W. Birkmayer / P. Riederer

Parkinson's Disease

Biochemistry, Clinical Pathology, and Treatment

Translated by Gavin Reynolds
with the assistance of Karl Blau
and Lindsay Reynolds

With a Foreword by Melvin D. Yahr

Springer-Verlag Wien NewYork

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Revised and enlarged translation of
"Die Parkinson-Krankheit. Biochemie, Klinik, Therapie"
Wien-New York: Springer-Verlag 1980

With 57 Figures

Softcover reprint of the hardcover 1st edition 1983

Library of Congress Cataloging in Publication Data. Birkmayer, Walther, 1910–
Parkinson's Disease. Bibliography: p. . Translation of: Die Parkinson-Krankheit, Biochemie, Klinik, Therapie. 1. Parkinsonism. I. Riederer, P., 1942– . II. Title. RC382.B5313. 1983. 616.8'33. 83–451.

ISBN-13:978-3-7091-7637-5 e-ISBN-13:978-3-7091-7635-1
DOI: 10.1007/978-3-7091-7635-1

Foreword

Parkinson's disease is one of the major causes of neurological disability in adult life. It has been encountered in all races, in every region of the world and shows no preference for either sex. In general, its initial manifestations begin in the fifth decade of life. With the world population showing an increase in numbers of people in the older age groups, Parkinson's disease will undoubtedly be encountered with increased frequency in the years to come. Though its cause is unknown, significant strides in understanding its nature and controlling its symptoms have been made during the past two decades. Contained in this volume is a comprehensive review of the present knowledge of Parkinson's disease.

Though James Parkinson is credited with the uncovering the illness which now bears his name, and his monograph on the Shaking Palsy written in 1817, is truly a medical classic, descriptions of this disease can be found in medical writings going back to the time of Galen. Indeed, he himself was the first to admit that he was not describing a new disease but bringing an old one to the attention of the medical researchers of his time so that it would become a subject of interest and investigation.

Specifically, his objective was the morbid anatomist whose efforts he hoped would bring to light the cause and nature of the disorder. This, then, would become a basis for treatment or even cure. Parkinson's faith in the morbid anatomists, I am afraid, was never realized, for not only did it take them over hundred years to establish the site of pathological change in this disorder, but no fruitful therapeutic measures resulted. Investigative studies in parkinsonism were indeed fallow until twenty years ago when it became a disorder of interest to the neurochemists and pharmacologists. Joining their efforts with that of clinical neurologists resulted in a most productive partnership from which the neurochemical pathology of Parkinson's disease was defined and a virtual explosion of research in this field occurred. In rapid succession: the underlying disordered homeostases of neurotransmitters in the striatum due to dopamine deficiency was shown, the importance of nigrostriatal mechanisms demonstrated and the reversibility of parkinsonian symptoms by the administration of

pharmacological agents capable of reactivating dopaminergic circuits, developed. Professor Birkmayer has been deeply involved in one way or another with these developments and it is from this prime vantage point that the present volume is written.

Professor Birkmayer's rich and extensive background in clinical neurology are melded together with the new concepts of neurochemistry and therapeutics which have evolved of recent date. Having participated in these developments, he is able to place them in exceptional perspective, not only in regard to present applicability to Parkinson's disease, but also as to future investigations which are needed to conquer this enigma of mankind. To have all the developments in Parkinson's disease of the past two decades brought together in a single volume is of untold advantage to the practicing physician as well as researcher in the field, that such is done by a pioneer investigator and master clinician is doubly rewarding.

Melvin D. Yahr, M. D.

Preface

25 years of work on Parkinson's disease (by Walther Birkmayer) and the experience aimed from four thousand cases are not in themselves a justification for writing this book. We wished rather to publish a collation of the advances made during the past 20 years, advances in which both authors took part. New research findings have been made mainly on the biochemical side and this is reflected in the emphasis of this book. These findings laid the foundations for a completely new approach to the treatment of Parkinson's disease, which is the first neurological disease in which the identification of a specific chemical defect has lead to the development of a novel pharmacotherapy.

This book is not a state-of-the-art textbook but rather reflects personal experience over the past two decades. We have, however, tried to be fairly comprehensive; in addition to the clinical problems and their treatment, an understanding of the basic research findings is, we feel, most important. Like no other, Parkinson's disease is ideally suited as a model for the investigation of other degenerative brain disorders.

This English edition is, in our opinion, an improvement on the original German edition for two reasons. Firstly, scientific English is clearer and simpler. Secondly, the translator, being a critical scientist, has removed superfluous comment from the text and thus provided the book with a more lucid and flowing style.

We thus wish to thank Dr. Gavin Reynolds who, assisted by Dr. Karl Blau and Dr. Lindsay Reynolds, provided us with an English translation of the original German edition "Die Parkinson-Krankheit". We are also most grateful to Dr. G. Stern for his invaluable and expert criticism of the English manuscript.

Vienna, January 1983 **W. Birkmayer** and **P. Riederer**

Contents

Generic and Trade Names

Generic Name	Trade Names		
	Federal Republic of Germany[1]	United Kingdom[2]	United States of America[3]
Amantadine	PK-Merz, Symmetrel, Contenton, Amantadin-Ratiopharm	Symmetrel	Symmetrel
Amitriptyline	Laroxyl, Saroten, Tryptizol	Domical	Amitriptyline, Elavil, Endep
Amitriptyline plus Chlordiazepoxide	Limbatril F	Limbitrol	Limbitrol
Benserazide	Madopar (+ L-dopa)	Madopar (+ L-dopa)	–
Benztropine	Cogentinol	Cogentin	Cogentin
Biperiden	Akineton	Akineton	Akineton
Bornaprin	Sormodren	–	–
Bromazepam	Lexotanil	–	–
Bromocriptine	Pravidel	Parlodel	Parlodel
Carbidopa	Nacom (+ L-dopa)	Sinemet (+ L-dopa)	Sinemet (+ L-dopa)
Chlorprothixene	Truxal, Taractan	Taractan	Taractan
Clopenthixol	Ciatyl	Clopixol	–
Deanol	–	–	Deaner
(–) Deprenyl	–	Eldepryl	–
Desipramine	Pertofran	Pertofran	Pertofrane, Norpramine
Diazepam	Diazepam, Lambra, Neurolytril, Tranquase, Tranquo-Tablinen, Valium	Atensine, Sedapam, Diazemuls, Evacalm, Solis, Valium	Valium
Dibenzepine	Noveril	–	–
Diclofenac N-Dipropylacetate (Valproic acid)	Voltaren Convolex, Ergenyl, Leptilan, Mylproin, Orfiril	Voltarol Epilim	– Dekapene
Dimenhydrinate	Dramamine, Epha, Novomina, Vomex A	Dramamine	Dimenhydrinate, Dramamine, Meni-D, Nico-vert, T-Circ
Domperidone	Motilium	–	–

Generic Name	Trade Names		
	Federal Republic of Germany[1]	United Kingdom[2]	United States of America[3]
L-dopa + Benserazide	Madopar	Madopar	–
L-dopa + Carbidopa	Nacom	Sinemet	Sinemet
Flunitrazepam	Rohypnol	Rohypnol	Flurazepam, Dalmane
Fluphenazine	Dapotum, Lyogen, Omca	Modecate, Moditen	Prolixin, Permitil
Flupentixol	Fluanxol	Depixol, Fluanxol	–
Haloperidol	Eukystol, Haldol, Haloperidol, Sigaperidol	Haldol, Serenace	Haldol
5-Hydroxytryptophan	Levothym	–	–
Imipramine	Tofranil	Tofranil	Imipramine, Janimine, SK-Pramine, Tofranil
Indomethacin	Amuno, Argun, Indohexal, Indomet, Indophlogont, Indotablinen	Imbrilon, Indocid, Mobilan	Indocin
Iprindole	–	Prondol	–
Levopromazine	Neurocil	–	Starine
Lorazepam	Tavor	Ativan	Ativan
Maprotiline	Ludiomil	Ludiomil	Ludiomil
Melitracen	Trausabun	–	–
Metoclopramide	Gastronerton, Gastrosil, Gastrotablinen, MCP, Metoclopramid, Paspertin	–	Reglan
Mianserin	Tolvin	Norval, Bolvidon	–
Nomifensine	Alival	Merital	–
Nortriptyline	Nortrilen	Aventyl, Allegron	Aventyl, Pamelor
Orphenadrine	Norflex, Orphenadrin	Disipal, Norflex	Banflex, Myophen, Myotrol, Norflex, Norgesil, Disipal
Oxprenolol	Trasicor	Trasicor	–
2-Phenyl-norbornane-2-carboxylic acid-γ-diethyl-aminopropylester (= Bornaprin)	Sormodren	–	–
Piracetam	Nootrop, Normabraïn	–	–
Procyclidine	Osnervan	Kemadrine, Osnervan	Kemadrin
Pyritinol	Encephabol	–	–
Thiethylperazine	Torecan	Torecan	Torecan
Thioridazine	Melleretten, Melleril	Melleril	Mellaril

Generic Name	Trade Names		
	Federal Republic of Germany[1]	United Kingdom[2]	United States of America[3]
Tiapride	Tiapridex	–	–
Tranylcypromine	Parnate	Parnate	Parnate
Triamcinolon	Delphicort, Extracort, Triam, Volon A	Adcortyl, Kenalog, Ledercort, Lederspan	Aristocort, Kenacort, Triamcinolone
Trihexyphenydil (Benzhexol)	Artane	Artane	Artane, Tremin, Trihexyphenidyl
Tryptophan	–	Pacitron	Amin A 21, Trofan, Tryptacin

– Indicates that the drug is not registered or is not mentioned in one of the available publications.

[1] According to "Rote Liste 1982" (Bundesverband der Pharmazeutischen Industrie, e. V., ed.). Aulendorf: Editio Cantor. 1982.

[2] G. Reynolds, personal communications.

[3] Physicians desk reference, 36th ed. (Baker, C. E., ed.). Oradell: Medical Econ. Comp. 1982.

According to the available References the following substances are not commercially available in Federal Republic of Germany, United Kingdom, and the United States of America:

1-Amino-3,5-dimethyladamantane (memantine)
Clozapine (a neuroleptic)
CU-32085 (a dopaminergic agonist)
Ethylbenzhydramine (an anticholinergic)
Lergotrile (a dopaminergic agonist)
Lisuride (a dopaminergic agonist)
Pergolide (a dopaminergic agonist)
α-Phenyl-α-(diethyl-aminoethyl-)glutarimide (an anticholinergic; Aturban)
3-PPP (stimulates preferentially autoreceptors)
Progabide (a GABA-ergic agonist)

Introduction

There is hardly any book on Parkinson's disease which starts without reference to the "Essay on the shaking palsy", in which James *Parkinson*, in 1817, first described this disorder of motor function. We would propose the first therapeutic advance to be that of *Charcot* (1892), who introduced treatment with the *Solanaceae*. This Atropa belladonna medication was practically the only available treatment until the introduction of the synthetic anticholinergic drugs (*Sigwald et al.* 1946). While the first autopsy finding was of a post-apoplectic cyst in the right thalamus (*Oppolzer* 1861), the decisive neuropathological observation was the description of a case of Parkinson's disease with a tubercle of the substantia nigra (*Blocq* and *Marinesco* 1894).

The work of *Tretiakoff* (1919) confirmed the substantia nigra as the pathogenic site of the parkinsonian defect. He reported on nine idiopathic and three postencephalitic parkinsonian cases in which there was a loss of pigmentation in the substantia nigra. *Hassler* (1938) definitively confirmed the involvement of this region in both idiopathic and postencephalitic parkinsonism, and was the first to infer a disorder of nigral cells from the diverse collection of syndromes. This was clinically most relevant since there are, for example, cases where the lower extremities are primarily affected, and other cases (albeit less frequent) where aphonia is the major symptom and movement is almost normal.

The discovery by Lewy (1912) of spherical inclusions in the brain stem has been confirmed by every subsequent investigator, although a correlation with a specific pathophysiological change has yet to be found. More recently *Stochdorph* (1979) found Lewy bodies in peripheral sympathetic ganglia. The Alzheimer fibrils found in the same regions are similarly unspecific indications of a degenerative process (Fig. 1).

In "typical" Parkinson's disease the average brain weight and volume of most subcortical nuclei are not significantly less than in age- and sex-matched controls (*Jellinger* and *Grisold* 1982, *Riederer* and *Jellinger* 1982), while rare forms of "atypical" parkinsonism show additional Alzheimer-like and other extranigral changes. Although most dopaminergic nerve terminals in the striatum degenerate, no ultra-

structural abnormalities of the synaptic organization of putamen have been found and there is no evidence for major neuronal degeneration or disorders of synaptic remodelling in the putamen (*Jørgensen et al.* 1982, *Forno* and *Norville* 1979). The aetiology of damage to the dopaminergic and other neuronal systems and the pathogenesis of neuronal degeneration in Parkinson's disease are unknown.

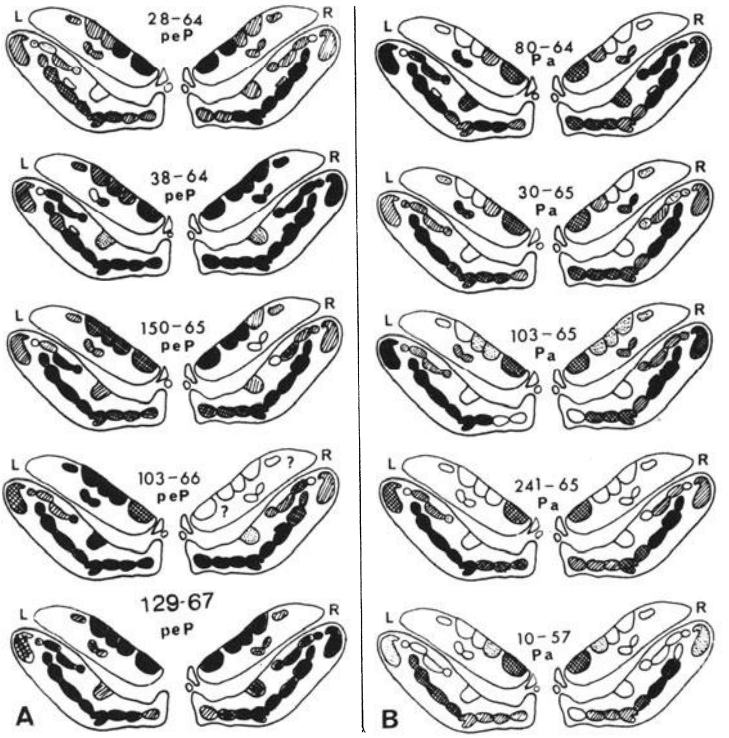


Fig. 1. Pattern and intensity of lesions of substantia nigra in postencephalic *(pe P)* and idiopathic parkinsonism *(Pa)*. ■ severe cell loss, ▩ moderate cell loss, ▨ slight cell loss, □ no lesion

The involvement of the brain stem points towards autonomic and psychopathological abnormalities as well as motor disorders in Parkinson's disease.

Economo (1929) first described postencephalitic parkinsonian symptoms when he identified encephalitis lethargica. Since then there has generally been a strong distinction made between the two syndromes of postencephalitic and idiopathic parkinsonism. A third syndrome, the so-called arteriosclerotic parkinsonism (*Critchley* 1929)

which has been described by numerous authors, should also be included. A widely held misconception is that parkinsonian symptoms appearing at or over 70 years are, in principle, arteriosclerotic.

In a broad study of 12 postencephalitic, 39 idiopathic and 7 arteriosclerotic parkinsonian cases (*Bernheimer et al.* 1973), characteristic clinical, neuropathological and biochemical results were found for each group. The age (given as $x \pm s.d.$) at first appearance of postencephalitic symptoms was between 32 and 68 years (average 42.3 ± 5.5) while for idiopathic and arteriosclerotic patients the corresponding data was 47–82 years (average 67.6 ± 1.3) and 62–83 years (average 74.7 ± 3.6) respectively. The disease duration of postencephalitic parkinsonism was 20.6 years (± 3.7, range 3–45 years), for the idiopathic disease 9.3 years ($\pm 0{,}9$, range 1–27 years) and for arteriosclerotic parkinsonism 2.7 years (± 0.16, range 1–4 years). It is notable that these average values are very similar to those of an earlier study (*Birkmayer* 1965).

Arteriosclerotic parkinsonism is a cerebral arteriosclerosis with softening and haemorrhaging in the substantia nigra, hence the parkinsonian syndrome. These foci are not only nigral but present in all parts of the brain. Thus other arteriosclerotic symptoms will be present (i.e. spasticity, disturbances of coordination and, above all, confusion and dementia).

