum of action of which was usually only incompletely understood. In particular, experiments utilizing reserpine were often criticized, with justification, as “polypharmacology”, as the concurrent depletion of several peripheral and central catecholamines rendered the interpretation of behavioural and motor responses difficult. Neurochemistry needed to be constructed from the basis up, not vice versa, and to be based upon secure knowledge concerning individual constituents, not the mass effects of interventions which simultaneously modulated a number of variables.\textsuperscript{293} Vogt had actually made a similar point in London, but arrived at a different conclusion to Carlsson; she adopted the almost nihilist view that nothing could be inferred about brain function from monoamine concentrations.\textsuperscript{294} In both cases, however, the caution was well advised. Carlsson then described his recent experiments with $\alpha$-methyl-DOPA in mice and rabbits; this could be metabolized, albeit slowly, by the DOPA decarboxylase of the extrapyramidal system to the MAO-resistant $\alpha$-methyl-dopamine, and further to $\alpha$-methyl-noradrenaline. As these substances were stored in the same manner as the natural transmitter, he proposed the use of this approach (‘false transmitters’) in the study of monoamine release and metabolism.\textsuperscript{295}

Pletscher and Gey (Hoffmann-La Roche, Basel) completed the biochemical session with a presentation on “drug-induced alterations of the metabolism of cerebral monoamines”, a review of the pharmacological agents available for this purpose. In Pletscher’s opinion, the relative roles played by 5-HT and the catecholamines in the effects of reserpine were yet to be determined; he, however, was now changing to the view that the catecholamines might play a greater role in this respect than allowed by the Bethesda group.\textsuperscript{296}

Seymour Kety delivered the resume of the biochemical session, as he had done three years previously at the Catecholamine Symposium in Bethesda. Eager to find points of

\textsuperscript{291} Carlsson and Lindqvist, 1962.
\textsuperscript{292} Ibid. One of the significant contributions of the 1961 meeting was the conclusive demonstration by Albert Zeller (Department of Biochemistry, Medical School of the Northwestern University, Chicago) that iproniazid was definitely a MAO inhibitor; Zeller, 1962; see also Zeller and Sarkar, 1962.
\textsuperscript{293} Carlsson and Lindqvist, 1962.
\textsuperscript{294} Vane \textit{et al.}, 1960, pp.574-575; Vogt, 1960.
\textsuperscript{295} Carlsson and Lindqvist, 1962.
\textsuperscript{296} Pletscher and Gey, 1962.
concordance, he concluded that it was “generally agreed that serotonin and norepinephrine were the amines of interest at the present time.” The major bone of contention was in fact, the depletion of which amine was responsible for reserpine-induced sedation. Kety was clearly leaning towards the catecholamine camp:

> It seems to me that Dr. Carlsson’s [1957] experiment is very difficult to get around, and the attempt to do so yesterday by invoking hypothetical alterations in the ratio of free serotonin to bound serotonin left me personally unconvinced. . . . Psychoanalytical theories have often been criticized as being dependent upon self-fulfilling hypotheses . . . It is comforting that this problem is not unique to psychiatry, but it is a danger whenever our hypotheses depend upon too many variables that have not been measured.

Brodie’s response to what must have been perceived as a solid reproof was not recorded. Kety noted that Carlsson’s 1957 results rendered it unlikely that 5-HT was involved in the awakening effect of DOPA in reserpinized animals, although it was still open whether it was DOPA itself or noradrenaline which directly led to alertness. Cronheim and Gourzis (Research Division, Riker Laboratories, Northridge, California) had recently reported that slow infusions of 5-HT or 5-HTP increased, rather than relieved, the sedation of reserpinized dogs; they, however, had interpreted these results as indicating that the depletion of noradrenaline is a prerequisite for the observation of 5-HT-related effects of reserpine. Kety commented that the behavioural effects of MAO inhibition were also problematic; while a rise in central noradrenaline levels was not usually measured in animal experiments, there was also a lot of evidence which suggested that 5-HT was not as intimately involved in its effects as the Brodie camp believed. Kety concluded that the general consensus was nonetheless that “the crucial experiment which implicates one or other amine remains to be done.” The crucial point was that the effect of manipulation of central amines on behavior and mood was now firmly on the agenda; it remained only to elucidate the details.

In his concluding comments, perhaps with an eye to the recent report of Degkwitz and his associates regarding the use of L-DOPA in humans, Kety referred to the attraction of studies in man:

> One of the speakers yesterday mentioned that the court of last appeal is the practical effect on patients. We must not forget, however, that basic research can also be done in man, and clinical studies can contribute a great deal to a fundamental understanding of how these agents act and what are the roles of the monoamines in the brain.

Experiments on humans, so Kety, are useful because they allow assessment of the subjective effects of the various agents; one of the criticisms up till now is that the behavioural endpoints which were assessed were often only vaguely defined and of a qualitative character. As it turned out, a number of the most significant contributions in the coming years would be reached by clinical investigators, as medical people began to turn their attention to the changes in the expanding field of neuropharmacology.

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298 Kety commented: “It is comforting to realize that there is as much disagreement between Hungary and Czechoslovakia as between Sweden, Italy and the United States in this matter.”
299 Ibid.
300 Ibid.
301 Cronheim and Gourzis, 1960.
303 Ibid.
Of the papers presented in the third session, “Corrélation clinique”, the most famous and the one relevant to the present work was the presentation by Barbeau, Sourkes and Murphy on the measurement of urinary dopamine in Parkinson’s disease and their first administration of oral L-DOPA to parkinsonian patients; this paper will be discussed in detail below. Ajuriaguerra presented the résumé of this session, discussing the role of monoamines in extrapyramidal syndromes specifically at the end. He briefly surveyed Barbeau’s report and noted that the urinary measurements in neurological akinesia might indicate that drug-induced parkinsonism was also the result of the interference of reserpine or the phenothiazines in monoamine metabolism; on the other hand, de Ajuriaguerra never specifically referred to dopamine in this discussion. Nevertheless, the recognition at a large international conference of the possible involvement of changes in catecholamine levels in a neurological syndrome was certainly indicative of the changing mood. As J. Elkes noted in his presentation:

There are periods in the evolution of any subject when the accumulated pressure of facts, rather than their lack, suggests a change in the direction of its future development. There are very many facts now from which a relationship between amines and behavior could justifiably be inferred.

This change did not only apply to Parkinson’s disease; de Ajuriaguerra had also noted the other presentations with approval concerning altered monoamine metabolism and its management in depression and psychosis. But the next step forward would be the empirical testing of this model in the brains of reserpinized humans, who had the advantage of being able to describe “from the inside” the effects of both reserpine and its putative antidote, DOPA.

Results accrued from various laboratories during the next few years which confirmed the significance of the biogenic amines in central nervous system transmission processes. The paradigm shift which had occurred is to be clearly read in the introductory remarks of Uvnäs at the Symposium on “Mechanisms of release of biogenic amines” (Stockholm, February, 1965):

[Biogenic amines] have already been the principle topics at a number of Symposia and other scientific gatherings. That may be so, but there is one aspect which has been relatively little discussed. Not only do these amines play an important role as chemical mediators in the peripheral and central nervous system; more and more drugs are found to exert a similar action via the release of amines or by interfering with the release. Release of amines is implicated in disturbances characteristic of various diseases.

This was an important point: the ‘catecholamine apostles’ tended to take a more functional approach to defining what constituted a transmitter substance than the views expressed by Crossland above. For example, Andén and colleagues defined the criteria for central monoamine transmission as follows:

1. Storage in neuronal synaptic substances.
2. Intraneuronal synthesis.
3. Release by electric stimulation or K+ ions.

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304 De Ajuriaguerra, 1962.
305 Elkes, 1962.
306 Uvnäs, 1966.
X. The dopamine and L-DOPA story

4. Functional effects of release into extraneuronal space (e.g. spinal reflexes, extrapyramidal effects, central excitation, rise in body temperature).
5. Efficient local inactivation (recapture, metabolism).
6. Turnover rate dependent on nerve activity.

While incorporating most of the classical physiological criteria for definition of a transmitter substance, the fourth point especially laid novel evidence on the fact that physiological responses to a substance, whatever their nature, should be considered in the evaluation of candidate substances; this was much broader than demanding that the putative transmitter be capable of eliciting an action potential.

The action of the drugs to which Uvnäs referred in neurological and psychiatric disease was yielding information both about the neurochemistry of the brain in health and disease, but also about the nature of the drugs themselves, which often exhibited initially unexpected characteristics. In this manner, a symbiotic relationship developed between laboratory and clinic. A particularly spectacular example of the value of this relationship was presented in the first years of the 1960s: Carlsson’s 1957 paper concerning reserpine-induced sedation in animals and its relief by L-DOPA was confirmed in humans suffering a natural dopamine deficiency.

XI. The first L-DOPA trials in the clinic: Frankfurt and Osaka

CRUCIAL TO THE EMERGENCE of L-DOPA as therapy for Parkinson’s disease was the report by Arvid Carlsson’s group in 1957 that this amino acid antagonized the effects of reserpine.\(^1\) This brief paper represented an interim high point in the elucidation of the role of catecholaminergic transmission in the central nervous system, a role which remained disputed until well into the first half of the 1960s. A number of groups around the world, however, were convinced that catecholamines played a critical role in central neurotransmission, and the results published by the Carlsson group in this and other papers provided much of the evidence which supported this presumption. Their 1957 paper was consequently widely and frequently cited (166 citations to 1969 are listed by the Science Citation Index)\(^2\) and became the basis on which a number of workers commenced investigations of the role of L-DOPA and dopamine in central neurotransmission.

The first administration of L-DOPA to humans was probably that by Oster and Zorkin (Department of Chemistry and the Medical Services of the Mount Sinai Hospital) in 1942. They reported that intravenous injections of 50mg L-DOPA produced a marked rise in blood pressure (usually accompanied by nausea and vomiting) in subjects with essential hypertension, but no significant change in those with normal blood pressure; the rise peaked four minutes after injection and lasted about 15 minutes.\(^3\) Holtz and Credner had also administered 50mg L-DOPA to their assistant at about this time, noting little more than an increased pulse which they suspected was at partially psychologically determined.\(^4\) Both these investigations, however, were more concerned with the biochemistry of L-DOPA and its role as catecholamine precursor than with any potential clinical application for the amino acid.

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1 Carlsson et al., 1957a.
2 This total does not include citations by members of Carlsson’s group.
3 Oster and Zorkin, 1942.
4 Holtz and Credner, 1942.
Frankfurt: demonstration of the anti-reserpine effects of L-DOPA in man

Amongst the few clinical groups which responded in a practical manner to Carlsson’s paper was a team of clinical psychiatrists at the Clinic for Nervous and Mental Disease of the University of Frankfurt in Germany. This group, which included Rolf Frowein and Rudolf Degkwitz, published their key paper on the subject, “On the effects of L-DOPA in man and their modulation by reserpine, chlorpromazine, iproniazide and vitamin B6”, in the German medical journal *Klinische Wochenschrift* in February 1960. The publication did not attract a great deal of immediate attention from clinicians or basic researchers; Science Citations Index lists a total of 32 references to the paper in the period 1960-1969. This is perhaps surprising, not only because Birkmayer and Hornykiewicz later nominated the paper as the basis of their clinical method in the famous report which appeared at the end of 1961, but also because it was an elegant and logical extension of the theoretical and animal investigations of catecholamine function which were exciting so much attention and controversy at the time.

Rudolf Degkwitz was the chief investigator in the Frankfurt group. His father, also named Rudolf, had been a prominent Hamburg pediatrician before the war; as an outspoken critic of the regime, he had been arrested by the Gestapo in 1943 and remained imprisoned until 1945. Immediately after the War, he addressed a critical assessment of German history and its relationship with the rise of National Socialism to German youth (*Das alte und neue Deutschland*, 1946), before leaving Germany until shortly before his death in 1973. The younger Rudolf Degkwitz was born in Munich on 20 June 1920 and studied in Berlin, Hamburg, Baltimore and Munich; he passed his State Exams in medicine in Munich in 1943 and completed his habilitation at Frankfurt University in 1959. His earliest publications were concerned with problems of cerebral circulation and their relationship to psychosis. In 1953, he received a grant from the German Research Council (DFG) to investigate the question of whether “a connection existed between the course of symptomatic psychoses in patients with cardiac or circulatory problems and changes in cerebral circulation and metabolism, simultaneously taking into account the type and course of the circulatory decompensation.”

From the end of the 1950s, he commenced a series of clinical experiments which aimed to examine the relationship of monoamine metabolism and endogenous psychosis. This experimental series had been stimulated, according to Degkwitz himself, by the results emerging from the laboratory of Peter Holtz at the Pharmacological Institute of the University, whose work was discussed in the previous
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In his classic 1942 paper with Credner, Holtz had proposed the following as the rationale for his investigation of whether mammals converted L-DOPA to dopamine in the manner which he had observed in the test-tube:

In this case, the interesting possibility would present itself in a more general way of achieving pharmacological effects by the application of substances which, in themselves pharmacologically inactive, are only converted in the body by means available there to the actually active compound, and thereby presumably eliciting a completely different pharmacological response as that which would have been expected from the administration of the complete, directly active pharmaceutical.11

Holtz had completed this key paper with the comment that the effects of the intravenous application of L-DOPA required further investigation to determine whether they might be clinically exploited.

The direct stimulus for the examination by Degkwitz of L-DOPA in humans, however, was the 1957 paper by Carlsson’s group. Reserpine cures were a commonly employed means of achieving sedation, particularly in psychiatric patients, during the 1950s; serious side-effects, especially extrapyramidal reactions which could be so severe as to produce a parkinsonian-like state, were, as already noted, often an unwelcome accompaniment of the therapy. The possibility that DOPA could be used to reverse such effects was thus clearly of clinical interest. There existed, however, a problem which would plague most clinical investigators of DOPA throughout the 1960s: DOPA occur as two optical enantiomers, but in man only L-DOPA can be converted to catecholamines. The preparation of the pure enantiomer was, however, difficult and expensive. The support of a chemical company was necessary in order to overcome this difficulty; for Degkwitz and his group, this company was Boehringer & Sons, Mannheim.12

On 25 October 1958, Frowein wrote to Friesewinkel concerning the investigation of reserpine and orphenadrine and “the biogenic amine issues connected with it.” In light of investigations involving the precise assessment of vegetative and metabolic responses to these agents, as well as psychopathologic aspects of the response to these drugs, Frowein ascribed the scientific value of this line of research such a high value that he had engaged the services of Dr Mohs and Dr Wichert for its continuation. In a separate letter of the same date, Frowein responded to an enquiry from Friesewinkel directed to Frowein’s research colleague Dr Kulenkampff regarding their ongoing research, and repeated his request for 5-hydroxytryptophan and DOPA.13 The answer to these letters is not held in the files, but on November 3, Frowein thanked Friesewinkel for the supply of 1g DOPA. A request for 5-hydroxytryptophan, both radioactively labelled and unlabelled, was also made, as was a request for larger quantities (20g) of tryptophan.15 A week later, Frowein requested an unspecified but large quantity of the

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11 Holtz and Credner, 1942.
12 The correspondence between the research group and the company was principally conducted by Rolf Frowein (Senior Consultant at the Clinic since 1956) and H. Friesewinkel (Boehringer Mannheim). It is clear from these letters that another psychiatrist at the clinic, Caspar Kulenkampff, also corresponded regularly with Friesewinkel, but these letters have not been located.
13 A handwritten note on the letter indicates that Kulenkampff had advised the writer of the note that DOPA had already been received.
14 The next letter from Frowein to Friesewinkel indicates that the reply was received on 28.10.58.
15 Letter, Frowein to Friesewinkel, 3.11.58.
MAO inhibitor ‘Marsilid’ (iproniazid);\textsuperscript{16} this latter request was satisfied within a couple of days, but Friesewinkel asked for patience regarding the fulfilment of Frowein’s other requests.\textsuperscript{17}

Early in the new year, it was clear that the investigation of DOPA was intensifying; on 9 January 1959, Frowein wrote:

\textit{Today another urgent request: We are currently in the middle of investigations which require a relatively high amount of DOPA. Could you please send us some more? We will probably use 5-10g in the near future. But I would be grateful if we could receive even 1 or 2g in order to avoid having to interrupt our investigation.}

Frowein also raised the concern which has been repeatedly expressed in connection with his method ever since. In their 1960 paper, Degkwitz and colleagues reported that they dissolved l-DOPA in boiling water. Surprise has subsequently been often expressed that this method did not oxidize the DOPA to a black, unusable form. Recently conducted experiments, however, have found that the recoverability of l-DOPA from solutions prepared in the manner described by Degkwitz et al. (1960) is effectively 100\% (table 11-1).

<table>
<thead>
<tr>
<th>Initial concentration</th>
<th>Measured concentration</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>50mg/10mL</td>
<td>46mg/10mL</td>
<td>92%</td>
</tr>
<tr>
<td>100mg/10mL</td>
<td>100mg/10mL</td>
<td>100%</td>
</tr>
<tr>
<td>200mg/15mL</td>
<td>197mg/15mL</td>
<td>98.5%</td>
</tr>
</tbody>
</table>

\textit{Table 11-1: Recoverability of l-DOPA prepared according to the method described in Degkwitz et al., 1961. These experiments were conducted in the laboratories of Professor Peter Riederer (Clinical Neurochemistry, Department of Psychiatry, University of Würzburg).}

From this letter, however, it is unclear whether the saline was boiled before or during the addition of DOPA in these initial experiments:

\textit{In our most recent experiments, we have not boiled the DOPA during solution (das Dopa beim Lösen nicht mehr gekocht), because we are not sure whether something is destroyed and rendered ineffective by this process.}\textsuperscript{18}

Whether an apparent lack of response to administered DOPA initially motivated the omission of boiling is not stated. In any case, Frowein was uncertain as to whether boiling the solution before injection had reduced the effectiveness of the drug; he was, however, principally worried about the sterility of the injected solution if it were not boiled, although the limited solubility of DOPA in saline was also a problem. Friesewinkel confirmed on January 20 that there could be some loss of DOPA during boiling, and suggested that Boehringer would provide ampoules of the drug if this were

\textsuperscript{16} Letter, Frowein to Friesewinkel, 10.11.58.
\textsuperscript{17} Letter, Friesewinkel to Frowein, 12.11.58. 25g ‘Marsilid’ was supplied.
\textsuperscript{18} Letter, Frowein to Friesewinkel, 9.01.59.
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more convenient for the investigators. Friesewinkel then provided a detailed discussion of the practical aspects of preparing DOPA for injection:

\[ \text{DOPA is normally dissolved in an oxygen-free atmosphere; i.e., under nitrogen. Its solubility at } 20^\circ \text{ is 1 part substance in 200 parts water, or } \frac{1}{2}\%. \text{ If the water is preheated to over } 100^\circ, \text{ the solubility is 1 part substance in 20 parts water, or } 2\% \text{ (sic). If you are not in a position to dissolve the substance in an oxygen-free atmosphere, it would be best if you first boiled dist. water or even tap water for about 10 minutes, in order to remove most of the atmospheric oxygen. Cooling the water to } 80^\circ, \text{ the DOPA can be dissolved at a concentration of about } 1.8\%, \text{ as calculated. In this manner, about } 45\text{mg DOPA can be dissolved in } 1\text{ccm water. The } DL\text{-form, or racemic, synthetic form, of DOPA is more and better soluble in water than the } L\text{-form. This } DL\text{-form is also well soluble in acids and alkaline solutions, somewhat soluble in benzol solutions and insoluble in ether, glycerine, chloroform, alcohol, etc.}^{19} \]

Using the indicated protocol, Friesewinkel saw no problems with respect to sterility of the injected solution. For further information on the technical aspects of DOPA preparation, Friesewinkel referred Frowein to Sealock’s protocol for its preparation from velvet beans in the first volume of *Biochemical Preparations* (1949), as well as to the older literature on the synthesis of (D,L)-DOPA.\(^{20}\) Frowein replied on January 30 that he would be glad to accept the offer of ready-made ampoules, and requested that he receive twenty-five each of 100mg, 50mg, 25mg and 10mg DOPA. The requirement for iproniazid had also increased; Frowein asked for 1000 tablets of 25mg each. He was also interested in obtaining a gram each of a number of “newly recognized metabolic products of adrenaline”: 5-hydroxyindole-acetic acid (5-HIAA), 3-methoxy-adrenaline (metanephrine), 3-methoxy-4-hydroxymandelic acid (VMA), 3-methoxy-4-hydroxyphenylacetic acid (DOPAC).\(^{21}\) On February 4, Friesewinkel wrote that the DOPA ampoules, the iproniazid tablets and the 5-HIAA could be supplied almost immediately.

On February 6, however, Frowein reported a setback: he had just received 10g DOPA from Boehringer, but it was unfortunately the \(D\)-form of the amino acid, which he recognized to be pharmacologically inactive as far as conversion to the biogenic amines in humans was concerned. He noted that his group had used D,L-DOPA in their investigations up until this point, although he now regarded the employment of L-DOPA as the correct approach. He therefore enquired as to whether Boehringer could supply the pure \(L\)-enantiomer, preferably in ampoule form. He also thanked Friesewinkel for the receipt of \(^{14}\)C-labelled D,L-5-HTP. Finally, Frowein excused himself twice for the efforts he was demanding, but expected that the results of the investigation would also be of interest for the company.\(^{22}\)

Unfortunately, the correspondence available in the archives breaks off at this point. Friesewinkel and Frowein were to discuss the project further during a colloquium which was to be held at the clinic on February 21.\(^{23}\) In a further letter from the end of May,

\(^{19}\) Letter, Friesewinkel to Frowein, 30.01.59.

\(^{20}\) Waser and Lewandowski, 1921; Hirai, 1926 actually discusses the synthesis of 2,4-dihydroxyphenylalanine, or resorcinylalanine); Harington and Randall, 1931. Sealock’s protocol was based on those of Torquati (1913), Guggenheim (1913) and Miller (1921), as discussed in chapter X.

\(^{21}\) Letter, Frowein to Friesewinkel, 30.01.59. Frowein had drawn a ring around 3-methoxyadrenaline on his list.

\(^{22}\) Letter, Frowein to Friesewinkel, 6.02.59.

\(^{23}\) *Ibid.*
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Friesewinkel thanked Frowein for his attendance at a symposium on reserpine at Lugarno; he mentioned that the proceedings were to appear “in the next few weeks” in the Schweizerische Klinische Wochenschrift, but this appears not to have taken place.24

This then was the background to the paper which appeared in the Klinische Wochenschrift in February 1960 under the authorship of Degkwitz, Frowein, Kulenkampff and V. Mohs; T. Wichert was acknowledged as having assisted on some of the work. The subjects employed in the investigation were “physically healthy patients (especially with regard to cardiovascular health) with psychiatric diseases, as well as the research leader” (presumably Degkwitz). L-DOPA was dissolved at a concentration of 10mg.ml–1 in physiological saline; in order to accelerate solution, the saline was boiled in advance, as advised by Friesewinkel, and, after the addition of DOPA, the solution was quickly cooled under running water, then injected intravenously over the next ten minutes.

Nine persons who were not being treated with any other medication received L-DOPA fourteen times at doses of 50-350mg. At doses of over 200mg, a dose-dependent increase in systolic blood pressure was noted, at 270mg all persons complained of not feeling well and were subject to a variety of vegetative reactions, at 350mg vomiting was induced in all subjects. Changes in electrocardiogram and electroencephalogram were unremarkable. The authors described the responses of the subjects quite graphically, and also included the reports of some of the subjects themselves, so that the effects of the drug on these individuals could be well envisioned.

More interesting perhaps were the responses of reserpine-treated patients to L-DOPA. Twenty-two persons received on various days (1st-27th days) of a reserpine treatment (average: 15mg/day) 350mg L-DOPA, for a total of thirty-five infusions. The systolic effects and the vomiting in response to L-DOPA was similar to those seen in the first group of subjects. Most importantly, from the 5th day of the reserpine treatment, the sedation which was elicited by reserpine for 2-3 hours following administration was reduced or even abolished in fifteen patients by 350mg L-DOPA. The effects observed by Degkwitz and his colleagues were in no way less dramatic than those reported a year later by Hornykiewicz and Birkmayer:

> After the unpleasant effects which L-DOPA induces had subsided, most subjects made reports such as this: “I’m feeling better than I have for the past few days. The feeling of exhaustion and the heaviness of my limbs have disappeared. I feel fresh and want to be active.” The investigator noted that the patients became more talkative; their sleepy, somewhat bloated faces were now fresh and lively. Their slow, lethargic movements became freer and quicker. Those whom reserpine had caused to be bed-ridden stood up and took part in activities in the patients’ common room.25

A slightly lower dose (270mg L-DOPA) was sufficient to elicit this response in only three patients who had responded to 350mg on the previous day.

Degkwitz and his colleagues also investigated the response to L-DOPA of patients who had been receiving any of a range of other medications:

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24 Letter, Frowein to Friesewinkel, 29.05.59.
25 Degkwitz et al., 1960.
• The blood pressure response to even small doses of L-DOPA (10-50mg) was enhanced and prolonged in patients who had also received the MAO inhibitor *iproniazid* (average: 150mg/day) for more than twelve days; nausea and vomiting, however, was not observed in these subjects.

• The sedation elicited by *chlorpromazine* (average: 380mg/day) was not relieved by treatment with L-DOPA (consistent with the 1961 report of McGeer and colleagues concerning the ineffectiveness of L-DOPA in drug-induced parkinsonism). The response to L-DOPA by these subjects, on the other hand, was blunted; in subjects who had received chlorpromazine over the previous seven days, doses of 500mg L-DOPA were tolerated without any noticeable reaction.

• The pressor effects of L-DOPA were enhanced in patients who had received 240-600mg *vitamin B6* (p.o. or i.m.) immediately before L-DOPA administration; additional treatment with reserpine did not modulate this effect. The authors had planned to employ vitamin B6 to counter the emetic effects of L-DOPA, but abandoned the idea following this experiment.

• L-DOPA (350mg) did not influence the narcosis induced by various *hypnotica* in five attempted suicides, nor was the hemostatic effect of L-DOPA modulated by prior exposure to these drugs.

The Degkwitz-Frowein group thus presented an impressive account of the effects of L-DOPA in humans under various pharmacological circumstances. The report was, however, unfortunately incomplete with respect to the design of the investigation and the responses of individual subjects; the results as presented are, in fact, somewhat incomplete. Most importantly, the authors did not mention whether parkinsonian effects had been elicited by reserpine treatment or reversed by L-DOPA. Such a comment may have drawn more attention, as the focus of clinical interest with respect to the effects of L-DOPA was certainly in the area of parkinsonism. A brief summary at the end of the paper concluded with the comment that:

*The sedation which occurs during treatment with reserpine could frequently, from the fifth day of reserpine treatment onwards, be impressively relieved for a time by L-DOPA.*

The authors did not, however, discuss the broader clinical potential of this phenomenon. On the basis that it antagonized the effects of reserpine, Carlsson had suggested in June 1959 (that is, probably before the submission of the Frankfurt paper) that L-DOPA could be of benefit in Parkinson’s disease. The Frankfurt group does not appear to have drawn this conclusion; there is certainly no indication that L-DOPA was tried in the few Parkinson’s disease patients at the clinic. A report on a Parkinson’s disease patient treated by Degkwitz in 1959 indicates that he prescribed only the belladonna extract which had been in use in Germany since the 1930s, ‘Homburg 680’.

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27 Degkwitz *et al*., 1960.
28 *Ibid*.
29 Record viewed in archives of Frankfurt Psychiatric Clinic. The record of a post-encephalitic patient treated by another neurologist from 1955 to 1959 indicated that his normal medication consisted of ‘Homburg 680’ and benzhexol. Interestingly, this patient was administered reserpine on one occasion in 1955, resulting in “lack of air, sialorrhea, intensification of the tremor”.
Further, dopamine was not regarded by these workers as mediating the effects of L-DOPA; in the introduction to their paper, they had remarked:

*Even if the results to be expected from our experiments can largely be predicted on the basis of already published animal experiments and the study of adrenaline and noradrenaline, it must also be remembered that DOPA differs from the catecholamines derived from it (adrenaline and noradrenaline), in that, amongst other factors, it is able to move from the blood into brain cells.*

There exists the outline of an application by Frowein (and signed by the Director of the Clinic, Professor Jürg Zutt) for support from the DFG for the continuation of the group’s investigations of biogenic amines; it is dated June 18 1959, and its contents indicate that it was written after the results described in their paper had been achieved. According to this application, reserpine had proved to be of especial benefit in psychotic states, and, according to the research of Holtz, probably exerted its effects by depleting central stores of adrenaline, noradrenaline and serotonin. The applicant argued that changes in biogenic amine metabolism might be involved in the production of endogenous psychotic states; up till this point, however,

*there has been, as far as we know, a complete lack of a more exact psychopathological elucidation of the effect of reserpine in humans, as well as of the attempt to correlate its effects with changes in the metabolism of the biogenic amines.*

Zutt proposed that his group would undertake these investigations:

*It is planned, by the administration of reserpine and of drugs which inhibit the catabolism of the biogenic amines on the one hand, and of precursors of the biogenic amines on the other, to alter the tissue content of biogenic amines, especially in the brain, to measure these changes and to correlate them with the elicited changes in the psychic state of humans, healthy as well as psychiatrically ill. We have conducted preliminary investigations in recent times which suggest that important results are to be expected from such an investigation.*

The application mentions that these preliminary investigations indicated that L-DOPA relieved the effects of reserpine treatment, and that its efficacy was dependent upon the length of the reserpine cure and possibly the underlying disease state. Metabolic changes, including water balance, carbohydrate metabolism and cardiovascular parameters, had also been assessed, as were changes in the EEG. Similar studies with monoamine oxidase inhibitors had also begun. The DFG was asked to support the costs of a physician and a technical assistant to carry out these investigations, and to grant 3,000DM per year for material costs; Professor Holtz was to be involved in the project as advisor.

It is not clear what became of this project. Degkwitz published a report in 1960 on his experiences following self-administration of iproniazid (275mg/day for two periods of three weeks). As already noted, this style of “auto-experimentation” was not at all uncommon in the history of neuropharmacology. In 1966, Degkwitz reported on his week-long self administration of each of no less than twelve “psycholeptica” (including

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30 Degkwitz et al., 1960.
31 Letter, Zutt to the Deutsche Forschungsgemeinschaft, 18.06.59.
32 Ibid.
33 Degkwitz, 1960.
orphenadrine, phenglutamic acid and biperiden), as well as of placebos. Degkwitz explained the philosophy underlying this approach:

Prescribing psychoactive agents for psychiatrically ill patients produces an interaction between the effects of the prescribed agents themselves (Eigenwirkung) and the reactivity of the patient. As doctors, we expect that this interaction results in a cure or, at least, an improvement with respect to the severity of the disease. If you attempt to approach this issue scientifically, the question must be answered as to what effects, psychic and somatic, these agents exert on healthy people.34

Following their 1960 paper, the next paper to emerge from the Frankfurt group as a whole (and the last which included both Degkwitz and Frowein as authors) appeared in March 1962; it discussed the “normal hourly excretion values of 5-HIAA in the urine of humans and factors which affect these values.”35 The continuity of philosophy with the previous work was recognizable, and the 1959 application to the DFG had mentioned the assessment of central biogenic amine metabolism via the urinary excretion of their metabolites. The focus of the group had now shifted, however, to serotonin and its modulation by reserpine, 5-HTP administration and monoamine oxidase inhibition. The influence of certain fruits and nuts (in particular, the walnut) on the excretion of 5-HIAA was also discussed. At the meeting of the Frankfurt Medical Society in mid-1962, Degkwitz held a talk on the “treatment of acute agitation and its theoretical basis”,36 while Frowein spoke on “the prognosis of degenerative brain processes.”37 E. Kirberger, who was co-author on the most recent paper from the group, made a presentation on the “investigation of serotonin metabolism”, in which the results of the group’s most recent paper were again discussed.38 This direction was further pursued by Degkwitz over the next few years; in 1963, he reported the elevation of urinary 5-HIAA following ingestion of caffeine, ‘Pervitin’ (methamphetamine) or phenmetrazine (‘Preludin’, an anti-anorexic agent);39 a short paper in January 1964 reported that the normal sleep-wake rhythm of 5-HIAA excretion was not observed in patients with depression or mania.40

By 1965, however, Degkwitz had concluded that no conclusions regarding central serotonin metabolism and its modulation by pharmacological agents could be drawn from measurements of urinary 5-HIAA.41 Kirberger, on the other hand, continued to pursue the question as head on the Central Laboratory at St Mark’s Hospital in Frankfurt.42 Kulenkampff was appointed associate professor at Frankfurt in 1962, before being appointed full professor in Düsseldorf in 1967. Apart from geriatrics, his major interests from this time were social psychiatry and the interaction between psychiatry, psychology and sociology.43

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34 Zlatníková et al., 1974.
35 Degkwitz et al., 1962a. The same themes were treated at the 1962 Symposion for Psychopharmacology: Degkwitz et al., 1962b.
36 Degkwitz, 1962.
37 Frowein, 1962.
38 Kirberger, 1962.
40 Degkwitz et al., 1964.
41 Degkwitz, 1965.
42 See, for example, Kirberger, 1966.
43 Strute and Doelken, 1981.
The *Reports of the DFG* indicate that grants were received by Zutt for projects entitled “Psychopharmacological investigations with particular reference to the biogenic amines” and “The modes of action of various groups of psychopharmaca” between 1960 and 1963, but I have not located any publications on these topics bearing Zutt’s name, and these titles probably refer to the work already discussed above. Neither Frowein nor Degkwitz appear to have returned to the investigation of the effects of L-DOPA. This is not surprising in light of the fact that they were psychiatrists and not neurologists, and that L-DOPA was ineffective in the treatment of phenothiazine-induced parkinsonism. Degkwitz, however, published in July 1963 a major review of the available drugs employed in the treatment of extrapyramidal motor disorders; the bulk of this paper concerned the treatment of parkinsonism. In his brief historical introduction, Degkwitz remarked that “a completely new approach” had become possible following the discovery by Ehringer and Hornykiewicz that dopamine, noradrenaline and serotonin levels were reduced in the parkinsonian brain; specifically, DOPA might be used to treat the disease, as dopamine is unable to cross the blood-brain barrier. In his catalog of pharmaceuticals, however, L-DOPA is not accorded any special emphasis; Degkwitz briefly noted its role as precursor of the catecholamines, the fact that it was soluble in boiling saline, that intravenous doses of up to 350mg were tolerated, and that its side-effects included nausea, palpitations, sweating and vomiting. He referred to papers by Birkmayer and Hornykiewicz and McGeer *et al.*, as well as to his own, for reports on clinical experience with the drug.

In the following detailed discussion of the treatment of specific parkinsonian symptoms, however, Degkwitz makes some interesting comments relating to the 1960 report which were not included in the original publication. He described the findings of Ehringer and Hornykiewicz and of Bertler and Rosengren, and wrote that they led to the attempt by the Frankfurt group:

> to compensate the deficit in patients. DEGKWITZ, FROWEIN, KULENKAMPFF and MOHS therefore gave reserpine-treated patients L-DOPA and could thereby break through the akinesia of the drug-induced Parkinson syndrome.

This interpretation of his own results was new; parkinsonian symptoms had not been mentioned in the 1960 paper, let alone that they were the stimulus for the use of L-DOPA. Degkwitz then described the method of Birkmayer and Hornykiewicz, which, as acknowledged by the Viennese pair, corresponded to that of the Frankfurt group. After describing in detail the Viennese findings regarding the relief of akinesia by L-DOPA, Degkwitz remarked in contrast:

> We have not been able to observe this effect with Parkinson patients in our clinic. We have thus far, however, treated only seven patients.

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45 Degkwitz, 1963. Extensive reference to this paper was made in chapter VII.

46 Ibid.

47 Ibid.

48 Ibid.
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Further, in his summation of the "relatively effective medications" for Parkinson’s disease, L-DOPA was not mentioned. He was not alone in this opinion at the time. There were a number of reasons for this, including the cost of producing L-DOPA; but Degkwitz was certainly not subject, on the other hand, to the same degree of skepticism regarding the role of catecholamines in central neural processes which inhibited the acceptance by many psychiatrists and neurologists of a neurochemical “replacement therapy”. As with Sano in Japan and McGeer’s group in Canada, his initial clinical observations were simply not sufficiently positive to motivate perseverance with a therapeutic approach which was far from problem-free. By 1965, Degkwitz was convinced that any benefit of L-DOPA (or of MAO inhibitors, for that matter) could be attributed to a placebo effect induced by the complicated method of administration, and he was not particularly impressed by either the magnitude or the reliability of even this effect.49

Degkwitz became an associate professor at Frankfurt in 1964; after a year as director of the district psychiatric hospital in Weissenau, he was appointed full professor and director of the Neurological Clinic at the University of Freiburg in 1968, where he continued his involvement in psychopathological and psychopharmacological research. From 1967 onwards, he authored a number of papers concerning extrapyramidal syndromes arising in the course of treatment with neuroleptics, including a detailed review in 1969 (“L-DOPA treatment of the Parkinson syndrome and the mechanisms underlying the effects of neuroleptics”).50 The opening of his concluding paragraph in this paper was highly interesting:

The agreement between the biochemical findings, the theoretical ideas and the clinical observations with respect to the Parkinson syndrome and the modi operandi of psycholeptics (collective term for neuroleptics and tricyclic thymoleptics) is striking. This is very rare in medicine. This concept will thus probably have to be modified.51

Apart from authoring a number of clinical textbooks (“Introduction to psychopharmacology for the clinic and practice”, 1967; “Mental illness. Introduction to psychiatry for clinical students” (with S.O. Hoffmann and H. Kindt), 1982), Degkwitz also edited the German edition of the “International Classification of Diseases” (1975) and a number of other books dealing with psychiatry and its history.

When addressing the question of the significance of the Frankfurt experiments with L-DOPA, it should be remembered that the Degkwitz-Frowein group was more concerned with psychiatric illness, especially depression and schizophrenia, than with specific disorders of old age, such as Parkinson’s disease. An examination of the patient lists for the Frankfurt clinic indicate that the number of Parkinson’s disease patients, of whatever etiology, was indeed quite small. The interests of this group were therefore of a fundamentally different nature to those being examined at approximately the same time in Vienna, Montreal and Osaka. It is therefore unsurprising that the application of L-DOPA in natural parkinsonism was not immediately pursued in Frankfurt; in any case, most cases of medicament-induced parkinsonism in psychiatric hospitals at this stage were attributable to halogenated phenothiazines, and such cases do not respond to L-DOPA therapy. A short time later, McGeer’s group would also report that the effects

49 Degkwitz, 1966a; this is a résumé of a presentation by Degkwitz at a Congress for Natural Healing Methods in 1965.
50 Degkwitz, 1969.
51 Ibid.
of L-DOPA described by Birkmayer and Barbeau could not be reliably reproduced in their own patients, who similarly suffered from drug-induced parkinsonism. This was probably one of the major reasons for the slow acceptance of L-DOPA therapy; it was generally acknowledged that neuroleptic-induced parkinsonism was easier to treat than either post-encephalitic or idiopathic parkinsonism, at least as far as the synthetic anticholinergic drugs were concerned. Because of its different mode of action, L-DOPA therapy did not, however, help these patients, arousing doubts in the minds of many neurologists.

Another reason for the failure of the Frankfurt group to extrapolate their results to natural parkinsonism was that Degkwitz and his colleagues, unlike the Vienna and Montreal groups in the next year, did not have any evidence of biochemical changes in Parkinson’s disease to guide them. For instance, Frowein wrote to Professor Faust (Freiburg University Psychiatric Clinic) in November 1959 that he felt it would not be useful in a review to be presented at an upcoming conference to describe individual research results which pertained to the biochemical basis of depression:

> In the end, one can indeed say that, from all the investigations which have been conducted, results have not emerged which enable us to say anything about the cause of depression, or even to be regarded as being its cause. . . . That the pathophysiological research has thus far “failed so miserably” (as it was once put) is actually surprising in the case of depression, in which the symptomatology and course suggest so strongly a biological basis.

Clinical neurochemistry was only beginning to emerge in 1960. Workers such as Frowein and Degkwitz believed in the biochemical foundation of nervous disorders and were assiduously searching for answers on this basis, principally by careful observation of the effects of various psychoactive agents both on patients and on healthy volunteers, including themselves. Direct evidence of the type which Ehringer and Hornykiewicz would present later in 1960, however, was lacking; and it was precisely this type of information which was required to enable an efficient pursuit of any rational biochemical therapy. The inductive reasoning which the Frankfurt other and groups applied to the questions they investigated was remarkably fruitful, but it was the development of reliable and sensitive assay techniques which could detect significant changes in human biochemistry which would expedite the development of neurochemistry. This was, indeed, the approach which Degkwitz and his co-workers adopted from 1960 onwards: not only to note subjective responses and measure physiological parameters such as blood pressure, but to analyze the effects of these drugs on the excretion of chemical neurotransmitters and their metabolites. That Degkwitz and his colleagues had recognized the significance for the clinic of the animal results of Carlsson’s group was in itself interesting, given the delay with which this occurred in the rest of the world; that they chose to apply L-DOPA, and not the racemic form of the amino acid, despite the cost involved, was even more momentous, and paved the way for its employment in Parkinson’s disease. At the same time, the focus for these workers had moved from the catecholamines to serotonin, and thus away from further involvement in the story of the treatment of Parkinson’s disease.

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52 McGeer et al., 1961.
53 Letter, Frowein to Professor C. Faust, 19.11.59 (held in Frowein file in archive of Frankfurt Psychiatric Clinic I).
XI. The first L-DOPA trials in the clinic: Frankfurt and Osaka

Following the Degkwitz paper, Pollin, Cardon and Kety (National Institute of Mental Health, National Institutes of Health, Bethesda) appear to have been the first to have applied L-DOPA in humans. This group was examining the effect of “amino acid feedings” in schizophrenic patients treated with iproniazid; none of nine amino acids tested had an effect on patient behaviour, with or without the MAO inhibitor. Four patients received intravenous L-DOPA once daily, starting with 6mg and increasing over a period of two weeks to 108mg (except for one patient, whose reaction dictated the cessation of treatment at 96mg); transitory hypertension, brachycardia and ventricular extrasystoles were observed at the higher doses. Interestingly, this was one of the few occasions on which L-DOPA or the intravenous route of administration was employed in America (apart from Friedhoff’s 1961 trial, to be discussed in chapter XII).

Isamu Sano and the first Japanese L-DOPA trial

The fact that DOPA therapy in parkinsonian patients was examined in Vienna and Montréal at the beginning of the 1960s is relatively well known, even by those who regard Cotzias as the true founder of L-DOPA therapy. Almost completely forgotten, on the other hand, is a paper presented by a Japanese group in 1960 which reported what is probably the first attempt to treat Parkinson’s disease patients with DOPA. This is all the more remarkable as the author, Isamu Sano, had also been responsible for two of the key papers which directly led to the consideration of the use of DOPA in Parkinson’s disease (as discussed in the previous chapter).

Sano’s group had commented in early 1959 that the depletion of dopamine, and not serotonin, was more likely to be responsible for reserpine-induced parkinsonism. Sano’s group had also observed the effects of DOPA administration on dopamine levels in reserpine-treated guinea pigs, but did not discuss the practical significance of these findings for human disease in this paper. But less than a month after the publication of the paper reporting these results, Sano reported at the First Symposium for Neuropathology in Tokyo (6 February 1960) the experimental treatment of parkinsonian patients with D,L-DOPA. This presentation then appeared in the October 1960 issue of the Japanese journal Shinkei Kenkyu no Shinpo (“Advances in Neurological Sciences”); this paper was recently published for the first time in English translation in Parkinsonism and Related Disorders. The paper, titled “Biochemistry of the extrapyramidal system”, discussed a variety of issues in current catecholamine research. Relevant to the present discussion is that in the middle of his presentation, Sano reported that he had examined the dopamine levels in specific brain regions of a deceased parkinsonian patient, and found them to be significantly reduced when compared with the levels reported in his 1959 paper; the most dramatic declines were found in the substantia nigra and striatum. The decline in striatal dopamine levels was comparable with that reported by Ehringer and Hornykiewicz later that year for two cases of idiopathic parkinsonism (table 11-2). He interpreted this finding cautiously, as he was aware that the patient had been treated with benzhexol and mepazine for the five months prior to death. Sano had also confirmed the effects of MAO inhibition on the catecholamine content of the animal brain reported in 1960:

54 Pollin et al., 1961.
55 Sano et al., 1960b.
56 Sano, 2000; with introductory remarks by myself and colleagues.
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[B]rain concentrations of DA and NA increased significantly following the administration of the monoamine oxidase inhibitors IIH (iproniazid) and JB516 (pheniprazine). Although serotonin levels were also increased, the most marked change was that of DA.57

As a result, Sano had treated an undefined number of patients with infusions of D,L-DOPA (200mg) or JB-516 (12mg). The results were promising, in that rigidity and tremor were improved by DOPA, at least for a few minutes; JB 516 appears to have had a more impressive effect on tremor in some patients, but was found to be “no better than trihexyphenidyl [benzhexol]”, a somewhat curious comment. Sano concluded that the DOPA effect was only transient, and that further studies were required to establish whether either DOPA or MAO inhibitors would play a role in Parkinson therapy. He reported the interesting fact that the patients themselves regarded the combination of DOPA and MAO inhibitor as the most effective treatment; despite the animal findings reported in his Klinische Wochenschrift paper, however, Sano does not seem to have explored this phenomenon further.58

<table>
<thead>
<tr>
<th></th>
<th>Normal NA (µg/g wet tissue)</th>
<th>Normal DA (µg/g wet tissue)</th>
<th>Parkinson's disease NA DA (µg/g wet tissue)</th>
<th>Parkinson's disease DA (% change)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N. caudatus: Sano</td>
<td>0.04</td>
<td>5.74</td>
<td>2.88</td>
<td>50%</td>
</tr>
<tr>
<td>N. caudatus:</td>
<td></td>
<td></td>
<td>0.08</td>
<td>69% (IP)</td>
</tr>
<tr>
<td>Hornykiewicz</td>
<td>0.09</td>
<td>3.5</td>
<td>0.02</td>
<td>94% (PE)</td>
</tr>
<tr>
<td>Putamen: Sano</td>
<td>0.07</td>
<td>8.25</td>
<td>0.24</td>
<td>97%</td>
</tr>
<tr>
<td>Putamen:</td>
<td></td>
<td></td>
<td>0.7</td>
<td>78% (IP)</td>
</tr>
<tr>
<td>Hornykiewicz</td>
<td>0.12</td>
<td>3.7</td>
<td>0.3</td>
<td>92% (PE)</td>
</tr>
<tr>
<td>Pallidum:</td>
<td></td>
<td></td>
<td>0.12</td>
<td>37%</td>
</tr>
<tr>
<td>Sano</td>
<td></td>
<td></td>
<td>0.23</td>
<td>80% (PE)</td>
</tr>
<tr>
<td>Pallidum:</td>
<td></td>
<td></td>
<td>0.15</td>
<td></td>
</tr>
<tr>
<td>Hornykiewicz</td>
<td></td>
<td></td>
<td>0.23</td>
<td></td>
</tr>
<tr>
<td>S. nigra/N. ruber:Sano</td>
<td>0.07</td>
<td>0.38/1.17</td>
<td>0.24</td>
<td>36%/89%*</td>
</tr>
<tr>
<td>S. nigra:</td>
<td></td>
<td></td>
<td>0.04</td>
<td>85%</td>
</tr>
<tr>
<td>Hornykiewicz</td>
<td></td>
<td></td>
<td>0.46</td>
<td></td>
</tr>
</tbody>
</table>

Table 11-2: Reported values for the dopamine and noradrenaline levels in several brain regions in normal and Parkinson’s disease brains. (Sano et al., 1959a and Sano, 1960; Ehringer and Hornykiewicz, 1960 (caudate, putamen, pallidum) and Hornykiewicz, 1963 (substantia nigra). IP, idiopathic parkinsonism; PE, post-encephalitic parkinsonism; otherwise, form of parkinsonism not indicated. *Sano et al. (1959a) reported separate figures for the substantia nigra and nucleus ruber, but Sano (1960) analyzed the two regions together; the figure calculated here can therefore only be seen as illustrative, as it cannot be determined in which nucleus the loss occurred.

58 Ibid.
This trial of DOPA as a treatment for parkinsonism thus preceded those of both the Viennese and the Montreal groups which will be discussed in the next chapter; why has it been forgotten? The fact that it was published in Japanese was certainly significant. But almost as important is the fact that Sano appears to have shared the general skepticism concerning the therapeutic value of DOPA which persisted in neurological circles throughout the 1960s. The report of his DOPA trial was made almost in passing as part of a broader discussion of the neurochemistry of the extrapyramidal system; with the stock comment that "further studies are required", he quickly passed on to the discussion of a novel degradation pathway for dopamine which he linked to melanin formation and, more speculatively, with the hallucinogenic properties of mescaline. This was related to the hypothesis of abnormal methylation reactions being involved in schizophrenia, which Sano also investigated in the late 1950s and early 1960s. It had also been recognized about this time that a series of alkaloids which showed methylation of the p- or 4-hydroxyl group of dopamine (that is, methylated phenylethylamine derivatives) elicited catatonia in a range of laboratory animals; one of these agents was bulbocapnine.59

It is clear that Sano regarded dopamine as more than merely an intermediate:

\[
\text{only a small portion of DA is converted to NA. DA has its own degradative metabolic pathway and its localization is independent, so we must consider that it has its own functional significance.}^{60}
\]

His disinterest in the fact that a combination of DOPA and MAO inhibitor elicited the greatest subjective response in his patients is thus all the more puzzling; he had already found that this combination elevated central dopamine levels five-fold, but noradrenaline concentrations were not so dramatically affected, being increased only two-fold. DOPA by itself elicited only small changes in noradrenaline concentrations in his animal experiments, but dramatic dopamine increases.61 Despite these results,

Nor did Sano’s audience at the 1960 Tokyo Symposium for Neuropathology express great interest in the use of DOPA in Parkinson’s disease; the only question touching on this part of Sano’s presentation was an (unanswered) enquiry from the biochemist Dr Makino as to whether methoxy-DOPA might elicit parkinsonian symptoms.62 It thus appears that Sano’s report did not excite much interest amongst his immediate colleagues, which probably discouraged him from further expensive experiments and certainly from submitting his preliminary observations to an international journal. Sano himself did not cite his own report until 1972. In fact, I am aware of its being mentioned in print only twice since its publication. The first citation was by Ohama and Ikuta (Institute of Brain Research, Department of Neuropathology, Niijjeka University, Niijjeka) in their 1976 investigation of the neuropathology of Parkinson’s disease, where Sano was listed amongst those who had first identified the dopamine deficiency in this disorder; the DOPA trial was, however, not mentioned in this paper.63 Secondly,

59 See Smythies and Levy, 1960; Ernst, 1962. The first paper was largely concerned with mescaline, one of the psychoactive substances which had interested Louis Lewin. Amongst the errors in the translated version of Sano’s 1960 paper is that mescaline is described as "trihydroxyphenylethylamine"; it is, in fact, trimethoxyphenylethylamine.

60 Sano, 1960/2000. Sano apologized at the end of this presentation for his apparent obsession with dopamine.

61 Sano et al., 1960.


63 Ohama and Ikuta, 1976.
Narabayashi (Department of Neurology, Juntendo University, Tokyo) referred to Sano’s DOPA trial in his 1985 review of the history of L-DOPA therapy in Japan, regretting that it had not attracted wider attention.\(^{64}\)

It is also significant that Sano was forced by financial considerations to use the racemic form of DOPA. This factor later motivated Birkmayer and Hornykiewicz to choose the intravenous route for the administration of L-DOPA, although these investigators had found that larger oral doses were equally effective. As D-DOPA is of no benefit for parkinsonian patients,\(^{65}\) it is also conceivable that the inactive isomer may reduce the efficacy of the L-DOPA component of the racemic form. The scientific climate of the time must also be considered. As already mentioned, it was by no means established in the early 1960s that chemical transmission plays a major role in the central nervous system, let alone that dopamine was a neurotransmitter. It is interesting that Sano’s 1959 paper was first cited in a 1960 review of “chemical transmission in the central nervous system” which examined a range of candidate substances, including acetylcholine, sympathin, serotonin, substance P, histamine and ATP – but not dopamine. Sano was instead cited regarding the distribution of noradrenaline in the human brain, while the dopamine results were not mentioned.\(^{66}\)

In the only other major paper from the Sano group regarding L-DOPA, published in 1964, the authors commented in their introduction that a function for amines as transmitters in the central nervous system “has never been supported by experimental evidence.”\(^{67}\) This was a surprisingly strong statement, given that Sano had spent a great deal of time in Europe and must have been aware of the emerging recognition there of a transmitter role for catecholamines in general and for dopamine in particular. The paper described their investigation of the effects of L-DOPA on carbohydrate metabolism in the mouse brain; they found that L-DOPA elicited an increase in brain glycolysis without an effect on inorganic phosphate levels. Parkinson’s disease was not mentioned in this paper, and the authors seemed unaware that earlier workers (including McCowan and colleagues in the 1930s and Birkmayer in the 1950s)\(^{68}\) had also identified aberrant carbohydrate and phosphate metabolism in Parkinson’s disease patients.\(^{69}\)

The fact is, however, that it was far from clear in 1961 what significance should be attached to the striatal dopamine deficit detected by Hornykiewicz and Sano, and the benefit of administering an amino acid long associated with nothing so much as intense vomiting seemed doubtful. L-DOPA therapy was thus initially trialled in only a few clinics, and was not generally rewarded with the spectacular success which marked Birkmayer’s initial experiments. It was characteristic for this period that the clinician exercised a great deal of freedom with regard to his experimentation with new medications, as explained above by Doshay. The testing of new therapies was consequently dependent on the attitude of the clinician to the disorder with respect to its underlying causes, its significant symptoms and the prospects of its being effectively managed, and to his interpretation of the responses of his patients to any particular drug. Sano, like many clinicians, was not impressed by the initial response of his patients to

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64 Narabayashi, 1985.
65 Birkmayer and Hornykiewicz, 1962.
67 Kakimoto et al., 1964.
68 McCowan et al., 1926a, 1926b; Birkmayer and Weiler, 1956.
69 Kakimoto et al., 1964.
XI. The first L-DOPA trials in the clinic: Frankfurt and Osaka

DOPA, and thus appears to have abandoned the therapy completely; Hornykiewicz has told me that Sano never mentioned the trial to him, although he was a frequent visitor to Vienna in the first half of the 1960s. Birkmayer, in contrast, was fortunate enough to achieve spectacular initial successes which carried him through the subsequent difficult period of systematically proving the worth of the drug.

The biochemical methods employed by Sano were both insensitive and non-specific compared with today’s methods, as were those of Hornykiewicz; it was the high dopamine concentrations in the basal ganglia and their sharp decline in parkinsonism which allowed the breakthroughs they achieved in this regard. Sano did not indicate from which form of parkinsonism his patients suffered. It is, however, noteworthy that the reduced dopamine concentrations observed in Vienna and Montreal were greatest in post-encephalitic parkinsonian patients; in fact, Barbeau’s group reported no difference between controls and idiopathic Parkinson’s disease patients with respect to urinary dopamine excretion,\textsuperscript{70} and the post-encephalitic patient group in Vienna also exhibited the most dramatic responses to L-DOPA.\textsuperscript{71} This luck with regard to the patient collective no doubt also played a role in the history of the therapy.

In the absence of a clearly defined mechanism of action for L-DOPA, and in light of the fact that the existence of the nigrostriatal pathway, which provided a link between the nigral lesion and reduced striatal dopamine levels, was not recognized in 1960, it is not surprising that the less than overwhelming success of L-DOPA as a monotherapy for the treatment of parkinsonism should have been regarded by so many workers with some suspicion. This is especially true given the series of disappointments with other “miracle drugs” for the disorder. Sano thus abandoned this particular avenue of research and turned his attention to other neurochemical questions concerning the role of biogenic amines in neurological disease. The next major paper from Sano’s group appeared in \textit{Nature} in 1963, and pursued the methylation hypothesis of schizophrenia alluded to in the paper on the biochemistry of the extrapyramidal system; it reported the increased excretion of 3,4-dimethoxyphenylalanine in the urine of schizophrenic patients, partially confirming the report from Friedhoff’s laboratory the previous year.\textsuperscript{72}

From the middle of the 1960s, Sano, together with Kakimoto and Kanazawa, was principally concerned with peptides and polyamines in the central nervous system, and published a major review on the subject in 1970.\textsuperscript{73}

Sano revisited monoamine therapy of parkinsonism in the early 1970s, but this time it was the employment of L-5-HTP in depression and Parkinson’s disease which he regarded as important. In 1972, his first paper on this subject commenced with a summary of his earlier findings regarding extrapyramidal dopamine, and included his only reference in an international journal to the D,L-DOPA trial of 1960; he explained that the expense of the drug had prohibited its further investigation.\textsuperscript{74} In a companion paper, however, he expressed disappointment that the success of DOPA therapy had since been overstated by many workers, and suggested that L-5-HTP was equally effective, albeit with a different profile of action, proving especially beneficial for the affective aspects of the disorder (depression). As L-5-HTP was particularly effective

\textsuperscript{70} Barbeau \textit{et al.}, 1962.
\textsuperscript{71} Birkmayer and Hornykiewicz, 1964.
\textsuperscript{72} Takesada \textit{et al.}, 1963.
\textsuperscript{73} Sano, 1970.
\textsuperscript{74} Sano, 1972.
against tremor, he was investigating a combined therapy of the two agents; to my knowledge, the outcome of this investigation has not been published. Sano also proposed that two forms of parkinsonism could be distinguished on the basis of the accompanying vegetative symptomatology, and related them to cell loss in different areas of the brainstem.\footnote{Sano and Taniguchi, 1972.}

What then was the role of Sano in the history of the L-DOPA therapy? He certainly deserves to be remembered as one of the pioneers in catecholamine research, and indeed as the first to identify a reduction of dopamine levels in the substantia nigra and striatum in Parkinson’s disease and to draw the appropriate conclusion. The solution to this problem was clear; but the clinical application of this solution was neither as simple nor as reliable as it first appeared, and it was also very expensive. It is, of course, not unusual that the significance of a particular finding is recognized only in retrospect; many examples of this phenomenon can be gleaned even from the pages of the present work. The persistence with which Birkmayer and Hornykiewicz pursued the L-DOPA therapy and its neurochemical basis was undoubtedly assisted by the dramatic effect achieved in their first patient; they also enjoyed the benefit of the support of a major pharmaceutical firm (Hoffmann-La Roche) and the associated access to L-DOPA. Sano lacked all of these advantages.
XII. Vienna tales:
Discovery of the dopamine deficit and introduction of \(\text{L-DOPA}\) therapy

Thudichum wrote in the German version of his pioneer work *The chemical constitution of the brain* that:

The connection between disturbances of brain function and abnormal chemical processes can be detected only with the finest chemical techniques before the disease manifests itself in an obvious manner.\(^1\)

Until the middle of the 1950s, the requisite techniques for the detection of chemical abnormalities in the brains of parkinsonian patients were unavailable; indeed there was no clear idea before this time as to what type of abnormality should be sought. By 1959, this had changed; it was now not only possible to assess monoamine levels in specific brain structures, but there was also ample reason to suspect that their assessment might yield important insights into the nature of the central nervous system deficit in parkinsonism. Carlsson's laboratory had provided the crucial impetus for such investigations with the work described above in chapter X; this group would continue to play an important role in elucidating the physiological basis of parkinsonism, as will be discussed in the next chapter. But the direct evidence for disturbed monoamine function in this disorder and the introduction of \(\text{L-DOPA}\) into antiparkinsonian therapy were made by two Viennese workers, the pharmacologist Oleh Hornykiewicz and the neurologist Walther Birkmayer.

Despite their fruitful collaboration, the relationship between the two later deteriorated. This was principally due to conflicting interpretations of the process by which \(\text{L-DOPA}\) was introduced into the clinic and the relative roles played by the two doctors in developments. Both have on many occasions spoken on and published separate accounts of their views of events in the early 1960s. As the basis for the

\(^{1}\) Thudichum, 1901.
following, I consulted all published material on the subject, especially that by Birkmayer and Hornykiewicz themselves, published scientific papers concerning the early investigation of \( \text{L-DOPA} \), and the private papers of Birkmayer.\(^2\) In addition, Hornykiewicz kindly granted me an interview of several hours in which the L-DOPA story, amongst other topics, was discussed in detail. Other researchers were also interviewed on the subject, and their memories of the events and their views have been acknowledged in the following account.

**Walther Birkmayer: Background**

Birkmayer was born on 15 May 1910 in Vienna, Austria. His father Hermann was a senior postal official, but the male Birkmayers (or Birkmeyers; both forms were used by the family until the end of the 1930s) were best known in Vienna as dancers, commencing with Hermann’s grandfather Adolf (*1836 †?), a dancer with the court theatre company, a tradition continued to the present by Walther Birkmayer’s younger cousin Michael Birkmeyer, well-known in the ballet. Birkmayer’s mother Franziska Margaretha was born in Vienna, her father Clement Jenisch, a smith, having been granted a residential permit for Vienna only in 1906; he came originally from Moravia, then part of the Austro-Hungarian Empire. Birkmayer’s maternal grandmother, Franziska Theresia, was a Bohemian Jew who converted to Catholicism on the day of her wedding. Birkmayer was an excellent pupil at school: he proudly noted in one of his biographical sketches that he was awarded the highest mark for the science project which formed part of the Matura (the leaving examination).\(^3\) Combining academic prowess with an aptitude for sports of all types, he enrolled at the University of Vienna in 1930 in both Medicine and Physical Education. These courses were also absolved with distinction, and on 5 February 1936 he was awarded his doctorate in medicine.\(^4\)

Birkmayer received a clinical appointment at the Psychiatric and Neurological Clinic of the University of Vienna, then under the leadership of Otto Pötzl (1877-1962), and had published a total of twenty-six papers in this capacity by 1940, mainly concerned with neurological impairment of movement, but also including a number biological aspects of sport.\(^5\) This period of Birkmayer’s career was brought to a sudden halt in 1940. Birkmayer had been a member of National-Socialist Party (NSDAP) and the Sturmabteilung (SA) since 1932; as leader of the Schutzstaffel (SS) Doctors’ Study Group “Donau” and member of the medical staff of the local SS section he bore the honorary rank of SS-Untersturmführer. In 1940, he applied for full membership of the SS, but was rejected because of his “incompletely Aryan pedigree”, the discovery of which by Birkmayer in 1939 could conceivably have motivated his application. He was allowed to retain his position in the university clinic but prohibited from teaching; Birkmayer thereupon volunteered for military service. He was posted as troop doctor to France and then to the Russian front; in July 1942, he was transferred back to Vienna, where he headed until April 1945 a special hospital for soldiers with head injuries.

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\(^2\) The major publications on the subject by the pair are Birkmayer, 1965, 1970a, 1971a, 1976, 1985, 1993; Birkmayer and Birkmayer, 1987; and Hornykiewicz, 1970a, 1973, 1992 and 1994. I was also granted unrestricted access to a great deal of unpublished material by Birkmayer’s daughter, Heidi Birkmayer-Ecker, to whom I extend my sincere thanks.

\(^3\) He had investigated the physical and chemical conditions which best facilitated carbon dioxide production by yeast from glucose; Birkmayer, *Licht und Schatten* (unpublished manuscript), p.34.

\(^4\) He also graduated as a licensed ski instructor.

\(^5\) For example: Birkmayer, 1938a, 1938b; 1939a, 1939b; Birkmayer and Schindl, 1939. A complete bibliography for Birkmayer is available from the author.
Despite recommendations from Pötzl (who was himself soon to be replaced as head of Psychiatry) and other neurologists, Birkmayer was relieved of all positions as a result of his political history, and was subsequently forbidden to practice medicine. In June 1948, his appeal against this decision was granted by the Austrian President.  

Birkmayer had used the years of reduced clinical activity (he had, in any case, not completely adhered to the conditions of his enforced retirement) to collate observations made by him during the war – over 3000 head injuries – in the book Hirnverletzungen (1950; English translation: Brain injuries, 1952). The monograph was a detailed analysis of the consequences of trauma to, or destruction of, specific brain regions. Several concepts were introduced in the book which Birkmayer would pursue for the rest of his life, including the potential for the rehabilitation of brain-injured patients and the multilayered nature of the individual perception of the world. One of the interesting concepts discussed in this book was that of “vegetative ataxia”, which Birkmayer had first discussed in the Wiener Medizinische Wochenschrift in 1947. It was generally believed at the time that the sympathetic and parasympathetic divisions of the autonomic, or vegetative, nervous system responded to change in an antiparallel fashion. The systematic re-examination of his patient collective had suggested to Birkmayer, however, that many patients with head injuries exhibited what he termed a “dissociated response” to a challenge with adrenaline or insulin; the expected rise in blood pressure was accompanied by a decline in pulse rate and leukocyte count. This “functional change” in vegetative responsiveness explained for Birkmayer the phenomenon whereby those who had sustained injuries to the brain, particularly in the area of the brainstem, responded abnormally to stress associated with alcohol, certain weather patterns and psychological change. That there was a physiological basis for all medical complaints, whether psychiatric or otherwise, was fundamental to Birkmayer’s understanding of medicine, combined with the constant and bi-directional interaction of environment and organism.

Under the influence of knowledge emerging during the 1950s regarding the biochemical basis of brain function, and particularly of the reticular activating system, Birkmayer developed this concept further in his second book (together with the internist W. Winkler), Klinik und Therapie der vegetativen Regulationsstörungen (1951, Vienna). He proposed that it was conceivable that vegetative ataxia could also be manifested in patients who had not sustained obvious physical brain trauma. An inborn error of metabolism or other illness, for example, could challenge the vegetative system to such an extent that spontaneous restoration of a balanced condition was no longer possible. This interest in the vegetative control functions of the brainstem would lead Birkmayer to the investigation of Parkinson’s disease.

The other major factor which led in this direction was the fact that Birkmayer, having been appointed Lecturer in Neurology and Psychiatry at the University, was in 1954 appointed Director of the Neurological Section of the Vienna Geriatric Hospital in the Viennese suburb of Lainz. This section itself accommodated about 300 patients, and the most common degenerative disorders were parkinsonism, multiple sclerosis and

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6 The details on Birkmayer’s biography presented here are based on letters and other documents contemporary with the events described.

7 The various aspects will be explored in a separate work dealing specifically with the life and work of Birkmayer, as will the controversy concerning his political activity during the period of the Third Empire.
dementia; the staff, however, were also responsible for the outpatient treatment of those with psychiatric-neurological complaints in the other departments of the hospital. In his book Institutional neurology. Clinic and therapy of chronic diseases, Birkmayer wrote that his experience in this institution had provided him with a solid basis for the discussion of the disease:

... apart from the 60 Parkinson's disease patients currently in the department, I also had access to the patient records and post mortem examination reports of the 100 postencephalitic parkinsonian, 41 Parkinson's disease and 50 arteriosclerotic parkinsonian patients who had stayed in the hospital during the previous ten years.

Birkmayer had concerned himself extensively with the vegetative responsiveness of his parkinsonian patients and had meticulously observed, for instance, the altered response of parkinsonian patients to challenge with adrenaline; although a rise in blood glucose occurred, its magnitude and duration was reduced in comparison with normal persons, and the decline in phosphorus levels normally observed to accompany this change was absent. The change was similar in postencephalitic and idiopathic patients. Further, he did not achieve a drop in blood pressure with \( \alpha \)-methyl-DOPA. Birkmayer saw this "vegetative rigidity" as characteristic for these patients.

Oleh Hornykiewicz: the background

Hornykiewicz was born in Sichov in Galicia (then part of the Austro-Hungarian Empire, now in Ukraine) on 17 November 1926. His father Theophil was a high school teacher; his mother Anna née von Jaworski was a member of an old aristocratic family. Hornykiewicz received his schooling in Lviv until 1940, when his parents left the Soviet Union for Vienna; after completing high school during World War II, he commenced medicine at the University of Vienna and was awarded his doctorate in 1951. After a brief period at the Rudolfiner Hospital, Hornykiewicz commenced his scientific career as a research assistant in the University Department of Pharmacology, then under the directorship of Franz (von) Brücke, a position he retained for the next sixteen years.

Hornykiewicz denoted as the turning point in this period the advice of his supervisor, Adolf Lindner, to apply for the British Research Council scholarship which provided him with eighteen months' valuable experience under the tutelage of Hermann Blaschko in the Department of Biochemistry at Oxford University (Dean: Hans Krebs). Hornykiewicz arrived in England at the end of 1956, and was immediately assigned the task of repeating in the laboratories of Professor J.H. Burn the 1942 experiments of Holtz and Credner concerning the effect of dopamine on blood pressure in the guinea pig. Blaschko’s contribution to the investigation of dopamine, together with the work which Carlsson’s laboratory was publishing at this point, has already been discussed above. Blaschko was dubious about Holtz’ interpretation that the depressor effect of dopamine was attributable to its acetaldehyde metabolite. He thus asked Hornykiewicz to examine the effects not only of L-DOPA and dopamine, but also those of epinephine
(which, like dopamine, could also be oxidized to 3,4-dihydroxyacetaldehyde) and the MAO inhibitor iproniazid. The crucial outcome of these experiments was the demonstration that dopamine itself, and not a metabolite, was responsible for the vasodepressor effect observed, the first indubitable demonstration that dopamine could exert specific physiological effects without further metabolism. This marked the commencement of Hornykiewicz’ involvement in the examination of a substance which up until this time was virtually unknown to him.

Hornykiewicz returned to Vienna in early 1958, eager to further pursue the biochemistry and function of dopamine (Blaschko had given him the advice on his return to Vienna: “Oleh, you should stick to dopamine – dopamine has a bright future”). Equally importantly, he had acquired in Oxford command of the best available methodologies for measuring catecholamines in biological tissues. But his interest now concerned its role in the brain rather than in the periphery, and he turned his attention to the effect of neuroleptics and MAO inhibitors on catecholamine (and, to a lesser extent, 5-HT) levels in the central nervous system. The first paper arising from his work in Vienna concerned an investigation of the effects of monoamine oxidase inhibition on dopamine levels in the rat brain, was published with Georg Holzer in 1959. Both harmine (reversible MAO inhibitor) and iproniazid (irreversible MAO inhibitor) elevated total brain dopamine levels (by 65% and 32% respectively); iproniazid also prolonged the duration of the rise in dopamine levels. Cocaine, chlorpromazine and bulbocapnine were without effect on central dopamine levels. The iproniazid effect could be blocked by prior administration of harmine, indicating a common point of attack for the two inhibitors (as also found by Pletscher and Besendorf). Interestingly, the effect of DOPA does not seem to have been investigated at this point. It was also established that the dopamine turnover rate in brain was high, suggesting to Hornykiewicz that dopamine might “be actively involved in the functional mechanisms of the brain.”

**Birkmayer, Hornykiewicz and Parkinson’s disease**

By 1958 at the latest, Birkmayer was convinced that abnormal transmitter release was responsible for the symptoms of Parkinson’s disease. In particular, his attention was drawn to the

> phasic crises involving vegetative and affective irritation, such as salivation, oiliness of the skin, seborrhea, sweating attacks, flushes, hyperthermia, edema in the legs, depression, phases of sleep, eating and crying disturbances, but also transitional phases of insufficient social adjustment.

This clinical picture led him to the hypothesis that disturbed transmitter function underlay parkinsonian symptomatology, and that, specifically, uncontrolled release of hypothalamic 5-HT was responsible for the vagomimetic effects, and that of noradrenaline for the akinesia and depression of parkinsonism. Walter Danieleczyk, who had come to Lainz complete his neurological training under Birkmayer, had stimulated

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12 Hornykiewicz, 1958.
14 Holzer and Hornykiewicz, 1959; Pletscher and Besendorf, 1959.
15 Holzer and Hornykiewicz, 1959.
16 Birkmayer, 1971a.
the interest of his mentor in 5-HT with a presentation at the regular Wednesday morning journal club meeting; as a result, Birkmayer had asked him to examine the effect of 5-HT on the vegetative nervous system.\textsuperscript{17} Further, von Euler and Gaddum had identified high levels of substance P in the brainstem,\textsuperscript{18} while Gaddum’s laboratory later reported that the highest levels above the brainstem were found in the caudate nucleus,\textsuperscript{19} so that Birkmayer suspected that substance P might also play a role in the disorder.\textsuperscript{20}

He was, however, unable to conduct his own biochemical investigations and was thus reliant on collaboration with pharmacologists and biochemists to test his hypothesis. His initial approach was made to Professor F. Lembeck (Pharmacological Institute, University of Graz) with regard to substance P in the parkinsonian brain; no significant differences, however, were found.\textsuperscript{21} In 1958, he approached Brücke in the University Pharmacological Institute with the idea of measuring 5-HT and sodium levels in the parkinsonian brainstem; Brücke suggested that Hornykiewicz, recently returned from Oxford, would be most suitable for this work, and the contact to Hornykiewicz was facilitated by Lindner. Hornykiewicz, however, was not enthusiastic about the suggestion, as his work commitments were already high, particularly as he was in the middle of establishing his own laboratory in the Pharmacological Institute. He was also much more interested in the investigation of dopamine than of 5-HT, especially as Carlsson’s papers on the reversal of reserpine sedation and the presence of high levels in the mammalian brain had recently been published.

In the meantime, Birkmayer’s assistant Danielczyk had examined for some months the effect on parkinsonian patients of what was then regarded as the best 5-HT antagonist, lysergic acid diethylamide (LSD-25). The positive effects on mood, rigidity and tremor, however, were manifested only at doses which were also hallucinogenic (10-30\textsuperscript{1039\textsuperscript{µ}g/day}).\textsuperscript{22}

It was not long after this, however, that the 1959 article by Bertler and Rosengren appeared in \textit{Experientia} which suggested that dopamine might possess a distinct physiological role in the basal ganglia. It was thereby clear to both Hornykiewicz and Birkmayer that dopamine levels in the parkinsonian brain should be assessed, both with respect to finding evidence for a specific function for dopamine in the human brain and as an investigation of the biochemistry of Parkinson’s disease in particular.

\textsuperscript{17} See Birkmayer and Danielczyk, 1957; Birkmayer and Loeb, 1958.
\textsuperscript{18} Von Euler and Gaddum, 1931.
\textsuperscript{19} Amin \textit{et al.}, 1954.
\textsuperscript{20} Birkmayer and Hornykiewicz, 1961.
\textsuperscript{21} This investigation was only ever mentioned by Birkmayer in his description of events leading to his trial of L-DOPA therapy; I am not aware of any relevant publications. Tenovuo would report in 1992 that substance P-like immunoreactivity, which in the human brain was greatest in the substantia nigra and striatum, was reduced in parkinsonian patients in several regions, including both parts of the substantia nigra and the internal segment of the globus pallidus; the losses in these two regions were attributed to degeneration of the nigrostriatal pathway. Loss of substance P-like immunoreactivity and substance P receptors in the nucleus basalis of Meynert was attributed to degeneration of cholinergic neurons in this region. Similar changes in the nucleus basalis were observed in Alzheimer’s disease brains (but not elsewhere).
\textsuperscript{22} This experiment was reported for the first time in the introduction to Birkmayer and Hornykiewicz, 1962. Already published, however, were the reports on self-experiments with a range of psychoactive drugs, including LSD, usually undertaken late at night when there was little to do on the ward; see Birkmayer and Seemann, 1957; Birkmayer and Danielczyk, 1957; Ambrozi \textit{et al.}, 1960; Danielczyk, 1985.
Hornykiewicz had by this stage established himself as the dopamine expert in Vienna; Birkmayer had discussed the significance of dopamine for parkinsonism with his colleagues during the past year, including the possible etiological role of reduced melanin concentrations.²³ Hornykiewicz was eager to undertake the necessary work immediately, applying the techniques he had been using in the rat brain to human post-mortem material, thereby initiating the first neurochemically based neuropathological investigation. He approached Birkmayer via Brücke concerning the availability of suitable material for investigation, and Birkmayer enthusiastically offered his support, as well as renewing his suggestion to assess 5-HT levels in Parkinson’s disease patients.

As the techniques available to Hornykiewicz would not have allowed the simultaneous determination of 5-HT, noradrenaline and dopamine in the amounts of brain tissue available, Hornykiewicz chose initially to examine only the levels of dopamine and noradrenaline in the brainstem and basal ganglia. Within months of reading the Experientia paper, he had procured post mortem brain samples from seventeen neurologically normal patients, two fetuses and of fourteen patients with extrapyramidal symptoms (four postencephalitic parkinsonian patients, two idiopathic Parkinson’s disease patients, two Huntington’s chorea, and six other patients exhibiting extrapyramidal symptoms).²⁴ He and his assistant Herbert Ehringer prepared the samples according to a modified version of the extraction procedure employed by Carlsson’s laboratory and detected the catecholamines using the colorimetric methods of von Euler and Hamberg for dopamine (detection limit: 2 µg) and Schaepdryver’s modification of von Euler and Flodding’s method for noradrenaline (detection limit not given).²⁵ Nineteen regions of the normal brain were examined (including the caudatus, putamen, pallidum and substantia nigra). The highest dopamine concentrations were found in the caudatus and putamen, as expected, while moderately high levels were found in the substantia nigra and area postrema. These results confirmed the results reported by Carlsson and Sano. More exciting were the results for brains from parkinsonian patients, as illustrated by Hornykiewicz’ reminiscence of his first examination of a parkinsonian sample:

Instead of the pink color given by the relatively high concentrations of dopamine in the control samples, the reaction vials containing the extracts of the Parkinson’s disease striatum showed hardly a tinge of pink discoloration. The brain dopamine deficiency in Parkinson’s disease, today standard textbook knowledge . . . – at that moment I literally could see it with my own naked eye!²⁶

Despite his impatience to publish his findings after examining three parkinsonian brains, Brücke prevailed upon Hornykiewicz to measure three more brains before submitting his report to the Klinische Wochenschrift in September 1960, where, incredibly, it appeared shortly before Christmas of the same year.²⁷ Brücke himself,

²⁴ The source of the material was the Pathological-Anatomical Institute of the University (H. Chiari) and the Geriatric Hospital of the City of Vienna/Lainz (Birkmayer and L. Haselhofer). The comparative accessibility of post mortem brain material to the Viennese researchers was one of the legacies of the medical reforms introduced under the patronage of Maria Theresia and Josef II and the direction of van Swieten. The emphasis of the “Old Vienna School” on pathologic-anatomic investigation led to royal guarantees of the availability of suitable material; Anton de Haen (1704-1776), a querulous believer in witches, is said to have been the first to have conducted regular autopsies as part of student training.
²⁷ Ehringer and Hornykiewicz, 1960.
XII. Vienna tales: Discovery of the dopamine deficit & introduction of L-DOPA therapy

Noradrenaline (µg/g tissue) | Dopamine (µg/g tissue)  
---|---

| Nucleus caudatus |  
|---|---|---|---|
| Normal | 6 | 0.06-0.14 | 0.09 | 10 | 2.7-5.5 | 3.5 |
| Post-encephalitic parkinsonism | 4 | 0.00-0.04 | 0.02 | 4 | 0.0-0.5 | 0.2 |
| Morbus Parkinson | 2 | 0.06-0.10 | 0.08 | 2 | 0.3-1.9 | 1.1 |

| Putamen |  
|---|---|---|---|
| Normal | 7 | 0.08-0.14 | 0.09 | 12 | 2.1-5.3 | 3.7 |
| Post-encephalitic parkinsonism | 4 | 0.01-0.05 | 0.03 | 4 | 0.1-0.5 | 0.3 |
| Morbus Parkinson | 2 | 0.06-0.08 | 0.07 | 2 | 0.3-1.2 | 0.8 |

| Globus pallidus |  
|---|---|---|---|
| Normal | 7 (4) | 0.05-0.30 | 0.15 | 13 (6) | 0.8-1.8 | 0.5 |
| Post-encephalitic parkinsonism | 4 | 0.13-0.46 | 0.23 | 3 | 0.0-0.2 | 0.1 |
| Morbus Parkinson | 1 | 0.06 | 0.06 | 1 | 0.3 | 0.3 |

| Hypothalamus |  
|---|---|---|---|
| Normal | 11 (5) | 0.80-1.67 | 1.25 | 11 (5) | 0.5-1.7 | 0.8 |
| Post-encephalitic parkinsonism | 3 | 0.27-1.99 | 0.98 | not determined |
| Morbus Parkinson | 1 | 0.53 | 0.53 | not determined |

Table 12-1: Post mortem noradrenaline and dopamine content of the human brain in normal and parkinsonian persons, as reported by Ehringer and Hornykiewicz, 1960. \( n \) = number of brains investigated; where pooled material from several brains was assayed, the number of determinations is given in parentheses.

however, had already alluded to what Hornykiewicz was doing at a conference in Liège in February 1960. After referring to levels measured in control brains, he remarked that:

> it was surprising that in two clinical cases of parkinsonian tactile agnosia, measurable levels of dopamine were found neither in the caudate nucleus nor in the putamen; this must become the focus of further research. If this observation were to prove true for other cases, one would perhaps have a reference point for evaluating the biological significance of dopamine in the extrapyramidal motor system. A normal value was found in one case of paralysis agitans.\(^{28}\)

In the final Ehringer and Hornykiewicz report, dramatically reduced dopamine concentrations were reported for three regions of the four postencephalitic parkinsonian brains (caudatus, putamen and pallidum); reduced noradrenaline levels in the caudate, putamen and hypothalamus were also measured. In one of the two idiopathic Parkinson’s disease patients, the decline in dopamine levels in the three assayed regions was comparable with that in the postencephalitic parkinsonian patients, while in the other the decline was still dramatic, but not to the same degree as in the postencephalitic

\(^{28}\) Brücke, 1960. This report indicated that the full paper would appear under the names “Brücke, Ehringer and Hornykiewicz”; Brücke did not, in fact, appear on the paper.
parkinsonian samples (table 12-1). As the patients were of similar age (not given) and the post mortem delay before the removal of their brains similar (3-20 hours), Hornykiewicz was convinced that the differences between the two groups could be confidently attributed to the different disease processes. Noradrenaline levels were reduced to a marked degree only in the hypothalamus. Nothing was known at this stage about the cellular localization of dopamine within the striatum, but the authors noted that three cell types needed to be considered: the numerous small ganglion cells, the large multipolar ganglion cells and the glia. The first could be eliminated as major sites of dopamine storage, as their massive loss in Huntington’s disease had been found by the authors to be unaccompanied by marked loss of dopamine; it was thus likely that dopamine was located primarily in the large multipolar cells. They noted, however, that the conclusion was only an interim one, as the histological lesion was characteristically small in parkinsonism; the disorder seemed more related to a functional than a structural loss.

The paper was submitted with a recommendation by Brücke to the *Klinische Wochenschrift* in September 1960, and published on 15 December. Although in time this paper would become one of the most cited in its field, despite being published in German, the response to the findings was at first lukewarm (figure 12-1). Hornykiewicz has designated the period 1960-1967 as the “seven lean years” of dopamine research; despite the start made at the end of the 1950s, interest in dopamine in the early 1960s was restricted to a small group scattered across the world. In his memoir on the history of L-DOPA, Hornykiewicz noted that his request to present his results at the Bel-Air Symposium on Monoamines in 1961 was not acknowledged; this is curious, given that the paper would have been the perfect partner for that of Barbeau’s group on reduced urinary dopamine levels and their first oral L-DOPA trials. His proposal to speak on central nervous system dopamine at the Second Symposium on Catecholamines in mid-1965 was also rejected.

In retrospect it seems obvious that the substitution of the dopamine lacking in parkinsonism should have been attempted, if not on the basis of Carlsson’s 1957 *Nature* paper alone then certainly after the publication of these results. Even Hornykiewicz, however, came upon the idea while correcting the page proofs for his paper while visiting Blaschko’s laboratory at the autumn of 1960. Perhaps the caution with which Hornykiewicz expressed his conclusions in the presentation to the Society of Doctors in Vienna on 10 November 1961 is some indication of the trepidation with which even he saw the matter:

*as the neostriatum clearly has an important control function in the extrapyramidal system, we proposed the working hypothesis that some of the extrapyramidal minus symptoms of the Parkinson syndrome could possibly be related to the demonstrated dopamine deficit in the neostriatum.*

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29. Taken together with the Brücke citation, this appears to indicate that the brain to which Hornykiewicz referred in the previous quotation was that of a postencephalitic parkinsonian patient, as were at least one of the other two brains examined in the initial experiments.


33. Hornykiewicz, 1975. The report on the meeting published in the *Wiener klinische Wochenschrift* at the end of 1961 includes only a short précis of Hornykiewicz’ talk; the entire text was published in 1975 by Hornykiewicz, dedicated to Birkmayer on his 65th birthday.
As Hornykiewicz noted in the next sentence, however, this hypothesis was actually double-pronged: it proposed not only that the dopamine deficit was connected with parkinsonian symptoms, it proposed also that dopamine had an important function in the normal human brain – and this had not yet been proved. The logical jump being undertaken was thus more daring than it might appear today. Further, in light of research into the disorder up to this point, neurologists were entitled to pose questions as to what this all had to do with the anticholinergic drugs currently in use, and to object that the major lesion in parkinsonism appeared to be in the substantia nigra. This region was too small to assay for dopamine in the current investigation.

It is nonetheless curious that the effect of DOPA on parkinsonian symptoms was examined in only a few clinics, most of them less than famous. This is especially the case given the relative freedom with which physicians could trial experimental therapies at this time. The shift in therapeutic initiative from the physician to the pharmaceutical firm which had occurred during the rise of the synthetic anticholinergics undoubtedly played a role in this reticence; the clinic had become dependent on the company for innovation in therapy, and, as Doshay noted, even somewhat obsequious.34 The introduction of L-DOPA into the clinic of parkinsonism was, in fact, the first major clinician-initiated innovation since the Bulgarian treatment, and the first since harmine and bulbocapnine to be suggested by an independently working pharmacological researcher.

Shortly after Hornykiewicz had identified the basal ganglia dopamine deficit in the parkinsonian brain, he invited Birkmayer to the Pharmacological Institute and suggested that the administration of L-DOPA to parkinsonian patients might improve their condition. On hearing of Hornykiewicz’ results, Birkmayer had initially considered whether the administration of dopamine might be employed to treat such patients., Hornykiewicz explained, however, that the blood-brain barrier was by now generally

34 Doshay, 1965b.
recognized as being impermeable to the catecholamines, so that administration of the precursor was the appropriate strategy. Hornykiewicz possessed at this stage about 2g of the substance, supplied to him by the director of research at Hoffmann-La Roche (Basel, Switzerland), Alfred Pletscher, for his investigation of dopamine metabolism in brain slices. Heartened by the encouragement of Brücke and Lindner concerning his “substitution” concept, Hornykiewicz placed the entire amount at Birkmayer’s disposal in January 1961, and recommended the protocol employed by Degkwitz’ group in Frankfurt.15 Birkmayer, however, was at this stage still convinced that changes in brain 5-HT levels were more likely to underlie parkinsonian symptoms; he was also still somewhat annoyed by the reluctance of Hornykiewicz to conduct the requested assays in 1958.36 It was thus only in July 1961 that he administered 50mg L-DOPA intravenously to his patient L.S. Nevertheless, the dramatic results achieved, which he recorded on film, quickly overcame any residual reservations he may have harbored.

