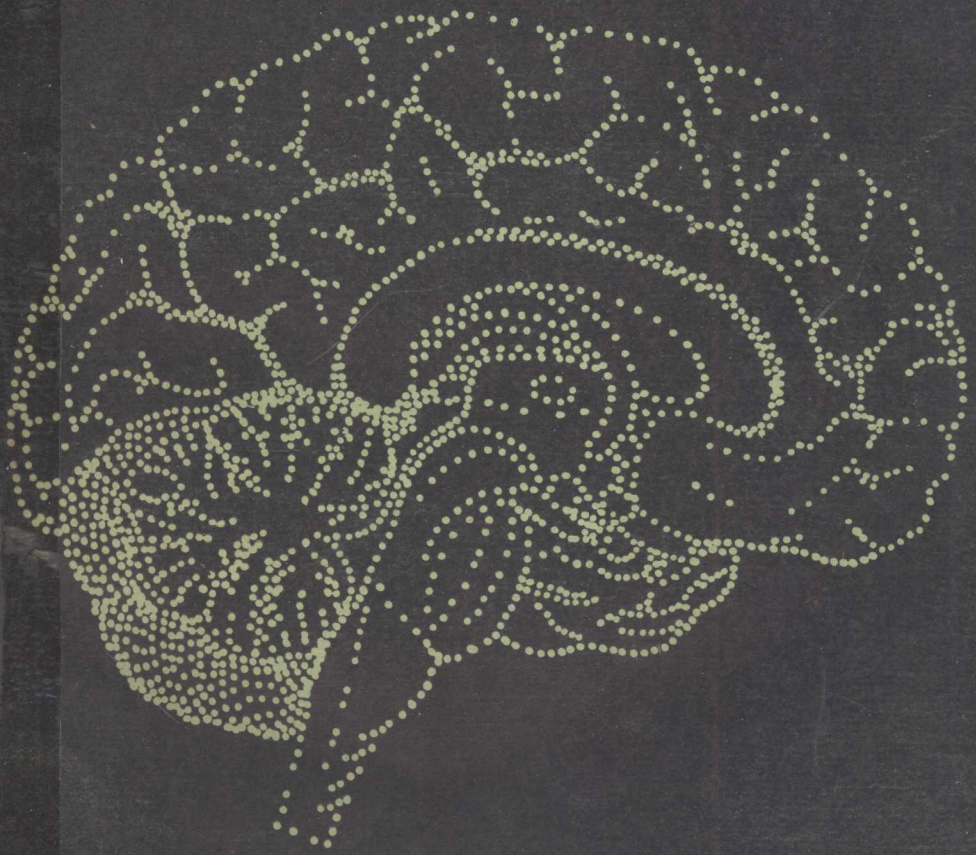
Advances in Neurology

Volume 3:

Progress in the Treatment of Parkinsonism

Edited by D. B. Calne



Advances in Neurology
Volume 3

Progress in the Treatment of Parkinsonism

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Edited by

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馆藏专用章

（内部交流）

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神经病学进展 第3卷

本书为专题性的著作。主要介绍关于帕金森氏病近年来在治疗方面的进展，重点介绍了左旋多巴及金刚烷胺等的治疗经验，以及其生化、药理学方面的进展及机理。可供内科、神经科临床医师及药物学工作者参阅。

目次：① Pre-Dopa 治疗：Pre-Dopa 内科治疗，帕金森氏病的外科治疗。② Levo-dopa 的治疗和副作用：帕金森氏病的治疗中长期使用 Levo-dopa 的效果，脑炎后和自发性帕金森氏病两者之间不同的反应。③现代应用的其他抗帕金森氏病的药物。④生物化学的发展：Levo-dopa 的血浆值及其代谢，帕金森氏病人中 Levo-dopa 耐量试验，脑脊液中胺代谢的表现，脑 Levo-dopa 的代谢。⑤药理学的发展：多巴胺的药理学，帕金森氏病治疗中应用 Levo-dopa 对心血管的影响，帕金森氏病的动物模型，帕金森氏病的治疗中类多巴胺的药物设计。