Parkinsonism can also be accompanied by an atrophy of cortical processes (*Jacob* 1978). In 1968, *Selby* demonstrated cortical atrophy which was related to a reduction in intellectual function. Of idiopathic parkinsonian patients, 81% exhibit mild to severe dementia (*Jellinger* 1974). Computer tomography (*Schneider et al.* 1978) has demonstrated severe atrophy, particularly in the cortical gyri.

Compared with typical parkinsonian symptoms (tremor, rigidity and akinesia), the persistant reduction in intellectual ability is relatively easy to understand in terms of this brain atrophy. Moreover we have no doubt that idiopathic parkinsonism represents a specific atrophy of a single system, the substantia nigra, yielding a typical pattern of symptoms and a characteristic prognosis (*Spatz* 1927). Of course, parkinsonian symptoms can occur individually in olivo-ponto-cerebellar atrophy, Alzheimer's disease and senile dementia. Nevertheless, it is undeniable that idiopathic parkinsonism is a separate disease entity *per se*.

The differential diagnosis of "postencephalitic" and "idiopathic" parkinsonism is meaningless nowadays since there are hardly any more postencephalitic cases. The one and only symptom which appears to be specific for postencephalitic disease is the oculogyric crisis. Phases of autonomic and affective dysfunction predominate in the post-

encephalitic patients although they are not specific symptoms since they also appear in idiopathic cases. From all our data about 90% of patients are idiopathic, which agrees with the studies of *Duvoisin* and *Yahr* (1972) who report 85% in that group.

Different pathogenic forms of parkinsonism have been described in the literature with an extraordinary precision. In over 25 years experience we have not come across a single concrete example of manganese or carbon monoxide parkinsonism at autopsy. Parkinson's syndrome from brain tumour is known to have occurred in cases of frontally localized meningeoma. Mechanical pressure on the basal ganglia has been put forward as an explanation of this; perhaps a more likely hypothesis is that of *Siegfried* (1968), who proposes a chemical cause in the form of a blockade of dopamine synthesis. A further cause which has been widely debated is the traumatic induction of the parkinsonian syndrome. However, *Kehrer* (1930) has found that not one case was reported in all the First World War literature. Similarly we have not come across a case of parkinsonian syndrome in 3000 brain damaged patients from the Second World War (*Birkmayer* 1951), nor did *Walker* and *Jablon* (1961) in their study of 739 such patients. It is apparent that, depending on the localization of the injury, single symptoms may appear, but a causal relationship between acute brain trauma and chronic progressive Parkinson's disease seems unlikely. But it is not exceptional to find long term narcosis, severe viral infection, high altitude oxygen deficit and even severe mental trauma as trigger factors for Parkinson's disease.

Finally, the appearance of parkinsonian symptoms after neuroleptic treatment is well known (*Steck* 1954); these features are often referred to as "parkinsonoid". However the typical picture of Parkinson's disease, with its akinesia, tremor, rigidity and progressive deterioration, cannot be observed. This pharmacological parkinsonian syndrome should be regarded as an extrapyramidal side effect of neuroleptic treatment. The blockade of dopamine receptors leads to akathisia, torsion dystonia and compulsive choreiform movements (*Haase* 1955). In most cases these symptoms disappear after withdrawal of medication. Only after long-term treatment – particularly in old patients – does tardive dyskinesia develop (*Ayd* 1961).

The susceptibility of old people points towards the pathogenesis of Parkinson's disease. There is, with increasing age, a loss in tyrosine hydroxylase activity, which is central to catecholamine synthesis (*McGeer et al.* 1971a). Depending on various factors in life, an individual will sooner or later reach a state of inadequate enzyme function and parkinsonian symptoms will appear. But while enzyme activity is genetically determined, our data show no genetic

contribution to Parkinson's disease. Of 4000 patients only 0.5% had a case in their family. However, our patient material is unsuitable for genetic studies; the multiplicity of geographic origins of the Viennese makes it difficult to construct family trees. In addition there is a tendency to deny any familial disease traits, a legacy of the National Socialist era.

The results of *Scarpalezos* (1948) and *Mjönes* (1949) indicated a hereditary component to the extent of 40% of 626 cases and 41% of 326 idiopathic cases, respectively. Recent studies by *Barbeau* and *Pourcher* 1982 delineated three familial forms of Parkinson's disease: an essential tremor-related familial Parkinson's disease, a familial akinetic-rigid syndrome, and a familial juvenile Parkinson's disease. Accordingly, familial Parkinson's disease can follow both the autosomal dominant model and the autosomal recessive model (*Barbeau et al.* 1982). However, the very low concordance rate for Parkinson's disease in monozygous twins shows that nongenetic factors are involved in its etiology (*Ward et al.* 1982).

The increase of stress in modern life could possibly explain the increase in Parkinson's disease and particularly its earlier appearence (our youngest case was 32 years old at the onset of the disease). This comment is also valid for depression. In any case it seems worth noting that syndromes involving biogenic amine metabolism (depression and Parkinson's disease) can be brought about by environmental factors, as opposed to schizophrenia which is in no way increased by environmental stress.

Biochemistry

General Principles of Biochemical Transmission

Introduction

Human behaviour can be influenced by drugs. For example, psychotomimetics produce hallucinations and other manifestations of psychoses, tranquillizers inhibit a wide range of psychiatric symptoms, antidepressants have a positive effect on mood, affect and interest, and neuroleptics have a strong calming influence on affect and psychological feeling.

For these substances, changes in neuronal transmission, including transmitter synthesis and metabolism, have been demonstrated in animal experiments, both *in vitro* and *in vivo*. These experiments are confirmed by clinical and experimental results from the study of extrapyramidal and psychiatric disorders in man.

From biochemical, pharmacological and histochemical studies it is now accepted that several of the compounds present in the brain are neurotransmitters. The neurochemistry of a few of those relevant to the study of Parkinson's disease will now be briefly described.

Acetylcholine

The biosynthesis and metabolism of this transmitter are shown in Fig. 2 and its mode of action is indicated in Fig. 3. Choline is taken up into the neuronal cytoplasm where choline acetyltransferase catalyses the synthesis of acetylcholine (ACh) from choline and active acetate. The synthesized transmitter is stored in vesicles within the nerve ending and, on arrival of a nerve impulse, is released into the synapse by a calcium-dependent mechanism.

Released ACh is subsequently hydrolysed by acetylcholinesterase, which is present in high concentrations in nerve endings. Reuptake of the liberated choline, but not of the short-lived transmitter itself, completes the cycle by acting as substrate for further ACh synthesis.

The determination of ACh in human brain is prevented by its rapid metabolism post-mortem. However, animal experiments have shown that ACh concentrations in the brain are parallelled by the activities of choline acetyltransferase and acetylcholinesterase so it is possible

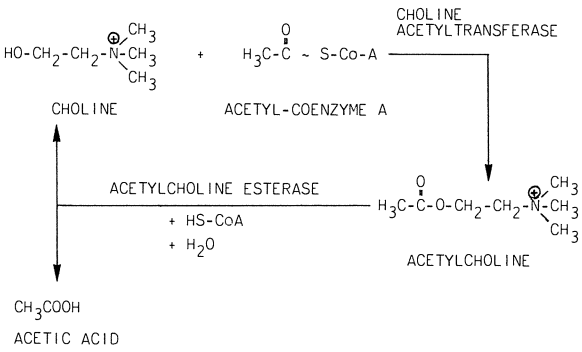


Fig. 2. Biosynthesis and metabolism of acetylcholine

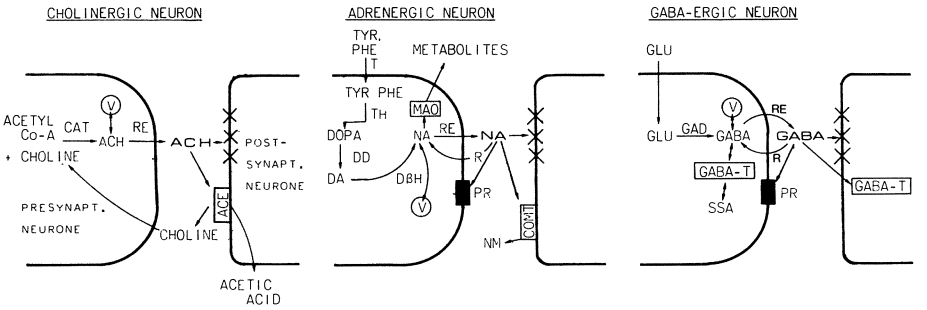


Fig. 3. Neurochemical events at cholinergic, adrenergic and GABAergic nerve-endings. *ACH* acetylcholine, *ACE* acetylcholine esterase, *CAT* cholineacetyl transferase, *V* vesicles, *RE* Ca^{++} dependent release, *NA* noradrenaline, *X* receptor unit, *MAO* monoamine oxidase, *COMT* catechol-O-methyltransferase, *NM* normetanephrine, *DA* dopamine, *DOPA* 3.4-dihydroxyphenylalanine, *TYR* tyrosine, *PHE* phenylalanine, *T* amino acid transport, *R* reuptake, *TH* tyrosine hydroxylase, *DD* dopa decarboxylase, *GABA-T* GABA-transaminase, *GABA* gamma-aminobutyric acid, *GLU* glutamate, *α-OKG* α-keto-glutaric acid, *SSA* succinic acid semialdehyde, *DBH* dopamine-β-hydroxylase, *GAD* glutamic acid decarboxylase

indirectly to determine the distribution of ACh in human brain. The striatum contains the highest activities of these two enzymes. Acetylcholinesterase is found in glial cells as well as in the cholinergic neurons.

Cholinergic nerves ascend from the reticular formation to innervate the thalamus, hypothalamus, hippocampus, basal ganglia and neocortex. This system may be part of the ascending reticular activating system and may be related to arousal and the conscious state.

ACh is an excitatory transmitter of the basal ganglia while dopamine is inhibitory. The akinetic symptoms of Parkinson's disease lie with the loss of balance between these cholinergic and dopaminergic

activities in these areas of the brain, an imbalance caused by the loss of dopaminergic inhibitory function.

Biosynthesis and Release of Catecholamines

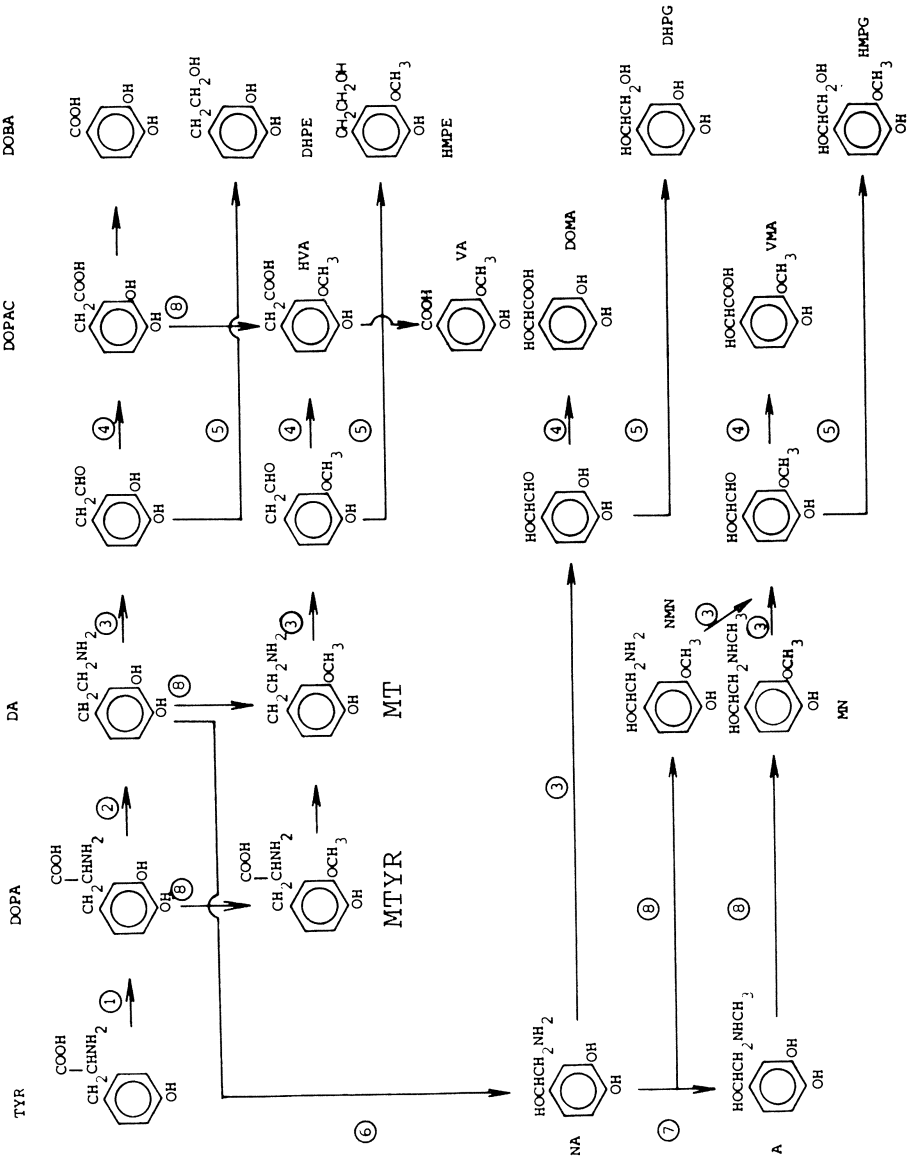
Dopamine and noradrenaline are synthesized from their precursor amino acid tyrosine, by hydroxylation and subsequent decarboxylation (Figs. 4, 5). Tyrosine is taken up into dopaminergic neurons via an active transport mechanism, where its transformation into dopa is catalysed by tyrosine hydroxylase. In the neuronal cytoplasm dopa is decarboxylated by aromatic amino acid decarboxylase (dopa decarboxylase) to form dopamine. Dopamine is then taken up into granular vesicles in which, in noradrenergic neurons, it is transformed into noradrenaline by dopamine-β-hydroxylase. The high intravesicular concentration of noradrenaline is brought about by a magnesium- and ATP-dependent transport mechanism. Vesicular catecholamines are stored partly bound (with ATP and binding proteins). Reserpine inhibits this active process.

The rate limiting step in the synthesis of catecholamines lies in the conversion of tyrosine to dopa. This tyrosine hydroxylase activity is controlled by the concentrations of dopamine and noradrenaline through a regulatory feedback mechanism. The synthesis of catecholamines in the adrenal medulla follows that of the neurons. However, adrenal noradrenaline is further converted to adrenaline by phenylethanolamine-N-methyl transferase within the granular vesicles.

Both in sympathetic neurons and in the adrenal medulla the catecholamines (along with ATP, binding proteins and dopamine-β-hydroxylase) are released by exocytosis. Plasma dopamine-β-hydroxylase has a longer half-life than the circulating catecholamines and thus the determination of its activity is a poor measure of actual sympathetic activity.

The major fate of released catecholamine transmitter is to be taken up from the synaptic cleft into the presynaptic terminal via an active reuptake mechanism to be stored for further release.

Fig. 4. Biosynthesis and metabolism of catecholamines. *1* tyrosine hydroxylase, *2* decarboxylase, *3* monoamine oxidase, *4* aldehyde dehydrogenase, *5* alcohol dehydrogenase, *6* dopamine-β-hydroxylase, *7* N-methyltransferase, *8* catechol-O-methyltransferase. *TYR* tyrosine, *DOPA* 3,4-dihydroxyphenylalanine, *DA* dopamine, *DOPAC* 3.4-dihydroxyphenylacetic acid, *DOBA* 3.4-dihydroxyphenylbenzoic acid, *DOMA* 3.4-dihydroxyphenyl mandelic acid, *HVA* homovanillic acid, *VA* vanillic acid, *VMA* vanilmandelic acid, *DHPE* 3.4-dihydroxyphenylethanol, *HMPE* 4-hydroxy-3-methoxyphenylethanol, *MHPG* 4-hydroxy-3-methoxyphenyl glycol, *DHPG* 3.4-dihydroxyphenyl glycol, *NMN* normetanephrine, *MN* metanephrine, *NA* noradrenaline, *A* adrenaline. Amines, acids and alcohols are partly bound and excreted as sulphates and/or glucuronides; dopamine, methoxytyramine and NMN can be N-acetylated


TYR
DOPA
DA
DOPAC
DOBA
MTYR
MT
NA
A
MN
DHPE
HVA
HMPE
VA
DOMA
DHPG
VMA
HMPG

The Catabolism of Catecholamines

Dopamine, noradrenaline and adrenaline are converted to inactive products by oxidative deamination and methylation by the enzymes monoamine oxidase (MAO) and catechol-O-methyl transferase (COMT), respectively (Figs. 4, 5).