The drama captured in the film of Birkmayer’s first patient is regarded as the beginning of the road to success of L-DOPA as the gold standard in the therapy of Parkinson’s disease. The first part of the film of L.S. shows a woman in bed with shaking hands who can only raise herself with the assistance of a nurse; once standing, she requires the greatest effort to commence walking, and then only in the classic parkinsonian inclined position, with hesitant steps, fixed eyes and an expressionless face. The second part depicts what has since been described as the “miracle cure”: following administration of L-DOPA, not only is movement no longer a problem and the trembling of the hands gone, the woman beams with pleasure and concludes her performance with a little dance. This dramatic response of the first patient was happily not unique: at doses of up to 150mg, remarkable improvements in the condition of all twenty test patients was achieved:

\[\text{The effect of a single intravenous injection of L-DOPA in Parkinson's disease was, in short, the total abolition or the substantial reduction of akinesia. Patients who, when lying in their beds, could not sit themselves up, who could, when sitting, could not stand, or who, when standing, could not start walking, were able to accomplish these tasks with ease after L-DOPA. They walked with the normal associated swinging movements, they could even run and spring. The voiceless, aphonic speech, with its unclear, palililalic articulation, became as strong and clear as that of normal persons. The patients could, for a short period, carry out motor activities to a degree which had been thus far achieved by no other medicament. This DOPA effect reached its peak within 2-3 hours and lasted (to a lesser degree) for 24 hours.}\]

Walter Danielczyk was also involved in the Lainz experiments; he remembered, however, that, although impressive, only careful observation over time revealed that a therapeutic breakthrough had been achieved:

\[\text{Our first experiments with intravenous L-Dopa in parkinsonian patients were conducted, with particular modifications, according to the observational protocol used for assessing vegetative responses to test agents. Hornykiewicz and Bernheimer were also invited to be present. Only these precise psychomotoric and vegetative observations, conducted over an extended period of time, as had become routine for us, allowed the recognition of the positive L-Dopa effect, which at that time was by no means readily apparent, as a breakthrough in the therapy of parkinsonism.}\]

35 Hornykiewicz, 1992; Birkmayer, unpublished preliminary manuscript of speech given in 1993.
36 Letter, Birkmayer to Hornykiewicz, 5.02.70; cited in Hornykiewicz, 1994.
37 Birkmayer and Hornykiewicz, 1961.
38 Danielczyk, 1985.
As acknowledged by Birkmayer and Hornykiewicz in a concluding footnote to their paper, Barbeau and Sourkes had already begun treating parkinsonian patients with oral L-DOPA by this time, and had communicated their experiences to Vienna; it was also reported at the international congress in Rome in September (see below).

Administration by infusion, as adopted in Vienna, had been suggested by Brücke as a means for conserving the limited L-DOPA supply; Birkmayer continued to favour it into the late 1960s, as the side-effects were less marked than when the amino acid was applied orally. Patients treated in the initial trial included both moderate and serious cases of all three major forms of parkinsonism; arteriosclerotic patients responded least to the therapy. A dose-dependent effect for the L-DOPA range tested was noted; the enhancement of the effect by the concomitant administration of the monoamine oxidase inhibitor isoproniazid (Marplan; Hoffmann-La Roche) was also noted in this first trial. The precursor of 5-HT, 5-hydroxytryptophan (5-HTP), was also first applied to patients at this time. A comment attached to the end of the paper noted lapidarily that preliminary results indicated that the intravenous injection of this amino acid also led to an improvement in certain parkinsonian symptoms.

Birkmayer’s and Hornykiewicz’ results were published as a two page paper in the Wiener Klinische Wochenschrift in November. The results were also presented by the two workers at the meeting of the Viennese Medical Society on 10 November 1961; Hornykiewicz held a presentation which lasted about thirty minutes on the scientific basis of the experiment, including the historical background to the suspicion that dopamine might play a role in basal ganglia function and his own assessment of dopamine levels in the parkinsonian brain. It is noteworthy that Hornykiewicz seems to have been unaware of the work by Sano’s group at this stage; only Carlsson’s group is referred to as having detected the basal ganglia concentration of dopamine, and Hornykiewicz recorded that his own measurements confirmed that this situation also prevailed in the human brain. This talk was followed by a presentation by Birkmayer of the film of the first patient treated with L-DOPA. The response of their colleagues was, in general, positive. The neurologists Franz Gerstenbrand and K. Pateisky

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39 5-Methyl-3-isoxazolocarboxylic acid 2-benzylhydrazide; also Ro 5-0831, isocarboxazid. U.S. patent to Hoffmann-La Roche: 1959.
40 Birkmayer and Hornykiewicz, 1961.
41 See footnote 33.
(Psychiatric and Neurological Clinic, Vienna University) reported that they had also treated patients with L-DOPA with and without isoproniazid, and had observed similar effects; they had also noted an effect on parkinsonian rigidity in some patients, and had monitored the effects electromyographically. This technique had indicated that rigidity and resting tremor were reduced for extended periods following L-DOPA administration, but intention tremor was either not affected or exacerbated. The head of the University Clinic, Hans Hoff (1897-1969), urged caution: “without wishing to denigrate the significance of the presented findings and the therapeutic success”, he did not believe that L-DOPA was likely to “cure” Parkinson’s disease, but merely alleviate some of its symptoms. Birkmayer accepted this caution: “It is at the moment a quite remarkable effect, but still not a therapy for Parkinson’s disease.” Nonetheless, he was willing to recommend as the best treatment for parkinsonism “a monoamine oxidase inhibitor, L-DOPA and one of the usual anti-rigidity medications.”

Hornykiewicz and his postdoctoral assistant Hanno Bernheimer had in the meantime carried out the requested assessment of 5-HT levels in several regions of the normal and parkinsonian brain; six parkinsonian brains (of undefined etiology) were used. This was, incidentally, one of the earliest investigations of the distribution of 5-HT in the human brain. Declines in 5-HT levels of about 50% were identified in most regions of

<table>
<thead>
<tr>
<th>Normal</th>
<th>Parkinsonian</th>
</tr>
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<tbody>
<tr>
<td>n</td>
<td>5-HT µg/g</td>
</tr>
<tr>
<td>Nucleus caudatus</td>
<td>6</td>
</tr>
<tr>
<td>Putamen</td>
<td>6</td>
</tr>
<tr>
<td>Pallidum</td>
<td>6</td>
</tr>
<tr>
<td>Thalamus</td>
<td>4</td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>6</td>
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<tr>
<td>Substantia nigra</td>
<td>6</td>
</tr>
<tr>
<td>Griseum centrale</td>
<td>6</td>
</tr>
<tr>
<td>Floor of the IV ventricle and formatio reticularis</td>
<td>4</td>
</tr>
<tr>
<td>Cortex (area 4)</td>
<td>1</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 12-2: Post mortem 5-HT levels in brain regions of normal and parkinsonian persons, as reported by Bernheimer et al., 1961. n = number of determinations; values for 5-HT levels are means, with range of values given in parentheses. ‘Parkinsonian’ encompassed both post-encephalitic and idiopathic parkinsonian patients.

42 Hornykiewicz and Birkmayer, 1961 (with discussion). One of the first press reports on this success appeared in the Viennese Arbeiter-Zeitung (‘Workers’ Press’) on 12 November 1961 under the title “Paralyzed can for a few hours again walk. Viennese doctors find a way that can lead to success against a hitherto incurable disease”; p.5.

43 Other early reports were Costa and Aprison, 1958; Bertler, 1961.
the parkinsonian brain normally rich in this amine, including the caudatus and substantia nigra (table 12-2). The consequences of this phenomenon were discussed, and reference made to the fact that Birkmayer had recently employed the MAO inhibitor harmine to improve parkinsonian symptoms (it had been particularly effective in reducing oculogyric crises), and to his use in 1950 of pyridoxine, the precursor of the cofactor for both DOPA- and 5-HTP-decarboxylases, to improve parkinsonian akinesia. Nevertheless, the first experiments with L-DOPA had already taken place, and the conclusion of the article left no doubt that future work would concentrate on this amino acid.44

**The controversy regarding credit for the L-DOPA experiment in Vienna**

There has been a great deal of discussion with regard to the distribution of laurels for the “discovery” of L-DOPA therapy. Having examined all the material published by Birkmayer and Hornykiewicz, having been granted access to letters and manuscripts regarding this question, and having spoken with a number of their colleagues, including Lindner, Danielczyk and Ehringer, I have concluded that the account given above accurately represents the course of events in Vienna in 1958-61. The conflict in the accounts of the two collaborators was ultimately rather one of accent and detail than of substance. The main points of dissension concern the question of who suggested the measurement of dopamine in the parkinsonian brain and the application of L-DOPA in parkinsonian patients. The publications of Birkmayer on the subject and his private correspondence support the account given here. Lindner, perhaps with an eye to history, had recommended to Hornykiewicz in 1960 that the authorship of the key ideas be specifically indicated in the published material, advice which was heeded.45 In his later years, Birkmayer claimed privately that he had motivated the investigation of dopamine in the parkinsonian brain, and also stated that he had been promised by Brücke that this role would be acknowledged in the Ehringer and Hornykiewicz paper; Birkmayer claimed to have waived his right to appear as co-author on this paper in order to emphasize Hornykiewicz’ role and thereby assist his habilitation (authors on papers emanating from Brücke’s department were generally listed in alphabetical order). This was not consistent with his earlier view of events; it should, however, be noted that these claims were made at a time in which time he was no longer in good health. As already noted, it would appear that at the beginning of 1960 it was intended to include Brücke’s name on this paper; it is conceivable that he forwent this privilege in order to leave only the two active investigators’ names on the paper.

The origin of this dispute is probably best encapsulated in a comment often made by Birkmayer with reference to the development of the new antiparkinsonian therapy, that he (Hornykiewicz) made the decisive step forward in suggesting the use of L-DOPA, but that Birkmayer himself had realized this idea and made the crucial observations regarding its effectiveness. Birkmayer thus distinguished between the idea and its implementation, while recognizing that the one without the other would have been inadequate. As late as the mid-1970s, this interdependence of the idea and its realization was still clear, at least to Birkmayer; it was only later that either of the collaborators began to view their achievement as being diminished by that of the other. As I have indicated at the beginning of this chapter, the dispute revolves around the emphasis to be accorded the roles of the two investigators. Birkmayer had certainly suggested the

45 Lindner, private communication.
investigation of the biochemistry of the parkinsonian brainstem; it was, however, Hornykiewicz who first saw dopamine, and not 5-HT, as the most important factor. It was also his training as a pharmacologist and his laboratory experience which allowed him to recognize that the precursor and not the transmitter should be administered. It was, however, Birkmayer’s powers of clinical observation and his perseverance in the following years, as it became clear that L-DOPA was not always as effective as it was in the first patients, which ensured that the Viennese L-DOPA story did not end as suddenly as it had begun.

I have spoken to several colleagues of Birkmayer who spoke of the warm friendship which bound Birkmayer and Hornykiewicz in the first half of the 1960s. This friendship was no doubt tested by the differing personalities of the two men. Birkmayer is remembered as a very outgoing and ebullient character, whereas Hornykiewicz has been described as a more reserved temperament. Birkmayer remarked in 1969 that, after he (Birkmayer) had overcome his resentment that Hornykiewicz had not immediately undertaken the requested examination of 5-HT levels in the parkinsonian brain, a highly satisfying collaboration and even friendship between the two had developed, a friendship remembered by many of their colleagues in interviews which I conducted. There is no indication of any dispute concerning the wording of the original papers concerning the L-DOPA experiment; for example:

*The suggestion made by one of us (Hornykiewicz) to improve parkinsonian symptoms by elevation of the dopamine levels in the brains of the patients was met with success.*

The friendship of the two researchers appears, however, to have been upset by an interview which appeared in the German issue of the *Medical Tribune* in 1969, in which Birkmayer is cited as referring to Hornykiewicz as his “assistant.” It had already been related to Hornykiewicz in Canada that Birkmayer had exploited his absence from Vienna to claim total credit for their joint contribution to the L-DOPA success, and the *Medical Tribune* incident appeared to confirm these stories. Birkmayer wrote to Hornykiewicz in June 1969 and explained that, despite the skepticism of the latter, he (Birkmayer) had been misrepresented by the journalist who had prepared the article. He protested that he consistently emphasized the crucial role played by Hornykiewicz whenever he wrote or spoke on the history of the therapy, and regarded Hornykiewicz’ suggestion as the major breakthrough: but he himself had implemented the idea and pursued it with determination and vigor. In all published material of this period, Birkmayer treats the subject fairly; for example, he wrote in July 1970 a brief review article, once again for the German *Medical Tribune*, in which he stated:

*The measurement of the biogenic amines serotonin and noradrenaline was proposed from the clinical side (Birkmayer), the pharmacologist Prof. O. Hornykiewicz also determined the dopamine levels.*

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46 Birkmayer and Hornykiewicz, 1962.
47 Birkmayer, 1969b.
48 Hornykiewicz, personal communication.
49 The mentioned letter contains much of historical interest with regard to the L-DOPA story, especially with regard to the relations between the two men in the 1960s. Professor Hornykiewicz gave me a copy of the letter during the preparation of my doctoral dissertation, but has regrettably refused me permission to cite it in any publication or lecture.
50 Birkmayer, 1970a.
It is perhaps true that over the years Birkmayer obscured who was responsible for which part of the research by his use of the word “we”, which is sometimes used by older style German-speaking professors as the first person pronoun singular as well as plural. Nevertheless, in all of Birkmayer’s published articles, the indispensable contribution of Hornykiewicz was recorded, if not emphasized. The two complemented each other in their work; Birkmayer was most productive when paired with someone with laboratory experience, whether a good experimental pharmacologist, neuropathologist or chemist (Hornykiewicz, Neumayer, Riederer); on the other hand, Hornykiewicz openly admitted that he did not “feel competent to discuss the therapeutic value of these findings” (the initial findings on the effects of L-DOPA in the Montreal and Vienna parkinsonian patients). The collaboration and friendship which bound the two in the period until 1968 was an exceptionally fruitful alliance of laboratory, theory and clinic, and it must be regretted that it ended with the bad feeling with which it did.

Further exploration of the “L-DOPA effect”

The next step was to convince Hoffmann-La Roche that L-DOPA represented a practical therapy for Parkinson’s disease; it would otherwise be unlikely that Birkmayer and Hornykiewicz could obtain the substance in the quantities necessary to continue their investigations. Birkmayer remarked in his talk at the International Conference of the Birkmayer Institute that he had first shown his film to a representative of Merck, Sharp & Dohme, who had immediately offered to buy the new agent; Birkmayer, however, felt that the first offer must be made to Hoffmann-La Roche, not only because of their historical connection with L-DOPA, but because of their support of the Viennese workers up to this point. He therefore presented his film to Alfred Pletscher and his colleagues in Basel only days after it had been made. Pletscher described the 1961 meeting in a presentation to the Austrian Parkinson Society in 1997:

Such a spectacular effect from such a small dose of the amino acid alone was difficult for us to accept. Rather, we believed that a psychological component could also be responsible for the success, a component based on the confidence which Birkmayer excited in his patients. Nevertheless, we decided to collaborate with Birkmayer, as we gained the impression that he was a doctor with a good feel for clinical effects and experience in the field of Parkinson’s disease. . . . The initial impression which the clinician Birkmayer had made upon us was subsequently confirmed. . . . He was no friend of formalized, clinical trials, such as double blind studies. He relied upon his clinical experience. I was particularly impressed by the care with which he adjusted the L-DOPA dosage according to the individual condition and situation of his patients.

Pletscher thus agreed to supply Birkmayer with ampoules of solubilized L-DOPA, although even the stock which Hoffmann-La Roche possessed was not great at this time. With this support, the further investigation of the “L-DOPA effect” was possible, and Hornykiewicz and Birkmayer undertook a uniquely thorough biochemical-clinical investigation which sought not only to determine the most effective means for treating parkinsonian patients but also the biochemical basis of the effects being observed. Their results were submitted in a paper in the Archiv für Psychiatrie und Zeitschrift für die

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51 Hornykiewicz, 1964a.
52 Birkmayer, 1990.
54 It should be noted, however, that Hoffmann-La Roche were also supplying a number of other clinics with L-DOPA in the early 1960s.
In July 1962, the speed with which they produced their second paper being indicative of the energy which they lent their investigation. For in the first half of 1962, they had examined the effects not only of various doses of L-DOPA, alone and in combination with MAO inhibitors, but also of a number of other substances.

During their investigations, patients were also treated with their usual anti-rigidity and -tremor medicaments, which may have obscured possible benefits of the new agents for these symptoms, but, as already discussed, this was standard practice at the time. The results of this investigation may be summarized as follows:

- L-DOPA in doses of 50-150mg i.v. had a moderate to marked motor effect in the twenty-one patients examined, with nausea, emesis and collapse the major side effects. Moderate cases responded better than older, more advanced cases.
- Orally or rectally applied L-DOPA (100mg) was less effective than intravenously applied L-DOPA, but was not associated with any increase in side effects.
- The L-DOPA effect could not be elicited by d-DOPA, dopamine itself or the L-DOPA derivative 3-O-methyl-DOPA.
- Neither the noradrenaline precursor D,L-threo-β-3,4-dioxyphenylserine (DOPS; 300mg i.v.) nor the 5-HT precursor D,L-5-HTP (50-100mg i.v.) had any significant effect on parkinsonian symptoms; the latter amino acid, however, exacerbated the symptoms of Huntington’s chorea patients.
- Pyridoxine was similarly without effect and did not modulate the response to L-DOPA.
- MAO inhibitors (isoproniazid, the experimental hydrazine MAO inhibitors Ro 4-2308 and Ro 4-2637, and the harman derivative Ro 3-1620) alone had only a small effect on parkinsonian akinesia. Together with 50mg L-DOPA, however, both the desired and undesired effects of the amino acid were intensified and prolonged. The unpleasant effects could be reduced by simultaneous infusion with caffeine (0.2g) or ‘Euphyllin’ (0.24g), or prior treatment with phentolamine methanesulfonate (15mg).
- The effects of L-DOPA on blood pressure were similar in control and parkinsonian patients. Following slow injection of 50mg L-DOPA, blood pressure was monitored at 10 minute intervals for three hours; a mean decline of 20mg Hg was measured.
- Both amphetamine and methamphetamine exhibited mild ant-akinetic effects. Carlsson had noted that amphetamine relieved reserpine-induced sedation; amphetamine was regarded at this time as a sympathomimetic, but its mode of action was unknown; its mild effect on akinesia suggested that it was, however, not acting directly at the same site as dopamine.

55 Birkmayer and Hornykiewicz, 1962.
56 DOPS can be converted by DOPA decarboxylase directly to noradrenaline: Blaschko et al., 1950.
57 ‘Euphyllin’ (Byk-Gulden) = theophylline compounded with ethylenediamine = aminophylline; ‘Euphylline L.A.’ (Valpan) is pure theophylline (1,3-dimethylxanthine). Both are used as bronchodilators; Birkmayer presumably used ‘Euphyllin’. Xanthine derivatives, including caffeine and theophylline, are widely distributed alkaloids which have long been employed for both medicinal and recreational purposes (possibly since Neolithic times). Amongst their multifarious pharmacological properties is their ability to increase blood pressure via increased peripheral resistance, stimulation of cardiac performance and actions at the level of brainstem regulatory centres.
59 Birkmayer and Hornykiewicz, 1962.
60 Carlsson, 1959b.
Another important feature of their results was that Birkmayer and Hornykiewicz claimed no success in the amelioration of rigidity or tremor with L-DOPA, although it was conceded that rigor could be improved secondarily to reduction of akinesia.61 This was a marked departure in the evaluation of new antiparkinsonian therapies: it was generally an effect on rigor or tremor which was sought, and the modulation of akinesia independently of the other symptoms was extremely rare in the literature. Nonetheless, they were aware that Barbeau had reported an improvement of rigidity with oral L-DOPA;62 they had no explanation for the discrepancy at this stage.

The significance of these results for explaining the L-DOPA effect in parkinsonism was then discussed in detail, and hypotheses on the possible site and mode of action of L-DOPA critically discussed in light of what was then known about catecholamine neurochemistry. The failure of peripherally administered dopamine or DOPS to ameliorate akinesia appeared to confirm that centrally synthesized dopamine mediated the effects of L-DOPA therapy, an interpretation consistent with the potentiation of this effect by MAO inhibition. The simplest explanation was that the hypothesis which had motivated the experiment was correct: the striatal dopamine deficit was responsible for parkinsonian akinesia, and that L-DOPA administration was capable of reducing this deficit:

... dopamine, which occurs in the human striatum at particularly high concentrations, is requisite for the normal function of these extrapyramidal centres, and the loss of dopamine in the striatum is specific for the akinesia of Parkinson’s disease.63

The pair were aware that this contradicted the then accepted dogma of Hassler that the degeneration of the substantia nigra was the central feature of the disorder.64 They attempted to bridge this gap by proposing that cell death in the latter region led to “biochemical inactivity atrophy” in the striatum, whereby they assumed, with Hassler, that pathways between the two nuclei were strictly striatonigral in direction. It was noted parenthetically that Bernheimer and Hornykiewicz had in the meantime also found reduced dopamine levels in the substantia nigra, although not to the same extent as in the striatum.65 On the other hand, Birkmayer and Hornykiewicz also recognized that Sourkes’ laboratory had presented evidence for a general metabolic defect of catecholamine metabolism in parkinsonian patients; Hornykiewicz’ laboratory, however, had found nothing to support this idea in the brains of parkinsonian patients.66

In any case, Birkmayer and Hornykiewicz concluded that L-DOPA, administered together with a MAO inhibitor, was a valuable addition to the therapy of parkinsonism. Whereas stereotactic surgery could reduce the positive symptoms of parkinsonism, and conventional medications for the relief of rigor could uncover a “residual potential for movement”, particularly early in the disease, akinesia in advanced cases was too severe to be amenable to hitherto available therapies. This was the niche which they anticipated could profitably be filled by L-DOPA replacement therapy.

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61 See Gerstmann and Schilder, 1921.
62 Barbeau, 1961b; Barbeau et al., 1962.
63 Birkmayer and Hornykiewicz, 1962. Emphasis stands in original text.
64 Hassler, 1953, pp.811-814.
65 The relevant paper was referred to as being “in preparation”.
66 Bernheimer and Hornykiewicz, 1962.
The attention of the Viennese group had thus by mid-1962 become firmly focused upon the role of central dopamine in Parkinson’s disease, and specifically upon akinesia. The aim from this point onwards was the prolongation of the effects of L-DOPA, initially with the use of MAO inhibitors. Birkmayer published two short articles concerning the “conservative treatment of Parkinson’s disease” in 1962; L-DOPA therapy was introduced as a useful, but not unproblematic treatment for akinesia:

In practice, therapy of Parkinson’s disease should today include:
1. atropine or belladonna preparations for the positive vegetative symptoms;
2. a combination of modern antiparkinsonian medicaments for the rigor and tremor, chosen according to the individual needs of the patient;
3. low doses of a MAO inhibitor which is tolerated by the patient together with infusions of 50-100mg L-DOPA, once or twice a week.67

In a subsequent publication, Birkmayer noted that this therapy was still only possible in the clinic.68 He also published a paper in 1962 (submitted at the end of October, 1961) concerning the differential diagnosis of tremor using a high speed camera; it is interesting that neither the dopamine deficit nor the use of L-DOPA was mentioned in this paper.69

**Dopamine and L-DOPA in other laboratories**

The growing interest in the significance of central nervous system dopamine and in the metabolism of DOPA is perhaps indicated by the growth in the citation rate of the Carlsson papers related to this work and of the Ehringer and Hornykiewicz paper at about this time (figure 12-1). Significantly, Guy Everett (Department of Pharmacology, Abbott Laboratories, Chicago), who had previously confirmed Carlsson’s work with L-DOPA in animals, felt emboldened to commence a paper in 1961 not only with the assertion that the central catecholamines were involved in “modulating the final behavioral motor output”, but also:

Most biochemical work has been directed to the determination of changes in norepinephrine only. Such data may be misleading because of the possible importance of Dopamine in motor behavior.70

Everett had continued to pursue the investigation of DOPA and dopamine which he had commenced at the end of the 1950s. In mice, the administration of D,L-DOPA (i.p.) to mice pretreated with a MAO inhibitor, such as MO-911 (pargyline),71 iproniazid or JB516 (pheniprazine), elicited a gradual behavioural response of increased activity and irritability, as well as of piloerection.72 Everett reported in 1961 that this response was in fact proportional to the degree of central MAO inhibition achieved; with the irreversible MAO inhibitor MO-911, a threshold level of 60% inhibition was required to achieve a marked behavioural response to D,L-DOPA. MO-911 was also shown to

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67 Birkmayer and Mentasti, 1962; see also Birkmayer, 1962a.
68 Birkmayer, 1964/65.
69 Birkmayer, 1962b.
70 Everett, 1961.
72 This response can be elicited with L-DOPA alone, but the doses required are much higher (∼100mg.kg\(^{-1}\) i.p. or even higher i.v.): see references in Sourkes, 1964a.
produce a dose-dependent increase in total brain catecholamines (up to 200mg.kg⁻¹ MO-911, which produced a 300% increase in catecholamine levels). This was interpreted as further evidence for a central action of catecholamines in mammals, and Everett argued that the behavioural response to D,L-DOPA was mediated by a metabolic product of the amino acid, although the precise mechanism remained unknown. In monkeys and rabbits, MO-911 elicited changes in the EEG indicative of increased arousal and irritability.⁷³ Similar evidence of increased motor activity in mice treated with L-DOPA or D,L-tyrosine (but not D-DOPA) was also reported by a number of other laboratories, including those of Blaschko⁷⁴ and Sourkes.⁷⁵ Everett was, however, at this stage not convinced that these catecholamines were transmitters in their own right, but rather that they functioned as "neuromodulators", either directly at the neuron or via the microglia. Nevertheless, he believed that a more precise understanding of these

⁷³ Everett, 1961.
⁷⁴ Blaschko and Chruściciel, 1960.
⁷⁵ Sourkes, 1964a.
functions could yield “a biochemical and physiological basis for the control of final motor output and at the same time show us further ways of modifying behavior by means of drugs.”

Notwithstanding this progress, the case for neuromodulation by central catecholamines still needed to be pleaded at the Second Symposium on Parkinson’s Disease in 1963:

> During recent years evidence has accumulated which indicates that the catecholamines – noradrenaline and dopamine – have specific functions in the central nervous system.

> . . . The evidence to support this view, however, lacks the rigor of a direct demonstration. . . . In no single set of experiments has it been unequivocally demonstrated that the observed effects, which were attributed to a direct action of the catecholamines on neural pathways, were not secondary to vascular changes within the brain, to reflex stimulation, or to some other chemical mediation.

Reference was made to the work of Carlsson’s group, but the events in Vienna were not mentioned; the only reference to dopamine was the fact that Carlsson had suggested it might function as more than a precursor for noradrenaline. In fact, the only other occasion on which dopamine was referred to at the conference was a discussion contribution by Barbeau, who noted that tremorine reduced central dopamine levels.

Other “true believers” in dopamine were also active in defining the metabolism of L-DOPA, even when their research interests were in different areas. Carlsson’s group, for example, was comparing the effects of L-DOPA administered to reserpinized cats either as the amino acid or in its methyl ester form. Lennart Hanson and John Utley (Pharmacology, Göteborg University) showed that the intraperitoneal injection of 100mg.kg⁻¹ L-DOPA methyl ester restored both brain catecholamines and the conditioned avoidance response in reserpinized cats to the same extent as the same dose of L-DOPA itself; similar results were gained in mice. The advantage of the ester lay in the fact that it was 100% soluble in water, while L-DOPA itself was only 5% soluble. This could have been of practical significance for the treatment of Parkinson’s disease, as it would have allowed a massive reduction of the required injection volume.

Pharmacology of the L-DOPA effect: Hornykiewicz and Bernheimer

Hornykiewicz has dubbed Guy Everett the “Dopamine Man” for his tireless campaign to promote the role of dopamine in motor activity during the “seven lean years” after 1960. Hornykiewicz himself, and his assistant Bernheimer, however, were responsible for a mass of research concerning the biochemistry of brain dopamine in humans during this period, quite apart from their collaboration with Birkmayer. Hornykiewicz was determined to elucidate the pharmacological basis of the L-DOPA effect. The application of this amino acid in Parkinson’s disease was the first rational neurochemical therapy of a neurological disease; that is, a neurochemical deficit had been identified in the brains of parkinsonian patients and the attempt was made to

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76 Everett, 1961.
77 Kirshner, 1966.
78 Hebb et al., 1966.
79 Hanson and Utley, 1965; see also Seiden and Hanson, 1964.
compensate this loss through the administration of its precursor. Hornykiewicz wished to improve the therapy by expanding the theoretical basis upon which it was build; Birkmayer applied his observational skills to determining whether theoretical expectations were converted into clinical reality. At this point Hornykiewicz was invited by the editor of the most important German medical journal, the Deutsche Medizinische Wochenschrift to write a review article on dopamine and Parkinson’s disease; the article, which appeared in September 1962, was subsequently translated into English and Greek. This was, in fact, the first review in any major medical journal concerning dopamine. The detailed overview concluded with the warning that it was still too early to speak of a “cure”. Most importantly, it was not yet even known where L-DOPA was acting; much spoke for its acting in the striatum, but an effect in the substantia nigra was also possible. The link between the nigral lesion and reduced striatal dopamine levels also remained a puzzle, given that the existence of the nigrostriatal pathway was not yet generally accepted; the only possibility at this stage remained the “biochemical atrophy” of the dopaminergic cells in the striatum subsequent to degeneration of the striatonigral pathway. This hypothesis, however, was presented with reservations, as functional atrophy in the absence of corresponding anatomical would represent a novel neurological phenomenon; further, it presupposed the existence of dopamine-releasing neurons in the striatum, also yet to be demonstrated. Hornykiewicz was cautious on all these points; he remarked that “our ignorance as to the actual function of the amine [dopamine] is still very profound”.

Hornykiewicz had by this point begun to investigate enzyme activity in the parkinsonian brain as a possible cause of the dopamine deficiency. There existed practical difficulties regarding measuring L-DOPA decarboxylase in human brain tissue; preliminary results from Bernheimer and Hornykiewicz nonetheless indicated that the activity of this enzyme was normal, as was that of MAO (in caudatus and cortex). Catechol-O-methyl transferase activity was not investigated at this point. Neither synthesis nor catabolism of dopamine thus appeared to be unusual in parkinsonism, which interpretation was at odds with that being promoted by Barbeau in Canada. Hornykiewicz noted at the time, however, that the manometric technique used to measure decarboxylase activity returned low and inconsistent values. It was therefore not overly surprising when he and his doctoral student, Kenneth Lloyd, should prove years later in work at the Department of Pharmacology in the University of Toronto that DOPA decarboxylase (and tyrosine hydroxylase) activity was, in fact, markedly reduced in the parkinsonian striatum. Glutamate decarboxylase activity, on the other hand, had been found by Hornykiewicz and Bernheimer to be reduced in parkinsonism;  

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81 Hornykiewicz, 1962.  
83 Hornykiewicz, 1962.  
84 See also Hornykiewicz, 1964a.  
85 Langemann and Ackermann, 1961.  
86 Bernheimer and Hornykiewicz, 1962.  
87 Bernheimer et al., 1962.  
88 Lloyd and Hornykiewicz (1970) found in more extensive studies that decarboxylase activity was greatly decreased in caudate-putamen, somewhat lower in the hypothalamus, and normal in cerebellum and cortex. Important was the fact that decarboxylase activity persisted at 5-10% of normal levels, even at advanced stages of parkinsonism. Riechert’s group (Freiburg) reported in 1969 that DOPA decarboxylase activity was decreased and MAO activity increased in biopsies of basal ganglia removed from parkinsonian patients during stereotactic operations in comparison with tissue from hyperkinetic patients. Most of the tissue, however, was from thalamus, and could be compared only with similar tissue from hyperkinetic patients, not with normal controls (Metzel et al., 1969; 1970).
XI. Vienna tales: Discovery of the dopamine deficit & introduction of L-DOPA therapy

this does not seem to have been further pursued. A final possibility was that the dopamine storage capacity of striatal neurons was for some reason reduced, perhaps by an endogenous reserpine-type molecule. In any case, these basic questions were left open for the time being, but enthusiastically discussed by Hornykiewicz and Birkmayer at the Café Schwarzspanierstrasse, around the corner from the Pharmacological Institute.

A series of neurochemical papers were published in the first half of the 1960s by the Viennese group under various lists of authors; the next important one was that of Bernheimer, Birkmayer and Hornykiewicz in the Klinische Wochenschrift of May 15, 1963: “The biochemistry of parkinsonism in humans: Influence of monoamine oxidase inhibitor therapy on the concentrations of dopamine, noradrenaline and serotonin in the brain.” Bernheimer and Hornykiewicz had once again measured amine levels in various brain regions, this time from three postencephalitic parkinsonian patients who had received MAO inhibitors in the weeks before their deaths (isocarboxazid, Ro 4-2637 or Ro 4-2308), as well as from an unstated number of similar patients who had not received MAO inhibitors, as well as from patients who had exhibited no signs of neurological disease. Different extraction and assay methods were employed to the 1960 Ehringer and Hornykiewicz report, leading to divergent values for measured catecholamine levels in some cases. The values reported in the two papers for dopamine and noradrenaline in the normal brain, however, were comparable in regions where the concentrations were relatively high. The differences were marked, however, for regions where transmitter levels were low; this was especially true for noradrenaline (table 12-3). The detection limits of both methods were high compared with modern techniques, and the meaningfulness of the lower figures cited in these papers is questionable, but there was, of course, no alternative at the time.

This problem might also be invoked to explain the fact that dopamine concentrations in the parkinsonian brain were much higher in this second study, although a dramatic difference when compared with the control brains was still noted (~75-90% decline in caudatus, putamen and pallidum), thus confirming the essence of the earlier results. New to this investigation was the determination on the effect of MAO therapy on amine concentrations: the administration of MAO inhibitors. These agents had already been found to completely eliminate MAO activity in the human brain; consistent with this, noradrenaline and 5-HT levels had been restored by MAO inhibitor treatment to normal levels in most regions (with excessive levels of both in thalamus and hypothalamus). Dopamine levels in caudatus and putamen, the regions richest in dopamine were, in contrast, still less than 15% of normal levels; those in the pallidum and hypothalamus, on the other hand, had been elevated to normal or supernormal levels (figure 12-4).

The group also measured amine levels in the brains of mice and rats treated with the three inhibitors; isocarboxazid and Ro 4-2637 elevated whole brain levels of all three

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89 Bernheimer and Hornykiewicz, 1962.
90 Also presented at the Gesellschaft der Aerzte in Wien in early 1963: Hornykiewicz et al., 1963. Some of the results had also been presented at the meeting of the German Pharmacological Society in Vienna at the end of September 1962: Bernheimer and Hornykiewicz, 1962. The extraction method was partly based on that of Weil-Malherbe (1961), while detection was now conducted using a spectrofluorimeter, as described by Sourkes and Murphy (1961).
92 Bernheimer et al., 1962.
transmitters, while Ro 4-2308 had no effect on dopamine concentration, as had been observed in the parkinsonian patients.\textsuperscript{93} Similar findings had been reported in animal experiments by Sano’s group.\textsuperscript{94} This might have indicated a species difference in the response to some MAO inhibitors. But Ganrot and colleagues had recently reported that MAO inhibition by iproniazid doubled dopamine concentrations in the human brain to the same extent as it did those of noradrenaline and 5-HT.\textsuperscript{95} This apparent discrepancy yielded a further insight into the biochemistry of parkinsonism: the Viennese group investigated a non-parkinsonian patient treated with nialamide, and found that striatal dopamine levels had indeed been increased together with those of the other biogenic amines in other regions. The failure of striatal dopamine levels to respond to MAO inhibition was apparently a feature of the parkinsonian brain.

This selective effect of MAO inhibition on monoamine concentrations was puzzling. The authors considered it unlikely that the MAO inhibitors employed selectively spared a specific ‘dopamine-MAO’; as changes in the synthesis and catabolism of dopamine had also been rendered unlikely by previous experiments, they proposed that disturbed dopamine storage might be responsible for the reduced levels found in parkinsonism. This was supported by the recognition that MAO inhibition alone lacked the ability to increase central amine levels in animals treated with reserpine (although it appeared to at least postpone the behavioural effects of reserpine if administered before the amine depleter). That dopamine levels were not restored by the enzyme inhibitor was

\textsuperscript{93} Bernheimer et al., 1963. \textsuperscript{94} Sano, 1960; Sano et al., 1960b. \textsuperscript{95} Ganrot et al., 1962. The levels of each of the monoamines were doubled.
consistent with the ineffectiveness of MAO inhibition alone in Parkinson’s disease patients; this further supported their earlier proposal of the central role of dopamine in the disorder and its treatment. These results confirmed the central role played by dopamine in the disorder, and that the regulation of its levels was independent of that of noradrenaline and 5-HT, so that its specific depletion in parkinsonism was possible. It was also consistent with the comparative lack of effectiveness of alternative approaches, such as MAO inhibitors alone, 5-HP and threo-DOPS. As the activities of metabolic enzymes associated with dopamine appeared to be normal, the only explanation available to the authors was that storage of the amine was specifically disturbed in parkinsonism; there was, however, no speculation on what might be responsible for this problem. At the presentation of these results to the Viennese Doctors’ Society, Gerstenbrand commented that Hornykiewicz’ findings were consistent with his clinical experience that MAO inhibitors could be useful as monotherapy in parkinsonism, but

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96 Bernheimer et al., 1963.
only in milder cases; he surmised that dopamine storage capacity in more severe cases was too low to permit much benefit from the inhibition of dopamine metabolism.97

The crucial paper regarding the physiological basis of Parkinson’s disease had appeared, however, a fortnight before under the sole authorship of Hornykiewicz: “The topical localization and behaviour of noradrenaline and dopamine in the substantia nigra of normal and parkinsonian persons.”98 The samples described in this paper were presumably assayed at the same time as those in the paper just discussed; certainly the same methods were employed, and the Bernheimer et al. paper was referred to as being “in press”. Hornykiewicz had identified that the noradrenaline concentration of the substantia nigra was low, and did not markedly differ between normal and parkinsonian brains. The dopamine concentration, on the other hand, was reasonably high (mean: 0.46µg/g tissue), although not as high as in the striatum; the concentration was higher in the zona compacta than in the zona reticulata. The range measured in the total substantia nigra was remarkably large, which Hornykiewicz attributed to the observed variability in the reticulata. Despite the use of pooled tissue for the assay of the two individual regions, rendered necessary by the high detection limits of the assay, there was the variance in dopamine concentration in this region was very large, especially when compared that of noradrenaline levels in the same region, which Hornykiewicz suggested might be attributable to the variability of number of melanin-containing neurons in this region. Most importantly, a decline to levels of 0.07µg/g (range: <0.01-0.17) was measured in parkinsonian substantia nigra. Hornykiewicz had thus now identified the dopamine deficit in both brain regions crucial to the neuropathology of parkinsonism (table 12-4).99

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Parkinson</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dopamine µg/g tissue</td>
<td>Noradrenaline µg/g tissue</td>
</tr>
<tr>
<td>Substantia nigra (total)</td>
<td>0.46 (0.10-1.46) n=13</td>
<td>0.04 (&lt;0.01-0.11) n=11</td>
</tr>
<tr>
<td>Zona compacta</td>
<td>0.76 (0.62-0.89) n=3 (13)</td>
<td>0.06 (0.06-0.07) n=3 (13)</td>
</tr>
<tr>
<td>Zona reticulata</td>
<td>0.34 (&lt;0.01-0.60) n=3 (13)</td>
<td>0.05 (0.04-0.06) n=3 (13)</td>
</tr>
</tbody>
</table>

Table 12-4: Dopamine and noradrenaline concentrations in the substantia nigra of normal and parkinsonian patients. Given are the mean values and (smaller italic type) the range of values measured; numbers in parentheses indicate the total number of substantiae nigrae employed in the assay. Taken from tables 1 to 3 in Hornykiewicz, 1963.

97 Hornykiewicz et al., 1963. Hans Hoff indicated in his contribution to the discussion that he regarded striatal destruction as underlying the symptoms of parkinsonism. A comprehensive review of MAO inhibitors at this point was delivered by Hornykiewicz in January 1964 as his inaugural university lecture: Hornykiewicz, 1964b.
98 Hornykiewicz, 1963.
99 Ibid.
In his discussion, Hornykiewicz approached the question of the significance both of dopamine and of melanin in the substantia nigra carefully. The differential distribution of the two substances suggested to him a functional difference in the two nigra regions. What these functions were could not be established until the source of the nigral dopamine was determined, because it was not clear at this stage whether it was of local origin or synaptic. With respect to the reduced dopamine levels, he noted that there appeared to be a correlation between the degree of nigral cell loss and the reduction of striatal dopamine levels:

\[
\ldots \text{cell death in the substantia nigra could well be the cause of the decline in striatal dopamine levels. For it is conceivable that the death of cellular elements in the subst. nigra, to which the striatum sends efferents, leads to a type of "biochemical inactivity atrophy" in the neostriatum. As support for this view might be offered the fact that the decline in dopamine levels in the neostriatum is much less marked in idiopathic than in postencephalitic parkinsonism, so that there seems to be a correlation between the degree of cell death in the subst. nigra and the disappearance of dopamine in the striatum.}^{100}
\]

A quantitative relationship between the two features of parkinsonism was thus expressly proposed for the first time. Further, Hornykiewicz wondered whether the site of action of L-DOPA might not be in the substantia nigra:

\[
\text{Hassler (1938), on the basis of precise histopathological studies, attributed akinesia and rigor to the loss of function of the subst. nigra}\ldots \text{An effect of L-DOPA on the subst. nigra in Parkinson's disease would, however, only be expected as long as this region still possessed functional nerve cells.}\ldots \text{That would be consistent with the clinical finding that in [\ldots] severe cases L-DOPA is not very effective against akinesia (Birkmayer and Hornykiewicz, 1962).}^{101}
\]

At end of 1964, Birkmayer and Hornykiewicz published another joint paper, in which they reviewed the situation three years after the first application of L-DOPA. It seems somewhat modest that the introduction to the paper, after discussing the specificity of the dopamine loss for parkinsonism and the restricted localization of dopamine in the mammalian brain, should conclude with the comment:

\[
\text{It does not, therefore, seem impossible that the symptom of akinesia (possibly also that of rigor) could be connected with the loss of dopamine in the striatum and substantia nigra.}^{102}
\]

Two hundred patients had now been treated with intravenous L-DOPA; these experiences will be discussed in the next section. The neurochemistry of the effect had also been further pursued by administering a number of alternative agents to parkinsonian and other patients; no benefit for any parkinsonian symptom was achieved by the administration of the L-DOPA precursors phenylalanine (50mg) or \(\beta\)-tyrosine (200mg), nor with \(m\)-tyrosine (40mg), which Blaschko and Chrusciel (1960) had found relieved reserpine-induced sedation. This proved to the investigators that the benefit of L-DOPA therapy could not be attributed to a placebo effect, but also suggested that a

\[\text{\footnotesize \cite{100}}\]
\[\text{\footnotesize \cite{101}}\]
\[\text{\footnotesize Birkmayer and Hornykiewicz, 1964.}\]
metabolic problem which prevented the conversion of tyrosine to L-DOPA might be involved in parkinsonism.103

An alternative explanation was favoured by those who believed that L-DOPA was only a precursor substance: that L-DOPA acted upon the reticular activation system in a non-specific manner. Hornykiewicz granted that this was possible, but emphasized from the beginning that the effects of L-DOPA were distinct from both those of amphetamine or apomorphine, which recognized as stimulating the activation system; specifically, amphetamine appeared to act as a psychic energizer, while apomorphine acted expressly upon tremor, which symptom, if anything, was exacerbated by L-DOPA. Further, the anticholinergic antiparkinsonian drugs were believed to act, at least in part, by depressing these centres. Finally, dopamine levels in the reticular formation were low in comparison with those of the basal ganglia. Hornykiewicz therefore viewed this alternative with skepticism, at the same time recognizing the structural similarities of dopamine and amphetamine, and the fact that apomorphine appeared capable of releasing central catecholamines.104

Birkmayer and Hornykiewicz also undertook an interesting experiment which would today probably fail to find the approval of the relevant ethics committee. They reasoned that if reserpine-induced parkinsonism shared the same neurochemical basis as natural parkinsonism, the administration of reserpine to less severe parkinsonian cases should result in a greater deterioration of the symptoms than in more advanced cases; this is because the amine stores of the latter patients are already severely reduced, and it would be difficult to reduce them further to any significant degree. The results were described thus:

Ten moderate cases, who could still move around, showed as early as three days after commencing administration of 0.75mg Serpasil per os per day an alarming deterioration of their symptoms, especially with respect to akinesia, so that the administration had to be stopped immediately. In contrast, the same dosage administered for eight days elicited no significant increase in the symptoms of five advanced, bedridden patients. It seems, however, interesting that the sedative effect of reserpine was similar in both groups.105

It was concluded that reserpine-induced parkinsonism was closely related to true parkinsonism, in that both involved on depletion of amine stores; as to the critical site of action of reserpine, the authors tended to the thought that it was the substantia nigra and not the striatum, as they had similarly demonstrated that reserpine could elicit parkinsonian symptoms in Huntington’s disease patients, where striatal neuronal loss was extreme.106 Further, they also noted that the increase in blood pressure elicited by noradrenaline (1mg s.c.) or tyramine HCl (10mg i.v.) was similar in Parkinson’s disease patients and normal controls; in reserpine-treated control persons, however, it was

---

103 Ibid. On the basis of its effects in animal models of drug-induced parkinsonism and in depression, Heller et al. reported in 1976 that 200 or 500mg D-phenylalanine improved the same symptoms as those modulated by L-DOPA in fifteen parkinsonian patients in an open field trial. The rationale for the approach was the proposed balance between dopamine/phenylethylamine and acetylcholine/5HT/tryptamine in the brain.

104 Hornykiewicz, 1964a.

105 Ibid.

106 On the other hand, other workers had used reserpine to control the abnormal movements in Huntington’s disease and other extrapyramidal hyperkinesias: Chuttani and Singh, 1959; Zmorski, 1959; Kempinsky et al., 1960; Markham et al., 1965; Forster and Markham in Forster et al., 1966.
known that an increased sensitivity to these agents was normally measured. It thus seemed that the analogy between Parkinson’s disease and reserpine-parkinsonism could not be extended to the periphery, a fact which was again difficult to reconcile with the notion of a general metabolic defect as proposed by Barbeau and Sourkes.  

In the meantime, Bernheimer and Hornykiewicz continued their study of dopamine metabolism in the brain, with Bernheimer measuring levels of the dopamine metabolite HVA as a control on reduced dopamine levels identified in the parkinsonian brain. Unlike dopamine, HVA was stable even in the presence of oxygen, so that its levels were less likely to be affected by post mortem conditions; the only caveat the researchers reported was that its post mortem levels might increase parallel to the oxidation of dopamine in the tissue. Sharman (Agricultural Research Council, Institute of Animal Physiology, Babraham, Cambridge) had recently identified HVA in brain and found that it was present at especially levels in the caudate nucleus, and several groups had found HVA levels could be used to assess dopamine turnover in the animal brain. Bernheimer, as the first to investigate the human brain, found high levels not only in the caudatus and putamen, but also in substantia nigra and pallidum. By early 1964, he and Hornykiewicz had established that HVA levels were significantly reduced in the caudate nucleus (78%; dopamine: 85%), putamen (82%; dopamine: 94%) and substantia nigra (82%) of parkinsonian patients. Further, the ratio of HVA/dopamine concentration in the striatum was shifted from about 1.0 to 1.75 (caudatus) or 3.58 (putamen), whereas the quotient was relatively stable in the substantia nigra (normal: 4.2; Parkinson’s disease: 4.6; figure 12-5). The authors hypothesized that this indicated increased activity of the surviving dopamine-producing neurons in the striatum to compensate the lost dopamine, an idea pursued further by Hornykiewicz in his 1966 review of the role of dopamine in extrapyramidal function. Reduced HVA concentrations were subsequently reported for the cerebrospinal fluid of parkinsonian patients, although the decline was not specific for this disorder. Further, these levels were not influenced in any patient group (parkinsonism or other neurological disorders) by the administration of L-DOPA.

This was the first indication of the high degree of functional reserve in the basal ganglia dopamine system; although this capacity for compensating loss appears in retrospect, at least to a certain extent, to be a phenomenon which one would expect of such a vital integration centre, this was not only the first evidence for such a capacity, but also an indication of the advantages which a neurochemical viewpoint brought to the analysis of brain function. Such a reserve capacity would have been difficult to explain in explicit terms with a purely anatomical model of brain function.

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107 Birkmayer and Hornykiewicz, 1964.
108 Bernheimer and Hornykiewicz, 1965. These results were first reported at the meeting of the German Pharmacological Society in Mainz in April 1964: Bernheimer and Hornykiewicz, 1964. See also Bernheimer and Hornykiewicz, 1966.
110 Carlsson and Hillarp, 1962; Andén et al., 1963b; Sharman; 1963b.
111 Bernheimer, 1964.
112 Bernheimer and Hornykiewicz, 1965.
113 In 1973, he and his associates would report that 80% of striatal dopamine could be lost before the presentation of clinical parkinsonian symptoms, consistent with the concept of increased turnover: Bernheimer et al., 1973.
114 Bernheimer et al., 1966.
Bernheimer and Hornykiewicz also pursued the effects of phenothiazine derivatives upon striatal dopamine turnover. Andén and colleagues in Carlsson’s laboratory had recently reported that chlorpromazine led to elevated HVA levels in the rabbit caudatus.\textsuperscript{115} Hornykiewicz’ laboratory had previously found chlorpromazine blocked the rise in catecholamine and 5-HT levels in the rat brain following iproniazid treatment, despite the fact that MAO activity remained effectively suppressed; similarly, the blockade of the antagonism by iproniazid of the catecholamine-depleting effect of reserpin was also reduced by chlorpromazine.\textsuperscript{116} Several potential mechanisms for these phenomena were discussed, but the authors leaned to the explanation first proposed by Brodie and Shore in 1957: that chlorpromazine “hinders the binding [of noradrenaline] to receptors, where its inactivation probably also occurs.”\textsuperscript{117} The Viennese workers now found that perphenazine and thioridazine also elevated HVA levels in the rabbit caudatus, but not the dopamine re-uptake inhibitors cocaine or imipramine, nor the α-adrenergic receptor blockers phenoxybenzamine or bulbocapnine. They concluded that the neuroleptic drugs probably elevated HVA levels by “blockade of specific dopaminergic receptors in the extrapyr. centres.”\textsuperscript{118}

Together with the clinical neurologist Gerhard Barolin (Vienna City Neurological Hospital Rosenhügel), Hornykiewicz and Bernheimer also published in 1964 the results of their assessment of amine levels in the brain of a patient who had suffered from untreated, partly unilateral parkinsonism. At the time of his death, tremor was restricted to the right arm and lower jaw, while he also exhibited bilateral akinesia, rigor and postural problems. Dopamine concentration was reduced by 50% in the left caudatus and by 80% in the left putamen (that is, the side contralateral to the tremor) compared to the corresponding right nucleus (the values of which, however, were reduced in comparison to normal controls). 5-HT levels were similar on both sides, as also in both halves of the thalamus. Dopamine levels were also reduced on both sides of the substantia nigra to less than detectable levels. Once more, the independence of

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure12-5.png}
\caption{Relationship between dopamine and HVA levels in selected brain regions = figure 1 from Bernheimer and Hornykiewicz, 1965. Q = HVA/dopamine ratio; * data from Hornykiewicz, 1963 (13 normal, 10 parkinsonian brains); ** data from Bernheimer et al., 1963 and unpublished findings (4 normal, 6 parkinsonian brains).}
\end{figure}

\textsuperscript{115} Andén et al., 1964b.
\textsuperscript{116} See also Gey and Pletscher, 1961, 1962; Carlsson and Lindqvist, 1963.
\textsuperscript{117} Ehringer et al., 1960; Brodie and Shore, 1957, see also Benfey et al., 1959.
\textsuperscript{118} Bernheimer and Hornykiewicz, 1965. Angelakos and McKenna (1965; Physiology, Boston University School of Medicine) reported at about the same time that chlorpromazine, but not prochlorperazine or mepazine, significantly reduced striatal dopamine levels in the cat (but not those of the rest of the brain), while mepazine specifically reduced striatal noradrenaline levels. Extrapyramidal signs were not correlated with degree of dopamine loss.
dopamine and 5-HT deficits was evident. More important, however, was the fact that the severity of the parkinsonian symptomatology was at least partially correlated with the greater dopamine deficit in the contralateral basal ganglia, supporting the Hornykiewicz-Birkmayer working hypothesis. Although interesting in this respect, the case was not unproblematic, as noted by the authors; there was no indication at this point that the striatum was involved in the generation of tremor, and the dopamine deficit had, up until this point, been more closely associated by the Viennese group with akinesia than with tremor or rigidity. On the other hand, these findings were not influenced by pharmacological intervention: the 76 year old patient had never received any antiparkinsonian medication.119

These successes in Hornykiewicz’ laboratory led to a broader biochemical-neurohistological study of parkinsonism, the preliminary results of which were presented in 1965. At the 8th International Congress for Neurology in Vienna (September 1965), Bernheimer, Birkmayer and Hornykiewicz, together with the neuropathologists Franz Seitelberger and Kurt Jellinger (Neurological Institute, University of Vienna), presented a paper which reported the preliminary results of their “comparative biochemical and neurohistological investigation” of the three major forms of parkinsonism. The aim was to establish whether biochemical and anatomical differences between the three forms could be identified which would allow their systematic demarcation. The investigators examined four cases of post-encephalitic parkinsonism, four of paralysis agitans, two arteriosclerotic patients and six cases involving “senile neuronal dystrophy”. The three major findings were:

- The striatal dopamine loss was related to the degree of parenchymal loss in the substantia nigra pars compacta.
- The anatomical lesions of postencephalitic parkinsonism could be qualitatively distinguished from those of the other forms. The dopamine deficit was also much greater in these patients; in two cases, no dopamine at all could be found in the caudate.
- Nevertheless, there existed a great deal of variability in the histology of the parkinsonian brain.120

But the results were recognized as preliminary and a larger, systematic study of the issues raised was needed. But in 1967, the driving force behind the neurochemical investigations, Hornykiewicz, departed to take up a position as visiting professor (from July 1968: full professor; from 1973: also Professor of Psychiatry) in the Departments of Pharmacology and Psychiatry at the University of Toronto in Canada, and the work was put aside for the time being and would not be published until 1973. The number of parkinsonian brains examined had increased by the second report (sixty-nine were examined morphologically, twenty-eight biochemically; of the latter, dopamine and HVA levels were assessed in the caudate and putamen (but not substantia nigra) of six post-encephalitic, thirteen idiopathic and five arteriosclerotic parkinsonian patients. The overall results did not differ significantly from the 1966 presentation; the major new findings were the positive correlations of both degree of akinesia and responsiveness to L-DOPA therapy with the degree of dopamine/HVA loss in the strio-pallidum.121

119 Barolin et al., 1964.
120 Bernheimer et al., 1965.
121 Bernheimer et al., 1973. For biochemistry of substantia nigra in parkinsonism, see Javoy-Agid et al., 1982.
Amongst the visitors at the Vienna meeting were Melvin Yahr and Roger Duvoisin of the newly constituted Parkinson’s Disease Centre at Columbia University in New York.\textsuperscript{122} Hornykiewicz showed the Americans the film of the 1961 L-DOPA experiment, and they were duly impressed. Hornykiewicz had been invited by Udenfriend to the symposium on the “Biochemistry and Pharmacology of the Basal Ganglia” held at the Parkinson’s Disease Centre in November,\textsuperscript{123} and Yahr took the opportunity to present Hornykiewicz and Carlsson to the press. As a result, two major articles appeared in the \textit{New York Times} concerning what Yahr was cited as describing as “the first indication that alterations in brain chemistry may underlie Parkinson’s disease”.\textsuperscript{124} This, together with Carlsson’s research since the mid-1950s, constituted “an important advance in research on the disease”.\textsuperscript{125} The dopamine deficit had arrived in the New World.

The last joint paper from Hornykiewicz and Birkmayer before the departure of the former was thus the report in the \textit{Wiener Klinische Wochenschrift} in May 1966 on reduced levels of the dopamine metabolite homovanillic acid (HVA) in the cerebrospinal fluid of parkinsonian patients.\textsuperscript{126}

### Further investigation of L-DOPA in the clinic: Birkmayer

Throughout these years, Birkmayer had continued his investigation of L-DOPA in the clinic, while Hornykiewicz and his laboratory advanced their research into the neurochemistry of Parkinson’s disease and the metabolism of dopamine. But in the meantime, the clinical results were less unequivocal than at the beginning: having regularly treated 200 parkinsonism patients over the three year period with L-DOPA (25mg i.v., once or twice/week), the results were now as follows:

- 20\% showed a \textit{general improvement in activity} (reduced akinesia) for a period of 1-3 days after L-DOPA infusion. All patients now also received a MAO inhibitor, either isocarboxazid (3×10mg daily) or nialamide (2×25mg daily).\textsuperscript{127}
- 30\% showed \textit{no response} to L-DOPA; there was nothing in their case histories which predicted whether a patient would benefit from L-DOPA or not.
- 50\% showed \textit{improvement of a specific impaired function}; that is, an improvement in one of propulsion, speech, posture, or of another symptom.\textsuperscript{128}

It is a tribute to the observational skills of Birkmayer that such individual responses were noticed. He was thus in a position to remark that even in cases where an abolition of the akinesia did not take place, that smaller but significant (for the patient) changes had occurred:

\textsuperscript{122} The multidisciplinary “Clinical Centre for Research in Parkinson’s Disease and Related Disorders” was organized by Yahr in 1963, and moved with him to the Mount Sinai School of Medicine in 1973; Elizan, 1988.

\textsuperscript{123} Costa \textit{et al.}, 1966.

\textsuperscript{124} Schmeck, 1965a, 1965b.

\textsuperscript{125} \textit{Ibid.}

\textsuperscript{126} Bernheimer \textit{et al.}, 1966. Gottfries, Rosengren and Rosengren had also reported reduced HVA levels in the striatum of a single parkinsonian patient in 1965.


\textsuperscript{128} Birkmayer and Hornykiewicz, 1964.
Some patients did not spend the night, as usual, lying completely rigid in bed, but could turn themselves and alter their position. Very advanced, completely immobile patients showed only an improvement in breathing and swallowing after L-DOPA, while the impaired motor function of the extremities remained untouched. Moreover, it was noted that the kinetic effect of L-DOPA was quite often asymmetric. The accompanying motions were restored in these cases on only one side; the patient could frequently carry out pushing motions of full extent and speed with only one hand, their ability to turn to the side was often improved in only one direction.\footnote{Ibid.}

Variability in the temporal features of the L-DOPA effect were also now emerging after extended usage. While improvement was usually evident within 10-30 minutes of injection, some patients responded only after one to two days, or required a series of injections to manifest improvement. The duration of the effect was also highly variable, ranging between one and five days (with the effect tapering off during this period). Birkmayer noted that the responses of his patients were highly individual, and that lack of response could not be overcome by increasing the amino acid dosage; such attempts only increased the untoward side-effects, mostly emesis and collapse. It was also noted that the intensity of these side effects was inversely proportional to the kinetic effectiveness of L-DOPA in a given patient. Birkmayer and Hornykiewicz suggested that this might be explained by the varying degree of extrapyramidal damage in his patients, as only those who retained sufficient numbers of cells capable of dopamine synthesis could be expected to benefit from L-DOPA supplementation. Interestingly, idiopathic Parkinson’s disease patients did not respond as well as postencephalitic parkinsonism cases; it had already been noted that the dopamine loss was greater in this latter group.\footnote{Ehringer and Hornykiewicz, 1960.} Finally, it was emphasized that all patients continued to receive their conventional antiparkinsonian medication (benzhexol, orphenadrine, benztropine mesylate, ethylbenzhydramine or methixene) throughout their investigations:

>If one of these agents was completely withdrawn, the consequent exacerbation of the rigor was so strong as to conceal the beneficial effect of L-DOPA on the akinesia.\footnote{Birkmayer and Hornykiewicz, 1964.}

That the Viennese group had not claimed that L-DOPA was a complete solution for the parkinsonian patient was often overlooked by subsequent investigators. Yahr noted in his review of the literature in 1969 that the "20%" success rate claimed by Birkmayer was "not very impressive",\footnote{Yahr et al., 1969.} and this was a view which he shared with most of the non-German-speaking world. Overlooked by this assessment, however, is the fact that it was an improvement in akinesia, a hitherto difficult to treat symptom, which was reported. Further, the "20%" claimed compares poorly only with the "60-80%" purportedly achieved by many of the synthetic agents if both claims are accepted on face value; as discussed above, however, the huge successes claimed with the cholinergic agents were often controversial, and often did not bear close inspection. It must also be remembered that "20%" of Birkmayer’s patients represented a much greater number of cases than the "50% of 16 patients" who formed the basis of Cotzias’ breakthrough paper.\footnote{Cotzias et al., 1967.}
Birkmayer also noted another aspect of parkinsonism which he discussed both in this paper and in separate publications. He noted that heat regulation in Parkinson’s disease patients is disturbed to the extent that hyperthermia (up to 40°C) could be a problem in summer, even lethal (a fatality rate of 4-5 deaths per 1000 patients per year was cited in 1970). This was part of the “vegetative decompensation” which had occupied his thoughts since the War, and was particularly marked in postencephalitic patients. This “vegetative rigidity” was not amenable to treatment with L-DOPA therapy, but could be managed by administration of 5-HTP and a MAO inhibitor. Further, since MAO inhibitors had been introduced as part of the regular therapy for Parkinson’s disease patients at Lainz, there had been no cases of central hyperthermia during the summer months. It was proposed that his beneficial effect could be attributed to restoration of noradrenaline and 5-HT levels in the hypothalamus, which were also reduced in Parkinson’s disease. The role of 5-HT in the vegetative symptoms of Parkinson’s disease had thus been confirmed.

By the end of 1966, three major possibilities presented themselves to Birkmayer as explanations for the dopamine deficit in parkinsonism:

- **Increased turnover of dopamine in the basal ganglia**: as cerebrospinal fluid levels of the dopamine metabolite homovanillic acid (HVA) were reduced in parkinsonian patients, this seemed unlikely.
- **Increased metabolism of dopamine by MAO**: administration of MAO inhibitors over a period of months led to increased central levels of noradrenaline and 5-HT, but not of dopamine. Increased MAO activity as the basis of the dopamine deficit was thus also unlikely.
- **Reduced dopamine synthesis**: phenylalanine and m-tyrosine elicited no kinetic effect in parkinsonian patients, but a combination of p-tyrosine (100mg) and NADH (200mg), the co-factor for tyrosine hydroxylase, produced an effect similar to that of L-DOPA.

Birkmayer especially was convinced that the essential problem in Parkinson’s disease involved tyrosine hydroxylase, and his experiments with α-methyl-p-tyrosine in parkinsonian patients and those of Spector and colleagues in chorea patients lent this interpretation some support. Hornykiewicz remarked that it was “as if a reserpine-like substance was continually acting upon the basal ganglia” in parkinsonism; indeed, he had earlier noted that “it may be tempting to assume that in Parkinson’s disease a reserpine-like principle might be active in the brain.”

Whatever the reason for the striatal dopamine deficit, Birkmayer was convinced by this point that L-DOPA should be regarded as the most useful agent available for the treatment of parkinsonism. This faith was assisted by his untiring observation of his patients’ responses to the amino acid, and also by the fact that he had added a peripheral decarboxylase inhibitor to his therapeutic approach. This potentiation of the central L-DOPA effect would ultimately permit a practical L-DOPA therapy for parkinsonism,

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134 Anonymous, 1970m.
135 Birkmayer and Neumayer, 1963; Birkmayer, 1964; Birkmayer and Hornykiewicz, 1964. Völler (Königin-Elena-Klinik, Kassel) added 5-HTP to antiparkinsonian therapy in 1967 and also noted the abolition of hypothermic crises and of leg edema; Anonymous, 1970m.
136 Birkmayer and Mentasti, 1967.
137 Spector et al., 1965.
138 Hornykiewicz, 1966a.
139 Hornykiewicz, 1964a; see also Hornykiewicz et al., 1963.
and will be discussed in detail in chapter XVI. Despite the promising early results and Birkmayer’s optimism, however, Hornykiewicz had becoming increasingly doubtful that a useful therapy would emerge from this work:

_I do not want to comment here on the therapeutic suitability of l-DOPA. That is a clinical problem which must be decided by the clinicians. It suffices here to note that a number of favourable conditions must be satisfied in order for a therapeutic effect, however interesting and surprising, to be able to become a real therapy: the agent must be well tolerated, it must be convenient to administer and the dosage easily adjusted, the duration of its effect should be as long as possible, it should not be incompatible with other medications, and so on. I am not sure that all of these preconditions have yet been met by l-DOPA._

He had no doubt, however, that the responses reported by Birkmayer were real. He was more inclined, however, to regard their value as yielding insights into the nature of Parkinson’s disease; their theoretical worth was of “exceptional significance.” His doubts had nothing to do with Birkmayer’s credibility, but rather the disheartening nature of the experiences which were being reported by a number of other workers who had experimented with l-DOPA in the treatment of parkinsonism. Before these experiences can be discussed, however, significant developments in Canada which complemented and augmented those occurring in Vienna must be recounted.

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140 Hornykiewicz, 1966a.
141 Ibid.
ON THE OTHER SIDE of the Atlantic, a second team of researchers had also reached the conclusion that dopamine was central to parkinsonism and that L-DOPA was the solution to the problem; they had, however reached these conclusions by a different pathway, although commencing from the same starting point. The partnership between the two major members of this team would not last as long as of Birkmayer and Hornykiewicz, but would similarly result in a number of papers now regarded as central to the emergence of L-DOPA as a viable therapy for Parkinson’s disease.

Theodore (‘Ted’) L. Sourkes was born in Montréal in 1920, the son of a businessman, and completed his high school studies in Quebec City. Having excelled at both Latin and mathematics, he surprised many by his choice in 1935 to study biochemistry at McGill University, then led by J.B. Collip, the first person to purify insulin and leading pituitary researcher. Financial constraints prevented him from proceeding directly to a doctorate after completing his basic degree; after periods at the Food and Drug Directorate in Ottawa, Queen’s University in Kingston (Ontario) and in the pharmaceutical industry, he finally commenced his Master’s degree in the Departments of Animal Nutrition and Chemistry at McGill University in 1945, before

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1 Collip had also described the preparation of a parathyroid extract in the 1920s, which had been popular for a time in the treatment of, amongst other disorders, postencephalitic parkinsonism. Incidentally, controversy surrounded the award of the 1923 Nobel Prize for Medicine or Physiology to Banting and Macleod for the discovery of insulin, as Banting’s chief assistant in the work had been the medical student Charles Best and Collip had actually purified the peptide; the two laureates therefore agreed to divide their prize money with Best and Collip. See Bliss, 1982 for the history of insulin.
proceeding to Cornell University in 1946. Here he completed in May 1948 his doctoral research (on the theme of transmethylation) under the supervision of James Sumner, the 1946 Nobel Prize laureate for chemistry.  

After a sojourn at Georgetown University in Washington, Sourkes was invited to join the Merck Institute for Therapeutic Research (Rahway, New Jersey) in 1949, where he was initially concerned with metabolism in the adrenal medulla. After important studies examining the specificity of adrenal decarboxylase, Sourkes was entrusted with testing a series of novel substances designed to block DOPA decarboxylase. Merck was attempting to develop a drug which reduced essential hypertension by blocking noradrenaline synthesis. At this point, DOPA decarboxylase was the only identified enzyme in this pathway (and thereby only tentatively), and the dominant research paradigm involved the development of an ‘anti-metabolite’ which reduced the activity of the enzyme. Stein and colleagues thus synthesized a panel of methylated α-amino acids, an approach suggested by the success of α-methylglutamate as an inhibitor of mammalian decarboxylase. Sourkes’ major achievement at Merck was the detailed exploration of one of these compounds, α-methyl-DOPA, as a result of which it which became the prototype anti-decarboxylase. By 1958, its antihypertensive capacity had been demonstrated in animals and humans, and the drug became famous as ‘methyldopa’ (‘Aldomet’). It would, in fact, prove to be the only decarboxylase inhibitor which proved useful in the treatment of blood pressure; the reasons for this would become clear only later.

In 1953, Sourkes moved to the Allan Memorial Institute of Psychiatry at the McGill University, where he remained until his retirement. He continued his investigation of DOPA decarboxylase, while his research student John Lagnado initiated MAO research in Sourkes’ laboratory; both enzymes would later be purified in Sourkes’ laboratory. At the end of 1955, Sourkes’ laboratory had begun to measure catecholamines in various tissues. This research direction was facilitated in 1959 by a special equipment grant

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2 James Batcheller Sumner (1887-1955) received his award as the first worker to crystallize an enzyme (urease in 1927) and to prove that it was a protein. This achievement was long ignored or disputed by most biochemists, so that the Nobel Prize served as vindication of his stance; his method had in the meantime been recognized as appropriate for the purification of any enzyme. Sumner received half the Prize; the other half was shared equally by the Americans John Howard Northrup (1891-1987), who had crystallized pepsin in 1930, and Wendell Meredith Stanley (1904-1971), who had investigated the tobacco mosaic virus in great detail, "for their preparation of enzymes and virus proteins in a pure form"; source: http://www.nobel.se/chemistry/laureates/1946/index.html (accessed 18.01.01).

3 See Sourkes et al., 1952.

4 Stein et al., 1955.

5 Pfister et al., 1955.

6 Sourkes, 1954; Stein et al., 1955.

7 U.S. patent to Merck: 1959; for resolution of isomers, U.S. patent to Merck: 1964. The commercial preparation consists of the l-isomer. For the further history of the mechanism of methyldopa, see below. Sourkes reviewed the early history of α-methyldopa in 1966 (Sourkes, 1966a) and 1967 (Sourkes and Rodriguez, 1967).

8 Sourkes, 1990.
which allowed him to acquire a spectrofluorophotometer, enabling him to adopt the latest fluorometric detection methods. Collaboration with clinicians also commenced at about this time, as his research interests focused upon the biochemical basis of psychiatric disease, encapsulated in his 1962 book "Biochemistry of Mental Disease."9

Towards the end of the 1950s, Sourkes and his graduate student Gerard Murphy were motivated by the work which had recently appeared concerning the localization of amines in the brain to concentrate on the biochemistry of diseases of the basal ganglia. The work emerging from Carlsson’s laboratory indicated that dopamine was probably involved in basal ganglia function, and its depletion probably underlay the sedative effects of reserpine. Sourkes’ familiarity with α-methyl-DOPA placed him in an excellent position to commence investigations of L-DOPA metabolism and its physiological significance.

This research interest also led Sourkes to take up contact with a young neurologist in the Section of Neurology at the University of Chicago, André Barbeau. Barbeau was born in 1931 in Montréal, the scion of an old French family which had settled in Canada in the seventeenth century. Barbeau’s first paper on Parkinson’s disease was a historical survey of extrapyramidal motor disorders, written during the completion of his postgraduate studies in 1957 (neurology at the University of Chicago).10 The paper betrayed a quite philosophical, even melodramatic approach to medicine which concluded with the following:

Many clinical varieties of extrapyramidal disorders have been observed, many pathological studies carried out, but the suffering humanity still goes on twisting, shaking, writhing, jumping and jerking when it does not want to... It is... possible that a chemical or metabolic abnormality will be found common to these entities, but until then there is still much work to be done and the physician, man above all, must know for the present the best he can offer is understanding, charity, hope and faith.11

Barbeau noted in 1984 that he had been inspired by a lecture by Carlsson during a meeting in Washington at about this time to turn his attention to “the specific excretion of dopamine in Parkinson’s disease”;12 he was studying neurology at the University of Chicago at this point, and was investigating the urinary excretion of catecholamines in neurological disease in general.

Direct collaboration between Sourkes’ laboratory and Barbeau commenced shortly after Barbeau transferred to the Montréal Neurological Institute at the beginning of 1960. The initial approach of the group was to determine whether urinary catecholamine excretion was abnormal in patients with basal ganglia disorders. In 1959, Sourkes, Murphy and Barbeau thus published in Canadian journals results of the assay of urinary adrenaline and noradrenaline using the trihydroxyindole method and of urinary dopamine using a modification of the Carlsson-Waldeck method; Sourkes’ first graduate student, Boris Drujan, had been principally responsible for the development of the technique employed in Montréal.13 This technique was used, for example, to

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10 Barbeau, 1958.
11 Ibid. For further biographical information, see Campanella, 1986; Chrétien et al., 1986.
12 Barbeau, 1984. One of his friends at Chicago was Melvin Van Woert, who a little later joined George Cotzias’ group.
13 Sourkes and Drujan, 1957; Drujan et al., 1959.
investigate the effects of electroshock therapy on urinary catecholamines. Murphy and Sourkes had also demonstrated the accumulation of dopamine in brain and kidneys of DOPA/iproniazid-treated rats; this rise in levels could be blocked with α-methyldopa.

The first major paper on catecholamines in basal ganglia disease, however, was published by Barbeau alone in Neurology in May 1960, having previously been read before the American Academy of Neurology in April 1959. The paper had been submitted for publication without Sourkes’ knowledge, which both soured the relationship between scientist and clinician from the beginning and explains the errors of biochemical fact contained within the paper. Barbeau had been investigating epinephrine secretion by various patients groups in 1957/58, and had found that increased levels of a “pressor substance” were excreted in the urine of parkinsonian patients. The current report was thus an extension of this investigation to other extrapyramidal disorders. Urine samples from thirty-two patients with a verified basal ganglia disease (most of whom apparently provided multiple samples) and one hundred twenty-six control persons were tested with a colorimetric detection method for catecholamines known as Simola’s reaction. Even at the time, the test was somewhat controversial. Although named for Simola, who discovered it, it was only later that Guyot and Isoard suggested that it might detect catecholamines, as these substances yield red compounds on oxidation by iodine; but even these workers remarked that it was not easy to employ, requiring some experience. The urine of forty-four patients and two hundred thirty eight controls was also tested using a bioassay based on the contraction of a strip of rabbit thoracic aorta; this test had been adapted from a method used for detecting pheochromocytoma. Twenty-seven patients were assessed by both tests, with the results proving consistent.

The Simola test indicated that a substance detected by this test was present in the urine of all five Huntington’s disease and six Wilson’s disease cases, as well as in nine of eighteen parkinsonian cases; the positive rate for the normal controls was 2.3%. The bioassay produced similar results (eleven of twenty-four parkinsonian cases were positive); the results for the controls was not reported, although a positive rate of 6-18% had been found by other cited workers. A positive response in this test could be blocked by adding phentolamine, an α-adrenergic receptor blocker, to the bathing solution. A number of substances had been examined with respect to the responses elicited in the two tests; only the three recognized physiological catecholamines and epinine produced positive responses in both tests. Barbeau interpreted the results cautiously, but appeared to be suggesting that increased dopamine levels were being detected in the urine of his basal ganglia disease patients. This impression was confirmed in his next paper on the subject as sole author, in which he explicitly hypothesized that “epinephrine

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14 Sourkes et al., 1958a,b. Other workers were also interested in the impact of therapy on urinary catecholamines at this time; for example, Kutschke and Ditfurth (1958; Medical and Neurological Clinics, Würzburg University) had reported a sharp reduction in catecholamine excretion in five psychiatric patients following reserpine treatment.
15 Murphy and Sourkes, 1959.
16 Barbeau, 1959. Barbeau falsely used the term “pressor substance” to indicate a substance which elicited a positive response in the Simola or rabbit aorta strip tests.
17 Simola, 1943.
18 Guyot and Isoard, 1957. The method essentially involved the heating of the urine sample with Lugol’s solution (5% w/v iodine and 10% w/v potassium iodide in water), followed by butyl alcohol extraction.
19 Helmer, 1957.
20 Barbeau, 1960.
(Adrenaline), nor-epinephrine (Nor-adrenalin) and especially dopamine (3-hydroxytyramine) could be excreted in the urine in increased concentration” in Parkinson’s disease.21

The interpretation of these results, however, is altogether problematic. Sourkes has noted that that the aorta strip test was designed for catecholamine levels associated with chromaffin tumors (>200µg/24hr), and was thus unsuitable for Barbeau’s purposes.22 Further, a positive response would be due more to the presence of noradrenaline than dopamine, as the latter is only 2% as potent in this test. Similarly, the identity of the substance detected by the Simola test had not been satisfactorily established. Curzon and Wald confirmed in 1963 that urinary levels of the Simola substance were increased in Wilson’s disease patients (and pregnant women), but not in parkinsonian or other extrapyramidal disease patients; further, the authors found that the spectrum and intensity of the Simola signal were inconsistent with the detected substance being dopamine or, indeed, any other catecholamine;23 the explanation that the substance detected was 3,4-dimethoxyphenylethylamine (DIMPEA), later investigated by Barbeau and others, was thus also excluded. It would ultimately be established that the chromogen resulted from the reaction between iodine, urea and tryptophan.24

Barbeau and Sourkes independently published reviews of the connection between dopamine and basal ganglia disease in 1961. Barbeau reviewed the literature concerning the specific localization of central nervous system catecholamines, with a particular emphasis on the work of Carlsson’s and Sano’s groups, and he concluded that there was some evidence for a striatal dopamine deficiency in parkinsonism. He recapitulated the results from his previous paper, noting that these results had been confirmed in the meantime by two other laboratories, albeit only in the form of personal communications; Sourkes and colleagues were also cited in a personal communication as having detected increased dopamine excretion in two parkinsonian and two Wilson’s disease patients with a specific chemical method.25 It was not clear how he reconciled increased urinary excretion of dopamine with its central deficiency. In any case, he wrote that further investigations into dopamine metabolism in extrapyramidal disease were being undertaken in co-operation with Sourkes’ laboratory.26

Sourkes’ review commenced with a detailed review of the investigation of the biochemistry of the basal ganglia to that point, before proceeding to describe the experiments which he and his doctoral student Murphy had conducted in 1960/61 concerning the metabolism of l-DOPA in the rat, with particular attention to the manipulation of dopamine levels in the brain. Intraperitoneal injections of l-DOPA (20mg.kg⁻¹) increased dopamine concentrations in the brain (but not as dramatically as in the periphery); urinary excretion of dopamine was also increased.27 It had been recognized that central and peripheral catecholamine levels were normal in pyridoxine-deficient animals, but Sourkes now reported that the conversion of administered l-DOPA to dopamine was markedly impaired in these animals. In rats treated with the

21 Barbeau, 1961a.
22 Sourkes, 1971a.
24 Schales, 1969.
25 None of these personal communications appears to have been published as full papers.
26 Barbeau, 1961a.
27 Murphy and Sourkes had also shown that D-DOPA can be converted in the rat to L-DOPA and thus used in dopamine synthesis: Murphy and Sourkes, 1961.
decarboxylase inhibitors α-methyldopa or α-methyl-m-tyrosine, brain concentrations of noradrenaline and dopamine (rat) and of 5-HT (guinea pig) were significantly reduced, as was the urinary excretion of dopamine, tryptamine, tyramine and 5-HT.²⁸ He further noted that l-DOPA (up to 40mg.kg⁻¹) had no obvious behavioural effects in the rat, but lower doses (10mg.kg⁻¹) could elicit a remarkable response in iproniazid-treated animals; 20mg.kg⁻³ l-DOPA was often fatal in such animals. Sourkes thus concluded that it was possible to elevate or depress central dopamine levels by administration of either l-DOPA or α-methyldopa:

it is worthwhile considering for the future what effects these or similar treatments would have upon animals bearing experimentally placed lesions of the basal ganglia and in patients with clinical disorders such as Parkinson’s and the striatal syndromes.²⁹

It was at this point the brief article appeared in Science (submitted 28 November 1960; published 26 May 1961) which would prove critical to future developments. By this time, the more specific methods which Sourkes’ laboratory employed had been applied to the question of urinary dopamine in parkinsonism, and the results presented by Barbeau, Murphy and Sourkes at the International Symposium on Neuroleptics in Montréal in November 1960.³⁰ The investigators noted that evidence had accumulated for a role for dopamine in basal ganglia function, and hypothesized that a metabolic change involving dopamine might underlie certain extrapyramidal disorders. Further:

It was presumed that the defect responsible for this difference, probably enzymatic in nature, was not limited to brain tissue and could thus produce general changes detectable by studying the urinary excretion of the catecholamines.³¹

The results reported at the Neuroleptics Symposium were recapitulated (in abridged form) in the Science paper: Barbeau, Murphy and Sourkes reported that urinary excretion of dopamine (but not of noradrenaline or adrenaline) was significantly reduced in parkinsonism (n=30), and increased in Wilson’s disease (table 13-1). The Canadian group had thus provided evidence for a disturbance in dopamine metabolism in parkinsonism, but noted that this would have to be substantiated in the brain. During their reading of the proofs of their paper, the Ehringer and Hornykiewicz report was published, which they acknowledged in an afternote.³² Barbeau noted in passing at a symposium in 1963 that urinary excretion of dopamine was also reduced in some relatives of idiopathic parkinsonian patients, although no clear pattern of inheritance could be established in what he described as a “preliminary study”.³³

Throughout the 1960s and 1970s, the Montréal report would be cited alongside Ehringer and Hornykiewicz (1960) as evidence of the dopamine deficiency in Parkinson’s disease. There were, however, a number of problems associated with the data which must be considered. The first is that Barbeau had previously reported increased excretion of a substance which he believed to be dopamine in Parkinson’s disease; the newer results, however, were gained using the specific fluorescent

²⁸ Some of these results were abstracted from Oates et al., 1960 and Smith, 1960.
²⁹ Sourkes, 1961.
³⁰ Barbeau and Sourkes, 1961. This paper actually constitutes a more thorough presentation of the results and their discussion than the much more frequently cited Science paper.
³¹ Ibid.
³² Barbeau et al., 1961.
³³ In Hebb et al., 1966.


<table>
<thead>
<tr>
<th>Group</th>
<th>Cases (No.)</th>
<th>Samples (No.)</th>
<th>Mean ± standard error</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Dopamine</td>
<td>Noradrenaline</td>
</tr>
<tr>
<td>Normal</td>
<td>24</td>
<td>24</td>
<td>316 ± 14.6</td>
</tr>
<tr>
<td>Parkinsonism (all types)</td>
<td>16</td>
<td>16</td>
<td>241 ± 21.5</td>
</tr>
<tr>
<td>Post-encephalic</td>
<td>6</td>
<td>6</td>
<td>177 ± 41.8</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>8</td>
<td>8</td>
<td>297 ± 36.2</td>
</tr>
<tr>
<td>Arteriosclerotic</td>
<td>2</td>
<td>2</td>
<td>(212)</td>
</tr>
<tr>
<td>Striatal syndromes (all types)</td>
<td>16</td>
<td>32</td>
<td>377 ± 23.9</td>
</tr>
<tr>
<td>Wilson’s disease</td>
<td>3</td>
<td>17</td>
<td>418 ± 24.8</td>
</tr>
<tr>
<td>Huntington’s chorea</td>
<td>4</td>
<td>5</td>
<td>272 ± 45.8</td>
</tr>
<tr>
<td>Dystonia</td>
<td>4</td>
<td>5</td>
<td>395 ± 45.8</td>
</tr>
<tr>
<td>Sydenham’s chorea</td>
<td>2</td>
<td>2</td>
<td>334</td>
</tr>
<tr>
<td>Familial tremor</td>
<td>1</td>
<td>1</td>
<td>334</td>
</tr>
<tr>
<td>Torticollis</td>
<td>1</td>
<td>1</td>
<td>328</td>
</tr>
<tr>
<td>Choreoathetosis</td>
<td>1</td>
<td>1</td>
<td>308</td>
</tr>
</tbody>
</table>

Table 13-1: Excretion of urinary catecholamines (µg/24hr), as reported by Barbeau et al., 1961 and Barbeau and Sourkes, 1961. Bold figures: p < 0.01; * p < 0.05. The figures cited in Barbeau’s presentation to the International Congress on Neurology (Rome, September 1961) diverge slightly from those here, in that the value given for post-encephalitic parkinsonian patients was 177 ± 18µg, and that for the idiopathic parkinsonian patients was 297 ± 31µg. The significance of the difference for dopamine levels in striatal syndromes (all types) was given as p < 0.01 in Barbeau et al., 1961, and as p < 0.02 in Barbeau and Sourkes, 1962. Dopamine excretion by the arteriosclerotic group was listed as significantly different (p < 0.01) in Barbeau and Sourkes, 1961. The mean was given as 211.5 ± 0.5). For adrenaline and noradrenaline excretion, only the figures in the shaded boxes were included in Barbeau et al., 1961.

techniques available in Sourkes’ laboratory, and would thus be considered more reliable. Interestingly, O’Reilly and colleagues later reported in a small study (five post-encephalitic cases and one other parkinsonian patient) that dopamine excretion was indeed increased in parkinsonism, as was 5-HIAA excretion.34 In 1961, Barbeau and colleagues observed that the degree of difference was related to the degree of akinesia,35 and Barbeau would ultimately qualify the original finding of the group by suggesting that reduced urinary dopamine levels were characteristic of akineto-rigid and late stage parkinsonian patients; where tremor or dyskinesia was dominant, normal or even increased levels could be found.36

The first major concern, however, must be the control group employed to define “normal” excretion: these were twenty-four laboratory personnel, presumably not age-matched with the patient group. This problem becomes clearer when one examines the more detailed presentation of the data published in the proceedings of the Bel-Air Symposium on Monoamines and the Central Nervous System, at which the results were presented in Geneva in September 1961 (table 13-2).37 By this point, the number of controls had increased to thirty-one, the number of parkinsonian patients to thirty. The

34 O’Reilly et al., 1965.
35 Barbeau et al., 1962.
37 Barbeau et al., 1962.
urine volume excreted in the 24 hour test period by the parkinsonian group was about 75% of that of the control group; when the results were expressed as ng/ml urine, however, rather than as µg/24h, the difference between the parkinsonian and normal groups disappeared. The authors were aware of this problem, and commented that:

one should regard these results [expressed as ng/ml] with suspicion, because they differ from those obtained by the analysis of covariance for the whole series.38

An admirable feature of the work of the Montréal group was their utilization of statistical analysis to determine the significance of their results, which habit Sourkes had brought to his work from his time at the Food and Drug Directorate; this was not yet usual practice in neurochemistry. However, the arguments employed in this presentation to justify the interpretation of their results appear convoluted and unconvincing. The fact remains, that when the figures are corrected for volume, dopamine excretion in the Parkinson’s disease patients was normal, while that of noradrenaline was increased. The question then arises of which figure possesses the greater physiological significance; this could only have been addressed by the use of an age-matched control group.

<table>
<thead>
<tr>
<th>Cases</th>
<th>Mean urinary volume (mL)</th>
<th>Dopamine µg/24hr</th>
<th>Noradrenaline µg/24hr</th>
<th>Adrenaline ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normals</td>
<td>31</td>
<td>1288</td>
<td>303.4</td>
<td>262.0</td>
</tr>
<tr>
<td>Parkinsonian</td>
<td>30</td>
<td>947</td>
<td>219.8</td>
<td>260.2</td>
</tr>
<tr>
<td>Post-encephalitic</td>
<td>12</td>
<td>904</td>
<td>188.4</td>
<td>24.4</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>15</td>
<td>1050</td>
<td>256.3</td>
<td>266.2</td>
</tr>
<tr>
<td>Arteriosclerotic</td>
<td>3</td>
<td>617</td>
<td>163.0</td>
<td>273.7</td>
</tr>
</tbody>
</table>

Table 13-2: Catecholamine excretion in parkinsonian patients and normal controls as reported by Barbeau et al., 1961.