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Preface

During the past few years the treatment of parkinsonism has undergone dramatic changes following the recognition of the crucial importance of striatal depletion of dopamine. On January 5 and 6, 1973, a meeting was held at the Royal Postgraduate Medical School, London, for European workers in this field. There were three major reasons for holding this symposium. First, it represented an effort to bring together clinical neurologists, pharmacologists, and biochemists for an interdisciplinary exchange of ideas. Second, it afforded an opportunity to review five years of widespread experience with levodopa, reassessing both the beneficial and the adverse reactions which have emerged. The third reason for this meeting was to provide a sounding board for discussing new aspects of the treatment of parkinsonism. These include attempts to augment the action of levodopa by modifying its metabolism with extracerebral decarboxylase inhibitors; studies on the biochemistry of brain, cerebrospinal fluid, blood, and urine of patients receiving levodopa; the investigation of drugs which selectively stimulate dopamine receptors; the evaluation of new anticholinergic agents; and the development of better animal models of parkinsonism.

The papers were divided into groups covering broadly similar topics, after which there were open discussions. These were allowed to develop quite informally and often extended into areas beyond the subject of the symposium. No attempt was made to curtail these diversions because it was considered preferable to allow participants to express themselves freely rather than to interrupt the flow of ideas with restraining comments from the chairmen. This policy resulted in the proceedings embracing, for example, speculations on the etiology of parkinsonism, controversies over its natural history, and an analysis of its neuropathology. However, such wanderings were brief, and did not deflect the general purpose of the meeting.

This publication is not intended to be a practical manual of therapy for parkinsonism. Detailed dose regimens for levodopa and anticholinergic drugs have been given in numerous review articles and can be found in the standard textbooks. It is intended for students, physicians, pharmacologists, and biochemists who are interested in the problems of evaluating recent therapeutic success in neurology, in searching for the causes of therapeutic

failure, and in attempting to establish a more favorable balance between the two. It is an appraisal of current achievements and deficiencies in the treatment of parkinsonism as well as a glimpse into what the future may hold.

Donald B. Calne
London

The costs of this symposium were generously met by Roche Products Ltd.

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Contents

"PRE-DOPA" THERAPY

1 "PRE-DOPA" MEDICAL TREATMENT
J. Purdon-Martin

5 SURGICAL TREATMENT OF PARKINSONISM
L. S. Walsh

6 DISCUSSION
C. Pallis

THERAPEUTIC AND ADVERSE EFFECTS OF LEVODOPA

11 THE "ON-OFF" EFFECT
Antonio Rosa Damásio, Alexandre Castro-Caldas, and Alice Levy

23 THE LONG-TERM THERAPEUTIC EFFECTS OF LEVODOPA IN THE TREATMENT OF PARKINSONISM
R. B. Godwin-Austen

29 DIFFERENCES IN RESPONSE BETWEEN POSTENCEPHALITIC AND IDIOPATHIC PARKINSONISM
K. R. Hunter

33 SPEECH AND LEVODOPA
C. Mawdsley

39 DISCUSSION
G. Stern

OTHER ANTIPARKINSONIAN DRUGS IN CURRENT USE

49 EFFECT OF INHIBITORS OF EXTRACEREBRAL DECARBOXYLASE ON LEVODOPA METABOLISM
Alfred Pletscher

59 TREATMENT OF PARKINSONIAN PATIENTS WITH LEVODOPA AND EXTRACEREBRAL DECARBOXYLASE INHIBITOR, RO 4–4602
U. K. Rinne, V. Sonninen, and T. Siirtola

73 STUDIES WITH CARBIDOPA (MK 486)
Sumant K. Rao and D. B. Calne

79 LONG-TERM TREATMENT OF PARKINSON'S DISEASE WITH AN EXTRACEREBRAL DOPA DECARBOXYLASE INHIBITOR (L-ALPHA-METHYLDOPAHYDRAZINE, MK 486) AND LEVODOPA
C. D. Marsden, J. D. Parkes, and J. E. Rees

93 DISCUSSION
D. B. Calne

97 STUDIES WITH BENAPRYZINE–A NEW ANTICHOLINERGIC DRUG–IN THE TREATMENT OF PARKINSONISM
O. P. W. Robinson

105 AMANTADINE TREATMENT OF PARKINSON'S DISEASE
J. D. Parkes, R. C. Baxter, A. Galbraith, C. D. Marsden, and J. E. Rees

115 MELATONIN AND METATYROSINE IN THE TREATMENT OF PARKINSONISM
K. M. Shaw, G. M. Stern, and M. Sandler

121 PYRIMIDYL-PIPERONYL-PIPERAZINE (ET 495) IN PARKINSONISM
S. D. Vakil, D. B. Calne, J. L. Reid, and C. A. Seymour

126 DISCUSSION
D. B. Calne

BIOCHEMICAL DEVELOPMENTS

131 PLASMA LEVELS OF LEVODOPA AND ITS METABOLITES
J. G. Allen

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137 LEVODOPA TOLERANCE TESTS IN PARKINSONIAN PATIENTS
J. G. L. Morris