MAO, being bound to the mitochondria, is widely distributed within the body. While mitochondria of adrenergic neurons are found to have high MAO activity, COMT has not been demonstrated in adrenergic nerve endings.

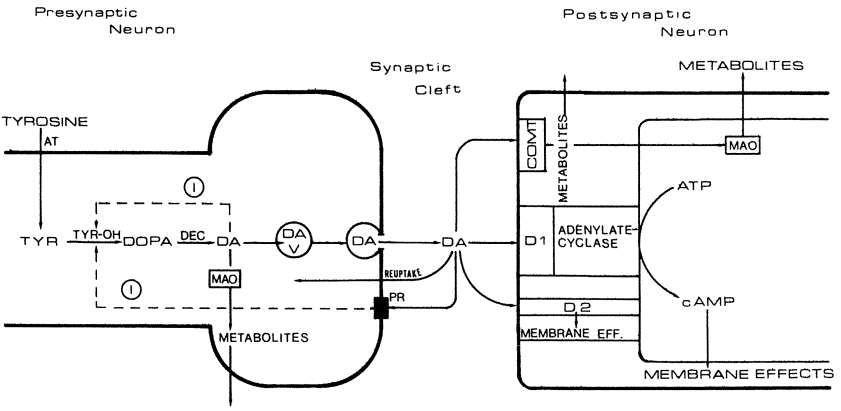


Fig. 5. Physiological processes in the pre- and postsynaptic dopaminergic neuron. *AT* amino acid transport, *TH* tyrosine hydroxylase, *DEC* decarboxylase, *V* vesicles, *I* feedback mechanism, *PR* presynaptic (auto)receptors, D_1 adenylate cyclase dependent postsynaptic receptor, *DA* dopamine, D_2 adenylate cyclase independent postsynaptic receptor, *ATP* adenosine-triphosphate, *CAMP* cyclic 3.5-adenosine monophosphate

In the neurons, the catecholamines are mainly metabolized by MAO, leading to the corresponding acid or alcohol (glycol). These are further converted to methylated endproducts, most probably by extraneuronal COMT. Further conjugation, to the sulphate or glucuronide, follows for most metabolites which, along with some of the unconjugated compounds, are then excreted. O-methylated catecholamines are excreted either unchanged, or after oxidation to the corresponding acid.

False Transmitters

It is possible that other compounds may also be synthesized in catecholaminergic endings, one example being octopamine. These so-called "false transmitters" can replace dopamine or noradrenaline in the storage granules and can be released instead of these

neurotransmitters. This will result in a decrease in noradrenaline or dopamine available for synaptic transmission as well as any effects due to a direct action of the false transmitter itself.

Dopamine

The distributions of dopamine and noradrenaline in human brain are very different. Table 1 shows that dopamine is concentrated particularly in the striatal nuclei while noradrenaline has higher concentrations in the nucleus accumbens and hypothalamus (Table 2). Dopamine-β-hydroxylase (catalyzing the conversion of dopamine to noradrenaline) shows an uneven distribution of activity which is related to that of noradrenaline.

Many dopaminergic neurons have their cell bodies in the midbrain, projecting from the substantia nigra to the striatum (nigrostriatal system). Other parts of the midbrain project to the olfactory tubercle, to the nucleus accumbens and to other limbic areas (mesolimbic system). A third dopaminergic system (tubero-infundibular system) projects from the cell bodies of the arcuate nucleus to the external

Table 1. *The dopamine content of various brain areas from parkinsonian patients with and without "akinetic crises" (Birkmayer and Riederer 1975a)*

Brain area	Dopamine (ng/g)		
	Parkinson's disease		Controls
	with akinetic crises	without	
	(n = 4)	(n = 6)	(n = 9)
Caudate n.	90 ± 25	401 ± 59	3843 ± 539
Putamen	40 ± 15	170 ± 44	4183 ± 742
S. nigra	40 ± 10	96 ± 12	582 ± 103
G. pallidus	55 ± 13	83 ± 10	846 ± 195

Data are given in mean values ± standard error per gram fresh weight. n = number of patients.

Neuropathology: complete loss of dopaminergic neurons in patients with "akinetic crises". Disability during an akinetic crisis: 80–100 (confined to bed). Drug response during "akinetic crises" (last stage): no response to L-dopa, anticholinergics, deprenyl, amantadine. Antipsychotic response during an "akinetic crisis" (last stage): neuroleptics = positive; tryptophan: in mild cases very good, in moderate cases good, in severe cases not sufficient.

layers of the median eminence of the hypothalamus. Dopamine neurons are also present in the cerebral cortex.

Parkinson's disease is a classic example of a disorder of the nigrostriatal dopamine pathway, reflecting the dopaminergic system's close involvement in motor function.

Dopamine is also concerned with the control of prolactin synthesis. It inhibits prolactin secretion by a direct action on the anterior lobe of the pituitary. Dopamine could thus be regarded as the inhibitory hormone of hypothalamic prolactin secretion. The administration of dopa (the dopamine precursor) inhibits prolactin secretion and has been used in the treatment of galactorrhoea. Dopamine agonists, in particular bromocriptine, also inhibit prolactin and are effective in treating this disease. On the other hand reserpine, which depletes stored dopamine, provokes these hormonal disturbances. It should be noted that recent results indicate that polypeptides are also involved in the regulation of prolactin secretion. Endocrine aspects of this dopaminergic system with reference to Parkinson's disease are given on p. 73.

Dopamine may participate in some symptoms of schizophrenia. The evidence for this includes experimental investigations with amphetamine, which stimulates dopamine release and can induce psychoses which in some cases are indistinguishable from schizophrenia. Additionally, some dopamine derivatives are hallucinogenic. These findings are supported by experimental results with neuroleptic drugs which have a favourable effect on various symptoms of schizophrenia and whose antipsychotic activity correlates to some extent with the blockade of dopamine receptors.

Presynaptic synthesis, the release mechanism and the metabolism of dopamine are all regulated by a "feedback" control through neuronal receptors. If these receptors are blocked (e.g. by neuroleptics), then synthesis, release and metabolism are stimulated. An activation of dopaminergic receptors (e.g. by apomorphine) has the opposite effect. This feedback regulation may involve both pre- and postsynaptic receptors. The presynaptic receptors are found on dendrites and cell bodies as well as on nerve endings (thus is "autoreceptor" a better description than "presynaptic receptor") (*Carlsson* 1975). Recently, a selective substance (3-PPP) has been synthesized and found to be suitable to characterize these autoreceptors (*Hjorth et al.* 1980) (D3 receptors according to *Seeman* 1980). For example, apomorphine stimulates dopamine autoreceptors at low doses, thereby causing an inhibition of dopamine synthesis. At these doses stereotyped behaviour cannot be observed. These small doses inhibit motor activity, but larger doses can stimulate it. In Parkinson's disease apomorphine probably

has a predominantly postsynaptic action, due to the presynaptic neuronal degeneration.

MAO inhibitors effect an increase in the concentration of dopamine, which in turn decreases the rate of tyrosine hydroxylation. This is not prevented by blockade of postsynaptic receptors with haloperidol, so a direct presynaptic endproduct inhibition must be responsible (*Carlsson et al.* 1976).

Other transmitters can influence dopaminergic transmission. Inhibitory GABA-ergic nerve endings, emanating from the striatum, impinge upon dopamine neurons of the substantia nigra.

Substance P, a putative transmitter which has its highest concentrations in the substantia nigra, may well have an excitatory effect on dopamine neurons (*Lembeck* and *Zettler* 1971). When injected intracerebroventricularly, it can stimulate dopa synthesis in all regions of the rat brain (*Magnusson et al.* 1976). Dopamine, noradrenaline and serotonin concentrations are diminished by substance P administration when their synthesis is inhibited. These data also provide evidence for the role of substance P as an excitatory transmitter.

Noradrenaline

The distribution of noradrenaline in the brain is similar to that of serotonin. The cell bodies of noradrenergic neurons are mainly found in the locus coeruleus and other nuclei of the pons and medulla. Some axons descend into the gray matter of the spinal cord, some extend to the cerebellum, while others innervate the dorsal bundle and thereby the dorsal hypothalamus, limbic nuclei and the neocortex (viz. *Kobayashi et al.* 1975).

Noradrenaline is important in various aspects of human behaviour. While unspecific pharmacological agents such as reserpine and MAO inhibitors induce behavioural changes in parallel with perturbations of noradrenergic systems, other transmitter systems may be equally important. However, specific biochemical and pharmacological manipulations can increase the availability of noradrenaline at postsynaptic receptors. The application of tricyclic antidepressants such as desipramine leads to increased noradrenergic activity by blockade of reuptake; a decrease in depressive symptomatology and improved vitality also results.

Hypothalamic noradrenergic neurons participate in regulating the secretion of anterior lobe hormones from the hypophysis. They apparently inhibit secretion of vasopressin and oxytocin and there is

Table 2. *Noradrenaline in control subjects and Parkinson's disease (Riederer et al. 1977)*

Brain area	Noradrenaline (nmoles/g)		
		Parkinson's disease	
	Controls (11)	without L-dopa (5)	with L-dopa[1] (4)
Lentic. N.			
Caudate n.	0.57 ± 0.11	0.26 ± 0.04*	0.29 ± 0.05*
Putamen	0.27 ± 0.06	0.15 ± 0.065**	0.20 ± 0.07
Gl. pallidus	0.24 ± 0.05	0.19 ± 0.08	0.22 ± 0.03
Diencephalon			
Thalamus	1.49 ± 0.15	1.04 ± 0.09**	1.15 ± 0.11
Hypothalamus	6.20 ± 0.68	2.31 ± 0.25*	2.68 ± 0.3*
C. mamillare	1.83 ± 0.27	0.71 ± 0.06*	0.85 ± 0.08*
Brainstem			
S. nigra	0.65 ± 0.13	0.20 ± 0.04*	0.31 ± 0.05*
N. ruber	1.43 ± 0.25	0.47 ± 0.05*	0.55 ± 0.07*
Raphe + form. ret.	0.19 ± 0.065	0.07 ± 0.02*	0.09 ± 0.022**
Limbic Structures			
G. cinguli	0.27 ± 0.065	0.13 ± 0.05**	0.14 ± 0.05**
N. amygdalae	4.73 ± 0.83	1.42 ± 0.19*	1.95 ± 0.2*
N. accumbens	5.83 ± 0.68	3.61 ± 0.41*	4.2 ± 0.45**

Number of patients in parenthesis.

Values as mean's ± standard error (s.e.).

The trend to higher values in Parkinson's disease treated with Madopar (3 × 250 mg daily) was not significantly different from untreated parkinsonism. [1] Last dosage was taken 4–11 hours before death.

Significance when compared to controls: * = $p < 0.01$, ** $p < 0.05$.

All other values were not significantly different from controls.

evidence that noradrenaline is involved in the control of feeding and self-stimulation. Noradrenergic neurons, as well as those of other transmitters, help regulate body temperature and noradrenaline also has inhibitory effects on the autonomic activity of the spinal cord.

Although there are PNMT-containing neurons in the medulla which project to the hypothalamus, the function of such an adrenergic system is at present unclear.

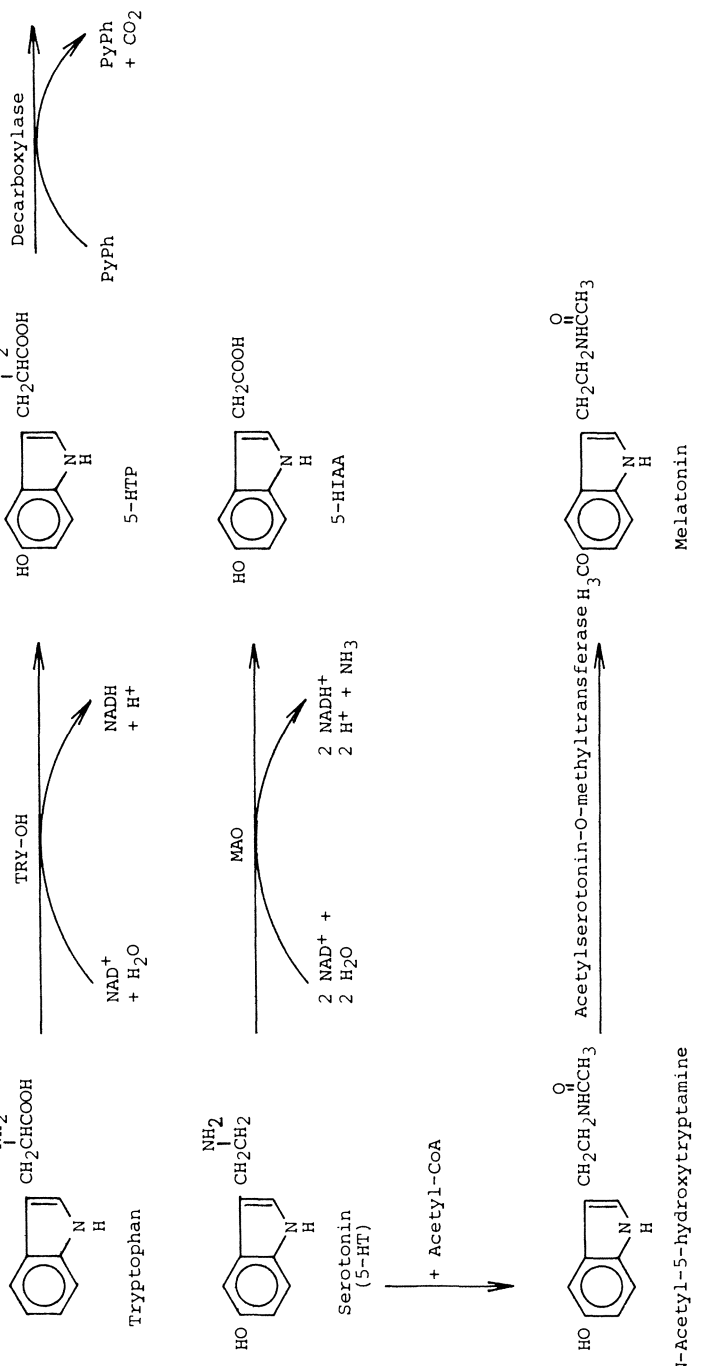


Fig. 6. Biosynthesis and metabolism of serotonin and melatonin. *TRY-OH* tryptophan hydroxylase, *5-HTP* 5-hydroxytryptophan, *5-HT* 5-hydroxytryptamine, *5-HIAA* 5-hydroxyindole acetic acid

Serotonin

Serotonin is synthesized from the essential amino acid tryptophan by hydroxylation to 5-hydroxytryptophan and subsequent decarboxylation (Fig. 6). The major metabolite is 5-hydroxyindoleacetic acid, formed from serotonin after oxidative deamination (with MAO) and further oxidation (with aldehyde dehydrogenase). Melatonin synthesis from serotonin occurs only in the pineal gland. Other derivatives of tryptamine and 5-hydroxytryptamine, notably psilocybin (a hallucinogenic constituent of some mushrooms) and bufotenin, have psychotomimetic effects.

Reserpine brings about a release of stored serotonin. Under suitable conditions this process can be inhibited, whereupon reserpine loses its tranquillizing properties. This provides evidence that the pharmacological properties of reserpine are due to a depletion of stored serotonin. But since reserpine also induces a release of dopamine and noradrenaline, it is not easy to assess which transmitter is primarily responsible for the effects of reserpine. The most illuminating study is still that of *Carlsson et al.* (1957) who describe how reserpine induced an akinetic state in rats which could be reversibly relieved by the administration of dopa.

The influence of various inhibitory compounds on MAO activity is described in detail elsewhere (see p. 106). It should, however, be mentioned that selective inhibition of MAO is possible; this permits the demonstration of specific effects of individual amine neurotransmitters.

Brain serotonin can be specifically depleted by p-chlorophenylalanine administration. This inhibits tryptophan hydroxylation and results in a sustained wakefulness in the animals. Serotonin is localized to specific serotonergic neurons, particularly those of the raphe nuclei. Additionally, from the investigations of *Maeda et al.* (1973) in cats (employing lesions of the reticular formation), there is substantial evidence for the participation of serotonin in sleep. However, p-chlorophenylalanine has not such a clear-cut effect in man, even in larger doses.

In the periphery, serotonin is found mainly in the enterochromaffin cells of the gastrointestinal tract. It can, however, be demonstrated in all other organs, often in considerable quantities (e.g. in liver, lungs, kidneys). Hyperperistalsis and diarrhoea can be observed as effects of a serotonin release, although the importance of serotonin in the peristaltic reflex is not entirely clear, since reserpine administration has only a slight effect on intestinal activity. The increased intestinal activity in carcinoid syndrome may be due to serotonin overproduction as it can be inhibited by serotonin antagonists. On the other hand this

treatment is ineffective against other characteristic symptoms of the disease.