The Science report included data for the individual Parkinson’s disease subtypes, whereby it was found that a statistically significant difference existed only between the dopamine excretion of the post-encephalitic parkinsonism group and controls; the arteriosclerotic group, although reduced, was too small in numbers to yield a significant difference, while the dopamine excretion of the idiopathic parkinsonian group was ‘normal’.39 The comment was made, however, that fourteen of the sixteen idiopathic patients had values below the normal mean, while two patients with family histories of other extrapyramidal disease had high values; the mean for the fourteen was 256µg/day.40 The expanded data found once again that dopamine excretion in this latter group was greater than in the other parkinsonian groups, but once again, the excretion rates corrected for volume showed no clear differences from the control group. It is

38 Ibid.
39 Barbeau et al., 1961. It was, however, listed as being significant (p<0.01) when first presented at the International Symposium on the Extrapyramidal System and Neuroleptics in Montréal in 1960: Barbeau and Sourkes, 1961.
40 Barbeau and Sourkes, 1961.
significant to note that the urinary volume was greatest in the idiopathic group and smallest in the arteriosclerotic group, suggestive of an age-related decline in urinary output.41

It was often emphasized that the excretion of catecholamines other than dopamine was normal in parkinsonian patients, as also reported by Nashold and Kirshner.42 Specifically, the sharp reduction of noradrenaline excretion observed in arteriosclerotic patients does not seem to have been discussed. The urinary excretion of this catecholamine, on the other hand, was higher in the hospitalized patients who were added to the expanded study, dramatically so if the output was corrected for urine volume. This phenomenon was not further discussed, except to suggest that it was probably responsible for the positive responses observed with the aortic strip test employed in Barbeau’s earlier investigation.43

Another detail given in the expanded report pointed to a problem in the experimental design which had dogged research in parkinsonism for years. Of the fifteen genuine parkinsonian patients examined in the Science report – it had proved on autopsy that one of the patients had probably suffered from Creutzfeldt-Jakob disease, not parkinsonism – eight were ambulant patients, seven were hospitalized. The fifteen patients who had been added to the study were all hospitalized cases; further, urinary volume and dopamine excretion (µg/24hr) was very much lower in these new subjects, the result of which was a further depression of mean daily dopamine output in the parkinsonian group. Parkinsonian patients of differing etiology had been pooled, and it would seem that the severity of the disorder varied also greatly in the group employed in the study; this renders interpretation of the results very difficult. The same criticism could be directed at Hornykiewicz’ investigation of brain dopamine, but in the differences detected in parkinsonian brains by the Viennese group differed only in degree, not direction. Equally importantly, Hornykiewicz directly assayed catecholamine levels in the brain, not their urinary excretion; this raises the most important question about the Montréal results. This is despite the fact that the group was aware of the complications involved in investigating heterogenous research populations; the second group of parkinsonian patients had, in fact, been carefully selected on the basis that their medication had been withdrawn for at least two weeks – a highly unusual practice – and were hospitalized.44

This final problem is the most important: whether the changes identified were physiologically significant or not, it would appear unlikely that they had any direct connection with a dopamine deficiency in the brain. Duvoisin noted in 1963 that most of the urinary dopamine was probably, in fact, produced in the kidney itself; further, the fact that the changes were greatest in the post-encephalitic patients suggested that, contrary to the Canadians’ interpretation, any change related to the central nervous system was the end result of a degenerative process, not the expression of a metabolic defect.45 Barbeau provided an unclear response to this question, but could assure Duvoisin that other tests had revealed no abnormalities in renal function, thus excluding the possibility that long-term treatment with other had damaged this organ. McGeer and

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41 Ibid.
43 Barbeau et al., 1962.
44 Ibid.
45 In Hebb et al., 1966.
Zeldowicz also noted in their negative report concerning the use of \textit{L}-DOPA in Parkinson’s disease:

> \textit{Only a tiny fraction of the total metabolism of the amines could pass through extrapyramidal cells, the major part being carried out in the gut, lungs, heart, adrenal medulla and other non-nervous tissue. Therefore, impairment of cells of the extrapyramidal system should not by itself noticeably affect the total excretion of amines or their metabolites.}\(^{46}\)

This would, in fact, be a complicating factor in the evolution of DOPA therapy for parkinsonism; the decarboxylase activity in the periphery is such that most exogenously applied \textit{L}-DOPA is metabolized before it can enter the brain.

A number of laboratories reported that they were unable to confirm the decreased urinary dopamine excretion.\(^{47}\) Bischoff and Torres (Santa Barbara Cottage Hospital Research Institute, Santa Barbara) were an exception. Using the similar techniques to the Canadians, they also reported that the mean amount of dopamine excreted by ten male controls during waking hours was 19 ± 4 µg.h\(^{-1}\) (range: 7-38) and 9 ± 1µg.h\(^{-1}\) during sleep (range: 5-15), while for seven cases of parkinsonism (three male) the mean excretion throughout 24 hours was 7 ± 1µg.h\(^{-1}\) (range: 3-11). A similar decline, however, was also found in seven cases of cirrhosis of the liver and sic cases of diabetes.\(^{48}\) Further, Hoehn’s group reported in 1976 that unconjugated urinary dopamine was negatively correlated with rigidity and akinesia in parkinsonian patients.\(^{49}\) Apart from these reports, however, corroborating evidence for the Canadian findings was sparse. This, however, casts doubt on the accuracy of the results reported by Sourkes’ laboratory; it must be remembered that there were only isolated efforts to replicate this work, as was also the case with Ehringer and Hornykiewicz’ identification of reduced basal ganglia dopamine concentrations.

Hornykiewicz did not address the question of dopamine excretion, concentrating his efforts on dopamine and metabolite levels in the brain itself. Greer and Williams found that HVA excretion was normal in parkinsonian patients of all three types; if anything, HVA excretion was elevated in post-encephalitic patients. Nor was the increase following administration of 2mg reserpine or 1g \textit{D,L}-DOPA markedly different from that seen in control subjects, although there was a tendency for the increase following \textit{D,L}-DOPA to be lower in parkinsonian patients; but the number of patients studied was too low to give any firm conclusions.\(^{50}\) This was consistent with the finding of Sourkes’ group that the metabolism of exogenous \textit{L}-DOPA was aberrant in parkinsonian patients (see below and table 13-3).\(^{51}\) Weil-Malherbe and van Buren examined both free and conjugated urinary dopamine (it was estimated that only 20-40% of excreted dopamine is unconjugated) in thirty-four parkinsonian patients of mixed type and a control group of nine students and eleven prisoner patients; the authors were unable to assemble an appropriate matched control group. The parkinsonian patients excreted about half as much urinary free dopamine as the control persons (67.5 ± 3.2 v. 126.4µg/24h); each group excreted about the same amount of conjugated dopamine (230 ± 12 v. 246 ±

\(^{46}\) McGeer and Zeldowicz, 1964.

\(^{47}\) O’Reilly et al., 1965; Westlake and Tew, 1966.

\(^{48}\) Bischoff and Torres, 1962.

\(^{49}\) Hoehn et al., 1976.

\(^{50}\) Greer and Williams, 1963. See similar results in Calne et al., 1969c.

\(^{51}\) Barbeau et al., 1962.
### XIII. Montréal and Göteborg: from dopamine deficit to the nigrostriatal pathway

<table>
<thead>
<tr>
<th>Cases</th>
<th>Dopamine (µg/6h)</th>
<th>DOPAC (µg/6h)</th>
<th>Volume (ng/mL)</th>
<th>Volume (mL/6h)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control period</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normals</td>
<td>6</td>
<td>79</td>
<td>23</td>
<td>673</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>8</td>
<td>58</td>
<td>31</td>
<td>272</td>
</tr>
<tr>
<td><strong>After dose</strong></td>
<td>(200mg L-DOPA)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normals</td>
<td>6</td>
<td>5224</td>
<td>1090</td>
<td>53,729</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>8</td>
<td>1301</td>
<td>540</td>
<td>24,707</td>
</tr>
</tbody>
</table>

Table 13-3: Metabolism of exogenous l-DOPA, as reported by Barbeau et al., 1962.

23µg/24h) and HVA (2528 ± 157 v. 2714 ± 168µg/24h), while DOPAC excretion was reduced by about 33% in the patients group (1273 ± 78 v. 1805 ± 182µg/24h), but this difference was not consistently significant. The authors related the difference in free dopamine excretion to long term therapy with anticholinergic drugs.52 Boulton and colleagues reported in 1967 that urinary tyramine levels were elevated in parkinsonism;53 it was suggested that this might be due to the decarboxylation of tyrosine resulting from a problem in tyrosine hydroxylase activity.54

Barbeau and Sourkes interpreted their results as indicative of either a general metabolic fault in parkinsonian patients or of a reduction in a specific autonomic activity. The authors themselves were aware of the difficulties involved in interpreting their findings; Sourkes discussed at length the problems associated with the Montréal study in 1970.55 While conceding that the urinary output was unlikely to reflect central metabolism, the results as published were defended. Once more, he dismissed the possibility of a volume effect on the grounds that there was no evidence of a correlation between dopamine excretion and urinary volume; the impact of age on either of these factors, however, was not discussed. By this stage, dietary effects and a general enzymatic defect affecting dopamine metabolism were also considered unlikely. Most importantly, Sourkes concluded:

> It is unlikely that urinary dopamine reflects directly the turnover rate of dopamine in the brain. The latter rate is not great enough to account for the output.56

More recently, Sourkes suggested that decreased urinary dopamine might “reflect a deficiency in some autonomic activity”, and that genetic studies might “yet explain this dual deficiency, occurring centrally and peripherally”.57 Another possibility suggested by Weil-Malherbe and Van Buren was that chronic treatment with antiparkinsonian drugs might be responsible for reduced urinary dopamine levels; as far as I can determine, this hypothesis has not been closely tested.58 The examination by Calne’s

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52 Weil-Malherbe and van Buren, 1969.
53 Boulton et al., 1967.
54 Watt, 1967.
55 Sourkes, 1971a.
56 Ibid.
58 Weil-Malherbe and van Buren, 1969.
group of L-DOPA metabolism in parkinsonian patients detected no general metabolic fault in this group.59

**L-DOPA therapy in Montréal**

Whatever the significance of these results, the paper became one of the most cited in dopamine and Parkinson’s disease research; more importantly, it motivated the group to undertake the next step, the administration of L-DOPA to compensate the presumed central deficit. It would not have been the first (or the last) time that the correct therapy was adopted for what proved to be doubtful or even false reasons. As discussed above, Sourkes and Murphy had already examined the modification of catecholamine levels in the rodent brain, and had shown that single doses of L-DOPA elevated central dopamine levels for up to eight hours following administration; the effect was greater when the MAO inhibitor iproniazid was also administered. They therefore proposed to Barbeau that he test the effect of the amino acid on parkinsonian patients.

Barbeau presented the preliminary results of this experiment at the Seventh International Congress of Neurology in Rome in September 1961. He reported a clear but short-lived (30min-2 hours) improvement of rigidity and akinesia in six patients treated with 200mg L-DOPA p.o. Four patients receiving L-DOPA alone exhibited 15-75% improvement, two who also received the MAO inhibitor tranylcypromine (Parnate, SK&F)60 showed 60-85% improvement; a seventh patient who received 5g tyrosine showed 40% improvement.61 In no case was tremor improved; in one case it was exacerbated. A further ten parkinsonian patients received 3×10mg tranylcypromine per day, and exhibited a 50-100% improvement in tremor 4-5 days after commencement of treatment, but only 20% in rigidity; two patients receiving α-methyldopa (3×250mg/day) showed a deterioration of both rigidity and tremor within two days. Barbeau concluded that dopamine was probably involved in the production of akinesia or rigidity, but not of tremor; further investigations of the use of L-DOPA, tryptophan and 5-HTP were underway.62 In a report published with Yves Duchastel the following year, Barbeau treated thirty parkinsonian patients with tranylcypromine alone; a mean improvement in tremor score of about 40% was noted at two weeks and three months, while rigidity scores were improved by about 25% and 40% at these two time points. The authors also found that the MAO inhibitor was effective against the trifluoperazine-induced extrapyramidal syndrome, whether administered together with the neuroleptic or subsequent to the development of symptoms.63

There were only a handful of other reports on Parkinson’s disease made at the Rome conference. The major volume of the proceedings consisted of over 1000 pages, of which twenty were occupied by the session on parkinsonism; and of these six reports, two were not actually concerned with Parkinson’s disease: one discussed Wilson’s disease, the other “neurological manifestations as the common denomination of somatic treatments in psychiatry”.64 Three of the papers in this session directly concerned therapy, including that of Barbeau. The others were by J. Nehlil (Paris), who spoke on

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59 Calne *et al*., 1969c.
61 A battery of tests described by Burns and de Jong (1960) were used for assessment of response.
62 Barbeau, 1961b.
63 Barbeau and Duchastel, 1962.
64 *Proceedings of the VII International Congress of Neurology*, pp.928-931 and 935-937.
the psychological effects of stereotactic surgery, and G. Ganев, who spoke on the work of a Bulgarian group with new agents for the treatment of parkinsonism, the isoniazid derivative, INHA-17, and ‘Bellazon’ (the combination of INHA-17 with ‘Bellapan’). INHA-17 alone (2-3××150mg/day, p.o.) effected improvement in twenty-nine of thirty-six cases, in seven a “marked improvement”. Reduction in rigor (83%), brady- (75%) and hypokinesia (72%), gait (80%), speech (56%) and affect (71%) were reported, and these were raised to almost 100% and prolonged in duration by concurrent use of Bellapan (2×0.5mg, p.o.) in twenty-five patients. Tremor was also improved in two-thirds of cases by INHA-17, but this was not significantly affected by ‘Bellapan’. Etiology of the disease did not seem important. Side effects were tachycardia, dryness of the throat and anxiety, but these were rare and reduced by dose adjustment.

A further paper on parkinsonism was presented in a different session. Its title, “Biopsy and post-mortem studies of basal ganglia in Parkinson’s disease” was interesting in light of the recent findings of Ehringer and Hornykiewicz, but failed to report anything remarkably novel. The study had the specific aim of examining DNA, RNA, lipids, iron and calcium in the basal ganglia and cortex; both electron microscope and histochemical studies revealed the presence of intracellular inclusions associated with eccentricity of the nucleus, but this had been known since Lewy. Other changes observed were altered RNA concentrations and distribution, varying amounts of an “iron stainable substance” and marked mitochondrial pleomorphism. What rendered the paper especially interesting was the fact that some of the material was taken from biopsies removed from sixteen patients undergoing pallidal surgery for parkinsonism. It was commented during the discussion following their presentation to the American Neurological Association the following year:

One cannot but admire a group of investigators who have the temerity to tackle a problem of this magnitude, utilizing human biopsy material with a battery of techniques which leaves one breathless.

The authors were cautious in the interpretation of the results. The major problem was the lack of an obvious source for control material; in the second report, biopsies collected from five schizophrenic patients were used “only for comparative purposes”. There were numerous questions to be addressed with respect to the possibility of artifacts associated with the techniques employed. It was nevertheless interesting to find that at least some of the changes identified in the past in post mortem material were also detectable in material from the living brain. It was also interesting that there was no mention of Ehringer and Hornykiewicz’ work.

65 ‘Bellapan’, a product of the Bulgarian Pharmaceutical Cooperative Company “Galenus” (Sofia), consisted of a total alkaloid extract of Bulgarian belladonna in the form of the tartrate; it was supplied in 0.5mg tablets (Ludwig et al., 1948, p.105). I have not found further information on INHA-17, except that it was used in Bulgaria in the therapy of tuberculosis (Beltschewa-Petrowa, 1965), and was also known in the clinic as ‘Nevropan’; see also Stolyarova, 1966, 1976. It should be noted that isoniazid was referred to by some European groups as INH (isonicotinic acid hydrazide).

66 Ganev et al., 1961. The sixth paper in the Parkinson’s disease session discussed the cog-wheel phenomenon of parkinsonism, and the differentiation of the neurological bases of resting and action tremor.

67 Roizin et al., 1961.

68 Roizin et al., 1962. Curiously, in this second study the results for only ten Parkinson’s disease and two post-encephalitic parkinsonian cases was presented; in the 1961 report, parkinsonian biopsies were reported. For use of human brain biopsy material, see also Kalyanaraman and Gillingham, 1964.

The experimental administration of L-DOPA to parkinsonian patients by the Canadians was reported in a more detailed report at the Bel-Air Symposium on Monoamines and the Central Nervous System in Geneva, also in September 1961. Six controls and eight parkinsonian patients (type not indicated) received 200mg L-DOPA orally (in the form of capsules); the increase in urinary excretion of dopamine following the dose was much smaller in the patients than in the controls (both absolute and corrected for volume), as was DOPAC excretion, though not as dramatically; this was tentatively interpreted as indicating that decarboxylase activity in these patients was reduced. The attempt was then made to elevate cerebral dopamine levels by use of MAO inhibitors, L-DOPA and a combination of the two. Tranylcypromine (3×10mg/day) improved tremor after 2-3 days and rigidity after one month; by three months, a 40% improvement in both symptoms had been achieved. The decarboxylase inhibitor α-methyldopa, on the other hand, was found to aggravate tremor, but not rigidity, in at least some parkinsonian patients. Finally, it was established that L-DOPA (100-200mg) exerted a noticeable effect on rigidity (improvement: ∼50%); despite the comment of the authors, there was no indication that this effect was enhanced by the concurrent administration of an MAO inhibitor. The improvement began about 30 minutes after ingestion and lasted 2-2½ hours. The effect on tremor of L-DOPA alone was not significant; combined with tranylcypromine, it exacerbated it. Tyrosine (5g) and meta-tyrosine (200mg) were also found to improve rigidity (∼30%) without altering tremor. The effect of L-DOPA could be blocked by α-methylldopa; D-DOPA was without effect on parkinsonian symptoms. Chronic administration of L-DOPA was also found to be beneficial for rigidity, although the benefit seen in the acute study could only be sustained when L-DOPA (3×100mg or 6×50mg/day) was combined with the traditional antiparkinsonian agent procyclidine (3×2.5mg/day) (table 13-4).

The results of this study were certainly encouraging. The authors were still speaking at this stage of a general metabolic fault involving dopamine synthesis, an hypothesis supported by the laboratory findings they reported at the symposium. More specifically, the Canadians saw this catecholamine problem, which probably involved MAO and DOPA decarboxylase, as being directly responsible only for the rigidity; “it will be necessary to discover a similar deficiency in the metabolism of other amines in order to explain the other symptoms.” The chairman of the clinical session at the symposium, de Ajuriaguerra, noted the findings of Barbeau’s group in his summation, but did not seem overly excited by them. He noted that Barbeau’s new results contrasted with his earlier work concerning increased excretion of a catecholamine – De Ajuriaguerra interpreted the new results as indicating that urinary excretion of both dopamine and noradrenaline was reduced – but was also impressed by the fact that the new results were consistent with Ehringer’s work. De Ajuriaguerra, however, appeared to be more interested in the insights into the role of monoamine metabolism in psychosis and neuroleptic action which experiments such as those of the Montréal group might yield.

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70 Marsh and colleagues, on the other hand, reported in 1963 some benefit for parkinsonian tremor of α-methyldopa; this was, however, unusual; Menon (1965) and Schwab and England (1968) also reported that α-methyldopa elicited or exacerbated parkinsonian symptoms.

71 Barbeau et al., 1962. Parkinsonism was a frequent side effect of methyldopa therapy of hypertension. Curiously, however, there were also reports its improving parkinsonian tremor (but not rigidity) or not affecting parkinsonian symptomatology: see Groden, 1963; Markham et al., 1963; Peaston, 1964.

72 Barbeau et al., 1962.

73 De Ajuriaguerra, 1962. The other five presentations in this session were also concerned with monoamines for the classification and treatment of psychosis. The biochemical session assembled the
XIII. Montréal and Göteborg: from dopamine deficit to the nigrostriatal pathway

<table>
<thead>
<tr>
<th>Precursor</th>
<th>Test</th>
<th>Other treatment</th>
<th>Number of tests</th>
<th>Mean % improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-DOPA (100mg)</td>
<td></td>
<td></td>
<td>2</td>
<td>50</td>
</tr>
<tr>
<td>L-DOPA (100mg)</td>
<td></td>
<td>Tranylcypromine</td>
<td>3</td>
<td>51</td>
</tr>
<tr>
<td>L-DOPA (200mg)</td>
<td></td>
<td></td>
<td>13</td>
<td>46</td>
</tr>
<tr>
<td>L-DOPA (200mg)</td>
<td></td>
<td>Aldomet</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>Tyrosine (5g)</td>
<td></td>
<td></td>
<td>3</td>
<td>30</td>
</tr>
<tr>
<td>Controls</td>
<td></td>
<td>Aldomet</td>
<td>4</td>
<td>-18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Procyclidine</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>D-DOPA (200mg)</td>
<td></td>
<td></td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Meta-tyrosine (200mg)</td>
<td></td>
<td></td>
<td>4</td>
<td>30</td>
</tr>
</tbody>
</table>

**Table 13-4: Summary of the experimental treatment of parkinsonism with dopamine precursors, as reported by Barbeau et al., 1962.**

Sourkes and Barbeau each reported their results at several meetings over the next few years; their findings and trial of DOPA in twenty-six patients even merited an article in the *New York Times* in April 1962. The article concerned a presentation on by Barbeau, Jasmin and Duchastel concerning the biochemistry of Parkinson’s disease at the annual meeting of the American Academy of Neurology in New York on 26 April 1962; Barbeau had “

> cited evidence that the brains of persons afflicted with Parkinson’s disease showed abnormally low concentrations of two related chemicals called dopamine and serotonin."

On the basis of this evidence, referring to the work of Hornykiewicz in Vienna, Barbeau had treated twenty-six patients with “dopa” and achieved rapid but fleeting results. The major problem, however, was scarcity of the drug; Barbeau estimated the cost of “giving one patient just one dose and testing him to gauge the drug’s effects” as lying around $100.77

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74 Leading monoamine researchers at this time: Brodie and Costa, Garattini and Valzelli, Carlsson and Lindqvist, Waelsch, and Pletscher and Gey, as well as the veteran of MAO research, Zeller.
75 For example, the L.B. Mendel Symposium on Nutrition and Mental Disease (Elgin; Sourkes, 1963b); Second International Pharmacological Meeting (Prague; Sourkes, 1964a); Galesburg Symposium on the Developing Brain (Sourkes, 1964b).
76 Later published as Barbeau et al., 1963.
77 Schmeck, 1962.
78 Ibid.
The Canadians had learned by now of the intravenous L-DOPA therapy introduced in Vienna (Barbeau and Sourkes visited Hornykiewicz in Vienna while in Europe for the two conferences, and also met Birkmayer), but there still remained a great deal of scepticism amongst other workers with regard to the use of L-DOPA in Parkinson’s disease; this was the period of “seven lean years” mentioned by Hornykiewicz in his history of L-DOPA. SOURKES AND BARBEAU recognized that they needed to examine post mortem brain tissue in order to solidify their hypothesis of decreased central dopamine levels in parkinsonism, but, like most researchers outside Austria, had no ready access to such material. SOURKES’ group, however, would later report that cerebral ventricular levels of HVA were decreased in Parkinson’s disease, consistent with Hornykiewicz’ findings in cerebrospinal fluid.

Barbeau and Sourkes had already ceased their collaboration by the mid-1960s; the differences of personality and approach to research determined that their relationship would not enjoy the relative longevity of that of Birkmayer and Hornykiewicz in Vienna. This problem first manifested itself in print in 1963. At the end of 1962, Barbeau had published a “new hypothesis” for the pathogenesis of Parkinson’s disease in the Canadian Medical Association Journal. After reviewing the major results of his work with Sourkes, Barbeau reported that he had extended this investigation by measuring the 5-HT metabolite 5-HIAA in urine, and found that the levels in Parkinson’s disease were much reduced compared to those in control persons; further, the increase in 5-HIAA excretion produced by challenging patients with D,L-tryptophan was also lower than normal. BARBEAU therefore hypothesized that DOPA/5-HTP-decarboxylase was the critical locus in Parkinson’s disease. He reported unpublished observations that 5-HTP improved parkinsonian tremor, and to a lesser degree, rigidity; the benefit of L-DOPA and 5-HTP together was greater than that of either agent alone. This would be in line with Carlsson’s finding of 1957, which has otherwise been largely forgotten, that 5-HTP enhanced the anti-reserpine effects of L-DOPA. But Barbeau noted that antiparkinsonian drugs had hitherto been judged according to their anticholinergic and antihistaminergic effects; he argued, however, that other potential transmitter substances, including Florey’s recently described “inhibitory factor I”, showed distributions in the central nervous system which suggested a role in extrapyramidal function. Discussion of the etiology of parkinsonian symptoms could thus not be restricted to the dopamine deficiency.

At the end of this discussion, Barbeau presented his new hypothesis, which was essentially an extension of McGeer’s recently proposed model of a balance between catecholaminergic/serotonergic and cholinergic/histaminergic function in the brain. BARBEAU noted that, on the basis of the observed responses to the various drugs then employed in parkinsonism, the three major symptoms of the disorder were probably associated with different transmitter systems or their interactions; specifically:

1. An imbalance or disequilibrium in a system linking dopamine and acetylcholine would result in symptoms such as rigidity and akinesia.
2. Disequilibrium of serotonin and histamine produced tremor and akathisia.

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78 Hornykiewicz, 1992.
80 See also Barbeau et al., 1963; but see Resnick et al., 1962.
81 Barbeau, 1962.
82 McGeer et al., 1961.
83 Barbeau, 1962.
In 1961, a more elaborate neurochemical hypothesis was not possible, and this scheme certainly allowed explanation of the difficulty in treating all three major symptoms of Parkinson’s disease with one agent. It was the first explicit statement of the hypothesis that Parkinson’s disease can not be attributed to a single fault, whether neurological or neurochemical; Barbeau would later express this concept in his description of Parkinson’s disease as a “systemic disease”, a viewpoint which he often vigorously defended against what he saw as an overemphasized concentration on dopamine alone:

One of the great misconceptions that has plagued research in Parkinson’s disease, is the assumption that because a dopamine deficiency had been demonstrated in the brains of patients and that some of the symptoms were corrected by levo-dopa therapy, it could therefore be concluded that the defect in dopamine metabolism was causal.\(^8\)

This problem was addressed only sporadically in the following thirty years, especially after the L-DOPA therapy had established itself; an attempt to specifically redress this conceptual imbalance came to clearest expression in the “balance hypothesis” of Birkmayer’s group\(^8\) and the pathohistological work of the Braaks.\(^8\) Sourkes, however, expressed his strong concern in a letter to the Journal that the hypothesis was overly speculative, a concern which he undoubtedly shared with many other workers at the time, judging by its lack of significant echo. There were also a number of factual errors and unclarities in Barbeau’s paper which undermined its authority to some degree.\(^8\)

Nevertheless, the proposal of a purely biochemical hypothesis for Parkinson’s disease was a novelty which pointed the direction of future developments.

Barbeau continued his search for the metabolic bases of the neurochemical changes he had discovered. He mentioned at the end of his “new hypothesis” paper that he had found serum magnesium levels to be reduced in parkinsonian patients, and also in those with familial tremor or delirium tremens; Schwab’s group, however, could not confirm this result.\(^8\) At the symposium held by the National Parkinson Foundation in Miami Beach in April 1964, Barbeau and his fellow neurologist Danielle Raymond-Tremblay reported once again significantly reduced blood magnesium levels (though not as dramatically as in his first report) accompanied by normal levels of calcium, sodium, potassium and phosphates in parkinsonian patients; parameters of hepatic and renal function were normal, as were blood β-lipoprotein values and parameters of thyroid function. Once again, urinary dopamine concentrations (expressed as µg.L\(^{-1}\) or µg.g\(^{-1}\) creatine) were significantly reduced; Barbeau had been careful in this study to use age-matched controls in order to facilitate intergroup comparisons. The novel part of this report was the finding that the dimethylated dopamine derivative 3,4-dimethoxyphenylethylamine (DIMPEA) occurred more frequently in the urine of Parkinson’s disease patients than that of control neurological patients; this substance had recently been identified in the urine of acute schizophrenics and was believed to reflect abnormal dopamine metabolism in these patients.\(^8\) Urinary concentrations of dopamine and DIMPEA were inversely correlated; further, DIMPEA excretion was positively correlated with the degree of akinesia. Barbeau interpreted his results more
carefully than in his previous papers, but suggested that low Mg\(^{2+}\) levels might lead to increased methylation of dopamine by catechol-\(\alpha\)-methyl transferase, acknowledging at the same time the unusual specificity for dopamine methylation which this hypothesis required. Interestingly, injection of DIMPEA was associated with an akinetic-rigid syndrome in both mice and monkeys.\(^{90}\)

<table>
<thead>
<tr>
<th></th>
<th>Urine volume (mL)</th>
<th>Dopamine (µg.L(^{-1}))</th>
<th>Noradrenaline (µg.g(^{-1}) creatine)</th>
<th>Adrenaline (µg.g(^{-1}) creatine)</th>
<th>5-HIAA</th>
<th>Blood Mg(^{2+}) mEq.L(^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Controls</strong></td>
<td>854</td>
<td>228 ± 31.2</td>
<td>225 ± 37.9</td>
<td>97.6</td>
<td>26.7 ± 2.9</td>
<td>5.83</td>
</tr>
<tr>
<td><strong>Parkinson’s disease</strong></td>
<td>869</td>
<td>97.8 ± 35.8</td>
<td>96.3 ± 31.6</td>
<td>98.2</td>
<td>27.3 ± 5.1</td>
<td>6.10</td>
</tr>
<tr>
<td><strong>Hemiplegia</strong></td>
<td>943</td>
<td>131 ± 20.6</td>
<td>129 ± 25.4</td>
<td>67.3</td>
<td>15.9 ± 4.2</td>
<td>4.52</td>
</tr>
</tbody>
</table>

**Table 13-5:** Urinary excretion of catecholamines and 5-HIAA and blood Mg\(^{2+}\) levels, as reported by Barbeau, 1965. Controls were patients who had been placed in the same hospital as the other subjects, but for reasons other than neurological or psychiatric illness; hemiplegia patients served as a second, ‘neurological’ control group. There were eleven patients in each group. Figures in bold are significantly different from control values (\(p < 0.02\)).

The hypothesis seems convoluted, but it must be remembered that workers at this time did not have access to the body of biochemical knowledge which is now available; in his presentation, Barbeau alluded carefully to the fact that dopamine “probably” plays a role as neural transmitter or modulator in extrapyramidal pathways:

*This could be facilitatory on \(\beta\)-adrenergic receptors and probably inhibitory on \(\alpha\)-adrenergic receptors. This would explain how, for example, dopamine could mediate transmission in the nigro-spinal pathway to produce initiation of movement and at the same time play an inhibitory role upon the globus pallidus and the thalamic centres related to the ascending activating system.*\(^{91}\)

There existed at this time no model of the motor loop (a question which today still provokes controversy) and no knowledge of specific dopamine receptors; a certain degree of fumbling in the dark was inevitable. DIMPEA will be mentioned again a little later, but this compound, interesting as it was, played no part in the development of antiparkinsonian therapy. Barbeau’s further pursued the investigation of parkinsonism until the mid-1970s alongside other research interests, including oculo-pharyngeal muscular dystrophy and heavy metal-induced epilepsy. After a decade devoted largely to research into the inherited ataxias, Barbeau returned to parkinsonism in the final years of his life, pursuing the interaction genetic and environmental factors in the disorder, with a particular interest in possible links between cytochrome P450 malfunction and parkinsonism.\(^{92}\)

\(^{90}\) Barbeau and Raymond-Tremblay, 1965.

\(^{91}\) Ibid.

\(^{92}\) For example: Barbeau and Pourcher, 1982; Barbeau et al., 1985, 1987.
The rediscovery of the nigrostriatal pathway

Sourkes himself published a comprehensive review in 1964 of the evidence for disturbed dopamine metabolism as the underlying cause in parkinsonism. Evidence for the involvement of various factors in this defect – DOPA decarboxylase, MAO, the storage of dopamine – were considered, but Sourkes concluded that the available data was as yet insufficient for speculation on the ultimate cause of parkinsonism. At the same time, he was already involved in putting the next major piece of the puzzle into place.

The identification of a problem in dopamine metabolism by the Viennese and Montréal groups was not greeted with the immediate excitement which one might have expected. This was partly due to problems with its logical correlate, the L-DOPA therapy (see next chapter); there was, however, also a theoretical difficulty. As discussed above, it had come to be broadly accepted by the early 1960s that the archetypal lesion in Parkinson’s disease involved the substantia nigra; the problem was explaining how this could be related to a dopamine deficiency in the striatum, a region where histopathological changes had not been consistently observed in parkinsonism.

The ostensibly obvious answer was that a nerve pathway originating in the substantia nigra delivered dopamine to the striatum, and that the degeneration of this pathway led to the observed striatal dopamine deficiency. Evidence for the existence of this pathway had been reported throughout the twentieth century. Harold Rosegay put his finger on the problem in 1944:

*The experimental determination of the striatal connections of the substantia nigra has proved to be one of the most elusive problems in brain-stem morphology.*

By the time of his paper, which described part of his doctoral work at Cornell University, the strionigral pathway had been described in the dog, monkey and man (von Monakow had described the loss of nigral cells following lesioning of the striatum in 1895); but as early as 1901, it had been suggested that there might exist a pathway in the opposite direction. Such a pathway had already been described in the dog (Holmes, 1901; Morrison, 1929), in cats, dogs and rabbits (Ferraro, 1928), rhesus monkey (Papez, 1938; Ranson, 1941) and the cat (Kimmel, 1942; Fox and Schmitz, 1944); during the 1950s, Johnston and Clemente (1959) also published a report concerning the identification of nigro-striatal pathways in cats.

During the first half of the century, the ‘Marchi degeneration method’ of staining was employed in Weigert sections of the brain to track neural pathways. The fibres connecting the striatum and substantia nigra are, however, thin and poorly myelinated; as a result, it was difficult with the Marchi method to demonstrate unequivocally whether any connection between the two structures existed, let alone to determine its polarity. Von Monakow, for instance, was of the opinion that the substantia nigra was directly innervated by the cortex and exchanged no contact with the neostriatum.

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93 Sourkes, 1964b.
94 Rosegay, 1944.
95 Details of these references are to be found in Rosegay, 1944, with the exception of Fox and Schmitz, 1944. See also Ranson and Ranson, 1942.
96 Von Monakow, 1925.
Ranson and Ranson commented upon the strionigral fibres identified by Papez in the following manner:

But no convincing evidence that they originate in the striatum has yet been presented. In our Marchi preparations we could see no evidence of their degeneration after lesions in the caudate nucleus, putamen or globus pallidus. Perhaps this failure to stain was due to the small amount of myelin they contain. But one must not overlook the possibility that they may be ascending fibers from the substantia nigra to the corpus striatum.\(^{97}\)

But Rosegay, with the assistance of Papez, had utilized a combination of techniques which included Marchi and Nissl staining as well as retrograde chromatolysis; in this manner he was able to conclude that the “fiber system joining the substantia nigra with the neostriatum is in part ascending, or nigro-striatal.”\(^{98}\)

It is thus surprising that, for example, Hornykiewicz felt obliged to resort to his explanation of “biochemical inactivity atrophy” to link the striatal dopamine deficiencies he had observed and the nigral lesions which characterized parkinsonism. The reason for this was the fact that the doyen of neurohistologists and the acknowledged expert in extrapyramidal matters, Rolf Hassler (1914-1984), did not believe that such a pathway existed. Since the appearance of his classic papers on the pathological anatomy of parkinsonism in 1938/39 (this work earned him his doctorate at the Charité in Berlin in 1939), it was difficult to oppose his views in this area; he had, after all, described the substantia nigra in health and disease in greater detail than before or (in certain respects) since. According to Hassler, the only rostral projections of the substantia nigra originated in the pars compacta and ended in the pallidum.\(^{99}\) In his 1960 account of the extrapyramidal system for the *Handbook of Physiology*, Hassler dismissed the existence of a nigrostriatal pathway with a single sentence:

_Extensive degeneration in the anterior part of the substantia nigra following destruction of these two afferent pathways [caudate nucleus to substantia nigra, cortex to substantia nigra] has been erroneously interpreted as indicating an ascending direction of striatal neurons (Rosegay).\(^{100}\)_

The inability to identify a nigrostriatal pathway using Nauta silver-impregnated sections had cast even more recent doubt on its existence.\(^{101}\) It is interesting that the views of Kinnier Wilson regarding the autonomy of the striatum (expressed most extensively in two classic papers in 1914 and 1925) and the absence of pathways connecting it and the cortex had also long been retained as dogma, despite the fact that Marinesco had demonstrated the existence of such pathways in 1895, as Wilson was well aware.\(^{102}\) He tended to a more open view by the end of the 1920s, but it was only in 1936 that Levin “re-discovered” the connections.\(^{103}\)

The discovery of the striatal dopamine deficiency in 1960 must therefore be seen as one of the preconditions which at least facilitated the “rediscovery” of the nigrostriatal

\(^{97}\) Ranson and Ranson, 1942.

\(^{98}\) Rosegay, 1944.

\(^{99}\) Hassler, 1953.

\(^{100}\) Jung and Hassler, 1960, p.869.

\(^{101}\) Carpenter, in discussion to Sourkes and Poirier, 1966b.

\(^{102}\) Marinesco, 1895, cited in Garai, 1951b. In fact, the pathway had been described even earlier by Muratoff, 1893 and Köölliker, 1889-1902, vol.2, p.623 (published 1893).

\(^{103}\) Levin, 1936.
tract; there existed the need to explain the link between the new neurochemical findings and well-established histological knowledge. Birkmayer had voiced this suspicion in 1965:

> It is curious that histological changes have been found in neither the nucleus caudatus nor in the putamen which would explain this dysfunction [reduced striatal dopamine turnover]. One is thus forced to consider tracts which normally run from the substantia nigra to the putamen and caudatus, whose stimulating influence leads to dopamine synthesis.\(^{104}\)

Hornykiewicz had also proposed in May 1964 at the meeting of the Society of Austrian Neurologists and Psychiatrists that a dopaminergic nigrostriatal tract would account for his growing collection of neurochemical data on extrapyramidal dopamine. This hypothesis would also solve the paradox that, in parkinsonism, striatal dopamine was depleted without obvious loss of striatal cellular material, while in Huntington’s disease the massive striatal cell loss was not accompanied by a decline in dopamine levels. He concluded that it was “however, in the absence of unambiguous neuroanatomical evidence, to leave the question open for now”.\(^{105}\) The issue would finally be solved by a series of findings which were reported by the neuroanatomist and experimental neurologist Louis J. Poirier (Neurological Sciences Laboratory and Department of Histology, University of Montréal) and Sourkes. Sourkes was aware both of the earlier work of Ferraro discussed above,\(^{106}\) and of the fact that the techniques to investigate his hypothesis were only becoming available at the beginning of the 1960s. Poirier, on the other hand, had previously demonstrated that electrolytic lesions in the tegmental area of the upper pons and midbrain (that is, immediately superior to the substantia nigra) of macaque monkeys resulted in contralateral postural tremor and hypotonia.\(^{107}\) In May 1963, Sourkes and Poirier began a collaboration which aimed to draw together and correlate for the first time neurological findings of this type and neurochemical data; specifically, the attempt was made to produce a monkey model of parkinsonism which reproduced more accurately the symptoms of the human disorder than did earlier attempts, such as the Vernier-Unna monkeys. At the same time, the pair aimed to determine whether a direct nigro-striatal pathway might provide the basis of a coherent explanation for the various neuropathological and neurochemical findings made thus far in the disorder.

The initial results were presented during the fall of 1963 at the Second Conference on Parkinson’s Disease in Washington;\(^{108}\) a progress report was presented at the 1964 meeting of French-speaking Physiologists in Clermond-Ferrand (France) and appeared as a brief communication in the *Journal de Physiologie*,\(^{109}\) before the crucial paper appeared in full in *Brain* in 1965.\(^{110}\) Nineteen macaques received uni- or bilateral electrolytic lesions in the upper pons or brainstem, and then killed one to nine months

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\(^{104}\) Birkmayer, 1965, p.186.

\(^{105}\) Hornykiewicz, 1964a; see also Hornykiewicz, 1964b. At the spring meeting of the German Pharmacological Society in Mainz, Hornykiewicz had argued for the existence of ‘dopaminergic’ neurons in the brain; he did not refer to a nigrostriatal pathway in this abstract; Hornykiewicz, 1964c.

\(^{106}\) Ferraro, 1928.

\(^{107}\) Poirier, 1960.

\(^{108}\) Poirier, 1966; Sourkes, 1966b.

\(^{109}\) Poirier and Sourkes, 1964.

\(^{110}\) Poirier and Sourkes, 1965. Hornykiewicz referred to this paper as being in press in his short 1964(b) article. The results were also presented at a number of other conferences between 1964 and 1966: see Sourkes and Poirier, 1966a, 1966b; Sourkes *et al*., 1969.
after the operation. The goal was not to destroy the substantia nigra, but to interrupt communication with the striatum; damage to both these structures was thus carefully avoided. The behaviour of the animals and their responses to certain drugs were also monitored after production of the lesion. The six animals which received unilateral lesions in the ventromedial tegmentum exhibited significant cell loss in the ipsilateral substantia nigra pars compacta (SNc); twelve animals with unilateral lesions in other parts of the tegmentum or brainstem showed no such loss. Most spectacular, however, was the finding that, in the same six animals, dopamine and noradrenaline concentrations in the ipsilateral caudatus and putamen were significantly reduced, while those of the other twelve animals were unaffected. Striatal 5-HT concentrations were also generally affected, but not consistently.111 It was also important that Poirier’s earlier observations that such lesions were associated with contralateral postural tremor and hypotonia were confirmed. The authors concluded:

*The results of the experiment suggest that the pars compacta of the substantia nigra normally exerts through its efferent nervous pathways a direct influence on the catecholamine concentrations of the corresponding (ipsilateral) striatum.*

The work described in this paper was further pursued, resulting in another major publication in *Brain* in 1966.113 It was established that while interruption of nigrostriatal fibres reduced striatal catecholamine levels, interruption of the most dorsomedial fibres of the cerebral peduncle reduced striatal 5-HT levels. Contralateral postural tremor was associated with the simultaneous disruption of both these pathways and of the corresponding rubro-tegmento-spinal tract; if the nigrostriatal fibres were spared, choreiform and ballistic movements in the contralateral limbs were observed. A panel of

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drugs were examined for their impact on these dyskinesias. Only the MAO inhibitors harmaline and harmine (5-10mg i.m.) had notable effects; both exaggerated the abnormal postures and movements (including tremor) in animals which exhibited these dyskinesias, and could induce hyperkinesia in lesioned animals who were otherwise normal with respect to motor activity. The related harmalol, which does not inhibit MAO, was inactive in this respect. These responses were attributed to protection by MAO inhibitors of continuously synthesized 5-HT in the striatum. L-DOPA and D,L-5-HTP were without effect, as were adrenaline, atropine, tranylcypromine, histamine and diphenhydramine. The authors concluded that abnormal movements resulted from chemical changes in the striatum (and, by inference, in the thalamus) resulting from such lesions.\(^\text{114}\) The work on both the dopaminergic and serotonergic fibres was presented together in the *Canadian Medical Association Journal* at the beginning of 1966.\(^\text{115}\)

Further investigation of the monkey model of parkinsonism clearly established the central role played by dopamine in parkinsonian tremor; further, the measured decline in striatal concentrations of the major dopamine metabolite, HVA, corresponded to changes identified by Hornykiewicz and his group in the parkinsonian brain.\(^\text{116}\) The effects elicited in the monkey by disruption of the nigrostriatal pathway were confirmed by other workers\(^\text{117}\) and could also be produced by similar lesions in the cat.\(^\text{118}\) Later work in Sourkes’ laboratory established that the dopamine deficit played the primary role in the parkinsonian symptoms exhibited in this animal model.\(^\text{119}\) But one of the most important concepts which emerged from the Sourkes’ and Poirier’s work which was at least as significant as this finding was the realization that multiple changes in amine concentrations were required to produce ‘parkinsonian’ symptoms; the idea that

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<th>Activity of the contralateral limbs</th>
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<td>Dopamine</td>
<td>Serotonin</td>
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<td>Nigrostriatal*</td>
<td>decreased</td>
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<td>Rubro-tegmento-spinal</td>
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<td>Rubro-tegmento-spinal and a cerebral peduncular tract**</td>
<td>normal</td>
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<tr>
<td>Nigrostriatal and cerebral peduncular tract</td>
<td>decreased</td>
<td>decreased</td>
</tr>
<tr>
<td>Nigrostriatal, Rubro-tegmento-spinal and cerebral peduncular tract</td>
<td>decreased</td>
<td>decreased</td>
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<td>None (intact animals)</td>
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*Table 13.7: Motor abnormalities associated with disruption of particular nerve tracts and striatal amine deficiencies, as reported by Sourkes and Poirier, 1966. * Leads to cell loss in substantia nigra; ** fibre group coursing in most dorsomedial portion of cerebral peduncle.*

\(^\text{114}\) I*bid.*

\(^\text{115}\) Sourkes and Poirier, 1966a.

\(^\text{116}\) Sharman *et al.*, 1967.


\(^\text{118}\) Poirier *et al.*, 1967; Lancaster *et al.*, 1970.

\(^\text{119}\) Larochelle *et al.*, 1971.
the disorder could be seen as a simple deficiency in one substance or the interruption of a single pathway was thus rendered unlikely. Parkinson’s disease probably involved multiple defects in a number of systems.

The importance of this work for neurochemistry cannot be overestimated, not only for its contribution to the theoretical analysis of Parkinson’s disease but also because, as the authors noted in retrospect, it:

*stimulated studies aimed at the identification of neurochemically defined pathways and their role in behavioral and psychoneuroendocrinological phenomena.*

It is easy to forget that the idea of ‘dopaminergic’ pathways or of other transmitter-defined pathways was unusual in 1964; neural tracts were defined by histological techniques based on reactions which were independent of their transmitter content. In a paper presented to the annual meeting of the German Pharmacology Society in mid-1964, Hornykiewicz had argued that the distribution of dopamine in the nuclei receiving efferents from the striatum was explained best by the hypothesis of dopaminergic tracts between this region and the substantia nigra and external segment of the pallidum; the existence of any ‘dopaminergic’ tracts at all, however, was still purely hypothetical.

Some residual suspicion persisted regarding the Sourkes and Poirier results; the integration of experimental neuroanatomy, neurochemistry and behavioural studies was a novelty, and the demonstration of the existence of the nigro-striatal pathway was clearly anything but classic histology. These doubts were soon allayed by functional investigations which provided further evidence for a direct dopaminergic nigro-striatal connection. The first unequivocal demonstration of a unity between physical lesion, neurochemical changes and behavioural abnormalities was a major step forward in establishing neurochemical investigations as the dominant research paradigm in the further investigation of neurological disease.

**Visualization of the nigrostriatal pathway**

Poirier and Sourkes had demonstrated with high probability the existence of a nigrostriatal pathway, but the methods for directly visualizing such a pathway were not yet generally available. This crucial step would be taken in Sweden, where Carlsson had been attempting to visualize catecholamines in the brain using fluorescent techniques since about 1958. This direction gained new impetus in 1959 through his collaboration with Nils-Åke Hillarp, a histologist who had attracted attention in the 1940s and 1950s with his work on the autonomic nervous system. Hillarp moved to Göteborg at the same time (1959) as Carlsson was appointed Professor in the newly built Department of Pharmacology. This allowed them to further pursue their common goals regarding visualization of central catecholamines, which benefited from the generous funding of equipment for the new laboratories by the University.

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120 Poirier and Sourkes, 1980.
121 Hornykiewicz, 1964a.
122 Classical methods were still inadequate for the visualization of the pathway at the end of the decade; see Faull and Carman, 1968.
124 Carlsson wrote that “he was delighted to learn that Hillarp wanted to join” him in Göteborg (Carlsson, 1987); others have said that Hillarp accepted the invitation of Carlsson to move to Göteborg. In the end, whoever took the initiative in this highly profitable collaboration was unimportant.
To detect catecholamines in the central nervous system, the Swedish pair required an extremely sensitive method; fluorescent detection was the obvious choice for their envisioned investigations. Hillarp had first described a method for the fluorescent demonstration of catecholamines in 1955, but the methods available in 1959 were insufficiently sensitive to visualize catecholamines at the levels with which they occur in the central nervous system, having been developed for use with chromaffin cells and adrenal tissue.\footnote{Falck and Hillarp (1959) attempted to visualize brain catecholamines with the techniques used for chromaffin cells, without success.} Carlsson and Hillarp initially applied the trihydroxyindole method which was used for the assay of catecholamines; it was capable of demonstrating adrenal catecholamine depletion by reserpine, but was not suitable for structures of the size of the nerve terminal. At this point, Hillarp and his pupil Bengst Falck (the latter in the Department of Histology, Lund) visited Olavi Eränkö in Finland; this worker had described a method for inducing fluorescence of adrenal catecholamines via formaldehyde fixation.\footnote{Eränkö, 1955.} A similar technique developed at Brodie’s laboratory in Bethesda for measuring tryptamine, where the spectrophotofluorimeter had also recently been introduced and published.\footnote{Hess and Udenfriend, 1959.} The fluorescence produced using this method was less impressive than with the trihydroxyindole method, but Hillarp was convinced that it could be improved. By the second half of 1961, following an exhaustive series of preliminary experiments, he and the research engineer Georg Thieme had developed a condensation method based on these forerunners whereby formaldehyde vapor was used to convert catecholamines in a dried protein layer to their corresponding tetrahydroisoquinoline condensation products (although the chemistry of the reaction was only confirmed later).\footnote{Corrodi and Hillarp, 1964.} The paper published by Falck, Hillarp, Thieme and Torp in 1962 describing the approach became one of the 100 most cited papers during the next twenty years.\footnote{See Carlsson, 1987. The authors were listed alphabetically.}

The method, however, still required some work if it were to be used to directly visualize catecholamines in tissue samples. Much of this work was conducted in Falck’s laboratory in Lund, as it was better equipped for such work than the pharmacology department in Göteborg. Cryostat sections exposed to formaldehyde vapor at 75°C produced the best results, but the results were still not entirely satisfactory. Late in August 1961, Hillarp visited Falck, and suggested that they attempt to air-dry stretch preparations of thin tissues, such as iris or mesentery, just as he had fifteen years previously for his thesis, and expose these preparations to formaldehyde vapor while heating. As Carlsson described the result of this weekend experiment:

\textit{The outcome was dramatic: in the fluorescence microscope Hillarp and Falck saw the same nerve-plexus pattern as previously observed by Hillarp following staining with methylene blue. But this time it was the adrenergic transmitter, which showed up as green fluorescence . . . In addition, yellow fluorescence derived from mast-cell 5-HT could be seen in the mesenterium preparations.}\footnote{Carlsson, 1987.}

The method had thus been developed to the point where individual neurons in peripheral tissue could be visualized, including terminal varicosities brilliant in their fluorescence. Despite immediate champagne celebrations, the experiment could not be
repeated until October, and was thus not mentioned in the first papers on the technique. The method needed to be further refined for the examination of embedded tissue samples, but it had been established that the principle underlying the approach was sound. This refinement was largely undertaken at Lund by Falck, but also continued in Stockholm by Hillarp in his new quarters.¹³¹ In 1962, Hillarp was appointed to the Chair of Histology at the Karolinska Institute, and set himself the task of reorganizing the department in line with his vision of the future of neuroanatomy, assisted principally by the young investigators who came together in the so-called ‘Monoamine Club’. Unfortunately, Hillarp was diagnosed in mid-1964 as having cancer, and he died less than a year later at the age of 47.¹³²

The first major paper on its application appeared in 1962 under the title “Cellular localization of brain monoamines”.¹³³ The technique was briefly described (more detail was offered in the following paper by Falck “on the possibilities of the cellular localization of monoamines by a fluorescence method”),¹³⁴ and the first examination of fluorescent structures in the brain reported, including the localization of central nervous system catecholamines in neuronal elements. A section devoted to the caudate nucleus of the rat and mouse described the fluorescence in this region thus:

*The fluorescence is quite diffuse and somewhat uneven: small irregular areas with somewhat higher intensity are present everywhere. In contrast to this the nerve cell bodies and fibre bundles fluoresce very faintly or not at all.*¹³⁵

The Swedish team had thus identified at the beginning of their studies the matrix construction of the striatum, as well as the fact that its dopamine content was probably associated with neurons of extrastriatal origin. Treatment of the animals with reserpine produced an almost total loss of fluorescence. Neither L-DOPA nor the MAO inhibitor nialamide had a significant effect on fluorescence when administered alone; together, however, they produced a marked increase in intensity. Nialamide did not block the effect of reserpine. These observations were correlated with the results of the biochemical research which had previously been reported by Carlsson’s laboratory, and the bright striatal fluorescence was thus attributed to high levels of dopamine in the caudatus; they hypothesized that it was “probably localized to submicroscopic structures belonging, for instance, to the neuropil.”¹³⁶

In June 1964, *Life Sciences* published a paper which had resulted from the collaboration between Carlsson’s group at Göteborg and that of Kjell Fuxe in the Department of Histology at the Karolinska Institute in Stockholm: “Demonstration and mapping out of nigro-neostriatal dopamine neurons”.¹³⁷ These workers actually started from the assumption that “the substantia nigra appears to send fibers to the corpus striatum”, citing indirectly the rediscovered Rosegay paper, and had set themselves the goal of determining whether these projections were dopaminergic. In contrast to the

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¹³² A brief history of the Hillarp story constituted the contribution of Dahlström and Fuxe (1999) to the special issue of *Brain Research Bulletin* dedicated to the most significant neuroscientific achievements of the 20th century.
¹³³ Carlsson et al., 1962a; see also Carlsson et al., 1965.
¹³⁴ Falck, 1962.
¹³⁵ Carlsson et al., 1962.
¹³⁷ Andén et al., 1964a.
Canadians, they placed electrolytic lesions directly in the substantia nigra of hooded and albino mice, but they also induced lesions to the ascending nigrostriatal fibres in a further three mice. Striatal catecholamine content was assessed in some animals by in situ fluorescence microscopy, and quantified in others using the standard fluorescent methods employed in the Carlsson laboratory. It was found that the dopamine-linked fluorescence of the ipsilateral caudatus and putamen was clearly reduced in animals in which the lesion was located in the SNc rather than the substantia nigra pars reticulata (SNr) or substantia nigra lateralis (SNI). This was also confirmed quantitatively: the dopamine content of the diencephalon/telencephalon was reduced from 1.4µg g⁻¹ tissue in normal animals to 0.75-0.87µg g⁻¹ in animals with unilateral nigral lesions, and to 0.44µg g⁻¹ in mice with bilateral lesions. Disruption of the nigrostriatal pathway also led to a clear-cut (~60%) reduction in the dopamine content of the ipsilateral striatum of one animal; the lesion was apparently too small to have an effect in the other two mice. Further, Fuxe and Dahlström had previously observed that the fluorescence of catecholaminergic neuron cell bodies increased two to three days after their being axotomized; this phenomenon was also observed in the current work with respect to neurons arising in the SNc. This was consistent with the more recent findings of Hornykiewicz that the dopamine content of the SNc was higher than that of the SNr. More importantly, the accumulation of dopamine in the substantia nigra following destruction of the striatum led the authors to the conclusion:

the data give strong evidence for the existence of nigro-neostriatal dopamine neurons, which probably contain most or all of the dopamine present in the neostriatum. They noted, however, that Rosegay had identified nerve bundles arising from the SNr, and that this probably indicated that two different pathways coursed from the substantia nigra to the neostriatum, one dopaminergic and the other using an unidentified transmitter. The authors did not appear at this stage to have been aware of the work of Poirier and Sourkes. Falck’s group in Lund (which now included Bertler) reported similar findings to their Swedish colleagues in the same year. Finally, Hökfelt employed electron microscope techniques to confirm the storage of dopamine in the terminal boutons of the nigrostriatal cells.

Andén, Dahlström, Fuxe and Larsson also published an important paper in 1966 which examined the functional role of the nigrostriatal pathway. Agents which either blocked or enhanced monoaminergic transmission were administered to rats after unilateral disruption of the nigrostriatal pathway or removal of the striatum. The behavioural changes in animals not receiving drugs were minor; but administration of agents blocking monoaminergic transmission (reserpine, haloperidol, chlorpromazine) induced contralateral turning, while those facilitating transmission (nialamide plus reserpine or L-DOPA) induced ipsilateral turning. D,L-5-HTP was without effect on turning behaviour. The authors concluded that the loss of neostriatal dopaminergic innervation was responsible for these responses, but also hypothesized that the concomitant disruption of an antagonistic cholinergic tract from the cortex was also involved in the behavioural changes. They noted, however, that, in primate models of parkinsonism, the symptoms were contralateral to the lesion; they assumed that this

139 Andén et al., 1964a; see also Andén et al., 1965.
140 Bertler et al., 1964.
141 Hökfelt, 1968.
species difference was explained by the organization of the striatal output in rodents, in which the pyramidal pathway is almost totally absent, not crossing as in primates.  

Despite the mounting evidence for a catecholaminergic nigrostriatal pathway, its existence remained controversial amongst traditional neuroanatomists for some time, as it could still not be demonstrated using conventional mapping techniques. By the end of the 1960s, however, the elegant studies of Fuxe’s group, and the demonstration by Sourkes and Poirier that disruption of the pathway produced parkinsonian-like tremor accompanied by striatal dopamine depletion in monkeys, had largely broken opposition to this idea. As late as 1969, however, Hassler was still resisting; in a classic study of “experimental interruption of strionigral connections in rat”, he and Bak concluded that:

> although many fibres terminating in the substantia nigra may come from the striatum or other rostral structures, relatively few fibres terminating in the corpus striatum originate in the substantia nigra or in mesencephalic or pontine levels.  

This was only the beginning of the mapping of the catecholaminergic systems of the brain, an exercise which became inextricably linked with the names of the Swedes Annica Dahlström and Kjell Fuxe, who published a classic series of papers in 1964/65 describing the demonstration of monoaminergic pathways and terminals in the central nervous system. Further significant contributions were made by Andén, Ungerstedt, Björklund and Hökfelt, not to mention those already named. The significance of this work was not restricted to the fact that it provided novel chemical maps of the brain, although this in itself was revolutionary. It also allowed for the first time the precise visualization of chemical transmission in the brain, and thus initiated a new era of the investigation of central neural function. It had previously been possible to measure catecholamine levels in tissue extracts, but now it was possible to identify precisely the cells and even organelles in which they were located, thus decisively ending the years of controversy about the origin of central catecholamines and expanding knowledge about the synaptic basis of monoaminergic transmission in a manner previously unimaginable.

With respect to Parkinson’s disease, the developments in Sweden were of fundamental importance. As Carlsson noted in 1987, the discoveries of dopamine deficits in parkinsonian patients and the beneficial effects of L-DOPA were important, but:

> the real breakthrough came with the histochemical techniques visualizing the cellular localization of the monoamines by means of the fluorescence microscope.  

Hornykiewicz was of similar opinion:

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142 Andén et al., 1966a. The results had been partly presented at the International Symposium on Mechanisms of Release of Biogenic Amines (Stockholm) in February 1965. Interesting comments made in this paper included the suggestion that striatal dopamine receptors were probably α-adrenergic-like receptors, and the assumption that striatal cholinergic fibres project beyond the striatum.

143 Hassler and Bak, 1969. See also Kim et al., 1970.

144 Dahlström et al., 1964; Dahlström and Fuxe, 1964a,b,c; Dahlström and Fuxe, 1965; Fuxe, 1965a, 1965b.

145 Much of this history has been described by Dahlström and Carlsson (1986).

Their [Fuxe and Dahlström] studies completely changed our understanding of the anatomy of the monoamine neuron systems in the brain and kept the interest in brain dopamine alive.\textsuperscript{147}

Hornykiewicz reported soon after this that the degree of striatal dopamine loss was correlated with the degree of loss of melanin-containing perikarya in the substantia nigra, consistent with the existence of the nigrostriatal tract observed in rodents;\textsuperscript{148} later in the decade he traced the course of the nigrostriatal pathway in the human brain by assaying HVA levels in discrete regions of the basal ganglia.\textsuperscript{149}

The demonstration of the nigrostriatal pathway by the Swedish and Canadian groups using a combination of anatomical, neurochemical, histological and behavioural techniques had revealed the vital relationship between striatum and substantia nigra which was central to the question of the pathology underlying Parkinson’s disease. More than this, the new fluorescence techniques marked the direction for the further research of the neurochemical basis of the disorder and represented a sensitive means for detecting changes in the catecholaminergic systems of experimental animals. The functional nature of this pathway was demonstrated at the end of the 1960s by groups which showed that stimulation of the substantia nigra led to the release of striatal dopamine and 5-HT.\textsuperscript{150}

It should, however, be noted that the fluorescent techniques were not immediately greeted with unmitigated approval; in his summary of the discussion of the session on adrenergic mechanisms at the Second Catecholamine Symposium in 1966, Nickerson commented that such an approach

\begin{quote}
\textit{cannot be considered to differ qualitatively from other histologic “staining” techniques just because the markers used are possible, or suspected, or postulated transmitters. It provides only an indication of “content”, which as yet can be validly related to function in relatively few situations.}\textsuperscript{151}
\end{quote}

He noted that the technique was new, and that many workers (including Marthe Vogt) harbored reservations about the quantitative aspects of the approach; “\textit{the urge to extrapolate is both understandable and dangerous}\textsuperscript{152}”. This caution was understandable, but the skepticism expressed seemed a remnant of the still persisting doubts about the role of central catecholamines. The same doubts were expressed about the Poirier and Sourkes work. The associations of amine loss and functional deficits following nigral lesions were merely correlations:

\begin{quote}
\textit{That the dopamine- and 5-HT-containing fibers function by releasing these materials, or are in fact the fibres responsible for the functional changes observed can be postulated from but not proved by such correlations.}\textsuperscript{153}
\end{quote}

Carlsson had made a similar point in the early 1960s when he advocated the use of amine precursors instead of therapeutic and chemical agents of incompletely defined

\textsuperscript{147} Hornykiewicz, 1992.
\textsuperscript{148} Hornykiewicz, 1964b.
\textsuperscript{149} Hornykiewicz et al., 1968.
\textsuperscript{151} Nickerson, 1966.
\textsuperscript{152} Ibid.
\textsuperscript{153} Ibid.
biochemical activity.\textsuperscript{154} The rigorous approach of classical physiology and pharmacology demanded that precise mechanisms of action be elucidated before definite conclusions about the function of any substance be drawn. The possibilities of such an approach, however, were restricted by the available technologies. Ultimately, however, the new techniques allowed the construction of the framework which would serve as a guide for further investigations. It must be borne in mind that the history of the therapy of parkinsonism has had only a limited association with well-planned predetermined investigations by rigorous scientists, and more to do with serendipity regarding the availability of effective agents and of technologies for assessing their usefulness.

\textsuperscript{154} Carlsson \textit{et al.}, 1960; Carlsson and Lindqvist, 1962.
S HORNYKIEWICZ HAS NOTED, the international “dopamine community” was quite modest at this point,¹ so that it is no surprise that the initial response to the reports out of Vienna was less than overwhelming. It must also be remembered that the two major papers by Birkmayer and Hornykiewicz concerning L-DOPA therapy were published in German language journals; while not as unusual in 1961 as it would be now, the rising importance of the United States in neurochemistry dictated that even at this stage a publication in English would have been of advantage. The peak citation rate for the two papers would occur much later, at the beginning of the 1970s. This was at the time at which L-DOPA was first licensed for regular use in the clinic, and referrals to the early papers was made more from a historical perspective than from a detailed interest in what had been said. The triumph of the biochemical models of brain function by this point had also enhanced their citability. If citations by the Viennese group itself are disregarded, Bernheimer and Hornykiewicz (1960) was cited in journals referenced by the Science Citations Index three times in 1961 (twice by the Montreal group), five times in 1962 (once by Barbeau, once by the McGeer group, once by Pletscher), before reaching fourteen citations in 1964. The start for Birkmayer and Hornykiewicz (1961) was similarly slow: from a single citation in 1962 (by Barbeau) to six in 1963 and eleven in 1964 (including the first citation by Cotzias), it dropped back to single figures before it reached thirty-seven in 1970 and more than twenty per year throughout the following decade. Both papers have in the meantime achieved “Citation Classic” status (Birkmayer and Hornykiewicz, 1961 had been cited 356 times by 1998), so that the initial slow response is perhaps a little surprising. It should, however, be remembered that the Science Citations Index did not catalog many German language journals at the beginning of the 1960s, so that these figures omit many possible German citations (for example, in the Wiener Klinische Wochenschrift).

¹ Hornykiewicz, 1992.
Initial response to the Viennese results

The first paper on the application of DOPA in parkinsonism had actually appeared in September 1961 in the *Journal of the American Medical Association*. Patrick McGeer’s group in the Department of Psychiatry at the University of British Columbia (Canada) were concerned with the extrapyramidal side effects induced by reserpine and many phenothiazine-class drugs, and were, like Hornykiewicz and Birkmayer, inspired by Carlsson’s work to hypothesize that disturbance of the normal function of dopamine might underlie these effects. Patients suffering drug-induced parkinsonian symptoms were thus administered large oral doses (up to 32g per day) of D,L-DOPA. Patients exhibiting mild extrapyramidal reactions to reserpine, chlorpromazine or thioproperazine generally showed some improvement after receiving 4-8g DOPA, but symptoms were still apparent; those exhibiting severe reactions were not helped even by large doses, but their symptoms could be controlled by 0.4-0.6g/day diphenhydramine. The authors concluded that:

\[\ldots\text{dopa has nothing to offer as a measure for the treatment of drug-induced Parkinsonism and lends little support to speculation that this syndrome primarily involves interference with the brain catecholamines, particularly dopamine. The results, however, do not disprove the theory, since we have no way of knowing, despite evidence from the urinary production of a generally enhanced catecholamine metabolism, that brain catecholamines were affected at all.}\]

McGeer’s group had noted that the urine and, in some cases, sweat of patients receiving large doses of DOPA was black and contained large quantities of dopamine and its metabolite HVA; the color was attributed to autooxidation of dopamine. The paper cited the work of Degkwitz’ group, but seemed unaware of both the Montréal and Viennese groups. The authors had previously observed the effects of DOPA in reserpine-treated animals, and suggested that species differences might underlie the lack of a significant DOPA effect in humans. Birkmayer and Hornykiewicz, however, suggested a short time later that resorption of orally administered DOPA by McGeer’s patients may have been less efficient than in their own study, as they themselves had had complete success in treating extrapyramidal responses to these drugs with intravenously applied l-DOPA. The Americans, however, had also added pyridoxine to the therapy of their patients; it would only be recognized later that they had thereby ensured that practically the entire administered dose of l-DOPA was decarboxylated in the periphery, while the d-DOPA would have done the patients more harm than good. Interestingly, Birkmayer and Hornykiewicz did not comment on the use of racemic DOPA instead of l-DOPA. It is a curious aspect of this early period that such details often remained unmentioned in many of the papers concerning DOPA therapy.

Following the publication of the first report by Birkmayer and Hornykiewicz, the first published l-DOPA trial by another group also emanated from Vienna. Franz Gerstenbrand and K. Pateisky, as already mentioned, had applied the drug by the end of 1961 at the Psychiatric-Neurological Clinic of the University after having heard of the therapy from Barbeau at the Neurological Congress in Rome of that year. The groups at

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5 Birkmayer and Hornykiewicz, 1962.
the Geriatric Hospital and the University Clinic operated completely independently of one another; nevertheless, Gerstenbrand and Pateisky also received their supply of \( L \)-DOPA from Hoffmann-La Roche, and applied the drug using the method of Degkwitz’ 1960 paper. Their first report specifically concerned the electromyographic assessment of the \( L \)-DOPA effect (in combination with a MAO inhibitor) in a 53 year old postencephalitic parkinsonian patient. They demonstrated that the duration of relief was greatest for akinesia, in agreement with the findings of Birkmayer and Hornykiewicz. But both rigidity and resting tremor were also relieved for about two hours following \( L \)-DOPA administration; the intention tremor, on the other hand, was unaffected.\(^6\)

Together with P. Prosenz, a broader account of their experiences was presented at the medical congress of the Czechoslovakian Medical Society “I.E. Purkinje” in November 1962. By this time, they had treated thirty patients with \( L \)-DOPA, either in the powdered form in capsules (à 100mg), as an infusion à la Degkwitz, or as a stabilized solution in ampoules. This report is, to my knowledge, the only one which indicated that a DOPA solution prepared according to the Degkwitz method must be used within half an hour of its preparation, as the solution was less effective after this period; deterioration of the solution was indicated by its development of a red color, indicative of oxidation. The kinetics of response to infused \( L \)-DOPA were similar to those reported by Birkmayer and Hornykiewicz for administration by this route. Gerstenbrand’s group found that the required dose was reduced when using ampoules, interpreting this fact as indicative of loss of substance during its preparation from fresh material. The oral administration of \( L \)-DOPA, which this group pursued to a greater degree than Birkmayer, required higher doses (200mg) to achieve comparable effects, divided into two doses during the day. The effects on akinesia were confirmed, as was a less marked effect on rigor in many patients; improvement of mood in parkinsonian patients presenting depression was also noted, and indeed to such an extent that the application of \( L \)-DOPA in non-parkinsonian depression was suggested. The results of their investigation were summarized in a figure (figure 14-1), and broadly confirmed the results of Birkmayer and Hornykiewicz with regard to the injection route; the oral route was clearly less effective. Especially

\(^6\) Gerstenbrand and Pateisky, 1962.
impressive was the improvement of akinesia in six patients who had already undergone stereotactic surgery to (successfully) treat their tremor and rigidity. Gerstenbrand’s group was therefore prepared to advocate L-DOPA therapy as appropriate for parkinsonism, despite the difficulties associated with its implementation. Their advice was to implement a fortnight of treatment with a MAO inhibitor (such as isocarboxazid), commencing with \(3 \times 10 \text{mg per day, reducing to } 2 \times 10 \text{mg/day after a week and to } 1 \times 10 \text{mg/day after a further five days.}\) Then, while maintaining this level of MAO inhibitor administration, 25-50mg L-DOPA was to be applied intravenously, 4-5 times at five day intervals; if tolerated, the therapy was implemented as \(2 \times 100 \text{mg oral doses twelve hours apart, every five days for six weeks. The protocol was to be repeated at two monthly intervals. Administration of the MAO inhibitor was also to be suspended for ten days every two months. Conventional anticholinergic therapy was to be continued.}\)

Gerstenbrand and Prosenz also reported in 1965 of their experiences with MAO inhibitors (isoproniazid, Ro 4-2637, Ro 4-2308) as antiparkinsonian substances, alone or in combination with L-DOPA. They themselves had gathered pathological evidence for disturbed amine metabolism in parkinsonian patients, including altered cerebrospinal fluid levels of dopamine and certain amino acids. They were therefore interested in pursuing a monoamine-based antiparkinsonian therapy, but their interest had shifted in the direction of MAO inhibitors. Response to each of the three MAO inhibitors in forty-five parkinsonian patients was similar. Administered alone, they each modulated the same symptoms as L-DOPA, but not with the same potency (twenty-five patients responded “moderately”, nine not at all), nor was the effect as reliable; less advanced patients responded best. MAO inhibitors enhanced the effects of intravenous L-DOPA in fifteen of twenty patients when administered together with the amino acid, consistent with Birkmayer’s findings. The side-effects associated with the inhibitors, however, were problematic: of forty-five patients, twenty-one exhibited significant side-reactions; of these, ten could not tolerate any of the inhibitors. The most common problems were emotional disturbances. Nonetheless, the authors concluded:

> The administration of MAO inhibitors alone also proved in part to be sufficiently effective and suitable for long-term treatment. We are therefore of the opinion that the Parkinson syndrome should be accepted as an indication for the administration of MAO inhibitors.

The tone of this paper was modulated by the fact that the authors found MAO inhibitors easier to handle in the clinic than L-DOPA, and, equally important, much less expensive. The L-DOPA therapy was, in fact, not further intensively pursued at the University Clinic. At this time, there existed a certain amount of ill-feeling between the Clinic and the University, but more importantly between Birkmayer and the leader of the clinic, Hans Hoff. As a Jew, Hoff had been forced to flee Vienna after the unification of Austria with Germany in 1938; following his exile in Iran and then the United States, he replaced Pötzl as leader of the Clinic in 1945. Birkmayer’s political background rendered it almost inevitable that his relations with Hoff would be difficult; it was partly on these grounds that he assumed the leadership of the Geriatric Hospital rather than a post at the University following his habilitation in 1954. L-DOPA therapy was, in any

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7 Gerstenbrand et al., 1963 (expanded version of presentation to I.E. Purkinje group).
8 Bruck et al., 1964, 1966.
10 Ironically, his habilitation in 1939 had been prevented by his part-Jewish background.
case, quite expensive and labour-intensive; Hoff therefore decided that it should no longer be employed. In June 1968, Avenarius and Gerstenbrand commented that investigations into the application of L-DOPA and MAO inhibitors had been promising, but had not yet led to the introduction of suitable new products for the therapy of parkinsonism.

The first reported application of L-DOPA in Parkinson’s disease in the United States was by Arnold Friedhoff’s group at the Department of Psychiatry and Neurology in the Psychopharmacology Research Unit of the New York University School of Medicine, who reported their experiences to date at the Annual Meeting of the American Medical Association on 27 June 1962. Friedhoff (together with Menek Goldstein and C. Simmons) had studied the metabolism of DOPA in rats at the end of the 1950s, and had proposed in 1959 that dopamine might act “in various tissues to protect epinephrine and norepinephrine from deamination by amine oxidase.” This interpretation of the presence in the brain of dopamine as a catecholamine-sparing substance had been quite popular until the early 1960s. Friedhoff’s group had, like McGeer, been studying extrapyramidal reactions to reserpine and chlorpromazine, which they noted were characterized more by rigidity than tremor. They were aware of Ehringer and Hornykiewicz’ paper and of the work of Sourkes and Barbeau. Friedhoff’s group selected patients “with a clear and uncomplicated diagnosis of parkinsonism” for their study, administering intravenously a 0.1% solution of L-DOPA in sodium lactate until a 15mm drop in systolic blood pressure was measured; this corresponded in practice to about 2.5mg/kg body weight, and was thus at the higher end of the range employed in Vienna. On the day before or after the infusion, a lactate solution without L-DOPA was administered in the same fashion; as only the physician knew which solution was being infused on a particular day, this was the first specifically “single blind” study employing L-DOPA. The positive effects on rigidity (but not on tremor) observed in eleven patients were sufficiently impressive, although of short duration, to encourage the authors to recommend further studies both into the usefulness of the therapy and into its neurochemical basis.

Interestingly, most of the other positive reports concerning L-DOPA and Parkinson’s disease originated in European clinics:

- **Johannes Hirschmann and Klaus Mayer** (Neurological Clinic and Polyclinic of the University of Tübingen; 1964): Using the same method as Degkwitz and Birkmayer, 25mg L-DOPA was found to abolish or markedly reduce akinesia in twenty-five long-term Parkinson’s disease patients. Electromyographic examination of five patients revealed an effect on rigor and tremor of short duration; this effect disappeared as the anti-akinesia effect set in. Tranylcypromine did not modulate the L-DOPA effect, but did achieve a slight reduction of tremor.

- **W. Umbach and D. Baumann** (Neurosurgical Clinic, University of Freiburg; 1964): A “movement and competence test” was employed to assess the motor skills of thirty patients before and after the injection of the stabilized L-DOPA

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11 Gerstenbrand, personal communication.
12 Avenarius and Gerstenbrand, 1968. See also Bruck et al., 1965.
13 Goldstein et al., 1959.
14 Friedhoff et al., 1962, 1963.
solution provided by Hoffmann-La Roche; the patients were examined before and after stereotactic operations designed to reduce tremor and rigor. MAO inhibitors were not employed. L-DOPA exhibited a strong but variable kinetic benefit. The effect was more marked following stereotactic surgery, which itself was of greater benefit than L-DOPA. The mode of administration and its side-effects were seen, however, as precluding its use on a long-term basis. This study had formed the basis of Baumann’s doctoral dissertation (1964).16

- In the following year, however, Umbach and O. Tzavellas reported that the intensity and duration of the L-DOPA effect (from 12 to 72 hours) could be increased by concomitant treatment with 20mg i.v. or p.o. of the MAO-inhibiting cyclexedrine HCl (‘Eventin’; Minden).17 The effect of cyclexedrine was interpreted as correction of insufficient cerebral perfusion which, together with the dopamine loss, was hypothesized to underlie akinesia.18 As a result of this experience, Umbach’s group treated 125 patients with 150-600mg L-DOPA and 25-50mg cyclexedrine (both orally) between 1965 and 1967, with satisfactory results.19 Cyclexedrine was employed by Völler to lengthen the effect of intravenous L-DOPA in primarily akinetic patients to six days.20

- E. Metzel, of the same clinic, also reported a positive effect of L-DOPA, with and without the MAO inhibitor Ro 4-2637/10, upon parkinsonian akinesia, but none upon the disturbed sense of spatial orientation which he had detected in such patients.21

- Carlsson mentioned in passing at a meeting in March 1963 that his group had seen positive effects of L-DOPA on parkinsonian patients.22

There were a trickle of positive assessments of intravenous23 and oral L-DOPA therapy24 from various other quarters, Hirschmann and Mayer were confident enough in 1964 to announce that:

*On the basis of observations and the results of investigations which have been conducted, it can no longer be doubted that a specific effect of L-DOPA exists, even if many questions regarding its mode and site of action remain open.*25

But this optimism was not shared by everyone. McGeer’s group had once again examined DOPA, this time examining its effects in idiopathic (n = 6), postencephalitic

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16 Umbach and Baumann, 1964.
18 Umbach and Tzavellas, 1965.
19 Tzavellas and Umbach, 1967.
20 Völler, 1968a.
21 Metzel, 1965.
XIV. The “lean years”: L-DOPA therapy 1961-1967

(n = 3) and arteriosclerotic (n = 1) parkinsonism. D,L-DOPA was administered orally as 250mg capsules, commencing at a dose of 250mg/day and increasing by one capsule per day until side effects were noted; this occurred at a dose of between one and five grams/day. Intravenous L-DOPA (three patients) and D,L-DOPA (one patient) was infused as a 1mg.ml⁻¹ solution in saline. For both routes of administration, placebo controls were also used. The duration of oral treatment ranged from a few days to two years (one patient had tolerated 3g/day for this period); the number of infusions per patient was not indicated, but appears to have been very low. Only two of ten patients showed objective improvement with oral D,L-DOPA (one idiopathic, one postencephalitic parkinsonian patient). Of three patients receiving intravenous L-DOPA, only one (postencephalitic) responded, and in fact to either 250mg L-DOPA or 500mg D,L-DOPA; interestingly, he did not respond to oral D,L-DOPA (5g). All patients showed increases in urinary dopamine excretion of two or three orders of magnitude, suggesting that metabolism of L-DOPA was no problem. Although the slight improvement shown by some patients was of theoretical interest given the findings of Ehringer and Hornykiewicz, McGeer concluded that “dopa has little to offer as a therapeutic agent in the treatment of parkinsonism.”

Birkmayer and Hornykiewicz countered that the response of McGeer’s group – 20% exhibiting objective improvement, 50% some slight improvement – corresponded to their own findings and should have been interpreted positively. It is interesting to note that McGeer and Zeldowicz assumed at this point that the decline in striatal dopamine was attributable to cell loss in the striatum itself; Hornykiewicz and Birkmayer replied that such a lesion was inconsistent with both anatomical findings (especially those of Hassler) and with measurements of other biochemical markers in this region.

But McGeer’s group was not alone in their skepticism. Melvin Greer and Clyde Williams (Pediatrics, Medicine and Radiology, University of Florida College of Medicine) found no effect of D,L-DOPA (1g, oral, once only administration) in two parkinsonian patients, and no difference in the urinary excretion rates of HVA compare with age-matched controls. There was also the occasional negative report from Europe. Clas Fehling (Department of Neurology, Sahlgren Hospital, Göteborg) conducted the first double-blind study of L-DOPA in parkinsonian patients, and was also the first to analyze the results with statistical methods. Twenty-five idiopathic Parkinson’s disease patients were treated with 1.5mg.kg⁻¹ body weight L-DOPA in a 0.45/0.50% solution over a period of 13-20 minutes. A placebo injection was given on the day before or after the L-DOPA injection. A battery of tests was administered to the patients before and after the injections, and the patients were also interviewed. The improvement on any parameter following L-DOPA injection was no greater than that following saline. Fehling offered many reasons for the difference between these results and those of other workers; significant were perhaps the facts that there were no postencephalitic cases in the patient collective investigated, and that the solutions employed were up to three weeks old; Fehling claimed that the L-DOPA solution could be stored for up to two months without loss of substance. Clearly significant, however, was the fact that each patient received only a single L-DOPA infusion.

27 Birkmayer and Hornykiewicz, 1964.
29 Greer and Williams, 1963. The paper had been read at the meeting of the American Academy of Neurology in April 1962.
30 Fehling, 1966.
Italian workers were also less than overwhelmed by the value of L-DOPA therapy. Two groups (Pazzagli and Amaducci: nine patients received 60-120mg \( \text{L-DOPA i.v.} \), one received 1200mg p.o.; Rinaldi and colleagues: ten patients received 50mg (i.m.) or 300mg (p.o.) \( \text{D,L-DOPA} \)\(^{31} \) saw no convincing evidence for a beneficial effect. Another group, on the other hand, reported the curious finding that forty schizophrenic patients who received 1-2mg.kg\(^{-1} \) L-DOPA intravenously exhibited significant symptomatic improvement of chlorpromazine- or haloperidol-induced extrapyramidal parkinsonism for a few hours following a single injection. Dystonia, akathisia, gait and bradyphrenia responded best, while tremor was largely unaffected.\(^{32} \) Most other workers found that neuroleptic-induced parkinsonism was not amenable to L-DOPA therapy, as the classic antipsychotic agents are potent dopamine receptor antagonists; this paper is thus unusual in the history of antiparkinsonian therapy.

At the beginning of 1967, K. Aebert (Neurosurgery Clinic, Bremen City Hospital) reported that he had repeatedly examined the effect of the amino acid on akinesia since 1963, but found no convincing effect on motor capacity of intravenously administered L-DOPA (ranging from a single 75mg dose to one patient receiving \( 3 \times 75 \text{mg} \), \( 1 \times 100 \text{mg} \), \( 9 \times 125 \text{mg} \) over as many days). Aebert saw the problem with previous L-DOPA trials as a practical one:

> However, one gets the impression that [Birkmayer & Hornykiewicz and Hirschmann & Mayer] do not give really comparable and measurable criteria for the anti-akinesia effect that later remain experimentally verifiable. Only Umbach and his associates have measured and rendered reproducible the achieved improvements by means of skills and time tests. . . . Objective investigations are made difficult by the strong influence of internal and external factors to which the parkinsonian patient is subject.\(^{33} \)

The conclusion reached by Aebert was clear; any “L-DOPA effect” was purely psychological; the familiar problem of suggestibility which had dogged antiparkinsonian therapy for as long as anybody could remember had not been banned. Together with many other investigators, he declared:

> [Our results] show no satisfying influence – or, to be blunt, no influence at all of treatment with intravenous L-DOPA on the akinesia of the Parkinson syndrome. We believe that an L-DOPA therapy in the current form is no longer meaningful, and we have therefore abandoned it.\(^{34} \)

More promising for Aebert, who regarded akinesia as the parkinsonian symptom requiring most urgent attention, was a combination of traditional anticholinergic compounds with other sympathomimetic substances, such as cyclexedrine or desipramine.\(^{35} \)

Umbach criticized Aebert’s study on the grounds that it included only eleven patients, and that four of them had developed akinesia only after stereotactic surgery, a not infrequently observed untoward repercussion of such operations. He emphasized the solid biochemical basis laid in Vienna and Montréal for the L-DOPA approach, but at

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\(^{31} \) Pazzagli and Amaducci, 1966; Rinaldi \textit{et al.}, 1966.

\(^{32} \) Bruno and Bruno, 1966. See also Brigida \textit{et al.}, 1965; Bruno and Brigida, 1965.

\(^{33} \) Aebert, 1967a.

\(^{34} \) \textit{Ibid.}

\(^{35} \) See also Aebert, 1967b (reply to Umbach).
the same time noted that it achieved its best effects only in combination with cyclexedrine, which he noted was probably a MAO inhibitor.36

**L-DOPA and depression**

Parkinson’s disease was not the only disorder in which the effects of L-DOPA were being investigated in the first half of the 1960s. Hermann Lenz (Neurological-Psychiatric Ward of the Hospital of the Brothers of Charity, Linz), investigating the role of catecholamines in psychosis, reported no differences between the increased urinary levels of DOPAC and HVA (assessed chromatographically) of healthy controls and four schizophrenic patients (one schizophrenia simplex, two paranoid cases, one hebephrenic) following intravenous application of freshly prepared 0.25-0.5g L-DOPA in saline containing ascorbate as stabilizer;37 the rise in excreted metabolite levels was reduced if iproniazid (75mg/day) was administered beforehand.38

Dale Friend (Harvard Medical School and Peter Bent Brigham Hospital, Boston) also investigated D,L-DOPA, initially as a noradrenaline precursor. In 1962, he reported to the New York Academy of Sciences that the administration of 200mg oral doses of D,L-DOPA to normal volunteers (27-54 years), both alone and after imipramine $(3 \times 25\text{mg/day}, 2\text{ days})$ or iproniazid $(3 \times 10\text{mg/day}, 2\text{ days})$ elicited neither psychological nor physical changes in the subjects. Total serum catechol levels, however, rose sharply an hour after D,L-DOPA alone, a change which was depressed by pretreatment with either of the two psychoactive agents. Friend was puzzled by these antidepressant effects, but also commented that the continuous administration of DOPA would be required if it were to be used in the clinic, as catechol levels had returned to normal within four hours. Urinary DOPA levels were increased by treatment with the amino acid, and these levels were even higher in subjects receiving one of the antidepressants, suggesting that DOPA inhibited their uptake by catecholamine synthesizing cells. Friend was relatively open as to whether dopamine or noradrenaline was the more important DOPA derivative. He had already tested MAO inhibitors and imipramine in Parkinson’s disease patients, “without any startling effect”, but was about to begin treating parkinsonian and depressed patients with a combined MAO inhibitor/D,L-DOPA therapy, with the aim of ensuring “the highest possible level of NE in the central nervous system.”39

In the discussion of this paper, where Sourkes mentioned his experience with the metabolism of DOPA isomers by rats, Friend claimed that he was had begun treating parkinsonian patients with oral doses of 400-600mg, four times daily, over a period of 2-3 weeks; at the end of this period, a MAO inhibitor would be added to the therapy of those patients not showing a positive response.40 This approach, however, suffered from the finding that transient hypertension occasionally resulted if L-DOPA, as he used in later papers, was combined with the MAO inhibitor nialamide; the authors could not determine whether the effect was due to noradrenaline or dopamine.41

36 Umbach, 1967. Cyclexedrine is, in fact, not a MAO inhibitor.
37 Nevertheless, with time a red coloring developed, at about the same time as the patients suffered emesis and collapse. The L-DOPA was donated by Hoffmann-La Roche (10g).
38 Lenz, 1962.
Friend’s group did report, however, a D,L-DOPA trial in depressed patients in 1963, testing the “catechol amine theory of affective disorders”. Aware of Carlsson’s and Everett’s work with DOPA in animals, as well as Degkwitz’ use of L-DOPA in humans, the authors administered 800-1200mg D,L-DOPA/day p.o. to seven female depressed patients for five weeks, or 120-800mg D,L-DOPA/day p.o. plus 45-60mg phenelzine/day p.o. for a similar period. Neither approach brought the patients any apparent benefit. Blood pressure increased in some patients receiving DOPA plus MAO inhibitor, a change correlated with elevated total blood catecholamines; the rise in spinal fluid catecholamine concentrations was less marked. A similar blood catecholamine level increase was observed in patients who had been pretreated with imipramine, but the pressor response was not observed in these patients; D,L-DOPA alone led to no rise in plasma catecholamine levels. The pressor response to DOPA following MAO inhibition had been reported by Degkwitz’, Pollin’s and McGeer’s groups, and also by those workers using intravenous L-DOPA administration. Sjoerdsma was in the audience at the presentation by Friend’s group of the second paper on this experiment, and remarked that he would “bet [his] bottom dollar” that the increase in blood catecholamines would be attributable to dopamine; he pointed out that in the assay technique employed (the Weil-Malherbe fluorescence method), dopamine fluorescence was low, so that it was easy to underestimate its contribution.

C.G. Ingvarsson (Neurological Hospital Central Hospital, Vänesborg), following the method described by the Viennese group, found, in contrast, that the intravenous administration of 22.5mg/day L-DOPA was sufficient to elicit a marked affective improvement of three depressed patients; the time-course of the effect was also similar to that described by Birkmayer.

There were also scattered reports of L-DOPA trials which were conducted to investigate more fundamental neuropharmacological issues. Bente, Stoerger and Tautz (Neurological Clinic, University of Erlangen-Nuremberg) examined the effects of L-DOPA in non-psychotic patients as part of their biochemical investigation of biogenic amine metabolism. Their description of the effect of 50-75mg L-DOPA is so descriptive as to merit citation in full here:

Following administration of L-DOPA, the same typical response is seen, even after repeated application. It can be divided into four phases of differing duration. An initial phase, lasting about 5 minutes, involves principally vegetative manifestations, such as feelings of warmth, intestinal nausea, involuntary swallowing and yawning without the experience of corresponding feelings of tiredness. There follows a second stage which lasts up to 20 minutes which is characterized by psychotropic effects. Most obvious is the heightened attention to one’s surroundings, to a degree which almost seems hypermetamorphotic, whereby discrimination between relevant and irrelevant aspects of the environment is somewhat reduced. As these effects subside, the shift to the third phase begins, which lasts for 60-90 min. This stage is dominated on the one hand by changes in affect, with a tendency to a shift in mood tinged with euphoria, and on the other by manifestations from the ideational area. A characteristic stimulation of associative processes takes place, with increased plasticity of the imaginative processes.