143 URINARY MONOAMINES AND THEIR METABOLITES IN PARKINSONISM: SOME RECENT STUDIES
Susan Bonham Carter and M. Sandler

154 DISCUSSION
M. Sandler

159 SIGNIFICANCE OF AMINE METABOLITES IN THE CEREBROSPINAL FLUID
Ian A. Pullar

165 THERAPEUTIC EFFECT OF LEVODOPA IN RELATION TO PRETREATMENT AMINE METABOLITE CONCENTRATION IN CEREBROSPINAL FLUID
G. Curzon

173 METABOLISM OF LEVODOPA IN THE HUMAN BRAIN
K. G. Lloyd, L. Davidson, and O. Hornykiewicz

189 DOPA METABOLISM BY INTESTINAL MICROORGANISMS
Olav M. Bakke

199 METABOLISM AND KINETICS OF ET 495 (PIRIBEDIL) IN MAN AND RATS
D. B. Campbell, P. Jenner, and A. R. Taylor

213 DISCUSSION
M. Sandler

PHARMACOLOGICAL DEVELOPMENTS

217 PHARMACOLOGY OF DOPAMINE
Marthe L. Vogt

223 CARDIOVASCULAR EFFECTS OF LEVODOPA IN PARKINSONISM
J. L. Reid and D. B. Calne

233 CHOLINERGIC-DOPAMINERGIC INTERACTIONS IN THE EXTRAPYRAMIDAL SYSTEM
G. Bartholini, H. Stadler, and K. G. Lloyd

243 ACTIONS OF 6-HYDROXYDOPAMINE ON CATECHOLAMINE-CONTAINING NEURONS IN THE CENTRAL NERVOUS SYSTEM
L. L. Iversen

252 DISCUSSION
P. D. Lewis

257 ANIMAL MODELS OF PARKINSONISM
U. Ungerstedt, A. Avemo, E. Avemo, T. Ljungberg, and C. Ranje

273 TOOLS IN THE TREATMENT OF PARKINSON'S DISEASE: STUDIES ON NEW TYPES OF DOPAMINE RECEPTOR STIMULATING AGENTS
Kjell Fuxe

281 NEUROPHARMACOLOGICAL STUDIES ON THE SITE AND MODE OF ACTION OF ET 495
B. Costall and R. J. Naylor

295 DESIGN OF DOPAMINE-LIKE DRUGS
Roger M. Pinder

305 MECHANISMS OF DRUG-INDUCED PARKINSONISM
D. F. Sharman

313 DISCUSSION
K. Fuxe

317 SUMMARY
A. Pletscher

321 INDEX

Advances in Neurology, Vol. 3
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"Pre-DOPA" Medical Treatment

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In undertaking to write on "pre-DOPA" therapy, I was not sure how far I was expected to go back. Parkinson himself (1817), you may remember, hoped for a great deal from the pathologists. "By their benevolent labours," he wrote, "its real nature may be ascertained and appropriate modes of relief or even of cure, pointed out." So far, however, the pathologists have done little to fulfill his expectations. More than 100 years later, when I was a student, the popular textbook of medicine was Osler's (1918), which had been written partly with the express purpose of debunking treatment by means of elaborate prescriptions embodying all sorts of peculiar substances. Osler wrote on the treatment of paralysis agitans: "There is no method which can be recommended as satisfactory in any respect. Arsenic, opium, hyoscine and the extract of the parathyroid gland may be tried and sometimes give relief, but are not curative. The friends should be told frankly that the disease is incurable, and that nothing can be done except to attend to the physical comforts of the patient. Regulated and systematised exercises should be carried out."