γ-Aminobutyric Acid (GABA)

The metabolic pathway of GABA is a "shunt" bypassing part of the citric acid cycle (Fig. 7). GABA is synthesized by decarboxylation of glutamic acid; the enzyme responsible, glutamic acid decarboxylase (GAD), has been shown by immunochemical methods to be localized within nerve endings. GABA is an inhibitory transmitter in the brain and is a mediator of presynaptic transmission in the spinal cord.

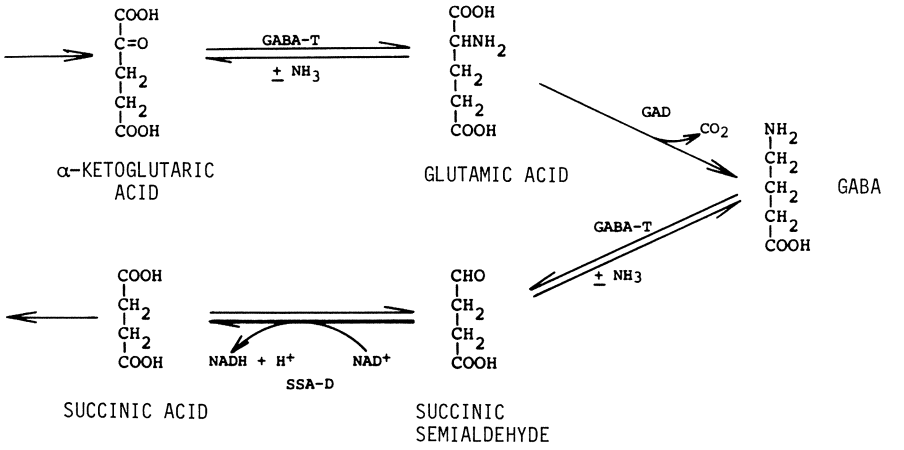


Fig. 7. Biosynthesis and metabolism of GABA. *GAD* glutamate decarboxylase, *GABA* gamma-aminobutyric acid, *GABA-T* GABA transaminase, *SSAD* succinic acid semialdehyde dehydrogenase

Albers and *Brady* (1959) demonstrated regional variations in GAD in the brain of the rhesus monkey. Gray matter was found to have generally higher activity than white matter, an observation confirmed in human brain by *Müller* and *Langemann* (1962). GAD activity is found particularly in the Purkinje cells of the cerebellum (*Kuriyama et al.* 1966), and 70–80% of activity is presented in synaptosomes (*Balazs et al.* 1966, *Bowen et al.* 1976, *Neal* and *Iversen* 1969, *Salganicoff* and *DeRobertis* 1965).

GABA is mainly metabolized by GABA transaminase (GABA-T) yielding succinic semialdehyde (*Waksman* and *Roberts*, 1965). Succinic semialdehyde dehydrogenase (SSAD) catalyzes the subsequent oxidation to succinic acid (*Miller* and *Pitts* 1967, *Sheridan et al.* 1967); both these metabolic steps are reversible.

The conversion of succinic semialdehyde to γ-hydroxybutyric acid (GHBA) by lactic acid dehydrogenase has also been described. GHBA, like its immediate precursor γ-butyrolactone, decreases neuronal activity in the CNS and in animal experiments GHBA leads to an increase in dopamine (*Laborit* 1964, *Walters* and *Roth* 1972). GABA-T and SSAD are distributed similarly in the brain and are mainly found in mitochondria. Only small quantities can be demonstrated in synaptosomal fractions.

The greatest accumulation of GABA is found in synaptic vesicles. The inhibitory GABA neurons are provided with a specific uptake mechanism (*Iversen* and *Johnston* 1971).

An increased outflow of GABA is required for synaptic transmission; the amount of GABA released is proportional to the size of the stimulus and requires the presence of calcium (*Otsuka et al.* 1966). Synthesis of GABA is apparently inhibited by hydrazines since its concentration decreases after administration of such substances. Hydrazines have convulsant effects which correlate with loss of GABA (*Balzer et al.* 1960). There has therefore been no lack of attempts to develop substances which increase GABA concentrations. Such GABA-T inhibitors include aminooxyacetic acid and cycloserine (*Baxter* and *Roberts* 1959, *Dann* and *Carter* 1964, *Gelder* 1966, *Wallach* 1961).

Substance P

Substantial amounts of this peptide have been demonstrated in the intestine, where it may be a mediator of the myoenteric reflex. Within the CNS, high concentrations have been demonstrated in the substantia nigra as well as in the hypothalamus and dorsal root of the spinal cord. The synthesis and metabolism of substance P are still under investigation.

Immunofluorescence techniques have demonstrated the presence of substance P pathways in several nuclei of the extrapyramidal system. An extensive network of these pathways occurs in the substantia nigra and in the subthalamic and interpenduncular nuclei (*Hökfelt et al.* 1975, *Nilsson et al.* 1974) and those of the substantia nigra originate from cell bodies in the caudate nucleus, putamen and globus pallidus (*Kanazawa et al.* 1977, *Hong et al.* 1977).

Dopaminergic Neurotransmission and Neuropeptides

The synthesis of the enkephalins and related peptides in the CNS has been demonstrated (*Elde et al.* 1976, *Simantov* and *Snyder* 1976, *Hökfelt et al.* 1980), while their physiological function and effect on behaviour are only beginning to be understood. Some investigations

do, however, point to the important role that these compounds play in behavioural control. Intraventricular administration of β-endorphin (but not other "opiate" neuropeptides) leads to a state of immobility and muscular rigidity in the experimental animal (*Bloom et al.* 1976, *Izumi et al.* 1977). The effect occurs fairly rapidly with the so-called "wet-dog shakes", total muscle rigidity and a state of akinesia (catatonia). It is dose-dependent: rigidity is predominant at low doses although external stimuli can still influence the behaviour of the animal. The intensity of rigidity is not so pronounced at night, when the animal is evidently more active.

However, β-endorphin is no "endogenous neuroleptic", since there are substantial differences in results from comparative investigations with haloperidol (*Bloom et al.* 1978). For example, naloxone has no effect on behavioural changes induced by haloperidol, while it completely removes the effects of β-endorphin. The marked effects of β-endorphin led to the view that these neuropeptides could be considered possible aetiological factors in mental disease (*Bloom et al.* 1976) and that opiate antagonists might offer a therapeutical approach. Results of clinical studies are contradictory, however. While *Gunne et al.* (1977) described naloxone to be beneficial in the treatment of auditory hallucinations, other workers were unable to verify this result (*Davis et al.* 1977, *Janowsky et al.* 1977, *Volavka et al.* 1977).

Other investigations have indicated a correlation between stress-induced analgesia and increased opiate-like activity in the brain (*Akil et al.* 1976, *Madden et al.* 1977), although *Fratta et al.* (1977) were unable to confirm this. On the other hand, investigations of lumbar CSF demonstrated a deficit in the concentration of endogenous opiates (*Akil et al.* 1978, *Terenius* and *Wahlström* 1975).

Terenius' group has detected an increase in endogenous opiate-like substances in the CSF of patients with schizophrenia (*Gunne et al.* 1977). Treatment with naloxone has, however, yielded mainly negative results which is probably due to the short period of action or the low dosage of this antagonist (*Bloom et al.* 1978, *Akil et al.* 1978). In fact, it has been shown that high doses of naloxone have significant effects on hallucinations and anxiety, but not on other symptoms of schizophrenia (*Akil et al.* 1978). Naltrexone, a longer-acting antagonist, has similar effects. Clinical investigations have so far shown that the opiate antagonists are only effective in selected patients and at high dosages.

Various animal experiments have shown that enkephalins reduce neuronal firing (*Frederickson* and *Morris* 1976), and that β-endorphin does not inhibit dopamine release (*Loh et al.* 1976).

The nigro-striatal dopaminergic pathway and the two efferent pathways from the caudate nucleus to the globus pallidus appear to be regulated by two independent feedback loops (*Costa et al.* 1978). One of these is the striato-nigral GABAergic loop which controls the activity of the dopaminergic cell bodies; the other is a short axonal loop in the striatum which impinges upon the dopaminergic nerve endings and which includes enkephalinergic neurons. This loop regulates the amount of dopamine released from nigro-striatal nerve endings via opiate receptors on these dopaminergic axonal terminals. Thus the dopamine release is regulated by a mechanism which is independent of any change in dopaminergic firing. The enkephalins inhibit GABA metabolism transynaptically but have no modulatory effect on cholinergic neurons. Enkephalins probably have an inhibitory influence on dopaminergic neurons (*Schwartz et al.* 1978).

It is probable that substance P, like GABA, acts on dendrites of dopaminergic neurons of the substantia nigra since it is also released from nerve endings of the striato-nigral pathway. While GABA inhibits, substance P stimulates dopaminergic neurons. If dopaminergic neurotransmission is blocked, the activity of cholinergic and substance P neurons increases. If it is correct to assume that the synapses between cholinergic and GABA-ergic neurons are inhibitory (*Costa et al.* 1978), then dopamine receptor blockade leads to increased cholinergic activity. This in turn will reduce the activity of the long GABA pathway innervating the substantia nigra, thereby resulting in a decreased inhibition of the nigral dopaminergic neurons.
GABAergic, cholinergic and enkephalinergic neurons are controlled, not only by dopamine, but also by a stimulatory afferent input from the cortex, a glutaminergic pathway.

Experiments designed to elucidate the influence of met-enkephalin and morphine on adenylate cyclase activity have shown no effect on either the basal activity or its sensitivity towards dopamine (*Racagni et al.* 1978). Enkephalins stimulate dopamine turnover in the striatum and limbic regions with a greater effect on the latter. Haloperidol leads to an increase in the striatal concentration of enkephalins.

The akinesia produced by β-endorphin can be antagonized by apomorphine and naloxone, while α-methyl-p-tyrosine exacerbates its effects. 5-HTP also enhances this akinesia, suggesting a connection between serotonergic systems and β-endorphin. β-endorphin increases serotonin levels, particularly in the mid-brain (raphé nuclei) and this region contains high densities of opiate receptors.

Met-enkephalin and leu-enkephalin are concentrated in areas which also have high concentrations of dopamine (for example the basal ganglia). Therefore possible interconnections between dopamine and

enkephalin systems are suggested. In fact, opiate receptors are located on striatal dopamine nerve terminals as well as on dopamine cell bodies in the substantia nigra. Opiates increase motor activity when injected into the substantia nigra and ventral tegmental area. Changes in the peptide neuromodulators in Parkinson's disease are described on p. 38.

Biochemical Changes in Parkinson's Disease

Introduction

Since 1960 there has been a great expansion in neurological and psychiatric research. Central to this have been the results of a decisive experiment crucial to the development of drug therapy for a neurological disorder, Parkinson's disease.

In the fifties *Brodie* and his colleagues discovered that reserpine is able to release serotonin from its storage sites, resulting in a depletion of this biogenic amine (*Brodie et al.* 1955). At the time it was assumed that this effect correlated with the antipsychotic action of reserpine. However, reserpine has the same effect on the catecholaminergic systems (*Carlsson et al.* 1957), and furthermore *Carlsson* demonstrated that dopa, the immediate precursor of the catecholamines, was capable of overcoming the effect of reserpine on animal behaviour. Subsequent investigations, showing that dopamine accumulates in the basal ganglia and noradrenaline in the brain stem (*Carlsson et al.* 1958, *Bertler* and *Rosengren* 1959), resulted in the proposal that dopamine in particular might be correlated with extrapyramidal motor effects.

One of us (W.B.) was interested in the clinical importance of these findings and proposed an investigation into the biochemical changes associated with autonomic and affective crisis in patients with Parkinson's disease. A collaboration was suggested with *Hornykiewicz*, which led to the demonstration of deficits in various neurotransmitters in particular structures of the human parkinsonian brain. The therapeutic studies which followed these investigations culminated in the antiparkinsonian therapy with dopa which is still in use today (*Ehringer* and *Hornykiewicz* 1960, *Birkmayer* and *Hornykiewicz* 1961).

Independent of this Vienna group, *Barbeau*, *Murphy*, and *Sourkes* (1961) found, at the same time, a reduced urinary excretion of catecholamines in parkinsonian patients and demonstrated an improvement of rigidity and tremor in these patients through the administration of L-dopa (*Barbeau et al.* 1962).

Thus it was found that biochemical correlates of a neurological disorder such as Parkinson's disease could be shown and that these biochemical disturbances could be influenced and improved, although

not cured, by drugs. This revolutionary recognition was a great stimulus to research into the biochemical pharmacology of the brain.

Although the parkinsonian syndrome is characterized mainly (but not exclusively) by a deficit of dopamine in the striatum, we cannot view dopamine in isolation. The behaviour of man is controlled by the combined action of a number of neurotransmitters and therefore disturbances in one system may be brought about by degenerative or functional disturbances in another such system.

Human Post Mortem Findings

Dopamine

It is accepted that in the parkinsonian syndrome there is a characteristic change in the chemistry of particular nuclei of the extrapyramidal motor system: the dopamine concentration in the striatum and substantia nigra is significantly below normal (*Ehringer* and *Hornykiewicz* 1960). This lack of dopamine is fairly specific to Parkinson's disease; however other diseases of the extrapyramidal motor system including supranuclear palsy and strionigral degeneration do feature a decrease in this transmitter (*Nagatsu et al.* 1981b, *Jellinger et al.* 1980). Although other nuclei also exhibit a dopamine deficit (Fig. 8), the extreme decrease in dopamine is limited to the striatum and substantia nigra. This dopamine loss can be correlated with the

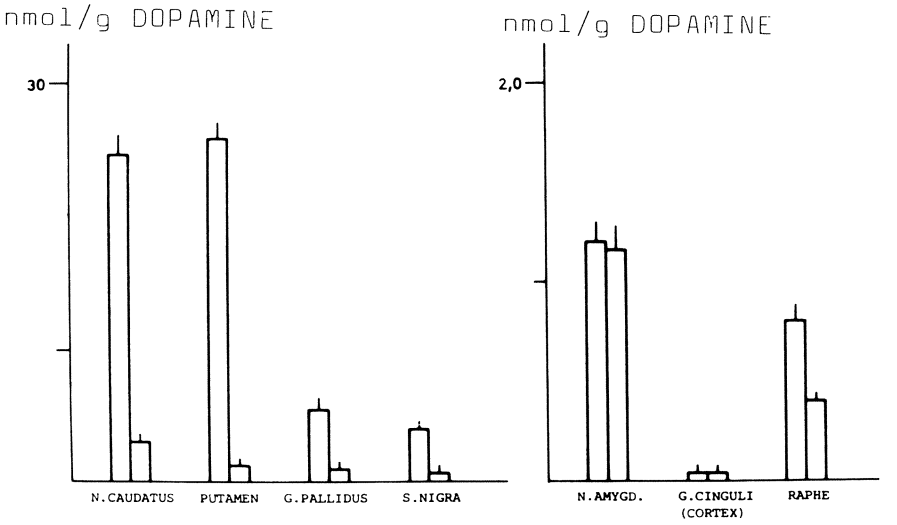


Fig. 8. Dopamine deficiency in Parkinson's disease. Left bars in each region are controls, right bars indicate Parkinson's disease (*Birkmayer et al.* 1977)

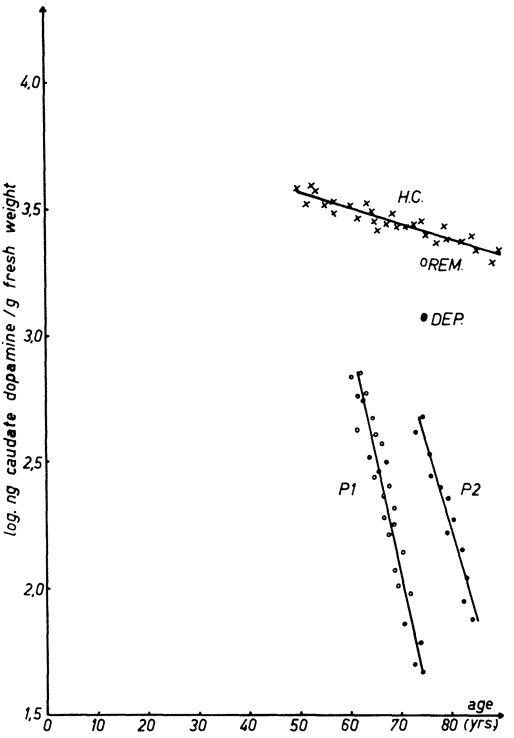


Fig. 9. Time course of nigro-striatal degeneration in parkinsonism (*Riederer* and *Wuketich* 1976). H.C. (x): Healthy controls clinical details see ref. Statistical analysis: number of cases: 28. Chi²-test: $CC_{corr} = -0.9660$, $r = -0.0092$, Oy = 3.88. P1 (○): Parkinsonian patients; age at onset of the disease = 60 ± 1 years; Statistical analysis: number of cases: 27. Chi²-test: $CC_{corr} = -0.9740$, $r = -0.0956$, Oy = 8.79. P2 (●): Parkinsonian patients; age at onset of the disease = 73 ± 1 years; Statistical analysis: number of cases: 12. Chi²-test: $CC_{corr} = -0.9768$, $r = -0.0835$, Oy = 8.885. DEP. (◖): Depressed patients; for clinical details see *Birkmayer* and *Riederer* (1975b). Number of cases: 3. REM. (O): Depressed patient during remission. Number of cases: 1.