42 Klerman et al. 1963.
43 Ibid.
44 Oster and Sorkin, 1942; Degkwitz et al., 1960; Birkmayer and Hornykiewicz, 1961; McGeer et al., 1961; Pollin et al., 1961.
45 Schildkraut et al., 1963.
whereby kinesthetic and proprioceptive coloring of qualities of feelings and experiences play a special role. . . . After the end of this phase, the Dopa effect transforms into a drift towards a contrary, morose, irritated mood, which can end in a final feeling of tiredness and exhaustion.\footnote{Bente et al., 1966.}

EEG analysis indicated increased vigilance in those patients for whom the normal vigilance level was low. Most of the administered dose was excreted via the urinary pathway within a couple of hours, principally as DOPAC, but also in significant quantities as HVA. The authors concluded that "dopamine . . . plays an important role in the regulation of the level of psychomotor activity."\footnote{Ibid.}

**Prospects for DOPA therapy in 1967**

As already mentioned, the early 1960s were lean years for those who sought to promote the role of dopamine in the central nervous system. At the Second International Pharmacological Meeting in Prague (August 1963), four papers dealt with the role of dopamine in the brain (presented by Bertler, Hornykiewicz, Sourkes and van Rossum); two years later at the Second Symposium on Catecholamines (Milan),\footnote{Proceedings published in *Pharmacological Reviews* 18: 29-803 (1966).} only Bertler and Rosengren were invited to wave the flag for the new catecholamine. In contrast to the clear tones of Carlsson at the meeting of the German Neurovegetative Society in March 1963, where he titled his presentation "Evidence for a role of dopamine in extrapyramidal functions,"\footnote{Carlsson, 1964a.} even his former students were not prepared to propose an unambiguous role for brain dopamine. In their review of the "possible role" of dopamine in the brain, they, too, were of the opinion that:

The effect of L-dopa is too complex to permit a conclusion about disturbances of the striatal dopaminergic system in Parkinson’s disease.\footnote{Bertler and Rosengren, 1966. Compare with Bertler, 1964.}

This reflected the mood of the audience, an interpretation bolstered by the discussion which followed. By 1966, the disappointments of L-DOPA therapy seemed to have overshadowed the great advances made in the investigation of catecholaminergic pathways with the fluorescence techniques developed in Sweden and the other insights regarding catecholamine function which had been gained during the previous ten years.

There was, admittedly, a decided lack of clarity regarding the exact physiological mechanism of the L-DOPA effect, if indeed, it exerted any specific effects. It was eminently possible, for example, following the work of Andén’s group on the effect of L-DOPA on spinal reflexes, that the amine was acting peripherally and not centrally.\footnote{Andén et al., 1963a, 1964c.} Bertler and Rosengren also noted that the noradrenaline precursor 3,4-dihydroxyphenylserine counteracted reserpine-induced sedation but had no impact on parkinsonian symptoms. It thus remained “probable” that dopamine was a central neurotransmitter, but it had not yet fulfilled many of the criteria which would allow definite judgement. Its regional co-localization with acetylcholine suggested to the authors, however, that dopamine "may merely modify the response of the cells when the
latter are acted upon by other agents. 53 They advised that anticholinergic agents remained the best drugs for parkinsonism, but no changes in cholinesterase had been identified in the parkinsonian brain. Caution was clearly indicated.

A basis for future developments was laid in November 1965 by the Symposium at the new Parkinson’s Disease Center (Columbia University, New York) on the “Biochemistry and Pharmacology of the Basal Ganglia”. The meeting gathered together most of the international dopamine research community for the first time, allowing an exchange of views from different research directions on dopamine in the central nervous system. Hornykiewicz recorded the fact that Duvoisin and Yahr had visited him in Vienna before the meeting, and were impressed by the video of the first patient treated with L-DOPA. They organized a press conference for him and Carlsson which led to the first sensational headlines in New York on the new therapy. These, however, were quickly forgotten in the absence of confirmation by an American clinic.54

It thus appeared by 1967 that the prospects for L-DOPA as a therapy for Parkinson’s disease were somewhat dim. Ironically, it was Degkwitz, who had led the way to L-DOPA being tried in Europe, who announced at a conference on natural medicine in 1965 that the amine could not to be recommended:

Firstly, the administration is complex. It is applied mostly as an infusion, possibly also as an injection; but even this mode is not so convenient. While the usual agents generally have a good effect on tremor and eye cramps, but less on tremor and akinesia, it is said that L-DOPA is particularly effective with respect to poverty of movement. Degkwitz, however, has thus far seen no convincing successes . . . The psychological effect of the impressive infusions probably plays the greatest role; strictly speaking it would all thus be a sort of placebo effect. It is probably similar with the MAO inhibitors . . . 55

In his 1965 review of antiparkinsonian therapy, Roger Duvoisin (Columbia University College of Physicians and Surgeons, New York) was even more severe with the apostles of the DOPA therapy:

[A] number of investigators, repeating a pattern that is all too familiar in the history of the treatment of parkinsonism, have studied the use of DOPA but have either been unable to confirm the described response to DOPA or have noted only an occasional and transient effect. Despite enthusiastic claims of therapeutic benefit, no evidence has been presented that the DOPA effect is in any way specific or that it differs from the effect of other sympathomimetic amines. Similar responses have been noted before with the use of amphetamine and other analeptics.56

Writing an information brochure for the United States Department of Health, Melvin Yahr and E.A. Bering wrote in 1966 that “no promising new forms of medical treatment

53 Bertler and Rosengren, 1966. As an interesting aside, Beani and colleagues (Pharmacology, Universities of Pisa and Florence) reported in 1966 that reserpine reduced acetylcholine levels in guinea-pig cortex and caudate nucleus, with the reduction especially marked in the latter region. DOPA administration, which did not influence acetylcholine levels in the normal animal, reversed reserpine-induced declines within 30 minutes.
55 Degkwitz, 1966a.
56 Duvoisin, 1965.
have been described in Parkinson’s syndrome”. At this point, even Hornykiewicz tended towards the view that L-DOPA therapy, while neurochemically sound, might prove to be impractical for regular use in the clinic:

[T]he effect of L-DOPA on akinesia and rigidity is undeniable. On the other hand, the question as to the therapeutic value of L-DOPA in parkinsonism seems still to be unsettled. This, in my opinion, is mainly due to the fact that, because of the unpleasant side effects of L-DOPA, it is practically impossible to inject doses of the drug which are high enough to increase the dopamine level in the striatum.

The second double-blind study of the effectiveness of L-DOPA therapy was published in 1968 by U.K. Rinne and V. Sonninen (Clinic of Neurology, Turku University). Thirty-six parkinsonian patients (twenty-four idiopathic, twelve postencephalitic) received on two successive days an injection of either 1.5mg.kg\(^{-1}\) L-DOPA in physiological saline or of saline alone. The Finnish workers found no effect on any symptom of the parkinsonian syndrome. They noted, however, a great interpersonal variation with respect to response to drug or placebo, and concluded that patient numbers in the study were too small to draw a decisive conclusion.

Nevertheless, it is interesting to note that on 24 May 1966, U.S. Patent 3,253,023 was granted to the Dow Chemical Co. (application: September 27, 1963) for a process for the extraction of L-DOPA from the beans of \textit{Vicia faba}; a kilogram of ground beans yielded 18.7g L-DOPA by this process, somewhat more efficient than Guggenheim:

\begin{quote}
A charge of 1 kg. ground beans (Vicia faba) was extd. with 9 l. 1% aq. AcOH at room temp. for 20 hrs. with occasional stirring during the first 4 hrs. The liquid was decanted and the bean pulp slurry vacuum filtered through a cake of acid-washed diatomaceous earth. The combined liquids were concd. in vacuo under N to 900 ml. The soln. was treated with acid-washed activated C, filtered as above, and concd. to 400 ml. To give 18.7g. 3-\textit{(3,4-dihydroxyphenyl)}-L-alanine, m. 284-6° (decompn.), [\(\alpha\)]\(_D\) –8.81.
\end{quote}

Hoffmann-La Roche had already developed methods for the industrial synthesis of L-DOPA from vanillin. But the demand for the amino acid declined after 1965, and interest in its commercial preparation waned.

**Problems of DOPA therapy in the early 1960s**

Many reasons underlie this initial failure of DOPA therapy to win recognition and approval. Not least was the cost of the drug; Barbeau cited a price for DOPA of about $US6,000 per kg in the first half of the 1960s. A second reason was perhaps the dramatic success in Vienna: not only Birkmayer, but most other workers were led to expect an instantaneous response to the drug, whereas experience would teach that most patients require continuous treatment with the drug over a period of time before they begin exhibiting a significant response. This is compounded by the fact that most clinicians expected a more or less prompt response to any pharmacological agent, even if the full benefit was manifested only after extended application; it was difficult, for

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57 Yahr and Bering, 1966, p.29.
58 Hornykiewicz, 1966b.
59 Rinne and Sonninen, 1968.
60 U:S. 3,253,023, abstract in \textit{C.A.} 65, 5529a.
example, to explain why the antidepressant effects of MAO inhibitors were manifested only after weeks of therapy, whereas laboratory investigations indicated that MAO activity was significantly suppressed within hours of the first administration of the drug. This was even more puzzling with antiparkinsonian medication: some response was to be expected after the first application of an agent, which is why so many of the negative reports on DOPA therapy involved single applications of the drug. Those who reported success with DOPA were usually those who employed only the L-isomer, combined it with a MAO inhibitor and patiently applied it over a period of time. The 1967 edition of the Martindale Pharmacopoeia concluded a one paragraph entry for “Dopa” with the lapidary comment:

*It has been tried in the treatment of parkinsonism in doses of 1 to 5 g. by mouth and 0.2 to 0.5 g. by intravenous infusion, but with doubtful benefit.*

The only reference given for this conclusion was the McGeer-Zeldowicz paper of 1964.

It should also be remembered that the animal models of parkinsonian tremor which had been developed during the 1950s also encouraged the view that an effective agent would exert immediate effects; the chronic effects of antiparkinsonian agents were never examined in these models, whether one thinks of lesioned macaques or tremorine-induced tremor. The fact that L-DOPA addressed the problem of akinesia rather than tremor (which L-DOPA often exacerbated in these early studies) or rigidity was in itself a problem. Parkinsonian researchers had traditionally sought agents which modified the two ‘major’ symptoms of the disorder, and understood akinesia as a secondary motor or psychic problem which would resolve itself when these two symptoms were brought under control, or could be managed by the use of stimulants such as amphetamine. There were many workers who regarded any effect which L-DOPA might exert as being simply a weak amphetamine-like stimulation – and as such, questioned the value of introducing a less effective agent which tended to induce emesis and hypertension as side effects.

Finally, DOPA therapy was suspect from the point of view of both clinician and pharmacologist at this point. The antiparkinsonian therapist had come to accept, after a century’s experience, that effective antiparkinsonian therapy was anticholinergic therapy, perhaps supported by spasmytic or antihistaminic agents. The pharmacologist, on the other hand, was trying to integrate not only dopamine but a range of other apparently neuroactive substances into his models of central nervous system function; in less than a decade, the arousing effects of DOPA in animals, the central distribution of dopamine in animal and man and its concentration in the basal ganglia, its deficiency in parkinsonism, and the therapy of this disorder by L-DOPA had all been reported: this rapid progression from basic research to at least partial clinical success was unprecedented. The developmental path taken by the agent was itself unusual: instead of being the result of rational modification of an existing antiparkinsonian by a pharmaceutical firm, L-DOPA was introduced as the rational outcome of theoretical insights gained by research pharmacologists and physiologists which were taken up by individual physicians and tried in the clinic.

L-DOPA, like reserpine, could never be the subject of a patent; only procedures for its extraction from natural sources or for its synthesis could receive such protection.

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There was thus only limited interest from pharmaceutical firms in promoting the use of the amino acid. Boehringer Mannheim, for example, supplied Degkwitz’ group with L-DOPA, but never became a major supplier of the agent as a pharmaceutical product. Hoffmann-La Roche had originally supplied Hornykiewicz with L-DOPA as a laboratory reagent. After reports of the initial successes in Vienna, they were prepared to supply other laboratories with the amino acid, but never aggressively promoted L-DOPA as a breakthrough in antiparkinsonian therapy. The company was prepared to wait and watch developments as individual clinicians, aware of one another but working independently, initiated their own research projects. This contrasts, for example, with the promotion of the company-developed diazepam (‘Valium’), launched by Hoffmann-La Roche in 1961. The initiative for its investigation therefore remained with individual physicians, whose judgement would depend on their clinical skills – especially their ability to notice an improvement in akinesia distinct from that of other symptoms, and to accept it as clinically significant – their patience and their luck with respect to the type and severity of the parkinsonism they attempted to treat. Despite the dramatic video of his first patient which he took to Basel, even Birkmayer was unable to completely convince Hoffmann-La Roche that L-DOPA represented a major advance in the treatment of Parkinson’s disease. L-DOPA was regarded rather as merely the latest in a series of potential new drugs for the disorder.

At the time, it was widely questioned whether the occasionally observed L-DOPA effect was actually connected with the dopamine depletion described by Hornykiewicz and Sano. It had, for instance, been reported that L-DOPA did not reach nervous tissue when administered to rodents, being metabolized instead by the endothelial cells of the capillaries. Andén’s group had, indeed, demonstrated that L-DOPA could modulate lower motor reflexes, providing an alternative locus of action. Later work by the same group, however, showed that exogenous L-DOPA does, in fact, facilitate nigrostriatal transmission in the rat; further, researchers at Hoffmann-La Roche were able to demonstrate the metabolism of applied L-DOPA by nervous tissue in humans. Any DOPA effect could thus be seen as being indirect and ultimately unreliable.

Could greater boldness in the application of L-DOPA have brought more rapid recognition for L-DOPA therapy? The reluctance to inject higher doses was thus, in contrast to what Wurtman later assumed, not principally because of fears concerning excessive noradrenaline synthesis and their impact on cardiac parameters following L-DOPA administration; larger doses were not administered of the apparent intolerance of the patients for such levels, not to mention the expense of the drug; most importantly, larger doses increased the severity of side effects without producing a greater therapeutic effect.

Further, the emetic effects of DOPA, which a number of pharmacologists and neurologists had experienced at first hand since Guggenheim swallowed 2.5g of freshly extracted DOPA in 1913, seemed in particular to represent an insuperable barrier to its achieving significance in the clinic. There were also unresolved concerns regarding the toxicity of DOPA in dopamine-deficient organisms. Weil-Malherbe had, as noted

63 Bertler et al., 1963.
64 Andén et al., 1963a, 1964c.
65 Andén et al., 1966b.
66 Bartholini et al., 1966; Pletscher et al., 1967.
67 Wurtman, 1970.
above, reported that the combination of MAO inhibitor and L-DOPA was often fatal in rodents, whether reserpine-treated or not.\textsuperscript{68} It was thus noteworthy that when the United States Food and Drug Administration (FDA) finally granted approval for the marketing of L-DOPA in 1970, an unusual proviso was imposed: after the licensing of the product, the two companies involved (Hoffmann-La Roche and Eaton Laboratories) were to supply the authority with on-going supplementary studies of the patients to whom it was administered. The major reservations of the FDA concerned the untoward side-effects of L-DOPA which were still regarded as limiting the value of the therapy.\textsuperscript{69}

It is noteworthy that the reduced dopamine concentrations observed in Vienna and Montréal were greatest in postencephalitic parkinsonian patients; in fact, Barbeau’s group reported no difference between controls and idiopathic Parkinson’s disease patients with respect to urinary dopamine excretion.\textsuperscript{70} The postencephalitic patient group in Vienna also exhibited the most dramatic responses to L-DOPA,\textsuperscript{71} Sano did not indicate which form of parkinsonism his patients exhibited. This luck with regard to the patient collective no doubt also played a role in the history of the therapy. It should also be noted that by 1968 Birkmayer had treated over 400 patients with L-DOPA (alone and in combination with other experimental agents), whereas Barbeau had employed it in only forty-three patients during the same period; this indicates the unusual energy with which the Viennese group pursued the somewhat troublesome therapy.\textsuperscript{72}

It must be emphasized that L-DOPA therapy represented a marked departure from the previous pathway for the pharmacological treatment of parkinsonism; the efforts of the major pharmaceutical companies were largely directed towards improving existing anticholinergic-based therapies. At the Second Symposium on Parkinson’s Disease (Washington, November 1963),\textsuperscript{73} Barbeau presented his and Birkmayer’s successes as part of his talk on the biochemistry of Parkinson’s disease;\textsuperscript{74} in the summation of the three day symposium, however, the session chairman (Boshes) mentioned neither catecholamines nor L-DOPA, concentrating rather on the prospects of neurosurgery.\textsuperscript{75} At the April 1964 conference held by the still young American National Parkinson Foundation in Miami, the leading Parkinson’s disease specialists Spiegel and Doshay reported their disappointment with DOPA:

\begin{quote}
\textit{I used DOPA in about 30 akinetic or rigid patients to see if it would help them get out of a chair and move faster. We were disappointed with the results. DOPA did not stimulate the patients to a greater degree than the monoamine oxidase inhibitors. We anticipated that our patients would start hopping about because of the accumulated serotonin and norepinephrine, but no such hoped-for response was observed and the survey terminated.}\textsuperscript{76}
\end{quote}

Doshay lamented that “\textit{during the past five years, not a single new drug has been added to the armamentarium of Parkinson’s disease}”.\textsuperscript{77} The chairman for this session,

\begin{itemize}
\item \textsuperscript{68} Vane \textit{et al.}, pp.550-551.
\item \textsuperscript{69} Anonymus, 1970b.
\item \textsuperscript{70} Barbeau \textit{et al.}, 1961.
\item \textsuperscript{71} Birkmayer and Hornykiewicz, 1964.
\item \textsuperscript{72} Barbeau, 1969b; Birkmayer, 1970a.
\item \textsuperscript{73} Proceedings published in the \textit{Journal of Neurosurgery} \textbf{24}: 170-477 (1966).
\item \textsuperscript{74} Barbeau, 1966.
\item \textsuperscript{75} Boshes, 1965.
\item \textsuperscript{76} Spiegel \textit{et al.}, 1965.
\item \textsuperscript{77} \textit{Ibid.}
\end{itemize}
Barbeau, pointed out, however, Doshay had used racemic DOPA (2-3×350mg capsules/day; supplied by Merck, Sharp & Dohme) and made weekly assessments of his patients; this was not the effective form of the drug, and the observation schedule was not appropriate given the expected duration of the drug effect. He emphasized, however, that the therapy was still experimental, and that its cost currently prohibited its long term application. Interestingly, he did not correct Doshay’s equally curious misapprehension about 5-HT and noradrenaline being involved in the probable mechanism of the L-DOPA effect; this presumably reflected American medical opinion on the question at this time. In his summation of the symposium, Boshes referred to the dopamine hypothesis only in passing:

Dr. Barbeau presented a concept that he has been developing over these past few years, and which has received a great deal of recognition already. Some may not accept all his results, but certainly something is happening in the area of dopamine metabolism that warrants further consideration.

The results of the Viennese and other German-speaking clinics as reported at the time would today be classified at least as being “interesting and worthy of further investigation”; it is difficult to escape the impression that the emerging American dominance of neurological science and the inability of Birkmayer and his colleagues to argue their case effectively in English delayed due recognition of their discovery. It is also some indication of the modesty of the original investigators with respect to their discovery that L-DOPA was not proffered as a general palliative for Parkinson’s disease; it was to be used specifically to improve akinesia, while the anticholinergic agents were to be retained for management of the other symptoms.

Perhaps the major impediment to the acceptance of L-DOPA therapy was the fact that neurology was simply not receptive for the concept of a monoamine replacement therapy in 1961. A few more years were required, during which ideas regarding monoamine transmission in the central nervous system were developed and clarified, before the value of the L-DOPA therapy could be properly assessed and recognized. It was still possible to assert in 1967 that there exited no consensus “as to whether there is a connection between altered [dopamine] metabolism and Parkinsonism in humans”. As already noted, the English neurologist Oliver published a handbook on parkinsonism in 1967 which made no mention of ‘neurotransmitters’; Onuaguluchi made no reference to chemical transmission in his 1968 review of the drug therapy of parkinsonism in the Handbook of Clinical Neurology.

The dopamine deficit was, however, mentioned in other contributions to this volume. Even here, however, there was some equivocation:

There can be little doubt that dopamine plays an important role in the physiology of the corpus striatum. Beyond this, however, we have no evidence that the depletion of this catecholamine in the brain of parkinsonian patients is a primary metabolic defect of this disease.

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78 Ibid.
79 Boshes, 1965.
80 See, for example, Birkmayer, 1964/65.
81 Friedman and Anton, 1967.
82 Oliver, 1967.
83 Onuaguluchi, 1968.
84 Selby, 1968.
Equally definitive was the assertion by the same author (George Selby; Neurology and Neurosurgery, Royal North Shore Hospital, Sydney) that:

*As yet, . . . , no convincing evidence has been provided that dopamine is a synaptic transmitter substance.*

And these views were expressed by a neurologist who remarked later in the same paper that both intravenous and oral L-DOPA could “relieve hypokinesia to a considerable degree”, albeit only temporarily. John Cumings (National Hospital, London) discussed the work of Carlsson, Sano, Hornykiewicz, Barbeau, Sourkes and Poirier in his chapter on the biochemistry of the basal ganglia in the same volume; he noted briefly that:

*the use of drugs which affect catecholamine metabolism have been used in an attempt to control the symptoms; thus both dopa and α-methyl dopa have been employed, the former with and without monoamine oxidase inhibitors. Unfortunately the results have been conflicting but Marsh et al. (1963) did have a limited success with α-methyl dopa.*

Selby and Cumings were aware of the presentations concerning L-DOPA at the International Congress of Neurogenetics in 1967 (to be discussed below), but it was clearly too early to be convinced of the efficacy of the new direction.

It is remarkable that the first assessment of dopamine concentrations in the parkinsonian brain by a laboratory other than that of Hornykiewicz, apart from Sano’s largely unrecognized report, was not published until 1971.\(^\text{87}\) In the absence of a clearly defined mechanism of action for L-DOPA, and in light of the fact that the existence of the nigrostriatal pathway was not definitively demonstrated until 1964/65, thereby establishing a link between the nigral lesion and the observed reduction in striatal dopamine levels, it is not surprising that the less than overwhelming success of L-DOPA as monotherapy for the treatment of parkinsonism should have been regarded with some suspicion. This is especially true given the century-long series of disappointments with other “miracle drugs” for the disorder. It was, in fact, the fortuitous discovery of a peripheral decarboxylase inhibitor in the mid-1960s which overcame many of the problems associated with L-DOPA therapy and paved the way to its becoming the standard treatment for Parkinson’s disease. But before this step could be taken, broader medical interest in L-DOPA was required, and it was an alternative approach which would awake this interest.

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\(^{85}\) *Ibid.*

\(^{86}\) Cumings, 1968.

\(^{87}\) Fahn *et al.*, 1971.
XV. The second coming: Oral L-DOPA therapy

GERMAN MEDICAL NEWS JOURNAL began an article in March 1970 on the “L-DOPA story” with the description of George Cotzias as “founder of the L-DOPA therapy of parkinsonism.”1 Perhaps nothing else illustrates the change in fortune for the therapy as views such as these, which were not at all uncommon. McDowell’s group introduced their 1970 paper on the use of L-DOPA in Parkinson’s disease with the much heard comment that the “first systematic evaluation of levodopa as a treatment for Parkinson’s syndrome was reported by Cotzias, Van Woert, and Schiffer in 1967.”2 This, despite the fact that he had also cited Birkmayer and Hornykiewicz’ and Fehling’s studies; the limited acquaintance with the German literature was perhaps indicated by the statement that all studies prior to Cotzias had employed D,L-DOPA.3 Birkmayer once remarked somewhat ruefully that he had discovered the L-DOPA therapy, Cotzias merely the side-effects.4 There is little doubt, however, for the reasons discussed in the last chapter, that by 1967 L-DOPA therapy had possibly reached its end; the intravenous route of administration and the short, unpredictable duration of action seemed to present insurmountable problems, no matter how well-founded its neurochemical basis. Birkmayer in Vienna was developing at this time a means to prolong the effect of intravenous L-DOPA, and the crucial paper on the subject was, in fact, published in the course of 1967.5 But by this time, attention had switched to the other side of the Atlantic, where L-DOPA therapy received the fillip it so desperately needed at this time.

1 Anonymus, 1970n.
2 McDowell et al., 1970.
3 Ibid.
4 The comment is remembered by many with whom I have spoken as having been made during discussion at the conference on Parkinson’s disease held in New York in 1969; it was also cited, for example, in Birkmayer, 1990.
5 Birkmayer and Mentasti, 1967.
George Cotzias, manganese and melanin

George Cotzias (1918-1977) was born on Crete into a prominent family. His father, royalist and reformist mayor of Athens before the Second World War and resistance leader during the German invasion, moved the family to New York in 1941 after King George requested that Cotzias act in the United States as representative of the Greek government-in-exile.6 Cotzias junior required only a further year to graduate in medicine, but had interrupted his study to volunteer for military service, and assisted a surgical team on the Albanian front. In America, he was rejected by several medical schools, partly on account of his poor English, before he was finally admitted to the Harvard Medical School. This surprising development was facilitated by an interview conducted in German (in which Cotzias was fluent) with Professor Weiss, himself a refugee; Cotzias graduated cum laude in 1943. Following internships in pathology at the Peter Bent Brigham Hospital and in medicine at the Massachusetts General Hospital, and a residency at the latter hospital in neurology, he joined the Rockefeller Institute in 1944, working with the famous biochemist Donald Van Slyke. Van Slyke was one of the first investigators in America to devote himself to the biogenic amines, his early work including the localization of MAO in mitochondria; he is often referred to as the “father of clinical chemistry”.7 Together with Vincent Dole and Lewis Dahl, Cotzias became involved in the investigation of monoamine metabolism and its relevance for hypertension.8 In 1954, Cotzias transferred with Van Slyke to the Brookhaven National Laboratory as executive officer (from 1955: head) of the Physiology Division and physician (from 1955: senior physician) at the Medical Research Center; in 1966, he became Head of the Hospital and Medical Research Center.9

Cotzias’ work at Brookhaven focused on the significance of trace metals for health and disease, with a particular interest in the biology of manganese. He was a pioneer in the use of radioisotope tracers in biological research, a direction inspired by the availability of a cyclotron at Brookhaven. Amongst his first papers from this period was the report that manganese accumulated in the liver, particularly in the mitochondria; in 1958, he described the highly dynamic and specific passage of manganese through the body which he had elucidated during the previous few years.10 Its excretion via the bile and fecal pathways suggested that manganese was somehow sequestered from the other transition metals in the body (such as magnesium, with which manganese shares many characteristics), which are excreted primarily in the urine.11 In 1958 he also wrote a detailed review of the role of manganese in health and disease for Physiological Reviews, outlining the problems and paradoxes which puzzled manganese researchers at the time; here his first contact with parkinsonism was recorded:

A diligent search for [an abnormality in the metabolism of manganese or another transition group metal] might be fruitful relative to human Parkinsonism. This view receives encouragement from the observations of Borg and Cotzias that some of the

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6 Cotzias returned to Athens after the War and was re-elected mayor in the first election (1951), but died soon afterwards. Cotzias Square, next to the Town Hall, is named for him.
7 See Anonymus, 1963; Rosenfeld, 1999.
8 See, for example, Dole and Cotzias, 1951. A selected bibliography covering all periods of Cotzias’ research is found in Dole, 1986.
9 For Cotzias biography, see Patten, 1983; Barbeau, 1984; Tang, 1984; Dole, 1986; Marketos, 1997.
Manganese was, ironically, one of the many treatments tried in the nineteenth century in Parkinsonism. It had long been recognized that manganese intoxication could induce parkinsonian symptoms in primates, including man. Cotzias mentioned in 1958 an ongoing study at Brookhaven into the "thesis that Parkinsonism might be a form of manganism," but the results of this study do not appear to have been published.

His expertise in manganese metabolism led to Cotzias’ assistance being sought in 1964 by the World Health Organization in the investigation of manganese poisoning in Chilean miners. Cotzias was moved by the plight of these workers, whose major symptoms were similar to those of Parkinsonism, especially their rigidity and akinesia. According to his colleague Lily Tang, this became the motivation for his search for a cure for Parkinson’s disease. Cotzias was initially surprised by the fact that tissue manganese concentrations (initially measured in hair, which accumulates the metal) were actually higher in healthy exposed workers than in those suffering from manganese; the turnover rate in the latter workers, however, was found to be higher than that of both their exposed but healthy comrades and of normal controls. The workers forced into retirement by their disability had long cleared their excess manganese levels by the time Cotzias examined them; the damage had already been done and clinical symptoms were no longer dependent on exposure. It was thus clear to Cotzias that continuing exposure to a high manganese load was not necessary for the expression of clinical symptoms; manganese toxicity was not directly related to accumulated exposure but rather to the rate of manganese turnover, which itself was determined by intake.

Cotzias had already been investigating manganese-binding proteins, and had identified a $\beta_1$-globulin in human plasma which he dubbed ‘transmanganin’ (in analogy to transferrin). Because of his biochemical findings, however, it was clear that post hoc administration of manganese chelators could play no role in therapy for the Chilean miners. His group also noted that chlorpromazine displaced manganese from its binding sites, thus establishing another link between manganese and extrapyramidal disease. In light of etiological theories for Parkinson’s disease involving oxidative stress which were developed later, it is interesting that manganese might be involved in the formation of free radical intermediates; the reaction between manganese and

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12 Cotzias, 1958.
13 W.A. Hammond, *A treatise on the diseases of the nervous system* (1891; Appleton, New York); cited in Forster, 1966. Potassium permanganate (up to 1g in a 0.1% solution) had also been employed in post-encephalitic patients, particularly in eastern Europe; such injections were of doubtful value but extremely painful: Majdan-Majdanskij, 1928; Gamarnik, 1934; Dejanov, 1935.
14 Embden, 1901; Edsall and Drinker, 1919; Lyon-Caen and Jude, 1935; also Schwab and England, 1968. For animal models: Mella, 1924; Pentschew *et al.*, 1963.
15 Cotzias, 1958.
17 Cotzias *et al.*, 1964b.
18 Mena *et al.*, 1967; Cotzias *et al.*, 1968b.
19 Copper chelators (most commonly penicillamine) are used in the therapy of Wilson’s disease, which shares some similarities with Parkinsonism.
20 Borg and Cotzias, 1962. Borg and Cotzias found that Mn$^{2+}$ and Mn$^{3+}$ formed colored complexes with phenothiazine derivatives; this property was shared with Fe$^{2+}$ and Co$^{3+}$, but not with Al$^{3+}$ or divalent meta ions. For references by other workers, see Cotzias *et al.*, 1964a.
chlorpromazine, for example, led to the formation of a semiquinone radical. Cotzias’ conclusion was that manganese might play a physiological role in free radical formation in oxidative metabolism.\textsuperscript{21}

The largely unexplored polymer melanin had been reported to contain high semiquinone concentrations, and the free radical concentration of hair samples was found to be related to its degree of pigmentation.\textsuperscript{22} Cotzias’ group established in 1964 that the manganese concentration was also greater in a number of heavily pigmented tissues (hair, feathers, bovine conjunctiva) than in the lightly pigmented structures from the same individuals.\textsuperscript{23} This led Cotzias to the hypothesis, expressed in the 1964 paper by his group entitled “Melanogenesis and extrapyramidal disease”:

\textit{the biological activities of some metals, some drugs, and some free radicals might converge on the function of a distinct species of intracellular organelles, the melanin granules.}\textsuperscript{24}

The view of Cotzias’ group was that there existed an analogy between the relationship of ‘melanosomes’, responsible for melanin synthesis in pigmented cells, and the mitochondria of non-pigmented cells, with both containing elevated free radical and manganese levels.\textsuperscript{25} Their 1964 paper was an exhaustive summary of the biochemical, physiological and other evidence for an involvement of melanin in extrapyramidal disease:

- Depigmentation of the substantia nigra is a feature of both Parkinson’s disease and phenylpyruvic oligophrenia; in man, pigmentation of the substantia nigra commences only during the eighteenth month post partum, and increases throughout life.
- Only mammals with a pigmented substantia nigra develop extrapyramidal disease spontaneously or experimentally (primates and horses; the latter exhibit a parkinsonian syndrome following the ingestion of yellow star thistle).
- In albinism without extrapyramidal disease, the pigmentation of the substantia nigra is normal. Regulation of peripheral and central melanogenesis were thus clearly independent processes.
- Melanin is rich in a number of metals, especially zinc, copper, iron and manganese, but also titanium, cobalt, nickel and molybdenum.
- A role for $\beta$-melanocyte stimulating hormone (MSH) as a neurohormone in higher species had recently been proposed. Some effects of chlorpromazine were reversed by MSH, while phentothiazine or reserpine administration caused increased MSH secretion in amphibians and fish. Both phentothiazine and reserpine therapy could elicit extrapyramidal symptoms in susceptible patients.
- Reduced catecholamine levels in various body tissues had been reported in Parkinson’s disease (referring to Barbeau, Ehringer, Hornykiewicz, Birkmayer, Sourkes, Greer and Williams) and phenylpyruvic oligophrenia. It had been suggested that catecholamines might serve as precursors for melanin formation in the brain. Further, L-DOPA had been found to be of symptomatic benefit in Parkinson’s disease (Birkmayer and Hornykiewicz, Barbeau \textit{et al.}, Friedhoff \textit{et al.}).
- Melanocytes and sympathetic cells both originate in the neural crest.\textsuperscript{26}

\textsuperscript{21} Ibid.
\textsuperscript{22} Kerkut \textit{et al.}, 1962.
\textsuperscript{23} Cotzias \textit{et al.}, 1964b.
\textsuperscript{24} Cotzias \textit{et al.}, 1964a.
\textsuperscript{25} Prasad \textit{et al.}, 1965; Van Woert \textit{et al.}, 1967.
\textsuperscript{26} Ibid.
The thesis proposed by Cotzias’ group on the basis of this and other evidence was:

burdening with semiquinone-free radicals of normally pigmented brain might induce extrapyramidal manifestations, while enrichment of the depleted organ with similar free radicals might relieve existing extrapyramidal disease. Melanin granules are said to capture free radicals.  

The same, he suggested, might also apply to “burdening” with metal ions; correction of metal deficiencies had been found to restore pigmentation in, for example, hair and retina. Much of Cotzias’ presentation is now known to be aberrant, and his conclusion sounds disturbing in light of modern etiological theories of Parkinson’s disease; he and his group, however, were nonetheless among the first to attempt a synthesis of the information relating to melanin and Parkinson’s disease. It might also be noted that it had been reported (albeit in a little known journal) that demelanization of the nigra had also been reported in patients treated with reserpine or phenothiazines. It should also be remembered that the spectral analysis studies of melanin carried out by Cotzias’ colleague Melvin Van Woert would not commence until 1967; nor was it yet known that the substantia nigra contains little tyrosinase, so that the peripheral pathway of melanogenesis is not as significant as auto-oxidation of dopamine in this region, contrary to the assumption made by Cotzias.

Not all workers agreed that manganese toxicity and Parkinson’s disease were similar; Duvoisin objected at the Second International Parkinson’s Disease Symposium that “a neurologist is struck not so much by its resemblance to parkinsonism as by dissimilarity.” Paul Yakovlev remarked that the first animal model to include rigidity, tremor and the characteristic flexion of the extremities was the manganese-treated Rhesus monkey in 1924, but Van Bogaert and Dallemagne had reported in 1945 that the neural lesion following manganese toxicity did not include consistent involvement of striatum or substantia nigra, but rather a diffuse damage to the cerebellum. Cotzias’ answer on this occasion was somewhat evasive; he was definitely struck by their similarity, although he conceded that he was not a neurologist and that the ores to which the Chilean workers had been exposed also contained many other metals. Everyone, including Cotzias, agreed, however, that, despite the similarities of the symptoms of the two disorders, manganism could not be equated with idiopathic Parkinson’s disease, especially as the former is a non-progressive disease. But Cotzias suspected that they might share common metabolic features, particularly with respect to the affected neuron populations.

A number of laboratories reported in the middle of the 1960s that melanin concentration was measurably reduced in the parkinsonian substantia nigra; the depigmentation of this region had been noted at the qualitative level since Trétiakoff’s

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27 Ibid.
28 Kaiser, 1963. See also references in Cotzias et al., 1964a.
30 Marsden, 1969; Rodgers and Curzon, 1975; van Woert, 1967, 1974; Van Woert and Ambani, 1974. Note, however, that there is evidence for the presence of tyrosinase in the substantia nigra: Miranda et al., 1984; Tief et al., 1998. Ikemoto et al., 1998, however, detected no midbrain tyrosinase using immunocytochemical techniques.
31 In Hebb et al., 1966.
32 Ibid., referring to Mella, 1924.
33 Cited in Lewis. 1971.
34 In Hebb et al., 1966.
work in 1919, and had recently begun to attract renewed attention. Cotzias’ group had noted that in extrapyramidal disease, even where pigmentation in the substantia nigra appeared normal, more sensitive chemical analysis often revealed subtle changes. Changes in skin pigmentation and other dermatologic changes had also been long reported in some patients undergoing long-term phenothiazine therapy. Cotzias thus began to consider means by which depigmentation in Parkinson’s disease might be halted or reversed. At the Miami meeting of the American Parkinson Association in 1964, Van Woert and Cotzias had presented results of their investigations of melanin isolated from the livers of two amphibians: the Congo eel (*Amphiuna tridactylum*) and the mud puppy (*Necturus americanus*). The melanin was found to be rich in MAO and to have accumulated previously injected radiomanganese. The authors postulated that biogenic amines were the precursors of melanin and that MAO was somehow involved in the synthetic process; an explanation linking this with the pathology of parkinsonism, however, was still lacking.

On the basis of these considerations, Cotzias attempted between 1964 and 1966 to treat parkinsonian patients with MSH: the result was an exacerbation of tremor accompanied by increased skin melanization. This was interpreted as possibly indicating that MSH had diverted available catecholamine precursors, especially DOPA, from brain to skin melanocytes. Not to be deterred, Cotzias then administered melatonin, which did indeed bring tremor under control to a limited degree, but was accompanied by excessive sedation of the patient.

Barbeau had twice presented the results of the Montréal group’s experiences with L-DOPA therapy in Brookhaven (1963 and 1966) and had discussed the prospects of the therapy with Cotzias. Cotzias had also turned his attention to the potentialities of this amino acid in 1965. Tang claimed that that this step was undertaken, “relying on reasoning rather than other’s (sic) experiments”. Cotzias was later cited as claiming that his success was due to his ignorance of the literature on previous trials of DOPA, which, he said, would only have dissuaded him from his own attempts. This might have been true to an extent, but Cotzias and associates indicated in their first major paper on their experience with D,L-DOPA that they were aware of the work of Hornykiewicz and Birkmayer (the Montréal group was not cited), although the success of the Viennese pair with L-DOPA was represented by the authors as being an isolated case; and their 1964 paper on the role of melanin in extrapyramidal disease had referred positively to L-DOPA trials in Austria, Canada and Germany, indeed citing...

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35 Foley and Baxter, 1958; Duffy and Tennyson, 1965; Pakkenberg and Brody, 1965.
36 See references in Cotzias *et al.*, 1964.
38 Cotzias *et al.*, 1967. Antón-Tay and Diaz (Neurobiology, Biomedical Research Institute, Ciudad University, Mexico) reported some benefit for parkinsonian symptoms of melatonin in 1971. These workers did not appear to be aware of Cotzias’ work with the hormone; they had observed an effect on the parkinsonian symptoms of a subject whose response to melatonin was being tested in another connection (thalamectomy). Shaw and colleagues (1973) observed no benefit in parkinsonian patients of melatonin.
39 Barbeau, 1984. Barbeau and Van Woert had also been friends since meeting during their training at the University of Chicago at the end of the 1950s.
41 Interview with the Munich medical magazine *Euromed*, 3 March 1970; reproduced in Kapp and Leickert, 1971, p.65. Also Cotzias *et al.*, 1973: “we were essentially ignorant of these developments at the outset, and did not know that levodopa had been abandoned by the profession as a drug.”
42 Cotzias *et al.*, 1967.
them as evidence for his hypothesis. Donald Calne also wrote that he was so impressed as a young clinician by the “integration of ideas and experimental findings on dopamine” in Hornykiewicz’ classic 1966 paper that he wrote to him for advice; in his reply, Hornykiewicz included a preprint of the much cited Cotzias et al. (1967) paper, which would suggest some contact between the group and Hornykiewicz. A sentence in a 1973 paper, on the other hand, is difficult to interpret:

In a recent review we did not say that we were essentially ignorant of these developments at the outset, and did not know that levodopa had been abandoned by the profession as a drug.

The sentence occurs at the end of a section on work by other investigators. If Cotzias wished to say that he was, in fact, aware of the work in Göteborg and Vienna at the time of his experiment, this would be accurate but inconsistent with many of his public utterances. The paper referred to is a detailed review of the background to L-DOPA therapy which essentially presents the dopamine and melanin deficiency hypotheses in parallel; there is a decided emphasis that replenishment of dopamine stores does not explain all the benefits of L-DOPA therapy, but there is no discussion of what motivated Cotzias to use DOPA in the first place. This renders the comment in the 1973 somewhat puzzling, which is apparently Cotzias’ response to accusations that he had made such a statement. That Cotzias initially chose to examine DOPA therapy on the basis of the deficient melanin hypothesis is, on the other hand, completely plausible; as he himself remarked, “The reasons for a wedding are not necessarily the same as those that sustain the marriage.”

In the first paper concerning DOPA in parkinsonism, Cotzias once more reported that MSH (20-40mg i.m.) aggravated the tremor, but not the rigidity, of six parkinsonian patients (type not stated). D,L-DOPA – used because it was cheaper than L-DOPA – was then administered to sixteen patients in increasing oral doses for varying periods of time; the DOPA was prepared in capsules of 500mg substance each. This approach was adopted in an attempt to saturate the synthetic enzymes which converted DOPA to active metabolites; this was, of course, not necessarily dopamine in the Cotzias model:

Its beneficial effects, if any, had to result from its enzymatic conversion into metabolites, among which only melanin and dopamine were known to us. It appeared that beneficial effects would be induced by saturating these and other enzymatic pathways, but without causing toxicity to the patients. A “controlled” double-blind study could therefore be neither safe nor conclusive, since it would preclude our being alert for signs of toxicity. Instead, we kept increasing the doses of levodopa (sic) slowly and waited for improvement or toxicity to emerge.

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43 Cotzias et al., 1964b.
44 Calne, 1988.
45 Cotzias, 1972/73, referring to Cotzias et al., 1971b.
46 Cotzias et al., 1971b.
47 Supplied by Nutritional Biochemicals Corporation; labelled “not for human use”. In his 1972/73 review, Cotzias stated that phenylalanine was then tested as the most obvious melanin precursor, but did not have any effect; for unexplained reasons, he “skipped the singly hydroxylated tyrosine” and tested D,L-DOPA as the next candidate precursor, a serendipitous choice, as he noted. Tang (1984) wrote that L-DOPA was not used because it was not available at that time, Cotzias (1972/73) that it was not available in sufficient quantity.
48 Cotzias, 1972/73.
Cotzias was even more specific in his Lasker Award speech:

*We recognized that the oral route of administration was necessary, but we did not know otherwise how to test this drug. We defined our need as follows: to saturate (and to keep saturating) either or both the enzyme, DOPA decarboxylase (which generates dopamine from DOPA) and the melanin-forming enzymes, ie, tyrosinase, within the brain. This simplistic notion conformed at the bedside with the method used by biochemists wishing to saturate an enzyme with substrate.*

Eight of sixteen patients treated with D,L-DOPA showed “either complete, sustained disappearance or marked amelioration of their individual manifestations of Parkinsonism.” The accompanying table indicated a 20-40% improvement in two patients, 40-60% in three patients and a greater than 60% improvement in a further three. Unfortunately, there is no indication of the means by which these figures were calculated; a number of symptomatic features (cogwheel phenomenon, rigidity, tremor and so on) and the performance of a variety of tasks (including handwriting, number of steps required to move 10 metres, ability to collect an object from the floor) were “tested periodically” during both drug and placebo treatment, but further details were not included in the paper. As the dose was increased, improvement was noted first in the rigidity; only at higher doses was tremor improved or even abolished. Cotzias noted that tremor, dysphagia and weakness were controlled in one patient who had failed to respond to benzhexol, ethopropazine, promethazine or benztropine. The optimal D,L-DOPA dose for the responsive patients ranged between a maximum of 3 and 16g/day (corresponding to 72-259mg.kg⁻¹) for a period of 34-347 days (total DOPA administered: 57-3892g). Oral administration of D,L-phenylalanine (1.6-12.6g), on the other hand, exacerbated parkinsonian symptoms in seven of eight patients who had benefited from DOPA administration. In two patients who had responded to D,L-DOPA therapy, neutron activation analysis detected a decline of approximately 30% in blood manganese concentrations before reaching a plateau at about 130 days, which Cotzias noted corresponded to the mean life-span of the erythrocyte.

The major complication observed was transient granulocytopenia in four patients treated with higher doses of D,L-DOPA, associated with extensive vacuolization of the less mature myeloid cells of the bone marrow. Athetoid movements were also noted in some patients who otherwise benefited from D,L-DOPA therapy. The authors thus concluded on a cautious note:

*Although D,L-DOPA emerges as an effective therapeutic agent, the hematologic complications indicate that caution is required in further studies of this compound.*

This was especially true because, as Cotzias conceded, the mechanism of the effect remained “obscure”, although it was acknowledged that reduced central dopamine levels in parkinsonism “might have some bearing on the improvement noted in our patients”. It was also noted that the onset of action of D,L-DOPA (about three hours; longer than in Vienna because of the route of administration) contrasted with the long period required to return to baseline after the termination of therapy (four to fourteen days); an effect on catecholamine storage granules was proposed as a potential

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49 Cotzias, 1969.
50 Cotzias et al., 1967.
51 Ibid.
52 Ibid.
XV. The second coming: oral L-DOPA therapy

explanation for this phenomenon. The failure of phenylalanine to reproduce the effects of DOPA, however, suggested to Cotzias that dopamine synthesis did not entirely explain the DOPA effect; it also indicated to him that defective hydroxylation processes might be involved in parkinsonism. Lack of phenylalanine hydroxylase (monoxygenase) underlies not parkinsonism, but the phenylketonuria; Cotzias thus presumably saw tyrosine hydroxylase as the potential enzymatic problem, which makes it even more curious that he did not test tyrosine in his patients in order to test the hypothesis.

Cotzias was doubtful that the dopamine hypothesis could explain the D,L-DOPA effect, as it was patients suffering only mild, unilateral parkinsonism who had failed to respond at all to extended D,L-DOPA treatment; concerns about toxicity had prevented him from using even larger doses in an effort to achieve a result in these cases. The authors had intimated in this paper that an investigation using L-DOPA would be desirable as soon as it became financially feasible. An anonymous editor in the British Medical Journal responded to Cotzias’ report with some interest in June 1967, noting that, as the traditional antiparkinsonian drugs were incapable of eliciting “dramatic improvement” in patients, it might be time to consider alternative directions. The 1962 paper of Birkmeyer (sic) and Hornykiewicz was cited as an early, disputed claim of the effectiveness of DOPA, but the reviewer did not distinguish between the two isomers of the amino acid. Cotzias wrote to the journal in August 1967 to thank the editors for their support, and to note that studies using L-DOPA were now underway and showing promise; higher doses were being used in an attempt to also reach milder cases.

Second International Congress of Neuro-Genetics and Neuro-Ophthalmology (Montréal, September 1967)

Cotzias’ group announced at the Second International Congress of Neuro-Genetics and Neuro-Ophthalmology in Montréal in September 1967 that a trial of L-DOPA in parkinsonism had begun, as the United States Atomic Energy Commission had agreed to underwrite the costs of Nutritional Biochemicals Corporation producing the L-amino acid. It was reported that:

> continuous oral administration of L-dopa may bring sustained relief to some parkinsonian patients, lasting for the several months of the trial practised thus far.

Dramatic films of the effects achieved were shown to underscore the benefit of the amino acid.

The paper from Cotzias’ group was not the only one presented at the 1967 Montréal conference concerning L-DOPA or dopamine in parkinsonism. The first session was in fact devoted to the “biochemistry of dopamine in extrapyramidal disorders”; it dealt mainly with anatomical studies aiming to determine the factors which regulated striatal dopamine, and included presentations from Hornykiewicz, Carlsson, Andén, Sourkes

53 Ibid.
54 Cotzias et al., 1967.
55 Anonymus, 1967.
56 Cotzias, 1967.
57 Cotzias and Papavasiliou, 1967; see also Cotzias, 1972/73.
58 Cited in Barbeau, 1969b.
and Poirier, Van Woert, the McGeers and Côté and Fahn (amongst others; twelve papers were presented). It is important to note that such work was stimulated by the recognition of a striatal dopamine deficit in parkinsonism, generally without reference to past or ongoing attempts to treat parkinsonism with DOPA. Spiegel’s group reported in this session that they had examined the effects of intracaudal injection of L-DOPA on bradykinesia elicited in the rat by caudal stimulation with alumina cream, tungstic acid or carbachol; in all cases, injection of L-DOPA increased locomotor activity, leading the referents to hypothesize that dopamine acted to relieve striatal inhibition of spontaneous motion.59

The clinico-biochemical session of the congress was, in comparison, quite brief, with six papers presented (including that of Cotzias’ group). The only other paper directly concerned with therapy was J.A. Rosen’s report that tranylcypromine improved bradykinesia and postural deficits in twenty-five of sixty-five patients. Interestingly, Rosen referred to experiments in which bradykinesia had been relieved in chimpanzees by intravenous administration of DOPA.60 The third session concerned specifically the biochemistry and pathophysiology of tremor; seven papers were presented, including discussions of tremorine-induced tremor and the anatomical substrates of extrapyramidal tremor, as well as the respective roles of ACh and catecholamines in the production of tremor. The final two sessions concerned abnormal urinary substances in Parkinson’s disease and schizophrenia (the so-called “pink spot”; ten papers) and the genetics of parkinsonism (four papers).61

The last paper in this final session was particularly interesting: Schwab and Poskanzer had analyzed about 1800 cases of parkinsonism seen at the Massachusetts General Hospital between 1875 and 1965 by the “cohort method”, and had determined that the increase in age of new cases of Parkinson’s disease matched that of the population which had experienced the epidemic encephalitis of the 1920s. This led them to the conclusion that new cases of parkinsonism were simply late manifestations of post-encephalitic parkinsonism and that parkinsonism as a nosological entity would virtually disappear with the winnowing of this population.62 This hypothesis had first been proposed by Schwab and colleagues (including Doshay) in 1956,63 and regularly reiterated in the meantime.64 As noted by the authors, Klaue had suggested in 1940 on the basis of his pathologic examinations that the etiology of both idiopathic and post-encephalitic parkinsonism was probably the same. The essential problem with Schwab’s approach was that it did not sufficiently consider the fact that Parkinson’s disease is a disorder of the aged; an analysis of the contribution of post-encephalitic parkinsonism to the total pool could thus be only assessed with the demise of the entirety of the population affected by the von Economo epidemic. This is illustrated by the epidemiologic prediction made on the basis of their analysis in their 1963 paper: the number of parkinsonian cases was expected to peak in the mid-1960s before rapidly declining by the mid-1980s to a level corresponding to about 10% of that of 1960. Schwab did not deny the existence of ‘paralysis agitans’; he expected, however, that by 1985 parkinsonism would be “occurring in a much reduced frequency and as a less

59 Spiegel et al., 1967; see also Spiegel et al., 1968.
60 Rosen, 1967.
63 Schwab et al., 1956.
64 For example, Poskanzer and Schwab, 1961, 1963.
important neurological problem." This has unfortunately not proved to be the case. Margaret Hoehn analyzed the distribution of patient ages in 1971/76 and concluded that the form of parkinsonism seen today is probably identical with that described by Charcot and others before the First World War, and that it was distinct from the epidemic of parkinsonism between 1920 and 1945. Even earlier, an Australian study had found that encephalitis lethargica was involved in only 13% of patients examined at Brisbane Hospital. This leaves the question of the relative frequency of parkinsonism before encephalitis lethargica untouched, but this issue is too complex to be discussed in the present work.

Third International Symposium on Parkinson’s Disease (Edinburgh, May 1968)

At the end of 1967, the dopamine hypothesis of Parkinson’s disease was fairly well established, but not the L-DOPA therapy. The breakthrough for the latter was achieved at the Third International Symposium on Parkinson’s Disease in Edinburgh in 1968. 116 participants were listed in the proceedings, compared with sixty-two at the previous symposium on Parkinson’s disease in 1963; twenty-five Americans, eleven Canadians and eighty Europeans (of whom twenty-one were from Edinburgh) participated, compared with forty-one Americans, sixteen Canadians and five Europeans (only one from continental Europe: Sem-Jacobsen from Oslo) at the Second Symposium. Equally significant was the fact that the proceedings of the symposium were published as a book, rather than as a supplement to the *Journal of Neurosurgery*. Of the eight sessions, the second, concerned with the pharmacology, biochemistry and histochemistry of the extrapyramidal system, was the largest, and most of the papers discussed aspects of monoamine metabolism and the nigrostriatal pathway. The sixth session, “medical neurology”, included one paper on the vegetative signs of parkinsonism and four on the use of L-DOPA: those of Cotzias’ and Yahr’s groups, a further contribution to its clinical application by Bettag and Holbach, and a paper by the Basel Hoffmann-La Roche research group concerning the use of decarboxylase inhibitors in combination with L-DOPA therapy. The thematic contrast with the program of the Second Symposium on Parkinson’s Disease could hardly have been greater.

At the annual meeting of the American Academy of Neurologists in April 1968 in Chicago, Cotzias’ group had reported that by November 1967 sixteen parkinsonian inpatients had been treated with slowly increased doses of L-DOPA for an average period of 200 days; the optimal dose (maximum improvement with minimal toxicity) was found to be 4-8g/day. All sixteen patients showed improvement of their major symptoms, although the changes in the more advanced cases were less impressive. Once again, all cardinal symptoms were improved, but tremor was controlled only at higher doses. Cotzias was now more positive: “the metabolic approach to the therapy of Parkinsonism deserves intensive study.”

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65 Ibid. The prediction attracted sufficient attention to be included on page 33 of the *New York Times* (front page of the second section) of 19 October 1962: “New theory links palsy to a virus. Two researchers believe Parkinsonism may vanish in 20 to 40 years”.

66 Hoehn, 1976; see also Hoehn, 1971.

67 Eadie et al., 1965.


69 Cotzias et al., 1968a.
Medicine (14 March 1968), Cotzias stated that twenty-one patients had now been successfully treated with L-DOPA; six were also receiving L-DOPA as outpatients. He noted that the blackening of the urine which had been associated with high dose D,L-DOPA therapy was not seen when L-DOPA was employed; the black compound was thus presumably associated with the D-isomer of the amino acid.\(^{70}\)

By the time of the Third International Symposium on Parkinson’s Disease (May 1968), the number of patients treated had risen to twenty-six, with the same pleasing results.\(^{71}\) Cotzias emphasized that all possibilities which might explain the improvement in these patients were being considered by his group. For instance, the chemical contamination of each L-DOPA batch was noted and was being prepared for publication; an often dramatic rise in plasma iodine levels was noted in many patients. Nor was Cotzias willing to abandon the melanin hypothesis:

> Specification of a neuronal role for [5-HT and dopamine] in the diseased brain is premature at best: we do not even comprehend why neurological improvement may emerge or increase long after the dose of l-dopa has become stabilized.\(^{72}\)

As an alternative, Cotzias chose “to stress the point” that L-DOPA and 5-HTP are metal chelators, and that L-DOPA and some catecholamines induce intracellular manganese accumulation. His major message, however, was the careful elevation of the L-DOPA dose over a period of weeks:

> the capsules containing l-dopa were given in gradually increasing oral doses so that the optimal dose was reached no sooner than after five to seven weeks. We cannot over-emphasize the importance of slow increments and of slow mobilization of these individuals.\(^{73}\)

The optimal daily doses achieved under this regime lay in the range 4 to 8g. Although Cotzias indicated that patients were withdrawn from anticholinergic medication in the weeks before the commencement of L-DOPA therapy, except in cases where this proved to be impractical, he also noted that the optimum L-DOPA dose was lower in individuals concurrently receiving such medication. It must also be emphasized that Cotzias’ protocol differed from that of many previous controlled studies in that L-DOPA was administered on a chronic basis; most studies which had reported negative results had done so after single or only a few administrations of the drug. In contrast to his D,L-DOPA studies, milder cases showed the most improvement in response to L-DOPA, a response which exhibited a characteristic course:

> we gained the impression that, with increasing doses of L-dopa, the history of the symptomatology was being retraced backwards. The sequence in which the signs of parkinsonism responded seemed to be as follows: first akinesia; then rigidity; finally tremor. Upon stopping the drug, these signs re-emerged in the reverse order, but a new plateau was reached between four days and four weeks. The new plateau seemed to be less severe than the basal state.\(^{74}\)

\(^{70}\) Cotzias, 1968.
\(^{71}\) Cotzias et al., 1969b.
\(^{72}\) Ibid.
\(^{73}\) Ibid.
\(^{74}\) Ibid.
There were also improvements in a range of other problems, including dysuria, lacrimation, dysphagia, aphonia and mood; the “awakening effect” of L-DOPA was, in fact, one of its most impressive qualities for Cotzias, bringing with it increased alertness, improved memory and greater interest, unaccompanied by insomnia or restlessness. These benefits, however, were not achieved without a price. Most ominous was the observation that ten of the twenty-six subjects developed “intermittent, dose-dependent reversible involuntary movements”. Minor side effects included transient nausea and vomiting, some sleeplessness and nervousness, and possible transitory biochemical changes (increased blood urea nitrogen and plasma bound iodine; eosinophilia). Cotzias, however, explicitly postponed discussion of these side effects to a later timepoint.

Cotzias also noticed a diurnal variability in motor performance in some patients during L-DOPA therapy, with expression of parkinsonian symptoms for one to two hours being seen in three patients in the early afternoon. These fluctuations could not be controlled in these cases by adjustment of the dosage schedule (6-7 times per day for most patients), but the duration of motor impairment could be reduced by employment of a reduced protein diet (11g/meal, compared with a high protein diet of 45g/meal). Oral phenylalanine (200mg.kg$^{-1}$) elicited similar episodes in these patients; in the other patients, it both exacerbated existing symptoms in those not receiving L-DOPA or blocked its effects in those who were.75

The discovery that slowly increasing the dose of L-DOPA reduced the problems of nausea and vomiting which were otherwise associated with high dose DOPA therapy, together with the demonstration of the viability of the oral route of administration using this method, were breakthroughs which revived worldwide interest in L-DOPA, including, most importantly for its future development, American interest. Cotzias’ success was reported as such in the *New York Times* of 8 May 1968, his first foray into the public domain with his new invention (figure 15-1). Hornykiewicz later noted:

[Cotzias] simply went far beyond what we would have thought possible with dosages of dopa. He did not see any effect with lower doses, so he kept going up, up, and up. That is, I think, the American approach to things, including medicine.76

It is, of course, interesting to note that Cotzias had achieved this interest with the results in so few patients, most of whom suffered from significant side reactions to L-DOPA which Cotzias chose largely to overlook for the time being; by this point, over six hundred cases of parkinsonism treated with L-DOPA intravenously had been published, most of them with a positive outcome.77 By 1970, the number of parkinsonian patients treated by Cotzias with L-DOPA had rise to forty-eight, of whom fourteen suffered from manganese-induced parkinsonism;78 this number had not altered by December 1971.79 With respect to manganism, it is interesting to note that even high

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75 Ibid.
76 Cited in Dow, 1990, p.63. Birkmayer had made a similar remark in a 1956 interview with Spiegel concerning multiple sclerosis research: “Americans also apply the carpet bombing approach in science. They destroy an entire district and in the process, of course, also hit the target factory.” 30 May 1956, p.44.
77 Barbeau, 1969.
78 Congress of the American Medical Association, Chicago, June 1970; cited in Kapp and Leickert, 1971, p.82. The authors noted that many of Cotzias’ patients suffered from postencephalitic parkinsonism.
79 Cotzias, 1971.
L-DOPA doses did not elicit the choreiform movements which bedevilled the therapy of ‘normal’ parkinsonian patients. In five of six manganism patients, L-DOPA proved to be of significant benefit for the motor symptoms. In the sixth, hypotonia was instead induced, a response also seen in normal subjects receiving high doses of L-DOPA (up to 1g/day); this patient responded well to D,L-5-HTP.80

As with Birkmayer, a great deal of Cotzias’ success can be attributed to his forceful and determined personality, interpreted by those not so enamored of the man as egoistic and ambitious. The neurologist Bernard Patten assembled a series of Cotzias citations in his “personal tribute” which illustrate well the propensity of the man to convey ambiguous impressions. For example, under the heading “How much suffering should the patient endure before the DOPA study is stopped?”:

We can’t turn back. Sure, the patients are suffering, but hell, what they’re going through ain’t nothing compared to what I went through when I was a sergeant in the Royal Greek Army... When the patients reach the degree of suffering that I experienced as a sergeant in the Greek Army, then we’ll stop the study. But right now there’s too much at stake.81

Cotzias, like Birkmayer, polarized those who came into contact with him; the words used by Patten to describe him could as easily be applied to his Viennese counterpart.

George was part of an era that has ended: an era before peer review and committee-approved protocols, a time before the quantification of biology – a time when guts, intuition, insight, and imagination were as important to the process of discovery as were material and methods.82

Whether such characters have a place in current medical research is a question which cannot be discussed here; it will suffice to note that extraordinary approaches and eccentric personalities are generally more tolerated in situations of desperation, both in medicine and elsewhere.

**L-DOPA: the start of the new beginning**

Cotzias’ presentation at the 1967 neurology congress in Montréal had already stimulated a great deal of interest amongst his colleagues, and the second American investigation of the therapy was also described in Edinburgh. Roger Duvoisin presented the initial results of an investigation by a group which also included Margaret Hoehn and Melvin Yahr (Parkinson’s Disease Research Center and Department of

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80 Cotzias et al., 1971b.
81 Patten, 1983.
82 Ibid.
Neurology, College of physicians and Surgeons, Columbia University, New York). Determined to extract the maximum information from their study, Duvoisin and his colleagues conducted a double-blind placebo-controlled investigation – in order to avoid the "lack of adequate controls" which characterized most studies to date – in thirty Parkinson's disease cases of varying severity. L-DOPA treatment was gradually introduced: after an observation period in which patients continued their normal medication, placebo capsules were given several times per day, and these were gradually replaced by L-DOPA capsules (250mg or 500mg). The dose commenced at 750-1000mg/day and increased until the appearance of side effects; this occurred at levels of 4-8g/day. Traditional medication was withdrawn before L-DOPA therapy in fourteen cases and after the response to the amino acid had been registered in nine. A number of symptoms were rated on a five point scale and summed to give a total rating for each patient; tasks of daily living were also assessed, as were a number of hematological parameters, electrocardiogram and electroencephalogram. Yahr's group found that all parkinsonian symptoms were improved by L-DOPA: the mean improvement for akinesia was 50%, for tremor 53% and for rigidity 64%. Tasks of daily living were performed with greater ease and competence; even drug-resistant oculogyria was resolved in the three post-encephalitic patients. Comparison of drug effectiveness in twenty-seven patients revealed that L-DOPA was superior to anticholinergic therapy in twenty-three cases and equally effective in two; in eleven patients, an additive effect of the two approaches was evident. The most common side effects were nausea (25 cases), vomiting (16) and postural hypotension (11); involuntary movements similar to those described by Cotzias were also seen in eight patients, mostly in the limbs least affected by parkinsonism. Mental disturbances, ranging from agitation to frank psychosis, were noted in five cases. The authors were thus confident that the L-DOPA effects described by Birkmayer and Hornykiewicz (1964) and Cotzias et al. (1967) were genuine reproducible effects of the amino acid.83 At the same meeting, Bettag and Holbach (University Neurosurgical

Figure 15-2: Diagrams used by Duvoisin et al. (1969) used to illustrate the effect of L-DOPA in parkinsonism. (a) Response of patient to L-DOPA therapy during a two month period as assessed by total neurological deficit score. (b) Scored performance of selected activities during different treatments: A 25mg/day benzhexol; B six days after withdrawal of benzhexol; C two weeks after 4.5g/day L-DOPA; D five days after withdrawal of L-DOPA; E ten days after resumption of L-DOPA therapy.

83 Duvoisin et al., 1967. These results were also presented three months later at the Annual Meeting of the American Neurological Association: Yahr et al., 1968.
XV. The second coming: oral L-DOPA therapy

<table>
<thead>
<tr>
<th></th>
<th>7AM</th>
<th>9AM</th>
<th>11AM</th>
<th>1PM</th>
<th>3PM</th>
<th>5PM</th>
<th>7PM</th>
<th>Total daily dose (g)</th>
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<tbody>
<tr>
<td><strong>Day 1</strong></td>
<td>0.1</td>
<td></td>
<td>0.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.3</td>
</tr>
<tr>
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<td>0.1</td>
<td></td>
<td></td>
<td>0.1</td>
<td></td>
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<td>0.1</td>
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<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>1.3</td>
</tr>
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<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
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</tr>
<tr>
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<td>0.2</td>
<td>0.3</td>
<td>0.2</td>
<td>0.2</td>
<td>0.3</td>
<td>1.7</td>
</tr>
<tr>
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<td>0.3</td>
<td>0.3</td>
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<td>0.3</td>
<td>0.3</td>
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<tr>
<td><strong>Day 17</strong></td>
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<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
<td>2.1</td>
</tr>
<tr>
<td><strong>Day 19</strong></td>
<td>0.4</td>
<td>0.3</td>
<td>0.4</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
<td>0.4</td>
<td>2.4</td>
</tr>
<tr>
<td><strong>etc.</strong></td>
<td>etc.</td>
<td>etc.</td>
<td>etc.</td>
<td>etc.</td>
<td>etc.</td>
<td>etc.</td>
<td>etc.</td>
<td>etc.</td>
</tr>
</tbody>
</table>

Table 15-1: Dosage schedule for the administration of L-DOPA, as presented in Cotzias et al., 1969c.

Clinic, Bonn) and Fasano (Neurosurgery, Turin University) also made presentations dealing with the positive experiences with L-DOPA, the latter employing intravenous L-DOPA as an adjunct to cryosurgical intervention.84

Cotzias and Duvoisin each showed films to the conference which illustrated graphically the effects of oral L-DOPA on parkinsonian patients. The English neurologist Donald Calne commented in a later memoir:

_The results seemed too good to be true, and many in the audience were skeptical; I recollect hearing my seniors asking whether the presenters “had ever heard of a controlled clinical trial”._85

The same doubts which had confronted the European workers in the first half of the 1960s thus raised themselves again. It should be remembered that the concept of the ‘double-blind trial’ may have been introduced in 1949, but its practice was still rather the exception in the mid-1960s, as discussed above.

But this time the ‘spell had been broken’86: enough workers had at least been rendered curious by what they had heard at the two conferences to return home and commence their own trials, including the young Calne. What was genuinely novel about the American rediscovery of the therapy was that all major symptoms of Parkinson’s disease could be controlled with L-DOPA, not just akinesia. Curiosity about the new therapeutic approach thus began to spread rapidly. The _Medical Letter_, a bulletin-type publication which advised physicians on developments in therapy, devoted its major article in the 6 September 1968 issue to “New and old drugs for parkinsonism”, the “new drug” being L-DOPA. The history of the agent from Ehringer and Hornykiewicz up until the recent conference of the American Neurological Association was reviewed, and the editor concluded that, despite the still scanty information on the drug, it was

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84 Bettag and Holbach, 1969; Fasano, 1969. See also Fasano et al., 1969, 1970.
85 Calne, 1988; presumably referring to Cotzias’ paper.
86 Kapp and Leickert, 1971, p.84.
showing such promise that “many . . . patients would gladly take whatever risks are involved in the use of L-dopa”. The editors expressed cautious hope that it might represent a “far more effective therapy for the symptoms of parkinsonism than any previously available drug”; indeed, the traditional anticholinergic drugs “have very limited effectiveness in most patients.”

Further:

The National Institutes of Health and the Parkinson’s Disease Foundation are now taking responsibility for increasing the numbers of studies in clinical research centers so that the Food and Drug Administration will have enough data when it acts on a new-drug application for marketing L-dopa.

1969: year of confirmation

Cotzias’ various presentations and the confirmation of his results by an independent clinic marked the beginning of real movement for the L-DOPA therapy in the United States. Indeed, the number of investigations being undertaken from the middle of 1968 was legion, if uncoordinated, devoid of a common approach and varying in quality. Several of the more prominent workers described their experiences at the IX International Congress of Neurology, held in New York at the end of September 1969.

It is an indication of the rising international public prominence of L-DOPA that, immediately before this meeting, the leading German news magazine Spiegel published its first report concerning the L-DOPA therapy. The magazine recorded that what the New England Journal of Medicine had described as “the most important contribution to medical therapy of a neurologic disease in the past 50 years” – that is, Cotzias’ work – was, in fact, presaged almost a decade earlier when Birkmayer and Hornykiewicz had discovered the dopamine deficit and trialled its correction by a substitution therapy. In the meantime, wrote the Spiegel, four German clinics and over 200 “medical teams” had investigated the therapy and verified the value of the Austrian discovery.

Interestingly, the magazine cited Oliver Sacks as one of the Americans who had reached the same conclusion; some of the patients had “vegetated for more than 40 years in hospital and were now released from their mummy situation”. This was one of the earliest references to the “Awakenings” story.

It was noted that scopolamine and atropine were still occasionally employed, but their peripheral activity made them less popular than the synthetic anticholinergics.
Chapter XII of the Congress was devoted specifically to “Parkinson’s disease and L-DOPA”, which in itself was indicative of the growing attention which the therapy was attracting. The following groups presented papers on the subject:

476. Hornykiewicz (Toronto): discussed monoamines in parkinsonism.
477. Rinne and Sonninem (Neurology, University of Turku): urinary dopamine and HVA excretion both before and after L-DOPA administration was similar in 65 parkinsonian patients and 23 controls.94
478. Cotzias et al.: involuntary movements were an increasing problem in parkinsonian patients, but not those suffering from manganism. It was emerging that the L-DOPA effect did not decline over time; the dose could, in fact, be reduced in some cases.
479. Duvoisin et al.: One hundred patients had now been investigated over a period of eighteen months. L-DOPA appeared to be the best drug in parkinsonism, but was often even more effective in combination with anticholinergic drugs.
480. Timberlake et al. (Harvard Medical School, Boston): double blind, internal placebo-controlled study in forty hospitalized ambulatory patients. L-DOPA (16×50mg/day) improved 25% of when compared with procyclidine; tremor, however, was not significantly affected.95
481. McDowell et al. (Cornell University Medical College, New York): 150 patients had been treated with L-DOPA, of whom half were treated for more than a year, the others for at least six months. Dosages of 1.5-8g/day achieved a 50% improvement in two thirds of patients.96
482. Barbeau and Gillo-Joffroy (Clinical Research Institute of Montréal) and Siegfried et al. (University Neurosurgical Clinic, Canton Hospital, Zürich): both these groups reported on the combination of L-DOPA with the decarboxylase inhibitor Ro 4-4602; this will be discussed below.
483. Steg (Neurological Department, Sahlgrenska Sjukhuset, Göteborg): this worker specifically addressed the side effects of L-DOPA therapy. Apart from hyperkinesia, these did not appear to represent a barrier to the use of L-DOPA in the clinic.97
484. Spiegel et al. (National Parkinson Institute, Miami; Temple University, Philadelphia): spoke on the work which they had initially described at the 1967 conference. They also added that they had successfully treated the a- and bradykinesia of parkinsonism (and, to a lesser degree, the tremor) with extracts of the velvet bean (Stizolobium deeringianum), which was less expensive than synthetic L-DOPA.98
485. Schwab (Massachusetts General Hospital/Harvard Medical School, Boston): estimated that of ten de novo parkinsonian patients, one was suitable for surgical intervention, six for immediate L-DOPA therapy and three for neither.99

A groundswell of support for the new therapy had thus developed, and greater attention was being paid to the benefits rather than the side effects of the new approach. It should also be remembered that the nine groups who had reported here their experiences with L-DOPA therapy during the previous year represented only a small minority of the number of clinics investigating the technique. The congress effectively gave its seal of

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94 See also Rinne et al., 1971.
95 See also Timberlake, 1970.
96 See also McDowell et al., 1970.
97 See also Andén et al., 1970; Steg, 1970.
98 See also Wycis et al., 1970.
99 Drake and Duvoisin, 1969.
approval to the new therapy, and this was due largely to reports from two groups, those of Cotzias and Yahr. Each group also published major papers during 1969, Cotzias prior to the conference, Yahr shortly afterwards, which would cement the new therapy in the clinic of parkinsonism. The following year, the German edition of the Medical Tribune published a special issue devoted solely to l-DOPA therapy, based to a great extent on the presentations at the IX World Congress of Neurology.100

In Europe, the major development at this time had been the introduction of DOPA decarboxylase inhibitors to the therapy of Parkinson’s disease, which would ultimately prove to be the second breakthrough necessary to establish the l-DOPA therapy as a viable tool in the treatment of the disorder. This aspect will be addressed in the next chapter. But Cotzias himself does not appear to have been aware of these moves as he published the paper in February 1969 which he saw as the culmination of his work during the previous two years. Cotzias commenced this presentation with the requisite caution:

Degenerative diseases like Parkinsonism are recurrently subjects of promising treatments that eventually prove disappointing. We have undertaken, therefore, to conduct controlled observations lasting long enough to be productive even for a slowly progressive, nonlethal disease.101

This would become a recurrent theme in the development of parkinsonian therapy: the question of whether symptomatic management offered more than a respite from the decline of the patient – and if so, whether the respite was significant. l-DOPA had now been administered to twenty-eight parkinsonian patients (all three forms) who had not responded satisfactorily to traditional therapy. During the first two weeks, other parkinsonian medications were discontinued as far as possible; in the following two to three weeks, placebo capsules were given six to seven times a day, and the patients’ condition monitored by neurologic, medical and laboratory examinations. l-DOPA was then introduced at a level of 100mg, three times a day, then gradually increased by 200-300mg per day until the optimal dose (maximally 8g per day) was achieved, normally after five to seven weeks. Cotzias also reported in this paper his first examination of combining l-DOPA therapy with a peripheral decarboxylase inhibitor; this aspect will be discussed in detail in the next chapter.102

The response of the patients to l-DOPA treatment was variable, but generally satisfying; Cotzias never claimed the dramatic responses which had met Birkmayer’s first attempts, but thirteen of the patients improved sufficiently to be discharged and henceforth treated on an ambulant basis. Nonetheless, his report that, for instance, two patients could return to their employment as carpenter or trial lawyer, was certainly impressive. Akinesia responded first to l-DOPA, then rigidity and tremor; tremor was, in fact, often not apparent until the other two symptoms had subsided. The l-DOPA dose required was generally half of the d,l-DOPA dose which had been necessary in patients who had received both forms. During the three years that he had observed these patients, significant diurnal fluctuations were noted in some patients, often associated with emotional or physical stress; the reduction in performance could last between a few minutes and several days. In general, however, the therapy appeared to maintain a steady state in the disorder of most patients for periods of up to two years. Notably, a

101 Cotzias et al., 1969a.
102 Ibid.
relapse into full parkinsonian following withdrawal of L-DOPA was most rapid in those patients experiencing diurnal fluctuations in its effect.\textsuperscript{103}

The side-effects included involuntary movements which varied in severity from passing to disturbing; the incidence of these movements, though reversible, appeared to be correlated with duration of disease, not with the degree of severity of the disorder. In a parallel experiment stimulated by this observation, Cotzias found that even 8g L-DOPA did not exacerbate the symptoms of a Huntington’s disease patient, but 3.75g α-methyl-DOPA was able to reduce his choreiform movements without eliciting signs of parkinsonism. Toxic effects were rare; mental changes included increased concentration and interest, improved memory, and a certain degree of sleeplessness and nervousness.\textsuperscript{104}

Despite the largely positive outcome of this investigation, Cotzias’ summation of his results was quite sober:

\textit{Despite their usefulness, the therapeutic effects are primarily tools for further investigation, of equal potential to the side effects.}\textsuperscript{105}

The bulk of the discussion concerned the location of the dopamine-responsive centres responsible for the side effects; his main interest at this point appears to have been the allocation of the various L-DOPA effects to either peripheral or central locations. It is thus all the more curious that the effects of the decarboxylase inhibitors used in the investigation were not considered in the discussion. This was despite the fact that it was hypothesized that saturation of peripheral tissues with L-DOPA preceded neurologic responses to the amino acid; akinesia was only improved at doses which also resulted in the urinary excretion of DOPA. Similarly, specific neuronal populations were saturated by different L-DOPA levels, a phenomenon which explained the presentation of positive and negative responses to the drug at different dose levels, which in turn differed according to the individual patient. Urinary excretion of dopamine and HVA were not correlated, suggesting to Cotzias that only a portion of the latter could be attributed to dopamine metabolism, the remainder representing the “siphoning off” of labile methyl groups from various tissues. Interestingly, there was no discussion in this paper of the role of melanin.\textsuperscript{106}

The most significant conclusion was that the L-DOPA effect does not seem to depend on the underlying cause of the parkinsonism, whether post-encephalitic, idiopathic, arteriosclerotic or even the consequence of manganese poisoning. As a result, \textit{“the effects of its administration might yield neurochemical information in neurodegenerative diseases whose signs are variants of those here.”}\textsuperscript{107} This was the reverse of the approach which had set Birkmayer and Hornykiewicz on the path to this point: Cotzias saw \textit{“biochemical dissection”} as a means for gleaning therapeutic clues concerning diseases whose underlying cause was not yet known, whereas Hornykiewicz regarded the systematic determination of those root causes as the better approach. This divergence reflected the traditional difference between investigative clinician and research scientist.

\textsuperscript{103} Ibid.
\textsuperscript{104} Ibid.
\textsuperscript{105} Ibid.
\textsuperscript{106} Ibid.
\textsuperscript{107} Ibid.
The first major confirmation of Cotzias’ results was the double-blind study first reported by the New York Neurological Institute group led by Melvin Yahr (and included Margaret Hoehn and Roger Duvoisin) at the Symposium on Parkinson’s disease in Edinburgh in May 1968, in expanded form at the meeting of the American Neurology Association in June 1968, and published in its final form a year later in the Archives of Neurology. The date of the initial presentation indicates that Yahr’s group had begun their L-DOPA trial soon after the 1967 congress. In their 1969 paper, Yahr’s group reviewed the history of DOPA therapy from its introduction in Vienna until the use of large doses of D,L-DOPA by Cotzias. This group reported that they had now found that the administration of 3-8g/day L-DOPA (as capsules, distributed as 3-5 doses/day) produced a significant overall improvement in forty-nine of sixty patients (mixture of etiologies and severity, but biased towards more severe cases) treated for up to eight weeks, with all major symptoms responding to the therapy; by twelve months this figure not only rose to 91%, but the degree of improvement in the patients had also increased, including an effect on the relatively therapy-resistant tremor. The degree of improvement compared with the traditional medical treatments was estimated as being about 250% greater (table 15-2). The description of a 59 year old patient (duration of disease: six years) allows comparison with Birkmayer’s patient L.S.; after his previous medication was withdrawn:

The patient became completely immobile and was confined to bed and chair. He could not arise, stand, or walk without support. His speech became barely intelligible. . . . Treatment with levodopa was then begun with 250 mg administered three times daily and progressively increased, until by the 16th day of treatment, the total daily doses had attained 5 gm. Significant objective improvement was noted as soon as the dose reached 2 gm/day, and a striking improvement was evident in the third week of treatment on the 5 gm. dose.108

Onset of benefit was more gradual than with Birkmayer’s approach, but the final result equally startling. A “placebo effect” was tested by substitution of blank capsules:

Abrupt withdrawal of levodopa by placebo substitution was followed in all cases by a gradual loss of the dopa effect. Little objective change was evident the first day on placebo; a marked deterioration occurred over the next several days, but even after six or seven days, some of the dopa effect was still detectable.109

Curiously, restoration of L-DOPA also restored the full therapeutic benefit, but only after a delay of about a week. The most common side effects in the study were the usual gastrointestinal responses (fifty-one patients), involuntary movements (thirty-seven patients) and cardiovascular responses (fourteen instances of postural hypotension, twelve of cardiac dysrhythmia). Only six patients, however, withdrew from therapy as a result of these side-effects. Despite conceding that their group had not “overcome all the difficulties of drug evaluation” and the fact that the precise mechanism of action of L-DOPA remained unknown, Yahr and his colleagues were convinced by their observations that:

levodopa at the present time appears to be the most effective pharmacological agent available for the treatment of parkinsonism regardless of cause, symptomatology, or degree of severity.110

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108 Yahr et al., 1969.
109 Ibid.
110 Ibid.
XV. The second coming: oral L-DOPA therapy

<table>
<thead>
<tr>
<th>Overall improvement (%)</th>
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<th>Follow-up trial period (4-12 months)</th>
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<td>20-49</td>
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<td>16</td>
</tr>
<tr>
<td>0-19</td>
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<td>4</td>
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<tr>
<td>Total number*</td>
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<th>Akinesia</th>
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<td>2</td>
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</tr>
<tr>
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<td>3</td>
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<tr>
<td>Mean improvement</td>
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<td>66%</td>
<td>57%</td>
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<td>53</td>
</tr>
<tr>
<td>L-DOPA, after 4-12 months</td>
<td>29</td>
<td>71</td>
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Table 15-2: Benefit of L-DOPA therapy for parkinsonian patients, as presented by Yahr et al., 1969.

Yahr’s group would even voice later in the year the exciting suggestion that L-DOPA might alter the progression of the disorder.111

Confirmation of the new status of L-DOPA therapy in England was confirmed by the publication 1969 of two important papers on its application in the *Lancet*. In April 1969, Calne, Sterne, Laurence (Medical and Neurological Units, University College Hospital, London), Sharkey (Highlands General Hospital, London) and Armitage (London School of Hygiene and Tropical Medicine) published there their double-blind study of the use of oral L-DOPA in post-encephalitic parkinsonism, one of the very few studies of L-DOPA in this class of patients to be published as a full paper. Calne had been interested in the possibilities of DOPA therapy since 1966, when he sought advice from Hornykiewicz during the preparation of his doctoral thesis. This group was also aware of problems of drug trial interpretation in Parkinson’s disease, and adopted the method previously described by Yahr’s group at the Edinburgh conference for the assessment of parkinsonian symptoms and the introduction of L-DOPA into therapy.112 Of the twenty patients who received L-DOPA for up to forty-seven days (initial dose: 1g/day; maximum tolerated dose was 0.5-2.5g/day; Calne’s group could not raise this dose to the same levels as Cotzias), seven improved “substantially”, three “moderately”, five

111 Duvoisin et al., 1969c.
112 Duvoisin et al., 1968. The assessment technique was most extensively described in Hoehn and Yahr, 1967, but this first description of what would become known as the ‘Hoehn-Yahr rating system’ received only few citations at this stage.
showed no response and five discontinued therapy because of the side-effects. All improvements were validated by comparison with a group receiving placebo. The most marked improvement was in control of walking, while tremor was one of the physical signs which benefited least. The side effects were quite severe in many cases, and mostly involved involuntary movements (ten cases), orthostatic hypotension (nine cases) and nausea (ten patients); all were controlled by lowering the L-DOPA dose.113

The Calne study was briefly reviewed a fortnight later in the *Lancet*, and compared with the more positive outcome reported recently by Cotzias with L-DOPA. Differences between the two studies were noted, including the double-blind design of the British study and the discontinuation of previous medication in the New York study, but no conclusions were drawn as to the causes of the discrepancy. Interestingly, the rationale in this brief review was the restoration of dopamine levels in the basal ganglia;114 in the 1967 *British Medical Journal* editorial on L-DOPA therapy, the melanin theory of Cotzias had held sway.115 A letter to the journal from the San Francisco neurologist Sean O’Reilly argued that the dose had been increased too steeply in the Calne study, and this explained the less convincing results. He recounted his own, successful experiences with L-DOPA, and had written only “to prevent any possible discouragement of investigators from treating severely disabled patients.” He believed that all parkinsonian patients, of whatever etiology, deserved a long-term trial of L-DOPA.116

The Cotzias and Calne reports were also briefly reviewed in a *Journal of the American Medical Association* editorial in September 1969, as was Schwab’s initial report on amantadine in Parkinson’s disease (see next chapter). Both approaches were praised as promising new directions in what had been until now the disappointing field of antiparkinsonian therapy; even should the long term outcome for these approaches be less spectacular than the promise, the journal noted, “the fresh metabolic approach at the molecular level will remain an important medical advance.” It was interesting that, at this point, the editor commented that dopamine was “in all probability . . . a synaptic transmitter.” The recent report by Tissot’s group that the peripheral decarboxylase inhibitor Ro 4-4602 reduced the requirement for large L-DOPA doses was also noted, including the observation that ten of twenty patients were “cured” and a further eight improved by the combined L-DOPA/inhibitor therapy.117

In November 1969, Calne’s group publish a companion report to their study of L-DOPA in post-encephalitic parkinsonism: this time the investigation involved twenty-six idiopathic Parkinson’s disease patients in a double blind, within patient study; that is, the patients’ individual responses to L-DOPA and placebo were compared. The duration and severity of disease was lower in this investigation than in their post-encephalitic parkinsonism study, and the maximum tolerated dose in this group was higher (1-8g/day). Six patients did not complete the program, for reasons which were not directly linked to L-DOPA therapy; about half the patients showed substantial improvement and a quarter some improvement. Hypokinesia, posture and rigidity responded best to L-DOPA, but tremor was also significantly reduced; the side-effects

113 Calne et al., 1969a.
114 Anonymus, 1969d.
115 Anonymus, 1967.
117 Anonymus, 1969a. Reference was made to Tissot et al., 1969a, to be discussed in the next chapter.
were similar to those seen in post-encephalitic cases, and similarly dose dependent. However, the improvement of motor signs was greater than that seen in the previous study, and the side effects less marked; however, unlike Yahr’s group, no further improvement was noted after the maximum tolerated dose had been received for two weeks.\textsuperscript{118}

In 1969, Barbeau published a detailed “critical review of nine years’ experience” of L-DOPA therapy of Parkinson’s disease; it was an excellent summary and discussion of the biochemical and clinical events of the past decade.\textsuperscript{119} The paper was something of a celebration; in a listing of published reports on low dose DOPA trials in Parkinson’s disease between 1961 and 1969, the number of favourable reports vastly outnumbered that of the unfavourable, whether the oral route or the intravenous was used; of the unfavourable, only one dated from after 1967. Following a discussion of the rationale behind the L-DOPA therapy, Barbeau discussed his own experiences: between 1960 and 1968, he had administered oral L-DOPA (300-2000mg/day) to a total of forty-three patients. The cost of the drug had prohibited him treating many patients on a chronic basis; two patients, about whom he had reported in 1961, had received 300mg/day for three months. Since 1968, he had treated eighty parkinsonian patients (one was post-encephalitic) with progressively increased doses of L-DOPA (maximum: 7g/day); nearly 80% showed improvement which he classified as “good” or “very good”.\textsuperscript{120}

As also reported by others at this time, hypotension (31%) and involuntary movements (50%) were the major side effects observed. Barbeau shared the concerns of many workers that this problem was an inevitable accompaniment of the beneficial effects of L-DOPA, and presented the first detailed analysis of the types of movements involved. Most authors up till now had commented on the presentation of choreiform involuntary movements, but Barbeau, who believed that these movements could be induced in any patient if the L-DOPA dose was raised to a sufficient level (and could not always be abolished by lowering the dose) thought otherwise:

\begin{quote}
At first these movements, particularly if they are limited to the face, are not noticed by the patient himself. They become bothersome mainly when they affect the limbs or when the peculiar wave-like nodding of the head becomes severe. Although most authors talk about chorea, dystonia or tics, it is our opinion that these dyskinesias differ markedly from what occurs in natural diseases of the basal ganglia. In some ways they resemble the dyskinesias seen during the acute phase of von Economo’s encephalitis or with some phenothiazines.\textsuperscript{121}
\end{quote}

Earlier, low dose L-DOPA trials had not been associated with the production of abnormal involuntary movements. The effects could be reduced by phenothiazine or pyridoxine treatment – which, however, also abolished the effectiveness of the L-DOPA therapy. Barbeau emphasized that these dyskinesias were seen only in parkinsonian patients receiving L-DOPA; multiple sclerosis and manganese intoxication patients, for instance, tolerated similar L-DOPA doses without manifesting involuntary movements.