For many years after my arrival at Queen Square, hyoscine was in vogue. Hyoscine provided a palliative treatment that was in many ways satisfactory and sometimes obtained quite remarkable results; it relieved both the rigidity and the tremor. If it was given in solution, so that the dose could easily be adjusted, and if it was taken after meals, so that the rate of absorption was relatively regular, then the results might be as good as any of those we have seen with the later anticholinergics. The trouble with hyoscine was not that it failed to produce the desired effects but that it produced so many undesired actions as well. Patients developed visual disturbances resulting from dilatation of the pupils and loss of accommodation; they complained of dryness of the mouth, confusion, and sometimes, especially after they went to bed, visual hallucinations. Nevertheless, hyoscine remained for many years, to my mind, the most satisfactory remedy at our disposal.

When the parkinsonian condition resulting from encephalitis lethargica became common, many other remedies were tried, the most important of

which were stramonium and atropine. Stramonium had previously been used for asthma, especially in the form of cigarettes, and some patients found that by lying down and smoking a stramonium cigarette they could terminate an oculogyric crisis. For some reason Bulgarian stramonium achieved a special reputation, and a whole regime of treatment was established which depended on increasing doses of the extract of the Bulgarian leaf. Both with stramonium and with atropine, optimum treatment depended on increasing dosage as the patient became more tolerant of the drug, and sometimes doses were achieved which, at first, would have seemed astronomical. The atropine regime was most popular in Germany, and I believe several well-known private therapeutic establishments were given over to its use. Starting with the pharmacological dose of 1/100th of a grain once or twice a day, the dosage was gradually increased until the victim might be taking more than ½ grain in 24 hr. Although the effect on the parkinsonian symptoms was very good and well maintained, what was remarkable about these large doses was that the usual side effects could be resisted. However, tachycardia and constipation might be troublesome. The danger of the regime was the state of collapse into which the patient fell if the regular dose was not forthcoming.

A little more than 20 years ago the synthetic anticholinergic drugs were introduced and before long they became confusingly numerous. Most of them are still in use, either as adjuvants to levodopa or as independent remedies. Artane®, the first on the market, was benzhexol, and other proprietary brands of the same chemical became available later as Pipanol® and Trinol®. Kemadrin®, which came next, was procyclidrine hydrochloride and so on—Disipal®, Lysivane®, Cogentin®, Akineton®, Tremonil®. These proprietary names are governed by regulations of the Home Office, which provide that the name must not give any indication of the chemical composition of the drug, and in many cases the name applies only in this country. For the clinician the great advantage of these preparations over the alkaloids and stramonium is the relative absence of side effects, visual disturbances, in particular, being virtually absent. The primary therapeutic effects were much the same with all of them, and all, with the possible exception of Tremonil®, relieved rigidity more than tremor. Several of them produced a slight euphoria which was an advantage, but toxic psychoses are apt to occur, and they have the peculiarity of being paranoic, rather than confusional, in type. At the Highlands Hospital, where there are still more than 50 postencephalitics, most of whom receive small doses of levodopa, the synthetic anticholinergic preparations mainly in use now after 20 years' experience are Disipal® and Artane®, with Lysivane® in third place but well behind.

Just as in the old days, a prescription contains a so-called corrective, such as Dexedrine®, Drinamyl®, or even chewing gum in association with these remedies. In practice I dislike ordering more than two preparations at the same time for any patient for regular use.

Finally, there is more to the treatment of parkinsonism than merely giving tablets – even levodopa – and one of the measures that interests me is hydrotherapy. It is well known that many parkinsonians feel better in water. I had a relative who was a quite severely affected postencephalitic, who lived in Madeira and for at least 6 months of the year he bathed in the sea daily. He said that when he was in the water he felt "just normal." Although he was intensively treated with successive regimes of medical therapy nothing that he took gave him the freedom that he experienced when he was in the water. I find the physiology of this difficult to understand; I presume it must depend on the reduction of excessive somatic reflex activities, and possibly healthy vestibular reflexes take over. Perhaps these are principles we could make greater use of, but so far the explanation of the phenomenon eludes me. Lest you feel inclined to try this therapy and encourage your parkinsonian patient to enjoy his swimming pool, let me warn you that, even if he is a good swimmer, he may be unable to hold his head up, especially in the water, and so it is absolutely essential that a competent attendant should be present.

To recapitulate, there was 100 years without any effective palliative; then 30 years of hyoscine-stramonium treatment; then the synthetics, still far from adequate, and so to surgery!

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