Patients	Age group (years)	Loss of dopamine in Caudate nucleus (%)
H.C.	45–55 (4)	15.3
	56–65 (7)	15.7
	66–75 (8)	9.8
	76–85 (6)	10.7
	86–95 (3)	
		mean = 12.87 ± 3.05 ± s.d. pro decade
P1	61–67 (14)	28.55 ± 9.00
	67–73 (13)	46.55 ± 6.85
P2	74–80 (9)	28.3 ± 4.16
	80–84 (3)	38.6 ± 5.79

symptom of akinesia; rigidity and tremor reflect other biochemical disturbances, since they respond less well to L-dopa treatment.

Fig. 9 indicates the time course of dopamine loss in the caudate nucleus from controls in comparison with two groups of parkinsonian patients (*Riederer* and *Wuketich* 1976). Even in the control group a loss of dopamine, of approximately 13% per decade, occurs with increasing age. Each Parkinson group, composed of patients whose first symptoms occurred at the same age but who died at different times thereafter, exhibits a very strong decrease in dopamine concentration as the disease progresses. From this investigation it was seen that a dopamine deficit of approximately 70% is necessary before the symptoms of Parkinson's disease become apparent. In addition dopamine is found to decrease with the degeneration of the nigro-striatal pathway. Since all these patients received L-dopa in some form, this therapy clearly cannot halt the progression of the disease. On the other hand it is also clear that L-dopa preparations will lose their efficacy as the disease advances. This progressive degeneration is, perhaps, not a linear process, but may accelerate, as suggested by the logarithmic presentation of data in Fig. 9. Aging has been discussed in more detail by *Carlsson* (1981).

Patients exhibiting the "akinetic crisis", as first described by *Danielczyk* (1973), have a very poor response to therapy and finally succumb in this akinetic state when dopaminergic drugs no longer have any effect. We have been able to carry out post-mortem investigations on a few of these cases (Table 1) and have found that the striatal dopamine content is even smaller than in other cases of Parkinson's disease. In cases with akinetic crisis, it seems that the presynaptic nerve endings have totally degenerated, since all therapeutic attempts fail. The fact that even postsynaptic dopaminergic agonists such as bromocriptine are also ineffective provides clinical evidence for the loss of, in addition, postsynaptic receptor function. This will be discussed further with more biochemical data in the chapter on therapy.

Data obtained from the measurement of tyrosine hydroxylase activity in various brain regions give support to the above results. Table 3, consistent with the dopamine values, shows that the greatest losses of activity of this enzyme occur in the striatum and substantia nigra. These findings, which presumably represent a decrease in catecholamine synthesis since the enzyme is rate-determining, are in agreement with those of *McGeer et al.* (1971a), *Nagatsu et al.* (1977) and *Lloyd et al.* (1975). The results cannot be explained by enzyme inhibition due to prior L-dopa therapy since this treatment is discontinued (for clinical reasons) 2–5 days before death, and because one patient who had never received L-dopa in any form also showed

Table 3. *Tyrosine hydroxylase activity in post-mortem tissue of different degenerative and metabolic disorders (Riederer et al. 1978a)*

	Normal subjects	Parkinsonian patients[1]	Senile P. without L-dopa (1)	Cerebral atrophy (2)		Hypertens. encephalop. (1)
Brain areas						
Caudate n.	27.8 ± 2.3 (15)	3.5 ± 1.0 (6)*	n.d.	–	3.7	3.0
Putamen	16.2 ± 5.9 (5)	1.2 ± 0.4 (6)*	n.d.	8.6	–	4.5
G. pallidus	19.9 ± 3.3 (3)	2.7 ± 0.8 (4)*	n.d.		–	–
S. nigra	19.4 ± 6.2 (4)	4.9 ± 1.8 (4)*	3.7	–	–	7.2
L. coeruleus	3.3 ± 0.1 (4)	2.0 ± 0.6 (2)	–	3.7	–	–
N. ruber	5.7 ± 1.9 (5)	2.1 ± 1.4 (3)	0.7	5.6	–	–
Raphe + ret. F.	0.9 ± 0.6 (4)	1.5 ± 0.4 (5)	1.8	–	0.8	–
Hypothalamus	3.1 ± 1.0 (5)	1.5 ± 0.3 (3)	–	1.5	2.3	–
C. mamillare	0.6 ± 0.4 (5)	0.5 ± 0.9 (2)	–	0.7	0.4	–
N. accumbens	2.0 ± 0.7 (5)	2.7 ± 2.2 (3)	–	1.2	–	–
Adrenal gland						
Medulla	186.2 ± 5.5 (5)	49.7 ± 12.4 (4)	159.2	138 (2)		144 (2)

Number of patients in parenthesis. – Not estimated. n.d. = not detectable. Means ± S.E.M. Values are given in nmoles dopa/hour/g. * $p < 0.01$.

[1] Combined L-dopa treatment discontinued 2–5 days prior to death.

activity significantly reduced below control values. Recent animals experiments confirm these results (*Melamed et al.* 1980).

In addition to the degeneration of nigral dopamine neurons in Parkinson's disease, a substantial decrease in tyrosine hydroxylase activity in the ventral tegmental area suggests a dopamine cell loss in this area and supports the existence of a dopaminergic mesolimbic system in humans (*Javoy-Agid* and *Agid* 1980). Moreover, there is evidence for a dopaminergic cortical projection from the substantia nigra and ventral tegmental area. Mesolimbic and mesocortical dopamine deficiencies might be responsible for in particular, psychiatric symptoms of the disease and side effects arising from drug treatment (*Birkmayer* and *Riederer* 1975a, *Javoy-Agid et al.* 1981).

We have shown that tyrosine hydroxylase is also significantly diminished in the adrenal gland (*Riederer et al.* 1978a). An effect of L-dopa therapy can be ruled out here too since, in animal experiments (*Dairman* and *Udenfriend* 1972), only very high doses (i.e. 1 g/kg) can bring about a 50% diminution of adrenal tyrosine hydroxylase activity; our patients had much lower activities (at low L-dopa doses:

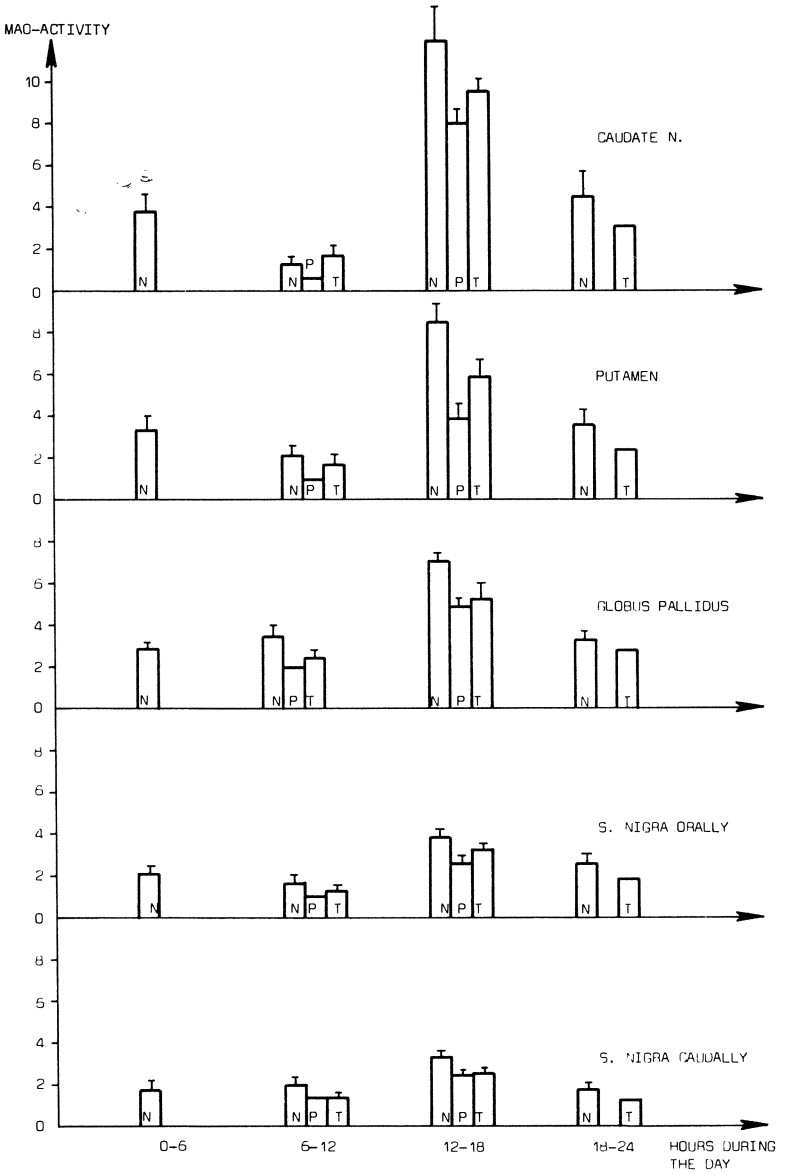


Fig. 10a

Fig. 10a, b. Circadian rhythm of monoamine oxidase activity in various areas of human brain. Kynuramine as substrate (nmoles 4-hydroxyquinoline/mg protein/20 minutes), mean values ± s.e. *N* controls, *P* Parkinson's disease without combined L-DOPA therapy, *T* Parkinson's disease treated with "Madopar" (*Birkmayer et al.* 1975)

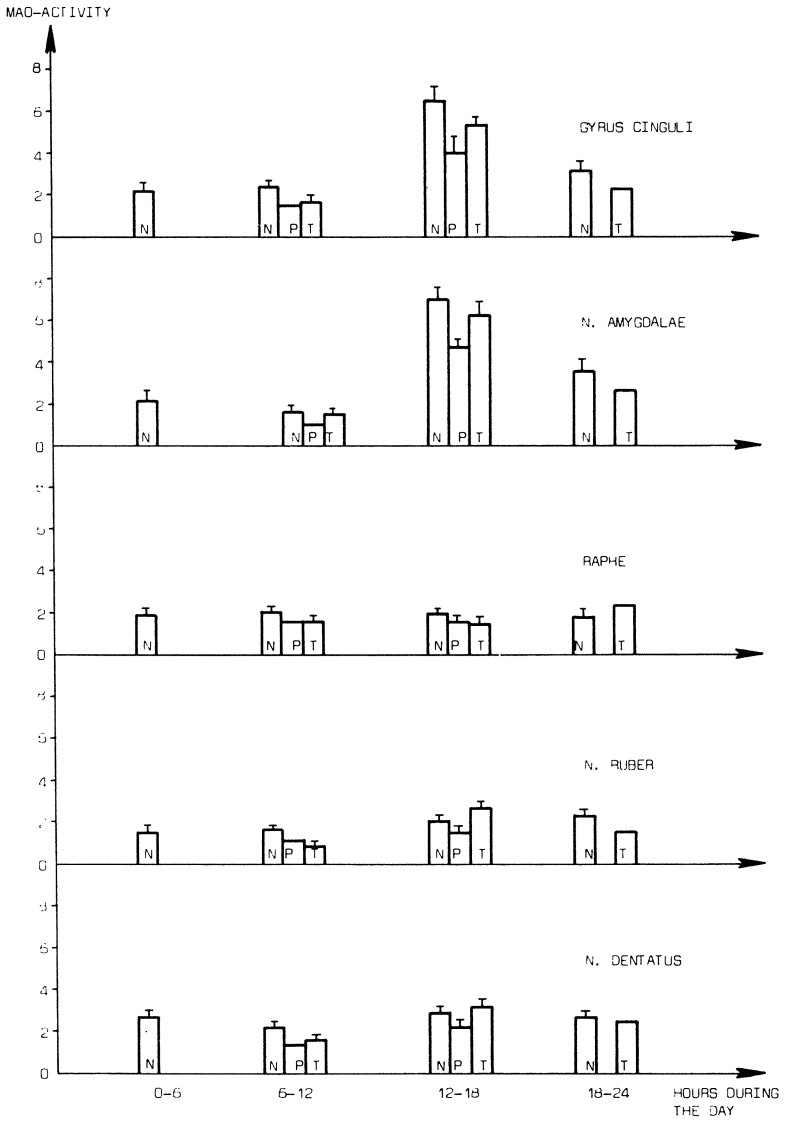


Fig. 10b

375–750 mg Madopar daily; Table 3). These results lead to the conclusion that either Parkinson's disease is a disease of the whole body, not just of the dopaminergic nigrostriatal pathway, or the reduction in adrenal tyrosine hydroxylase is due to the imbalance of central neurotransmitter systems. Experimental evidence validates the

latter view: the stimulation of central dopamine receptors is associated with an increase in adrenal tyrosine hydroxylase activity. Destruction of serotonergic neurons also increases this activity (*Quik* and *Sourkes* 1977) and exemplifies the inhibitory effect of serotonin systems on the activity of dopaminergic neurons. Other investigations suggest that the reduction in adrenal tyrosine hydroxylase is an effect of the disturbed balance between dopamine and ACh function in the brain (*Ulus et al.* 1977, *Lewander et al.* 1977).

In contrast to this synthesizing enzyme, the activity of the metabolizing enzyme monoamine oxidase (MAO) is unchanged in Parkinson's disease (Fig. 10a, b). This is in agreement with the results of *Bernheimer et al.* (1962) and *Lloyd et al.* (1973). The data in Fig. 10a, b is subdivided according to time of death and provides an interesting insight into the circadian rhythm of this enzyme. Activity of MAO is highest in the afternoon. This could relate to the increase in "off" phases at this time, since dopamine would be deaminated more rapidly. The therapeutic success with deprenyl, a "clean", selective MAO inhibitor (see p. 106), may provide evidence for this assumption although other effects, such as competition with dopa for transport into the brain from amino acids deriving from the mid-day meal, may also be relevant. These normal values for MAO are an important finding; they indicate that the morphological structures containing MAO are not involved in the degenerative process.

Biochemical Aspects of Dopaminergic Agonists

The presynaptic portion of the dopamine neurons is believed to degenerate as a consequence of the degenerative process, while the postsynaptic part may remain relatively intact. According to *Ungerstedt* (1971) degeneration causes supersensitive receptors and this assumption has stimulated research into the development of dopamine agonists leading to novel therapeutic approaches in Parkinson's disease and providing further knowledge of the function of neurotransmitter receptors. However, from the first reports (*Calne et al.* 1974, *Corrodi et al.* 1973, *Flückiger* and *Vigouret* 1981 for reviews, *Fuxe et al.* 1974, *Horowski* and *Wachtel* 1976, *Schachter et al.* 1980) until today, no other dopamine agonist has been so widely investigated and employed as has bromocriptine, found to be effective both on its own and in conjunction with conventional L-dopa therapy. However a range of other ergoline derivatives are under investigation or have already been found to be successful antiparkinsonian drugs (see p. 122).

Dopamine agonists are limited in that they are unselective both in acting on all dopaminergic systems and in occasionally acting at presynaptic sites (*Carlsson* 1975). In Parkinson's disease the

degenerative process is progressive, and there is evidence that receptor units change both in their number and in their affinity towards ligands. Whereas experimental data suggest there is a compensation of presynaptic functional loss by change in receptor function, confirmation of these data in man is still lacking. In contrast, post-mortem brain studies have provided evidence for both increased and decreased receptor number in Parkinson's disease. This discrepancy between animal experiment and post-mortem brain analysis can be explained by the assumption that supersensitive receptors are the expression of acute experimental lesions or of the "compensated phase" in Parkinson's disease, whereas subsensitive receptors derive from further postsynaptic degeneration or result from drug therapy (see p. 32; *Riederer* and *Jellinger* 1980, *Yahr* 1981).