Barbeau also reviewed data concerning “Dopa potentiators” – the decarboxylase inhibitors employed by Birkmayer and Cotzias – for he had concluded that:

\begin{flushright}
118 Calne \textit{et al}., 1969b.
119 Barbeau, 1969b.
120 \textit{Ibid}.
121 \textit{Ibid}.
\end{flushright}
1. Cephalic dyskinesias
(a) Ophthalmic: pseudo-exophthalmos; rapid blinking, blepharospasm; sudden lateral deviations; internal strabismus; intermittent mydriasis
(b) Facial: unilateral rictus with or without hemifacial spasm; trismus; asymmetric choreic/myoclonal cheek movements
(c) Oro-bucco-lingual: rapid, short duration tongue protrusion; longer protrusion with rolling and licking; clicking and smacking of lips and tongue; rumination-like movements of lips and chin; rhythmic clicking of dentures; rare palatal myoclonus; altered vocalization
(d) Cervical: latissimi contractions; wave-like anteroposterior rocking of head; lateral tremor of head (rare); torticollis; synchronized shrugging of shoulders; sudden massive unilateral shoulder contraction with inclination of head to affected shoulder

2. Truncal dyskinesias
(a) Respiratory: hyperventilation with panting; myoclonal jerks of diaphragm and intercostal muscles
(b) Postural: whole body rocking in sitting position; swaying while standing; belly dancing movements of pelvis; scoliosis; opisthotonia; acute akathisia anxiety reactions

3. Upper extremity dyskinesias
(a) Proximal: slow wing-like lapping of entire arm; internal rotation of arm; ballistic movements; athetosis
(b) Distal: rapid jerking finger movements; restlessness of hands and increased gesticulation; saccadic lateral movements of hand from wrist; increased tremor at commencement of therapy accompanied by reduced rigidity, followed by decreased rate and amplitude

4. Lower extremity dyskinesias
(a) When lying down: extension spasms of leg; akathisia
(b) When sitting: balancing motion of leg from knee with lateral and/or anteroposterior movement; lateral oscillation of knee or ankle; rocking motion of foot on floor; rhythmic splaying of toes
(c) When standing: movement from one foot to other (akathisia)
(d) When walking: internal rotation of ankle progressing to whole limb circumvolution; athetosis; ballismus

Table 15-3: Classification of L-DOPA-induced dyskinesias by Barbeau (1969b).

L-dopa, as it is presently used (November 1969), cannot yet be marketed because of the cost, the cumbersome dosage schedule and the possible dangers of unsupervised usage.\(^\text{122}\)

The drug, however, should be made available to “qualified investigators”, in order to investigate the advance of the therapy; Barbeau listed ether or ester derivatives of L-DOPA, chemical analogues of either L-DOPA or dopamine, and the employment of suitable dopamine receptor agonists as possible steps towards “eventual success” in the treatment of Parkinson’s disease.\(^\text{123}\)

In November 1969, the advances made thus far were discussed at a small symposium (sixty participants) organized by Barbeau and McDowell in Val David, near Montréal; Calne described it as “the most memorable neurological meeting that I have ever

\(^{122}\) Ibid.
\(^{123}\) Ibid.
XV. The second coming: oral L-DOPA therapy

Most of the leading researchers in the field were present; by its conclusion, any doubts about the value of L-DOPA therapy had been cleared, as least in the minds of those who attended the meeting. The major topics of discussion no longer concerned whether L-DOPA was an advance in the therapy of parkinsonism, but rather means by which L-DOPA therapy could be improved. It had, however, also emerged that the new approach was not without its problems; these will be discussed below.

L-DOPA in post-encephalitic parkinsonism

Neither of the editorials which appeared in the major British medical journals following the publication of the results published by Calne’s group concerning the employment of L-DOPA in post-encephalitic parkinsonian patients appeared to find the selection of a purely post-encephalitic group as significant in the interpretation of the group’s results. Other reports followed which indicated that L-DOPA did not benefit post-encephalitic cases to the same extent as idiopathic patients, primarily because of their low tolerance for the amino acid; this was consistent with the lower maximal doses reported by Calne and his colleagues. Members of the group wrote in a letter to the Lancet at the end of the following year that slow elevation of the dose and a lower maintenance level (average of thirty-two patients: 750mg; range: 250-1750mg) could allow some improvement in such patients, but the danger of adverse effects was much more acute than in idiopathic parkinsonism. Oliver Sacks (Beth Abraham Hospital, New York) and his associates had also investigated L-DOPA therapy in post-encephalitic patients, and noted in particular the various forms of respiratory crisis (attacks of gasping, panting, sniffing or similar; respiratory and phonatory tics; tachypnoea, bradypnoea; respiratory asymmetries) seen in these patients. These responses were seen with low L-DOPA doses (under 2g/day), and seemed to represent an exacerbation of pre-existing respiratory abnormalities in these cases; the phenomenon was never observed in idiopathic parkinsonian patients. Riddoch had also observed that respiratory abnormalities were common in post-encephalitic patients. Krasner and Cornelius (Stobhill and Ruchill Hospitals, Glasgow) detected this sort of response in only one of twelve post-encephalitic patients, but also a range of other unpleasant side effects, including depression, euphoria and involuntary movements. Curiously, their assessment of the benefits of therapy restricted itself to tremor, rigidity and writing, which in the most cases did not respond to L-DOPA.

Another side effect observed by Sacks in post-encephalitic patients was particularly interesting: “forced reminiscence” or “incontinent nostalgia”:

One of the most astonishing effects of L-dopa, when given to certain post-encephalitic patients, is the reactivation of symptoms and behaviour-patterns present at a much earlier stage of the disease, but subsequently “lost”.  

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125 Barbeau and McDowell, 1970.
126 Hunter et al., 1970.
128 Riddoch, 1927.
129 Krasner and Cornelius, 1970. These authors remarked that most of their post-encephalitic patients did not respond to the drug, and those that did exhibited the most disturbing side effects.
This included the renewed re-emergence of old symptoms (such as respiratory tics), but also included the emergence of “‘dormant, primitive symptoms” such as myoclonus, bulimia, polydipsia and satyriasis. Even more intriguing was the case he reported of a 63 year old woman who had suffered post-encephalitic parkinsonism since the age of 18; following release from oculogyria and other parkinsonian signs, followed by psychomotor excitement and increased libido, she experienced, to her own surprise, the vivid recollection of the period in which she had fallen ill:

*The period was marked by nostalgia, joyful identification with a youthful self, and uncontrollable upsurge of remote sexual memories and allusions.*

This nostalgia was accompanied by mannerisms, linguistic colloquialisms and references to the events and night-life of the 1920s. Continued excitement led to a decrease in the L-DOPA employed, resulting in immediate loss of the memories. Sacks related the phenomenon to excitement rather than to the disinhibition which can elicit vivid recall in old age and inebriation, and thus similar to forced reminiscence associated with migraine and epilepsy.

Duvoisin and colleagues, on the other hand, were reasonably satisfied with the effects of L-DOPA therapy in thirty post-encephalitic parkinsonian patients. Twenty-six cases exhibited symptomatic improvement, including a reduction in two of the most aggravating hallmarks of post-encephalitic parkinsonism, oculogyria and sialorrhea, although choreiform dyskinesia was exacerbated. Abnormal involuntary movements (nineteen cases) and behavioral responses (ten cases) were the major adverse side effects; seven patients discontinued therapy because of side effects, mostly of a motor nature. The group attributed their more positive results to the longer period of their trial; they emphasized that adjustment of dosage was more critical in post-encephalitic patients than in idiopathic parkinsonism. They also noted that their results were consistent with the report by Solomon’s group in 1937 that amphetamine was of greater benefit for post-encephalitic parkinsonian patients than in paralysis agitans.

Sacks published the most comprehensive depiction of the effect of L-DOPA in post-encephalitic patients in the book *Awakenings*. Sacks was regarded with some suspicion by the scientific community; he had been reporting some of his results in letters to the editors of British medical journals since 1970, some of which have been discussed above, but had never published a complete paper on his investigation, which at its peak encompassed seventy patients. He explained in 1983 that the impression which the L-DOPA effect in his patients made upon him was of a nature which could not be conveyed in a conventional scientific article:

*Thus I was impelled, willy nilly, to a presentation of case histories or biographies[,] for no “orthodox” presentation, in terms of numbers, series, grading of effects, etc, could have conveyed the historical reality of the experience.*

Sacks was a neurologist, but was evidently more concerned with the psychic aspects of L-DOPA upon his patients, both those resulting directly from the application of the

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131 See also Jankovic and Nour, 1986, regarding respiratory dyskinesia in parkinsonism.
132 Ibid.
133 Ibid. See also Sacks, 1982.
134 Duvoisin *et al.*, 1972
136 Sacks, 1983.
drug and those which occurred in response to the motor improvements achieved. This
highly individualized analysis of patient response reflected his extraordinary devotion
to his patients, but did not produce the type of data required by a scientific paper on L-
DOPA at this point in time. This is not to criticize Sacks as a neurologist; until the mid-
1960s, journals were filled with medical papers on parkinsonism and other neurological
disorders which essentially consisted of collections of case studies. Nor were Cotzias’
1967 and 1969 papers supported by either the case numbers or the statistical analysis
which characterized publications by other workers on the effects of L-DOPA. It must,
however, be noted that some of Sacks’ statements on the therapy were difficult to
reconcile with wider neurological thinking:

our data not only show us the inadequacy of classical neurology . . . but give us the
shape of a new neurophysiology of quantum-relativistic type. . . . If the first half [of the
awakening needed in neurology] was Einsteinian, the second half is Freudian . . . the
realisation that all forms of behaviour – Parkinsonism, catatonia, tics, no less than
fantasies dreams or neuroses – are creations or expressions of the individual; . . . [they]
have a relational or referential or linguistic structure analogous to that of dreams or
ideas.\textsuperscript{137}

Sacks’ astute observations were best published as a book of case studies, and this is how
they appeared in 1973. In the meantime, his attempts to write a paper for medical
journals had been rejected; the only full “publication” on his experiences had appeared
in the British Broadcasting Corporation magazine, the \textit{Listener}, in October 1972.\textsuperscript{138}

Sacks’ book includes case histories for twenty patients, eighteen of whom were post-
encephalitic patients. The results depicted were extraordinary. The described patients
suffered extreme akinesia and rigidity, many had been largely immobile for at least a
decade, many for nearly half a century. Initially, most responded well to L-DOPA
(administered in gram quantities), many with an “explosion” of motor and psychic
activity. Unfortunately, the post-encephalitic cases also began to manifest untoward
motor and psychiatric effects within a very short period – usually within weeks of
commencing therapy – to an extent which compelled the suspension of L-DOPA
therapy. A peculiar sensitivity to L-DOPA was noted, in that administration of the drug
led to a rapid increase in abnormal movements, followed by a return to the previous
akinetoc state; the period of ‘normalcy’ which intervened between ‘up’ and ‘down’
phases had disappeared. The most famous of the patients were perhaps Aaron E., an
idiopathic Parkinson’s disease patient pictured in the \textit{New York Times} as the first
parkinsonian patient to ever walk from the hospital grounds,\textsuperscript{139} and the post-encephalitic
patient Leonard L., portrayed by Robert de Niro in the motion picture, \textit{Awakenings}.
Aaron E. continued to derive benefit from L-DOPA for some time, but suffered from a
particularly malignant form of parkinsonism which led to his being re-institutionalized
sixteen months after the commencement of therapy; L-DOPA was thereafter
successively withdrawn and restored without ever reproducing the original benefits.
Leonard L. had manifested serious psychiatric problems within a month of commencing
L-DOPA therapy; therapy was terminated after five months due to the dangers posed by
Leonard to himself and others. Subsequent attempts to restore L-DOPA revealed an
extraordinary sensitivity – 50mg sufficed to elicit adverse reactions – until immediately

\textsuperscript{137} Sacks, 1972.
\textsuperscript{138} Ibid.
\textsuperscript{139} Shenker, 1969.
before his death in 1981, at which point he demanded that he not receive the agent in order to be able to die in peace.140

In summary, Sacks provided a valuable documentation of both the motor and psychiatric response to L-DOPA in post-encephalitic parkinsonian patients. His patients developed many of the side effects seen in idiopathic parkinsonian patients, but more rapidly and with greater severity; psychiatric problems of a magnitude not normally seen in idiopathic patients were also common. It seems clear that the basal ganglia damage suffered by these patients, combined with decades-long experience of disability, prohibited any great chance of symptomatic improvement, let alone a return to normal functioning.

Response of physicians, patients and industry to news about L-DOPA

It was clear that by early 1969 the enthusiasm for L-DOPA in America had reached boiling point. Letters had begun appearing in medical journals the previous year containing enquiries from physicians who had themselves read about L-DOPA or had been brought up to date on the subject by their patients.141 Potential commercial suppliers had begun jockeying for position. Hoffmann-La Roche (USA) announced a multimillion dollar program to produce L-DOPA in commercial quantities. Eaton Chemicals, a Norwich Pharmacal daughter, was conducting animal toxicity and clinical studies; Nutritional Biochemical (Cleveland) had been supplying L-DOPA for non-human use for many years (as well as to Cotzias); Premium Chemicals (Freeport, Rhode Island) had initiated a pilot plant for the isolation of L-DOPA from natural products, its president estimating that L-DOPA therapy would currently cost patients $10/day. In 1970, Bio-Derivatives (Deer Park, New York) also announced its intention to produce L-DOPA in commercial quantities by a natural route, while Stauffer Chemicals (Edison, New Jersey) was expanding its benzol products plant, partly in order to supply chemical intermediates for the synthesis of L-DOPA.142

Press coverage in America of the new agent portrayed a “wonder drug”: a half-page report in the New York Times in August 1969 was titled “Drug brings Parkinson victims back to life”. The article was concerned mainly with the Abraham Hospital in the Bronx and the supervisor of L-DOPA therapy in this institution, Oliver Sacks. A large number of the patients here were post-encephalitic parkinsonian patients, recognized as the more difficult than even idiopathic Parkinson’s disease patients to treat. Nevertheless, Sacks reported that “close to 90 per cent” of his patients, including “25 severely disabled post-encephalitics, some of whom have been institutionalized for more than 40 years” had benefited from the therapy; in 30% the success was spectacular, in a further 30% substantial, and in yet another 30% moderate improvement had been achieved.143 This interest was no doubt also spurred – and attempts made to spur the interest of government authorities – directly by clinicians themselves. For example, a full page advertisement appeared on the last page of the New York Times on 27 June 1969. It depicted in the left-hand corner the handwritten testimony of a parkinsonian patient, addressed to the Chairman of the Parkinson’s Disease Foundation at Columbia University, William Black:

141 For example: Cotzias, 1968b.
142 Anonymus, 1969e; 1970c,d,e.
143 Shenker, 1969.
How much satisfaction it must give you to see in your lifetime the breakthrough of a cure for Parkinson’s disease. I finished four weeks of L-Dopa therapy and the results are miraculous.

Black replied in the printed letter dated 26 June which occupied the bottom half of the page:

I will admit that I had to hold back the tears when I saw “before and after” film of our first successful L-Dopa patient. I realized right then we can now truthfully say that Parkinson’s Disease is reversible. . . . L-Dopa is the best so far but . . . L-Dopa is not the complete answer. . . . If there were some way that I could convey the glow that I get when I receive a letter such as yours, I know that everyone who can afford to give would open their hearts and pocketbooks for medical research.144

L-DOPA was clearly the most spectacular medical breakthrough in many years, and its proponents were pulling out all the stops to ensure that its research was funded and the drug received the imprimatur of the relevant authorities as rapidly as possible.

In Great Britain, public interest in the new drug had also reached new heights, with reports in the press from parkinsonian patients who had travelled to the United States to partake of the cure which was still largely denied them at home. L-DOPA had not appeared in the trade magazine The Pharmaceutical Journal until the second half of 1969, but was thereafter a constant theme. In response to the massive interest, the Medical Research Council, which had set up a working party to examine whether L-DOPA should be accepted as a treatment for parkinsonism, and the Department of Health and Social Security issued a joint statement on the availability of the drug in August 1969. L-DOPA would continue to be available only for the purposes of supervised clinical trials until the safety of the drug had been assured. Further, sudden withdrawal from L-DOPA was supposed to be associated with severe reactions, so that it could not be responsibly prescribed until adequate, safe supplies were available. In any case, according to the statement, L-DOPA was only of benefit for some patients and undesirable side effects “are common”.145 Both patients and clinicians, however, were impatient. An Oxford neurologist, John Potter, wrote to the British Medical Journal in September to express his “bewilderment” about the “lukewarm” official statement; he argued that Cotzias’ 1967 paper in particular and the work of others in general was sufficient proof of both the efficacy and safety of L-DOPA, and that the need for further clinical trials was doubtful. He argued that the Department of Health should abandon its “ paternalism” and allow the long suffering patient to decide whether they were willing to risk trying the new agent; further, the estimated cost of £1 per day per patient would represent a saving on the costs of hospitalization and stereotactic intervention.146 In November, an advertisement appeared in the Evening Standard demanding that L-DOPA be made available under the National Health Service; sufferers of Parkinson’s disease were asked to complete a coupon indicating that they were aware of the risks associated with the therapy and were nonetheless demanding the right to make their own decision on the matter. The issue was also discussed in an editorial of the same paper.147

146 Potter, 1969.
There were repeated warnings from the Committee on the Safety of Drugs that the use of laboratory-grade L-DOPA by some doctors was not necessarily safe; the Committee wished to assure the public that they were processing the assessment of the agent as rapidly as possible:

*The committee is impressed by the evidence of the value of L-dopa in the treatment of some forms of Parkinson’s disease and is doing all in its power to ensure that the supply of L-dopa in a safe and satisfactory form is encouraged as rapidly as possible.*

The *Lancet* reported in December 1969 that there was considerable confusion about the availability of L-DOPA; following the extensive media interest in the drug, many patients had assumed that it was freely available through the National Health Service. According to the report, supplies in England were growing, but this Japanese product, reportedly used in most American and English trials to this point, contained “at least a 1% impurity”. The Committee on the Safety of Drugs had, however, been satisfied by the safety of the Roche product, and had quickly released it for clinical trials. Although Hoffmann-La Roche had constructed a new factory in Switzerland for its production, the available quantities in Britain sufficed only for the clinical trials in five designated Medical Research Council centres. No other companies had supplied the Committee with corresponding data regarding their products; this did not, however, prevent individual doctors from prescribing laboratory-grade L-DOPA.

In September 1969, a year after its first L-DOPA review, the American *Medical Letter* opined that the evidence for the effectiveness of L-DOPA therapy was mounting; “No investigator has failed to report favorable results in a majority of patients.” Hoffmann-La Roche, Eaton Laboratories and Nutritional Biochemicals were all sponsoring clinical trials, but they had “not yet asked the Food and Drug Administration to approve the marketing of the drug, nor are they expected to do so in the near future.” The most serious side effects at this stage were regarded as being orthostatic hypotension, which appeared to diminish with time, and cardiac arrhythmia; dyskinesias, especially of the head region, had only been observed at extremely high doses. Apart from those clinics sponsored by the manufacturing firms, individual physicians could apply for permission from the FDA to purchase the agent on an investigational new drug (IND) basis; it could be procured from Eaton, Nutritional or Calbiochem for 25¢/500mg tablet. Hoffmann-La Roche had also indicated that they were prepared to supply the agent to a further 10,000 patients under appropriate controls without charge. It was also noted, however, that many physicians administering the drug to private patients were unacquainted with the relevant literature, and thus of the appropriate treatment schedule and precautions to be taken regarding its combination with other drugs. The magazine urged collaboration between the FDA, Department of Health and the pharmaceutical firms in order to expedite its orderly marketing, a more efficient and safer alternative to the prevailing situation. As early as March 1969, however, there was considerable pressure from the medical community for a rapid certification of the agent by the FDA, and the National Institute of Neurologic Diseases and Stroke had “proposed to pool available data in a computer study which would speed up approval”.

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149 Anonymous, 1969f.
150 Anonymous, 1969c.
151 *Ibid*.
152 Anonymous, 1969e.
The Hoffmann-La Roche multicentre trial of L-DOPA therapy

The reported successes of Cotzias’ and Yahr’s groups had justified the first great multicentre trial of oral L-DOPA by Hoffmann-La Roche from the beginning of 1969 in America; a report on the study as at 15 April 1970 was published in the special issue of Clinical Pharmacology and Therapeutics (volume 12, number 2, part 2) which appeared at the beginning of 1971. The introduction to this issue (by Fletcher McDowell) explained that the motive for the study was not the necessity of proving the efficacy of L-DOPA, but rather the need to clarify its position in antiparkinsonian therapy:

The study was designed at a time when there was little understanding of the potential of levodopa and considerable confusion about how to proceed rapidly with a study to evaluate its efficacy.153

The readiness of the participants to “lose their identity and primacy in the development of a new therapy” was praised, especially as there was no question of L-DOPA being patented in the United States, as it was a natural substance. While McDowell was no doubt correct in describing the cooperative study as one “of the most important developments in American medicine in the past fifteen years”, it is to be doubted that altruism played the major role in this case; there was no real indication that any of the major players were willing to surrender their share of the fame attached to the new therapy. But the days were long past when a single clinician could hope to introduce a major new therapeutic direction alone; this was especially true in the case of L-DOPA, where Hoffmann-La Roche had made the drug available to so many clinics from the early 1960s that thoughts of a therapeutic monopoly by a single clinic were immaterial. The control of pharmaceutical development had shifted from the individual to the collective, and more specifically to the pharmaceutical industry. This was recognized in the discussion of the symposium by Udenfriend:

[Scientists and clinicians are developing a sophistication in the application of biochemistry to pharmacology and therapeutics to a degree they had not realized before. . . . Researchers, many of them in pharmacology departments, clinical departments, and in laboratories of pharmaceutical companies have said that there is nothing biochemistry can contribute to therapy. In fact, I’ve heard many say that nobody has ever developed a drug on biochemical grounds and they doubted that anyone ever would. . . . Today we find that one must not only use biochemistry to introduce a drug on logical grounds but also that the concepts that emerge thereby must be followed up with chemical reasoning.154]

This bridging of the gap between laboratory and clinic was a major difference from the situation in the 1950s, when ‘neurochemistry’ and ‘neurology’ were two separate fields with little in common: the one an analytical, theoretical research field, the other an applied art which relied on the observational gifts of the empirical clinician for progress. This was one of the reasons for the slow acceptance of the L-DOPA phenomenon in the first place: the encroachment of biochemistry into pharmacology was necessary in order to bestow the biochemical changes identified in the laboratory with recognized validity in the clinic. One must, however, ask how slowly this process might have progressed if it were not for the partnerships of, for example, Hornykiewicz and Birkmayer, which brought together solid biochemical reasoning with clinical

154 Udenfriend et al., 1971.
acumen. Further, as Udenfriend argued later in the same session, the relationship between clinic and laboratory was bilateral: L-DOPA was also a valuable research tool for other disorders, such as chorea.\textsuperscript{155}

Twenty-seven clinics were involved in the Hoffmann-La Roche-sponsored multicentre study, which employed a uniform protocol for assessing the responses of 1,120 patients to L-DOPA, none of whom had previously been treated with the agent (‘group A’).\textsuperscript{156} Standard antiparkinsonian medications were continued throughout the trial, but MAO inhibitors, α-methyl-DOPA, major neuroleptics and barbiturates were not allowed. Rigorous entry criteria were applied to ensure that all subjects were genuinely parkinsonian, although the type does not appear to have been considered. In addition, the respective reports of six centres which had previously employed L-DOPA and adopted the standard protocol after the initiation of the study, involving a further 413 patients, were included in the investigation, although assessed as a separate group (‘group B’). Finally, an extended program was initiated in October 1969 in a further ninety-three centres to assess therapeutic and tolerance levels for L-DOPA, but this part of the investigation did not contribute analyzed data to the study.\textsuperscript{157}

The results were extremely positive; there was even a small minority in whom “signs of parkinsonism were no longer to be detected.”\textsuperscript{158} Not only were all three major symptoms responsive to high dose L-DOPA therapy, but many vegetative symptoms were also improved in a significant number of patients (table 15-4). In summary:

- Most patients were treated on an ambulant basis.
- The majority of patients received a maintenance dose of 3.5-6.5g L-DOPA per day.
- Thirty-six signs/symptoms of Parkinson’s disease were assessed at each visit. The percentage of patients classified as “improved” increased with duration of treatment. At 15 April 1970, all major symptoms had improved in about two-thirds of group A and three-quarters of group B.
- About one-third of patients did not improve overall or worsened during the study.
- 84% of group A and 93% of group B experienced side-effects of L-DOPA therapy. Early in treatment, these were of a gastrointestinal nature; later, behavioural changes were observed (group A: 26.5%, group B: 43.0%), although it was not clear whether they were to be attributed to L-DOPA or to a concomitant psychiatric syndrome. Cardiovascular side-effects were not as frequent (A: 14.6%, B: 30.2%). The most disturbing side-effects were the choreiform involuntary movements which appeared as the maintenance dose was reached (group A: 54.8%, group B: 72.9%); these could be reduced by lowering the L-DOPA dose.
- Laboratory abnormalities were frequent (for example, a tendency to increased serum glutamic oxalacetic transaminase (SGOT) activity), but could not be directly attributed to L-DOPA therapy.
- 127 patients discontinued therapy; the most frequent causes were psychiatric reasons (16), ineffectiveness of therapy (15) and depression (12).
- None of the thirty-one deaths during the study could be linked to L-DOPA therapy (most common causes: pneumonia, 6; suicide, 5; pulmonary embolus or cardiac arrest, 3 each).

\textsuperscript{155} Ibid.
\textsuperscript{156} A preliminary statistical assessment of the results involving 825 patients was published as part of a review by Kaeser et al. in the Schweizerische Medizinische Wochenschrift in 1970.
\textsuperscript{157} Langrall and Joseph, 1971.
\textsuperscript{158} Kaeser et al., 1970.
XV. The second coming: oral L-DOPA therapy

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<td>52</td>
<td>64</td>
<td>54</td>
<td>75</td>
</tr>
<tr>
<td>General activity</td>
<td>50</td>
<td>65</td>
<td>69</td>
<td>73</td>
</tr>
</tbody>
</table>

Table 15-4 (a): Results of treatment with L-DOPA in the Hoffmann-La Roche multicentre trial, as reported by Langrall and Joseph, 1971.

The extended program examined the responses of more than 3,000 patients to L-DOPA over a period of therapy from 2 to 11 months, and indicated that:

side effects of sufficient severity to warrant cessation of treatment are infrequent and that, among these, adverse reactions of a psychiatric nature appear to be the most troublesome.

The most frequently reported side-effect had been twelve cases of psychosis.\(^{159}\)

In contrast to Birkmayer’s early results but consistent with the findings of Calne’s group, post-encephalitic patients tolerated high doses of L-DOPA less well than idiopathic patients. Stereotactic surgery was to be preferred in cases of unilateral parkinsonism. Otherwise, L-DOPA was recommended for all parkinsonian cases in which akinesia and rigor dominated the clinical picture.\(^{160}\)

\(^{159}\) Langrall and Joseph, 1971.

\(^{160}\) Ibid.
At the same time as this study, similar studies had been initiated by Hoffmann-La Roche in Germany; they had yielded similar promising results. Völler at the Queen Elena Clinic in Kassel had been investigating the use of DOPA as early as 1964/65, but lack of access to the drug and the changing policies of the clinic management had prevented an intensive trial. This had changed in early 1966, since when the drug had been employed in selected patients (over 1500 by 1971). In combination with traditional anticholinergic drugs, it was found that lower doses were required than reported in America, although different symptoms responded to different levels of the drug: a- or hypokinesia at 1-1.5g/day, bradyphrenia at 2-2.5g/day, rigidity (and in some cases the tremor) at 2.5-4g/day. Völler advised, however, that DOPA was not the wonder drug promoted in some sections of the press, while at the same time regretting that production bottlenecks currently restricted its availability. Similarly, Umbach’s group in Berlin had continued their examination of a combined DOPA/MAO inhibitor therapy as an adjunct to stereotactic surgery. The results achieved in 220 patients treated between 1967 and 1970 (for periods of minimally 8.3 months; seventy-two treated on an ambulant basis) were published in the doctoral thesis of Kluge in 1970. The conventional medications were found to have no effect on akinesia, while having a significant effect on rigidity and tremor; combined with depot cyclexedrine, however, the akinesia was also improved, though not to the same degree as DOPA with cyclexedrine (table 15-5). Umbach continued to find that stereotactic surgery was the best solution for tremor and rigidity; the prior treatment with DOPA of patients whose akinesia rendered stereotactic surgery difficult, however, rendered about 60% of such cases operable. The authors recommended in conclusion that the choice of therapy must be based on the degree of severity of the individual symptoms of the patient.

<table>
<thead>
<tr>
<th></th>
<th>Akinesia</th>
<th>Rigidity</th>
<th>Tremor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional medication</td>
<td>0%</td>
<td>57.9%</td>
<td>52.7%</td>
</tr>
<tr>
<td>Biperiden + cyclexedrine</td>
<td>45.5%</td>
<td>63.6%</td>
<td>72.7%</td>
</tr>
<tr>
<td>DOPA*</td>
<td>76.5%</td>
<td>41.0%</td>
<td>29.0%</td>
</tr>
<tr>
<td>Stereotactic surgery</td>
<td>5.6%</td>
<td>85.2%</td>
<td>88.0%</td>
</tr>
</tbody>
</table>

Table 15-5: Symptomatic improvement in 220 patients undergoing various forms of antiparkinsonian therapy, as reported by Umbach in Kapp and Leickert, 1971, p.63. * Some patients receiving DOPA also received cyclexedrine.

Similar trials were also conducted in other countries, including Australia, where the following two summations from editorials from the Medical Journal of Australia illustrate graphically the change in mood in the course of 1970:

It is probable that DOPA and amantadine will prove to be significant advances in the therapeutics of Parkinsonism, and further advances may follow as related compounds are synthesized. However, these advances should not be allowed to overshadow the value of stereotactic surgery, . . . [April 11 1970]"
In summary, l-dopa is the most effective drug available for the treatment of Parkinson’s disease of any aetiology, severity or duration, particularly in relation to rigidity and bradykinesia. The ultimate role of amantadine will probably be in the management of the Parkinsonian patient unsuitable for l-dopa therapy, or in conjunction with l-dopa to facilitate a reduction in the dosage of the latter drug . . . [October 3 1970]166

The first publications in this journal concerning L-DOPA therapy appeared in this latter issue, together with a number of papers on amantadine therapy. Positive results, similar to those achieved elsewhere, were reported.167 A year later, Jenkins and Schwieger (Prince Henry’s Hospital, Melbourne) confirmed in a more extensive study (over 100 patients, 18 months) that “at least 70% respond far beyond the effects obtained by conventional anticholinergic drugs.”168 An article on a trial out-patient program for L-DOPA therapy appeared in the same issue.169

The commercial introduction of L-DOPA

Despite a number of unresolved problems, a consensus that oral L-DOPA therapy was a viable treatment for the disorder had been accepted; the necessary support from the American research and neurology community had been won by the work of Cotzias and Yahr. In Great Britain, the Department of Health announced in early 1970 that L-DOPA supplies, principally from Brocades and Roche, were increasing rapidly; by May there should be enough to treat about 10,000 patients, by the end of the year 27,000 (there were an estimated 60,000 parkinsonian patients in England and Wales at the time).170 Warnings against the use of L-DOPA not cleared for clinical use were reiterated; this was partly provoked by the announcement that Chemica Laboratories intended to release L-DOPA for therapeutic purposes without seeking approval from the Committee on the Safety of Drugs. The official response to this move prompted the editors of the Pharmaceutical Journal to plead for the prompt release of cleared L-DOPA in order “to oust what may be termed the black market in L-dopa”.171 Public expectations and demands concerning a new antiparkinsonian therapy had not been this high since the promise of harmine in the 1920s.

The last hurdle to overcome in America was the licensing of the drug for use in humans by the Food and Drug Authority (FDA); this organization, however, was in early 1970 not yet totally convinced that this stage had yet been reached. The new “miracle therapy” had also become something of a media event in the United States, and the few clinics with access to the agent were besieged by hopeful patients and their relatives. It was reported that 40-80 researchers were applying the drug “to a major degree”, while a further 200 used it to “a minor degree”.172

A symposium was organized by the Eaton Laboratories division of Norwich Pharmaceutical Company for 14 January 1970 to complement a collaborative study which they had funded.173 Held at Georgetown University in Washington, D.C., the “L-

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166 Anonymus, 1970g.
167 Landy, 1970.
168 Jenkins and Schwieger, 1971.
169 Hicks and Rischbieth, 1971.
172 Anonymus, 1970h.
DOPA experts were reported to have assured the assembled 350 physicians that that the drug was effective, safe in the context of its intended use and that it even functioned as an aphrodisiac for many patients. For a time, this latter potential threatened to overshadow the major significance of the drug. One of the leading American L-DOPA experts, William O’Malley (Department of Neurology, Georgetown University), cited the hypersexuality reported in a minority of cases as indicating that the amino acid could influence behavioural aspects not directly connected with parkinsonism, and described the use of L-DOPA in Parkinson’s disease as a foretaste of further developments:

*God has opened up a path to mankind. Immeasurable human suffering could be prevented in the future if we only take up the challenge and dedicate unlimited efforts and resources to this cause.*

It had been shown by this drug that areas of brain function not affected by this particular disorder could be manipulated biochemically, indeed “fundamentally altered”. Such sentiments in 1970 were doubtless a worry for the FDA and distracted from the real value of L-DOPA, which O’Malley sought to promote in his appeal to President Nixon to release L-DOPA for clinical use. In 1969, the FDA had rejected an application from Eaton laboratories to market the drug without even granting a New Drug Application (NDA) number, but O’Malley argued that the division in scientific ranks over the value of L-DOPA had now dissipated. In his emotional plea, O’Malley noted that Eaton had stockpiled huge amounts of L-DOPA which they had produced in the hope of its licensing, which they could release for the relief of patients at a moment’s notice. He argued that this release was ultimately inevitable; but:

*every day that this release is postponed means death or a wheelchair for further hundreds of Americans. There are no guidelines set by Congress that are so holy that they cannot be broken.*

This was certainly a change since 1967; O’Malley now spoke of the “overwhelming” mass of evidence for the effectiveness and safety of L-DOPA in Parkinson’s disease, that its use was unanimously supported by all those involved in the treatment of the disorder, and that the only barrier to the full exploitation of this gift to mankind was the bureaucracy and stubbornness of the FDA and Congress. He claimed that 80% of 220 patients treated at the Georgetown University Hospital had derived benefit from L-DOPA therapy, in 65% the improvement was classified as “marked”: “We don’t know if L-DOPA arrests or cures the disease, but we know it improves it.”

John Campbell (Cincinnati University) opined further that L-DOPA was more a food than a drug, an opinion which he shared with Cotzias.

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174 So called by the reporter for the *Chemical & Engineering News*; Anonymus, 1970a. There were nine presentations by ten of the invited participants. Hornykiewicz was present; Cotzias was not.

175 For example: O’Malley, 1970.

176 Press release, cited by Kapp and Leickert, 1971, p.67. I have not been able to obtain an original copy of this press release in English, and have thus translated the German translation back into English, explaining any verbal discrepancies which may have thus arisen.

177 Ibid.

178 Ibid.

179 Cited in Anonymus, 1970h.

180 Ibid.

181 See, for example, Cotzias et al., 1971b.
In retrospect, the reticence of the FDA to license the drug and, indeed, of the supplier firms to make the amino acid more freely available, might appear difficult to comprehend. It must, however, be borne in mind that l-DOPA and, a short time later, the decarboxylase inhibitor benserazide were regarded at this time as highly toxic substances with undefined long term effects. The Val David meeting at the end of 1969, discussed above, devoted a great deal of its time to the side effects of l-DOPA and treatment failures; in particular, it was emerging that a great many, if not all, patients treated with l-DOPA could expect to be afflicted at some point by abnormal involuntary movements. There were thus very strong arguments for at least delaying the introduction of l-DOPA as a commercial drug; it was ultimately the absence of comparably effective antiparkinsonian agents at this point in time and the public pressure on the American Congress which delivered the impetus for its licensing despite the reservations of the FDA (and of many medical authorities). Amongst the “important therapeutic considerations” listed by Eaton Laboratories in their advertisements for ‘Dopar’ were, indeed the following warnings:

(a) Dopar (levodopa, Eaton) is not curative and its mechanism of action is unknown;
(b) Long-term safety and efficacy of Dopar (levodopa, Eaton) have not been established;
(c) . . .
(d) About one-third of patients or more will not experience clinical improvement on Dopar (levodopa, Eaton), and virtually 100% of patients will experience side effects of some degree . . .

As with many agents employed in the treatment of disorders such as cancer and AIDS, the otherwise hopeless situation of the patient was allowed to override qualms with regard to the absolute safety of the agent, and it was hoped that such problems might find a solution at some time in the future.

The culmination of the meeting was a summary of the results of the ‘Eaton Collaborative Study’ of l-DOPA in parkinsonism. Twenty-two institutions were involved in the study (all American, except for the Clarke Institute in Toronto (Hornykiewicz)); the results from sixteen were included in the summary, while the others undertook “strict double-blind or other special studies” which were to be reported elsewhere. Of 601 patients who began the study, twenty-four terminated their involvement because of side effects, twenty-two because of lack of benefit, fourteen for personal reasons and five as the result of another illness; there were ten deaths, and forty-one patients lost to follow-up. All but ten subjects were between 61 and 80 years of age, with twice as many men as women; 470 were paralysis agitans cases, 80 postencephalitic parkinsonian and five arteriosclerotic parkinsonian patients. The Hoehn and Yahr classification of disorder severity placed 47 patients in grade I, 92 in grade II, 156 in grade III, 171 in grade IV and 80 in grade V. Patients served as their own collective controls, in that they were successively assessed on a variety of performance and biochemical parameters while receiving each of their hitherto normal medication, placebo and an empirically determined optimal level of l-DOPA. Twenty-two symptoms were rated (0 = absent, 4 = very severe) to give a neurological index ; six

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182 Information included in Dopar package; also in advertisements: for example, Medical Times, Sept. 1970, pp.119-123.
183 Of the remainder, five were classified as ‘familial parkinsonism’, one as hydrocephalus and two ‘unreported’.
tasks of daily living were also assessed (0 = normal, 10 = patient hinders rather helps assistant in performance of task) to give a disability index. The two indices were then summed to give an overall index of function. The findings of the study can be summarized as follows:

- Improvement of neurological signs commenced a few weeks after commencement of L-DOPA therapy. Bradykinesia improved most rapidly and dramatically, tremor was less responsive.
- Eleven patients (grades I to III) showed total remission of symptoms, of whom at least six were women.
- 234 patients showed 50-99% improvement; this included about half the patients in grades I-II, one-third of those in grade IV and one-quarter of those in grade V.
- Sixty-seven patients were treatment failures; these included a single grade I patient, about one-tenth of grades II and III, and one-sixth of grades IV and V.
- As assessed by the patients themselves, twenty-eight reported total symptomatic remission (including two from grade V and four from grade IV), 340 (67% of those reporting) felt that improvement was moderate or better, and fifty-two (10%) regarded themselves as treatment failures.
- Response was inversely related to duration of disease.
- Response was unrelated to optimal L-DOPA dose, age and gender.
- On average, about 60% improvement was registered in each of the cardinal symptoms.
- Most common side effects were nausea and/or vomiting (more than half), involuntary movements (184 cases), mental disturbances (194 cases) and transient hypotension. Increased libido was often reported “but was rarely looked upon as an adverse effect.”
- No consistent effect of L-DOPA on any of a variety of assessed laboratory variables was detected.¹⁸⁴

The symposium also heard reports by individual investigators who had taken part in the collective study, but whose data derived from strict double blind or other special studies, and were thus not included in the collective analysis. Manfred Muenter (Neurology, Mayo Clinic, Rochester) reported to the symposium similarly positive results from a double-blind, placebo-controlled study in twenty-six patients,¹⁸⁵ as did John Campbell (University of Cincinnati School of Medicine) for an open trial in 168 patients conducted over two years,¹⁸⁶ while William Timberlake (Harvard Medical School and Lemuel Shattuck Hospital, Boston) reported that a double-blind in a total of eighty-five patients indicated that the effect of L-DOPA on rigidity, akinesia (as assessed by the Schwab bulb ergograph test for myasthenia and by walking a defined distance) was about 30% greater than that of procyclidine.¹⁸⁷ And by the time of the Symposium, the participating clinicians in the Cooperative Study were so impressed with L-DOPA that they were already treating a further 1,906 patients.¹⁸⁸

Robert Keenan, Director of the Clinical Pharmacology Division of Eaton Laboratories, indicated at the beginning of his presentation that Cotzias’ 1967 paper had motivated Eaton laboratories to shift their antiparkinsonian research from anticholinergic agents to L-DOPA.¹⁸⁹ During the final discussion at the symposium, he

¹⁸⁴ Keenan, 1970.
¹⁸⁵ Muenter, 1970.
¹⁸⁶ Campbell, 1970.
¹⁸⁷ Timberlake, 1970.
¹⁸⁸ O’Malley et al., 1970.
¹⁸⁹ Keenan, 1970.
### Table 15-6 (a): Response to L-DOPA therapy in the Eaton Collective Study according to Hoehn-Yahr grade of disease at outset of therapy, as reported by Keenan, 1970. Figures represent patient numbers.

<table>
<thead>
<tr>
<th>Improvement (%)</th>
<th>Original grade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
</tr>
<tr>
<td>100</td>
<td>4</td>
</tr>
<tr>
<td>50-99</td>
<td>29</td>
</tr>
<tr>
<td>20-49</td>
<td>11</td>
</tr>
<tr>
<td>1-19</td>
<td>2</td>
</tr>
<tr>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total number of patients</td>
<td>47</td>
</tr>
</tbody>
</table>

### Table 15-6 (b): Response to L-DOPA therapy in the Eaton Collective Study by neurological component, as reported by Keenan, 1970. Figures represent patient numbers.

<table>
<thead>
<tr>
<th>Improvement (%)</th>
<th>Rigidity</th>
<th>Tremor</th>
<th>Brady-kinesia</th>
<th>Finger dexterity</th>
<th>Postural stability</th>
<th>Sialorrhea</th>
<th>Sweating</th>
<th>Facial expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>90</td>
<td>130</td>
<td>114</td>
<td>81</td>
<td>156</td>
<td>138</td>
<td>115</td>
<td>105</td>
</tr>
<tr>
<td>50-99</td>
<td>202</td>
<td>136</td>
<td>191</td>
<td>165</td>
<td>106</td>
<td>53</td>
<td>26</td>
<td>203</td>
</tr>
<tr>
<td>20-49</td>
<td>113</td>
<td>76</td>
<td>91</td>
<td>93</td>
<td>37</td>
<td>12</td>
<td>6</td>
<td>77</td>
</tr>
<tr>
<td>1-19</td>
<td>25</td>
<td>18</td>
<td>0</td>
<td>38</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Average improvement (%)</td>
<td>57</td>
<td>61</td>
<td>62</td>
<td>54</td>
<td>68</td>
<td>67</td>
<td>64</td>
<td>63</td>
</tr>
</tbody>
</table>

commented that the company was working closely with the FDA on the licensing of the drug, and that the FDA was “being extremely cooperative and reasonable with this drug”; nevertheless, he was not prepared to speculate as to when it might be commercially available. The session concluded with the following exchange:

**DR. KEENAN:** I think that both we at Eaton Labs and FDA are anxious to make this available as soon as possible.

**VOICE:** Is that a matter of months, or years? (Laughter.)

Eaton was importing L-DOPA produced from fish flour in Japan; Hoffmann-La Roche was increasing its American production, hoping to market their product Larodopa within six months, and several other companies had indicated their interest in entering the field. The industry journal *Chemical & Engineering News* commented:

> No wonder that drug companies are eager to gain approval: 500,000 patients taking an average 4 grams per day would eat up 730,000 kg. of L-dopa per year. Even if increased production drops the wholesale price to 5 cents per gram (as one maker predicts) from its present 40-cent-per-gram level, it still adds up to a cool $36.5 million annually.

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190 O’Malley et al., 1970.
The production costs for L-DOPA had dropped from $5,000-$10,000/kg in 1968 to around $500/kg, of which 20% was import duty; the cost per patient had thereby dropped from $1000 to $100/month. It was reported that 6000 to 7000 patients were now being treated with L-DOPA in America; of these, about a third were “dramatically” improved and able to lead fairly normal lives, a third were “markedly or moderately” improved, while the other third was only slightly improved or still totally disabled.\(^{192}\)

In giving credit to those responsible for the discovery, the *Chemical & Engineering News* named Hornykiewicz (who was collaborating with Eaton at the time) and Cotzias. Although the journal had interviewed Hornykiewicz for their article, it seems to have confused the story somewhat; with reference to the L-DOPA trial of 1961 in Vienna:

> His [Hornykiewicz’s] experiments were not very successful, for three reasons (it turned out): not having L-dopa, he had to use the racemic mixture; he didn’t give big enough doses; he quit too soon.\(^{193}\)

These comments were presumably meant by Hornykiewicz to apply to the many workers who had doubted the L-DOPA effect in the early 1960s. In any case, this version allowed the journal to introduce Cotzias as being responsible not only for the breakthrough with L-DOPA itself, but also as the discoverer of the synergistic effect of decarboxylase inhibitors. The significance of the discovery, however, was not missed by the journal:

> L-dopa may be the vanguard of a coming breakthrough in biogenic amines comparable in importance to the proliferation of antibiotics in the 1940’s and 1950’s.\(^{194}\)

Keenan indicated that Eaton intended to resubmit their application to the FDA, but did not wish to say when; he had, however, met with FDA representatives prior to the recent symposium “to iron out minor differences and proposed package insert details, usually the last pre-approval step”.\(^{195}\) Anticipation amongst researchers, physicians and patients alike was mounting; the Eaton symposium was reported in major articles in the *New York Times*, both on 15 January, and in the weekend news review.\(^{196}\) The tone of the reportage was hopeful but cautious; it was noted that L-DOPA was certainly no miracle cure, and that side effects and general lack of response could mean that as many as 40% of patients derived no benefit from the agent, leading the article writer to pose the philosophical question:

> If a drug is found that may dramatically help a small percentage of persons afflicted with a debilitating and often devastating disease, should its use be publicized or would this raise false hopes in the majority of sufferers who would not be aided?\(^{197}\)

Most workers, however, were impatient to have L-DOPA licensed as rapidly as possible. The wait did not last long. In June 1970, the FDA granted approval for the commercial distribution of L-DOPA by Hoffmann-La Roche (as ‘Larodopa’) and Eaton Laboratories (as ‘Dopar’). Conditions which were described by the agency’s

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\(^{192}\) Anonymus, 1970a, 1970h.

\(^{193}\) Anonymus, 1970a.

\(^{194}\) Ibid.

\(^{195}\) Anonymus, 1970h.

\(^{196}\) Lyons, 1970a, 1970b.

\(^{197}\) Lyons, 1970b.
commissioner, Charles C. Edwards, as unusual, were attached to the permits: the two firms were required to continue monitoring patients using the drug in order to ascertain whether the side-effects were acceptable. Further, the agency regarded the doses employed as being very high in comparison with most other licensed pharmaceuticals. At the same time, Edwards described L-DOPA as showing “promise of being one of the major discoveries of recent years”\(^{198}\). Two agents were being commercially promoted in America as possible solutions with regard to these issues: the decarboxylase inhibitor MK 486 (carbidopa) by Merck, Sharp and Dohme, and aminoacidamantane (amantadine; Symmetrel) by DuPont, which Klawans believed slowed the metabolism of brain dopamine. In any case, the L-DOPA dosage required also needed to be reduced because production levels were capable of satisfying the needs of only 100,000 patients, but the number of potential “customers” was 500,000-1,000,000 in America alone.\(^{199}\) Further, a worldwide shortage of vanillin, the base product for the synthesis of L-DOPA, had been reported at the beginning of 1970; world consumption had reached 8 million pounds in 1969 and was growing at the rate of 10% per annum. One American firm which manufactured vanillin, Monsanto (Seattle, Washington), had announced plans to double its capacity to 4 million pounds (ca. 2 million kg) by the middle of 1970.\(^{200}\)

FDA approval for L-DOPA was of such public interest that it was announced on the front page of the New York Times on 5 June 1970; it was noted, however, that it would not be available in most clinics until adequate supplies had become available.\(^{201}\) Two weeks later, the annual convention of the American Medical Association honored the significance of the licensing of L-DOPA by holding a symposium devoted to the drug, unofficially declared “medicament of the year”, as reported on the front page of the German doctors’ magazine, the Praxis-Kurier.\(^{202}\) Roche announced the release of ‘Larodopa’ in America with a five page advertisement in the 29 June edition of the Journal of the American Medical Association, including two pages which reproduced the package insert. L-DOPA therapy was described as the “culmination of a quest” which had been particularly intense during the previous two and a half years; the company was now in a position to offer L-DOPA of the highest purity, synthesized by an exclusive process “that relies entirely on domestic sources of supply”. Supplies would be restricted in the short term to approximately four hundred hospitals, clinics and medical researchers, but the company would be able to “meet the nation’s medical needs on a sustained basis within a very short time”.\(^{203}\) By the end of 1970, L-DOPA was also freely available in the United Kingdom, even if a quota system was temporarily imposed on hospitals in order to limit the number of patients receiving the drug; supplies of the drug were initially quite limited, and it seemed undesirable to allow patients to commence therapy if it was likely that it would have to be terminated after a few months.\(^{204}\) Over the next few years, a rash of reports appeared concerning the employment of L-DOPA in Parkinson’s disease, all more or less positive (figure 15-3); the doubt about the therapy had now been largely abolished, and attention now turned to refinement of the L-DOPA effect and the control of its unwanted side-effects.


\(^{199}\) Anonymous, 1970h. Amantadine will be discussed in the next chapter.


\(^{201}\) Schmeck, 1970: “A drug for Parkinson’s disease gets cautious F.D.A. approval”.

\(^{202}\) Anonymous, 1970j.


Industrial production of L-DOPA

Strangely enough, it was not at first clear which production method or methods would be most important for the commercial preparation of L-DOPA. Roche, a division of the American daughter of Hoffmann-La Roche, had synthesized L-DOPA for some time, and needed only to expand production. Eaton Laboratories purchased their material from Ajinomoto (Yokkaichi, Japan), while Nutritional Biochemicals (part of International Chemical & Nuclear; ICN) intended to market L-DOPA in conjunction with Smith, Kline & French, also with materials purchased in Japan (Sankyo Chemical Industries). Much secrecy surrounded such activities; Ajinomoto, for instance, announced that they were expanding their capacity (currently 10 tonne per month) and were shifting from vanillin as base product to an “abundant and cheap” alternative, but were not specific about either aspect. The company predicted a drop in the current price of up to $130/kg to about $100/kg. Sankyo (current capacity: 25 tonne per month; 20% exported to Europe, 80% to ICN) would not disclose which of tyrosine, vanillin or piperonyl aldehyde was used as base product.205

The problem with the synthesis of L-DOPA had always been the separation of the two optical isomers. Bio-Derivatives consequently argued that their intention to isolate the amino acid from beans could make them financially competitive, despite their smaller size; in October 1970, the company announced its aim to raise production from 100kg per month to 150 tonne per year by 1972. The estimated cost to the clinic was 24c per gram; the company had stockpiled enough beans for six months’ production. The United States Agricultural Department had already screened 1000 plants for their potential as natural sources of L-DOPA, and identified a number of likely candidates; if velvet beans currently grown in the southern states as animal feed were used, yields of about 36lb per acre (~40kg/ha) were estimated. B.H. Natelson (Neurology, Albert Einstein College of Medicine, Bronx) had written to the Lancet in September 1969 with

205 Anonymus, 1970k.
the suggestion that 250g of *Vicia faba* would provide therapeutic doses of L-DOPA a great deal more cheaply than synthetic amino acid; crude extracts might also prove a palatable alternative. A patent had also been applied for by workers associated with the Koninkijke Pharmaceutische Fabreken (Netherlands) for a process whereby L-DOPA was synthesized naturally by bacteria from L-tyrosine.206

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206 Anonymus, 1969e, 1970k; Natelson, 1969; see also report in *Chemical & Engineering News*, 16 February 1970, p.21. For further reports on beans as sources of L-DOPA, see Bell and Janzen, 1971; Daxenbichler *et al.*, 1971.
L-DOPA: the next steps

By 1970, the medical world had accepted L-DOPA as a legitimate agent in the treatment of Parkinson’s disease. At the Bel-Air Symposium on Catecholamines at the end of the year, Duvoisin declared in his summation of the treatment session that the efficacy of L-Dopa is now well established. Indeed, there is a remarkable agreement among all the investigators who have reported their experiences and among the several discussants regarding the clinical effects of L-Dopa. About two-thirds of patients enjoy a 50% or better improvement of their symptoms and many achieve a better than 80% improvement. In general, the results have improved with the passage of time in part because there seems to be a fairly long period of six months or more during which improvement continues to accumulate and partly, no doubt, because we have all benefited from increased experience in using L-Dopa in clinical practice.207

Carlsson emphasized another facet in his review of the biochemistry session at this symposium: L-DOPA therapy was not only effective, it also rested by 1970 on a sound, if still incomplete, morphological and biochemical basis.208 In contrast to earlier therapies for parkinsonism, basic scientific investigation had provided the impetus for the introduction of the therapy, and was also helping to explain its negative side effects and to indicate the direction for its further refinement. A further step in this direction was the first confirmation of the Ehringer and Hornykiewicz results in 1971 by Fahn and colleagues. The striatal dopamine deficit was confirmed in two parkinsonian patients: the level in the putamen was reduced by more than 90% in both patients, in the caudate by up to 62%, depending on the region examined. Notable reductions in 5-HT levels (putamen: 20-60%; caudate: 9-85%) and noradrenaline (50-70% in inferior head of the caudate, the only region assessed with significant noradrenaline levels) were also measured. On the basis of these results and other clinical and laboratory reports in the literature, the authors concluded that the dopamine deficit underlay the akinesia of parkinsonism and was involved in rigidity; the combined dopamine/5-HT loss was associated with tremor; and chorea was associated with an increased dopamine to receptor ratio.209

The broadening acceptance of high dose oral L-DOPA therapy effectively put an end to the widespread use of intravenous L-DOPA administration, although isolated reports concerning this approach continued to appear.210 Birkmayer also saw the retention of this avenue as useful in patients with marked gastrointestinal responses to oral L-DOPA.211 Hornykiewicz noted that this method remained useful for examining the pharmacodynamics of the drug, which he now regarded as “the most effective single antiparkinson drug currently available.”212 Incidentally, he also noted in 1971 that there

207 Duvoisin, 1971.
209 Fahn et al., 1971. There had, however, been reports from outside Hornykiewicz’ laboratory which provided indirect evidence for reduced dopamine turnover in parkinsonism, including reduced cerebrospinal HVA concentrations: for example, Guldberg et al., 1967; Johansson and Roos, 1967; see also Chase and Ng, 1972.
210 For example, Kaufmann et al., 1970.
211 Birkmayer, 1970a, 1971. It is interesting to note that Rivera-Calimlim et al. (1970) attributed some treatment failures to problems with gastric resorption of the drug; this could be overcome by administration of an antacid thirty minutes before L-DOPA.
212 Hornykiewicz, 1971a.
were as yet no reports on the assessment of central dopamine-β-hydroxylase, catechol-O-methyltransferase or tyrosine hydroxylase activities in the human brain; further, his own laboratory had produced most of the data on L-DOPA-decarboxylase, and his 1962 paper on MAO was also without successor.213

By 1972, the position of L-DOPA therapy in the therapy of parkinsonism was so established that the German medical magazine Selecta could title a review of the current status of antiparkinsonian therapy “L-dopa maintains central position”.214 The question was no longer whether L-DOPA worked, but what could be done to make it work better. Clas Fehling, who had conducted one the controlled studies of low dose L-DOPA which had produced negative results, published one of the first reports on the successful treatment of Parkinson’s disease with L-DOPA on an outpatient basis. By 1972, the majority of patients were treated in this manner, but this was the first reasonably large study to systematically examine the outcome of the approach.215 Fehling pointed to two important factors which made such an investigation important. Firstly, the general physician in such a situation was confronted with a range of patients with various coexistent disorders and who were not as directly amenable to medical supervision as hospitalized patients; for instance, the titration of the L-DOPA dose was more difficult in such patients. Fehling then noted that studies on the effects of L-DOPA tended to fall into one of two groups:

- studies in which the success rate and the improvement noted are both impressive: the patients tended to be more selected in such studies;
- studies with a less differentiated patient base often resulted in good improvement in one-third, moderate change in a further third, an no benefit in the final third.

The second situation corresponded to that of the physician treating patients on an outpatient basis, and Fehling’s results were not unexpectedly similar to those of this type. Secondly, Fehling found that neither cardiac nor circulatory problems were elicited by long term L-DOPA treatment, which included a large proportion of older patients. This was encouraging in light of the still unresolved concerns about the effects of large L-DOPA doses on circulatory parameters.216

The two major adjuncts discussed in the Selecta paper were stereotactic surgery and amantadine, but it was also emphasized that the anticholinergic drugs were “not yet unnecessary”.217 R.C. Hughes and colleagues (General Hospital, Newcastle-on-Tyne) reported in 1971, for instance, that the abrupt termination of anticholinergic therapy (primarily orphenadrine and/or benzhexol) after the stabilization of L-DOPA treatment was not tolerated well by most patients, and even the gradual withdrawal was often problematic; of thirty-four patients, only eleven were able to abandon traditional therapy completely, with the major complaints being “increases in slowness”, tremor and excessive salivation. Further, they reported evidence that the anticholinergic agents potentiated some effects of L-DOPA, and suggested that anticholinergic agents might

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213 Ibid. Nagatsu et al. reported in 1979 that the activity of tyrosine hydroxylase was markedly reduced in the parkinsonian brain.
215 See also Hicks and Rischbieth, 1971; Kofman, 1971. Fehling used L-DOPA purchased from Japan (Ajinomoto) or custom produced by Astra in Sweden.
216 Fehling, 1972. For the issue of hypotension associated with L-DOPA therapy, see editorial by McDowell and Lee, 1970.
217 G.S., 1972.
slow the inactivation of central dopamine.\textsuperscript{218} R.K. Whyte and colleagues (University College Hospital Medical School and London School of Hygiene and Tropical Medicine) also detected an increased benefit conferred by orphenadrine in L-DOPA-treated patients in a double-blind crossover trial (n = 15); part, but not all, of this effect was undoubtedly the central anti-emetic effect of orphenadrine.\textsuperscript{219} The referents at the 1970 Bel Air Symposium generally reported that most patients could not rely on L-DOPA as a monotherapy; two-thirds required the continued administration of anticholinergic medication to achieve optimal results.\textsuperscript{220} More recently, both benztropine\textsuperscript{221} and orphenadrine\textsuperscript{222} were reported to improve the response to L-DOPA.

Broe and Caird (University of Glasgow), on the other hand, found that the addition of orphenadrine to L-DOPA therapy in elderly patients (over 68 years), most of whom also suffered from dementia, led to an exacerbation of their cognitive disabilities. Interestingly, these authors, in contrast to a number of other workers at the time,\textsuperscript{223} found that the parkinsonian symptoms of the older patients responded well to L-DOPA, as did mental function in many cases; in fact, both neuropsychiatric complications and the production of involuntary movements was quite rare in their study.\textsuperscript{224} Martin and colleagues (University of Minnesota Health Sciences Centre, Minneapolis) found no added benefit of benzhexol in L-DOPA therapy in a placebo-controlled trial in thirty patients over 6–8 months; nor were significant differences in the presentation of undesirable side effects noted. The authors could not decide on the basis of this study whether this was due to the maximum possible improvement being achieved by L-DOPA alone, or because of a pharmacological reason for the non-additivity of the effects of the two drugs; it had been reported for example, that patients using benzhexol had lower plasma L-DOPA levels than those receiving L-DOPA alone.\textsuperscript{225} Fermaglich and O’Doherty suggested that reduced gastrointestinal motility might impede absorption of oral L-DOPA.\textsuperscript{226} An interesting comment by Martin and co-workers was that:

\begin{quote}
Our findings are consistent with the results of studies that have failed to demonstrate a therapeutic effect of this drug in Parkinson’s disease\textsuperscript{[227]} These results must be reconciled with other reports alleging a small but definite beneficial effect of trihexyphenidyl hydrochloride in some patients.\textsuperscript{228}
\end{quote}

Benzhexol had thus suffered the same fate as many antiparkinsonian therapies before: once lauded as the most effective agent for the treatment of all parkinsonian symptoms, it had joined the list of agents whose effectiveness was regarded at best as somewhat limited, and this only a few short years after the arrival of its successor.

\begin{thebibliography}{9}
\bibitem{Hughes} Hughes et al., 1971.
\bibitem{Whyte} Whyte et al., 1971.
\bibitem{Sigwald} Sigwald, 1971; Duvoisin, 1971.
\bibitem{Tourtellotte} Tourtellotte et al., 1982.
\bibitem{Bassi} Bassi et al., 1986.
\bibitem{Boshes} Boshes et al., 1969 (see also Boshes et al., 1979); Jenkins and Groh, 1970. But see Cotzias et al., 1969a; Beardsley and Puletti, 1971; Marsh et al., 1971a,b.
\bibitem{Broe} Broe and Caird, 1973.
\bibitem{Martin} Martin et al., 1974; Bianchine et al., 1971. See also Contin et al., 1991.
\bibitem{Fermaglich} Fermaglich and O’Doherty, 1972.
\bibitem{Kaplan} The papers referred to were Kaplan et al., 1954 and Brumlik et al., 1964.
\bibitem{Doshay} Martin et al., 1974. The papers supporting benzhexol were Doshay et al., 1954, a 1957 review by Hamlin, Burns et al., 1964 and Marsden, 1969.
\end{thebibliography}
Some attention was devoted during this period to the comparison of the side effects associated respectively with anticholinergic and L-DOPA therapy. Dyskinesias were a particular problem noted early in the use of L-DOPA therapy, but this response was also seen with anticholinergic agents; further, L-DOPA-induced dyskinesia could be exacerbated by such drugs.\(^\text{229}\) It was also noted that L-DOPA therapy appeared to lead to a certain cholinergic supersensitivity; physostigmine induced “off-periods” both in long term anticholinergic patients\(^\text{230}\) and in long term patients suffering from fluctuations.\(^\text{231}\) Weintraub and Van Woert found, on the other hand, that L-DOPA therapy decreased cholinergic sensitivity; this, however, might also be related to a compensatory increase in cholinergic sensitivity subsequent to the withdrawal of anticholinergic medication from these patients.\(^\text{232}\) Yahr’s group suggested that cholinergic sensitivity returns during the course of long term L-DOPA therapy, and that the development of anticholinergic agents directed specifically against striatal receptors might be of use in parkinsonism; anticholinergic agents were found to be helpful in the management of fluctuations in response to L-DOPA.\(^\text{233}\) Procyclidine was reported to relieve foot dystonia in L-DOPA-treated patients.\(^\text{234}\)

The article on L-DOPA in the 26th edition of the Martindale Extra Pharmacopoeia (1972) was now over four tightly printed pages long. Nor was the employment of the agent restricted to parkinsonism; it was also listed as having been (at least partially) successfully applied in:

- Congestive heart failure
- Depression
- Dystonia musculorum deformans
- Hepatic coma
- Supranuclear palsy
- Hepatolenticular degeneration
- Manganese poisoning
- Migraine
- Seborrhoeic dermatitis

No negative reports were listed for its use in Parkinson’s disease. It is perhaps interesting to note, however, that of the eight references cited with respect to the efficacy of L-DOPA in parkinsonism, only one (Tissot \textit{et al.}, 1969) was not published in the \textit{British Medical Journal}, the \textit{Lancet} or the \textit{New England Journal of Medicine}; amongst the list of “reviews” and “other references” (twenty papers in all), not a single worker from continental Europe was mentioned. All references to pre-1969 experiences were omitted, except for a passing reference to Cotzias \textit{et al.} (1967). L-DOPA had been accepted, but had, in effect, required “rediscovery” by the English-speaking world. Several commercial preparations of L-DOPA were available by this time: ‘Brocadopa’ (Brocades; capsules and tablets), ‘Bendopa’ (ICN), ‘Larodopa’ (Roche; tablets), ‘Weldopa’ (later: ‘Veldopa’; Smith & Nephew Pharmaceuticals) and ‘Dopar’ (USA only: Eaton Laboratories); in Germany, ‘Helfodopa’ (Helfenberg, Wevelinghoven) and in Italy ‘Dopaidan’ (De Angeli) was also available, while the Japanese company Sankyo marketed ‘Syndopa’ (capsules) via various licensees in some countries.\(^\text{235}\)

\(^{229}\) Birket-Smith, 1974, 1975; Fahn and David, 1982.
\(^{230}\) Duvoisin, 1967.
\(^{231}\) Yahr \textit{et al.}, 1982.
\(^{232}\) Weintraub and Van Woert, 1971.
\(^{233}\) Yahr \textit{et al.}, 1982; Clough \textit{et al.}, 1984.
\(^{235}\) Extra Pharmacopoeia, 1972, pp.70-75. In 1988, Sittig listed another twenty-three L-DOPA preparations available in various countries.
Theoretically, these preparations should have been chemically and pharmacologically identical. But Birkmayer commented in 1970 that the Hoffmann-La Roche product, produced in a factory dedicated to its synthesis, was 99.9% pure, whereas the Japanese product included 33% α-methyl-DOPA.236 The source of this information is not given, but the remark is interesting in light of a letter which appeared in the Medical Journal of Australia in November 1971. The author, an associate professor at the Royal Adelaide Hospital, had been treating three patients for some time with the Japanese product ‘Syndopa’; the patients were stabilized at 3-4g/day, and had shown great improvement with regard to rigidity, tremor and other symptoms. He had noted in the past few weeks, however, a deterioration in their condition; upon inquiry, he found that the trial supply of ‘Syndopa’ had been exhausted, and the patients were now receiving instead ‘Larodopa’ tablets. By increasing the dose by 33%, the former benefit could be restored, suggesting that the Roche preparation was somehow less potent than the Sankyo offering.237 It is unlikely that the presence of α-methyl-DOPA would explain this difference (see next chapter), but the anecdote is nonetheless intriguing.

The decline in striatal dopamine levels in Huntington’s chorea, although not as dramatic as in Parkinson’s disease,238 suggested that the amino acid might be of some benefit. Unfortunately, the reverse was observed in most cases.239 Similarly, most clinicians found that L-DOPA was not appropriate for the reversal of neuroleptic-induced parkinsonism,240 which was not surprising in light of Carlsson’s determination that such agents act by blocking dopamine receptors.241 It is, however, noteworthy that one of the few reports which reported positive results in such a case found that akinesia, but not rigidity or tremor, was improved.242

**Official recognition and priority questions regarding L-DOPA therapy**

George Cotzias’ achievement in resuscitating interest in L-DOPA was increasingly recognized in an official manner from 1969 onwards. In this year, he was appointed Professor of Medicine at the State University of New York (Stony Brook) and Professor of Neurology at Mount Sinai School of Medicine; for his contribution to the research of Parkinson’s disease he was also awarded the Albert Lasker Medical Research Award in this year. Amongst the other awards which he received was an honorary degree from the National University of Athens and his election to the National Academy of Sciences in 1973. He continued to conduct research into means by which the problems associated with L-DOPA therapy might be overcome. At the time of his death he was Professor of Neurology at Cornell University Medical College and Attending Neurologist at New York Hospital and Memorial Sloan-Kettering Cancer Center, having moved from Brookhaven with his laboratory in 1973.243 He died in 1977 as the result of lung cancer.

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236 Letter, Birkmayer to Hornykiewicz, 5.02.70.
237 Lander, 1971. The author also mentioned that L-DOPA was to become freely available in Australia on 1 December 1971.
239 See, for example, Tan et al., 1972; Simanyi et al., 1973; Low et al., 1974; Sishta and Templer, 1976. See also Klawans et al., 1972 for use of L-DOPA in detection of Huntington’s chorea.
240 For example: Yaryura-Tobias et al., 1970.
The award of the prestigious Lasker Prize provoked something of a scandal, with many members of the prize committee resigning in protest. The reason for this was the fact that Cotzias enjoyed the publicity which he attracted as the “inventor of the L-DOPA therapy” and tended to overlook the major contributions of others to the field. The award was made to Cotzias for “his demonstration of the effectiveness of large daily dosages of L-DOPA in the treatment of Parkinson’s disease.”\footnote{Barbeau, Hornykiewicz and Birkmayer were affronted by this attitude, introducing an element of bitterness into the field for many years. Birkmayer, himself no stranger to publicity, wrote pointedly in 1970 that “in numerous glossy magazines, more and more indications and new discoverers of the Dopa therapy are presented every week”. He nevertheless accorded Cotzias the achievement of a “quantum leap” in the therapy.\footnote{The American Association for Research into Nervous and Mental Diseases recognized the achievements of Hornykiewicz in this field soon afterwards.\footnote{The question of who “invented” the L-DOPA therapy was heatedly discussed from the beginning. A month before the meeting of the American Medical Association in Chicago (June 1970), attended by Cotzias and at which L-DOPA was honored as “medicament of the year”, the therapy was a central theme at the Neuropsychiatric Symposion in Pula (Hungary).\footnote{Regular symposia were held in Pula during the period of the Cold War in order to facilitate contact with Eastern Bloc scientists unable to travel freely in the West.}}}} Barbeau, Hornykiewicz and Birkmayer were affronted by this attitude, introducing an element of bitterness into the field for many years. Birkmayer, himself no stranger to publicity, wrote pointedly in 1970 that “in numerous glossy magazines, more and more indications and new discoverers of the Dopa therapy are presented every week”. He nevertheless accorded Cotzias the achievement of a “quantum leap” in the therapy.\footnote{The American Association for Research into Nervous and Mental Diseases recognized the achievements of Hornykiewicz in this field soon afterwards.\footnote{The question of who “invented” the L-DOPA therapy was heatedly discussed from the beginning. A month before the meeting of the American Medical Association in Chicago (June 1970), attended by Cotzias and at which L-DOPA was honored as “medicament of the year”, the therapy was a central theme at the Neuropsychiatric Symposion in Pula (Hungary).\footnote{Regular symposia were held in Pula during the period of the Cold War in order to facilitate contact with Eastern Bloc scientists unable to travel freely in the West.}}} The American Association for Research into Nervous and Mental Diseases recognized the achievements of Hornykiewicz in this field soon afterwards.\footnote{The question of who “invented” the L-DOPA therapy was heatedly discussed from the beginning. A month before the meeting of the American Medical Association in Chicago (June 1970), attended by Cotzias and at which L-DOPA was honored as “medicament of the year”, the therapy was a central theme at the Neuropsychiatric Symposion in Pula (Hungary).\footnote{Regular symposia were held in Pula during the period of the Cold War in order to facilitate contact with Eastern Bloc scientists unable to travel freely in the West.}}

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Mr. C. would have been well advised to invite Mr. B. to his international symposium on L-DOPA, suggested Mr. S. thoughtfully over a glass of wine. The Pula panel discussion of L-DOPA, led by Mr. B., had been a great success, added Mr. S. But that doesn’t help much, for Mr. C. is an American and has the support of the massive U.S. medical publicity machine which emphasizes his priority again and again, to the extent that everyone believes that Mr. C. invented L-DOPA. Why would you invite the almost forgotten but actual discoverer?\footnote{The editorial traced the origins of the therapy to Birkmayer and Hornykiewicz, and criticized in no uncertain terms the “greed for glory” which it detected not only in Cotzias’ attitude, but also in that of American authorities; for instance, an American journal was cited as praising Cotzias as one of the great physicians “who initiated their work on their own”.\footnote{The author of the editorial had asked Cotzias his opinion on the discrepancy between the L-DOPA doses employed in Europe and America; he “received as answer merely an impolite and dismissive ‘ask Birkmayer’”.\footnote{Such attitudes did not endear Cotzias to many of his overseas colleagues, who, while acknowledging Cotzias’ achievement in introducing the therapy in America and thus cementing its place in the clinic, regarded the previous work of many European workers, in particular that of Birkmayer, as more extensive and systematic. Gert Völler (Königin-Elena-Klinik, Kassel), for example, lamented a short time later that articles in}}
both the lay and medical press had led to the false impression that L-DOPA therapy was “a purely American development”.  

The significance of L-DOPA therapy has also often prompted the question of whether the Nobel Prize for Physiology or Medicine might not have been appropriate recognition of its importance. The major problem lay in the fact that the Nobel committee is bound by its statutes to award the prize to a maximum of three investigators. The question then arises as to which three persons would be the most deserving candidates. A number of those involved in the L-DOPA story have unashamedly campaigned privately for the prize:

> My contribution was that I used the big doses. I opened a new era in the therapy of chronic nervous system diseases, and the medicines that will be used will be natural body chemicals. It’s a great discovery and worth the Nobel prize.

But none achieved their dream. I have been granted access to a confidential letter from Birkmayer to a German colleague who proposed nominating him for the Nobel Prize in 1977; Birkmayer wrote that such a nomination would be appropriate only if it also included Hornykiewicz and Carlsson. Birkmayer maintained until his death that it was this triumvirate which deserved the laurels for the discovery of L-DOPA therapy: Carlsson for establishing the significance of central nervous system dopamine, Hornykiewicz for identifying the dopamine deficit in parkinsonism, and himself for implementing the logical outcome of these investigations. I have not been able to determine whether the nomination was ever made; the fact is that one of the greatest achievements in 20th century medicine was long passed over for perhaps the ultimate acknowledgement. Claims to the honour were certainly also justified for Cotzias for his role in the introduction of oral L-DOPA therapy, as also for Sourkes for his measurement of urinary catecholamine levels and for his exploration of the nigrostriatal pathway. Despite the excitement engendered by Cotzias’ 1967 and 1969 papers, however, he may have remained an isolated if enthusiastic proponent of the therapy, not unlike the situation of Birkmayer in 1966, if Melvin Yahr had not confirmed his work as promptly and as thoroughly as he did. Indeed, if patient numbers are indicative, Yahr’s group pursued oral L-DOPA therapy with even greater vigor than Cotzias’; further, the papers from this group offered much more detail regarding both the effectiveness and adverse effects of the therapy. There were thus at least six major candidates for the award at the time it might have been made, and it would have been impossible to have done so without provoking a great deal of controversy and ill-feeling, particularly in light of the strained relations between some of the candidates.

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251 Völler, 1970.
252 “§4. A prize amount may be equally divided between two works, each of which is considered to merit a prize. If a work that is being rewarded has been produced by two or three persons, the prize shall be awarded to them jointly. In no case may a prize amount be divided between more than three persons. Work produced by a person since deceased shall not be considered for an award. If, however, a prizewinner dies before he has received the prize, then the prize may be presented.” Source: http://www.nobel.se/nobel/nobel-foundation/statutes.html
253 Cotzias, cited by Patten, 1983.
254 In the June 1969 letter to Hornykiewicz referred to on page 473, Birkmayer referred to disquiet arising from rumors of a Nobel Prize for the L-DOPA therapy in 1968; Hornykiewicz would be honoured for his discovery of the dopamine deficit in parkinsonism and his proposal of the L-DOPA therapy, Birkmayer for his elaboration of the practical therapy and particularly for his clinical observations regarding the effects of the decarboxylase inhibitor Ro 4-4602. Cited in letter circulated to colleagues by Hornykiewicz, 19 April 2001.
Although many awards and honorary doctorates would be bestowed upon many participants in the L-DOPA story, only Arvid Carlsson would receive the Nobel Prize. He shared the 2000 award equally with Eric Kandel and Paul Greengard for their contributions to the investigation of neurotransmission in the central nervous system; Carlsson was specifically rewarded:

for his discovery that dopamine is a transmitter in the brain and that it has great importance for our ability to control movements. His research has led to the realization that Parkinson’s disease is caused by a lack of dopamine in certain parts of the brain and that an efficient remedy (L-dopa) for this disease could be developed. Arvid Carlsson has made a number of subsequent discoveries, which have further clarified the role of dopamine in the brain. He has thus demonstrated the mode of action of drugs used for the treatment of schizophrenia.255

This was thus a recognition of Carlsson’s lifetime work in the field of dopaminergic transmission, although the popular press inevitably seized upon his role in the development of L-DOPA therapy as the most accessible of his achievements to present to the public. This aroused, however, some dissatisfaction amongst Hornykiewicz and certain of his colleagues, who interpreted the award as resting solely on his role in the history of L-DOPA therapy and argued in an open letter to the journal Parkinsonism and Related Disorders that Hornykiewicz was the rightful recipient of this honour (Cotzias had died in 1977, Birkmayer in 1996).256 This regrettable attack on the Nobel Committee overlooked not only the precise wording of the press release describing the grounds for Carlsson’s honour, but also the collective nature of the three men who shared the prize. The 2000 Nobel Prize for Physiology or Medicine should be seen as the seventh in a series of awards recognizing progress in the research of neurotransmission:

1906 Camillo Golgi and Santiago Ramón y Cajal “in recognition of their work on the structure of the nervous system”
1932 Charles Sherrington and Edgar Douglas Sherrington: “for their discoveries regarding the function of the neurons”.
1936 Henry Dale and Otto Loewi “for their discoveries relating to the chemical transmission of nerve impulses”.
1944 Joseph Erlanger and Herbert Spencer Gasser: “for their discoveries regarding the highly differentiated functions of single nerve fibres”.
1963 John Eccles, Alan Hodgkin and Andrew Huxley “for their discoveries concerning the ionic mechanisms involved in the excitation and inhibition in the peripheral and central portions of the nerve cell membrane”
1970 Julius Axelrod, Bernard Katz and Ulf von Euler “for their discoveries concerning the humoral transmitters in the nerve terminals and the mechanism for their storage, release and inactivation”257
2000 Arvid Carlsson, Paul Greengard and Eric Kandel “for their discoveries concerning signal transmission in the nervous system”.

Awards have thus been made on a fairly regular basis in recognition of conceptual advances in the neurosciences,258 but has rarely acknowledged an individual medical

256 Abrusseau et al., 2001; see also Helmuth, 2001.
258 The significance for neuroscience of the awards to Neher and Sakmann (1991) for work concerning the function of single ion channels in cells and to Gilman and Rodbell (1994) for the discovery of G protein-coupled receptors cannot be overlooked, although the Prizes recognized the development of
therapy or specific application for an individual neurological disorder. Indeed, the recognition of the invention of the integrated circuit with the 2000 Nobel Prize for Physics was widely criticized on the basis that it departed from the traditional reservation of the Nobel Prize for conceptual advances. With respect to the Prize for Physiology or Medicine, the only departures from this principle in neurology have been the 1927 Prize for Julius Wagner-Jauregg “for his discovery of the therapeutic value of malaria inoculation in the treatment of dementia paralytica” and the share of the 1949 Prize awarded to Egas Moniz in 1949 “for his discovery of the therapeutic value of prefrontal leucotomy in certain psychoses”.

Carlsson’s contribution to the basis of L-DOPA therapy was ultimately only one of his many achievements in fundamental research acknowledged by the Nobel Committee; correspondingly, Carlsson mentioned the therapy only briefly in his Nobel Prize lecture, and attributed its introduction to Hornykiewicz and Birkmayer and its broader acceptance to Cotzias. The 2000 Prize was thus only tangentially concerned with antiparkinsonian therapy; its focus was, in contrast, conceptual advances in the investigation of neurotransmission in general.

**Cotzias: further directions**

In 1971, Cotzias addressed the issue of “chemical memory” of drugs by tissues, including the brain. In most cases, such a memory led to reduced sensitivity for a particular drug; Cotzias thus noted that most antiparkinsonian drugs eventually lost their potency and needed to be substituted by alternative medications. He had initially expected that the same would apply to L-DOPA, but after six years’ experience with the drug doubted that this was the case. It seemed that once stable management of symptoms had been achieved, this level could be maintained for years, although the L-DOPA dose needed to be adjusted according to the changing needs of the patient. A downward adjustment was often required because of the emergence of involuntary movements, hypotension and positive Coombs tests; this, however, did not appear to be associated with a deterioration of the patient’s parkinsonian symptoms. That some sort of “chemical memory” for the drug could develop was supported by his observation that patients who had previously received D,L-DOPA developed abnormal involuntary movements at lower L-DOPA doses than those who were de novo subjects; this was true even in cases where the exposure to D,L-DOPA had occurred many months previously. He also noted that the dopamine receptor agonist apomorphine controlled parkinsonian symptoms more effectively if administered after a period of L-DOPA therapy.259 Interestingly, he also found that the combination of L-DOPA with D,L-5-HTP was toxic in mice, and did not therefore pursue this combination in parkinsonian patients.260 Cotzias believed, in fact, that L-DOPA was capable of halting the progression of the disease.261 In his “Overview of the present treatment of parkinsonism with l-DOPA”262,
he indicated that he was still unconvinced that elevation of basal ganglia dopamine levels was sufficient to fully explain the benefit of l-DOPA for parkinsonian patients. Its effects on melanogenesis, release of growth hormone and competition with other amino acids for transport mechanisms were discussed. He hypothesized that l-DOPA therapy “may be changing spare parts of brain cells besides supplying consumables.” In particular, he suggested that, by “scavenging” labile methyl groups from tissues, it led to a central depletion of methionine, noting that the methyl groups represented by the HVA levels excreted following an average l-DOPA dose accounted for about 75% of the groups available in the typical American diet. This would have consequences for both protein synthesis and RNA function. Although the link between these consequences and the antiparkinsonian effect of l-DOPA was unknown, he concluded:

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\text{the supply of dopamine to the brain is a necessary but by no means sufficient explanation for the action of levodopa. We further propose that regulation of the transmethylation processes is a more fundamental function of this drug.}\]

Although not explicitly discussed in this paper, there was probably some reference to the transmethylation hypothesis of schizophrenia which at least suggested this idea to Cotzias. He regarded l-DOPA as possessing two distinct sets of actions: “those of a nutrient and those of a drug.” Cotzias specifically proposed that:

\[
l\text{-dopa is a methyl group acceptor which restores some degree of normalcy to transmethylation reactions and therefore probably to the macromolecular composition of the Parkinsonian brain.}\]

To this phenomenon Cotzias attributed the fact that the benefit of l-DOPA therapy did not disappear immediately if the drug was withdrawn, and also the apparent slowing of the progression of the disorder. Wurtman’s group reported in 1973 that chronic l-DOPA loading depleted S-adenosylmethionine and methionine in the rat brain, and suggested that the consequent deficiency might lead to reduced O-methylation of l-DOPA and dopamine, thereby extending their effectiveness. This contrasted with other suggestions that 3-O-methyldopa might play a role in the benefit of l-DOPA therapy.

Cotzias also continued to pursue the link between manganese and l-DOPA. For instance, the bones and brain of a mutant mouse exhibiting ataxia and other central nervous system abnormalities (‘Pallid’; C^57BI/6J) not only contained less manganese than normal mice, the animals were also resistant to the effects of administered l-DOPA. Further, chronic administration of l-DOPA (10mg.g^{-1} diet) to normal mice led to a small but significant increase in manganese levels in the brain; an enriched manganese diet did not modulate central dopamine levels. These observations suggested to Cotzias the possibility of a genetic basis for the divergent responses of individual patients to the amino acid. His group also detected a high correlation between the levels of manganese and dopamine in various regions of the cat brain and at various stages of

\[263\text{ Cotzias et al., 1971a.}\]
\[264\text{ Ibid.; see also Cotzias et al., 1971b.}\]
\[265\text{ There had also been generally increased interest in the role of methylation in the regulation of gene expression at this time: Cotzias cited reviews by Arber and Linn, 1969; Glassmann, 1969; Yarus, 1969.}\]
\[266\text{ Cotzias et al., 1971b.}\]
\[267\text{ Ibid.}\]
\[268\text{ Ordonez and Wurtman, 1973; also Wurtman, 1972.}\]
the developing mouse brain; he thus hypothesized that the maturation of central
dopaminergic systems is manganese-dependent. This was supported by experiments in
which the dietary intake of manganese was controlled in young mice. Experiments
towards the end of his life indicated that a diet supplemented with high levels of L-
DOPA increased the life expectancy of mice.

With respect to manganese, it is interesting that in 1978, Weiner and colleagues
reported that not only L-DOPA, but also the D2 receptor agonists bromocriptine and
lergotrile produced increases in manganese levels (accompanied by decreased copper
levels) in most brain regions of guinea pigs treated with these agents. This phenomenon
was suggested to underlie some of their toxic effects.

Cotzias shared with many of the other characters in the L-DOPA story the conviction
that he had made the most significant contribution to the development of the therapy,
and this overview exemplified his tendency to forget his forerunners and important
European research. Nevertheless, Cotzias’ contribution to the field was crucial to the
ultimate breakthrough of L-DOPA therapy. The bravado of Cotzias and his group in
administering large doses of L-DOPA, though perhaps partly inspired by the gradual
increases used in high dose anticholinergic therapy of parkinsonism since the 1920s,
was undoubtedly a major milestone in the therapy of Parkinson’s disease. It is, however,
clear, that his antecedents in Göteborg, Vienna, Montréal and other places made
contributions to these developments and to the development of neuropharmacology in
general which were of at least equal significance. Further, it is highly doubtful that L-
DOPA therapy would today be of significance if the dose employed had not been
reduced by the co-administration of adjunct agents, especially the decarboxylase
inhibitors. The adulation of certain authors for Cotzias’ role in the L-DOPA story often
leads to the impression that he single-handedly discovered and developed the approach,
and was also responsible for the age of neurotransmitter-based neuropharmacology. It
in no way demeans his contribution to note that the “first miracle in neurodegenerative
disease” was the result of a series of events by workers in different parts of the world.

Problems with L-DOPA therapy

The literature on the untoward effects of L-DOPA presents what initially appears to
be a frightening catalog of negative side effects, a litany of motor, psychiatric and other
forms of suffering. On the one hand, this can not be surprising; it would be
unreasonable to expect that the complete panel of effects elicited by supplying an amino
acid which plays a role in a range of metabolic pathways central not only to
neurological but also general somatic function could be predicted in advance. Secondly,
although the purpose of L-DOPA therapy is to overcome the extrapyramidal dopamine
deficit identified by Hornykiewicz, oral administration of the precursor cannot be
expected to deliver a “magic bullet” to precisely those regions which require it, or even
to modulate, dopamine transmission in a physiological manner in those regions which
require therapy. Finally, however, it must be borne in mind that no previous
antiparkinsonian therapy had been investigated from even before its inception with such
intensity, by so many workers and with such advanced technology as L-DOPA therapy.

271 Weiner et al., 1978.
272 Kordoer and Goetz, 1999.
Indeed, L-DOPA therapy is probably safer than all its predecessors, precisely because its evaluation has not been limited to determining whether symptomatic relief is afforded at doses which do not intolerably burden the patient with undesired reactions; each side effect of L-DOPA therapy has quickly been noted and analyzed as it emerged, and, even if solutions for many problems are still wanting, the problems themselves are neither surprising nor ignored.

L-DOPA is readily absorbed from the gastrointestinal tract, but must be protected from peripheral metabolism by the use of decarboxylase inhibitors if significant amounts are to reach the brain. Critical for the following discussion is a phenomenon which has been described as the “all or none” rule. A certain threshold plasma concentration is required in order to achieve the benefits of L-DOPA treatment, this generally lies in the region of 400-600ng.ml⁻¹ in long-term patients. Increasing plasma L-DOPA levels above this point does not increase the benefit for a given patient; it will, however, intensify the untoward side effects which limit the usefulness of L-DOPA.²⁷³

At the time it was introduced into the clinic, the remarkably low toxicity of L-DOPA was one of its most attractive features, and the lack of adverse interactions with other agents often employed in the treatment of older patients was also welcome.²⁷⁴ But even before L-DOPA had been licensed for use in parkinsonism, it was clear that it did not represent a problem-free solution for the disorder. As noted by Cotzias:

"The next thing to do is to learn how to use levodopa... I don’t think we really know how to use it yet."²⁷⁵

All early workers noted the presentation of a range of side effects. Efforts were already underway to find adjunct therapies which would either increase the effect achieved by L-DOPA or to reduce the amount which needed to be administered; 70% of patients could tolerate 1-8g/day, but the use of such large doses of a drug – moreover, a drug proposed to modify central catecholamine levels to an unknown degree – on a chronic basis was unprecedented, and the long term consequences for the patient could not be foreseen. Hornykiewicz commented that, although L-DOPA was the most natural solution to the problem underlying parkinsonism, some of the side effects elicited by the agent would have been classified by classic pharmacology as lying in the "sub-toxic" range.²⁷⁶ This was quite apart from the discomfort (gastrointestinal symptoms, nausea, occasional hypotension) which many patients experienced even under the regimen of slowly increased doses. Further, even the opening of a mass market for the amino acid and the associated drop in price would not render it an inexpensive drug; it was estimated in 1969 that each 500mg capsule was priced at 40-50c in America, so that the therapy cost $6-7 per day.²⁷⁷ The use of decarboxylase inhibitors, as will be discussed in detail in the next chapter, reduced these problems, and there were immediate calls that a combination L-DOPA/decarboxylase inhibitor would be most useful for the therapy of parkinsonism. In 1969, however, it was probably easier to gain a licence for L-DOPA

²⁷³ The pharmacological data estimated by Robertson et al., 1969 (and listed in the 1996 edition of Goodman and Gilman’s The Pharmacological Basis of Therapeutics) are: oral availability 41 ± 16%; oral availability when administered with carbidopa: 86 ± 19%; clearance: 23 ± 4mL.min⁻¹.kg⁻¹ (with carbidopa: 9 ± 1); volume of distribution: 1.7 ± 0.4L.kg⁻¹ (0.9 ± 0.2); half-life: 1.4 ± 0.4h (1.5 ± 0.3); effective concentration: 8 ± 3nmol.mL⁻¹.
²⁷⁴ Hunter et al., 1970
²⁷⁵ In Udenfriend et al., 1971.
²⁷⁶ Hornykiewicz, 1970b.
²⁷⁷ Natelson, 1969.
### Table 15-7: Side effects reported in early studies of L-DOPA therapy in parkinsonism.