Receptors change their affinity towards the endogenous ligand with respective loss of receptor sites and in the final "decompensated phase" the akinetic final stage of Parkinson's disease correlates with a terminal switch of D_2-receptors into the high affinity state. This suggestion has been confirmed experimentally by *Fuxe et al.* (1981) who found supersensitive receptors in experimentally lesioned animals. However, these chronic experiments eventually lead to a loss in receptor function, and after one year subsensitive receptors develop (*Fuxe et al.* 1981).

D_1 Receptor Activity

Dopamine sensitive adenylate cyclase (*Kebabian et al.* 1972) is associated with postsynaptic membranes and is present in the nigro-striatal and mesolimbic structures of the human brain. Recently, *Kebabian* and *Calne* (1979) have named this receptor D_1 whereas other dopamine receptor units, labelled by neuroleptic drug binding techniques, are referred to as D_2. Basal level of cAMP are not changed in parkinsonian patients who died of bronchopneumonia or heart failure due to secondary causes (group A) while lower levels of cAMP were seen in patients who died during long lasting akinetic crises (group B). Stimulation of cAMP by 100 μM dopamine in group A showed a significant increase above basal levels, but this was significantly less pronounced in comparison to controls. The adenylate cyclase system was not stimulated at all by 100 μM dopamine in parkinsonian patients with therapy resistant akinetic crises (Fig. 11, Table 4). Long term drug treatment failed to change the capacity of dopamine to stimulate cAMP production (*Riederer et al.* 1978b). These findings indicate a disturbance of the postsynaptic neuronal activity in Parkinson's disease.

These results are in accordance with findings by *Shibuja* (1979), who found a lower basal activity of adenylate cyclase in the caudate

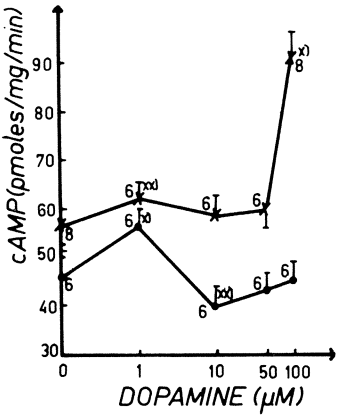


Fig. 11. In vitro stimulation of adenylate cyclase in caudate nucleus by dopamine. Mean values ± s.e.m. (cAMP pmol/min./mg protein). * $p < 0.01$ compared to basal value, ** $p < 0.05$ compared to controls (100 μM dopamine), X controls; ● Parkinson's disease with akinetic end stage (*Riederer et al.* 1978b)

Table 4. *Stimulation of adenylate cyclase in caudate nucleus by dopamine dependence on drug treatment (Riederer et al. 1978b)*

	cAMP (pmoles/mg/min.)	
	Basal level	Dopamine stimulated (100 μM)
Controls (4)	54.2 ± 7.3	90.3 ± 16.5^{+}
Liver cirrhosis (5)	65.1 ± 13.8	45.2 ± 8.9
Carcinoma (4)	47.9 ± 12.9	33.7 ± 11.6
Parkinson's disease		
A. Kinetic patients (4)	53.4 ± 5.3	73.6 ± 4.3^{+} *
a) Nomifensine (2)	54.2	65.3
B. Therapy resistant akinetic crisis (8)	46.7 ± 11.9	44.3 ± 8.6**
a) Madopar (6)	79.9 ± 13.9	57.8 ± 10.9
b) (–)Deprenyl (6)	61.7 ± 14.9	47.9 ± 9.2
c) Bromocriptine (4)	76.6 ± 3.3	65.3 ± 10.6
d) Amantadine (5)	78.5 ± 10.6	61.4 ± 9.2
e) Clomipramine (4)	69.3 ± 8.3	62.1 ± 8.9
f) Anticholinergics (3)	47.2 ± 6.4	33.0 ± 9.9**

$^{+}$ $p < 0.01$ compared to basal levels; * $p < 0.01$ compared to controls (100 μM dopamine); ** $p < 0.01$ compared to kinetic parkinsonian patients (100 μM dopamine).

nucleus and putamen with a low stimulation by dopamine. However *Nagatsu et al.* (1978) found an increased stimulation of adenylate cyclase by dopamine in the caudate nucleus obtained from three parkinsonian patients with an overlap between patients and controls. cAMP dependent protein kinase has been shown to be decreased in Parkinson's disease (*Kato et al.* 1979).

Denervation Supersensitivity or Subsensitivity of Dopamine Receptors in Parkinson's Disease

Animal experiments have shown that presynaptic denervation can induce a supersensitivity of postsynaptic receptors. These findings are relevant to Parkinson's disease where, as a result of dopaminergic neuronal loss, the efficacy of L-dopa treatment declines, culminating in a terminal phase characterized by lack of response to all antiparkinson drugs with increasing frequency of side effects. Moreover, there is an increase in daily oscillations and a loss of tolerance to drug application. These clinical observations are in line with a "denervation supersensitivity" where overactivity of postsynaptic dopamine receptors compensate for the functional lack of degenerating presynaptic neurons.

Neuroleptic drug binding techniques, labelling D_2 receptors in post-mortem brain striatum, have shown controversial results in Parkinson's disease with increased (*Lee et al.* 1978), normal (*Spokes* and *Bannister* 1981) or decreased receptor density (*Rinne et al.* 1979, 1981, *Winkler et al.* 1980) in L-dopa-free patients. L-dopa has been reported to decrease neuroleptic drug binding sites (*Lee et al.* 1978), although it has been shown not to influence receptors in other studies (*Rinne et al.* 1979). *Reisine et al.* (1977) found normal and low density of D_2 binding sites in L-dopa treated parkinsonians, and *Winkler et al.* (1980) conclude that there is a subsensitivity of D_2 receptor activity.

Preliminary results comparing different drugs on D_2 receptors in post-mortem putamen of patients with Parkinson's disease are shown in Table 5. As all our patients were on some type of antiparkinsonian drugs, D_2-receptor activity after agonist treatment can only be compared to controls and a group of three Parkinson's disease patients treated either with amantadine (given in one patient; 400 mg/day) or L-dopa (given in two patients; 3×125 mg Madopar/day) until death. Only a very slight reduction in B_{max} values is notable in this group compared to controls. A more pronounced drop in receptor activity can be seen in patients who had been treated with the dopamine agonists lisuride and CU-32085 for about two months before death. In contrast, neuroleptics increase the number of binding sites, in agreement with results of *Rinne et al.* (1979) and our own studies on

Table 5. *^{3}H-Spiroperidol-binding in post-mortem putamen*

	(n)	Sex (M/F)	Age (years)	Post-mortem time (h)	B_{max} (pmol/g)[2]	K_D (nM)
1. Controls	(18)	4/14	73.6 ± 3.1	7.7 ± 1.2	23.3 ± 1.2	0.13 ± 0.016
2. Parkinson's disease						
Amantadine, L-dopa	(3)	0/3	77.3 ± 0.7	8.8 ± 3.0	21.7 ± 2.25	0.12 ± 0.03
Lisuride	(3)	0/3	71.7 ± 2.9	9.0 ± 3.0	17.4 ± 4.6	0.39 ± 0.20
CU-32085	(1)	0/1	61.0	9.0	13.5	0.31
Neuroleptics	(3)	0/3	81,7 ± 5.2	10.8 ± 5.2	25.9 ± 2.0	0.12 ± 0.014
3. Alzheimer's disease	(3)	0/3	67.3 ± 4.1	7.8 ± 2.8	16.2 ± 3.1	0.32 ± 0.028
4. SDAT						
without neuroleptics	(5)	2/3	80.0 ± 6.1	4.7 ± 2.8	23.06 ± 3.8	0.13 ± 0.036
with neuroleptics	(2)	0/2	80.0 ± 0	1.0/2.5	39.8 ± 41.5	0.77 ± 1.50
5. Senile vascular Enc.	(4)	2/2	82.0 ± 8.28	5.8 ± 0.8	25.8 ± 8.48	0.16 ± 0.074
6. Hypertension (Reserpine treated)	(1)	0/1	76.0	2.5	38.3	0.23
7. Schizophrenia[1]						
short-term neuroleptics	(5)	2/3	73.8 ± 3.0	2.3 ± 0.4	18.2 ± 1.96	0.17 ± 0.024
long-term neuroleptics	(10)	2/8	67.6 ± 2.4	2.1 ± 0.2	29.1 ± 4.1	0.92 ± 0.295
neuroleptic-free	(3)	1/2	60.0 ± 4.0	3.2 ± 2.4	15.5 ± 3.3	0.17 ± 0.018

[1] Neuropathology: age-related normal brains. [2] Student's t-test: lisuride versus controls $p < 0.005$; neuroleptics (Parkinson's disease) versus controls $p < 0.005$; amantadine, L-dopa versus neuroleptics $p < 0.05$; M. Alzheimer versus controls $p < 0.0005$; controls versus schizophrenia + short-term neuroleptics $p < 0.05$; controls versus schizophrenia + long-term neuroleptics $p < 0.01$; schizophrenia + long-term neuroleptics versus schizophrenia + short-term neuroleptics $p < 0.01$; neuroleptic-free versus controls $p < 0.02$.

neuroleptic treated schizophrenics (*Reynolds et al.* 1981a, *Riederer et al.* 1982a, *Riederer* and *Jellinger* 1982). Desensitization of D_2 receptors by dopamine agonists have been shown in long-term treated animals, in which the density of D_2 receptors was reduced by about 30% (mean) (reviewed by *Seeman* 1980, *List* and *Seeman* 1980).

Thus the concept of denervation supersensitivity is of little more than theoretical interest except perhaps in the early (untreated) stages of the disease when it might compensate for the loss of dopamine neurons. This certainly does not reflect a total loss of presynaptic structures as shown by electron microscopy (*Forno* and *Norville* 1979) and immunocytochemical studies (*Jørgenssen et al.* 1982). It is apparent from our results that drug treatment, particularly with dopamine agonists, may induce a drop in receptor number which would correlate with a functional subsensitivity of the neuronal system. This underlines the importance of using the lowest possible dose of such therapeutic agents in order to obtain an effect without stimulating too great a "down regulation" of the postsynaptic receptors. However, it is relevant to note that some of the beneficial effects of dopamine agonists seem to be attributable more to a psychomotor activation than to motor function, these being related to different brain structures (see *Birkmayer* and *Riederer* 1982).

Noradrenaline

In addition to the degeneration of the nigro-striatal dopaminergic system in Parkinson's disease, other biochemical losses can be detected. Investigations into the noradrenergic system have shown a deficit of noradrenaline in almost all brain regions (reviewed by *Riederer et al.* 1977). Since this transmitter is particularly important in the function of the autonomic nervous system, both noradrenaline and its major metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) have been measured in our post-mortem brain studies.

Table 2 shows the noradrenaline concentration in brain regions from parkinsonian patients. While all patients have significantly lower values than controls, the dopa-treated patients have, on average, more brain noradrenaline than the untreated group. A similar although generally more pronounced trend is shown by MHPG (Table 6).

Morphological examination of the pigmented brain stem nuclei showed that the locus coeruleus, as well as the substantia nigra, exhibits some degeneration. The increased turnover of noradrenaline could represent a compensatory phenomenon resembling the changes in the dopamine-HVA system (*Bernheimer et al.* 1973). Since noradrenaline pathways emanating from the noradrenaline-rich coeruleus innervate a large number of brain regions (reviewed by *Kobayashi et al.* 1975), this

degeneration leads to a reduced activity of dopamine-β-hydroxylase (*Nagatsu et al.* 1981b) and a decrease in noradrenaline elsewhere. Furthermore, the independent regional variations in the losses of dopamine and noradrenaline suggest that these changes are, at least in part, independent processes. The clinical relevance of these findings are discussed elsewhere (see the chapter on "side effects").

Table 6. *3-Methoxy-4-hydroxy phenylglycol (MHPG) in control subjects and Parkinson's disease (Riederer et al. 1977)*

	MHPG (nmoles/g)			
	free	free + bound	free	free
	controls (5)	controls (4)	Park. dis. without L-dopa (3)	Park. dis. with L-dopa (4)
Lentic. N.				
Caudate n.	0.72 ± 0.21	0.82 ± 0.19	0.28 ± 0.17*	0.52 ± 0.19**++
Putamen	0.66 ± 0.25	0.79 ± 0.17	0.13 ± 0.06*	0.41 ± 0.12*+
G. pallidus	0.14 ± 0.06	n.e.	0.14 ± 0.07	0.16 ± 0.055
Diencephalon				
Thalamus	0.97 ± 0.54	n.e.	1.19 ± 0.43	1.25 ± 0.15
Hypothalamus	1.31 ± 0.25	1.65 ± 0.18	1.29 ± 0.35	1.55 ± 0.145
C. mamillare	0.16 ± 0.06	n.e.	0.27 ± 0.16	0.30 ± 0.092
Brainstem				
Raphe + ret. form.	0.51 ± 0.06	0.70 ± 0.083	0.35 ± 0.065*	0.55 ± 0.075++
S. nigra	0.92 ± 0.1	1.12 ± 0.09	0.51 ± 0.14*	1.14 ± 0.11+
N. ruber	0.22 ± 0.04	n.e.	0.21 ± 0.13	0.23 ± 0.10
Limbic Structures				
G. cinguli	0.15 ± 0.09	n.e.	0.14 ± 0.08	0.17 ± 0.055
N. amygdalae	0.87 ± 0.38	1.20 ± 0.12	0.55 ± 0.18	0.92 ± 0.14++
G. dentatus	0.86 ± 0.39	n.e.	0.43 ± 0.2	0.66 ± 0.12
N. accumbens	1.10 ± 0.28	n.e.	0.38 ± 0.17*	0.75 ± 0.11
Dentate N.	0.18 ± 0.02			

n.e. = not estimated. Number of patients in parenthesis. Values are the means ± standard error (s.e.). Significance when compared to controls: * = $p < 0.01$, ** = $p < 0.05$. Significance between L-dopa treated and untreated patients suffering from Parkinson's disease: + = $p < 0.01$, ++ = $p < 0.05$.

Serotonin, Competition of Aromatic Amino Acids

Serotonin is significantly reduced in almost all parts of the parkinsonian brain (*Bernheimer et al.* 1961). In contrast to dopamine, however, this loss is on average only about 40–50% (Fig. 12) and can be much less. Interestingly there is no further loss in serotonin concentration after long-term dopa medication (Table 7), although a

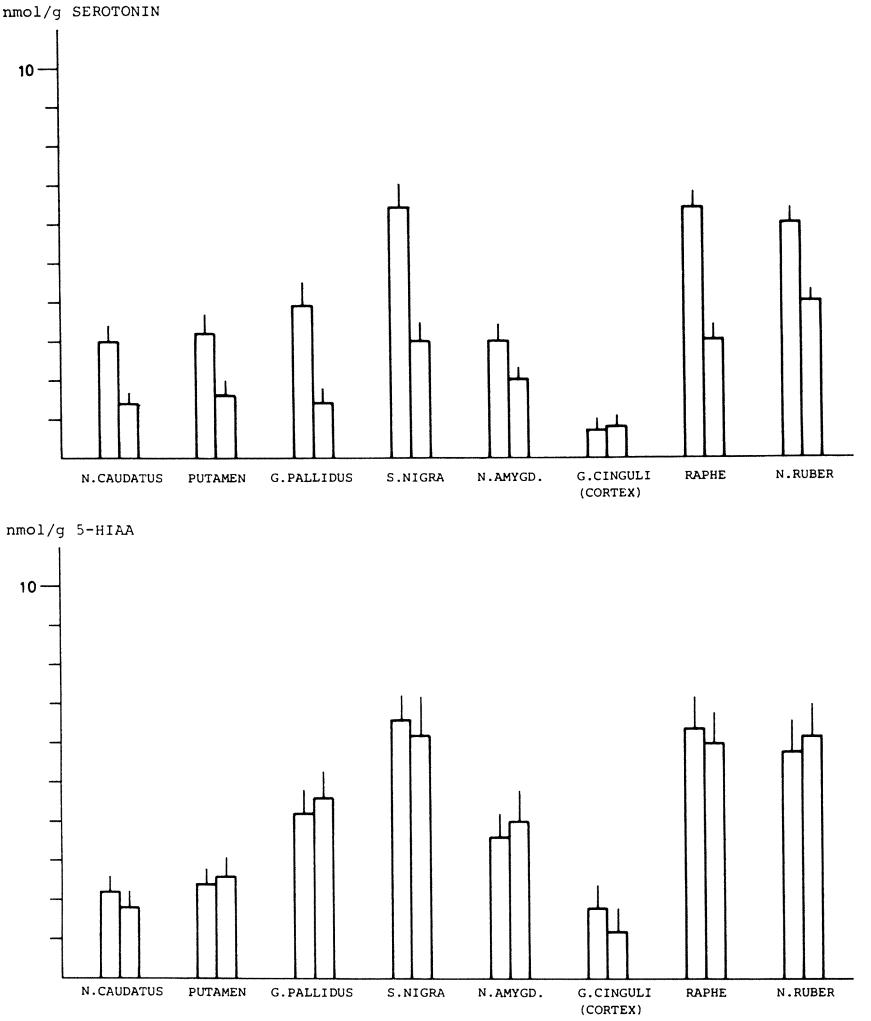


Fig. 12. Serotonin and 5-hydroxyindole acetic acid in various areas of human brain. Left bars of each region are controls, right bars indicate Parkinson's disease (*Birkmayer et al.* 1974)

Table 7. *5-Hydroxy-tryptamine in L-dopa-resistant and Madopar-treated parkinsonian patients compared to age-matched controls (Riederer and Wuketich 1976)*

	5-Hydroxy-tryptamine (ng/g) mean ± s.d.		
	L-dopa resistant parkinsonian patients (n = 4)	Parkinsonian patients on long-term Madopar treatment (n = 5)	Controls (n = 18)
Caudate nucleus	115 ± 14	125 ± 12	275 ± 19
Putamen	140 ± 13	135 ± 12	260 ± 21
Pallidum	135 ± 12	150 ± 14	380 ± 26
Substantia nigra oral part	265 ± 20	280 ± 23	545 ± 32
Substantia nigra caudal part	354 ± 24	370 ± 32	553 ± 27
N. amygdalae	190 ± 16	215 ± 19	272 ± 15
Gyrus cinguli	75 ± 10	63 ± 10	70 ± 12
Raphe + ret. form.	385 ± 35	409 ± 32	510 ± 30
Red nucleus	410 ± 32	395 ± 35	565 ± 33

L-dopa resistant parkinsonian patients: drug treatment during the last years before death: Amantadine, anticholinergics. No antiparkinson therapy 3–7 days before death. Age of patients: 75 ± 1 years.

Madopar treated parkinsonian patients: Madopar 3 × 250 mg daily in the mean for 5–7 years; antiparkinson-therapy 6–24 hours before death. Age of the patients: 75 ± 2 years.

Controls: age: 75 ± 3 years; 10 males, 8 females.

Autopsy interval: 9 ± 3 hours for all cases; storage time of dissected material: 42 ± 5 days at −70 C.

competitive effect between the individual aromatic amino acids has been described (*Fernstrom et al.* 1973, Table 8a, b). The extent of this competition is a question of dosage since the animal experiments employed doses higher than the total dopa dose taken by the patients. Fig. 40 shows the dopa levels of treated parkinsonian patients and demonstrates that the striatal uptake of dopa is greater than in other regions. This reflects the conversion to dopamine and subsequent vesicular storage in the terminals of nigro-striatal dopaminergic neurons which is the major fate of dopa after passing into the brain. If these presynaptic endings are destroyed, very little dopa, if any, can be

Table 8a. *Human brain tyrosine level with and without L-dopa treatment*

	Tyrosine μg/g (12)	Tyrosine after L-dopa μg/g (11)	Tyrosine WD / Tyrosine AD	Decrease %	Dopa level after L-dopa[1,2] μg/g (11)
Caudate nucleus	39 ± 2.1	31 ± 2.2*	1.26	21.5	1.95 ± 0.11
Putamen	42 ± 2.9	32 ± 2.8*	1.31	23.8	1.75 ± 0.12
G. pallidus	34 ± 3.1	27 ± 1.9*	1.26	20.6	0.85 ± 0.07
S. nigra	74 ± 4.8	48 ± 4.3*	1.54	35.1	1.2 ± 0.20
Raphe + ret. form.	27 ± 2.0	16 ± 1.5*	1.69	40.7	0.8 ± 0.05
N. ruber	35 ± 3.0	23 ± 2.1*	1.52	34.3	1.15 ± 0.09
N. amygdalae	44 ± 3.3	31 ± 2.7*	1.42	29.5	0.75 ± 0.04
G. cinguli	61 ± 4.6	49 ± 3.2*	1.25	19.7	0.63 ± 0.03

Values are mean ± standard error of the mean; number of patients in parentheses. * = $p < 0.01$. WD = without L-dopa treatment, AD = after L-dopa treatment.

[1] 3 × 250 mg Madopar daily.

[2] Dopa values of controls in the range of 10–30 ng/g.

Table 8b. *Human brain tryptophan levels without and with L-dopa treatment*

	Tryptophan μg/g (12)	Tryptophan after dopa μg/g (11)	Tryptophan WD / Tryptophan AD	Decrease %
Caudate nucleus	17.0 ± 1.4	8.2 ± 0.55*	2.07	51.8
Putamen	15.2 ± 0.90	7.3 ± 0.50*	2.08	52.0
G. pallidus	15.0 ± 0.85	7.7 ± 0.32*	1.95	48.7
S. nigra	19.2 ± 1.10	6.0 ± 1.30*	3.20	68.7
Raphe + ret. form.	23.3 ± 1.85	7.3 ± 0.95*	3.19	68.7
N. ruber	22.7 ± 1.7	9.8 ± 1.35*	2.32	56.8
N. amygdalae	17.5 ± 0.75	5.5 ± 0.70*	3.18	68.6
G. cinguli	14.9 ± 0.60	5.9 ± 0.85*	2.53	60.4

Dopa levels are shown in Table 8a. Values are mean ± standard error of the mean; number of patients in parentheses. * = $p < 0.01$. WD = without L-dopa treatment, AD = after L-dopa treatment (3 × 250 mg Madopar daily).

decarboxylated and so more is available to other intact regions of the brain. This might result in psychosis, the side effect found particularly in the end stages of the disease (see chapter on therapy).

In addition, serotonin receptor binding has been found to be unchanged in the striatum and in the frontal cortex and is not influenced by L-dopa or neuroleptics (*Rinne et al.* 1980). However, a slight decrease of serotonin receptor density has been noted in the frontal cortex (*Kienzl et al.* 1981). Serotonin receptor binding is, however, decreased in patients dying in coma and this might have influenced the latter study.

Neuropeptides

Although there is a wide spread reduction of dopamine in Parkinson's disease and a neuronal interrelationship between dopamine and several neuropeptide systems (see p. 18) dopaminergic denervation does not result in a reduction of met-enkephalin in the caudate nucleus, putamen, nucleus accumbens, nucleus amygdalae and hippocampus although a substantial reduction can be noted in substantia nigra, ventral tegmental area and globus pallidus externus (*Javoy-Agid et al.* 1982a). Degeneration of enkephalinergic fibres and/or nerve terminals in the mesencephalon of parkinsonian patients seem to accompany the loss of dopamine neurons. The decrease of met-enkephalin binding in the substantia nigra (pars compacta) from parkinsonian patients suggests a direct contact between enkephalinergic neurons and dopamine cells.

Furthermore, met-enkephalin, CCK-8, enkephalinase activity and D-Ala^2-met^5-enk A receptor binding are decreased in the substantia nigra (*Javoy-Agid et al.* 1982) and somatostatin is reduced in CSF (*Christensen et al.* 1980). Leu-enkephalin binding has been measured by *Rinne et al.* (1981) who found a significant increase in putamen, but not in caudate nucleus and nucleus accumbens. Moreover, an increase in receptor number was noted in the limbic cortex and hippocampus, but not in frontal cortex, nucleus amygdalae and hypothalamus.

The importance of enkephalinergic neurons in controlling dopamine systems and motor function in animals is well established. However, preliminary clinical trials of opiate agonists in Huntington's chorea or of naloxone in Parkinson's disease have not shown an improvement from which definite conclusions can be drawn (reviewed by *Javoy-Agid et al.* 1982a).

GABA

In Parkinson's disease, the inhibitory effect of GABA on nigro-striatal dopamine neurons is diminished. This is characterized by reductions in GABA in the substantia nigra and GAD in the nigra and basal ganglia (*Bernheimer* and *Hornykiewicz* 1962, *McGeer et al.* 1971b, *Hornykiewicz et al.* 1976).

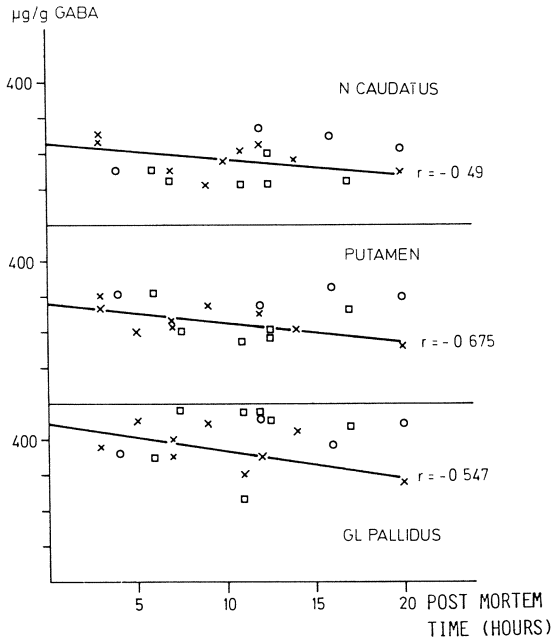


Fig. 13a

Fig. 13a–d. GABA in various brain regions–post-mortem dependence. x Controls, □ Parkinson's disease, ⊡ D Parkinson's disease plus Madopar, ⊡ PS/DD Parkinson's disease plus Madopar and Deprenyl (pharmacotoxic psychosis), ○ endogenous depression

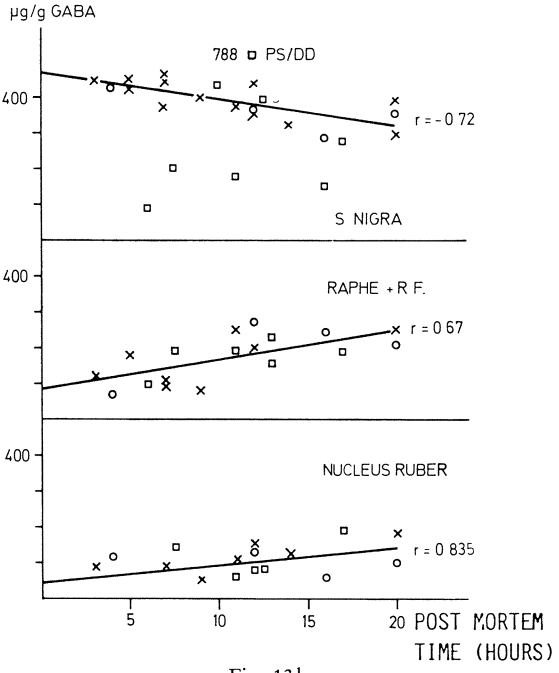


Fig. 13b

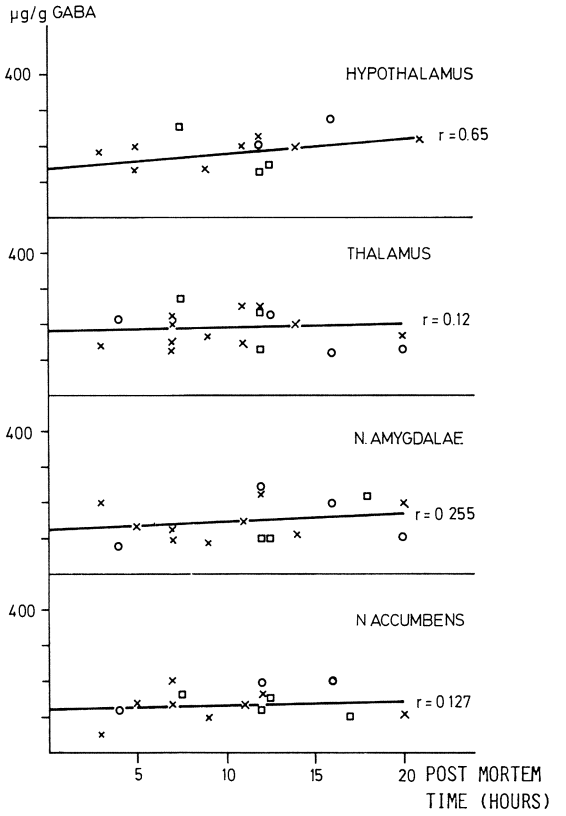


Fig. 13c

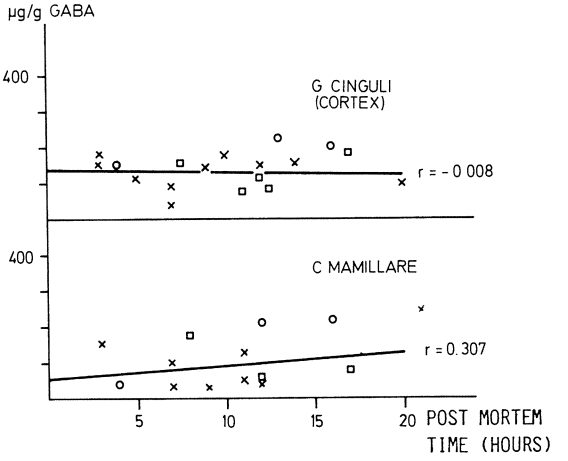


Fig. 13d

Table 9. *Activity of GABA-transaminase in Parkinson's disease*

Brain area	Controls	M. Parkinson
Caudate N.	15.7 ± 4.4 (4)	8.54 ± 1.7 (5)
Putamen	16.6 ± 7.9 (3)	–
S. nigra	11.6 ± 1.1 (6)	11.2 ± 4.8 (3)
Raphe + ret. form.	7.3 ± 2.5 (3)	–
Frontal cortex	10.8 ± 1.8 (4)	12.3 ± 1.4 (5)

Values are means ± S.E.M. (nmoles GABA/mg tissue/h). Number of patients in parenthesis. – = not determined.
Age: Controls 70 ± 4.4 (10) Post-mortem time: Controls 4.75 ± 1.1 (10)
Parkinson 77.6 ± 5.0 (5) Parkinson 6.5 ± 3.9 (5)

After determining the post-mortem changes in GABA in human brain tissue, we studied samples of various brain regions from patients with Parkinson's disease (Fig. 13a–d). In this condition GABA is found to be decreased in the substantia nigra in some but not all patients, consistent with a lower GAD activity in this brain region (*Bernheimer* and *Hornykiewicz* 1962, *McGeer et al.* 1971b, *Lloyd* and *Hornykiewicz* 1973). On the other hand no other area of the brain, with the exception of the ventral tegmental area (*Javoy-Agid et al.* 1982) showed any significant loss. It would follow that, in Parkinson's disease, there is a reduced activity of the GABAergic input to the substantia nigra from the striatum. Moreover, it should be mentioned that GABA concentrations may be normal (Fig. 13a, b), possibly as a consequence of reduced GABA-T activity in caudate nucleus (Table 9) or as a result of L-dopa treatment, which has been shown to increase GABA in CSF (*Lakke et al.* 1982, *Manyam* 1982). Low CSF GABA concentrations have been shown to correlate with on-off symptoms (*Teychenne et al.* 1982).

On this evidence it would appear that the disturbance of the GABA system in Parkinson's disease is more functional than degenerative. Investigations with brain tissue from parkinsonian patients who had received long-term dopa therapy, compared with those who received no dopa, indicated that this treatment increases GAD activity (*Rinne et al.* 1974, *Hornykiewicz et al.* 1976, *Lloyd et al.* 1981).

In addition it has been shown that (^{3}H) GABA receptor binding is decreased in the substantia nigra, although not in the striatum (Table 10). Thus GABA receptors may be localized on the cell bodies or dendrites of the nigro-striatal dopaminergic neurons which degenerate in Parkinson's disease. The lack of any change in

benzodiazepine binding in various human brain areas including striatum and substantia nigra suggest that these receptors are localized elsewhere (*Möhler et al.*, unpublished data).

Table 10. [^{3}H]*GABA-binding in substantia nigra*

Reference	Controls	Parkinson's disease	Treatment	% Controls
Rinne et al. 1980	85.0 ± 11 (11)	38.0 ± 15 (5)*	with L-dopa	44.7
		52.0 ± 11 (7)	without L-dopa	61.2
Lloyd et al. 1977	30.8 ± 5.0 (11)	9.7 ± 2.9 (6)**	?	31.4

Mean values ± S.E.M. (fmoles/mg protein); * = $p < 0.05$; ** = $p < 0.01$.