*Nausea and vomiting were listed together. **Thirteen cases of confusion, hallucinations or vivid dreams were reported; there were also nine cases of depressive episodes, but it is not possible to determine how many of the thirteen patients were also in this category.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Yahr et al., 1969 (n = 60)</th>
<th>Barbeau, 1969a (n = 80)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Peripheral</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>51</td>
<td>35</td>
</tr>
<tr>
<td>Vomiting</td>
<td>31</td>
<td>*</td>
</tr>
<tr>
<td>Hypotension</td>
<td>14</td>
<td>25</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Cardiac dysrhythmia</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Myocardial infarct</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>19</td>
<td>1</td>
</tr>
<tr>
<td>Polyuria</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td><strong>Central</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Involuntary movements</td>
<td>37</td>
<td>40</td>
</tr>
<tr>
<td>Psychic changes</td>
<td>10</td>
<td>13+**</td>
</tr>
<tr>
<td>Somnolence</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td><strong>Biochemical</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Elevated serum urea nitrogen</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>Transient increase in uric acid (blood)</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>Elevated SGOT</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Transient increase in alkaline phosphatase</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Positive LE cell preparation</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Postural hypotension attracted a great deal of early attention, especially with regard to whether it was of central or peripheral origin.\(^{278}\) It was also observed in patients receiving concomitant decarboxylase inhibitor therapy, suggesting an at least partially central mechanism. In any case, it did not appear to unacceptably increase the risk associated with L-DOPA therapy in patients with a history of cardiac disease, in which respect it was superior to anticholinergic therapies.\(^{279}\) Barbeau reported in 1969 that plasma renin activity was low in akinetic parkinsonian patients; plasma aldosterone and plasma volumes were normal, but these were also the patients who tended to have reduced urinary dopamine levels.\(^{280}\) It was noted by Yahr that parkinsonian patients tend

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\(^{278}\) A session was devoted to it at the Val David symposium in 1969: Barbeau and McDowell, 1970, pp.255-318.

\(^{279}\) See, for example, Jenkins et al., 1972.

\(^{280}\) Barbeau et al., 1969.
to have lower blood pressure than matched controls, and they also have a lower incidence of cerebrovascular and myocardial infarcts. It is perhaps ironic that hypotension should be regarded as a problem in L-DOPA therapy, given that concerns originally centered on the possibility of its inducing hypertension; hypotension secondary to deprenyl administration would also cause anxiety. In any case, it is now generally accepted that lower blood pressure (with standing systolic level as low as 70mm Hg) is more a feature of parkinsonism than of pharmacological therapy.

Peripheral side effects of L-DOPA therapy were not unexpected, and problems for which simple solutions could reasonably be expected. But with longer term application of L-DOPA, more perplexing problems of presumably central origin began to emerge; foremost amongst these were the abnormal movements (dyskinesias) which most patients appeared to develop after an extended period of treatment with L-DOPA. Despite the enthusiasm for the new agent, there must have been some thought given to whether these problems would eventually capsize the success of L-DOPA and relegate it to a place in history alongside banisterine and the Bulgarian treatment. Cotzias was the first to observe frequent presentation of these side reactions, experienced by some of the initial patients receiving up to 16g d,l-DOPA per day. Barbeau had also addressed this question in his otherwise celebratory review of nine years experience with L-DOPA, and had also proposed a classification system with the hope that this might lead to some understanding of their origin and thus of means of alleviating them. The problems associated with L-DOPA therapy were of such concern even at the end of 1969 that they were the subject of the first two parts of the conference (40% of its agenda) organized by McDowell and Barbeau in Val David; no less than fifty presentations on the theme are recorded, including twenty-eight on the topic which many found most disturbing, abnormal involuntary movements. Clinical, pharmacological, anatomical, physiological and biochemical aspects of the problem were considered; it was thereby an excellent example of the clinical experience stimulating further basic research.

By 1974, Duvoisin reported that 20% of patients exhibited dyskinesia within a month of the commencement of L-DOPA therapy; by a year, this figure increased to 81%. Melvin Yahr commented in 1984 that “few parkinsonians on levodopa for more than five years do not have some elements of dyskinetic phenomena.” The manifestation of these often disturbing choreiform reactions becomes more frequent with long-term use of L-DOPA, but it cannot be predicted when a particular patient will begin manifesting such reactions. Particularly violent presentation of dyskinesia was often noted in post-encephalitic parkinsonian patients, who, in any case, were relatively intolerant for L-DOPA. The most frequent form of dyskinesia, “peak dose dyskinesia”, occur during periods when the patient is most mobile and plasma levels of L-DOPA are at their peak. Further, the only means of controlling them appeared to be reduction of the L-DOPA dose, with consequences for control of the parkinsonian symptoms. Many patients, in

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281 Barbeau and McDowell, 1970, p.266.
282 Duvoisin et al., 1963.
283 Nutt et al., 1992, pp.126-130.
284 Cotzias et al., 1967.
285 Barbeau, 1969b. See also Barbeau et al., 1971b.
286 Barbeau and McDowell, 1970.
287 Duvoisin, 1974.
fact, presented dyskinesia just at the time when L-DOPA had begun to show its maximum benefit. But even then, satisfactory results were not always possible: those patients who suffered from these abnormal movements appeared to also have developed an increased sensitivity to the untoward effects of L-DOPA, so that even low doses were sufficient to elicit upsetting side reactions. This was later related to supersensitivity of striatal dopamine receptors associated with L-DOPA therapy, but it was also found that such dyskinesias could also be elicited in persons with normal receptor sensitivity.289

Whereas Cotzias had reported that withdrawal from L-DOPA in order to control dyskinesia did not affect the response to a subsequent L-DOPA course,290 Birkmayer had observed from the beginning of his application of oral L-DOPA that once dyskinesia emerged, the sensitivity of the patient to L-DOPA in this respect was permanently elevated.291 This paralleled his finding that discontinuation of L-DOPA therapy led immediately to a decline in the kinetic state of the patient – “the parkinsonian patient requires L-DOPA for the term of his life, just as the diabetic requires insulin”292 – whereas American reports had indicated that interruption of L-DOPA therapy after several months was not associated with an inevitable immediate decline in condition.293 Further, Hippius and Logemann reported that L-DOPA also exacerbated hyperkinesia resulting from long-term neuroleptic treatment in twelve of forty patients, and was associated with an increase in drive and mood, suggesting that these changes were associated with the reactivity of the extrapyramidal system.294

Most workers associated these dyskinesias directly with the pharmacology of L-DOPA – indeed, many argued that naturally occurring dyskinesia of various types should now be re-examined with respect to altered dopaminergic function295 –, although alternative suggestions were also made. Proctor and McGinnis (University of Texas Graduate School of Biomedical Sciences; later: Department of Physics), for example, suggested that the electron-donor properties of L-DOPA might be involved in the production of these symptoms, consistent with Cotzias’ group’s finding that other electron donors, such as the phenothiazines, could induce dyskinesia in animals possessing the electron acceptor melanin in the substantia nigra.296 In light of later hypotheses of oxidative stress in parkinsonism, Proctor’s proposal is extremely interesting:

_l-dopa is an electron donor and might be expected to form charge-transfer complexes with brain melanin, perhaps leading to the unpairing of electrons and to the generation of free radical species (or conversely, to the quenching of existing free radical species). It is also possible that l-dopa may catalyze oxidation reactions as a consequence of its ability to activate molecular oxygen by participating in a charge-transfer complex with the latter molecule. This reaction might lead to the generation of the free radical species of the oxidatized (sic) substrate. On the other hand, it should also be noted that the quinone oxidation products of l-dopa have excellent electron-acceptor properties and might serve as a sink for excess unpaired electrons._297

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289 Klawans et al., 1977; Fahn, 1989.
290 Cotzias et al., 1969a.
291 Birkmayer, 1971; Barbeau (1969) was of the same opinion.
292 Ibid.
293 Cotzias et al., 1969a.
294 Hippius and Logemann, 1970.
Electrophysical considerations of this type were rare in applied pharmacology in 1970. It is intriguing that increased production of free radicals induced by L-DOPA be seen as contributing to the long-term benefit of L-DOPA therapy; Proctor noted that electron-donating purines, such as caffeine, had been found to improve phenothiazine-induced dyskinesia in the 1950s. Further, Proctor noted that both dyskinesia and psychosis were associated with hyperpigmentation, and proposed that correlations between these symptoms and the levels of electron-donating and -accepting entities should be further pursued in order to elucidate crucial biochemical pathways in a number of other disorders, including alkaptonuria and Lesch-Nyhan syndrome. Somewhat later, Proctor and McGinness suggested instead that melanin functioned as free radical sink, more consistent with current views.

With even more extended employment of L-DOPA, “peak dose dystonia”, a more serious and painful form of dyskinesia, appeared alongside the by now familiar choreic dyskinesias. Further, it was observed in the late 1970s and early 1980s that such dystonia could also occur during the “off” phase of the drug effect; even worse was the identification of diphasic dyskinesia, whereby dyskinesia was seen on a cyclic basis at both the beginning and the end of the dose period.

A range of supplementary agents were examined in an effort to control dyskinetic movements, including the traditional anticholinergic medications. Yahr reported in 1969 some success with 5-HTP (up to 1½g/day), but by 1984 it was regarded as being ineffective. Trifluoperazine and pyridoxine, and later haloperidol and reserpine, were found to reduce the intensity of abnormal movements, but only at the cost of deterioration of the parkinsonian symptoms. Large doses of nicotinamide (up to 4.5g/day) or melatonin (up to 6.6g/day) were found to be ineffective in very small studies (six and eleven patients) in the control of involuntary movements.

This problem still awaits its ideal solution. According to the current standard model of the motor loop, the corpus striatum projects to the substantia nigra pars reticulata and the internal segment of the pallidum both directly and by an indirect route via the external segment of the pallidum and the subthalamic nucleus (corpus Luysii). Both pathways are modulated by dopaminergic projections from the substantia nigra pars compacta to the striatum, but in opposite directions by the two dopamine receptor types: D1 receptor activation excites the direct striatonigral pathway, while D2 receptor activation inhibits the output to the external segment of the pallidum. Dyskinesia associated with long term L-DOPA administration is interpreted by this model as indicative of an imbalance between the activity of the direct and indirect output pathways of the striatum. This phenomenon has been attributed to a number of factors:

300 Muenter et al., 1976; Melamed, 1979; Marsden et al., 1982.
301 Yahr, 1970. Up to 15g/day tryptophan was also tried, but this was without effect on both the abnormal movements and the parkinsonian symptomatology.
303 Ibid.
304 Cotzias et al., 1972. Cotzias’ group had reported in the previous year that melatonin corrected the development of adventitious movements in L-DOPA-treated mice. It had been found that melatonin increased brain 5-HT (but not 5-HIAA) levels, but the melatonin effect could not be produced by treatment with 5-HTP.
inappropriate conversion of L-DOPA to dopamine by intact and degenerating neurons, pulsatile activation of dopamine receptors, neurotoxic effects due to oxidative stress, and motor fluctuations arising from inadequate pulsatile stimulation of other components of the motor circuit. Interestingly, the D2 receptor and D2/D3 receptor agonists currently used in Parkinson’s disease, such as lisuride, bromocriptine, ropinirole and pramipexole, are not associated with this problem, whereas the mixed D1/D2 receptor agonist pergolide is reported to be similar to L-DOPA in its propensity for inducing dyskinesia. It might appear that dopaminergic agonists which specifically activate the indirect pathway are less associated with dyskinesia. However, selective D1 receptor stimulation with ABT-431 elicited an improvement in motor symptoms comparable to that achieved by L-DOPA, also with significantly less problems with respect to dyskinesia.

It is perhaps also interesting to note that involuntary movements were considered one of the features of post-encephalitic parkinsonism which distinguished it from true paralysis agitans:

*Mme Lévy has grouped the involuntary movements of encephalitis lethargica as follows: (1) choreiform movements, (2) bradykinesia, (3) myoclonic movements, and (4) tremors. But, in addition, there are many others – for example, innumerable tics, shuffling and stamping movements of the feet, ocular or glossal spasm, complex automatic actions of the whole body, and the “imitative” movements described by Babinski and Klebs.*

Apart from the tremor, these movements received little attention as far as therapy was concerned; they also appear to have subsided as the disease progressed. All were reported to be exacerbated by emotional stress and to disappear during sleep, where sleep was possible.

A second issue considered extensively at the Val David conference were “treatment failures.” One of the frequent criticisms directed at investigators of the older anticholinergic therapies was their often unrealistic optimism regarding the outcomes of treatment with certain agents. The fact that not all patients responded dramatically to L-DOPA therapy, and that there existed patients who did not respond at all, was addressed fairly frankly from the beginning by those involved in its investigation; even Birkmayer had conceded as early as 1964, despite his conviction regarding the value of the therapy, that the response of Birkmayer’s first patient L.S. was far from typical of the benefits obtained with the drug. He noted at Val David that the substantia nigra of non-responders proved to be bleached of melanin at autopsy, and this seemed a reasonable explanation for many treatment failures; the progression of the disease had reached such a stage that L-DOPA supplementation could no longer be of benefit for the patient. This concurred also with the clinical experience of the following years: about 60% of

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306 See, for example, Lees and Stern, 1981; Baronti et al., 1992; Pearce et al., 1998.
308 See Fici et al., 1997.
309 Shiosaki et al., 1996.
312 Birkmayer and Hornykiewicz, 1964.
313 Birkmayer, 1970b.
patients lost about 30-40% of the initial benefit after therapy had been continued for three years. Yahr, however, also observed that “drug holidays”, during which the patient was temporarily withdrawn from L-DOPA, were often sufficient to restore the efficacy of the agent. It is thus likely that changes in receptor sensitivity induced by L-DOPA therapy itself, which were also invoked to at least partly explain the emergence of abnormal involuntary movements, were involved in this desensitization, a familiar experience from the days of the anticholinergic agents. Interestingly, Yahr reported in 1982 that long-term L-DOPA use was indeed associated with an increase in the sensitivity of the cholinergic system as determined by administration of physostigmine.

A third problem not so clearly recognized at the time of the Val David meeting was the occurrence of diurnal motor fluctuations which accompany L-DOPA therapy. These first attracted greater attention at the beginning of the 1970s. Barbeau remarked that patients tended to regard dyskinesias less seriously than their families and physicians; the often unpredictable fluctuations in the L-DOPA effect itself, on the other hand, were viewed with much greater concern. Variations in the intensity of parkinsonian symptoms had been recognized for decades, although the role of such changes in the “benefits” achieved by medication were often not considered. In patients treated with L-DOPA, however, these fluctuations tended to be more accentuated, to an extent which was distressing for the patient. They occur in two principal forms. The first is the “end of dose” or “wearing off” decline in symptom control which generally occurs at the end of the dose period; it would seem to relate to the physiological decline in the availability of L-DOPA. This effect can be counteracted by administration of a dopamine receptor agonist or the continuous infusion of L-DOPA, for which reason research in both these directions has been intensely pursued; the pharmacodynamics of orally administered L-DOPA does not seem adequate for long term management of parkinsonism. Such fluctuations can be first seen a few years after the commencement of therapy.

More than 50% of patients are reported to experience the second form of fluctuation problem, the so-called “on-off” phenomenon, two to five years after commencing therapy, and usually after having experienced end of dose problems. The duration of benefit of a given dose is reduced, and the superimposition of coexistent dyskinesia often results in unpredictable, sudden switches between profound akinesia and uncontrolled hyperkinesia; the switch from a- to hyperkinesia is usually precipitate. Attempts to control this problem have included the administration of lower doses of L-DOPA at more frequent intervals, the use of dopamine receptor agonists and MAO-B inhibitors as adjunct therapies and the employment of controlled release L-DOPA preparations. All these efforts are essentially designed to reduce potential fluctuations in central L-DOPA/dopamine levels, although the drugs employed may also have other significant beneficial effects.

Birkmayer’s group regarded such fluctuations not as side effects, but rather as an exaggerated form of the normal symptom variations of the natural disorder; their management was, nevertheless, the same.

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315 Ibid.
316 Yahr et al., 1982.
317 Sweet and McDowell, 1974.
318 Barbeau, 1981.
320 Claveria et al., 1973; Sweet and McDowell, 1974; Fahn, 1974; Markham, 1974; Yahr, 1974.
321 Birkmayer et al., 1987.
Other problems were recognized as experience with L-DOPA increased. Particularly disturbing was the suggestion that L-DOPA therapy was associated in the longer term with a range of untoward psychiatric effects over the years. It was noted early that in America, where higher L-DOPA doses were employed than in Europe, 12.3% of patients experienced psychic disturbances such as agitation and restlessness. 322 Most common amongst psychiatric side effects are depression and fatigue, but anxiousness, confusion, hypersexuality, hallucinations, delusions and even frank psychosis have also been reported. Confusional states occur less frequently with L-DOPA than with anticholinergic therapies. Early estimates suggested that the frequency of psychiatric side effects in L-DOPA therapy could be as high as 50%, although 20% was the mean rate identified. 323 Barbeau hypothesized that at least some of these states might be attributable to the metabolism of L-DOPA to abnormal methylated compounds. 324 But it is not clear to what degree these changes reflect responses to L-DOPA or rather underlying psychiatric problems, perhaps associated with the pathology of parkinsonism itself. Cognitive changes in parkinsonism have been recognized sporadically for more than a century; 325 König commented in 1912:

*The symptomatology of paralysis agitans includes in a great many cases an abnormal temperament, usually in the form of a hypochondriac depression with a tendency to irritability and feelings of persecution . . . In many cases, these mood anomalies progress to genuine psychosis . . As a more frequent combination of purely external character, dementia senilis or arteriosclerotica, or, towards the end of life, the manifestations of delirium are also possible.* 326

The discrimination of disease and drug effects, however, has always been difficult in a patient group subject to continuous and varied pharmacological interventions. 327 The co-presentation of Parkinson’s disease and Alzheimer’s disease is not uncommon, and

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confusion, delirium</td>
<td>40</td>
<td>4.4</td>
</tr>
<tr>
<td>Depression</td>
<td>38</td>
<td>4.2</td>
</tr>
<tr>
<td>Overactivity, restlessness, agitation</td>
<td>33</td>
<td>3.6</td>
</tr>
<tr>
<td>Psychosis, delusions, paranoia</td>
<td>33</td>
<td>3.6</td>
</tr>
<tr>
<td>Hypomania</td>
<td>14</td>
<td>1.5</td>
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<tr>
<td>Hypersexual behaviour</td>
<td>8</td>
<td>0.9</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>14</td>
<td>1.5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>180</td>
<td>20%</td>
</tr>
</tbody>
</table>

*Table 15-8: Major psychiatric symptoms in 908 patients treated with L-DOPA, as reported by Goodwin, 1971. The figures were compiled from twenty-one studies in which adverse psychiatric side effects were specified.*

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322 Anonymus, 1970j.
324 Barbeau, 1970.
325 See Ball, 1882 for review.
326 König, 1912. This paper includes a good review and bibliography of the subject to this point.
327 As examples of the literature on this subject throughout the century, see: Souques, 1921; Hauptmann, 1922; Marshall, 1936; Schwab et al., 1951a; Porteous and Ross, 1956; Loranger et al., 1972; Anonymus, 1974; Sweet et al., 1976.
incidences of 20-50% for dementia in parkinsonism have been reported, the prevalence in idiopathic Parkinson’s disease patients is estimated at 10-30%. It has been proposed that both diseases form part of a spectrum of central neurodegenerative disease. If a major tranquilizer appeared indicated, thioridazine was often chosen as the phenothiazine least associated with the induction of parkinsonian symptoms.

Other problems of l-DOPA therapy which were frequently registered included:

- **Akinetic crises:** total immobilization without loss of consciousness, lasting from minutes to days, have been attributed both to an overly rapid withdrawal from medication and to a total failure of the nigrostriatal system and the reduction of striatal dopamine levels below a required threshold (∼10% of normal).
- **“Freezing”:** the loss of ability to initiate leg movement for periods lasting from seconds to minutes has been attributed to noradrenaline deficits, and therefore neither caused by nor responsive to l-DOPA therapy. There are often associated with incidents of emotional stress.
- **Vegetative problems:** obstipation, incontinence, sweating crises, heat intolerance, breathing disturbances.
- **Melanoma:** Skibba and associates reported in 1972 a case in which l-DOPA therapy appeared to be associated with the development of multiple primary melanoma; Fermaglich and Delaney reported a further six similar cases in 1977. This phenomenon has been repeatedly discussed in the literature, but there appears to be no clear causal link between l-DOPA therapy and cancer.

These latter problems have also been observed in patients not treated with l-DOPA, and it is probable that they are symptoms of the disorder which are amplified by therapy. It is perhaps interesting in this regard to consider the list of major complications in parkinsonism noted by Onuaguluchi in 1964, as given on page 339 (DOPA therapy was not considered in his review).

A summary of adverse side effects in l-DOPA therapy is presented in table 15-9; it is not appropriate in a historical work to discuss these in greater detail than has already been done so above. It suffices to note that, in spite of these many problems, the value of l-DOPA therapy itself was never in question; the same Cooper who had eight years earlier dismissed the potential benefit of drug therapy for parkinsonian patients and had treated 6,000 patients surgically since 1952, had used l-DOPA in 600 patients since Cotzias had presented his results; he concluded that “treatment failures are relatively insignificant if compared with value as a therapeutic agent.” He had undertaken 900 stereotactic operations on parkinsonian patients in 1967; in 1970 the number was 50. It was reported in most of the therapeutic trials following the publication of Cotzias’ results that around 80% of patients exhibited significant benefit from l-DOPA therapy, an important improvement on what could be achieved with anticholinergic agents. More

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328 Cole and Clyde, 1961. For an early case of coexistent parkinsonism and dementia, see Bergesio, 1885.
329 Mayeux and Marder, 1996, and references therein. See also Aarsland et al. (2001), who discuss the problems involved in estimating the incidence of dementia in Parkinson’s disease patients. The authors’ own study indicated that risk of dementia in Parkinson’s disease was six times higher than in other aged persons.
331 Skibba et al., 1972; Fermaglich and Delaney; 1977. For recent reviews on the subject see Kleinhans et al., 1996; Pfutzner and Przybilla, 1997.
332 Cooper, 1971.
Peripheral side effects

Gastrointestinal symptoms
Cardiac symptoms
Melanoma

Central side effects

Dyskinesia
  Chorea
  Dystonia
  Myoclonus
  Simultaneous dyskinesia and parkinsonism

Dyskinesia
  Mental changes
    Dementia, confusion, agitation
    Psychiatric: depression, hallucinations, delusions, mania

Tachykinesia with hypokinesia
  Loss of efficacy

Fluctuations
  “Wearing off”
  “Sudden off”
  “Yo-yoing”
  “Delayed on”
  Others

Freezing

Table 15-9: Adverse side effects of long term L-DOPA therapy in parkinsonian patients, as classified by Fahn, 1989.

Importantly, it was also possible to achieve results in those advanced patients for whom all hope had long been abandoned; rather than a mild amelioration of the worst symptoms which amounted to little benefit for the severely handicapped; restoration of independent movement and care was achievable, even if the complete cure remained elusive.

It was thus clear that the introduction of L-DOPA therapy did not represent the discovery of a panacea for Parkinson’s disease, but a giant step forward had nonetheless been taken. There was no doubt that the quality of life of a great many patients had been improved; even restoration to partial mobility and autonomy represented a major and unexpected change in the lives of many who had formerly resigned themselves to inexorable creeping decrepitude which would soon or later result in full-time institutionalization. Further, the benefits of L-DOPA therapy appeared to include increased life expectancy for responsive patients. In 1967, life expectancy for parkinsonian patients was about seven years less than that for the general population; by 1981, it was being suggested that this difference had been cut to one and a half years in L-DOPA-treated patients. This was probably not a direct effect of the drug, but largely the result of:

333 Hoehn and Yahr, 1967.
a marked reduction in the infectious and degenerative complications of the sedentary state induced by the disease, and to the better general medical care which accompanies regular visits for L-DOPA therapy monitoring.334

Birkmayer had noted similarly that “The Parkinson patient doesn’t die as the result of rigidity, he dies because of his akinesia”.335 Life for parkinsonian patients had become increasingly mobile and thereby more healthy – and, as a result, more livable.

The success of L-DOPA therapy also sparked the most intense and fruitful period of parkinsonism research in the history of the disorder, a development stimulated by the new direction and hope which L-DOPA therapy offered and made possible by technical developments which allowed investigations of central nervous function with a degree of intimacy which previously was not even imaginable. The attempt to explain phenomena such as L-DOPA-linked dyskinesia has, in particular, stimulated intensified investigation of the neuroanatomy and neurochemistry of the motor system and the relationships which exist between its components.

The first “rational therapy” for parkinsonism: Mechanism of the L-DOPA effect

L-DOPA therapy of parkinsonism has often been apostrophized as the first “rational therapy” for the disorder.336 This claim is based on the fact that a series of biochemical observations, culminating in the determination of reduced dopamine levels in the substantia nigra and striatum of the parkinsonian brain, led to the attempt to compensate this deficit with the appropriate precursor. That is, pharmacological intervention was based upon the defined neurochemical consequences of a specific nervous lesion. The therapy was thus the logical answer to a defined problem, whereas the anticholinergic therapies were empirical; the response of patients to anticholinergic agents was of greater consequence for theoretical considerations regarding parkinsonism than vice versa, and even then the impact was minimal. It is certainly true that this logical flow from “brain homogenate to treatment”337 was pursued in Vienna, and a similar process was at work in Montréal. But this logic was not otherwise widely recognized at the time. It is, for instance, somewhat surprising that no attempt was made by other laboratories to verify the dopamine deficit identified in Hornykiewicz’ laboratory until the early 1970s. Further, the logical clinical conclusion of his work was drawn only in a few, generally less prominent clinics. On the other hand, the significance of urinary levels of dopamine and its metabolites as an indicator of central nervous function was controversial, so that the major evidence upon which the rational basis of the L-DOPA therapy rested were the measurements undertaken at the beginning of the 1960s in Vienna. Hornykiewicz’ laboratory and several other workers had subsequently investigated dopamine metabolites in the parkinsonian brain and the effects of various agents on dopamine and metabolite levels in the animal brain; but the essential, basic phenomenon of reduced dopamine levels in parkinsonism was not immediately pursued elsewhere.

334 Barbeau, 1981.
335 Anonymus, 1970m.
Although the L-DOPA approach would appear logical, the idea that a peripherally administered amino acid might reach basal ganglia synapses and restore their normal function was a daring supposition, and rendered plausible only by empirical success. Indeed, most would argue that the ultimate success of L-DOPA was due to the discovery by Cotzias of the feasibility of “high dose L-DOPA” therapy; and he claimed that his work, in turn, was motivated by the dubious theory of compensating the melanin loss which characterizes the disease. In a very real sense, then, the success of the L-DOPA therapy, at least initially, had less to do with its rational neurochemical basis than with the fact that a number of respected clinicians demonstrated that it worked; that is, it was to thus some extent as empirical as the anticholinergic approaches.

This is further underscored by the fact that that the question of how and where L-DOPA achieves its beneficial effects has been continuously posed and variously answered since the introduction of the therapy. Hornykiewicz conceded in 1969 that the rectification of the basal ganglia dopamine deficit was only one of several possibilities for the mechanism of its action. He concluded, however, that the effects of L-DOPA were due to:

- **an action in the central nervous system**: neither dopamine nor noradrenaline administered peripherally exerted an antiparkinsonian effect, and peripheral decarboxylase inhibitors allowed the reduction of the required L-DOPA dose.
- **an amine formed from L-DOPA**: the alternative L-DOPA metabolite 3-methoxy-DOPA was found to have no antiparkinsonian effects, while the concurrent use of a MAO inhibitor reduced the required dose of L-DOPA by up to 85%.
- **probably dopamine**: catecholamine metabolites were excluded by the enhancing action of MAO inhibitors, while the noradrenaline precursor threo-DOPS possessed no antiparkinsonian effects.\(^{338}\)

He urged caution on the last point, however, as little was known about the metabolism of threo-DOPS in the human brain. Nevertheless, Hornykiewicz assumed that replenishment of dopamine stores in the striatum probably underlay the therapeutic effect of L-DOPA, assuming that adequate levels of DOPA decarboxylase were still available to convert the precursor to the active amine. Results which he and Bernheimer had gained with respect to this question in the mid-1960s had been inconclusive, due largely to the variability of enzyme activity in the control brains they had examined;\(^{339}\) Other workers, on the other hand, had detected a decline in the activity of this enzyme in the striatum following transection of the nigrostriatal pathway.\(^{340}\) This would, in fact, be predicted, and at the same time presented a paradox; if the nerve endings responsible for dopamine synthesis had degenerated, how could supplementation with L-DOPA be of any benefit? The standard answer was that the surviving nerve endings were induced by the higher levels of the precursor to increase the rate of synthesis of the transmitter, and thereby to increase extracellular levels either by stimulated release or simple leakage. This was consistent with the shift in the striatal HVA/dopamine ratio to higher values in the parkinsonian brain which Hornykiewicz’ laboratory had detected, and with data later reported by Rinne’s group concerning catecholamine metabolite levels in the parkinsonian brain (see below).\(^{341}\)

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\(^{338}\) Hornykiewicz, 1970b; see also 1970a.

\(^{339}\) See Bernheimer and Hornykiewicz, 1962; also Langemann and Ackermann, 1961.

\(^{340}\) See references in Hornykiewicz, 1970b.

\(^{341}\) Bernheimer and Hornykiewicz, 1965; Rinne and Sonninen, 1973.
Hornykiewicz also emphasized that differences between some of the effects seen with small doses of intravenous L-DOPA and massive doses of oral L-DOPA might exist. Hyperkinetic side effects, for instance, were notably absent from therapy with the former. One potential problem was that exogenously administered L-DOPA had been shown in animal studies to be accumulated by brain regions which did not normally synthesize dopamine or noradrenaline; further, as the aromatic amino acid decarboxylase was also present in serotonergic neurons, dopamine could be synthesized and presumably released in regions where it did not normally occur. This was invoked as an explanation for the observation that L-DOPA administration appeared to lead to reduced 5-HT levels and to certain side effects which were associated with serotonergic mechanisms. Birkmayer described his concurrent use of L-tryptophan or L-5-HTP with L-DOPA as an effort to drive L-DOPA from serotonergic neurons.342

Hornykiewicz retained the view, however, which he had first articulated in detail in 1966:343 that Parkinson’s disease was essentially a “striatal dopamine deficiency syndrome” (although he was careful to note that the existence of a dopaminergic nigrostriatal pathway in man had not yet been definitively demonstrated) and that the beneficial effects of L-DOPA were attributable to the correction of this deficit.344 Other workers, however, had posited that L-DOPA might also achieve results in other brain regions; there were those, for example, who saw the main effect of L-DOPA as being the stimulation of the reticular arousal system. Barbeau emphasized the value of the side effects in the clarification of both the basic etiological problem in parkinsonism and the mechanism of action of L-DOPA. He noted, for instance, that abnormal movements were elicited by L-DOPA only in parkinsonian and certain other patients, and then only after extended treatment with high doses, and were usually manifested with a characteristic pattern. He proposed that different brain regions were responsible for different effects:

- Stimulation of striatal dopaminergic autoreceptors: stereotypic orobucofacial grimaces of the choreiform type.
- Displacement by dopamine or one of its methylated derivatives of transmitters, probably in the brainstem: slow, large amplitude tremor and hypotonia.
- Displacement by dopamine of 5-HT in the brainstem or limbic nuclei: toxic psychotic symptoms.345

It must also be understood that at the time these hypotheses were being advanced, little was known about the local physical or biochemical topography of the striatum or, indeed, of most brain regions. The hypotheses proposed at the beginning of the 1970s were thus similar in nature to those advanced by Feldberg at the end of the 1940s to explain the benefit of atropine therapy in parkinsonism: in both cases, they were largely based on interpretations of empirical clinical data. This was partly due to the continued absence of a suitable animal model of parkinsonism: while the biochemical and behavioral effects of various drugs could be investigated in a variety of species, there still existed no means of comparing the effects on parkinsonian symptoms, except to test them directly in patients.

342 Birkmayer et al., 1974.
343 Hornykiewicz, 1966c.
344 Hornykiewicz, 1970b.
345 Barbeau, 1970b.
Concluding the Val David conference, Carlsson noted that the peripheral side effects could probably be reduced by the use of decarboxylase inhibitors, some of the psychic side effects by dopamine β-oxidase inhibitors; but even at this stage it was clear to him that “a deeper analysis of the underlying mechanism” involved in the production of abnormal movements would be required before this problem could be resolved. Nevertheless, he was optimistic about the prospects for the future of parkinsonism research:

> There are still discoveries to make in this field, and I would now like to suggest that we go home and make them.  

This they did. The editorial article by Richard Wurtman in the *New England Journal of Medicine* for its New Year’s Day edition of 1970 was titled “Catecholamines and neurologic diseases” and commenced with the encouraging lines:

> Nature has been unusually kind to research scientists who work with the catecholamines: it has endowed their work with instant relevance. In few other areas of biomedical science has it been possible to achieve so rapid a translation of basic biochemistry into practical therapy.

The relevance of catecholamine research for psychiatric and cardiovascular medicine was mentioned, but Wurtman then moved to the fact that “Cotzias, Yahr, Barbeau and a host of other gifted investigators have carried the catecholamine revolution to neurology.” “Compelling evidence” suggested that a sizable proportion of the parkinsonian population derived benefit from L-DOPA therapy. Nevertheless, the author turned his attention to some of the problems which had to be faced in the 1970s:

- He noted a lack of direct evidence for the theory that L-DOPA achieved its effect by elevating brain dopamine levels (the melanin theory was not mentioned); according to Wurtman, the therapy had thus far derived its theoretical support from animal experiments. This was curious, as it both ignored Cotzias’ stated rationale for his trials, and ignored Ehringer and Hornykiewicz’ 1960 paper (although he cited Hornykiewicz’ 1966 review article).
- Wurtman’s point became clearer in the following section: most L-DOPA was probably metabolized by decarboxylases and methylases in the periphery, and thus lost to the brain. Inhibitors needed to be found to circumvent this problem.
- Wurtman argued that not only was there no evidence for L-DOPA increasing the catecholamine content of the surviving nigrostriatal neurons, the presence of excessive catecholamine levels in these neurons would be of questionable benefit.
- The surprising failure of L-DOPA to induce hypertension via its conversion to adrenaline was “a boon to the clinician but a puzzle to the biochemist.” There had, in fact, been reports of cardiac arrhythmias, but these could be controlled by reduction of the L-DOPA dose.

His concluding assessment that the mechanism of action of L-DOPA would probably “be resolved in the within a year or two” proved to be a little optimistic. More accurate was his opinion that “the success of L-DOPA therapy owes as much to chance as to the theoretical foundations that generated its initial use.” Nevertheless, Wurtman

347 Wurtman, 1970.
348 Ibid.
It was, in fact, the case that, if it was increasingly accepted that real benefits could be achieved with L-DOPA, the mechanisms by which it achieved its effects were still controversial. This uncertainty as to the precise nature of the L-DOPA effect was naturally encouraged by the untoward side effects which emerged with its extended use. This was not entirely justified; that the dopamine deficit was crucial to the expression of parkinsonian symptoms did not mean that its rectification would be sufficient to return a patient to ‘normality’. The aim of L-DOPA therapy was, after all, limited to compensating dopamine losses in the basal ganglia, not to restoring the natural physiological balance of the extrapyramidal system which presumably existed before the onset of disease. The L-DOPA therapy was by no means a ‘cure’ for Parkinson’s disease, a fact which seems to have been overlooked by some workers at the time; knowledge concerning what would become known as the “motor loop” for example, was scanty, so that the therapeutic approach was necessarily simplistic.

It was generally agreed that the positive results achieved in the earlier intravenous L-DOPA trials could largely be attributed to its replenishment of basal ganglia dopamine stores, as reviewed by Hornykiewicz in 1966. It was initially questioned by some workers, however, whether exogenous L-DOPA actually reached the brain to an appreciable degree; Bertler’s group had demonstrated at Lund, for example, that there existed a barrier in rodents at the level of the vascular endothelium not only against the entry of peripherally administered D-DOPA and dopamine, but also against L-DOPA and L-5-HTP. This was due to the presence of significant DOPA decarboxylase and MAO activity in the capillary walls. Pletscher’s group had demonstrated in 1966, however, that the level of radioactive HVA detected in the cat cerebrospinal fluid was greater following intravenous administration of L-[14C]-DOPA than of [3H]-HVA, indicating that the level of HVA in the cerebrospinal fluid reflected, at least in part, metabolic processes in the brain. Rinne’s group found somewhat later that dopamine and HVA concentrations were massively elevated (compared to both a control and an untreated parkinsonian patient) in the basal ganglia of a patient treated with 5g/day L-DOPA, but also in the cortex, thalamus, hypothalamus and cerebellum, while noradrenaline levels were unaffected; 5-HT concentrations and, to an even greater extent, 5-HIAA levels were also increased in most regions. This contrasted with later findings in animal experiments that L-DOPA loading produced falls in central 5-HT and 5-HIAA, probably by displacement of 5-HT from its natural storage sites. In 1973, Rinne and Sonninen confirmed the elevation of dopamine and HVA levels, but not of noradrenaline concentrations, across the brain in twelve parkinsonian patients who had received L-DOPA, of whom four had also received a decarboxylase inhibitor (benserazide). The increase in HVA levels was more marked than that of dopamine, indicative of rapid dopamine turnover in these patients, but there was a great deal of variability in the dopamine/HVA levels measured, differences which were related to the interval between the final L-DOPA dose and death. Interestingly, employment of a
The effects of high dose oral L-DOPA could conceivably elicit a second set of effects not induced by direct application, either via the presence of large concentrations of L-DOPA itself or of another of its metabolites, such as methoxy-derivatives. It was noted that L-DOPA therapy led to the accumulation of high levels of 3-O-methyl-DOPA throughout the brain; its long half-life rendered it possible that it served as a depot for L-DOPA release. Birkmayer and Hornykiewicz had earlier reported that the intravenous administration of this putative derivative had no effect on parkinsonian signs, but more recent reports had indicated that it had a slight effect when administered in high oral doses. Other methylated dopamine derivatives also possessed some receptor activity, but were regarded as less likely to be involved in the antiparkinsonian action of peripheral decarboxylase inhibitor, if anything, was associated with more moderate elevations in central dopamine levels (table 15-10).

Table 15-10: Dopamine (white boxes) and HVA concentrations (shaded boxes) in the human brain, abstracted from report by Rinne and Sonninen, 1973. Values for controls and parkinsonian patients not receiving L-DOPA are given as mean ± standard error of the mean; figures for L-DOPA-treated patients are ranges. In all cases the units are µg.g⁻¹ brain tissue; numbers in brackets are number of patients is given in parentheses.

<table>
<thead>
<tr>
<th>Caudate</th>
<th>Putamen</th>
<th>Pallidum</th>
<th>Substantia nigra</th>
<th>Thalamus</th>
<th>Hypothalamus</th>
<th>Cerebral cortex</th>
<th>Cerebellar cortex</th>
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<tr>
<td>Controls</td>
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<tr>
<td>1.37 ± 0.23 (13)</td>
<td>2.34 ± 0.45 (12)</td>
<td>0.95 ± 0.11 (13)</td>
<td>0.54 ± 0.09 (11)</td>
<td>0.31 ± 0.07 (9)</td>
<td>0.35 ± 0.08 (9)</td>
<td>0.19 ± 0.05 (13)</td>
<td>0.23 ± 0.06 (13)</td>
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<tr>
<td>2.59 ± 0.31 (24)</td>
<td>4.82 ± 0.45 (24)</td>
<td>3.10 ± 0.42 (23)</td>
<td>1.66 ± 0.17 (21)</td>
<td>0.30 ± 0.06 (15)</td>
<td>0.62 ± 0.04 (12)</td>
<td>0.09 ± 0.07 (15)</td>
<td>0.03 ± 0.02 (15)</td>
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<tr>
<td>Parkinsonian patients</td>
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<tr>
<td>0.17 ± 0.05 (6)</td>
<td>0.16 ± 0.05 (6)</td>
<td>0.08 ± 0.04 (6)</td>
<td>0.06 ± 0.03 (5)</td>
<td>0.20 ± 0.07 (5)</td>
<td>0.21 ± 0.09 (5)</td>
<td>0.10 ± 0.07 (5)</td>
<td>0.17 ± 0.10 (5)</td>
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<tr>
<td>0.97 ± 0.35 (6)</td>
<td>0.70 ± 0.12 (6)</td>
<td>0.87 ± 0.28 (6)</td>
<td>0.47 ± 0.14 (6)</td>
<td>0.11 ± 0.05 (5)</td>
<td>0.17 ± 0.08 (5)</td>
<td>0.01 ± 0.01 (5)</td>
<td>0.02 ± 0.01 (5)</td>
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<tr>
<td>Parkinsonian patients receiving L-DOPA</td>
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<tr>
<td>0.21-4.61 (8)</td>
<td>0.22-3.96 (8)</td>
<td>0.13-5.63 (7)</td>
<td>0.13-5.35 (6)</td>
<td>0.13-2.76 (7)</td>
<td>0.10-0.43 (6)</td>
<td>0.21-2.93 (8)</td>
<td>0.02-2.50 (7)</td>
</tr>
<tr>
<td>0.46-10.09 (8)</td>
<td>0.67-16.49 (8)</td>
<td>0.61-25.87 (8)</td>
<td>0.76-21.89 (8)</td>
<td>0.50-11.05 (8)</td>
<td>0.46-6.92 (8)</td>
<td>0.34-3.60 (8)</td>
<td>0.07-6.65 (8)</td>
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<tr>
<td>Parkinsonian patients receiving L-DOPA and benserazide</td>
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<tr>
<td>0.12-0.60 (4)</td>
<td>0.11-0.40 (4)</td>
<td>0.09-0.40 (3)</td>
<td>0.10-0.29 (4)</td>
<td>0.10-0.28 (4)</td>
<td>0.11-0.62 (4)</td>
<td>0.14-0.28 (4)</td>
<td>0.02-0.68 (4)</td>
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<tr>
<td>0.66-4.53 (4)</td>
<td>1.15-3.95 (4)</td>
<td>1.28-3.14 (4)</td>
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<td>0.84-2.07 (4)</td>
<td>0.79-1.26 (4)</td>
<td>0.22-0.81 (4)</td>
<td>0.09-1.87 (4)</td>
</tr>
</tbody>
</table>

354 Chalmers et al., 1971; Davidson et al., 1971; Sourkes, 1971c; Bartholini et al., 1972; Geissbuhler et al., 1972.
355 Birkmayer and Hornykiewicz, 1962.
356 Gauthier et al., 1971; but see de Ajuriaguerra et al., 1971.
L-DOPA. It had also been suggested that tetrahydropapaveroline-like condensation products of L-DOPA might undergo transformation to active noraporphine products. This possibility had become particularly interesting following the recognition of the dopamine-like activity of apomorphine, particularly in the striatum. Ericsson and colleagues also reported that the dopamine metabolite DOPAC and two derivatives (dihydroxyphenylpyruvic acid and dihydroxymandelic acid) were at least as effective as L-DOPA in reversing reserpine-induced depression of motor activity in rats, and suggested that DOPAC might, in fact, be active in its own right.

The effects of L-DOPA therapy on other transmitter systems were also obscure. With the identity of the DOPA and 5-HTP-decarboxylases now accepted, it was conceivable that dopamine was produced in regions where it did not normally occur, or that it inhibited 5-HT synthesis. The effects of large L-DOPA doses on competition for amino acid transporters was also unknown. The effectiveness of the oral therapy also introduced the possibility that dopamine levels being restored or even increased above normal physiological levels in some regions could have decisive consequences for the function of other transmitter systems.

Finally, it was probable that some effects of L-DOPA were mediated peripherally; Barbeau’s group, for example, had found that L-DOPA reduced the already depressed plasma renin activity of parkinsonian patients, which fact they suggested might have some connection with the reported hypotensive effects of L-DOPA. Andén’s group at Göteborg had also reported as early as 1963 that intravenous L-DOPA (67mg.kg⁻¹) increased the flexor response elicited by pinching the skin in acute spinal cats, indicating that exogenous L-DOPA could have effects at the spinal level.

In September 1975, the Fifth International Symposium on Parkinson’s disease was held in Vienna under the appropriate chairmanship of Birkmayer and Hornykiewicz and the sponsorship of Hoffmann-La Roche. The bulky volume of the proceedings is divided into three almost equal sections:

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357 Ericsson et al., 1971.
358 Ernst, 1965; Andén et al., 1967; Walsh et al., 1970; Sourkes, 1971b; see also Hornykiewicz, 1973a.
359 Barbeau et al., 1969b.
360 Andén et al., 1963a; see also Carlsson et al., 1963; Andén et al., 1966b.
biochemistry, neurophysiology and neuropharmacology of parkinsonism;
• tremor and akinesia;
• medical treatment of the disorder.361

The first section represented evidence for the massive strides which had been taken since 1970; whereas at the time of the commercial introduction of L-DOPA, the neurochemistry of the disease was largely restricted to the work of Hornykiewicz’ and Sourkes’ groups in the early and mid-1960s, a variety of directions were now being pursued, including the relationships between dopaminergic and cholinergic systems in the basal ganglia, the roles played by other transmitters, especially 5-HT and GABA, and the regulation of the synthesis, release and turnover of the various neuroactive substances. What had shortly before been rather vague and controversial ideas of specific neurochemical pathways and systems and their interrelationships were now beginning to assume definite contours. This had been made possible partly by the pioneering work of investigators such as Carlsson and Hornykiewicz, and also by the extensive mapping of the various central pathways in the second half of the 1960s, principally by Swedish groups; it was also promoted, however, by the success of the L-DOPA therapy and the exploitation of L-DOPA itself as a research tool, both in animals and man.

As Melvin Yahr noted in his concluding address, the meeting was the culmination of a process which had commenced with the Third International Symposium on Parkinson’s Disease in 1969, in which biochemistry of the disorder began to assume the role as major topic of discussion rather than thalamotomy and other surgical interventions, where the form of the meeting changed from an intimate gathering to the now familiar larger format. It is also represented the realization of the ideal which Doshay had promoted at the end of the 1950s: the cooperation of clinicians and scientists in the solution of a problem which was of both clinical and theoretical importance. This required the openness on both parts of the partnership exemplified in an anecdote related by Yahr.

I remember very well sitting next to a very seasoned clinician [at the 1969 meeting] that (sic) was watching some of the material being presented on the clinical effects of dopa in parkinsonism who kind of said to me, ‘Oh, I have seen lots of these drugs over the years, and this one will go up in smoke in a short period of time like all the others did.’ But what impressed him the most at that time was the demonstration by one of the Swedish group of what happened to a rat who had a nigral lesion.362

The section on medical treatment at the 1975 Vienna conference was largely devoted to long term experience with L-DOPA and the assessment of a variety of “adjuvant therapies”. L-DOPA therapy was not only no longer questioned, it had assumed the central position once occupied by the belladonna alkaloids and more recently by benzhexol and orphenadrine. It was reported that L-DOPA extended the life expectancy of the patients receiving it, and also returned a financial benefit to the community as a whole, principally through the reduction in stationary treatment of parkinsonism and in many cases the return of the patient to the workforce.363 The major issues now were the management of the side effects of L-DOPA therapy, particularly the involuntary movements which most speakers recognized as yielding further clues to the pathology

361 Birkmayer and Hornykiewicz, 1976.
of Parkinson’s disease (which, however, required decoding, a task which still demanded a great deal of work) and the choice of appropriate adjuvant therapy. Paul Pierre Castaigne and colleagues (various neurological clinics, Paris and Tours) and G. Selby (North Shore Hospital, Sydney) reported that the effects of L-DOPA declined with time; the progression of the disease might be slowed by L-DOPA, but it ground inexorably onwards.\footnote{Castaigne et al., 1976; Selby, 1976.} As a possible solution to this problem, the MAO-B inhibitor deprenil was introduced at the meeting by Birkmayer and his colleagues.\footnote{Birkmayer et al., 1976.}

The fact that tremor was not adequately controlled by L-DOPA was also addressed; Albrecht Struppler (Technical University of Munich) and Siegfried saw this as remaining the province of stereotactic surgery,\footnote{Struppler et al., 1976; Siegfried, 1976.} while Umbach and Völler argued that this indicated the need to retain some form of anticholinergic therapy for the foreseeable future, although he conceded that surgery was the only permanent solution for this symptom.\footnote{Umbach and Oppel, 1976; Voeller, 1976.} Tremor had long been a difficult symptom to treat; doubts were expressed at the end of the 1960s that the synthetic anticholinergic agents were more effective than the older belladonna alkaloids in this regard.\footnote{For example, Yahr and Duvoisin, 1968.} The response of resting tremor to L-DOPA therapy appears to be more variable than that of other cardinal symptoms, although improvement in about 50% of patients has been reported.\footnote{Koller, 1986.} It appears to be inferior to anticholinergic agents and dopamine receptor agonists, however, in the management of this symptom.\footnote{Laihinen et al., 1992; Deuschl, 1999.}

By 1975, L-DOPA therapy had thus firmly cemented its place in the therapy of Parkinson’s disease, and the 1975 conference in Vienna was both a celebration of this achievement – a more informed celebration that that of 1969 – and a sober assessment of the problems which still awaited resolution. Pelton and Chase wrote in this year that:

\begin{quote}
At least half of parkinsonian patients obtain more than a 50% improvement with L-dopa; included in this group are perhaps 10% of patients who experience a total remission of parkinsonian signs. Another 25% of patients have a fair response to L-dopa (20-49%), which equals or exceeds the response to conventional anticholinergic agents. . . . The remaining 20-25% of patients experience little (< 20%) or no benefit from relatively high doses of L-dopa, or more frequently are unable to tolerate ordinary therapeutic dose levels because of intolerable adverse effects.\footnote{Pelton and Chase, 1975. In this review, one page discussed the therapeutic benefits of L-DOPA therapy, nearly four the adverse side effects.}
\end{quote}

These treatment failures, and the frequency of untoward side effects in those who were responsive to therapy, however, were reminders that the ultimate therapy had not yet been achieved. The conditions for solving these problems, on the other hand, were better than in the past; not only had basic knowledge concerning the anatomical and neurochemical organization of the central nervous system greatly expanded in the previous twenty years, the research community – basic and clinical research – had also grown and become integrated on an international basis in a manner which would have been unthinkable in the 1950s. The preconditions for the rapid exchange of ideas and
results and for large scale cooperative studies ensured the maximum possible rate of advance would be achieved in the following years. Unfortunately, the magnitude of the problems to be addressed proved to be greater than initially expected; considerable advances have nevertheless been achieved.
XVI. Adjuncts and alternatives: The extension of dopamine-based therapy

By the end of 1970, it had been generally accepted that L-DOPA was the most effective therapy yet devised for parkinsonism, but was nonetheless not the final answer. There were many aspects of L-DOPA therapy which could be improved: the duration and reliability of its benefit, the peripheral and central adverse side effects, the degree and nature of the improvement achieved: all these issues demanded solutions, and it became quickly apparent that L-DOPA monotherapy probably required a series of adjuncts if it were to be exploited to its maximum capacity. At the Bel-Air Symposium on Catecholamines in December of this year, Carlsson listed the following as the best candidates for enhancing the effectiveness of L-DOPA therapy:

A. Dopa-potentiating agents:
   1. Peripheral decarboxylase inhibitors
   2. MAO inhibitors
   3. COMT inhibitors
   4. Amphetamine
   5. Membrane-pump blockers (e.g. desipramine)
   6. Anticholinergic agents
   7. Amantadine (mechanism unknown).

B. Dopa analogues (e.g. meta-tyrosine).

C. Agents stimulating dopamine receptors directly (apomorphine).

D. Receptor blocking agents.

E. Dopamine-β-hydroxylase inhibitors.¹

Most of these approaches would, in fact, be tried in the succeeding years, although not all within the time-frame of the current manuscript; many had already been tried during the pre-L-DOPA period. The first major advance was the use of peripherally acting decarboxylase inhibitors; ironically, the effect of one such agent had been examined and found praiseworthy before Cotzias had published his first paper on DOPA therapy.

¹ Carlsson, 1971; see also Carlsson, 1972.
Benserazid(e) (Ro 4-4602): the first peripheral decarboxylase inhibitor

The significance of this major development in the L-DOPA story had not been immediately widely recognized. Even those workers who found a positive effect with the DOPA therapy in the early 1960s were frustrated by the problem that its duration of action was quite short. This rendered the therapy somewhat impractical, especially if the intravenous route were to be further employed, as it was difficult to envisage how the therapy could be implemented outside the doctor’s clinic. If, on the other hand, the oral route was to be preferred, the amount of L-DOPA required was likely to make the therapy too expensive to be viable. There thus existed the urgent need for a means of prolonging the effectiveness of L-DOPA. Chance would play a remarkable role in the discovery of one such means.

Birkmayer and Hornykiewicz recognized that the duration of the L-DOPA effect might be extended if dopamine metabolism could be slowed. Their first attempt to prolong its benefit was thus the administration of MAO inhibitors. About 10% of patients, however, suffered side-effects sufficiently serious (including paranoia and hallucinations) to necessitate the termination of MAO inhibition. Nevertheless, some of Birkmayer’s success with L-DOPA throughout the 1960s might be ascribed to his continued employment of MAO inhibitors in those patients who could tolerate them, as will be discussed below. A second alternative would have been a depot form of L-DOPA which released amino acid continuously; this had been suggested by Birkmayer and was considered by Hoffmann-La Roche in the early 1960s, but the galenic difficulties associated with approach could not be overcome.

The major solution for the problem came, in fact, from an unexpected direction. Alfred Pletscher and his research group at Hoffmann-La Roche had concerned themselves with the investigation of enzyme inhibitors since the fortuitous discovery of the antidepressive and anti-anginal effects of iproniazid. Amongst these was the DOPA decarboxylase inhibitor α-methyl-DOPA, discovered by Sourkes in 1954. The compound was found to be useful in the clinic as a hypotensive agent, presumably by inhibiting noradrenaline synthesis. As its potency as a decarboxylase inhibitor was, however, rather moderate, the search for more potent inhibitors was initiated at a number of pharmaceutical companies, including Hoffmann-La Roche. One such candidate, Ro 4-4602 (= benserazide HCl), was an extremely potent decarboxylase inhibitor. This compound, synthesized by B. Hegedüs of Hoffmann-La Roche, was also of interest for another reason: it was the first decarboxylase inhibitor identified which did not interfere with other aspects of monoamine metabolism. The α-methylated aromatic amino acids, for instance, also appeared to stimulate monoamine release; carbonyl reagents, such as isoniazid and hydroxylamine (NH₂OH), were fairly weak decarboxylase inhibitors and seemed to require pyridoxal-5’-phosphate as cofactor. NSD 1034, was quite potent as a decarboxylase inhibitor but also acted as a MAO and dopamine-β-oxidase inhibitor. Brodie, Drain and colleagues, on the other hand, found

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3 Pletscher, 1985.
5 Burkard et al., 1962; Kuntzman et al., 1962. Nissbrandt et al. (1988) later reported that it also exhibited amphetamine-like dopamine-releasing properties in the rat; striatal DOPA accumulation was greater following the administration of this inhibitor than the more commonly employed NSD 1015.
that NSD 1034 (200mg.kg\(^{-1}\)) did not significantly affect 5-HT or dopamine levels in mice brain, but selectively reduced noradrenaline concentrations.\(^6\)

The agent was found to be a potent in vitro inhibitor of decarboxylase (using 5-HTP as substrate), and its action was independent of pyridoxal-5'-phosphate levels in the incubation medium. In vivo, it inhibited brain and peripheral decarboxylase in mice and guinea pigs without affecting MAO activity; this inhibition was reflected by a decline in catecholamine and 5-HT levels in the assayed organs.\(^7\) Unfortunately, even large doses of Ro 4-4602 (up to 10g) did not elicit a hypotensive effect, or indeed any notable effects, in human subjects. It was later recognized that this was due to the fact that DOPA decarboxylase is present at most physiological sites in excess, so that even 90% inhibition does not markedly reduce noradrenaline synthesis. It is now believed that the blood pressure-reducing effect of \(\alpha\)-methyl-DOPA is not due to decarboxylase inhibition, but rather to its conversion in the central nervous system to the “false transmitter” methyl-noradrenaline; this compound is then released from neurons by the same stimuli which release the actual transmitter. Its specific site of action is believed to be \(\alpha\)-adrenergic receptors in the brainstem, the stimulation of which reduces sympathetic outflow from the central nervous system. It is also possible that its further conversion to methyl-adrenaline may play a role in its hypotensive effect.\(^8\)

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\(^6\) Brodie \textit{et al.}, 1962; Drain \textit{et al.}, 1962.

\(^7\) \textit{Ibid.}

\(^8\) Hardman \textit{et al.}, 1996, pp.786-787.
The accounts of what happened next diverge slightly. Pletscher initially regarded the L-DOPA effect which Birkmayer had presented to him on film on October 26 1961 as "the best placebo effect that I had ever seen." According to Pletscher himself, as Ro 4-4602 was released for clinical examination in 1964, he recommended to Birkmayer that he administer the drug together with L-DOPA; should the L-DOPA effect be real and attributable to its conversion to dopamine, Ro 4-4602 should block its benefit. According to Birkmayer, Pletscher had advised him to try the drug in patients suffering from hypertonia and anxiousness. But Birkmayer had already observed the calming effect of α-methyl-DOPA on Huntington’s disease patients and decided to test the more potent decarboxylase inhibitor in these patients first; this was also logical, as Huntington’s disease and Parkinson’s disease were regarded in many ways as being mirror images of one another; atropine and scopolamine, for instance, act as anti-parkinsonian agents, but exacerbate the symptoms of Huntington’s disease. It was thus conceivable that a substance which reduced central amine levels might reduce choreic movements. In any case, Birkmayer administered the new decarboxylase inhibitor (3×150mg/day, p.o.) to Huntington’s disease subjects, only to find that their condition deteriorated to such an extent that the experiment had to be discontinued. Birkmayer reasoned that an agent which exacerbated Huntington’s disease might improve Parkinson’s disease, and so administered the drug to fifteen parkinsonian patients. The results were curious: he found that Ro 4-4602 intensified and extended the effect of L-DOPA.

Birkmayer discussed these results with Hornykiewicz; both were puzzled that a substance which blocked dopamine synthesis could have a positive influence on the L-DOPA effect. Hornykiewicz ultimately counselled Birkmayer that he should advise Pletscher of his observations if he were certain that there was no error; he himself would not ask to appear on any publication which resulted from the experiment, as he had not been directly involved and could contribute no rational pharmacological explanation for what Birkmayer had described. Birkmayer thus contacted Pletscher seven months after he had received Ro 4-4602 with the results of the experiment. Pletscher described his response thus:

This unexpected finding, which had been made through observational skills of indubitable integrity, . . . , made the researchers at Roche even more uncertain, but also more thoughtful. Pletscher’s group had in the meantime further advanced their investigation of Ro 4-4602, and soon afterwards discovered the solution to the apparent paradox. Ro 4-4602, in contrast to α-methyl-DOPA, is able to cross the blood-brain barrier only to a very small degree; the consequence was that it inhibited peripheral DOPA decarboxylase to a much greater extent than central nervous system DOPA decarboxylase. The result of this selectivity was that the combined administration of Ro 4-4602 and L-DOPA led to a much higher blood concentration of L-DOPA than when the amino acid was administered alone; further, the proportion of applied L-DOPA which reached the brain
was significantly increased, as was consequently the elevation of central dopamine levels. Pletscher and Bartholini’s finding appeared in *Nature* in 1967, and represented the biochemical basis for a combined L-DOPA/peripheral decarboxylase inhibitor therapy in Parkinson’s disease.\(^{15}\) Now assured that there was a rational explanation for his observations, Birkmayer’s paper (together with Maria Mentasti) describing the benefit of decarboxylase inhibitor supplementation of L-DOPA therapy appeared shortly afterwards, almost three years after he had first applied L-DOPA and Ro 4-4602 together.\(^{16}\)

At about the same time, Udenfriend’s group had found that the decarboxylase inhibitors D,L-\(\alpha\)-hydrazino-\(\alpha\)-3,4-dihydroxybenzylpropionic acid (MK 485; Merck, Sharp & Dohme);\(^{17}\) and 3-hydroxy-4-bromobenzylxoyamine (NSD-1055 = brocresine; also inhibits dopamine-\(\beta\)-oxidase) increased the \([3H]DOPA\)-induced increase in labelled brain dopamine and heart noradrenaline, but not brain noradrenaline in the guinea pig.\(^{18}\) Although animal experiments indicated that brocresine had at least limited access to the brain, a small study reported in 1973 that the inhibitor reduced the required L-DOPA dose in parkinsonian patients.\(^{19}\) It never achieved widespread application in antiparkinsonian therapy; as a histidine decarboxylase inhibitor, on the other hand, it has found some employment in the treatment of pruritis and chronic urticaria.\(^{20}\)

The use of a decarboxylase inhibitor allowed a number of changes to L-DOPA therapy:

- Improved intestinal absorption of L-DOPA, as gut decarboxylase was inhibited.
- The L-DOPA dose required could be reduced by about 80%, with a consequent reduction in the cost of the therapy. This was even more critical with oral L-DOPA therapy: Calne and colleagues would report in 1969 that only 1% of administered L-DOPA in this manner was available to the brain after peripheral metabolism.\(^{21}\)
- The inhibition of peripheral decarboxylation itself further reduced the incidence of peripherally mediated side effects: gastrointestinal reactions were reduced from 50% to 10%, serious cardiovascular responses from 20% to 5%.\(^{22}\) This rendered the therapy more acceptable for patients and reduced the number of those who terminated the treatment despite experiencing significant benefit.
- Greater ease of handling: it was possible to reduce the number of capsules required to 3-4 per day, as the effect of an individual L-DOPA dose was prolonged.
It was also possible to more rapidly determine the optimal maintenance dose for a patient, a process which could previously take months, and to achieve a therapeutic plateau. The first definite benefits of L-DOPA therapy could be achieved within two weeks rather than a month, as with L-DOPA alone.

According to some workers, the effect on tremor was more marked than with L-DOPA alone.23

There was initially, however, problems which threatened to prevent the broader application of Ro 4-4602 in Parkinson’s disease. It was noted in rats that chronic treatment with Ro 4-4602 led to bone deformations reminiscent of labyrinthism. Bone problems were the last thing to which parkinsonian patients could be exposed. It was discovered, however, that patients did not exhibit the deformities observed in the rat, and it was subsequently established that the decarboxylase inhibitor only had this effect on still developing bones; in rats this process is life-long, in humans it ends shortly after puberty. The hepatotoxicity of Ro 4-4602 in animal models also proved to be less significant in humans. Nevertheless, the toxicity seen in rats prevented the introduction of benserazide in America, and also inhibited Hoffmann-La Roche in releasing the drug for immediate use in Europe.24

Birkmayer had thus achieved another significant breakthrough in the treatment of Parkinson’s disease; the discovery of the benefits of the combined therapy is, indeed, reckoned by many observers to have been his greatest achievement in this field. It is thus somewhat surprising that his long delayed 1967 paper on the subject was so much more modest than his earlier papers on L-DOPA itself. This may have had many reasons. It was, for instance, amongst his first major research papers in the treatment of Parkinson’s disease which was prepared without Hornykiewicz. In his autobiographical writings, Birkmayer often emphasized the luck he had experienced in his collaboration with a series of colleagues who could complement his acute clinical skills with a deeper understanding of the biochemical and pharmacological issues involved.25 The discussion of the biochemistry of the Ro 4-4602 effect in this paper is limited to a précis of the Pletscher findings (which had been privately communicated to Birkmayer before the appearance of the paper). The second reason is that Birkmayer regarded the decarboxylase inhibitor at this stage as only one of several potential improvements of L-DOPA therapy; in the same paper, he also described how the tyrosine hydroxylase inhibitor α-methyl-p-tyrosine (200mg i.v.) led to a marked deterioration of parkinsonian symptoms (and sedation of choreic patients). Birkmayer attempted to stimulate tyrosinase activity26 by supplying p-tyrosine (200mg i.v.) and the co-factor for the enzyme, nicotinamide adenine dinucleotide diphosphate (NADH; 20mg i.v.); the combination produced a kinetic effect in some patients comparable with that of L-DOPA /Ro 4-4602, supporting Birkmayer’s suspicion that the conversion of tyrosine to L-DOPA was deficient in parkinsonism. This therapeutic approach, however, was not further pursued at this stage.27

23 Fazio et al., 1972.
24 Pletscher, 1985; see also discussion in I.I., 1970a,c.
26 At the time that these experiments commenced (1965), tyrosine hydroxylase had only recently been discovered (Nagatsu et al., 1964a, 1964b); Birkmayer continued for many years to use the terms ‘tyrosinase’ and ‘tyrosine hydroxylase’ interchangeably.
27 Birkmayer and Mentasti, 1967.
In the period 1967-1969, the combination of L-DOPA and Ro 4-4602 was intensively investigated in Vienna, Zürich and Geneva.28 Pletscher, Bartholini and Tissot argued at the Third Symposium on Parkinson’s Disease (Edinburgh, 20-22 May, 1968) that the “selective increase of cerebral dopamine [was] a therapeutic possibility in Parkinson’s disease”, referring to their own tracer studies in the rat and the preliminary results from Birkmayer’s clinic (as a personal communication).29 Shortly afterwards, further reports of positive experiences with the combination therapy in Switzerland were published by Siegfried (Neurosurgery Clinic, State Hospital, Zürich)30 and by Tissot and their colleagues (Psychiatric and Neurological Clinic, Geneva University, Geneva), who also demonstrated increased plasma L-DOPA concentrations in patients co-treated with the inhibitor.31

In the following years, Birkmayer became more confident of his finding, both as a result of its confirmation by other groups, and also as result of the renewed interest in L-DOPA itself stimulated by the high dose therapy being introduced by Cotzias in New York; Birkmayer noted this latter event, however, a little ruefully: “Gifted children are often claimed by several fathers. L-DOPA is such a gifted child.”32 After a résumé of the history of the DOPA therapy up until 1969, Birkmayer reported an experimental series with ten parkinsonian patients; their responses to the combined L-DOPA/Ro 4-4602 therapy was analyzed objectively with a physiological acceleration transducer, which measured the force of a thrusting motion. He showed that the combination therapy (each 450mg p.o.) was more effective than L-DOPA alone; it is significant that Birkmayer was now prepared and able to administer L-DOPA orally, having recognized the Cotzias challenge. The significance of this result was clear:

A report from the year 1967 by Cotzias confirmed the beneficial DOPA effect in parkinsonian patients with high doses of L-DOPA (sic) (up to 16g per day), although with increased side-effects, above all leukocytopenia. Duvoisin and Yahr have also recently reported the beneficial kinetic effect after high oral L-DOPA doses (6g pro die). One must however keep in mind that by such high doses not only is the presentation of side-effects increased, but that genuine toxic side-effects are also possible, especially as a therapy for parkinsonian patients stretches over a period of decades.33

For Birkmayer, the avoidance of these reactions was as important as extending the duration of the kinetic effect of L-DOPA, and that was why he regarded the decarboxylase inhibitor adjunct as so important. By 1971, he had treated eighty cases with oral L-DOPA and Ro 4-4602, achieving significant kinetic improvement in fifty-five (60%).34 He now regarded the essential parkinsonian therapy as a combination of

28 Birkmayer, 1969a; Siegfried et al., 1969; Tissot et al., 1969b, 1969c. For comprehensive list of references, see Birkmayer and Kapp, 1975.
29 Bartholini et al., 1969.
30 Siegfried et al., 1969. Curiously, Siegfried’s group cast doubt on the early positive results gained with L-DOPA alone on the basis that only small amounts of the amino acid reach the blood from the gastrointestinal tract; they seemed unaware that both Viennese groups applied L-DOPA intravenously.
31 Tissot et al., 1969a, 1969b, Geissbühler et al., 1972b.
32 Birkmayer, 1969a. In 1971(a), Birkmayer listed the “decisive steps in the development of the L-DOPA therapy for the Parkinson syndrome”, commencing with his own 1958 suggestion to measure brain amines, via Carlsson, Hornykiewicz, Degkwitz, Barbeau and Sourkes and Pletscher, and ending with the high dose therapy of Cotzias. He ended with: “If these data were fed into a computer, the percentage contribution of the individual contributions could be calculated. Whatever the result, Vienna would certainly not do badly.”
33 Birkmayer, 1969a.
34 Birkmayer, 1971a.
anticholinergic drugs, L-DOPA and decarboxylase inhibitor, together with an antidepressant to potentiate monoaminergic function; even now he did not see L-DOPA as a possible monotherapy.35

Interestingly, the following brief news item appeared in the Deutsches Ärzteblatt on 30 August 1969:

_The Canadian A. Barbeau, University of Montreal, has reported promising experiences with a combination of the anti-parkinsonian drug L-DOPA and the experimental substance RO-4-4602, developed in Switzerland. This substance appears to work as a sort of pacemaker for L-DOPA and allows it to enter the brain in greater concentrations. This combination therapy consequently allows a lower dosage of L-DOPA and a corresponding restriction of its undesirable side-effects on other tissues._36

The news had thus travelled around the world and back. Barbeau’s group, the first to employ the Roche decarboxylase inhibitor in North America, made their first major presentation on the combination therapy at the Bel-Air Symposium in Geneva in September 1970 (Monoamines noyaux gris centraux et syndrome de Parkinson).37 This assembly of many of the leading basic and clinical researchers in field of extrapyramidal disease devoted a great deal of its attention to the new therapeutic possibility; Cotzias’ demonstration of the effectiveness of the L-DOPA therapy was not sufficient to conceal the problems which still plagued its implementation. Barbeau commenced his presentation with the bold “_The efficacy of L-dihydroxyphenylalanine (L-DOPA) in Parkinson’s disease has now been proven beyond any reasonable doubt._”38 Comparing oral L-DOPA alone and in combination with Ro 4-4602 in two groups of twenty patients each – and claiming incorrectly that this had never been done before – the Canadians found that the a number of advantages for the combination therapy:

- The maintenance dose after three months was 4300mg/day in the L-DOPA group, 800mg/day in the combination group.
- In the combination group, there were nine patients in the “excellent” response group, compared with three in the L-DOPA group; similarly, there was only a single patient in the “poor” response category, compared with three in the L-DOPA group.
- The incidence of some side-effects was reduced: nausea (20 v. 45%), psychic disturbances (5 v. 20%), bradykinesia (0 v. 30%). Involuntary movements (30-40%) and hypotension (15-20%) were similar in the two groups.39

The reduction in centrally determined adverse effects of L-DOPA therapy was an unexpected bonus of decarboxylase inhibition: Barbeau noticed in particular the absence of freezing episodes and a reduction in abnormal movements, although he also remarked that if they did appear, the latter tended to appear earlier and to be more resistant to amelioration.40

35 Birkmayer, 1971b.
38 Barbeau _et al._, 1971c.
39 _Ibid._
40 _Ibid._
adjuncts and alternatives: extension of dopamine-based therapy

In his summation of the biochemistry session, Carlsson placed decarboxylase inhibitors at the head of his list of possible modifications of the L-DOPA therapy, reflecting the interest in the approach which had been expressed at the meeting. Ziegler’s group at Hoffmann-La Roche (Basel) and Theiss und Schärer (Basel) reported on the lack of toxicity of the therapeutic combination in animals and humans. An interesting finding reported at this meeting was reported by Constantinidis and Geissbuhler (Hoffmann-La Roche, Basel); they presented evidence that Ro 4-4602 penetrated the capillary cytoplasm more efficiently than it did the brain parenchyma, thus providing a further element in the explanation of the benefit provided the combination therapy. As discussed above, capillary decarboxylase acted as an enzymatic barrier against the passage of L-DOPA into the central nervous system; indeed, only at concentrations of greater than 50mg.kg\(^{-1}\) did L-DOPA enter the brain in significant quantities. The findings of the Roche investigators meant that differing doses of Ro 4-4602 would be required to achieve inhibition of the enzyme in the capillary beds of various brain regions; the fact that the activity in the substantia nigra capillaries was particularly low explained the preferential accumulation of dopamine in the basal ganglia following L-DOPA administration. The same group had presented evidence that decarboxylase inhibition also increased the preferential localization of brain L-DOPA in the basal ganglia, thus possibly contributing to reduction of central adverse effects. (table 16-1; figure 16-3). Carlsson also mentioned in his summation that both he and Bertler’s group had found that injected L-DOPA was converted into dopamine in the brain capillaries, so that the blood-brain barrier was at least partly enzymatic with respect to the passage of L-DOPA; this finding corresponded well with the findings of Constantinidis and colleagues.

At the 1970 conference on the Hoffmann-La Roche Cooperative Study in America, Pletscher and Bartholini reported that of the available options for inhibition of peripheral decarboxylase, α-methyldopa was too weak. The hydrazine derivatives

<table>
<thead>
<tr>
<th>Region</th>
<th>Benserazide dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral cortex</td>
<td>10mg.kg(^{-1})</td>
</tr>
<tr>
<td>Cerebellar cortex</td>
<td>15mg.kg(^{-1})</td>
</tr>
<tr>
<td>Striatum</td>
<td>8mg.kg(^{-1})</td>
</tr>
<tr>
<td>Substantia nigra</td>
<td>4mg.kg(^{-1})</td>
</tr>
<tr>
<td>Raphe</td>
<td>50mg.kg(^{-1})</td>
</tr>
</tbody>
</table>

Table 16-1: Benserazide dose required to eliminate L-DOPA-induced fluorescence of capillary epithelium in defined brain regions of the rat, as reported by Constantinidis et al., 1970.

Figure 16-3: Distribution of labelled catecholamines in rat brain two hours after intraperitoneal administration of 5mg.kg\(^{-1}\) \(^{14}\)C-L-DOPA, as reported by Bartholini and Pletscher, 1968.

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42 Ziegler et al., 1971; Theiss and Schärer, 1971.
43 Constantinidis and Geissbuhler, 1971; see also Constantinidis et al., 1970, and Bartholini and Pletscher, 1968.
NSD1015 and Ro 4-4602 were potent compounds, the effects of which on the elevation of central catecholamines levels increased with dose to a maximum point, and then declined; the range for NSD 1015, however, was very narrow, possibly due to its greater ability to cross the blood-brain barrier. MK-485 (see below) was less potent than the other hydrazines, but showed no tailing off of its effect in the normal therapeutic range (figure 16-4); its penetration of the brain parenchyma was also negligible at these doses. These authors also reported a phenomenon which would later be invoked to explain some of the side effects of L-DOPA therapy: L-DOPA together with Ro 4-4602 reduced central 5-HT levels, presumably by competition of L-DOPA with 5-HTP for penetration of various tissues, including the brain, the displacement of 5-HT from its normal stores by dopamine and the competitive inhibition of 5-HTP decarboxylation by L-DOPA.45

![Figure 16-4: Effect of various decarboxylase inhibitors on 14C-L-DOPA induced rise in rat brain 14C-catecholamine levels, as reported by Pletscher and Bartholini, 1971. Each inhibitor was administered 30 minutes before 3mg.kg^-1 L-DOPA; the animals were sacrificed 60 minutes following L-DOPA administration.]

This response had been suggested by some workers to be involved in the increase in tremor seen in some L-DOPA-treated patients.46

Following this meeting, the combination therapy was trialled in a number of clinics around the world (forty-seven centres in seven countries by 1973)47, meeting with great approval. The question was addressed of the appropriate relationship of dose of the two agents; Birkmayer tended towards 1:1, but adjusted the ratio according to the responses of individual patients, but the 4:1 ratio (L-DOPA: Ro 4-4602) was gradually accepted as appropriate in the most cases.48 Rinne's group found in 1972 that this ratio reduced the required dose of L-DOPA by 80% to produce a given plasma level. The authors noted, however, that both Birkmayer's and Siegfried's groups found that the incidence of involuntary movements was reduced with a ratio of 1-1½:1, a finding which contrasted with the experiences of those using the higher ratio.49 Nevertheless, the 4:1 ratio was ultimately accepted as standard.

45 Pletscher and Bartholini, 1971.
48 Barbeau, 1971a; Birkmayer, 1971a. The combination received the test designation Ro 8-0576.
49 Rinne et al., 1972.
Carbidopa (MK 485/MK 486)

Cotzias first described the use of decarboxylase inhibitors in his classic 1969 paper on the use of L-DOPA in parkinsonism. They chose to use D,L-α-methyl-DOPA hydrazine (MK 485, D,L-α-hydrazino-α-3,4-dihydroxybenzylpropionic acid; Merck, Sharp & Dohme); the source for the choice was identified as Carlsson, and the rationale for this approach was the finding by Udenfriend’s group that the substance potentiated the elevation of central dopamine levels by DOPA in animals.\(^{50}\) Inhibition of DOPA decarboxylase by the hydrazino derivative of α-methyl-DOPA had been reported in the early 1960s;\(^{51}\) Pletscher and Bartholini reported in the same year as Cotzias’ publication that MK-485 did not appreciably inhibit brain decarboxylase in animals, even at higher doses.\(^{52}\) Cotzias regarded MK-485 as superior to “another such inhibitor used in Europe” (benserazide was not actually named) on the basis that it “remained exclusively outside the brain regardless of dose.”\(^{53}\) The effects of α-methyl-DOPA, the best characterized decarboxylase inhibitor and the only one licensed for use in the clinic in America at the time, were also examined in a single Huntington’s disease patient.

As described above, Cotzias administered L-DOPA to twenty-eight therapy-resistant parkinsonian patients after discontinuing previous medication. The administered dose of L-DOPA was gradually raised from 3×100mg/day until the optimal dose (maximally 8g per day) was achieved after five to seven weeks. The same protocol was used when examining the effect of α-methyl-DOPA. When testing the effect of MK-485, L-DOPA therapy was abruptly discontinued until symptoms and urinary dopamine and HVA concentrations indicated a return to pre-treatment levels. The inhibitor was then administered six times a day, commencing at 100mg and increasing over a week to 250mg per administration; L-DOPA was then added, initially at 3×5mg/day, and increased until the response matched that for L-DOPA alone.

It is apparent from the results reported that Cotzias administered MK-485 together with L-DOPA to only three patients; two were suffering severe side-effects with L-DOPA alone (one with nausea, the other with choreiform movements), while the third was virtually “normal”. A gradual steady improvement was observed in two patients; but in the third, who had previously complained of abnormal movements, the sharp symptomatic improvement in the parkinsonism following the combined therapy was matched by the worsening of this side effect. In all cases, the required L-DOPA dose was markedly reduced. The clinical potential of decarboxylase inhibitors in parkinsonism, however, was not further discussed at this point.\(^{54}\)

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\(^{50}\) Udenfriend et al., 1966.

\(^{51}\) Porter et al., 1962; Sjoerdsma et al., 1963.

\(^{52}\) Bartholini and Pletscher, 1969.

\(^{53}\) Cotzias, 1972/73. In 1972, Cotzias referred to Ro 4-4602 simply as “the one used abroad”; Papavasiliou et al., 1972.

\(^{54}\) Cotzias et al., 1969a.
There was no indication in this paper that a major advance had been introduced – Cotzias seemed more interested in the use of decarboxylase inhibitors for “dissecting” the L-DOPA effect into its putative components –

*Despite their usefulness, the therapeutic effects are primarily tools for further investigation, of equal potential to the side effects.*

But this attitude quickly changed. As early as the licensing of L-DOPA by the FDA, suggestions had been made to potentiate the effect of the amino acid with either a decarboxylase inhibitor or amantadine. Research by various groups confirmed that MK-485 potentiated the central effects of L-DOPA while reducing its peripheral consequences, and investigation of brain decarboxylase also received greater attention, with Lloyd and Hornykiewicz reporting reduced striatal decarboxylase activity in parkinsonian patients. This stimulated wider interest in the possibilities of a topographically specific decarboxylase inhibitor in antiparkinsonian therapy. From 1972, Cotzias published a number of papers promoting the combination of L-DOPA and the L-isomer of the inhibitor (MK-486; carbidopa). The same benefits as were achieved with Ro 4-4602 were accomplished by MK-486; most impressive for Cotzias was the fact that diurnal fluctuations in response to L-DOPA were dampened, although the price for this benefit was often the earlier presentation of more severe abnormal involuntary movements. He was also satisfied with the biochemical dissection of the disorder which the drug permitted him: for instance, hypotension, involuntary movements and mental aberrations could be potentiated by the agent, strongly suggestive of their central origin. Cotzias also established that the employment of MK-486 was compatible with that of conventional antiparkinsonian drugs. Thomas Chase (National Institutes of Health, Bethesda) reported to the 1970 Eaton Laboratories-sponsored symposium that the combination of MK-485 with L-DOPA allowed a reduction in the dose of the latter by up to 75% in eight patients he had tested; the side effects of nausea and emesis were abolished, but the involuntary movements associated with high dose L-DOPA therapy were still present. A series of studies by a number of (mostly) American groups were published during the next few years confirming Chase’s report and Cotzias’ earlier findings.

As with L-DOPA itself; however, Cotzias tended to overlook European research; for example, he wrote that this decarboxylase inhibitor:

*is unique both in therapy and in research, in that it remains strictly within peripheral tissues whenever the blood-brain barrier is intact.*

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55 Ibid.
56 Anonymus, 1970b.
57 For example: Butcher and Engel, 1969; Butcher et al., 1970; Lotti and Porter, 1970; Strömberg, 1970.
60 Papavasiliou et al., 1972.
62 Yahr et al., 1971; Calne et al., 1971; Marsden et al., 1973a,b; Schwartz et al., 1973; Lieberman et al., 1975a.
63 Cotzias et al. 1973. Similarly, in his 1972/73 paper on the use of carbidopa, his reference for reduced dopamine and 5-HT levels in parkinsonism was one of his own reviews (Cotzias, 1971).
The Swiss product benserazide was presumably disregarded on the basis it was not licensed for the clinic in America, and did have some access to the central nervous system, albeit an extremely limited access. The priority issue was of such concern (not without some justification) to Wolfgang Kapp (Hoffmann-La Roche, Basel) that he and Birkmayer released a brochure in 1975 describing in detail the emergence of the concept in Switzerland and Austria. Nevertheless, Cotzias’ contribution to the field cannot be overestimated, and both the clinical and theoretical conclusions which he drew on the basis of the effects of the combined L-DOPA/decarboxylase inhibitor therapy were invaluable, especially when validated by parallel results with benserazide in Europe.

Cotzias had also been confronted by the problem that a large proportion of the administered L-DOPA was converted to dopamine before it had crossed the blood-brain barrier. But, as might be expected, he also cited at various times a number of other motives for trying decarboxylase inhibitors in antiparkinsonian therapy. In December 1971, Cotzias was being frustrated by both the abnormal movements and the diurnal fluctuations of response which his patients exhibited. Part of the problem, he hypothesized, was that L-DOPA or one of its metabolites “was imprinting a memory of the drug’s passage upon the tissues including the brain.” This was explored by use of the dopamine receptor agonist apomorphine, as will be discussed below. The other possibility which occurred to Cotzias was that dopamine or a peripherally produced metabolite was responsible for the observed adverse effects; according to this review, he had therefore used MK-485 – by this point, in a total of fifteen patients and at doses of up to 1500mg – to block the production of this putative metabolite. This is clearly different from the rationale given in his 1969 paper. The early emergence of abnormal movements convinced him that the hypothesis was aberrant, but diurnal fluctuations were reduced by this approach, leading Cotzias to the new hypothesis:

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\text{metabolites located in the periphery compete for the entrance of levodopa into the brain, thus imposing a block in the path of levodopa. Whenever this block was in effect, hypokinetic episodes would ensue. Whenever the block was overcome by levodopa, the brain would be flooded with the drug. If that flooded brain had been previously sensitized to the action of levodopa, involuntary movements would emerge during such flooding.}
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Cotzias examined this blocking effect of L-DOPA metabolites dopamine or DOPAC in an animal model, and also found that their effect was enhanced by MK-485. The behavioral effects of apomorphine, however, were not affected by the three substances. Cotzias thus concluded that his hypothesis was correct, and that an L-DOPA analog might overcome the block which inhibited the passage of L-DOPA itself. The methyl ester of L-DOPA, first examined by Carlsson in the early 1960s, was tested, and appeared to pass the presumed block, but its effectiveness was also enhanced by MK-485, so that Cotzias decided that its major advantage was its more efficient gastrointestinal absorption.
According to his 1972/73 review, on the other hand, his motivation for the use of a decarboxylase inhibitor in combination with L-DOPA by the observation on the ward that the effect of L-DOPA was negated in some patients by a high protein meal; this effect could occur immediately after the meal or with a delay of some hours. Two possibilities were considered:

- the amino acids in the meal competed with L-DOPA either at the level of gastrointestinal absorption or at the level of entry into the brain;
- excessive catabolism of L-DOPA was occurring in peripheral tissues.69

Cotzias conducted dietary experiments with his patients which ultimately led him to dismissing the first of these alternatives.70 Cotzias had thus linked his introduction of MK-485/486 in the clinic to a variety of hypotheses; ultimately, however, it was accepted because it worked.

Another interesting benefit of treatment with a decarboxylase inhibitor which was that it allowed the use of pyridoxine in L-DOPA-treated patients. As was discussed earlier, vitamin B₆ had been used in parkinsonian patients since the 1940s, albeit with disputed benefit. As the vitamin is the co-factor for DOPA decarboxylase, many workers added pyridoxine to their treatment schedule after the introduction of L-DOPA therapy, and were both dismayed and puzzled to find that even very small doses were capable of abolishing the benefits (and central side effects) of L-DOPA.71 Stimulation of peripheral L-DOPA decarboxylation was presumed to underlie this effect, leading to the preparation of special pyridoxine-free vitamin preparations and diets for parkinsonian patients. As expected, use of a decarboxylase inhibitor removed this obstacle, and pyridoxine could again be freely used in combination with L-DOPA therapy.72 It is interesting to note that hydrazines, such as MK-486, were reported at this time as being capable of inducing pyridoxine deficiency.73

**Combination preparations**

The combination of L-DOPA with a decarboxylase inhibitor was commercially launched in Europe in 1973 by Hoffmann-La Roche as ‘Madopar 125’ capsules (100mg L-DOPA, 25mg benserazide)74 and in the United States in 1972 by Merck, Sharp & Dohme as ‘Sinemet’ tablets (250mg L-DOPA, 25mg carbidopa)75. Pletscher noted in a historical review in 1997 that sales of Madopar had continually risen since its introduction; despite the marketing of a number of alternative agents, it had maintained its place in the arsenal of the clinician treating parkinsonism.76 The major advantages of the combination therapy have been recognized in the long term as the following:

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69 Cotzias, 1972/73.
70 Cotzias et al., 1973.
71 Duvoisin et al., 1969b; Jameson, 1970; Leon et al., 1971.
72 Papavasiliou et al., 1972a; Calne et al., 1971; Klawans et al., 1971.
73 Holtz and Palm, 1964, Sourkes, 1966a; Cornish, 1969.
74 Also available as Madopar 250 (200mg L-DOPA, 50mg benserazide). Madopar was initially introduced in Switzerland, then Austria; according to Sittig (1988), it became available in Italy in 1974, and in England, France and Germany in 1975.
75 Also available as Sinemet 110 (100mg L-DOPA, 10mg carbidopa). According to Sittig (1988), Sinemet became available in Italy and England in 1974, and in France, Germany (where it was named ‘Nacom’) and the United States in 1975.
76 Pletscher, 1997.
• Reduction of the optimal L-DOPA dose by about 75-80%.
• Peripheral side-effects are significantly reduced (but not abolished);\textsuperscript{77} in particular, nausea associated with stimulation of the medullary emetic centre is avoided, and cardiovascular effects are minimized.
• Achievement of the therapeutic dose is accelerated by the fact that development of tolerance of the peripheral side-effects is not as necessary.
• Antagonism of the L-DOPA effect by pyridoxine is not a problem.
• The percentage of “good responders” is increased compared with L-DOPA as monotherapy.\textsuperscript{78}

The major side-effects include, not unexpectedly, the exacerbation of the untoward responses associated with the central effects of L-DOPA itself; abnormal involuntary movements, oscillations in performance and disturbing mental effects appear to be the major problem in this regard, appearing earlier in the course of the therapy and often in a more severe form. Neither benserazide nor carbidopa themselves appear to be associated with any significant degree of toxicity, which is somewhat surprising, given their non-specific suppression of aromatic amino acid decarboxylation processes in the periphery; high levels of decarboxylase activity and the availability of alternative metabolic pathways presumably underlie the apparent innocuous nature of the drug.\textsuperscript{79} In America, benserazide has not been licensed for use in humans, so that only the alternative, carbidopa, is employed here; both inhibitors may be used in most other countries. It has generally been found that the two are equally effective, although there have been reports of individual patients tolerating one or the other better. Lieberman and colleagues, for example, reported that L-DOPA levels were higher, but with a shorter half-life, in four patients when treated with ‘Madopar’ than with ‘Sinemet’; there was no difference in symptomatic relief, but L-DOPA levels were lower and half-life was shorter in patients with on-off phenomena.\textsuperscript{80}

It is interesting to note that the two decarboxylase inhibitors examined in the 1960s remain the only members of this class licensed for use in the therapy of parkinsonism.

**MAO inhibitors: the beginnings**

MAO plays a major role in the in vivo inactivation of biogenic and diet-derived amines in both the central nervous system and in peripheral neurons and tissues. The most important substrates for the enzyme in the central nervous system are the catecholamine neurotransmitters (dopamine, adrenaline and noradrenaline), 5-HT and β-phenethylamine (PEA). The monoamine deficiency hypothesis of parkinsonism required that this deficiency be compensated. Apart from direct supplementation of the missing transmitter, inhibition of its catabolism would also be expected to be of benefit, assuming that synthesis of the transmitter was adequate. An advantage of this approach was that it was not necessary to identify whether the crucial transmitter was dopamine, norepinephrine or 5-HT, as all three are catabolized by MAO. Further, if, for example, L-DOPA was used to elevate central dopamine levels, the concurrent use of a MAO inhibitor would be expected to prolong its effects by delaying dopamine catabolism.

\textsuperscript{77} Rinne and Mölsä, 1979.
\textsuperscript{78} Examples of reports on combination treatment: Przuntek, 1973; Steinhäusl, 1973; Völler and Muschard, 1973; Feise and Paal, 1974; Gehlen and Eisenlohr, 1974.
\textsuperscript{79} For interference in tryptophan and niacin metabolism, see Bender et al., 1979, Bender, 1980.
\textsuperscript{80} Lieberman et al., 1978. See review in Pinder et al., 1975.
Oxidative deamination of primary amines had been described as early as 1877 by Schmiedeberg, but MAO was first described and assayed by the Bathurst (doctoral) Student Mary L.C. Hare (Biochemical Laboratory, Cambridge; later Mary Bernheim (1902-1997), Department of Biochemistry, Duke University School of Medicine, Durham) in 1928; she named it tyramine oxidase. It had previously been assumed that the major deamination pathway for amines involved their hydrolysis to the corresponding alcohol. Hare was unlucky in that when she chose to examine adrenaline as the substrate of her assay, and found that it was not “attacked” by the enzyme; auto-oxidation of the catecholamine precluded any success with the method used (the Barcroft differential manometer), and thus obscured the full significance of her discovery. A number of other substances, including tyrosine, phenylalanine and DOPA were also found to be unaffected by the enzyme. She recognized that it was distinct from tyrosinase, because it was not inhibited by cyanide; she also noted that it represented the first departure from Warburg’s rule that all cellular oxidation requires iron. She concluded that it was possible, but unlikely, that tyramine oxidase might normally act to metabolize endogenous tyramine or a related compound; this, however, would presuppose the decarboxylation of tyrosine, and thus of an entirely new mode of amino acid catabolism.

Bernheim-Hare’s papers did not attract the attention they deserved, and the enzyme was rediscovered nearly a decade later by Pugh and Wastel (in the brain: “amine oxidase”) and Blaschko’s group (“adrenaline oxidase”) in 1937; Zeller recommended in 1938 the name “monoamine oxidase” in order to distinguish it from diamine oxidase. In the same year, Gaddum and Kwiatkowski (University College, London) suggested that some agents, including ephedrine, might achieve some of their effects by inhibition of amine oxidase. It was Blaschko’s group which subsequently delivered most of the information regarding distribution, reaction paths and substrates which constituted the basis of knowledge regarding the enzyme until the 1960s. Blaschko, however, always acknowledged Hare in his historical reviews of the subject. The role of MAO was not initially clear; Blaschko himself hypothesized that it might prevent dietary amines from entering the circulation.

With remarkable prescience, Hans Birkhäuser (University Medical Clinic, Basel) suggested in 1940 that the distribution of MAO in the human brain might yield clues regarding central nervous system disease, and, employing a modification of the Warburg manometric method used by Blaschko’s laboratory, found the highest levels in thalamus and caudatus, somewhat lower activity in putamen, with lower values in pallidum and cortex. A quarter century would pass before the next report on regional MAO levels in human brain.

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81 Schmiedeberg, 1877.
82 Hare, 1928. It is notable that she should have identified the substrate which would later prove to be a problem in the clinical application of MAO inhibitors.
83 Ibid.; see also Bernheim, 1931. Hare married Frederick Bernheim, a biochemist later noted for his research on anti-tuberculosis agents, shortly after the publication of her first paper on tyramine oxidase. It is thus a little ironic that the first recognized MAO inhibitor should later arise from research into tuberculostats.
84 Blaschko et al., 1937; Pugh and Quastel, 1937.
85 Zeller, 1938.
86 Gaddum and Kwiatkowski, 1938.
87 For example: Blaschko, 1952; 1972.
88 Blaschko, 1952.
89 Birkhäuser, 1940.
Hoffmann-La Roche had discovered the hydrazine derivatives *isoniazid* (‘Rimifon’) and *iproniazid* (‘Marsilid’) in the course of their search for more effective drugs for the treatment of tuberculosis; isoniazid was first synthesized in 1951 as a pyridine analog of the German *thiacetazone* (‘Tibione’; Riker). Zeller demonstrated in 1952 that iproniazid, in contrast to isoniazid, was a MAO inhibitor. By this time the energizing effects of iproniazid, but not isoniazid, had surprised staff in tuberculosis wards, and it was suggested that it might be useful in the treatment of depression. George Crane was one of the first to realize that such an agent might also be serviceable in the treatment of psychiatric patients, having noted its psychiatric ‘side effects’ in tuberculous patients. The first journal reports of its successful application in psychiatric patients was published in 1957 by Loomer, Saunders and Kline; twelve of seventeen chronically institutionalized depressed patients responded favorably to $3 \times 50\text{mg/day}$ iproniazid. The authors concluded:

> Whatever the mechanism of iproniazid may be, it would appear as though with it a new pharmacological approach is now available for adjunctive therapy in psychiatry.

Within a few years, a number of other hydrazine derivatives were produced by various pharmaceutical companies, the most successful of which was phenelzine sulphate (Nardil; Warner-Chilcott). Iproniazid itself lost FDA approval in the early 1960s due to concerns about hepatotoxicity.

The MAO-inhibiting properties of iproniazid thus became known at a time when interest in the neurochemistry of central catecholamines was increasing. Brodie’s group reported in 1956 that the consecutive administration of iproniazid and reserpine to rats led to increased motor activity in rats rather than the sedation to be expected from reserpine. Carlsson established in 1957 that iproniazid alone did not reverse reserpine-induced sedation, but also that it enhanced the waking effects of D,L-DOPA in reserpinized animals. England and Schwab had tried low doses of iproniazid in parkinsonian patients without success in 1959, but feared that the potential hepatotoxicity of the hydrazine derivative rendered it too dangerous for regular use. Hornykiewicz and Holzer had reported in 1959 that the MAO inhibitors harmine and iproniazid elevated central dopamine levels in the rat; harmine had, as discussed, been

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90 4-Pyridinecarboxylic acid hydrazide; isonicotinoylhydrazine (INH). U.S. patent to Hoffmann-La Roche: 1952.
91 4-Pyridinecarboxylic acid 2-(1-methylethyl)hydrazide.
93 Zeller and Barsky, 1952; Zeller *et al.*, 1952a, 1952b.
94 Crane, 1956.
95 Loomer *et al.*, 1957. The rationale for the use of iproniazid in depression led to legal proceedings in 1981 between two of the erstwhile colleagues involved in this breakthrough; Kline maintained that it was suggested by the animal studies of iproniazid reported by Brodie’s (1956) and Chessin’s (1956) groups (this rationale was cited in the 1957 paper), which reported that animals pretreated with iproniazid were not sedated by reserpine, becoming instead overactive. Saunders claimed in 1959 that he had suggested its use in psychiatric patients in 1955 as a result of his theoretical considerations regarding the effect of MAO inhibition on brain catecholamines. Saunders won the case in the U.S. Supreme Court in 1980; he also won the appeal. Maxwell and Eckhardt, pp.148-149; see also Kline and Cooper, 1980.
97 See Kline, 1970.
98 Brodie *et al.*, 1956.
100 England and Schwab, 1959.
used thirty years earlier to treat parkinsonism, but had since fallen out of favour.\textsuperscript{101} Harmine, in contrast to iproniazid, is a reversible inhibitor of MAO, so that its effects are much more short-lived. In order to achieve a significant change in central catecholamine levels, however, sustained suppression of MAO inhibition is required.

Sano found that either of the MAO inhibitors iproniazid and pheniprazine\textsuperscript{102} enhanced central dopamine levels in the normal and reserpinized rat; he also found that these drugs produced some improvement in the rigor and tremor of a small number of parkinsonian patients, and recorded the observation that they themselves felt best when treated with it in combination with D,L-DOPA.\textsuperscript{103} Muether and colleagues (St Louis University School of Medicine, Clayton 5) reported in 1961 that they had treated seven parkinsonian patients (four arteriosclerotic, three doubtfully post-encephalitic) with the new MAO inhibitor $\alpha$-ethyltryptamine acetate (‘Monase’, Upjohn; 50mg).\textsuperscript{104} The three post-encephalitic cases showed no response to this addition to their treatment, two of whom experienced “irritability, a strange indescribable sensation, and unpleasant dreams.” The four arteriosclerotic patients showed fair to good improvement, with no side effects; in one case, tremor was abolished during treatment. The authors, who were investigating the possible benefit of MAO inhibition for a range of disorders which they believed involved impaired

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\textsuperscript{101} Holzer and Hornykiewicz, 1959.
\textsuperscript{102} Withdrawn in America due to induction of transient red-green color blindness through retrobulbar neuritis.
\textsuperscript{103} Sano, 1960/2000.
\textsuperscript{104} Etryptamine. British patent to ICI: 1963.
circulation, recommended further investigation of the drug in parkinsonism.\textsuperscript{105} Doshay had also reported an anti-akinetic effect of the antidepressant nialamide in 1961;\textsuperscript{106} Ramirez achieved an increase in muscular strength and a reduction in tremor with the same drug.\textsuperscript{107}

Given the neurochemical background of their proposal to use L-DOPA in parkinsonism, it was hardly surprising that Birkmayer and Hornykiewicz examined the combination of MAO inhibitor with L-DOPA from the beginning of their trials of the latter. Degkwitz and colleagues had already observed the enhancement of the L-DOPA effect by the addition of iproniazid.\textsuperscript{108} Birkmayer had, in fact, examined the use of harmine before the advent of L-DOPA, but without satisfactory results.\textsuperscript{109} He also suspected that disturbed 5-HT metabolism might be involved in parkinsonism, and had thus measured 5-HIAA levels in urine and cerebrospinal fluid; these results provided no support for his hypothesis. Nevertheless, he was confident of its correctness, and thus treated a patient suffering an oculogyric crisis with 25mg iproniazid. Unfortunately, the attack lasted several days instead of the normal few hours, an unwelcome response which, in any case, suggested to Birkmayer that 5-HT was, indeed, involved in parkinsonian symptomatology.\textsuperscript{110}

After he had commenced employing L-DOPA in parkinsonian patients, a number of MAO inhibitors supplied by Hoffmann-La Roche were examined in Birkmayer’s hospital, including isocarboxazid (‘Marplan’) and the harman derivative Ro 3-1620. As already discussed, they all intensified both desired and undesired effects of L-DOPA, as well as extending its duration of action.\textsuperscript{111} Both he and Hornykiewicz were puzzled, however, that the symptomatic effects of MAO inhibition alone were so disappointing. This was quickly explained by Hornykiewicz and Bernheimer as they examined brains of parkinsonian patients who had received MAO inhibitors in the weeks before their deaths; noradrenaline and 5-HT levels were restored to normal levels and even increased to supernormal levels in most brain regions, whereas dopamine concentrations were still about 15% of those of normal controls.\textsuperscript{112} Further, MAO inhibition did not restore monoamine levels in the reserpined animal.\textsuperscript{113} The solution to the paradox was thus evident: MAO inhibition slows the degradation of existing transmitter, but in the parkinsonian basal ganglia, dopamine was not being synthesized at a sufficient rate to allow compensation of low levels by MAO inhibition. The role of MAO inhibitors would be restricted to protecting from rapid metabolism the dopamine formed from exogenous L-DOPA. Despite the risks associated with MAO inhibitors, Birkmayer was of the opinion that “a Parkinson therapy without the addition of a MAO inhibitor is incomplete.”\textsuperscript{114}

Barbeau and Duchastel found that one of the first non-hydrazine MAO inhibitors, tranylcypromine, was of benefit for tremor and rigidity, but not akinesia.\textsuperscript{115} On the

\textsuperscript{105} Muether \textit{et al.}, 1961.
\textsuperscript{106} Doshay, 1961b.
\textsuperscript{107} 1960; cited in Sourkes, 1964b.
\textsuperscript{108} Degkwitz \textit{et al.}, 1960.
\textsuperscript{109} Bernheimer \textit{et al.}, 1961.
\textsuperscript{110} Birkmayer and Hornykiewicz, 1961.
\textsuperscript{111} Birkmayer and Hornykiewicz, 1962, 1964.
\textsuperscript{112} Bernheimer \textit{et al.}, 1962, 1963.
\textsuperscript{113} Weil-Malherbe \textit{et al.}, 1961.
\textsuperscript{114} Birkmayer, 1964/65.
\textsuperscript{115} Barbeau and Duchastel, 1962.
advice of Hornykiewicz, Birkmayer had also examined tranylcypromine in the treatment of parkinsonian akinesia, but was not particularly impressed by the benefit achieved; it was useful, however, for depression. He had treated over two hundred patients with the inhibitor by 1963, with results 40% greater than those achieved with standard anticholinergic preparations. The effect on tremor was evident within a few days, the effect on rigor required a few weeks. Duvoisin, on the other hand, remained skeptical, as he commented during a discussion at the Second Symposium on Parkinson's Disease; Barbeau replied on this occasion that he was aware of fifteen groups who had used MAO inhibitors in parkinsonism, twelve with positive results.

Most of the workers in the first period of the L-DOPA therapy (1960-1966), in fact, co-administered MAO inhibitors, including the Hoffmann-La Roche products as well as nialamide (‘Niamid’; Pfizer), pargyline (‘Eudatin’; Abbott) and clorgyline (May & Baker); a few even found that these drugs alone were adequate. Dandiya and Bhargava investigated the effects of MAO inhibitors in a number of animal models of tremor in 1968, and found that they fared poorly in comparison with the anticholinergic agents. Only in the suppression of nicotine-induced tremors did most (but not iproniazid) offer protection. The authors, however, interpreted their results more optimistically, suggesting that the mild protection afforded by nialamide, isocarboxazid, pargyline and phenelzine in some models supported the hypothesis of McGeer and his colleagues that MAO inhibition should have antiparkinsonian effects.

**MAO inhibitors: the temporary setback**

But there existed a further problem which rendered the MAO inhibitor approach, promising as it was, difficult: the side effects of MAO inhibition, especially the cardiovascular effects, were too severe, and could even be fatal. The MAO inhibitors used in the 1960s not only had the desired effect of elevating central nervous system catecholamine levels, but also potentiated the sympathomimetic action of indirectly acting amines, including tyramine, in the periphery; hypertensive crises, particularly following the consumption of tyramine-containing foods, especially cheese, but also broad beans, certain red wines and yeast products (‘Marmite’), were thus a dangerous side-effect of such inhibitors (the "cheese effect"). Scattered reports of hypertensive crises associated with phenelzine and, especially, tranylcypromine had been reported throughout 1961 and 1962, and a number of physicians subsequently reported that their patients had already recognized the connection between cheese and their attacks, but
Barry Blackwell (Psychiatry, Maudsley Hospital, London) was the first to publish the link with cheese intake in a letter to the Lancet in August 1963. In an earlier letter (January), he had warned that, despite a number of reports by various groups during the previous eighteen months, the dangers associated with tranylcypromine were still largely overlooked.\textsuperscript{123} Blackwell now noted that the presentation of side effects during tranylcypromine therapy, including paroxysmal hypertension, intracerebral hemorrhage and headache, appeared to be fairly random; some patients who responded negatively were often found to tolerate the drug at a later timepoint. This suggested to him the involvement of an exogenous factor in the precipitation of the syndrome. He had recently received a letter from a pharmacist who reported that his wife had exhibited the syndrome following her consumption of cheese. “\textit{Despite the unlikely nature of this observation}”, Blackwell examined the dietary histories of all his patients, and found that eight of ten had definitely eaten cheeses within two hours of presenting symptoms.\textsuperscript{124} A representative of Smith, Kline & French Laboratories (manufacturer of ‘Parstelin’, the major form of tranylcypromine employed in Britain) responded in the same journal that the company had been aware of the possible link for several months; although the evidence was still inconclusive, it was advised that cheeses should not be eaten by patients receiving tranylcypromine.\textsuperscript{125} Shortly afterwards, Asatoor and colleagues (Westminster Hospital, London) drew attention to the fact that tyramine (and possibly β-phenylethylamine) contained in the cheese, as reported at the beginning of the century by a number of workers and confirmed by Asatoor’s group, was probably responsible for these untoward side effects of tranylcypromine.\textsuperscript{126} A flurry of letters describing the response with this and other MAO inhibitors appeared in the following months in the Lancet.\textsuperscript{127}

It was subsequently confirmed that the combination of cheese and MAO inhibitor elicited an effect on blood pressure which matched that of intravenous administration of tyramine.\textsuperscript{128} The use of these agents thus required certain dietary restrictions which were seen as too inconvenient by some workers; Völler noted that many physicians were not especially acquainted with what was required.\textsuperscript{129} Liver damage associated with MAO inhibitor usage also began to be reported in the mid-1960s.\textsuperscript{130} Duvoisin felt that the benefits of MAO inhibitors were too doubtful to justify the risk involved.\textsuperscript{131} It was also disturbing that MAO inhibitors could not be co-administered with the tricyclic antidepressants, which at this stage enjoyed a better reputation in the treatment of depression; negative responses to such combinations ranged from dizziness and nausea to death.\textsuperscript{132} These problems appeared insurmountable, and by 1970 the employment of MAO inhibitors in parkinsonian therapy had largely been abandoned, although still employed in many German-speaking clinics. The 1972 Martindale Extra

\textsuperscript{123} Blackwell, 1963a.
\textsuperscript{124} Blackwell, 1963b, 1963c.
\textsuperscript{125} Weber, 1963.
\textsuperscript{126} Asatoor \textit{et al.}, 1963.
\textsuperscript{127} The story of the discovery of the cheese effect, and the initial disbelief expressed by many, has recently been related by Blackwell himself (1998; see Blackwell, 1970 for more extensive referencing). He includes the interesting detail that tyrosine was first isolated from cheese in 1846 by Liebig; it was named from the Greek for cheese, τυρός.
\textsuperscript{128} Natoff, 1964.
\textsuperscript{129} Völler, 1968a.
\textsuperscript{130} Goldberg, 1964.
\textsuperscript{131} Duvoisin, 1965.
\textsuperscript{132} Clinical Psychiatry Committee of the Medical Research Council, 1965; Cole, 1964; Sjöqvist, 1965.
Pharmacopoeia specifically advised against administering L-DOPA to patients who had received a MAO inhibitor during the previous two weeks.\textsuperscript{133} In the United States, pheniprazine had already been removed from the market because of its association with hepatitis and amblyopia, \( \alpha \)-ethyltryptamine in 1961 because of agranulocytosis. Iproniazid had also been removed by now, and tranylcypromine was also withdrawn for a short time. Understandably, MAO inhibitors were regarded as wonderful research tools, but suffered from a rather tarnished clinical reputation.\textsuperscript{134}

It is somewhat ironic that the danger posed by tyramine-containing foods, especially cheese, had been suggested before the First World War. Indeed, Hippocrates had disapproved of cheese as a “bad article of food, in that it gives pain to anyone who eats it in excess”.\textsuperscript{135} More specifically, the Royal Society of Medicine in London had been concerned immediately before the First World War with the question of whether putrefaction of food in the large intestine could be held responsible for a syndrome which included headache and fluctuations in blood pressure. It was suggested that the end products of protein digestion might enter the general circulation if there were “some inability on the part of the oxidizing machinery to keep pace with the formation of putrefactive products”.\textsuperscript{136} As discussed above, the presence of tyramine in certain cheeses had been recognized since the first decade of the century. Cheese was thus immediately involved in the intestinal toxemia discussions:

\begin{quote}
The simplest way by which the harmless amino-acids are made toxic is by decarboxylation. . . . in each case the law holds that the amino-acid [tyrosine, histidine, tryptophan, arginine, leucine, phenylalanine] is non-poisonous, whilst the base [tyramine, histamine, tryptamine, agmatine, iso-amylamine, phenylethylamine] exerts distinct physiological activity. . . . Tyramine has also been shown to occur in ripened cheese, being in this case produced from tyrosine by bacterial action in much the same way as it is formed in the alimentary canal.\textsuperscript{137}
\end{quote}

Although the function of intestinal MAO was still unclear at the end of the 1950s, Blaschko had suggested in 1952 that it might serve to protect the organism from dietary amines. The “cheese effect” would thus have been less of a surprise than it was, had those who employed MAO inhibitors been more acquainted with medical history.

The report by Hodge and colleagues (Wellcome Medical Research Institute and Department of Biochemistry, University of Otago, Dunedin) concerning the consumption of broad beans (specifically identified as \textit{Vicia faba}) by patients treated with pargyline was particularly interesting in light of the history of L-DOPA and dopamine. In one patient, the rise in systolic blood pressure amounted to 120mm Hg within twenty minutes; it could be restored to normal levels by the administration of phentolamine. The authors prepared an ethanol extract of the beans which proved to have pressor activity when administered to rats; the only amine present in the extract was found to be DOPA, and the activity of the extract was blocked by co-administration of \( \alpha \)-methyldopa. The authors appear to have been unacquainted with the work of

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\textsuperscript{133} Extra Pharmacopoeia, 1972, p.72. See also Hunter \textit{et al.}, 1970a.
\textsuperscript{134} For comprehensive review of situation, see Marley and Blackwell, 1970.
\textsuperscript{135} Cited in Blackwell, 1970.
\textsuperscript{136} Sommerville, 1913.
\textsuperscript{137} Dixon, 1913. The discussion of “alimentary toxæmia” covered 380 pages of the Proceedings of the Royal Society of Medicine (10 March-7 May 1913), with contributions from more than fifty participants.
\end{flushright}
Guggenheim. In the same year, Shaw noted in passing that MAO inhibitors could enhance the effects of antiparkinsonian medication, but did not specify which agents were involved.

**MAO-B inhibitors: deprenyl and relatives**

The solution to what appeared to be an insurmountable problem, however, had been provided by two separate discoveries in the mid-1960s, the full significance of which were recognized only in the middle of the next decade. The second of these discoveries was the recognition that MAO actually occurs as two distinct isozymes, distinguishable on the basis of their substrate preferences and sensitivity to inhibition by a new MAO inhibitor, M&B 9302 (clorgyline):

- **MAO Type A (MAO-A):** selectively and irreversibly inhibited by low concentrations (nM) of clorgyline. In the human central nervous system, it is chiefly responsible for the deamination of 5-HT and noradrenaline; in the intestine, it metabolizes the oxidation of tyramine.
- **MAO-B:** relatively insensitive to clorgyline. MAO-B inhibition in the human brain principally reduces the catabolism of dopamine and PEA.

There were suggestions that two enzymes existed as early as 1961, but it was first demonstrated conclusively by J.P. Johnston in 1968 (May & Baker, Dagenham). The recognition of the existence of two MAO forms ultimately led to the development of a range of inhibitors which are relatively specific for one or the other type; MAO-A inhibitors have found greatest application in the treatment of depression, MAO-B inhibitors in the therapy of neurodegenerative disorders, including Parkinson’s disease. As tyramine was the main problem with respect to MAO inhibitor-induced hypertensive crises, a specific inhibitor of MAO-B would be expected to provide the benefits of reduced central dopamine catabolism without the risks of non-specific inhibitors.

As it proved, the ideal candidate had already been synthesized in 1962 by the Chinoin Pharmaceutical Company in Budapest. The ultimate reason which led to its synthesis is unclear. The leader of the research division, Zoltan Ecseri, had ordered the synthesis of 250 derivatives of phenylalkylamine and pargyline as potential centrally acting hypotensive agents. The scientific advisor for this project, Jozsef Knoll (*1925; Department of Pharmacology, Semmelweis University, Budapest), later asserted that these compounds had been designed from the start as "psychic energizers", with the aim being to combine the short-term stimulant effects of methamphetamine with the uplifting effects of MAO inhibition. It is conceivable that the project leader and his advisor had different motivations, so that the ostensible change in aim probably developed in the course of the project under the strong influence of Knoll’s existing interest in psychopharmacology. He had previously been

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139 Shaw, 1964.
140 Johnston, 1968.
141 This is the version found in Parnham, 1993. In the original paper, Knoll *et al.* (1965) mention that “more than 30 compounds” were examined; it is not clear how this relates to the “250” which were later mentioned.
142 Which later proved to be a reversible MAO inhibitor: Suzuki *et al.*, 1980.
143 Knoll *et al.*, 1965; Knoll, 1983.
investigating the behavioural effects of different amphetamine doses in rats, and had initiated a broad study of structure-activity relationships of methamphetamine derivatives, the aim being the development of more specific agents for use in the clinic. This had led to the identification of substances such as p-bromo-methamphetamine, which Knoll described as “serotonergic methamphetamine”, and \( \text{N}^1\text{-O-carboxyphenyl-N}^2\text{-p-[2-methylaminopropyl-1]-phenylacetamidine} \), a prototype “catecholaminergic amphetamine” \(^{144}\). In any case, the Hungarian patent for compound E-250, the last of the product series synthesized in Ecseri’s laboratory, \(^{145}\) a potent MAO inhibitor and psychostimulant which combined the propargyl group of pargyline and the basic structure of methamphetamine, was issued in December 1962, a report in 1964 and the first English paper on the compound appeared in 1965. \(^{146}\) Animal experiments showed that it possessed the two qualities which had been sought in the project:

> Compound E-250 is a potent psychic energizer of broad spectrum of action, which acts both as an acute psychostimulant and a chronic psychic energizer in animal experiments, but unlike amphetamine, it does not increase motility significantly and lowers blood pressure. \(^{147}\)

E-250 displayed a range of properties which were unusual for \( \beta \)-phenylalkylamines: it combined the stimulant effect of amphetamine, was found to be antidepressant in animal models of depression, and was also a potent MAO inhibitor. The latter property was tested using tyramine as substrate, a logical choice in view of problems with the cheese effect and also fortunate, as it is a mixed MAO-A/MAO-B substrate.

![Chemical structures](image)

**Figure 16-9:** Deprenyl and its parent monoamine oxidase inhibitor, pargyline, and the natural amine PEA. * Chiral carbon in deprenyl; # methylation of this carbon gives amphetamine.

Interestingly, the same compound had been synthesized in 1963 as one of a series of propargyl-containing derivatives by Swett and colleagues in the laboratories which had first produced pargyline (Abbott Laboratories; North Chicago). Their interest, however, was short-lived, as they found it to be only a weak MAO inhibitor in vitro; they had, ironically, used 5-HT as the substrate for screening potentially interesting MAO

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\(^{144}\) Knoll, 1983 and references therein; Parnham, 1993.

\(^{145}\) (±)-Phenyl-isopropyl-methyl-propinylamine. French patent (for racemic compound) to Chinoin: 1965; Dutch patent (for (−)-isomer) to Chinoin: 1966. Patents nominated depression as possible area of application.

\(^{146}\) Hungarian patent 151090; Knoll et al., 1964; Knoll et al., 1965. The Hungarian patent nominates as inventors Ecseri (32.5%), Elizabeth Müller (the chemical engineer who conducted the syntheses: 32.5%), Knoll (25%) and Somfai (patent lawyer: 10%).

\(^{147}\) Knoll et al., 1965.
inhibitors ("serotonin pigment test"). Even more ironic was the fact that that compounds identified in this screening process were then examined in vivo – by assessing the degree of activation achieved in mice when administered before 200mg D,L-DOPA.\textsuperscript{148} This was a curious oversight; one of his colleagues in this work, Guy Everett, published at the same time a paper on another of the compounds they had examined, MO-1255.\textsuperscript{149} This compound was completely inactive in the serotonin pigment test; but it was found to be an effective in vivo inhibitor of murine liver and brain MAO. Further, it was found to be as effective as pargyline in promoting elevated central catecholamine levels following administration of DOPA; motor activity following DOPA administration was also increased by concomitant treatment with MO-1255.\textsuperscript{150} It was thus clear that there existed potentially interesting MAO inhibitors which would not be identified by the serotonin pigment test. In retrospect, the existence of different MAO isomers can be invoked to explain this phenomenon, and it is also now recognized that the in vivo and in vitro activities of an enzyme are not necessarily identical.

Preliminary trials in the Soviet Union and Poland indicated that E-250 might be of some use as an antidepressant, and did not exhibit the "cheese effect" even under conditions aimed at deliberately provoking this reaction; doses of up to 150mg were employed, massive in comparison with those now used in Parkinson's disease.\textsuperscript{151} But the synthesis of E-250/deprenil coincided with the period in which the "cheese effect" had become a topic of great concern, resulting in the temporary withdrawal from the market of many MAO inhibitors; Chinoin consequently shelved plans for the further development of E-250. Knoll continued his own investigations, and found in 1967 that the amphetamine-like qualities of the (+)-isomer were much greater than those of (–)-E-250; the latter, however, was a 500-fold more potent MAO inhibitor in vitro.\textsuperscript{152} In the same year that Johnston defined the two MAO types, Knoll’s group published further evidence that (–)-E-250 actually antagonized the physiological effects of tyramine in vitro and in vivo (in the rat and cat), so that it exhibited something akin to a "negative cheese effect";\textsuperscript{153} this, however, appears to have been largely unnoticed by the wider scientific world. Considerable skepticism regarding the very possibility of a MAO inhibitor lacking the "cheese effect" would persist amongst many workers well into the 1970s. Ironically, it would later prove that the affinity of L-deprenyl for MAO-B is actually not much higher than that for MAO-A, but the kinetics of the irreversible, covalent binding step in the reaction between inhibitor and enzyme determine its high specificity.\textsuperscript{154}

But Johnston’s paper had stimulated a revival of interest in MAO and its role in the central nervous system. In London, Moussa Youdim and Merton Sandler (Queen Charlotte Hospital) had examined the distribution of MAO isozymes in brains of depressed patients who had been treated with a variety of MAO inhibitors. They were surprised to find that the highest levels of MAO-B were found in the basal ganglia, as

\textsuperscript{148} Swett \textit{et al.}, 1963. That this compound was of no interest to Abbott is indicated by the fact that it was not covered by the patent for propargylbenzylamine monoamine oxidase inhibitors filed in April 1962 and granted in January 1964 (US 3,118,941).
\textsuperscript{149} Ethyl N-benzylcyclopropanecarbamate; encyprate.
\textsuperscript{150} Everett \textit{et al.}, 1963.
\textsuperscript{151} Cwynar \textit{et al.}, 1966; Varga and Tringer, 1967; Varga \textit{et al.}, 1967; Knoll \textit{et al.}, 1968.
\textsuperscript{152} Magyar \textit{et al.}, 1967.
\textsuperscript{153} Knoll \textit{et al.}, 1968.
\textsuperscript{154} Gaál and Hermecz, 1993.
the predominant form in these nuclei in the rat brain was MAO-B.\textsuperscript{155} Further, patients treated with the non-specific MAO inhibitor tranylcypromine had elevated levels of norepinephrine, 5-HT and dopamine, while clorgyline (MAO-A inhibitor)-treated patients showed no increase in dopamine levels, also contrary to what had been predicted by rat studies; it was believed that if dopamine was a preferential substrate for either of the two forms, it was for MAO-A.\textsuperscript{156} It was beginning to emerge at this point that the neurochemistry of the rat brain could not always be extrapolated directly to the human brain.

A conference was convened in June 1971 at Cagliari on Sardinia to commemorate the 70th birthday of Blaschko, responsible for many of the contributions concerning MAO from the 1930s until the 1950s and recognized by many as the “discoverer” of MAO, to discuss the current research status of the enzyme. It was attended by many of the leading catecholamine investigators of the day; the most recent previous symposium devoted to the enzyme had been the 1963 New York Academy of Sciences meeting (at which Swett had spoken on the work of his group with pargyline derivatives, including deprenil). Knoll presented a comprehensive review of the effects of deprenil (as he now designated the substance) on catecholamine release, uptake and deamination; he compared its effects with those of other current MAO inhibitors and emphasized the puzzling lack of a “cheese effect”.\textsuperscript{157} Deprenil was confirmed by another worker at the same meeting to be a specific MAO-B inhibitor (except in the rabbit).\textsuperscript{158} The idea that the world’s first specific MAO-B inhibitor should be an Eastern Block product, however, was received with some skepticism, as was the crucial lack of the “cheese effect”. Youdim, who was present at the meeting, has remarked that he “doubted that anyone had really paid attention to this pharmacological action . . . or the possible clinical significance of this drug.”\textsuperscript{159}

There the matter lay until 1974. At this time, a young colleague of Birkmayer, the biochemist Peter Riederer, was working in Sandler’s laboratory in London, where he befriended Youdim. Riederer and Birkmayer had been considering the possibilities of selectively modulating MAO activity as a means of increasing the value of L-DOPA therapy; Birkmayer had continued searching since the end of the 1960s for the appropriate adjunct therapy which would maximize the benefit of the increased central dopamine levels achieved by decarboxylase inhibition. Riederer, in particular, was convinced that a selective MAO-B inhibitor could reduce the “on-off” fluctuations which were being increasingly regarded as a critical problem in the L-DOPA therapy of akinesia, having noted a cyclical pattern of basal ganglia MAO activity, particularly in the striatum. Youdim had been invited by Knoll to visit Budapest in October 1974, and accepted a request to break his journey in Vienna and to hold a lecture on MAO inhibitors in the Neurology Institute. Riederer and Youdim then retired to a Viennese wine-restaurant, where a “symposium of two” took place. Riederer instructed an admittedly uninterested Youdim in the problems of antiparkinsonian therapy, particularly the “on-off” phenomenon; Riederer related this to normal diurnal fluctuations in MAO activity which he had recently been investigating, and was eager to


\textsuperscript{156} See Fowler \textit{et al.}, 1984.

\textsuperscript{157} Knoll and Magyar, 1972.

\textsuperscript{158} Squires, 1972.

\textsuperscript{159} Youdim \textit{et al.}, c.1990.
find a suitable selective inhibitor to dampen the consequences of these fluctuations. Youdim spoke of l-deprenyl (as it was now generally known) and his own work on the distribution of MAO isozymes in human brain. The outcome of the “meeting” was that Youdim agreed to procure l-deprenyl from Knoll for a trial of its effects in parkinsonian patients in Vienna.160

Neither Youdim nor Knoll were convinced that l-deprenyl could be of benefit in this disorder. Both agreed with the majority of the scientific community that dopamine was a substrate for MAO-A, not MAO-B, as this had been conclusively demonstrated in the rat. Knoll was aware of neither Birkmayer’s work in parkinsonism nor of Youdim’s human brain studies. He personally regarded the future of the drug as involving its role in depression and saw β-phenylethylamine (PEA) as its major natural substrate. Nevertheless, Youdim brought 3g l-deprenyl back to Vienna (10g had been requested). Youdim feared the likelihood of hypertensive crises which might accompany the co-administration of l-DOPA and a MAO inhibitor, and advised Birkmayer and Riederer against using large doses; the pair thus cautiously administered less than a milligram of l-deprenyl with 25mg l-DOPA in their first trial (November 1974). Within weeks, however, the Viennese group had established that a dose of 10mg l-deprenyl was not only safe, it also reduced and in many cases abolished the “on-off” periods in forty-four of their patients. Riederer presented these results at the 5th International Symposium on Parkinson’s disease (Vienna, September 1975),161 and the full results were presented in the much cited paper which appeared in the Journal of Neural Transmission in the same year.162 A more detailed study involving over two hundred patients confirmed this initial success and appeared in the Lancet two years later.163

Riederer’s presentation stimulated a great deal of discussion at the conference. Sandler commented that the deprenil effect was not only of clinical importance, but was also of theoretical significance; if a MAO inhibitor enhanced l-DOPA therapy and reduced some side effects, it indicated that dopamine metabolites, such as tetrahydroisoquinoline, might be responsible for side effects but not the therapeutic benefit of l-DOPA (contrary to what he and Sourkes had suggested). On the other hand, he was not convinced that the specificity of deprenil for MAO-B was necessarily significant. Calne noted previous failures with MAO inhibitors were now apparently due to the wrong choice of inhibitor; Zeller and Boshes reported that they had successfully employed pargyline in l-DOPA-resistant patients, having found that one of the preconditions for response to l-DOPA appeared to be a 50% reduction in MAO activity (measured in platelets). There were also suggestions that deprenil improved parkinsonian patients simply by virtue of its antidepressant qualities. Fahn, on the other hand, while noting that its mechanism of action remained to be determined, entertained the hypothesis that it increased synaptic dopamine concentrations by inhibiting its catabolism.164 In his summation of the symposium, Melvin Yahr commented:

But, hopefully, in some of the newer approaches pointed out at this meeting that the ability now to use MAO inhibitors of particular types whether, as Dr. Birkmayer indicated, it is A or B we do not know, but the ability to now use these in parkinsonism

161 Birkmayer et al., 1976.
162 Birkmayer et al., 1975.
163 Birkmayer et al., 1977; see also Birkmayer et al., 1982.
164 Birkmayer and Hornykiewicz, 1976, pp.399-403.
and combining them with dopa and extending the actions, the central pharmacological action, may have increasing importance in increasing its therapeutic efficacy.\textsuperscript{165}

Not everyone was convinced that a new breakthrough had emerged from Vienna; in particular, the mechanism and the safety of the drug were still questioned. At the Ciba Foundation Symposium on Monoamine Oxidase and its Inhibition (1975), Knoll interpreted the results as indicative of a role of PEA in Parkinson’s disease.\textsuperscript{166} Many workers remained convinced that dopamine was a MAO-A substrate. Youdim finally persuaded Gerald Stern and Sandler to conduct a trial in London; their reluctance stemmed from their previous unhappy experiences with tranylcypromine as a clinical MAO inhibitor.\textsuperscript{167} Stern had also reported in 1970 that quite small oral doses of L-DOPA (50mg) induced rapid rises in blood pressure and pulse in a patient who had been receiving the common antidepressant phenelzine. These effects were alleviated by administration of the $\alpha$-adrenergic receptor blocker phentolamine.\textsuperscript{168} Their first move was to try l-deprenyl personally in order to convince themselves of its safety; then it was administered to four normal and six parkinsonian volunteers together with increasing doses of tyramine, in order to be absolutely certain that the drug possessed no “cheese effect”. Only after this had been achieved were they prepared to try the drug as a therapy for Parkinson’s disease, an approach somewhat different to that of their Viennese colleagues. The results of this trial were positive, although not as dramatic as in Vienna. Their findings were published in the \textit{Lancet} shortly after those of the Viennese group had appeared there, and a more detailed report was published in \textit{Psychopharmacology} at the beginning of 1978.\textsuperscript{169}

Deprenyl was launched as a commercial product in Hungary in 1977 (under the name ‘Jumex’), the same year in which Sandler’s group reported that dopamine was, in fact, a MAO-B substrate in the human brain,\textsuperscript{170} and its licensed production by foreign pharmaceutical firms quickly followed. The rights to produce l-deprenyl in Britain and most of western Europe were assigned by Chinoin to a Finnish company, and were ultimately transferred to a British subsidiary of the Finnish Sugar Corporation, Forum Holdings; no major western pharmaceutical firm was interested at this point in what was seen as a questionable adjunct therapy for a small group of advanced parkinsonian patients. By 1982, the value of l-deprenyl as an adjunct therapy with L-DOPA had been established by a number of open and double-blind studies in numerous countries, and the drug became commercially available in Britain under the name ‘Eldepryl’ (Somerset).\textsuperscript{171} Its status as a major addition to the therapy of Parkinson’s disease was confirmed in May of the following year at a special symposium in Turku, Finland (“\textit{A new approach to the treatment of Parkinson’s disease’’}), where groups from all over Europe reported their experiences with l-deprenyl;\textsuperscript{172} a similar symposium four years later (“\textit{MAO-B-inhibitor selegiline (R(−)-deprenyl). A new therapeutic concept in the treatment of Parkinson’s disease’’}, Berlin, January 1987) marked its launch onto the German market as ‘Movergan’ (ASTA Pharma, Frankfurt).\textsuperscript{173}

\textsuperscript{165} Yahr, 1976.
\textsuperscript{166} Knoll, 1976.
\textsuperscript{167} Youdim \textit{et al.}, c.1990.
\textsuperscript{168} Hunter \textit{et al.}, 1970a.
\textsuperscript{169} Lees \textit{et al.}, 1977; Elsworth \textit{et al.}, 1978.
\textsuperscript{170} Glover \textit{et al.}, 1977.
\textsuperscript{171} Dow, 1990; p.90.
\textsuperscript{172} Rinne, 1983.
\textsuperscript{173} Riederer and Przuntek, 1987.
As Riederer had hoped, L-deprenyl was found to control the “on-off” fluctuations in patients who had been receiving L-DOPA for long periods, especially those fluctuations which occurred at the end of a dosing period; random fluctuations were also responsive, but not to the same extent. Most studies at this time failed to identify a therapeutic effect on akinesia when given without L-DOPA, but most of the patients investigated with the new drug were at an advanced stage of the disease and thus probably less amenable to help provided by the inhibition of dopamine catabolism. Later studies found that L-deprenyl delayed the need to commence L-DOPA therapy in early cases of Parkinson’s disease; this was considered a positive sign, both because it appeared to indicate that a slower progression of the disease could be achieved, and because evidence began to emerge in the mid-1980s that L-DOPA might be cytotoxic in the brain under certain conditions. It was also at about this time that Fahn’s group published a detailed analysis of the complications of long-term L-DOPA therapy in which the authors, while acknowledging the undoubted benefits of L-DOPA, suggested that:

levodopa itself may induce cerebral changes that are cumulative over time. Since our data suggest that longer duration of disease prior to levodopa therapy does not adversely affect clinical response, and since patients with clinical fluctuations, especially if severe, tended to be younger when they began levodopa therapy, there seems little reason to initiate therapy early, when the disease is relatively mild or responds to other medications.

An alternative approach which reduced L-DOPA dosage or delayed the necessity for using it would thus have been welcome. L-deprenyl appeared to offer this means. Although it potentiated not only the positive effects of L-DOPA but also its unwanted side effects, including abnormal involuntary movements, these could be controlled in most cases by simply reducing the dose of L-DOPA employed. In fact, a 30-40% reduction of the required L-DOPA dose was usually reported. Further, side effects attributed directly to L-deprenyl have been minimal; suggestions that it might be associated with hypotensive crises have remained largely anecdotal.

Several additional features associated with L-deprenyl therapy began to emerge with its long-term use. Reviewing the results that they had obtained over the previous seven years, Riederer and his colleagues noted in 1982 that the response to the agent did not, as with many antiparkinsonian agents, decline with chronic use; even more startling, it also appeared to be associated with increased longevity of the patient. This finding was reinforced by a more comprehensive retrospective study completed three years later by Riederer and Ambrozi which compared the performance of patients who had

174 Reviewed: Fahn, 1996, 1998; Agid, 1998; see also the statement arising from a consensus meeting at the end of 1998, which concluded that “there is no convincing evidence that levodopa causes or accelerates neuronal cell death”. Agid et al., 1999. The suspicion that L-DOPA might accelerate the degenerative process in parkinsonism had been expressed on the basis of clinical experience from as early as the mid-1970s; it was only at the end of the 1980s, however, that experiments in animal models suggested that L-DOPA could increase local oxidative stress. Cotzias’ group, on the other hand, had found that mice adapted to large amounts of dietary L-DOPA (40mg.g⁻¹ feed) lived longer on average and appeared more youthful than their normally fed compatriots, but at the expense of a higher mortality rate in the first months of life and the development of corneal opacities: Cotzias et al., 1974b; See also Cotzias et al., 1974c.

175 Lesser et al., 1979.

176 Knoll, 1978; Rinne et al., 1978; see also review in Wessel, 1993.

177 Reported at Heidelberg MAO Symposium in 1983: Birkmayer et al., 1983.
received Madopar alone (377 patients) with those who had also received l-deprenyl (564 patients); longevity was increased in the latter group by a mean 15.3 months.\textsuperscript{178}

The Viennese study was criticized because of its open nature and because of the fact that the research hypothesis had not been proposed before the commencement of the trial, but it nonetheless stimulated a great deal of interest. This would prove to be the beginning of controversy about whether l-deprenyl, in fact, slowed the progress of the disorder, thus moving antiparkinsonian therapy at least a step closer to its long sought Holy Grail, an issue which is still debated with great heat. Such an effect presumably involved a reduced rate of degeneration of the nigrostriatal pathway; the only means by which this seemed possible was the reduced production of a toxic substance by the action of MAO, possibly of cytotoxic oxidizing free radicals. Other workers, however, found that the effect did, in fact, diminish after a number of years; the authors were not willing to speculate as to whether this was the result of long-term MAO inhibition or to progression of the disease.\textsuperscript{179}

The solution of this question required large, multicentre trials, and these would be most convincing if conducted in America. But the United States had until now remained largely inured to the new agent; another event was required to stimulate broader interest in the introduction of yet another new agent to antiparkinsonian therapy. It was about this time that the ability of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) to induce parkinsonism in humans attracted attention. The first case of a heroin addict contracting the disease from a contaminated batch of the meperidine analog 1-methyl-4-propionoxy-4-phenylpyridine (MPPP) was actually identified in 1976, but the identification of four further victims in 1981 raised the alarm.\textsuperscript{180} After releasing the news to the press, an intense search for the cause of its toxicity began, and in 1983 Langston and colleagues announced that the conversion of MPTP to the 1-methyl-4-phenylpyridinium ion (MPP\textsuperscript{+}) by glial cell MAO-B was required for its toxic effects to be expressed; MPP\textsuperscript{+} is actively transported into the neuron by the dopamine transporter, explaining its specific toxicity for the nigrostriatal pathway.\textsuperscript{181} The mechanisms by which MPP\textsuperscript{+} exerts its toxic effects lie outside the scope of the current work; it suffices here to note that interactions with mitochondrial electron transport chain and the consequent generation of highly oxidative free radicals is generally believed to be among the processes involved in the resultant cell death. In any case, the MPTP phenomenon ignited the search for a “natural toxin” which might underlie the pathogenesis of idiopathic parkinsonism.\textsuperscript{182}

\textsuperscript{178} Birkmayer et al., 1985.
\textsuperscript{179} Yahr, 1987.
\textsuperscript{180} Reported in Davis et al., 1979. The story of the discovery of MPTP was reviewed by Roger Lewin in 1984. Amongst the “ironies” in the MPTP story which he recorded was the fact that Hoffmann-La Roche (where MPTP was first synthesized by Ziering and colleagues in 1947 in the search for potent pethidine analogs) had examined MPTP as a potential antiparkinsonian drug in animals at the end of the 1950s and in six humans in 1960. Lewin wrote that this was based on the resemblance of MPTP to certain transmitters, but a number of reports in the late 1950s regarding the potential utility of MPTP-like molecules as spasmolytics and analgesics was the more probable reason for this research direction. See Schmidle and Mansfield (1956; Rohm & Haas Co.) for alternative synthesis; also Randall and Lehmann (Hoffmann-La Roche, Nutley, U.S.A) for further work on piperidine derivatives as analgesics.
\textsuperscript{181} Langston et al., 1983.
\textsuperscript{182} For review of MPTP and other current animal models of parkinsonism: Gerlach and Riederer, 1996.
It was recognized by several groups that inhibition of MAO-B protected against MPTP intoxication in several species. Up until this point, l-deprenyl had struggled to find approval in the United States, but this phenomenon paved the way to its being finally accepted. The businessman Donald Buyske, who had maintained contacts with Chinoin regarding E-250 as a potential antidepressant from as early as 1970, had obtained a licence from the Hungarian firm in 1981 for the synthesis of the drug by S.C. Johnson & Co.; due to lack of interest by the company, the licence was transferred to Buyske’s own company, Somerset Pharmaceuticals, in the following year. The FDA had repeatedly declined his applications for approval of the agent, even as a so-called “orphan drug”. This is a special status granted for agents of potential clinical significance, but without initially specifying a particular application; this would have extended his patent rights without needing to provide the detailed clinic evidence required for a regular drug licence. This was partly because until 1991 the FDA required toxicity tests of twelve month duration (six months was usual in Europe), and was not prepared to licence the drug for human use on the basis of European clinical data. The situation had thus changed from the time at which l-DOPA was introduced, and even more dramatically since the situation which Doshay had described at the beginning of the 1960s (chapter VIII); and while individuals expressed impatience, it appears that the American medical community had by this time not only accepted but also internalized the need for controlled, double blind, placebo-based studies in American clinics before the introduction of any new drug. The required study was finally conducted by Roger Duvoisin, Abraham Lieberman and Manfred Muenter in ninety-six patients, and the results published in 1988. The American investigators were not as enthusiastic as their European colleagues, but agreed that a mild symptomatic benefit was evident in patients experiencing disturbing L-DOPA-related motor fluctuations, and this was achieved with minimal side effects.\textsuperscript{183} The FDA finally granted its approval in mid-1989.\textsuperscript{184}

By this stage, a range of new synthetic MAO-B inhibitors was being investigated with the aim of producing more specific agents without amphetamine metabolites. It is not my intention to discuss in detail here these developments; their major characteristics

\textsuperscript{183} Golbe \textit{et al.}, 1988.
\textsuperscript{184} Parnham, 1993. Deprenyl has also found application in veterinary medicine; the Pfizer product ‘Anipryl’ is employed in the management of canine cognitive dysfunction syndrome (CDS) and of uncomplicated canine pituitary dependent hyperadrenocorticism (PDH). Hypothalamic dopamine deficiency may be involved in this latter disorder. The most common adverse reactions leading to discontinuance of the drug (in 4\% of 404 animals) were restlessness/agitation, vomiting, disorientation, diarrhea, diminished hearing, possible drug interaction (weakness, confusion, loss of coordination and “seizure-like” activity while being treated concurrently with metronidazole, prednisone, and trimethoprim sulfa), increased destructive behavior in a dog with separation anxiety, anorexia, anemia, stiffness and polydipsia (Pfizer product information for Anipryl and references therein).
are listed in table 16-2.\textsuperscript{185} Most currently investigated MAO-B inhibitors are irreversible, including rasagiline (AGN-1135), mofegiline and MDL-72145; the Hoffmann-La Roche product lazabemide is the major reversible MAO-B inhibitor being considered for use in Parkinson’s disease. Deprenyl, or selegiline as it is now known,\textsuperscript{186} remains the benchmark against which new MAO-B inhibitors are measured. In 1991, the drug was awarded the Claudius Galenus Prize of the German Ärzte-Zeitung in recognition of its position as an “outstanding drug” on the German market.\textsuperscript{187}

**MAO inhibitors: mechanism of action**

Further surprises regarding MAO and its inhibitors emerged with further investigations. Given the substrate specificity of the two MAO forms, their distribution in the human brain is perhaps surprising: the highest MAO-A concentrations are in the catecholaminergic neurons of the locus ceruleus, and of MAO-B in the serotonergic and histaminergic neurons of the raphe and posterior hypothalamus; there are especially high concentrations of both forms in the human basal ganglia.\textsuperscript{188} The dopaminergic neurons of the substantia nigra in both rodents and primates express MAO-A, but not MAO-B.\textsuperscript{189} Although Westlund and colleagues identified a dense distribution of MAO-B-immunoreactive nerve terminals in the substantia nigra, which contrasted with the weak signal for the striatum, nigral MAO-B is located primarily in glial cells.\textsuperscript{190} Richards and associates employed quantitative enzyme autoradiography to identify a three-fold higher level of MAO-B than of MAO-A in the substantia nigra; however, the levels of the A-form were higher in the pars compacta than in the reticulata, while the opposite distribution was noted for MAO-B.\textsuperscript{191} The topographic location of MAO types thus does not coincide with that of their presumed natural substrates, and it has been suggested that the role of MAO is principally to protect the local environment from excess levels of foreign monoamines. MAO-B could also indirectly regulate extraneuronal transmitter levels, particularly those of dopamine, by regulating the levels of a release-promoting substance, such as PEA.

Central nervous system MAO-B (but not MAO-A) activity increases with age in both humans and animals, perhaps as a result of glial cell proliferation associated with neuronal loss.\textsuperscript{192} In humans, this increase commences at 50-60 years of age, but is not observed in the substantia nigra.\textsuperscript{193} Increased blood platelet MAO-B activity has been reported in both Alzheimer’s and Parkinson’s diseases, although the increased activity in the latter disorder might be associated with the frequently coexistent Alzheimer’s disease, rather than directly with Parkinson’s disease.\textsuperscript{194} Fowler and associates reported that MAO-B activity was reduced by 40% in the brains of smokers; tobacco use is associated both with psychiatric disease and a reduced risk for Parkinson’s disease.\textsuperscript{195}

\textsuperscript{185} For detailed discussion of MAO-B inhibitors in neurology and psychiatry, see Szelenyi, 1993.
\textsuperscript{186} The suffix ‘-giline’, derived from pargyline or pargiline, is now used to denote a specific MAO-B inhibitor; *USP dictionary of USAN and international drug names*, p.850.
\textsuperscript{187} Rudolph, 1991.
\textsuperscript{188} Overviews: Oreland et al., 1983; Westlund, 1994; Saura et al., 1996.
\textsuperscript{189} Westlund et al., 1985.
\textsuperscript{190} Westlund et al., 1988; Konradi et al., 1989.
\textsuperscript{191} Richards et al., 1998.
\textsuperscript{192} See, for example, Strolin-Benedetti and Dostert, 1989; Fowler et al., 1997.
\textsuperscript{193} Saura et al., 1997.
\textsuperscript{194} Danielczyk et al., 1988.
\textsuperscript{195} Fowler et al., 1996.
Table 16.2: Major selective MAO-B inhibitors which have recently been investigated for use in antiparkinsonian therapy.

<table>
<thead>
<tr>
<th>Name</th>
<th>Synonyms</th>
<th>Structure</th>
<th>Action on MAO-B</th>
<th>Selectivity in vitro</th>
<th>Selectivity in vivo</th>
<th>Amine transport inhibition</th>
<th>Anti-oxidative effects</th>
<th>Current status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lazabemide</td>
<td></td>
<td>[Chemical Structure]</td>
<td>Reversible</td>
<td>26,568</td>
<td>&gt;18,867</td>
<td>Weak</td>
<td>Yes</td>
<td>Discontinued</td>
</tr>
<tr>
<td>Ro 196327</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mofegiline</td>
<td></td>
<td>[Chemical Structure]</td>
<td>Irreversible</td>
<td>74,000</td>
<td>1,740</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>MDL 72145</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rasagiline</td>
<td>AGN 1135, TVP 101(2)</td>
<td>[Chemical Structure]</td>
<td>Irreversible</td>
<td>50</td>
<td>100</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Deganyl</td>
<td></td>
<td>[Chemical Structure]</td>
<td>Irreversible</td>
<td>233</td>
<td>69</td>
<td>Yes</td>
<td>No</td>
<td>Phase II trials (Alzheimer's disease)</td>
</tr>
<tr>
<td>Deprenyl</td>
<td></td>
<td>[Chemical Structure]</td>
<td>Irreversible</td>
<td>100</td>
<td>49</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Rasagiline</td>
<td></td>
<td>[Chemical Structure]</td>
<td>Irreversible</td>
<td>233</td>
<td>69</td>
<td>Yes</td>
<td>No</td>
<td>Phase II trials (Alzheimer's disease)</td>
</tr>
<tr>
<td>Mofegiline</td>
<td></td>
<td>[Chemical Structure]</td>
<td>Irreversible</td>
<td>100</td>
<td>49</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>MDL 72145</td>
<td></td>
<td>[Chemical Structure]</td>
<td>Reversible</td>
<td>26,568</td>
<td>&gt;18,867</td>
<td>Weak</td>
<td>Yes</td>
<td>Discontinued</td>
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</tr>
<tr>
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<td>Weak</td>
<td>Yes</td>
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<tr>
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<td></td>
<td>[Chemical Structure]</td>
<td>Reversible</td>
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<td>Yes</td>
<td>Discontinued</td>
</tr>
<tr>
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<td>[Chemical Structure]</td>
<td>Reversible</td>
<td>26,568</td>
<td>&gt;18,867</td>
<td>Weak</td>
<td>Yes</td>
<td>Discontinued</td>
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<tr>
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<td></td>
<td>[Chemical Structure]</td>
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<td>Yes</td>
<td>Discontinued</td>
</tr>
<tr>
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<td></td>
<td>[Chemical Structure]</td>
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<td>Weak</td>
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<td>Discontinued</td>
</tr>
</tbody>
</table>

Data taken from Henriot et al., 1994; selectivity = ratio of IC50 for MAO-B (substrate was PEA) and MAO-B (G, H); not known.
Surprises regarding the possible actions of MAO-B inhibitors in the central nervous system have also emerged. In vitro and vivo studies have suggested that, in addition to their enzyme-inhibition, these agents have a number of other beneficial effects:

- inhibition of dopamine reuptake and increase stimulated dopamine release by chronic (but not acute) administration
- increased expression enzymes involved in protection of the cell against oxidative stress
- prophylactic protection against a range of neurotoxins
- “neurorescuing” effects when administered after certain toxins or injuries, possibly via inhibition of apoptotic processes; these effects are elicited by L-deprenyl concentrations too low to significantly affect MAO-B activity
- altered protein expression in both glia and neuronal elements
- stabilization of mitochondrial membrane potential
- increased cytokine concentrations
- stimulation of immune function
- reduced polyamine turnover.196

These phenomena are almost certainly partly related to one another as aspects of a complex pattern of interacting effects and partly independent of one another. Which of these phenomena is involved in the beneficial effects of L-deprenyl in Parkinson’s disease also awaits clarification. One factor which caused early concern was the fact that L-deprenyl is metabolized to L-amphetamine and desmethyl-selegiline (DMS).197 The former is, however, not regarded as playing a role in the actions of L-deprenyl, as its “amphetamine-like” qualities are only a fraction of those of the D-isomer. It should nevertheless be remembered that Coyle and Snyder observed that L-amphetamine was as potent an inhibitor of striatal catecholamine uptake as the D-isomer in the striatum, in contrast to other brain regions.198 DMS, on the other hand, exhibits a number of interesting properties, and also inhibits MAO-B, although less potently than the parent compound, and may play an important role in its effects.199 This, however, like so much concerning L-deprenyl, remains controversial.

That the search for a highly specific pharmacological agent should produce compounds with such “dirty” pharmacological profiles is not surprising, that these agents should function as well as they do is perhaps somewhat puzzling. Further, whether these various actions will all ultimately be linked to MAO-B inhibition is unlikely. It is, on the other hand, conceivable that this broad palette of actions is the basis of the success of L-deprenyl; by intervening at several points in the neurochemistry of the neuron and perhaps glia, it is possible that a better result is achieved than with a highly specific compound. Once again, serendipity may have played an important role in the improvement of therapy, but only, as always, if the opportunity is recognized and seized.

Whatever the confusion regarding its mechanism of action, these laboratory findings have provided an experimental underpinning for the suspicion that L-deprenyl provides a certain degree of neuroprotection in Parkinson’s disease (and perhaps in other neurological diseases, including Alzheimer’s disease), thus slowing the rate of its

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196 Reviewed in Foley et al., 2001.
197 Reynolds et al., 1978. See also Elsworth et al., 1982; Riederer et al., 1983.
198 Coyle and Snyder, 1969.
199 Heinonen et al., 1997.
progression. This was first suggested by the analysis by Riederer and associates of their first eight years’ experience with the drug;\textsuperscript{200} similar results were reported by Tetrud and Langston in 1989,\textsuperscript{201} the news of which was sufficiently spectacular as to merit a front page story in the \textit{New York Times} in August 1989, in which experts were reported as being “elated” by the results, although the findings were to be regarded as “preliminary and in need of confirmation”.\textsuperscript{202} The study was small in comparison with that reported by the Viennese group, involving only fifty-four patients (one hundred were originally to be enrolled). The major findings were that deprenyl-treated, early stage parkinsonian patients required L-DOPA after 549 days compared with 312 days in the control group, and there appeared to be no serious side effects associated with the use of the inhibitor.\textsuperscript{203} Despite the preliminary nature of the findings, Olanow told the \textit{New York Times} that the results were “pretty convincing” and that he was “delighted” with them.\textsuperscript{204} By quirk of bureaucratic fate, deprenyl became available as a prescription drug in America the following month.

The Tetrud-Langston study inspired a great deal of interest in America and elsewhere, as the possibility of slowing the progress of a neurological disorder – a neuroprotective strategy rather than symptomatic treatment – would clearly represent a revolutionary medical breakthrough of the greatest magnitude; not only would a major step towards the long sought ‘cure’ for parkinsonism have been achieved, but also a great advancement in both the understanding and therapy of neurodegenerative diseases in general. Workers around the world therefore looked forward with great anticipation to the results of the much larger multicentre DATATOP (Deprenyl And Tocopherol Antioxidative Therapy Of Parkinson’s Disease) study. L-deprenyl and α-tocopherol (vitamin E) were the first agents whose neuroprotective properties were specifically examined in a controlled clinical study, the conceptual basis of which was provided by the oxidative stress model of neurodegeneration. L-deprenyl (10mg/day) and/or tocopherol (2000mg/day) were administered over a period of up to two years to 800 Parkinson’s disease patients who were both in an early stage of the disorder and previously untreated.\textsuperscript{205} The criterion chosen for assessment of neuroprotection was the time-point at which deterioration of the patient necessitated initiation of L-DOPA therapy. α-Tocopherol had no significant effect on disease progression, either alone or in combination with L-deprenyl; the latter, however, postponed the necessity of L-DOPA therapy by up to nine months. L-deprenyl, however, also produced a small but measurable symptomatic effect, confounding the interpretation of the results. Nevertheless, the presentation of disability was delayed even in patients whose symptoms were not improved during the study.\textsuperscript{206}

But in a follow-up to the DATATOP study, the beneficial effects of L-deprenyl were not sustained, nor did L-deprenyl significantly alter the presentation of side-effects associated with L-DOPA therapy.\textsuperscript{207} It thus appeared that L-deprenyl was not capable of

\begin{flushleft}
\textsuperscript{200} Birkmayer \textit{et al.}, 1985.
\textsuperscript{201} The study had commenced in 1986.
\textsuperscript{202} Kolata, 1989.
\textsuperscript{203} Tetrud and Langston, 1989.
\textsuperscript{204} Kolata, 1989.
\textsuperscript{205} Parkinson Study Group, 1989.
\textsuperscript{206} Parkinson Study Group, 1993. More recently, the Rotterdam Study of 5342 non-demented individuals between the ages of 55 and 95 years suggested that high intake of vitamin E might protect against the occurrence of parkinsonism: de Rijk \textit{et al.}, 1997.
\textsuperscript{207} Parkinson Study Group, 1996.
\end{flushleft}
halting the course of the disease in the longer term. Olanow, however, criticized the design of the follow-up study, in that the groups compared were not actually matched; assignment of patients in the follow-up study was based on their outcome in the initial study, with the consequence that baseline disability was not equal in the compared groups at the commencement of the extension study.\textsuperscript{208}

Olanow’s group described a fourteen month randomized, double-blind, prospective controlled study which aimed to minimize the symptomatic effects of L-deprenyl within the experimental design (the “Sindepar study”). In contrast to the DATATOP study, all patients received symptomatic treatment from the onset. One hundred and one patients were treated for twelve months with L-deprenyl or placebo and an agent directed at the symptoms of Parkinson’s disease (Sinemet or the dopamine receptor agonist bromocriptine); L-deprenyl/placebo was discontinued after twelve months, the symptomatic treatment a week before the end of the study. The test parameter employed was the change in Unified Parkinson’s Disease Rating Scale (UPDRS) score between the start and end of the study. At the end of the study period, L-deprenyl had been discontinued for two months and would thus be expected to be “washed out”, and MAO-B activity to have returned to normal. L-deprenyl treatment was found to be significantly superior to placebo in inhibiting deterioration of UPDRS score (mean deterioration: L-deprenyl group, 0.4 ± 1.3; placebo, 5.8 ± 1.4 points), with the choice of symptomatic treatment having no significant effect on the outcome. Both because of the experimental design and the fact that the effect observed was greater than that which could be explained by the symptomatic effect of L-deprenyl, the influence of L-deprenyl was interpreted as indicative of a reduced rate of deterioration, and thus of a neuroprotective role for L-deprenyl.\textsuperscript{209} Long-term studies carried out in Denmark and Norway, Finland and Germany also indicated that the early combination therapy of L-deprenyl and L-DOPA had a long-term favorable effect on daily L-DOPA use.\textsuperscript{210}

The question of whether L-deprenyl exerts a neuroprotective effect, and if so, how, thus remain open. L-Deprenyl does not halt the course of degeneration in Parkinson’s disease, but may significantly slow its progress. It must be noted that the investigation of neuroprotection in the clinic is fraught with inherent theoretical and practical difficulties. For example, the fundamental neurochemical nature of neurodegeneration has not yet been defined; although several mechanisms thought to be involved have been identified, it remains to be definitively demonstrated that such processes are responsible for specific features in any neurodegenerative disease. Parkinson’s disease is probably a multifactorial disorder, and oxidative stress alone is insufficient to explain all aspects of the disease. The lack of effect of the free radical-scavenging vitamin E in the DATATOP study seemed to exclude an explanation based on a purely antioxidant effect, although the question of whether the vitamin dose employed was adequate for achievement of significant benefit must also be entertained. Other pathomechanisms – excitotoxicity, disturbance of Ca\textsuperscript{2+} homeostasis, metabolic dysfunction, apoptosis – are probably involved, interacting with each other in a complicated manner, the temporal and causal relations of which remain to be elucidated. It is thus conceivable that, even if L-deprenyl exerted a significant neuroprotective effect, the impact on the further course of the disease might not have been great enough to be detectable in the DATATOP study. The situation is further complicated by the fact that it is difficult to distinguish

\textsuperscript{208} Olanow, 1996.
\textsuperscript{209} Olanow \textit{et al.}, 1995.
\textsuperscript{210} Larsen and Boas, 1997; Myllylä, \textit{et al.}, 1997; Przuntek \textit{et al.}, 1999.
between the symptomatic and neuroprotective effects of a drug, as the withholding of symptomatic treatment in order to more conveniently investigate a putatively neuroprotective agent is ethically problematic.\textsuperscript{211}

Equally important is that the dynamic of the neurodegenerative process dictates that only a narrow therapeutic window is available in which even a highly effective neuroprotective strategy will be meaningful (figure 16-11). Neuroprotective treatment would ideally be initiated during the “latent” phase of the disorder, before the manifestation of clinical symptoms; unfortunately, Parkinson’s disease cannot be diagnosed with certainty before the appearance of symptoms. Glenda Halliday’s group (Prince of Wales Medical Research Institute, Randwick; Neuropathology, Department of Pathology, Sydney University; Neurology, Westmead Hospital) reported that the areal fraction of pigmented neurons in the substantia nigra was already reduced by 70% (in comparison to young controls) at the first presentation of symptoms of Parkinson’s disease, late onset Parkinson’s disease or diffuse Lewy body disease; despite reduced brain volume, no significant decline was measured in the substantia nigra of normal controls. Further, only the cell loss in the dorsolateral cell cluster was correlated with duration of disease; cell loss in this region increased dramatically from about 20% at time of diagnosis to almost 100% within 15-18 years.\textsuperscript{212} Gerlach and Riederer estimated a maximal period of seven years between the first manifestations of Parkinson’s disease and the point at which a neuroprotective strategy would be pointless (less than 10% of

\textsuperscript{211} Foley and Riederer, 1999, 2000b; Riederer and Foley, 2000.
\textsuperscript{212} Halliday \textit{et al.}, 1996.
substantia nigra neurons still viable). As many patients involved in long-term trials are at an advanced stage of the disorder, the chances for detecting a neuroprotective effect may be small.

The tantalizing fact remains that L-deprenyl and, in certain respects, other MAO-B inhibitors exhibit neuroprotective and -restorative effects in vitro which, if they are significant in vivo, promise the possibility of therapies which halt the presently inexorable decline of central nervous system function which characterizes disorders such as Parkinson’s and Alzheimer’s disease. Correspondingly frustrating is the fact that the design and interpretation of trials which aim to assess the neuroprotective efficacy of such drugs will continue to be difficult until specific biochemical or other events are identified which can act as direct indicators of the impact of the therapy. Equally intriguing is the recent finding in a controlled Scottish study over seven years that mortality in 97 parkinsonian patients receiving antiparkinsonian medication for the first time was greater than in the general community (999 controls; determined using the Kaplan-Meier method), and that this difference was attributable to mortality in patients receiving L-DOPA alone as their initial medication (64 patients). Those receiving deprenyl, however, regardless of whether they were also receiving L-DOPA (13 of 28 patients initially receiving deprenyl also received L-DOPA; by end of study, only four patients still received selegiline as monotherapy), exhibited the same mortality as the control group.

The use of MAO inhibitors in Parkinson’s disease has a long history and promises to play a major role in future developments. It should be remarked that it was a major stroke of luck that basal ganglia dopamine is metabolized by MAO-B and not by MAO-A, as in the rat; otherwise, the development of specific inhibitors would have not brought the same benefits for antiparkinsonian therapy as have been seen with L-deprenyl. Birkmayer regarded the employment of L-deprenyl into the clinic as the third major breakthrough in the therapy of the disorder (after L-DOPA and decarboxylase inhibitors), and it has certainly contributed a great deal to advancing the quality of life of parkinsonian patients. The introduction of deprenyl into the clinic was, if anything, the result of a more rational process than that of L-DOPA therapy; Riederer had recognized the significance of laboratory investigations of MAO activity in the parkinsonian brain, and specifically sought an agent with particular characteristics for solving the problem he had identified. Luck then played its usual role: the agent for which he was looking existed, and could be provided by his friend and colleague Youdim, an expert in the relevant field who nevertheless had no interest at the time in antiparkinsonian therapy. Riederer’s suggestion, implemented by Birkmayer, was blessed with a success which, although initially controversial, was never in danger of experience the years in the wilderness which had postponed the recognition of the value of L-DOPA therapy.

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214 Mitchell et al. (1997), on the other hand, found in a review of randomized controlled trials of antiparkinsonian drugs between 1966 and 1996 that subjects over 75 years of age were practically excluded from study. The design and interpretation of clinical controls are rendered easier if such factors are borne in mind.
215 Donnan et al., 2000. Risk ratios: patients v. controls: 1.76; L-DOPA monotherapy v. controls: 2.45; selegiline as ‘adjuvant’ therapy: 0.92. The remaining patients received the following on their initial prescription: benzhexol, 3; benzhexol plus deprenyl, 1; orphenadrine, 1.
Knoll has vigorously urged on many occasions that l-deprenyl be used as a prophylactic agent by the aging population, not only in the scientific literature but also in the popular press, its potential as an aphrodisiac has been especially promoted, paralleling the early years of l-DOPA in America.\^216 Similar sensationalization of the benefits in a number of quarters, including by the publicist Alastair Dow, have led to its massive popularity as the “anti-ageing pill”;\^217 doses of 5mg per week have been recommended for those in their fifth decade of life as a means of staving off the effects of old age. Not unnaturally, its alleged benefits for longevity, libido and cognition are its major selling points.\^218

While l-deprenyl is far from being the “fountain of youth” or even the ultimate solution for Parkinson’s or any other neurological disease, it would appear that it has brought that solution closer, and in combination with l-DOPA will remain the standard by which new therapies will be measured – at least until the basic cause of the disorder becomes known, presuming that such knowledge will also suggest a practicable means of addressing it.

**Chloramphenicol and aberrant mRNA in parkinsonism**

An interesting attempt to treat parkinsonism at a more fundamental level should also be briefly mentioned here. Stefanis and Issidorides (Neurology and General Biology, Athens National University) reviewed in 1970 evidence that an unknown agent stimulated synthesis of glial mRNA for growth factors and other proteins associated with cell division. They proposed that this defect might elicit similar changes in associated neurons, resulting in “de-differentiation”, loss of function and, ultimately degeneration. Amongst the evidence cited for this hypothesis was the fact that reserpine stimulates increased transcription and translation, as well as glial proliferation, in animals, that parkinsonian patients who died early in the disease exhibited increased levels of nigral RNA (inversely correlated with the level of melanization), and that blood cell protein analysis had revealed abnormalities in parkinsonian patients. The authors consequently proposed that the antimicrobial agent chloramphenicol, which inhibits protein synthesis in proliferating but not that in differentiated cells, might both block “proliferation [and might] also restore the ‘differentiated’ state of the cell” in parkinsonian patients. Eighteen subjects received 1.5-2g chloramphenicol orally for a period of 3-6 weeks; three controls received

![Figure 16-12: Chloramphenicol.](https://www.altavista.com/cgi-bin/query?pg=r&n=2&i=ORuhm7i&m=17&u=lef.org/magazine/mag95/95sep1.htm; accessed 1.02.01.)

\^216 For example: Knoll et al., 1983; also “Prof. Knoll: I have discovered the pill of eternal youth!”, which appeared in the Austrian boulevard magazine Die ganze Woche on 7 February 1991.

\^217 Dow, 1993.

\^218 Deprenyl was recently listed on an internet site (“Life Extension Magazine”) as the third highest recommendation for “life extensionists”; in the first two positions were melatonin and acetyl-L-carnitine, while it was followed by (amongst others) phosphatidylserine, centrophenoxine, GH3/KH3 (procaine), dehydroepiandresterone and human growth hormone. Source: http://www.altavista.com/cgi-bin/query?pg=r&n=2&i=ORuhm7i&m=17&u=lef.org/magazine/mag95/95sep1.htm; accessed 1.02.01.
placebo. Only one subject receiving the inhibitor exhibited no improvement, while one experienced “complete restoration to normal”. Improvement was first manifested 4 to 17 days after initiation of treatment, with dyskinesia and rigidity ameliorated before tremor, and the maximum effect achieved by 1.5 to 4 weeks, at which time tremor was abolished in some patients despite the persistence of significant rigidity and dyskinesia. Symptoms gradually deteriorated to their original level in some cases within two weeks of termination of administration, while in others some benefit remained evident at three months. Stefanis and Issidorides noted that stimulation of nucleic acid synthesis by dopamine had also been reported.

Intriguing as these results were, the untoward effects associated with long term chloramphenicol therapy, particularly hematological changes, precluded further pursuit of this direction. The authors had not observed signs of toxicity during their study, but had, in any case, not intended that chloramphenicol be adopted into antiparkinsonian therapy, but wished rather to “indicate possible new approaches to the study of the pathogenesis and treatment of the disease”. The theoretical basis of their investigation remains relevant, especially in light of more recent interest in the role of glia and programmed cell death in nigral neurodegeneration in parkinsonism.

**Apomorphine: the first dopaminergic agonist in antiparkinsonian therapy**

With the broad acceptance of the dopamine hypothesis of Parkinson’s disease, it was a logical step at the end of the 1960s to examine the impact of dopamine receptor agonists on the disorder. It would be expected that direct stimulation of the appropriate receptors would be a more specific therapy than the administration of large quantities of the monoamine precursor, and thus elicit fewer untoward side effects. It was also recognized by the early 1970s that as many as 25% of patients did not respond significantly to L-DOPA therapy (with or without a decarboxylase inhibitor); it was suspected that this might be due to the deficiency in striatal aromatic amino acid decarboxylase reported by Ken Lloyd and Hornykiewicz in 1970. On the other hand, excessive synthesis of norepinephrine or displacement of 5-HT from its natural stores in as a result of large L-DOPA doses might be associated with some of the untoward side effects seen in L-DOPA-treated patients. The longer half-lives of receptor agonists compared with L-DOPA would also allow a more continuous stimulation of dopamine receptors, which many saw as a more physiological approach and more likely to overcome problems such as motor fluctuations. Directly acting dopamine receptor agonists thus seemed the ideal solution to many of the problems associated with L-DOPA therapy.

Two such agonists had already been examined before dopamine had been recognized as a transmitter: bulbocapnine in the 1920s and apomorphine by Schwab’s group in the

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219 Stefanis and Issidorides, 1970. See also Gomirato and Hydén (1963) for discussion of a ‘glial error’ in the pallidum in parkinsonism.

220 Gilman et al., 1990; pp.1127-1129. The initial experiment was almost immediately attacked as a dangerous "misuse" of chloramphenicol (Cronkite, 1970), a charge emphatically denied by Stefanis (1970).

221 Stefanis and Issidorides, 1970. In the response to Cronkite’s criticism of the study, Stefanis (1970) noted that hemotoxic effects observed in early experiments with high dose oral DOPA had not prevented its investigation.
early 1950s (see above). In the early 1960s, the Dutch pharmacologist Ernst drew attention to the structural similarities of apomorphine and dopamine; his group and that of Andén in Sweden then demonstrated that apomorphine elicited stereotypic behaviour in rodents by stimulating dopamine receptors.222

The first group to re-examine apomorphine in parkinsonian patients after this recognition was that of Cotzias in 1970. Cotzias was not aware of Schwab’s employment of apomorphine in parkinsonism until after he had submitted his paper to the New England Journal of Medicine. He was still promoting the view at this stage that melanin synthesis was involved in the therapeutic effect of L-DOPA, but as he noted in his paper on apomorphine:

*The therapeutic effects of L-dopa might also be assigned to dopamine if they could be duplicated by apomorphine.*223

He asserted that L-DOPA was used in place of dopamine itself not because it cannot cross the blood-brain barrier, but because it “is degraded extensively by monoamine oxidase. Given in large doses, it will cause toxicity before it can trickle into the brain.”224 Apomorphine, on the other hand, mimicked some of the effects of dopamine, and might thus be used to more efficiently stimulate dopaminergic centres.225 Fifteen patients were treated with apomorphine HCl (0.25-2.0mg s.c.) in a placebo-controlled investigation, of whom six were parkinsonian cases (four had previously received L-DOPA, with great success) and four suffered from chronic manganism. The subjects were scored according to a method developed by the Parkinson’s Disease Information Center in New York which rated the motor and vegetative signs to give a total score of between 0 (normal) and 100 (total incapacity). A sharp improvement in scores following apomorphine administration was measured in five of the six parkinsonian patients and in all manganism cases; one parkinsonian patient who had not yet received L-DOPA was not responsive to apomorphine, while one manganism victim (whose condition had previously been aggravated by L-DOPA) showed only a decrease in tremor, while his other symptoms worsened. The beneficial effect peaked at 30-60 minutes and lasted for about two hours. The authors felt that these preliminary results were worthy of further pursuit, both because they allowed the use of milligram amounts of drug rather than grams, and because of the insights which it might yield into the chemistry of the disorder. Apocodeine (the monoethyl ether of apomorphine) and bulbocapnine were suggested as alternative agonists.226 These findings were broadly confirmed by other groups soon afterwards.227

In a further study, the curious observation was made by Cotzias group that patients who had never received L-DOPA did not respond as well as those who had; further, the side effects induced by apomorphine were less severe in L-DOPA-treated patients. Overall, the clinical effects of the two agents appeared to be additive, but their adverse effects cancelled each other out; for instance, L-DOPA-induced nausea was sometimes

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222 Ernst, 1965; Ernst and Smelik, 1966; Andén et al., 1967; Ernst, 1967. For review: di Chiari and Gessa, 1975.
223 Cotzias et al., 1970.
225 He had previously noted the similarity between some of the side effects of L-DOPA therapy and the primary effects of apomorphine: Cotzias et al., 1969.
226 Cotzias et al., 1970.
227 Braham et al., 1970; Castaigne et al., 1971.
counteracted by apomorphine. This was related by Cotzias to the "chemical memory" imprinted upon these tissues by L-DOPA, as discussed earlier. Apomorphine also appeared to enhance the effects of L-DOPA itself.\textsuperscript{228} The use of oral apomorphine was later examined by the group (up to 1440mg/day – compared with the maximal 10mg recommended by the U.S. Pharmacopoeia for inducing emesis), but the higher doses required proved to be damaging to the kidney.\textsuperscript{229}

The group then turned their attention to the use of N-propylnoraporphine alone or in combination with L-DOPA. It was found to be moderately beneficial as an adjunct to L-DOPA/carbidopa therapy, and without major side-effects. This encouraged the investigators to synthesize a range of N,N-disubstituted dopamine derivatives for use as dopamine receptor agonists in parkinsonism.\textsuperscript{230} By this time, however, alternative agonists had been developed which rendered the new candidates superfluous. The only effect of tetrahydropapaveroline (norlaudanasoline), an alkaloid derivative of dopamine and possible apomorphine precursor, was to exacerbate tremor.\textsuperscript{231} More recently, Campbell and associates reported that S(+)N-n-propylnorapomorphine selectively antagonized dopamine receptors in the limbic forebrain but not extrapyramidal basal ganglia, whereas R(-)N-n-propylnorapomorphine was a dopamine receptor agonist. The two agents could be administered to rats as the corresponding methylenedioxy-derivatives and metabolized to the active aporphines in vivo.\textsuperscript{232}

In 1979, Corsini’s group tried apomorphine injections once again, together with the peripheral dopamine receptor antagonist domperidone to inhibit peripheral side effects, but the drug was generally forsaken about this time.\textsuperscript{233} Apomorphine had been used for almost a hundred years as an emetic, and this effect certainly hindered its success in other situations, as did its peripheral side effects, including hypotension and bradycardia. Its major deficit, however, was that its therapeutic lasted little more than an hour, hardly sufficient to justify its side effects.

\textsuperscript{228} Düby \textit{et al.}, 1972.
\textsuperscript{229} Cotzias \textit{et al.}, 1972.
\textsuperscript{230} Cotzias \textit{et al.}, 1976b, 1978; Ginos \textit{et al.}, 1975; 1978.
\textsuperscript{231} Cotzias \textit{et al.}, 1975, 1976c; Papavasiliou \textit{et al.}, 1978; see also Walsh \textit{et al.}, 1970; Dordain \textit{et al.}, 1974.
\textsuperscript{232} Campbell \textit{et al.}, 1982; 1987.
\textsuperscript{233} Corsini \textit{et al.}, 1979.
Apomorphine experienced its most recent renaissance at the end of the 1980s. Lees and Stern demonstrated that subcutaneously administered apomorphine (either as a bolus injection or continuously infused) effectively reversed “off” periods in fluctuating parkinsonian patients. The usual dose required is 2-5mg, and the effect is achieved within fifteen minutes. Sublingual and rectal application of apomorphine has also been described, but the latency period is about as twice as long as with subcutaneous administration. Apomorphine has also proved useful in the management of a number of other side effects of L-DOPA therapy, including abnormal involuntary movements. Portable minipumps for continuous apomorphine administration are now available for patients who otherwise experience frequent oscillations in response to L-DOPA.

**Piribedil**

Nevertheless, results from a number of groups with apomorphine were no doubt compared with early experiences with L-DOPA, so that the search for a similar agent but with less daunting side effects was initiated. Corrodi and colleagues had discovered a new potent dopamine receptor agonist in 1971 which was subsequently dubbed piribedil (‘Trivastal’; Pharmacodex, Munich); clinical trials by a number of groups in the period 1971-1976 found a moderate effect on tremor, especially when combined with L-DOPA, but it was also a potent emetic. More significantly, dyskinesias and adverse psychiatric reactions were quite common, so that it was not further investigated.

**Bromocriptine and other D₂ receptor agonists**

Agalactia in pigs associated with ergot-contaminated feed had been known for many years; in 1962, it was demonstrated that ergotoxin has a direct prolactin-inhibiting effect upon the hypothalamus, and the search for an alkaloid which specifically inhibited prolactin secretion began. 2-Bromo-α-ergocryptine methanesulfonate (bromocriptine) was subsequently (1967) selected by Sandoz (Basel) for development for use in humans as such an inhibitor, but was accorded only low research priority, as the existence of neither a distinct hormone “prolactin” in humans nor of a receptor for the inhibition of its release was generally accepted at this stage. With the recognition of

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234 Stibe et al., 1987, 1988; Poewe et al., 1988; Frankel et al., 1990a.
236 Lees et al., 1989; Hughes et al., 1991a, 1991b, 1993; Kleedorfer et al., 1991. Intranasal application has also been explored: Kapoor et al., 1990.
237 Poewe and Granata, 1997.
239 Corrodi et al., 1971; Vakil et al., 1973; Sweet et al., 1974a; Lieberman et al., 1974, 1975b; Callaghan et al., 1975; McLellan et al., 1975; Feigenson et al., 1976. It continues to be used as a peripherally acting vasodilator.
240 Mixture of ergocornine, ergocristine and ergocryptine.
241 German (1969) and U.S. patents (1973) to Sandoz (Swiss priority: May 1968).
XVI. Adjuncts and alternatives: Extension of dopamine-based therapy

the existence of human prolactin at the beginning of the 1970s, bromocriptine was
initially employed in the investigation of the regulation of its secretion. Fuxe and
Höckfelt (Department of Histology, Karolinska Institute, Stockholm) thus discovered
that it reduced dopamine turnover in the hypothalamus and striatum. These results were
extended in 1973 by studies with H. Corrodi (Department of Pharmacology, Göteborg
University and Astra Pharmaceuticals, Södertälje), in which they found that
bromocriptine exerted a number of effects on central catecholamines. Although it
lacked the stimulating action of apomorphine in rats with normal central dopamine levels,
bromocriptine appeared to be active at dopamine receptors. Most importantly:

The present results underline the importance of actions on dopamine synapses in the
neostriatum and limbic forebrain. The main action appears to be a direct dopamine
stimulation of long duration.

As a result of these observations, they suggested that it might be useful in the treatment
of Parkinson’s disease. This hypothesis was tested even before the confirmation of the
dopaminomimetic properties of bromocriptine by other workers; the period which
elapsed between a laboratory finding and its attempted application in therapy by other
workers was becoming shorter.

At the end of 1974, a group at the Department of Medicine (Neurology) at the
Hammersmith Hospital in London headed by Donald Calne were the first to report a
trial of bromocriptine in parkinsonian patients. The double blind study involved twenty
patients, nineteen of whom were receiving L-DOPA and eleven anticholinergic drugs;
they continued their regular medication throughout the trial. Bromocriptine was initially
administered at a dose of 2.5mg per day and gradually increased until untoward side
effects emerged, a maximum of 30mg/day; the dose was then maintained for a period of
6-12 weeks, followed by six weeks on placebo. The blind evaluator assessed various
functional and physical signs on a five point scale at fortnightly intervals. The side
effects of the therapy were similar to those seen with L-DOPA, and could be reduced by
dose adjustment; it was tolerated better than either apomorphine or piribedil.
Neurological deficits were improved by about 20% in severely disabled patients, but

242 Reviewed in Lataste, 1984. Bromocriptine was originally approved by the FDA in 1978 for the
treatment of amenorrhea/galactorrhea secondary to hyperprolactinemia and was subsequently
244 Corrodi et al., 1973. This group knew bromocriptine as CB 154.
245 Miyamoto et al., 1974; Johnson et al., 1976a,b; the effect of bromocriptine on prolactin secretion was
only decisively demonstrated in 1976 by Flückiger et al.
only by 10% in milder cases; this was interpreted as being the result of “the greater room for improvement” in the more severe cases. The authors remained cautious about the potential of bromocriptine therapy, reasoning that inhibition of dopamine release via stimulation of presynaptic receptors represented a possible theoretical problem.²⁴⁶ Nonetheless, they persisted with the approach. Shortly afterwards, the group reported that by increasing the bromocriptine dose even further – in one case, to 75mg/day – it was possible to reduce the required L-DOPA dose by an average of about 65%; six patients had abandoned L-DOPA altogether, preferring the agonist. The greatest benefit was experienced by more advanced patients, leading Calne to hypothesize that the agonist overcame the problem of a decline in decarboxylase levels in these patients to a point where L-DOPA alone was no longer sufficient as therapy.²⁴⁷ After an interruption caused by his transfer to the Institutes of Health in Bethesda, Calne reported an investigation in which ninety-two patients were treated with bromocriptine with high doses of bromocriptine (gradually raised to 40-90mg per day; Calne estimated that 20mg bromocriptine was equivalent to a gram L-DOPA) for periods of up to thirty months. The greatest benefit was seen in patients receiving L-DOPA; the L-DOPA dose could be reduced by an average of 40% in these patients. Most interesting was that those cases exhibiting “on-off” problems or severe dyskinesia derived the most benefit from the agonist; at this stage, Calne had never seen a patients who developed “on-off” fluctuations for the first time while receiving bromocriptine. The major side effects were hypotension which manifested itself at low doses (“first dose phenomenon”), and could be life-threatening; psychiatric changes similar to those which can be produced by L-DOPA, but more profound (visual and auditory hallucinations); and dyskinesia, but to a lesser extent than with L-DOPA. Erythemelalgia (warm, edematous feet) was an unusual side effect, related to epidermal mononuclear infiltrating vasculopathy. 52% of patients continued to receive bromocriptine with benefit; 32% discontinued therapy because of untoward side effects, 9% because of lack of response.²⁴⁸

Calne is now generally credited as having introduced dopamine receptor agonists as a new approach into the therapy of Parkinson’s disease. A number of other groups also investigated bromocriptine in the next few years, generally with positive results with regard to control of motor fluctuations, although it was generally found to be less effective than L-DOPA as monotherapy.²⁴⁹ Bromocriptine (‘Parlodel’; Sandoz) became the first dopamine receptor agonist to be licensed as an adjunct therapy in Parkinson’s disease in 1976. Calne’s experiences suggested to him that low doses of bromocriptine and of L-DOPA should be co-administered as early as possible in the disorder.²⁵⁰ This view has been supported by studies conducted by Rinne which found that the early combination of bromocriptine with low dose L-DOPA achieved similar results to L-DOPA monotherapy, but with a reduction of later complications.²⁵¹ While some workers have advocated the addition of as little as 7.5mg/day bromocriptine to L-DOPA therapy, 20-40mg/day is required where bromocriptine is employed as monotherapy.²⁵²

²⁴⁶ Calne et al., 1974a.
²⁴⁷ Calne et al., 1974b.
²⁴⁸ Calne et al., 1978a, 1978b.
²⁴⁹ Debono et al., 1975; Lees et al., 1975; Kartzinel et al., 1976a,b (including Calne); Lieberman et al., 1979a; Lees and Stern, 1981a; U.K. Bromocriptine Research Group, 1982. For more recent references, see Piccoli and Riuggeri, 1995; Tolosa et al., 1998.
²⁵⁰ Calne, 1983.
²⁵¹ Rinne, 1989 and references to earlier reports therein.
²⁵² Poewe and Granata, 1997.
Studies involving bromocriptine were also responsible for a more general advance in neurochemistry. It had been noted that bromocriptine, unlike existing dopamine receptor agonists, did not stimulate “dopamine-sensitive adenylate cyclase” activity. Further, Calne had noted that not all dopamine receptor agonists elicited the same responses; in particular, bromocriptine, in contrast to apomorphine, did not provoke emesis, leading to the suggestion that the existence of different types of dopamine receptor might allow separation of the desired and adverse effects of dopaminergic antiparkinsonian therapy.\(^\text{253}\) In 1979, John Kebabian and Calne proposed that there exist two classes of dopamine receptors, \(D_1\) and \(D_2\), principally on the basis that the former stimulated adenylyl cyclase and the latter did not.\(^\text{254}\) The concept was initially disputed and later expanded, but the essential idea has prevailed. The authors recognized from the start that both types occur at various sites within the striatum, but could not allocate a function with regard to motor control to either class. With respect to Parkinson's disease, it was proposed on the basis of the effects of the \(D_2\) receptor agonists that the disorder involved a defect in transmission at this receptor.\(^\text{255}\) This view has prevailed until recent times, largely because the function of the \(D_1\) receptor in basal ganglia activity has long remained something of a mystery. A paradox which has not been completely resolved was the observation that bromocriptine (and other ergot-derived dopamine receptor agonists) rarely induce dyskinesia in patients who had never been treated with L-DOPA; L-DOPA-treated patients, even after withdrawal from the amino acid, are, however, at increased risk of bromocriptine-induced dyskinesia.\(^\text{256}\)

Following the initial success of bromocriptine, a number of other agonists were trialled in quick succession, all, like bromocriptine, are ergolines, derivatives of the ergot alkaloids contained in the fungus *Claviceps purpurea*:

- **Lergotrile mesylate**: a promising candidate in the mid-1970s for the treatment of major parkinsonian symptoms, producing less severe dyskinesia and more pronounced initial hypotension than L-DOPA; it was also less expensive than bromocriptine. But interest had waned by 1979 because of its significant hepatotoxicity. Other side effects included mental changes (exacerbation of those associated with L-DOPA therapy); it was, however, effective in addressing the “on-off” phenomenon of L-DOPA therapy.\(^\text{257}\)

- **Lisuride (lysuride)**: semisynthetic ergoline first synthesized in Czechoslovakia in 1960;\(^\text{258}\) originally seen principally as a serotonergic agent, Horowski (Schering, Berlin) identified its principally dopaminergic nature in animals and man.\(^\text{259}\) It is a highly water soluble \(D_2\) receptor agonist and partial \(D_1\) receptor agonist/antagonist with some activity at 5-HT\(_1\) receptors. Side effects include hallucinations and related psychic effects. Although less effective than bromocriptine in the relief of end-of-dose akinesia, its solubility makes it ideal for infusion; further, its low effective dose meant that it was the first dopamine receptor agonist that could be used parenterally. Employed in Europe under the name

\(^{253}\) Calne, 1974b.

\(^{254}\) Kebabian and Calne, 1979. Kebabian (1978) had first proposed the designations “\(\alpha\)-” and “\(\beta\)-dopaminergic receptors”, but recognized the inevitable confusion with adrenergic receptor types. See reviews in Calne, 1988; Bennett, 1998.

\(^{255}\) Kebabian and Calne, 1979.

\(^{256}\) Calne, 1988.


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Lergotriole

Lisuride (‘Dopergin’)

Pergolide (‘Permax’)

Cabergoline (‘Destinex’)

α-Dihydroergocriptine (‘Daverium’)

Terguride (‘Dironyl’)

Figure 16-16: Ergoline-class dopamine receptor agonists trialed in antiparkinsonian therapy

‘Dopergin’ (amongst others); its use in America is currently limited to prolactin inhibition and the management of migraine.260

• Pergolide: a potent D2 and (to a lesser extent) D1 receptor agonist. It manages parkinsonian symptoms at lower doses than bromocriptine, with a longer duration of action (leading to a greater reduction in “off-time” and end-of-dose phenomena) and with fewer side effects (nausea, hypotension). It is also reported to be useful in some patients who longer respond to bromocriptine.261


Further ergot derivatives were introduced in the 1990s (including cabergoline and α-dihydroergocryptine). An interesting aspect of these agonists is the observation that patients who become unresponsive to one agonist may often be switched with success to one of the alternatives, similar to the earlier situation with the largely interchangeable synthetic anticholinergic agents. Side-effects common to these agents include insomnia, nausea and vascular disturbances, including orthostatic hypotension; these reactions can be sufficiently severe as to restrict use of the medication.  

The partial agonist terguride (‘Dironyl’; Schering) is an interesting compound, in that structurally it is almost identical with LSD; earlier investigations suggested its efficacy as an antiparkinsonian agent, but later reports have not been as optimistic, although its combination with a D₁ receptor agonist may prove useful.  

Attempts to synthesize dopamine receptor agonists without these problems by omission of the ergot alkaloid structure resulted in the 1990s in the synthesis of a multitude of new dopamine receptor agonists, including pramipexole, ropinirole, quinagolide (CVC 205-502) and N-0923, the latter being developed as a transdermal therapy for Parkinson’s disease. The D₃ receptor agonist, talipexole (‘Alefexole’,

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263 Corsini et al., 1985; Brücke et al., 1987; Krause et al., 1990; Ruggieri et al., 1991; Baronti et al., 1992b; Pacchetti et al., 1993; Akai et al., 1995. Also marketed as ‘Mysalfon’ (Leciva/Spořa, Czechoslovakia).

264 Olanow et al., 1989; Poewe et al., 1990; Calabrese et al., 1998; Schrag et al., 1998; Calne, 1999; Factor, 1999; Wachtel, 1999. The primary indication for which quinagolide (‘Norprolac’; Novartis) is employed is suppression of prolactin secretion.
Nippon Boehringer-Ingelheim), is employed as an antiparkinsonian agent in Japan; *piroheptine* (‘Trimol’; Fujisawa), structurally related to the imipramine-class amine uptake inhibitors and the anticholinergic *elantrine*, has also been used in this capacity.\(^{266}\) It is still too early to determine whether the pharmacological profiles of these agents makes them better choices than the older ergot derivatives, especially as they have themselves been associated with novel side effects, such as narcolepsy.\(^{266}\)

Finally, there is evidence that the dopamine D\(_2\) receptor agonists, like the MAO-B inhibitors, exert direct anti-oxidative and neuron-rescuing effects;\(^{267}\) this may involve reduced dopamine turnover produced by stimulation of autoreceptors, leading to reduced availability of extracellular dopamine for oxidative processes, as well as also the direct “scavenging” of free radicals.

The dopamine receptor agonists currently used in the therapy of Parkinson’s disease are listed in table 16-3. Their employment in therapy is now accepted, but controversy regarding their exact role in the treatment of Parkinson’s disease has persisted for a number of years. Specifically, the question of whether these agents should be applied early in the disorder or only when the familiar problems associated with long term L-DOPA therapy begin to manifest themselves has been long debated.\(^{268}\) A number of studies of *de novo* Parkinson’s disease patients have found that the timepoint at which L-DOPA therapy becomes necessary can be delayed by treatment with dopamine receptor agonists such as lisuride and ropinirole,\(^{269}\) or that the required dose of L-DOPA is reduced;\(^{270}\) further, the probability of the presentation of dyskinesia is significantly reduced when therapy begins with dopamine receptor agonists instead of L-DOPA.\(^{271}\) Bromocriptine, lisuride and pergolide have all proved to be effective as monotherapies in *de novo* parkinsonian patients, often as effective as L-DOPA itself, but are rarely employed as such in more advanced patients. Some authorities believe that the early combination of a dopamine receptor agonist (bromocriptine and lisuride are best investigated in this respect) with L-DOPA delays the onset of motor fluctuations associated with the latter.\(^{272}\)

This controversy overlaps that of the question of whether L-DOPA therapy itself should be delayed as long as possible. The grounds for such a postponement are provided by animal studies which suggest that L-DOPA itself may be cytotoxic (as discussed above), by the observation that L-DOPA-associated dyskinesia is related to the duration of the therapy, and by the potential exacerbation of oxidative stress by excessive dopamine levels. On the other hand, it has been argued that the development of dyskinesia is more closely related to the progression of the disease than to the

\(^{265}\) Hitomi *et al.*, 1972a, 1972b; Ohashi *et al.*, 1972; see also Saithoh, 1988, for effects of *piroheptine* (and benzhexol) in MPTP-treated monkeys. Nippon Boehringer-Ingelheim arose from co-operation between C.H. Boehringer Sohn and Tanabe Seiyaku in 1955 in the production of ‘Buscopan’, the scopolamine derivate used in antiparkinsonian therapy.

\(^{266}\) Most recent review of dopaminergic agonists in antiparkinsonian therapy at time of writing: Factor, 1999.


\(^{268}\) See, for example, Calne *et al.*, 1984; Rascol *et al.*, 1984; Lieberman *et al.*, 1984b; Fahn, 1996b; Montastruc *et al.*, 1999.

\(^{269}\) For example: Runge and Horowski, 1991; Sethi *et al.*, 1998.

\(^{270}\) Przuntek *et al.*, 1996; Rinne, 1999.


Table 16-3: Pharmacological profiles of dopamine receptor agonists. α₁, α₂, adrenergic receptor subtypes; β-adrenergic receptors; D₁, D₂, dopamine receptor subtypes (involvement in dopamine-mediated motor responses is established); D₃, dopamine receptor subtype (involvement in dopamine-mediated antidepressive effects is not indubitably established); 5-HT, serotonergic receptors. –, antagonist; 0, agonist (very low affinity); +, agonist (low affinity); ++, agonist (moderate affinity); ++++, agonist (high affinity); ±, partial agonist; ?, no information available. Table compiled by Gerlach et al. (2000) from information in Brecht (1998) and Watts (1997).
XVI. Adjuncts and alternatives: Extension of dopamine-based therapy

Figure 16.18: Selected D1 dopamine receptor agonists of possible value in antiparkinsonian therapy. ABT-431 and dihydrexidine reached clinical testing; SKF 82958 is a full D1 receptor agonist, except in the human caudate nucleus, where it is a partial agonist.

less associated with dyskinesia. However, selective D1 receptor stimulation with ABT-431 was recently found to elicit an improvement in motor symptoms comparable to that achieved by L-DOPA, and also with significantly less problems with respect to dyskinesia. Clearly, this field requires a great deal more investigation.

Amantadine

Amantadine HCl (‘Symmetrel’; Ciba-Geigy), a curious water-soluble triamine, was originally introduced in 1963 as an antiviral agent for the prophylaxis of A2 influenza. With an effectiveness comparable with that of influenza vaccines, it appears to inhibit a late stage of virus assembly, but the precise mechanism is unknown. As an antiviral agent it was somewhat controversial; it offered protection only if used immediately on exposure to the virus, and the recommended dose (200mg/day, 10 days) only granted limited protection (~50%) and a high incidence of side effects, particularly those of a neurological nature (ranging from insomnia and lack of concentration to confusion, hallucinations and seizures).

In 1968, a patient with mild bilateral parkinsonism described to Robert Schwab the remission of her symptoms while taking amantadine (2×100mg/day) in order to forestall the flu, and of their return after she had ceased using the drug. Acuity of observation is not restricted to the clinician or chemist. Schwab then contacted the manufacturer to enquire whether this was an isolated report, discovered that it was, and thereupon commenced a small trial in ten parkinsonian patients. Observing no adverse side effects, he then undertook a larger, placebo-controlled study over six months which found

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278 Fici et al., 1997.
279 Shiosaki et al., 1996; Rascol et al., 1999. See also Gilmore et al., 1995; Blanchet et al., 1998; Calne, 1999.
280 1-Adamantanamine. Also marketed as ‘Virofral’ (Boehringer, Mannheim) and ‘Contenton’ (Dauelsberg, Göttingen), and the sulphate as ‘PK-Merz’ (Merz, Frankfurt). British (1963) and U.S. patents (1964) to Studiengesellschaft Kohle; Belgian patent (19643) to Du Pont.
281 Tyrrell et al., 1965; Hay, 1992; Hardman et al., 1996, pp.1209-1211.
282 Schwab wrote: “Such serendipitous findings are not rare in the literature especially in chronic diseases for which there are no cures”; Schwab et al., 1969.
that 66% of 163 patients showed signs of objective or subjective improvement in all three major parkinsonian symptoms while taking amantadine (up to 200mg/day) together with their usual medication; in 58% of the responsive patients, the benefits were sustained for three to eight months. Side effects were not disturbing (nervousness, depression, vertigo, abdominal disturbances) and could be controlled by adjusting the dose.\textsuperscript{283}

An editorial in the same issue of the \textit{New England Journal of Medicine} expressed the simultaneous surprise and curiosity with which many were struck by Schwab’s report. After L-DOPA had brought excitement back into antiparkinsonian therapy following years of standstill, yet another novel effective agent was surprising enough, let alone an antiviral agent. The writer, however, also pointed to the many curious points of Schwab’s report: the potentiation of the effects of anticholinergic antiparkinsonian agents – but only after amantadine had been employed for weeks; the sudden failure of the drug after several months in some patients; the precipitous return of akinesia in some cases within twenty-four hours of discontinuance of the drug. There was also its unusual structure, which the author felt was unprecedented in the history of antiparkinsonian drugs. There were many questions, but the agent was worth further examination.\textsuperscript{284} The editor in the \textit{Medical Journal of Australia} was also intrigued by the discovery of amantadine at precisely the time L-DOPA therapy had been officially sanctioned; it was suggested that the role of amantadine in antiparkinsonian therapy remained unclear, but would probably be employed in patients unsuitable for L-DOPA

\textsuperscript{283} \textit{Ibid.}
\textsuperscript{284} Anonymus, 1969h.
therapy or as a means of reducing L-DOPA dosage in order to control the side effects of the latter.\textsuperscript{285}

Further clinical trials confirmed the original observation, and amantadine had become a popular adjunct to parkinsonian therapy even before it was approved for this indication by the FDA in 1971; it was thus introduced to the therapy of parkinsonism at about the same time as L-DOPA. Response to amantadine developed within a few days, but tended to wane after several months (or even weeks) of use; it remained, however, a useful addition to L-DOPA therapy when the effectiveness of the latter declines. As a monotherapy, it was less impressive than L-DOPA, but more effective than anticholinergic agents. Other interesting findings were the facts that the benefit of amantadine was specific for parkinsonian tremor, and that amantadine also potentiated the side effects of anticholinergic drugs.\textsuperscript{286}

Side effects associated with amantadine in parkinsonism have, in general, been relatively few and mild. Tyrrell and associates reported in 1965 that volunteers who consumed 400mg amantadine per day experienced nausea, emesis, tremor and general physical weakness; 200mg/day was occasionally associated with insomnia and nervousness.\textsuperscript{287} Gessler reported that amantadine did not influence kidney function except in those with a pre-existent problem.\textsuperscript{288} Psychiatric disturbances, including hallucinations and anxiousness, may occur when the drug is combined with anticholinergic agents, but this is reversible. There are some suggestions that side effects are due to the amplification of concurrent medication; Dallos and colleagues, for instance, found that hallucinations in two patients were controlled by adjusting the dose of benzhexol used.\textsuperscript{289} Enthusiasm was temporarily dampened by the reports of livedo reticularis in the legs associated with its long term use; this is caused by local vasoconstriction resulting from catecholamine release, and has only cosmetic consequences for the patient.\textsuperscript{290} The significance of amantadine has again increased recently with the discovery that amantadine sulphate infusions, followed by oral administration, are an effective means for alleviating motor fluctuations and dyskinesias in Parkinson’s disease.\textsuperscript{291}

As with its antiviral action, the mechanism by which amantadine benefits the parkinsonian patient remains unknown after thirty years. It has, for instance, no known metabolites in man, and the administered dose can be recovered almost completely from the urine.\textsuperscript{292} Its therapeutic profile resembles that of dopamine (although, like bulbocapnine, it is reported to exhibit mixed agonist and antagonist properties), and it was suggested that it might have an amphetamine-like effect on dopamine release.\textsuperscript{293} Strömberg and colleagues found that it released a reserpine-resistant catecholamine pool

\begin{itemize}
\item \textsuperscript{285} Anonymus, 1970f, 1970g.
\item \textsuperscript{286} Appleton et al., 1970; Dallos et al., 1970; Gilligan et al., 1970; Hunter et al., 1970b,c; Parkes et al., 1970a,b, 1971; Schwieger and Jenkins, 1970; Völler, 1970b; Mawdsley et al., 1972; Fahn and Isgreen, 1975; Voeller, 1976; Umbach and Oppel, 1976.
\item \textsuperscript{287} Tyrell et al., 1965.
\item \textsuperscript{288} Geßler, 1968.
\item \textsuperscript{289} Dallos et al., 1970.
\item \textsuperscript{290} See references in Lang and Blair, 1989.
\item \textsuperscript{291} See, for example, Ruzicka et al., 2000.
\item \textsuperscript{292} Tyrell, 1965; Lang and Blair, 1989.
\item \textsuperscript{293} Grelak et al., 1970; Strömberg et al., 1970; von Voigtlander and Moore, 1971b; Farnebo et al., 1971; Strömberg and Svensson, 1971; Bailey and Stone, 1975.
\end{itemize}
dependent on catecholamine synthesis, which action Carlsson compared to that of catecholamine release by d-amphetamine.\textsuperscript{294} Mawdsley and colleagues, however, found that cerebrospinal fluid HVA (and 5-HIAA) levels were unaltered by amantadine treatment.\textsuperscript{295} Peaston and colleagues, using labelled L-DOPA in three parkinsonian patients, found that amantadine reduced peripheral metabolism of L-DOPA.\textsuperscript{296} In animal studies, amantadine released peripheral dopamine in animals treated with the transmitter; in vitro, it facilitated evoked dopamine release and inhibited dopamine re-uptake.\textsuperscript{297} The potent dopamine re-uptake inhibitor, mazindol, however, does not seem to be of benefit in Parkinson’s disease.\textsuperscript{298} In his review of amantadine and its actions, Allen suggested that the major effect of the drug might be to promote the high affinity state of the striatal D$_2$ receptor by an interaction with membrane lipids.\textsuperscript{299}

Amantadine elicits occasional side effects reminiscent of those of the anticholinergic drugs, but is not anticholinergic in any of the major tests of such activity (guinea pig ileum, vasodepressive response to acetylcholine in dogs, inhibition of oxotremorine-induced tremor).\textsuperscript{300} It was reported, on the other hand, to inhibit NMDA-evoked acetylcholine release in the rat and rabbit striatum, and to suppress the electrical conductivity of the acetylcholine receptor in denervated muscle;\textsuperscript{301} further, physostigmine was used as an antidote in a case of attempted suicide with a huge dose of amantadine.\textsuperscript{302} Its mechanism thus awaits clarification; what is clear is that amantadine is the only agent described as an indirect dopaminergic agent which has maintained its place in the therapy of parkinsonism. Kornhuber and colleagues identified the NMDA receptor antagonizing properties of amantadine, a characteristic shared by memantine (‘Akatinol’; Merz),\textsuperscript{303} which possesses both antiparkinsonian and muscle-relaxing properties.\textsuperscript{304} More recently, it has been reported that amantadine increases tissue decarboxylase activity, an intriguing suggestion.\textsuperscript{305} The question of its exact mode of action, however, remains unresolved, and the empirical employment of antiparkinsonian agents is thus not quite at an end.

Schering examined congeners of amantadine as potential antiparkinsonian agents in the first half of the 1970s, including carmantadine\textsuperscript{306} and dopamantine (which, as the name indicates, combined amantadine and DOPA structures);\textsuperscript{307} these did not prove to be as effective as the parent compound, which thus remains in a class of its own. A single Russian report reported positive experiences with the glucuronide derivative of amantadine, gludantane.\textsuperscript{308} The structural analog rimantadine\textsuperscript{309} was also ineffective in

\textsuperscript{294} Carlsson, 1971.
\textsuperscript{295} Mawdsley \textit{et al.}, 1972.
\textsuperscript{296} Peaston \textit{et al.}, 1973.
\textsuperscript{297} Grelak \textit{et al.}, 1970; von Voigtlander and Moore, 1971b.
\textsuperscript{298} Delwaide \textit{et al.}, 1983.
\textsuperscript{299} Allen, 1983.
\textsuperscript{300} Vernier \textit{et al.}, 1969.
\textsuperscript{301} Albuquerque \textit{et al.}, 1978; Lupp \textit{et al.}, 1992; Stoof \textit{et al.}, 1992b.
\textsuperscript{302} Casey, 1978.
\textsuperscript{303} 1-Amino, 3,5-dimethyladamantane. U.S. patent to Lilly: 1968.
\textsuperscript{304} Fischer \textit{et al.}, 1977; Kornhuber \textit{et al.}, 1994.
\textsuperscript{306} 1-(1-Adamantyl)-2-azetidine-carboxylic acid.
\textsuperscript{307} N-(3,4-Dihydroxyphenethyl)-1-adamantane-carboxamide.
\textsuperscript{308} Cited in Vernier, 1996.
parkinsonism; its advantage over amantadine with respect to viral prophylaxis was, in fact, the absence of central nervous system side effects. It is an ironic footnote that the emergence of influenza A2 virus strains which are resistant to amantadine were reported as early as the first half of 1970.

**Serotonin-related agents**

At the end of the 1950s, 5-HT was attracting “far more attention than any other pharmacologically-active substance”; in a 1958 review of the serotonin research between 1954 and 1958, Page cited no less than 529 references. Yet it would be the middle of the 1960s before a transmitter role for the amine would be generally acknowledged. Serotonin or 5-hydroxytryptamine had been known for decades under various names as a peripheral humoral agent. It was then discovered in 1953 by two groups in the brain, much to their own surprise and that of others, and was in 1957 demonstrated by Costa and Aprison in human brain. It exhibited a highly specific distribution in the central nervous system, with the highest levels in the substantia nigra, nucleus ruber and hypothalamus. Brodie and Shore proposed in the same year that 5-HT acted in the central nervous system as a transmitter, but the idea met with a great deal of resistance.

As with the catecholamines, there existed a number of alternative explanations for the presence of 5-HT in brain. The American neuroendocrinologist Woolley had noted, for example, that oligodendrocytes in cell culture exhibit a pulsating behaviour which was inhibited by serotonin: “the pulsations of the oligodendroglia, and their anatomical situation in the [comparatively poorly vascularized] brain, suggests that these cells are little stirring devices which circulate the extravascular fluid” and thus help to maintain the exchange of metabolites. He hypothesized that serotonin, by inhibiting these

![Figure 16-20: Serotonin, its precursor (5-hydroxytryptophan, 5-HTP) and its major metabolite (5-hydroxyindoleacetic acid, 5-HIAA).](image)

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309 α-Methyl-1-adamantanemethylamine. Dutch (1965) and U.S. patents (1967) to Du Pont.
310 See, for example, Evidente et al., 1999.
311 Oxford et al., 1970.
312 Crossland, 1960.
313 Page, 1958.
314 Twarog and Page, 1953; Amin et al., 1954.
315 Read before the Society of Biological Psychiatry in June 1957; published in Costa and Aprison, 1958.
316 Amin et al., 1954.
317 Brodie and Shore, 1957; Shore et al., 1957.
pulsations, might induce local anoxia, thus explaining, for example, LSD-induced hallucinations.\footnote{Woolley, 1957.} John Crossland also felt at this stage that the evidence for a transmitter role for 5-HT was inadequate:

> If 5-hydroxytryptamine is a transmitter substance, it would seem to exert its action over a very narrow area of the central nervous system. It can hardly be responsible for general non-cholinergic transmission.\footnote{Crossland, 1960.}

Crossland also noted the major problem with 5-HT research, which also affected dopamine research:

> The most embarrassing feature of 5-hydroxytryptamine is its relationship with adrenaline. The similarity of their structures, distribution and metabolism makes it difficult to decide which is involved in any experimental situation, and also raises the question of whether 5-hydroxytryptamine and adrenaline may not reflect different aspects of a common process.\footnote{Ibid.}

The biochemical tools available to the researcher tended to modulate all the monoamines in an indiscriminate manner:

- reserpine depleted stores of all central monoamines;
- DOPA decarboxylase and 5-HTP decarboxylase appeared to be similar and probably identical enzymes;
- monoamine uptake inhibitors of the time were not specific for particular monoamines;
- all monoamines were metabolized by the single enzyme MAO.

It was thus not surprising that differentiating between the effects and roles of the various monoamines was a problem. This was especially true, as most workers appeared determined to restrict the number of central transmitter substances to an absolute minimum, resulting in unnecessary competition between the champions of the various candidates. One gets the impression that some of the pioneers would have been appalled by the explosion in numbers of not only transmitter classes and species, but also of the subdivisions of receptors with which they interact. That serotonergic transmission occurs in certain specific regions but does not exclude the possibility of other transmitters, even in these same regions, is no longer surprising; in the 1950s, this was often not the case. Models of brain function were much more simplistic, still heavily reliant on concepts derived from studies of nerve-muscle interactions – and certainly easier to comprehend in a holistic manner. In any case, it was principally Brodie and Shore who championed the role of 5-HT as a transmitter, persisting until it was finally accepted a decade after they had proposed the idea.

As already discussed, Birkmayer was initially of the opinion that Parkinson’s disease involved primarily a deficit in central serotonergic function, principally because of the vegetative aspects of the disorder.\footnote{Birkmayer and Hornykiewicz, 1961.} This suspicion was well grounded; the reserpine model of parkinsonism, for instance, was seen by many as evidence for the involvement of 5-HT in the disorder, as the leading American reserpine investigators Brodie and Shore were able to support with compelling evidence the concept that its central effects...
were related to 5-HT release. There were several other reasons which suggested that 5-HT might be involved in parkinsonism. Firstly, the highest levels in the human brain were found in the mesencephalon and diencephalon, and it was certain nuclei of these regions that exhibited the clearest signs of neurodegeneration in the disorder. Further, both reserpine and the phenothiazines were regarded as chemical antagonists of the effects of serotonin, and both were known to be capable of eliciting parkinsonian symptoms in man, as discussed in chapter X.

Birkmayer approached Hornykiewicz in 1957 with the idea of measuring 5-HT in the brains of deceased parkinsonian patients, but Hornykiewicz’ interest at this time already concerned dopamine. Birkmayer had tried lysergic acid diethylamide-25 (LSD) in parkinsonian patients in the late 1950s, but improvement of tremor and rigidity was achieved only with doses which were hallucinogenic. No evidence for a serotonergic defect was detected in measurements of 5-HIAA in urine and cerebrospinal fluid, but Birkmayer found that 25mg iproniazid extended an oculogyric crisis in one of his patients from a normal duration of a few hours to a period of three days; this further convinced him of the assumption of serotonergic involvement, although other amines also came into question. In the meantime, Carlsson’s work with reserpine and the reversal of its effects with L-DOPA stimulated his interest in dopamine, although he remained convinced that 5-HT played a role in the vegetative symptomatology. The suggested assessment of brain 5-HT in parkinsonism was finally conducted by Hornykiewicz and Bernheimer in 1961, and revealed that there was a reduction in the levels of 5-HT in many regions of the brain, including striatum and substantia nigra, but these reductions were not as marked as those of dopamine. Sourkes and Poirier reported in 1965 a lack of consistent correlation between surgical lesions in the substantia nigra and striatal 5-HT content.

As discussed above, both McGeer’s group and Barbeau proposed in the early 1960s that 5-HT was involved in some parkinsonian symptoms, particularly tremor, but neither converted this view into a practical therapeutic strategy. Barbeau had identified a reduced urinary 5-HIAA level in parkinsonian patients (both basal levels and following challenge with D,L-tryptophan), but the value of such a test is doubtful (see Degkwitz below) and the same caveats with respect to experimental design must be exercised as with urinary dopamine levels. On the basis of these results and the report that 5-HTP allayed nicotine-induced tremors in animals, Barbeau administered 5-HTP to parkinsonian patients, and found some improvement in tremor and, to a lesser extent, rigidity; the patients were reported to notice a greater benefit from the combination of this drug with L-DOPA than from either agent alone. The approach does not appear to have been further pursued, nor were the detailed results ever published.

The hypothesis that 5-HT/histamine balance was involved in tremor, however, continued to be investigated into the 1970s, by which time interest in central histamine was rapidly declining. Agnoli’s group reported in 1972 that the Sandoz agent BC 105...
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(pizotyline), a drug which combined anti-serotonergic and anti-histaminergic actions, was reported to be as effective as promethazine against tremor, but with less marked side effects; it was, however, not successful as a commercial antiparkinsonian agent.

In their first paper on the L-DOPA effect, Birkmayer and Hornykiewicz attached a comment to the end to the effect that preliminary experiments with 5-HTP in parkinsonian patients indicated that improvement of certain unspecified negative symptoms of the disorder could be achieved with this amino acid. This was pursued further in the second paper; in this case, however, 50mg (i.v.) 5-HTP elicited no significant kinetic effect in any of sixteen patients; 100mg produced vomiting and hypotension. Oculogyric crises were resolved in about half the patients, if only temporarily; agitated patients were sedated and slept for one or two hours. In contrast, the same dose led to an exacerbation of the motor symptoms of two chorea Huntington’s patients; this effect persisted for a number of days. Finally, the blood pressure-sinking effect of 5-HTP (and of L-DOPA) was similar in both parkinsonian and normal persons, evidence against a general decarboxylase insufficiency in parkinsonism.

Birkmayer was convinced by these experiments that 5-HT was probably not crucially involved in the motor symptoms of Parkinson’s disease, but its involvement in vegetative symptoms was another question. In 1963, he noted that it was recognized that parkinsonism patients feel uncomfortable in warmer conditions; during summer heat waves, Birkmayer had encountered patients whose temperatures remained at 40°C for days, unresponsive to antipyretic medication, a condition which often proved fatal (on average: five deaths in his hospital per year). He had noticed, however, that during the two years of applying the L-DOPA/MAO inhibitor therapy, there had not been a single case of fatal hyperpyresis, prompting him to investigate the physical discharge of heat by his patients. He employed the method of Auerswald and Bornschein, whereby the ratio between the temperature gradient between thigh and large toe of the naked and the clothed subject was used as an index of the functionality of heat economy. Birkmayer discovered that the value for this ratio was about 2 in normal persons, but 1.1 in untreated parkinsonian patients, indicating disturbed heat management in the latter, although core temperature was normal. He found that 50mg L-DOPA shifted this index only marginally, but 50mg 5-HTP moved the parkinsonian value to 2.1. As only a few of his patients had previously received 5-HTP (for experimental purposes), he attributed the observed decline in mortality to the regular use of MAO inhibitors; about this time Hornykiewicz and Bernheimer had found that such therapy led to a great increase in central levels of 5-HT and noradrenaline, but not of dopamine. As a consequence, Birkmayer treated heat crises in his patients after this time with 50mg 5-

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330 Agnoli et al., 1972. It is interesting to note that Garbarg et al. (1983b) found the highest brain histidine decarboxylase activity after that of the hypothalamus was in the substantia nigra. Enzyme activity was decreased neither in this region or any other assessed area of the parkinsonian brain.
331 Birkmayer and Hornykiewicz, 1961.
332 Birkmayer and Hornykiewicz, 1962.
HTP, and found that they were invariably resolved within thirty minutes. The effect lasted for up to twenty-four hours, and could be repeated as often as desired. It was also at about this time that Feldberg and Myers reported that serotonergic mechanisms were central to heat regulation in the cat.

It is difficult to know whether the heat crises experienced by Birkmayer’s patients were entirely attributable to the disorder, and how much they were the result of anticholinergic therapy. Untreated parkinsonian patients also exhibit dysfunctional heat management and reduced sweating, but these features of the disorder are exacerbated by any form of anticholinergic therapy. Hyperthermia associated with atropine treatment of parkinsonism was recognized in the 1930s:

> It is not uncommon to find a small rise in temperature after taking a large dose of atropine. This is probably a direct effect on the thermogenic centre. It cannot be due to a diminished loss of heat because the amount of heat dissipated is actually increased. In severe cases of poisoning the temperature sometimes rises very high, even to 107° or 108°F [≈42°C].

Many workers also reported a reduced tolerance for the Bulgarian treatment during summer. Hyperthermic crises during summer months, often with fatal outcomes, had thus been a problem associated with parkinsonism for many years, the only solution having been careful observation and adjustment of the atropine dose.

In 1962, Robert Resnick and colleagues (Harvard Medical School/Peter Bent Brigham Hospital/Lemuel Shattuck Hospital, Boston) assessed 5-HT metabolism in ten paralysis agitans patients using essentially the same approach as that employed by Barbeau and colleagues had applied to assess dopamine and 5-HT metabolism; as controls, however, the Americans used eleven neurological patients on the same ward as the parkinsonian patients. Although baseline urinary 5-HT and 5-HIAA concentrations were lower in the control than in the parkinsonian group, the differences were not statistically significant. Levels of the two indoles following administration of 0.66mg.kg⁻¹ D,L-5-HTP were also lower in the paralysis agitans cases, but the range of values in each group rendered the result non-significant. The authors were aware that their results primarily reflected gastrointestinal metabolism, which was interesting in light of the more speculative interpretation which the Canadians afforded their results, but noted that it was clear that there was no general metabolic defect in 5-HT metabolism in parkinsonism; a localized lesion in the central nervous system, however, “remains a speculative possibility.” Degkwitz reached the conclusion a few years later that urinary 5-HIAA levels were not at all informative about 5-HT metabolism in the organism; like Resnick, he found that only 50-70% of administered 5-HTP could be recovered as hydroxyindoles in the urine, casting doubt on the assumption that 5-HIAA was the only 5-HT metabolite.

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336 Feldberg and Myers, 1963.
337 Dixon (1936), cited in Hall, 1937. Sollmann (1936) wrote that low doses of atropine suppressed perspiration and thus increased body temperature, while high doses led to a fall in temperature.
338 For example, Neuwahl, 1939; Panegrossi, 1940, p.19.
339 Resnick et al., 1962.
Roos and Steg (Departments of Pharmacology and Physiology, University of Göteborg) reported in 1964 experiments which contrasted with those of the famous 1957 Carlsson et al. paper: they found that the infusion of 200mg.kg\(^{-1}\) 5-HTP was sufficient to relieve the rigidity and tremor in the rat calf muscle elicited by 3.6mg.kg\(^{-1}\) i.p. reserpine, and also to relieve the effect of the latter on \(\alpha\)- and \(\gamma\)-motoneuron excitability. The results cannot, however, be seen as contradicting Carlsson’s earlier findings. As the authors noted, they achieved their results using electromyographic techniques which did not measure akinesia, the major parameter assessed by Carlsson’s group. Tremor and rigidity, on the other hand, had not been obvious in Carlsson’s animals (mice and rabbits), reflecting possible species difference in the response to reserpine.\(^{341}\) On the other hand, the new results were interesting from the viewpoint of antiparkinsonian therapy, but the paper did not attract a great deal of attention.

The work of Sourkes and Poirier in the mid-1960s also provided evidence for the involvement of basal ganglia 5-HT in motor function.\(^{342}\) Hassler and Bak reported in 1969 that increasing the levels of striatal 5-HT in the rat with drugs such as harmaline led to rigidity and tremor-like jerking; using iproniazid to increase striatal dopamine levels produced hyperactivity. If the rat was subjected to hemidecerebration, dopamine levels dropped by 50\% without a change in 5-HT levels, and a slight contralateral tremor and ipsilateral turning were seen; tremor could be amplified by administration of harmaline. These results were interpreted as indicating that the ratio of 5-HT to dopamine in the striatum determined motor activity: if less than unity, rigidity and tremor resulted; if greater than unity, hyperactivity.\(^{343}\) These results suggested that it should be thus possible to treat these two symptoms in parkinsonism with serotonin antagonists, but this approach does not appear to have ever been further investigated.

Duvoisin reported in 1971 that he had tried 5-HTP in parkinsonian patients, but succeeded only in inducing ataxia and vomiting; there was no modification of symptoms or of \(\text{L}-\text{DOPA}\)-induced dyskinesias.\(^{344}\) Cotzias’ group treated one case of parkinsonism resulting from chronic manganese poisoning with 5-HTP after \(\text{L}-\text{DOPA}\) had proved to be counterproductive; all symptoms were relieved by the treatment, and it was suggested that the amino acid might be considered in cases which were not responsive to \(\text{L}-\text{DOPA}\).\(^{345}\) They also tried \(\text{L}-\text{tryptophan}\) and \(\text{D,L}-5\text{-HTP}\) (amongst other amino acids) in gram doses in an effort to control \(\text{L}-\text{DOPA}\)-induced dyskinesias, but without success.\(^{346}\) Barbeau’s laboratory reported in 1969 that reserpinized rabbits exhibited reduced striatal acetylcholine content, and that \(\text{L}-\text{DOPA}\) acted to restore normal levels. Obversely, physostigmine led to an increased acetylcholine content in this region, an effect which could be counteracted by treatment with 5-HTP. It was suggested that cholinergic function in the striatum was subject to opposing controls by dopamine and 5-HT; opposing roles for the two amines had also been reported by other workers in other brain regions.\(^{347}\) Once again, however, little attention appears to have been given this phenomenon.

\(^{341}\) Roos and Steg, 1964.
\(^{342}\) Sourkes and Poirier, 1965, 1966a; Poirier et al., 1966.
\(^{343}\) Hassler and Bak, 1969; also Kim et al., 1970.
\(^{344}\) In Udenfriend et al., 1971.
\(^{345}\) Mena et al., 1970.
\(^{346}\) Cotzias et al., 1971b.
\(^{347}\) Orzeck and Barbeau, 1970.
Isamu Sano, mentioned above regarding his early L-DOPA trial, returned to the idea of “precursor therapy with monoamines” in the 1970s, publishing a number of papers in Japanese journals (one of them in German) on the use of L-5-hydroxytryptophan (L-5-HTP) in depression. Sano also promoted this therapy at the international symposium on depressive illness held at St. Moritz in January 1972, which was also attended by Birkmayer. Although he did not present a paper, Sano emphasized during his contributions to the symposium discussions that the success of his version of the 5-HTP therapy, which contrasted with the disappointing results gained by earlier workers, could be attributed to his employment of the L-isomer, which, like L-DOPA, had been difficult and expensive to procure in the required quantities. Later that year, Sano published a pair of papers in the *Münchner Medizinische Wochenschrift* concerning the employment of L-5-HTP in both depression and Parkinson’s disease. In the second paper, he expressed disappointment that the success of DOPA therapy had been exaggerated, and suggested that L-5-HTP was equally effective, albeit with a different profile of action, proving especially beneficial for the affective aspects of the disorder (depression). As L-5-HTP was particularly effective against tremor, he was investigating a combined therapy of the two agents; to my knowledge, the outcome of this investigation has not been published. Sano also proposed that two forms of parkinsonism could be distinguished on the basis of the accompanying vegetative symptomatology, and related them to cell loss in different areas of the brainstem.

Although a number of the newer “dopamine receptor agonists” also exhibit activity at some 5-HT receptors, these papers appear to have been the last attempt to specifically design a therapeutic strategy for the motor symptoms of Parkinson’s disease involving serotonin. Some side effects of the L-DOPA therapy were attributed to the accumulation of dopamine in neurons which normally stored 5-HT; tryptophan was thus employed by Birkmayer to compete with L-DOPA for uptake into such neurons. L-Tryptophan was especially recommended by Birkmayer for the treatment of those rare cases in which L-DOPA therapy results in a psychotic reaction involving hallucinations and paranoid ideation (“DOPA psychosis”); the authors reported that in the previous year, sixteen such cases had presented in a total of three hundred patients. These crises did not appear to be related to length of therapy or to the dose being administered. It was found that L-tryptophan (3×500-100mg/day) was able to overcome these crises without interrupting L-DOPA treatment, as had been previously necessary. The authors commented that the genesis of these responses was of theoretical interest: Almost all long-term L-DOPA patients experienced dyskinesia, but only a few suffered psychosis. On the other hand, Birkmayer had also seen similar dyskinesia in patients receiving only L-tryptophan. Gehlen and Müller noted in 1974 that the estimated incidence of DOPA psychosis ranged as high as 20%, with estimates normally around 14-15%. They also had success with L-tryptophan in four of five patients with such a psychosis. This phenomenon was related by Birkmayer’s group to reports by Chase’s and other groups that striatal 5-HT levels declined during L-DOPA therapy. Further, there were reports that tryptophan-poor diets and L-DOPA administration both exacerbated psychic symptoms.
in schizophrenia, with which Barbeau had compared the nature of the DOPA psychosis. A double blind study failed to confirm these findings, although it has also been suggested that there exist distinct patient populations with respect to responsiveness to L-tryptophan therapy.

It was also suspected that the increase in peripheral 5-HT concentrations following the use of peripheral decarboxylase inhibitors might explain some of the side effects of combined L-DOPA therapy. Karobath and colleagues reported a decline in cerebral levels of 5-HT treated with L-DOPA. Neither \( p \)-chlorphenylalanine (PCPA), which depletes 5-HT stores, nor the central serotonergic antagonist methysergide influenced parkinsonian symptoms.

Neither tryptophan nor 5-HTP have maintained a regular place in the therapy of Parkinson’s disease, although both are sometimes employed as “natural sedatives” to assist with sleep problems. The problem with both amino acids is their lack of specificity; tryptophan is not only the precursor for 5-HT, but is also the substrate for the kynurenine pathway; in fact, 90% of administered tryptophan is probably metabolized in this manner. 5-HTP, on the other hand, is decarboxylated in all neurons with aromatic amino acid decarboxylase, including those which do not normally synthesize 5-HT; neither it nor L-DOPA can be regarded as ‘magic bullets’ which exclusively target normal physiological sites of action for 5-HT and dopamine.

Interest in the involvement of serotonergic mechanisms in the parkinsonian problem has recently been revived in part by the beneficial effects of clozapine in the management of tremor reported by some workers. The 5-HT\(_3\) receptor antagonist ondansetron and the 5-HT\(_2\) receptor antagonist mianserin have both been investigated as potential antiparkinsonian agents, but their place in the therapy of this disorder has not yet been established.

**Figure 16.22: 5-HT receptor antagonists which have been examined in the therapy of parkinsonism.**

**Ondansetron**

**Mianserin**

**Melanocyte stimulating hormone inhibitory factor**

Another novel chemical approach to be introduced into the therapy of parkinsonism in the period covered by this work was the use of the melanocyte stimulating hormone inhibitory factor (L-propyl-L-leucyl-glycine amide; MIF) as a potentiator of L-DOPA by Kastin and Barbeau in 1972. Work being undertaken in Kastin’s laboratory at this time

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355 Cited in Gehlen and Müller, 1974.
356 Beasley et al., 1980; Bryant, 1980.
357 Karobath et al., 1971; Klawans and Ringel, 1973; Chase, 1974a.
358 Birkmayer and Riederer, 1980.
359 Reviewed in Kuhn and Müller, 1997b; Deuschl, 1999.
360 Miyawaki et al., 1997.
indicated that MIF potentiated the effects of \( L-DOPA \) in intact and hypophysectomized animals,\(^{361}\) prompting the initial trial of infused MIF in parkinsonian patients. Some symptomatic benefit was achieved,\(^{362}\) but oral administration (250-1500mg/day), proved to be ineffective.\(^{363}\) A second trial in six patients with i.v. MIF (200mg) indicated a beneficial effect in five patients which Barbeau described as far better than “any of the numerous antiparkinson drugs which we have tested in our laboratory over the last 15 years, including levodopa alone.” No changes in brain catecholamine levels were detected.\(^{364}\) Short half-life of MIF in blood, or administration of oral doses that were much higher than required, were explanations offered for the failure of MIF to be as effective as the infused hormone. The results obtained with infused MIF were consistent with the negative effect of MSH on parkinsonian symptoms described by Cotzias and the finding of higher serum MSH levels in Parkinson’s disease,\(^{365}\) but other developments rendered the approach superfluous and it was abandoned. The Chase group found no benefit for parkinsonian symptoms or \( L-DOPA \)-induced dyskinesia of the intravenous administration of either MIF or thyrotropin releasing hormone (TRH).\(^{366}\)

**Electroconvulsive therapy**

Two depressed patients who also suffered from parkinsonism were treated with electroconvulsive therapy (ECT) by Lebensohn and Jenkins in 1975; sustained improvements in both the depressive and motor aspects of their clinical picture were achieved after four sessions. One patient was described as suffering “classic idiopathic Parkinson’s disease” but was also reported to have suffered severely from influenza during the 1918 epidemic; the other patient had not been exposed to phenothiazines for at least eleven years.\(^{367}\) Another author noted that ECT improved parkinsonian symptoms in a patient before the depression for which he primarily received the treatment had been relieved, and suggested that the two conditions were biochemically linked.\(^{368}\) The reports remain anecdotal but interesting, in that the effect of ECT on depression is believed to be related to increased catecholamine turnover, although the reason for this biochemical change is not understood. The use of ECT in patients with severe rigidity is often declined by clinicians, and its use in depression at all is controversial in many countries; despite its possible benefits, it therefore remains an unlikely therapeutic direction. On the other hand, if the precise regions involved in the therapeutic benefit were to be identified, local electrical stimulation might provide benefit to the patient.

Costain and colleagues reported in 1982 that the growth-hormone (GH) response to subcutaneous administration of apomorphine was increased following ECT, and suggested that dopaminergic transmission was enhanced by the procedure.\(^{369}\) Balldin

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362 Kastin and Barbeau, 1972.
364 Barbeau, 1975.
365 Cotzias *et al.*, 1967; Shuster *et al.*, 1973a. The latter group proposed that increased MSH levels were secondary to reduced regulation by midbrain dopamine, and was responsible for seborrhea in parkinsonism. The same authors reported that this seborrhea could be managed with \( L-DOPA \) (Burton *et al.*, 1973). See also criticism by Sandler *et al.*, 1973 and reply by Shuster *et al.*, 1973b.
367 Lebensohn and Jenkins, 1975.
369 Costain *et al.*, 1982.
and associates found that ECT could be beneficial in patients in whom “on-off” fluctuations were particularly aggravating; both symptomatic improvement and reduction in severity of fluctuations was achieved in three of five patients, with the effect lasting several months. It was proposed that ECT reversed post-synaptic loss of sensitivity resulting from long term L-DOPA administration.370

After 1980

I have now reached the end of my discussion of the major therapeutic directions which had made a significant impact on the treatment of parkinsonism by 1980. The “ultimate therapy” had not yet been achieved, and the search continued for yet further alternatives. Amongst the major attempts to manipulate catecholaminergic systems in parkinsonism were the following:

- **Catechol-O-methyl transferase (COMT) inhibitors** had been suggested at the end of the 1960s, as dopamine is metabolized not only by MAO but also by this enzyme.371 Further, L-DOPA can be metabolized in vivo to 3-O-methyl-DOPA (OMD), a reaction particularly favored in the periphery in the presence of decarboxylase inhibitors.372 OMD is not substantially further metabolized, and competes with L-DOPA for uptake into the central nervous system.373 Two groups noted in the early 1970s the deterioration of their parkinsonian patients following OMD administration; although it was also found that OMD accumulated in the plasma of poor responders to L-DOPA therapy, such patients respond poorly to direct dopamine receptor agonists.374 The first reported trial of a COMT inhibitor (GPA 1714; N-butyl-gallate) was that of Ericsson in 1971; despite its beneficial effects, its toxicity prohibited its further use.375 Since then, a number of COMT inhibitors have been developed, including the peripheral inhibitors entacapone (‘Comtan’; Orion/Novartis) and nitecapone and the peripheral/central COMT inhibitor tolcapone (‘Tasmar’; Hoffmann-La Roche). Reduction of adverse side effects associated with L-DOPA therapy was achieved, but hepatotoxicity of the COMT inhibitor itself remain a problem.376

- On the other hand, it was suggested that 3-O-methyl-DOPA itself might be useful in the treatment of parkinsonism, serving as a depot for L-DOPA; it crossed the blood-brain barrier easily, and its plasma half-life (12-15 hours) was much longer than that of L-DOPA. Despite isolated positive reports, this proved to not be the case, as little demethylation of the derivative occurs in vivo in humans.377

- **Dopamine β-hydroxylase inhibitors**, which would block the conversion of dopamine to adrenaline, received limited attention at the beginning of the 1970s. Neither fusaric acid378 nor disulfiram379 appeared to benefit parkinsonian patients, although they were reported to reduce severity of L-DOPA-induced dyskinesia.380

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370 Balldin et al., 1980.
371 Carlsson et al., 1962b.
372 Sharpless et al., 1972.
373 Bartholini et al., 1972; Sharpless et al., 1972; Wade and Katzman, 1975.
374 Calne et al., 1973; Muenter et al., 1972-1974; Reilly et al., 1980.
377 Geissbuhler et al., 1972a; Bartholini et al., 1972; Calne et al., 1973; Muenter et al., 1973.
378 5-Butyl-2-pyridinecarboxylic acid. First isolated from the fungus *Fusarium heterosporium* in the 1930s and subsequently used as an antibiotic, its inhibition of dopamine β-hydroxylase was reported
XVI. Adjuncts and alternatives: Extension of dopamine-based therapy

- **Atypical neuroleptica**, in contrast to the classic antipsychotic agents, such as haloperidol and chlorpromazine, do not generally elicit extrapyramidal side effects. **Clozapine** exerts effects at not only dopaminergic but also at serotonergic, α-adrenergic and cholinergic receptors; it has been used to reduce psychiatric side effects of L-DOPA therapy and to reduce motor fluctuations and resting tremor. There is, however, a risk of agranulocytosis associated with use of clozapine. Prothipendyl had been used in antiparkinsonian therapy as early as the 1950s; it was reported that tremor was improved in eleven patients receiving the agent as adjuvant therapy. Other atypical antipsychotics employed in parkinsonian patients include olanzapine and quetiapine.

- **Dopamine D2 receptor antagonists**: Corsini and colleagues employed domperidone to control the peripheral effects of oral apomorphine therapy. A number of selective antagonists have since been examined with varying success in the control of peripheral side effects of L-DOPA therapy, and thus as an alternative to decarboxylase inhibitors; domperidone remains the major representative in this area. Tiapride (‘Tiapridex’, related to sulpiride, Synthelabo) has been employed as an anti-dyskinetic agent in a number of conditions, including Huntington’s disease, essential tremor and L-DOPA-induced dyskinesia.

- **Adrenergic agents**: The fact that norepinephrine levels and tyrosine hydroxylase activity are also generally reduced in the parkinsonian brain has often been disregarded in favor of correction of the dopamine deficit. The α2-adrenergic agonist clonidine was found to be ineffective in Parkinson’s disease. Narabayashi and colleagues, however, reported a marked improvement in freezing and micrographia following treatment with L-threo-DOPS (‘Dops’; Sumitomo), and some improvement of the cardinal symptoms.

- **Budipine** (‘Parkinsan’; Byk Gulden) combines an incredible range of pharmacological properties: mildly anticholinergic, a non-competitive NMDA receptor antagonist; it does not appear to be a direct dopamine receptor agonist, but may release dopamine from presynaptic sites as well as inhibiting MAO-B. It blocks tremorine-
Figure 16.23: Selection of newer agents trialed in antiparkinsonian therapy. (a) COMT inhibitors; (b) Dopamine β-hydroxylase inhibitors; (c) Budipine; (d) threo-DOPS; (e) Atypical neuroleptica; (f) Peripheral D₂ receptor inhibitor; (g) Nicotine analog.
induced tremor, various experimental catalepsies and MPTP toxicity. Peripheral
effects are minimal. In parkinsonian patients, it is reported to primarily relieve all
three cardinal symptoms to varying degrees with minimal side effects.392

- **Nicotinamide adenine dinucleotide** (NADH) was first employed in antiparkinsonian
  therapy in the early 1960s by Birkmayer on the basis that it is the cofactor for
tyrosinase.393 More recently, it was recognized that tetrahydrobiopterin (BH4) is the
coenzyme for tyrosine hydroxylase; NADH is the cofactor for the rate-limiting
enzyme in BH4 synthesis, quinonoid dihydropteridine reductase. As the blood-brain
barrier is fairly impermeable to BH4, Birkmayer tried both oral and intravenous
NADH therapy in parkinsonian patients and reported great success; these
experiments, however, are somewhat controversial due to a number of shortcomings
in experimental design. Two subsequent trials by other groups have produced
contradictory results.394

- **Iron therapy**, in the form of ‘Oxyferriscorbone’ (Theraplix, France),395 was also
  revived at Birkmayer’s clinic in the 1980s, supported by the demonstration that iron
stimulated tyrosine hydroxylase activity in vitro by up to 20-fold.396 Campbell and
  colleagues, on the other hand, found that concurrent administration of ferrous iron
reduced the bioavailability of both l-DOPA and carbidopa.397 Despite the probable
involvement of disturbed iron homeostasis in Parkinson’s disease398 and the report
that ‘Oxyferriscorbone’ (but not ferrous iron) is anti-oxidative in vitro,399 the clinical
efficacy in this disorder of iron or iron chelator therapy remains to be established.

- The nicotine analog, **SIB-1508Y**, has a high affinity for substantia nigra α4β2
  receptors which release dopamine upon stimulation. It has thus been examined as
one of the more unconventional candidate antiparkinsonian agents, thus far with few
results.400 Nicotine itself was found to synergize with l-DOPA but not with a D2
receptor agonist in MPTP-treated monkeys.401

With the growth in knowledge regarding not only the neuroarchitecture and
neurochemistry of the basal ganglia but of the central nervous system in general, a
wealth of new opportunities have been considered with regard to restoration of as
normal as possible motor function, including the use of neurotrophic factors, free
radical scavengers, NMDA channel blockers and even gene therapy as part of ambitious
neuroregenerative and neuroprotective approaches. These cannot be discussed here, but
have been summarized in my recent reviews on the subject.402

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Budipine is also employed in the treatment of migraine.
393 Birkmayer and Mentasti, 1967.
394 Birkmayer et al., 1993; Dizdar et al., 1994; Kuhn et al., 1996; see further references in Kuhn and
Müller, 1997b.
395 As injection or powder; a 3mL ampoule contained 15mg ferrous/ferric iron-dehydroascorbic acid
complex, 15mg ferric iron- alloxaanic acid complex. Prior to its withdrawal from commercial
availability in 1990, ‘Oxyferriscorbone’ was most commonly employed in the treatment of gastric
ulcer. Interestingly, it was also supplied by Theraplix in combination with 0.5mg atropine/ampoule.
396 Rausch et al., 1988; Birkmayer and Birkmayer, 1989.
397 Campbell et al., 1990.
398 Most recently reviewed in Double et al., 2000.
399 Dostert et al., 1991.
400 Cosford et al., 1996; Menzaghi et al., 1997; Lloyd et al., 1998.
401 Domino et al., 1999.
402 Foley et al. (in press); Riederer and Foley, 2000. See also Koller and Tolosa, 1998.
Table 16-4 (next page): Recommended agents for the treatment of parkinsonism according to the Extra Pharmacopoeia, 1972-1989. Notes: AADI: aromatic amino acid decarboxylase inhibitors (benserazide, carbidopa). After 1989, the Extra Pharmacopoeia no longer included an index of clinical applications; by this point, most antiparkinsonian agents were, in any case, included in the category ‘Dopaminergic agents’.
### XVI. Adjuncts and alternatives: Extension of dopamine-based therapy

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<td>(‘NeyDop’/‘NeyDop N’)</td>
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Table 16-5: Current antiparkinsonian therapy as indicated in the most recent handbooks in Australia, Germany and Great Britain:
(a) as listed in the 2000 annual edition of the Australian ‘MIMS’ (‘Monthly Index of Medical Specialties’; pp.3-319 to 3-331).
(b) as listed in the 2000 (4th quarter) edition of the German ‘Gelbe Liste’ (pp.110-111).
The two belladonna preparations, the organ preparation and benztrpine and pridinol were also listed in the 1997 edition of the ‘Rote Liste’ but not the 2000 ‘Gelbe Liste’; items marked with an asterisk did not appear in the 1997 ‘Rote Liste’ (section 70). ‘NeyDop’ is a mixture of mostly bovine tissue (20% cerebrum, 40% diencephalon, 20% cerebellum, 20% fetal placenta) in saline; ‘NeyDop N’ also includes L-DOPA, lithium chloride and ascorbate.
(c) as listed in the 1999 edition of the ‘Martindale’ (pp.1128-1146; * drug being investigated as antiparkinsonian therapy).
XVII. Concluding remarks:
From alkaloids to neurochemistry

When the normal composition of the brain shall be known to the uttermost, then pathology can begin its search for abnormal compounds or derangement of quantities . . . it is probable that by the aid of chemistry many derangements of the brain and mind, which are present obscure, will become accurately definable and amenable to precise treatment, and what is now an object of anxious empiricism will become one for the proud exercise of exact science.

Thudichum,
A treatise on the chemical constitution of the brain (1884)

One is constantly impressed by the fact that, throughout the history of antiparkinsonian therapy, three parallel strands of investigation developed which often showed little regard for one another: the clinic of parkinsonism (and other neurological disorders), the neuroanatomical pathology and the neurochemistry. Only at the end of the 1960s were these three strands wound together to yield a more complete and rounded view of the parkinsonism. The history of these three fields and their relationships to one another cannot be traced here in detail, but a few comments which briefly explore the reasons for this development are required in order to complete the present story.

The essential problem has always been limitations imposed by available technology. Neuroanatomists of the 19th and early 20th centuries were able to detect only relatively gross pathologies in their brain samples. As a result, the sometimes unremarkable changes in the substantia nigra were overshadowed by larger changes elsewhere in the brain, even when these changes were inconsistent or infrequently encountered. Further, most reports concerned only a few examined brains, many, indeed, described single specimens. There was also the fact that it was expected, despite the comments of Parkinson himself, that the major lesion would be found in the striatum, known to be involved in control of motor activity, or the cortex; the function of the brainstem was seen principally as a relay station for fibres passing to the muscles. As Lewy noted, it was technical advances in the early part of the 20th century which allowed his own important work and that of the Vogts, Hassler and others in which both the normal basal ganglia and the changes evident in extrapyramidal disease could be explored and defined.1 This allowed the identification of specific lesions in certain brain regions in

1 Lewy, 1942.
parkinsonism, especially the substantia nigra, subthalamic nucleus (corpus Luysii) and nucleus ruber. Nevertheless, this had little immediate impact on the therapy of parkinsonism.

With regard to brain neurochemistry, there were already voices early in the 20th century which suggested that “humoral transmission” occurred in the brain as it did in the periphery, but this was much more difficult to demonstrate in the central nervous system than in muscle. Further, precise localization of putative humoral agents was impractical with available techniques, so that the concept of a pathway associated with a particular neurosubstance could not be developed. Finally, “neurochemistry” as we know it was itself in its embryonic stages. The first major text on the subject, Chemistry of the Brain by Irvine Page, appeared in 1937, but was concerned principally with general metabolic pathways, for which Page explicitly stated that “no apology is necessary”. Twenty-one enzymes had thus far been identified in neural systems, but the author noted that they had been little studied in the brain. More surprising for the present reader would be the thoughts included in his final chapter:

\[\text{Mind and matter may be two aspects of universal stuff. . . . thought is a spiritual manifestation . . . energy itself may be of spiritual origin.}\]

Neurochemistry was still in the phase initiated by Thudichum in the last quarter of the 19th century: cataloging and measuring the contents of the system, without yet producing a synthesis of the information which might explain specific neural functions or disorders. By the 1930s, there was a certain awareness of the possibility that altered brain metabolism might be involved in neurological disease:

\[\text{Hedged about as it is with delicate restrictions, surely it is more possible to understand how pathologically the brain in its metabolism may not only be subjected to the action of toxins (the usual view), but occasionally fail owing to self poisoning with its own misguided machinery. So should we envisage a possible occasional development of mental abnormality.}\]

In a broad sense, this view is still valid today; but at the time it was written (1940), this review of the “biochemistry of brain tissue” was concerned principally with factors modulating oxidative respiration, and even acetylcholine was mentioned only in passing.

But the move towards a more intimate analysis of central nervous system biochemistry had already begun; Page himself was very much involved in research into the function of serotonin in neural systems. In his review of the “biochemistry of the nervous system” (1944), Derek Richter (Central Pathological Laboratory and Mill Hill Emergency Hospital, London) included a section on acetylcholine, noradrenaline and related enzymes in the brain; the mechanism of action of such molecules, however, was still regarded as controversial: (“other investigators are unwilling to consider acetylcholine as anything more than an incidental by-product of nerve metabolism”),

\[\text{Page (1937) cited in McIlwain, 1999.}\]
\[\text{It is interesting to note that Thudichum himself largely spurned the idea of an integration of brain chemistry and physiology; he was particularly spiteful in his polemics against the work of investigators such as Wilhelm Kühne (who coined the term ‘enzyme’) and Hoppe-Seyler; see McIlwain, 1975.}\]
\[\text{Peters, 1940. He commenced his essay (in an industry journal) with: “Brain tissue is the most important biological invention in Nature.”}\]
\[\text{Richter, 1944.}\]
and their function in the brain a complete mystery. There was some discussion of the effects of pharmacological agents in the central nervous system, but even this was limited to the impact of convulsants and narcotics on central respiration.

In 1953, Blaschko distinguished between two types of effect which a catecholamine might exert on an effector cell:

*I think the metabolic studies make it likely that for adrenaline and related compounds we shall have to distinguish between first-phase effects, exerted upon the cell membrane from the outside, and second-phase effects, which depend upon the presence of the amine inside the cell. It may be that in the first phase, we see the sympathomimetic effects *sensu strictiori*, while in the second phase we observe the effects upon carbohydrate metabolism.*

Such views were also conditioned by concepts of transmitter-receptor interaction which closely resembled those of enzymes and their substrates.

At this point, however, there was little opportunity to integrate the available biochemical information with anatomical maps of the brain or with specific clinical pictures. There had, however, been suggestions even by his stage that specific changes in brain biochemistry might underlie the symptoms of psychiatric and neurological disease. As early as 1940, Hans Birkehäuser (University Medical Clinic, Basel) had noted that evidence had accumulated that anticholinergic acted as a transmitter substance not only in the periphery, but also in the central nervous system. Further:

*It is probable that high [choline] esterase levels in a particular tissue are indicative of significant nervous activity. Certain motor disturbances, as observed, for example, in schizophrenia, might be attributable to problems in enzymatic activity. Reduced AChE levels would lead to the accumulation of ACh, resulting in constant stimulation of the affected region of the central nervous system. . . . Before one can investigate pathologic brains for enzyme levels, the occurrence of these substances in the normal organ must be established.*

Birkehäuser noted that David Nachmansohn (1899-1983) had already published a great deal in recent years concerning the distribution of choline esterase in the brain (including the human brain), Nachmansohn had concluded that:

*The great differences in esterase activity in different regions suggests that acetylcholine is involved not only in the transmission of nervous impulses in the autonomic system and at the neuromuscular junction, but also in the central nervous system.*

No information had yet been published concerning monoamine oxidase, diamine oxidase or choline oxidase. Birkehäuser therefore undertook the task of investigating these enzymes, and emphasized the need to report not only absolute values, but also the number of brains investigated and the variation in levels observed; further, the effects of age, gender, pathological and anatomic abnormalities and the post mortem delay prior to assessment of the tissue. The results of these investigations have been mentioned
above;\textsuperscript{10} at this point, it is more important to note this paper as an early example of the applied awareness that measurement of biochemical parameters might yield insights into the etiology of central nervous system disorders.

The next major step was the mapping of various neurosubstances in the brain, as it was accepted (although not unequivocally) that localization was probably an indicator of function.\textsuperscript{11} Amongst the various substances mapped at this stage, that of central nervous system sympathin by Marthe Vogt proved to be most significant; adrenaline and noradrenaline were already recognized to exercise neurohumoral functions in the periphery, and their localized presence in the brain suggested similar possibilities in this tissue. Further, the methodological approach employed by Vogt was also adopted by many who followed her, including Sano’s group in 1959. It also provoked workers such as Carlsson and Brodie to experiments in the pharmacological manipulation of central neurosubstance levels; the significance of the discovery of the effects of reserpine and of their reversal by the administration of amino acid precursors must be reckoned as one of the most significant advances in science this century.\textsuperscript{12}

It was about this time that the connection between neurochemical findings and neurological conditions first received wider attention. Workers had begun to correlate the central biochemical actions of drugs with their pharmacological or behavioural actions; this shift was potentiated by the introduction of the first psychopharmaca, chlorpromazine and reserpine. In particular, the role of 5-HT in mental disorders was discussed.\textsuperscript{13} Holtz noted the significance of this development in 1958:

\emph{When one reviews the results to date of serotonin research, it is perhaps especially impressive that the emphasis which was initially given entirely to the investigation of the periphery, of smooth muscular organs, . . . on the basis of which it was discovered, has undergone a shift, in that the central effects of the biogenic amine which also occurs in the brain has been the focus of research in recent years and remains as such.}\textsuperscript{14}

5-HT was the most investigated amine during the second half of the 1950s. Pharmacological investigations repeatedly underscored its significance: the psychotropic effects of lysergic acid diethylamide (LSD) and other indole-based compounds, the depletion of central 5-HT by reserpine, the elevation of its levels by the precursor 5-HTP or the MAO inhibitor iproniazid. In other words, the research tools available to pharmacology at this point all favoured the investigation of 5-HT – regardless of the fact that these tools would later prove to be far from specific for serotonergic systems – and prompted investigators to ask whether altered levels in the human brain might be involved in neurologic or psychiatric disease; there were undoubtedly some who were already pondering whether the pharmacological manipulation of its levels might provide solutions to some of these problems. In the meantime, the empirical value of the psychopharmaca in the modulation of mood, arousal and cognition, advances built upon foundations laid long ago by alkaloids such as scopolamine, ensured that they remained objects of intense laboratory investigation.

\textsuperscript{10} See pages 256 and 634.
\textsuperscript{11} See, for example, discussion in Burn, 1950.
\textsuperscript{12} See chapter X.
\textsuperscript{13} See, for example, Woolley, 1957; Costa \textit{et al.}, 1962.
\textsuperscript{14} Holtz, 1958.
These developments completed what McIlwain has described as the regaining by neurochemistry of its specific biological components;\textsuperscript{15} the neurochemistry of the brain was no longer a laboratory curiosity, it was a system which could be manipulated by pharmacological intervention, thus paving the road to neuropharmacology. Curzon has also examined the development of neurochemistry from this period as reflected in the articles appearing in \textit{Journal of Neurochemistry}, the first journal devoted to neurochemistry (founded 1956). A few figures will suffice to indicate trends:

- In 1956/7-1960, around 40\% of papers concerned brain constituents, under 25\% transmitters; in 1975-1980, these figures were about 15\% and 40\% respectively (1985-90: 15\% and 60\%).
- This rise in the focus on transmitters applied to all classes: investigations involving amines rose from 10 to 20\% (1985-1990: 25\%) of papers, amino acids from 3 to 9\% (15\%), acetylcholine from 4 to 7\% (10\%), peptides from 0 to 3\% (6\%).\textsuperscript{16}

The founding of the \textit{Journal of Neurochemistry} was in itself a departure, marking the emergence of neurochemistry as a field distinct from general physiology and biological chemistry. The trend to neurotransmitter investigations marked the direction that this evolution was bound to take. The journal was clearly not clinically oriented, nor was neurochemistry in itself, but the confluence of clinic and chemistry was made possible by this emancipation.

The philosophy of this change was summarized by Blaschko at the 1960 Ciba Symposium on Adrenergic Mechanisms:

\begin{quote}
\textit{Biochemistry has ceased to be a refined kind of cookery; we no longer destroy all the structural elements in attempts to separate the chemical constituents of the tissues as pure compounds. This must still be done, but we also try to break up the tissues in a more controlled fashion, so as to keep the structures of subcellular size intact; and there is the parallel study by cytological methods . . . to find out where the structures isolated are situated in the intact cell.}\textsuperscript{17}
\end{quote}

He noted that little had emerged to date from the convergence of physiology and pharmacology, as the active substances occur at concentrations too small to localize precisely; nonetheless, methods were emerging which would change this situation. It is, of course, interesting that it was the laboratory scientists and not the clinicians who made this connection. It is also ironic that, at the same symposium, the pathfinding work of Carlsson in this connection was received with such scepticism. The change which was imminent was presaged in the comment made by Houston Merritt at the commencement of the meeting of the Association for Research in Nervous and Mental Disease in 1957:

\begin{quote}
\textit{The ultimate aim of pharmacotherapy in diseases of the nervous system is to correct any functional disturbance of a physiological or biochemical nature, or to modify morbid structural disease in such a manner that physiological function becomes more normal.}\textsuperscript{18}
\end{quote}

\textsuperscript{15} McIlwain, 1991.
\textsuperscript{16} Curzon, 1993.
\textsuperscript{17} Vane \textit{et al.}, 1960; p.437.
\textsuperscript{18} Merritt, 1959.
Although the meeting at which this remark was made was concerned mostly with the prospects of pharmacological therapy in psychiatry, two papers discussed anticonvulsants (one by Yahr), one spinal reflexes, and one movement disorders. More importantly, the idea that a biochemical functional deficit might be relieved by pharmacological therapy had been presented, even if at this stage it remained a hypothetical notion.

The final stage in this phase of the journey was initiated in 1960-1961 in Vienna. Firstly, Ehringer and Hornykiewicz provided the first evidence which associated a particular disorder with a specific central neurochemical defect in a defined region. There had been earlier reports linking brain disorders to possible chemical anomalies, based on the effects of therapeutic drugs; but these remained hypothetical in the absence of direct proof. Ehringer and Hornykiewicz had provided provocative evidence, but one more step was required to confirm its clinical significance. The change that they had detected was in way linked with the standard therapy of parkinsonism, their results could not have been predicted on the basis of previous clinical experience. But this was also a problem; it was entirely possible that the striatal dopamine deficiency described by these workers was purely incidental to the disorder. The successful treatment of parkinsonian patients with L-DOPA by Birkmayer was thus the crucial proof of the clinical significance of their discovery. Equally importantly, however, was that it confirmed and underscored the validity and utility of the neurochemical approach to the investigation and therapy of neurological disorders; not only mood and arousal, but also motor deficits attributed to irreversible and probably progressive damage of the central nervous system could, in principle, be managed – and perhaps cured – by the administration of specific neurochemical compounds. Even the limited success experienced with low dose L-DOPA therapy was sufficient to confirm the significance of the discovery of a striatal dopamine deficiency. The revolutionary nature of this development can hardly be overstated. In the space of less than a decade – between Vogt’s mapping of brain sympathin in 1954 and the successful therapy of parkinsonian patients with L-DOPA in 1961 – both psychiatric and neurological disease of the central nervous system had become valid targets for directed neurochemical investigation and, ultimately, therapy.

The introduction of L-DOPA therapy for parkinsonism represented the provisional culmination of this phase in the evolution of neurochemistry: it was at this stage that clinic, neurochemistry and neuroanatomy converged, although it was not immediately recognized. Were Ehringer and Hornykiewicz to report the dopamine deficiency for the first time today, there would be a rush of papers from other workers in a very short time confirming, refuting and qualifying their findings. The early successes of Birkmayer and others with L-DOPA, though not entirely satisfactory, would stimulate much greater interest in further examination of the therapy today than they did in 1961. But the situation in the 1960s was different. This was a new situation, altering the manner in which neurological disease was addressed, and as such was not immediately accepted.

It is also interesting that at about the same time, the lead in pharmacological research moved from the clinic to the laboratory. Whereas the history of parkinsonian therapy had previously been punctuated by the introduction by individual clinicians of novel or modified therapies, the move to “rational therapeutics” placed the emphasis on laboratory testing and theoretical justification of new approaches. This was not only the

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19 See chapter XII.
result of advancing knowledge and technology, but also of the new style of management of drug development. The requirement for long term large scale trials before a drug could be marketed with specific claims placed such investigations well outside the scope of individual scientists or clinicians; cooperation between various types of investigators and between different institutions became an absolute requirement. This also meant that the role of the drug company was altered; the cost and scale of such projects could only be managed by a large organization. Further, it is rather unusual today for a drug promoted by an individual or extracted by a plant collector to attract much attention in the general scientific or medical community; the pharmaceutical firms thus control to a significant degree the direction in which new development occurs.

It is also appropriate here to recapitulate the question of what constitutes a ‘rational therapy’. Empirically determined therapies of parkinsonism, such as the employment of belladonna alkaloids, were by no means ‘irrational’; to classify them as such would be to dismiss most attempts at pharmacotherapy before the 20th century as irrational. The anticholinergic therapies functioned to a degree, and the continued employment of these substances, and not of others, is entirely attributable to this fact; that is, they were the subject of rational and scientific trial and selection. Both this success and the problems associated with these therapies, in turn, had an impact on the development of neurosciences; this impact, however, was limited until the concept of the central nervous system as a chemical system had been developed and, equally importantly, accepted. In other words, pathological states yielded clues regarding the function of the normal or healthy brain, and parkinsonian patients were, in a certain sense, the experimental subjects in an extended experiment.20

L-DOPA therapy turned this relationship on its head. A string of findings in the laboratory, from Brodie’s discovery of the amine-releasing properties of reserpine to Carlsson’s discovery that DOPA countered the behavioural effects of reserpine, and finally the identification of dopamine accumulation in the basal ganglia of animals and then of humans (which depended on the availability of suitable techniques), combined with clinical observations that reserpine induced parkinsonism-like state in man and that both the motor and vegetative symptoms of natural parkinsonism suggested that the neurochemical substances being examined in the laboratory might play a role in these deficiencies, hinted that basal ganglia dopamine deficiency might underlie the symptoms of parkinsonism, which was then sought and found: and then, as the practical outcome of this chain of events, L-DOPA was finally administered to patients. That was the real scientific triumph of L-DOPA therapy: the successful extrapolation of basic research into the clinic, the demonstration that medical research by chemists, biologists and others would play a far more active role in the development of novel therapeutic strategies than had previously been possible with the largely descriptive research of the neuropathologist.

This was achieved because L-DOPA therapy addressed a phenomenon actually relevant to the pathology of natural parkinsonism. It was of secondary importance, what position the dopamine deficiency occupied in the temporal chain of events leading to parkinsonism; significant was the fact that this deficiency actually existed in the brains of real patients. The definition of what constituted ‘parkinsonism’ and the significance of different symptoms for the quality of the patient’s life had often been problems in interpreting the value of various therapeutic approaches, as discussed above; rigidity

20 See Sourkes, 1964a, for a similar discussion.
and tremor were each considered at various stages to be the primary target of antiparkinsonian therapy, while akinesia, poorly defined and understood, was often neglected; there was also the confusion of phenomena such as tremor and motor unrest, of rigidity, cramp and spasm, leading to inappropriate therapeutic choices. Finally, the development of animal models of tremor – most animal models of ‘parkinsonism’ were, in fact, models of nothing more than tremor –, while not actually hindering the development of new approaches, also created a number of false trails. A problem with any model is that it is an analogy: and all analogies enjoy only limited validity, the problem being that one can rarely know in advance how close the identity of model/analogy and reality actually is. This was especially true in the case of animal models of parkinsonism: neither the lesion models of the 1950s nor tremorine were ultimately terribly relevant to physiological parkinsonism; the human disease involves more than tremor, which, in any case, is a symptom produced by any of a range of etiologies. The basal ganglia dopamine deficiency, on the other hand, is a real and relevant phenomenon, and its discovery provided the first secure basis for the scientific investigation of the underlying causes of the disorder.

That l-DOPA is not the long sought cure for parkinsonism is not surprising. Parkinsonism is clearly more than an amino acid deficiency which can be overcome by a dietary supplement. It is improbable that exogenous l-DOPA can re-establish the physiological pattern of dopamine synthesis, storage and release which prevailed prior to the loss of basal ganglia cells which cannot be replaced. It has also become clear that the disorder is a ‘multisystem disorder’ with respect to anatomy, neurochemistry and function, and thus requires multilevel solutions. At the same time, the ultimate trigger or (more probably ) triggers for the processes leading to the changes in the basal ganglia and other regions which ultimately result in the parkinsonian syndrome remain hidden. Nevertheless, l-DOPA has earned its title as the ‘gold standard’ in the therapeutics of parkinsonism, in that it and other agents directed at reinforcement of dopaminergic mechanisms provide greater relief and maintenance of quality of life for the patient than any currently recognized alternative. As recently noted succinctly at a consensus meeting of many of the world’s leading Parkinson’s disease experts:

Levodopa is the most effective antiparkinsonian drug and reduces the mortality rate in Parkinson’s disease.\(^{21}\)

In 1975, an anonymous editor reviewed the history of “miracle cures in Parkinson’s disease” in a page and a half in the British Medical Journal, noting the variety of approaches which had been explored, the relative roles of directed development and serendipity in these various directions, and the trail of discarded therapies once hailed as breakthroughs.\(^{22}\) The clear lesson to be drawn from this story was that caution is still required when assessing the value of any new antiparkinsonian therapy, and that the ultimate answer will have to wait until a great deal more has been discovered concerning the details of the etiology of parkinsonism.

But, as the editor of the cited article concluded, there is good reason to regard l-DOPA as the agent which has more closely approached an ideal ‘miracle cure’ than any previous candidate. The outlook for the parkinsonian patient in 2001 is without doubt

\(^{21}\) Agid et al., 1999. Warren Olanow, Stanley Fahn and Gerald Cohen appended a statement registering their concerns regarding the toxicity of l-DOPA.

\(^{22}\) Anonymus et al., 1975.
much improved on the situation which existed forty years ago, and incomparably better than when Parkinson first drew attention to the neglected disorder nearly two centuries ago. The need for further intensive research, however, is also clear, and it is to be hoped that L-DOPA will itself be one day consigned to the history books, made obsolete by an approach which renders all symptomatic therapy superfluous.
I have come to the end, gentlemen,
and believe that I have demonstrated that,
despite our quite advanced clinical knowledge of this peculiar and
difficult disease,
our knowledge regarding its nature and its pathogenesis is still
very incomplete and our capacity regarding its treatment and cure
is still highly unsatisfactory.

May the new century bring a happy change to this situation!

Wilhelm Erb, 1906
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XVII. Concluding remarks: From alkaloids to neurochemistry


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Summary

The author presents the first detailed review of the pharmacological therapy of parkinsonism from ancient times until the near present (1980). It is not clear whether parkinsonism as it is now defined – a progressive neurodegenerative disorder of the basal ganglia characterized by sharply reduced striatal dopamine levels, particularly in the striatum – has affected a significant minority of aged persons at all points in history, but suggestive evidence to this effect has been identified in the older literature and is reviewed. The major discussion commences, however, with the administration of various plant alkaloids to parkinsonian patients in the second half of the 19th century. Antiparkinsonian therapy since this time may be divided into a number of phases:

1. The employment of alkaloids derived from solanaceous plants: initially hyoscyamine, then hyoscine/scopolamine and atropine. The discovery and characterization of these alkaloids, and the gradual recognition that other pharmacologically useful solanaceous alkaloids (such as duboisine) were identical with one or other of these three compounds, is discussed.

2. With the outbreak of encephalitis lethargica following the First World War, parkinsonian patient numbers increased dramatically, leading to a multiplicity of new directions, including the use of another solanaceous plant, stramonium, of extremely high atropine doses, and of harmala alkaloids.

3. The so-called “Bulgarian treatment” was popularized in western Europe in the mid-1930s. It was also a belladonna alkaloid-based therapy, but associated with greater efficacy and fewer side effects. This approach, whether as actual plant extracts or as defined combinations of belladonna alkaloids, remained internationally dominant until the end of the 1940s.

4. Synthetic antiparkinsonian agents were examined following the Second World War, with the aim of overcoming the deficiencies of belladonna alkaloid therapy. These agents fell into two major classes: synthetic anticholinergic (= antimuscarinic) agents, such as benzhexol, and antihistaminergic drugs, including diphenhydramine. These agents were regarded as more effective than plant-based remedies, but certainly not as cures for the disease.

5. A complete change in direction was heralded by the discovery in 1960 of the striatal dopamine deficit in parkinsonism. This led to the introduction of L-DOPA therapy for parkinsonism, the first approach directed against an identified physiological abnormality in the disorder.

6. Subsequent developments have thus far concentrated on refinement or supplementation of the L-DOPA effect. Recent attempts to develop neuroprotective or -restorative approaches are also briefly discussed.
The thesis also discusses the mechanisms by which the various types of antiparkinsonian agent achieved their effects, and also the problems confronting workers at various periods in the design and assessment of novel agents. The impact of attitudes regarding the etiology and nature of parkinsonism, particularly with regard to symptomatology, on such measures is also considered. Finally, the history of antiparkinsonian therapy is discussed in context of the general development of both clinical neurology and fundamental anatomical, physiological and biochemical research throughout the period in question. In particular, the deepening understanding of the neurochemical basis of central nervous system function is emphasized, for which reason the history of dopamine research is discussed in some detail. This history of antiparkinsonian therapy also illustrates the fact that the nature of experimental clinical pharmacology has markedly changed throughout this period: No longer the preserve of individual physicians, it is now based firmly on fundamental laboratory research, the clinical relevance of which is not always immediately apparent, and which is only later examined in (large scale) clinical trials.

It is concluded that antiparkinsonian therapy was never irrational or without basis, but has always been necessarily rooted in current knowledge regarding neural and muscular function. The achievements of L-DOPA therapy, the first successful pharmacological treatment for a neurodegenerative disorder, derived from the fruitful union of the skills and contributions of different types by laboratory scientists, pharmacologists and clinicians.
Zusammenfassung


2. Mit dem Ausbruch der Encephalitis lethargica nach dem Ersten Weltkrieg stieg die Anzahl von Parkinson-Patienten dramatisch an, was zu einer Vielfältigkeit neuer therapeutischer Richtungen führte, darunter der Einsatz des auch zu den Solanazeen gehörenden Stramonium, die Verabreichung von extrem hohen Atropindosen, und die Benutzung von Harmala-Alkaloiden.


Lebenslauf

Der Verfasser dieser Schrift wurde am 25. August 1961 in Katoomba (New South Wales, Australien) geboren. 1974-1979 besuchte er St. Dominic’s College, Penrith (N.S.W., Australien); 1979 wurde ihm das Higher School Certificate verliehen (australisches Gegenstück zur deutschen Abitur).

1980-1984 studierte er Biochemie und Physiologie an der Macquarie University (Sydney, Australien); nachdem er sehr erfolgreich ein Forschungsjahr abgeschlossen hatte, wurde ihm das Bachelor of Science Degree with First Class Honours (B.Sc. (Hons)) verliehen (School of Biological Sciences, Macquarie University, North Ryde, Sydney, Australien). Sein Forschungsprojekt betraf die Zirbeldrüsenfunktion der Ratte.

Es folgten viele Jahre in der biologischen Forschung: zunächst in der School of Biological Sciences, Macquarie University (Einfluß von Antidepressiva auf Zirbeldrüsenfunktion der Ratte; 1984-87), dann in den Departments of Infectious Diseases and Virology, Sydney University (im Institute for Clinical Pathology and Medical Research, Westmead Hospital, Sydney: Auswirkungen von Infektion mit HIV auf die Funktion der Monozyten des Menschen; 1987-90) und schließlich im Centre for Neurosciences, School of Medicine, Flinders University (Adelaide, Australien: Einfluß der Schilddrüsenhormone auf dopaminerge Rezeptorfunction in der Ratte, mit Rücksicht auf ihre Relevanz für psychiatrische Krankheiten; 1990-1994). Während dieser Zeit war der Autor auch als Lehrer an den verschiedenen Universitäten tätig, hauptsächlich bei präklinischen Kursen für Medizinstudenten und Krankenschwestern (Anatomie, Physiologie und Biochemie).

Erklärung

Gemäß §4 Abs.3 S.3, 5 und 8 der Promotionsordnung für die Fakultät für Biologie der Bayerischen Julius-Maximilians-Universität Würzburg erkläre ich als alleiniger Verfasser dieser Dissertation ehrenwörtlich:

1. Ich habe die Dissertation selbständig angefertigt und keine anderen als die von mir angegebenen Quellen und Hilfsmittel benutzt;
2. Ich habe die Dissertation weder in gleicher noch in ähnlicher Form in einem anderen Prüfungsverfahren vorgelegt;
3. Ich habe früher mit Erfolg die folgenden akademischen Grade zu erwerben versucht:
   - Bachelor of Science Degree with Honours (Macquarie University, Sydney, Australia)
   - Magister Artium (Universität Würzburg)