The Cholinergic System

Cholinergic neuronal activity has been followed by measuring choline acetyltransferase activity and decreases have been reported in globus pallidus, putamen, frontal cortex and hippocampus in Parkinson's disease (reviewed by *Ruberg et al.* 1982). Muscarinic binding sites were increased in putamen, globus pallidus, and frontal cortex. However, the increase in receptor number seems to reflect the influence of anticholinergic drugs (*Ruberg et al.* 1982). Reduced activity of choline acetyltransferase in Alzheimer's disease (without anticholinergic therapy) in cortex, hippocampus, putamen and amygdala is accompanied by a simultaneous reduction of muscarinic receptor number (see *Ruberg et al.* 1982 for review).

Huntington's Chorea

Huntington's chorea is an autosomal dominant hereditary disease which could be regarded, on the basis of its characteristic hyperkinetic movement, as the opposite of Parkinson's disease. In this disorder there is a degeneration of the small interneurons of the striatum (*Greenfield* 1958) which results in a progressive atrophy of this region. There is evidence that cortical areas and, in severe cases, the thalamus and substantia nigra are also affected. Investigations have demonstrated that the dopaminergic nigro-striatal system is not involved (*Bird* and *Iversen* 1974, *Bernheimer* and *Hornykiewicz* 1973, *Bernheimer et al.* 1973, *Birkmayer* and *Riederer* 1978, *Bird* and *Kraus* 1981).

However, the majority of cases have a significant reduction in GABA concentrations in the nigro-striatal region (*Perry et al.* 1973, *Bird* and *Iversen* 1974, *Cross* and *Waddington* 1981). But, as has been

Table 11. *Summary of biochemical changes in Parkinson's disease*

	Changes in Parkinson's disease (advanced stage) compared to normal aging
Dopamine	↓↓↓
Homovanillic acid	↓↓
Tyrosine hydroxylase	↓↓↓
Biopterin	↓↓
Dopa decarboxylase	↓(↓)=
Monoamine oxidase	=
Catechol-O-methyltransferase	=
cAMP-dependent protein kinase	=
D_1-receptors	↓↑=
D_2-receptors	↓↑=
Noradrenaline	↓(↓)
Dopamine-β-hydroxylase	↓(↓)
Phenylethanolamine-N-methyl transferase	↓
Serotonin	↓(↓)
5-hydroxytryptophan decarboxylase	↓=
5-hydroxyindoleacetic acid	↓(↓)
Serotonin receptors (S1)	↓=
γ-Aminobutyric acid (GABA)	↓(↓)
Glutamate decarboxylase	↓(↓)
GABA receptors	↓(↓)
Substance P	↓(↓)
Leu-enkephalin binding	↓=↑

↓↓↓ severely, ↓↓ moderately, ↓ slightly affected
= not affected

mentioned, GAD measurement gives more valuable information about GABAergic activity. Since the post-mortem instability of acetylcholine prevents its determination, the only way to assess cholinergic function is to measure the activity of choline acetyltransferase (CAT), the enzyme synthesizing acetylcholine. Both CAT and GAD are reduced in the striatum in Huntington's chorea (*Bird et al.* 1973, *McGeer* and *McGeer* 1973, *McGeer et al.* 1975, *Stahl* and *Swanson* 1974) although, in a relatively high proportion of patients, normal CAT levels have been measured (*Bird* and *Iversen* 1974). On the basis of these results there is a general agreement that the striatal cholinergic and GABAergic systems are affected in Huntington's chorea. Lesion experiments in animals indicating the presence of GAD-containing interneurons of the neostriatum are also consistent with these results. Evidence for a

strio-nigral GABAergic pathway has also been described (*McGeer* and *McGeer* 1976). Thus the nigro-striatal dopaminergic nerve endings can exert an inhibitory effect on the cholinergic interneurons of the neostriatum (*McGeer et al.* 1976).

Over the past years there has been no shortage of attempts to find substances which influence GABAergic systems. Administration of GABA itself is of little use as it cannot cross the blood-brain barrier (*Roberts* and *Kuriyama* 1968, *Kuriyama* and *Sze* 1971). The close endothelial connection and impossibility of pinocytosis in capillary membranes prevents the entry of hydrophilic (lipophobic) molecules such as GABA. Nevertheless penetration of such substances is possible if there are pathological changes in the membrane, which provides an explanation for the effect of high doses of GABA reducing, for example, the frequency of epileptic fits (*Tower* 1960). Partial success has also been reported in Huntington's chorea (*Purpura et al.* 1958, *Fisher et al.* 1974), although the concurrent administration of high doses of GABA with an inhibitor of GABA-T, n-dipropylacetate, did not produce any substantial improvement. This is presumably due to the compartmentation of GABA (introduced into the brain by adding lipophilic groups to the GABA molecule); an increase in neuronal GABA would only be possible after inhibition of GABA uptake into glial cells.

Administration of the precursor, glutamic acid, is ineffective due to its inability to cross the blood-brain barrier. Glutamic acid is also involved in a series of other processes including oxidative metabolism, protein synthesis and possibly neurotransmission. As with GABA, compartmentation is presumably important. Since GAD is the rate limiting enzyme in the formation of GABA, the administration of glutamate has little chance of success.

An increase in GABA concentration can be produced by inhibition of GABA metabolism. Various substances have been tested; they include isoniazid and phenelzine (also an MAO inhibitor), which are found to increase GABA in the brain, although the high concentrations necessary are potentially toxic (*Perry* and *Hansen* 1973). Structural analogues of GABA such as hydrazine propionic acid and ethanolamine-O-sulphate also inhibit GABA-T and thus increase GABA concentrations, although they have not yet been tested therapeutically. Aminooxyacetic acid has been tested as a GABA-T inhibitor, but induces cramps at high concentrations. Another GABA-T inhibitor, N-dipropylacetate, has been successful in the treatment of epilepsy (grand mal and petit mal) despite side effects which included vomiting, nausea and somnolence (*Boilley* and *Sorel*

1969). However, it has been unsuccessful in the treatment of Huntington's chorea (*Gelder* 1966).

A disadvantage of GABA-T inhibition lies in the increase in glial GABA content; it is not certain whether this effect also occurs in GABA neurons. Inhibitors of GABA uptake block both glial and neuronal uptake processes. At present there are no specific inhibitors without clinically unacceptable side effects.

A substantially more significant result has been produced by research into GABA receptors. Imidazole-4-acetic acid, a breakdown product of histamine, appears to be a GABA receptor agonist, although its administration to patients with Huntington's chorea has had no effect on their hyperkinetic symptoms (*Shoulson et al.* 1975).

More recently, the search for GABAergic agonists has stimulated interest in muscimol and progabide, only the latter substance being of clinical importance in diseases with a presumed GABA-deficiency (*Lloyd* and *Dreksler* 1979, *Lloyd et al.* 1981, *Löscher* 1981). This direct action on GABA-receptors might be a useful alternative since GABA-T inhibitors are limited by the regulatory effect of GABA on its own synthesis and release. The reduction in the efficacy of GABA-mimetic substances in long-term treatment seems to be an expression of feedback control. A further disadvantage is the poor regional selectivity of GABA-mimetics and the small therapeutic dose range.

The Clinical Pathology of Parkinson's Disease

The symptoms of Parkinson's disease include tremor and rigidity, both positive motor symptoms, and akinesia. Akinesia can be thought of as a negative symptom, being characterized by the inability to convert a potential for movement into kinetic energy (*Birkmayer* 1965), while tremor is due to the emergence of a primitive pattern of motor behaviour and rigidity results from current stimulatory and inhibitory neuromuscular activity.

Tremor

Resting tremor is one of the fundamental criteria for the diagnosis of Parkinson's disease. This rhythmic, involuntary back-and-forth motion has been recorded and measured by many and various methods in the past hundred years. *Herz* (1931) employed film analysis, *Jung* (1941) analysed action potentials, *Steinbrecher* (1961) used EMG and *Boshes* (1976) recorded the tremor with an accelerometer. We have used a high-speed camera at 880 frames per second (*Birkmayer* 1962). In all these investigations the frequency approximated to 5 Hz (range 3–8 Hz). This resting tremor occurs in only one plane while intention tremor occurs in all possible directions.

Our high-speed camera analyses of tremor yielded objective values of the time and amplitude from which the parameters of velocity, acceleration, force, work and power could be calculated (*Birkmayer* 1962). Tables 12 and 13 show such a calculation. The average velocity of the parkinsonian tremor is found to be 0.45 $m.sec^{-1}$ and that of intention tremor 2 $m.sec^{-1}$. The greatest acceleration for the parkinsonian tremor is 16.8 $m.sec^{-2}$ while that for intention tremor is 104.6 $m.sec^{-2}$. The equivalent values for the greatest force, work and power are 0.513 kp and 42.75 kp, 0.0216 kg.m and 0.697 kg.m, and 0.432 $kg.m.sec^{-1}$ and 17.4 $kg.m.sec^{-1}$ respectively.

All values for parkinsonian tremor are much smaller than those for the intention tremor. Thus a parkinsonian patient can maintain a resting tremor all day, while a patient with intention tremor (as in Wilson's disease) will need to rest for much of the day since these stronger movements use up much more energy. The rhythmicity and small energy requirement of the parkinsonian tremor suggest that it has its origin in primitive brain structures. It may be that it is an expression of

Table 12. *Parkinsonian tremor analysis by high speed camera*

Time (sec.)	Distance (m)	Velocity (m/sec.)	Acceleration (m/sec.^{2})	Force (Kp)	Work (kgm)	Power (kgm/sec.)
0.04	0.0210	0.53	13.3	0.407	0.00854	0.2140
0.05	0.0218	0.44	8.8	0.269	0.00587	0.1170
0.04	0.0052	0.13	3.25	0.099	0.00051	0.0128
0.04	0.014	0.35	8.75	0.268	0.00375	0.0940
0.05	0.042	0.84	16.80	0.513	0.02160	0.432
0.04	0.008	0.20	5.0	0.153	0.00122	0.0305
0.04	0.019	0.48	12.0	0.367	0.00678	0.170
0.06	0.024	0.40	6.7	0.205	0.00492	0.082
0.03	0.012	0.40	13.3	0.407	0.00488	0.163

Table 13. *Intention tremor analysis by high speed camera*

Δ t Time (sec.)	Δ s Distance (m)	Velocity m/sec.)	Acceleration (m/sec.^{2})	Force (Kp)	Work (kgm)	Power (kgm/sec.)
0.04	0.022	0.55	13.8	5.64	0.124	3.10
0.04	0.163	4.18	104.6	42.75	0.697	17.4
0.04	0.163	4.18	104.6	42.75	0.697	17.4
0.04	0.019	0.475	11.9	4.87	0.0924	2.31
0.04	0.018	0.45	11.25	4.60	0.0828	2.07
0.04	0.130	3.15	78.8	32.20	0.418	10.5
0.04	0.086	2.15	53.8	22.0	0.189	4.72
0.04	0.076	1.90	47.5	19.4	0.148	3.70

a particular rhythm of the spinal cord which is analogous to the motion of the medulla fish (*Holst* 1939), a proposal that has also been made by *Jung* (1941).

Hassler (1953) postulated that the emergence of this basic rhythm of spinal interneurons is brought about by the degeneration of the substantia nigra. Common to both parkinsonian tremor and the flickering of primitive flagellata is a regular rhythm and a particular sensitivity towards various stressful stimuli. Thus the increase in parkinsonian tremor due to affective or emotional stimulation compares with the "Bewegungssturm" of primitive organisms. *Kretschmer* (1926) compared such basic motor patterns to hysteria in man. This also applies to all types of hyperkinesia (e.g. that due to the side effects of

L-dopa therapy). Related to this is the "sham dead" reflex in animals which *Kretschmer* compared to hysteric paralysis. The freezing effect, a symptom of blocked motor activity which will be described later, should be mentioned in this respect. Both the positive symptoms of tremor and hyperkinesia and the negative "freezing" phenomenon – analogous to the "sham dead" reflex – are ancient patterns of behaviour which emerge when the higher brain centres are "switched off". In fact the successful stereotactic disconnection of the ventral oral anterior nucleus of the thalamus provided evidence for this central regulation of the spinal rhythm (*Hassler* and *Riechert* 1958).

Mettler (1946) has demonstrated a parkinsonian-like tremor induced by central lesions. Lesions of the ventromedial region between the upper pons and the caudal hypothalamus (*Poirier et al.* 1966), through which pass ascending nigral pathways, result in a resting tremor of the contralateral extremities. This defect is associated with a reduction in dopamine and serotonin in the caudate and putamen on the damaged side (*Andén et al.* 1966, *Goldstein et al.* 1969, 1973). Homovanillic and 5-hydroxyindolacetic acids are also diminished in these regions, as are the activities of tyrosine- and tryptophan hydroxylases and even dopa- and 5-hydroxytryptophan decarboxylases (*Poirier et al.* 1969). Lesions induced by α-methyltyrosine at various points in the rubro-olivo-cerebellar-rubro loop also evoke a tremor, although surgical lesions have no such effect. α-Methyltyrosine – an inhibitor of dopamine synthesis – brings about a tremor on the same side as the lesions. In monkeys this can be prevented by administration of dopa. Inactivation of the nigro-striatal pathway leads to a deficit of dopamine which is the essential factor in the emergence of tremor (*Sourkes* and *Poirier* 1966, *Poirier et al.* 1976). The globus pallidus and the ventrolateral thalamus participate in the production of tremor. In addition the premotor region and the motor cortex, which are connected to the ventrolateral thalamus, play an important role in the maintenance of the tremor. Thus destruction of the motor region can remove parkinsonian tremor (*Bucy* and *Case* 1949). Integrity of the cortico-thalamo-cortical pathway is also vital to the tremor, hence we find that the only totally effective method to remove it is by stereotactic lesioning of this cortico-thalamic loop.

The variety of these controlling mechanisms is clinically important in that one or other of the major antiparkinsonian drugs – anticholinergics, L-dopa, amantadine or bromocriptine – will be able to ameliorate parkinsonian tremor. A multiplicity of regulatory disturbances requires a multiplicity of therapeutic measures, although the neurosurgical approach is the most effective. Such operations can also prevent any increase in the resting tremor, while L-dopa and

anticholinergic drugs cannot stop the exacerbation of tremor through affective or emotional stimuli. It is also notable that if one trembling hand is restrained the tremor will transfer to the other hand, or to the foot on the same side of the body. Similarly a stereotactic operation for tremor often transfers the tremor to the other side of the body, greatly limiting the efficacy of this procedure.

Tremor can be blocked for a short time by an effort of will, but it eventually breaks through with an even greater intensity. Resting tremor is generally in abeyance in sleep, only reappearing during the REM phases (*Struppler et al.* 1976). Presumably the thalamo-cortical loop is biochemically "switched off" during sleep.

The affective exacerbation of tremor is particularly troublesome since it puts a strain on interpersonal relationships. Thus, a parkinsonian patient entering a bus or restaurant will attract everyone's attention which will serve to intensify his tremor. On sitting quietly, he will no longer be noticed and the tremor will diminish back to a pathophysiological "ticking over".

The resting tremor of the completely relaxed, supine patient can be distinguished from a postural tremor occurring while sitting or standing. The increase in parkinsonian tremor by affective stimulation shows that this tremor is not a single, isolated symptom, like segmental muscular atrophy, but is connected with emotional and autonomic regulatory systems. The tremor frequently exhibits a diurnal rhythm which correlates with endogenous depression insofar as it is more severe in the morning and substantially less pronounced in the evening. The reverse can, however, also be observed since tremor, like all parkinsonian symptoms (whether those of affect or the autonomic or motor systems), is sensitive to the weather. Finally tremor can serve as a gauge of general health conditions. In infections such as pneumonia or influenza it will completely disappear, but on recovery will return. In akinetic crises and before death the tremor will also abate.

Rigidity

Another classical symptom appearing in practically all patients is rigidity. An EMG activity is apparent at rest, as well as in passive or active movement (*Höfer* and *Putnam* 1940; Fig. 14).

The rigidity is particularly strong in the muscles adjacent to the trunk, i.e. those of the shoulders and the pelvic girdle. This frequently leads to pain in these areas, the neck or the lumbar region. These pains of the joints are a feature of the whole course of the disease; many parkinsonian patients receive antirheumatic treatment for up to several years. Rigidity leads to a blockade of the nutrient flow to the surfaces

of the joint which is normally maintained by the continual changes in pressure. In the later stages of the disease this is compounded by the increasing pressure of body weight upon the joints due to muscular weakness. Arthritis of the hip can often result; this is painful during walking and standing, but is notably free of pain when the patient sits or lies down.

Rigidity, unlike tremor, can be produced in animals by strictly defined stereotactic procedures (*Poirier et al.* 1976).

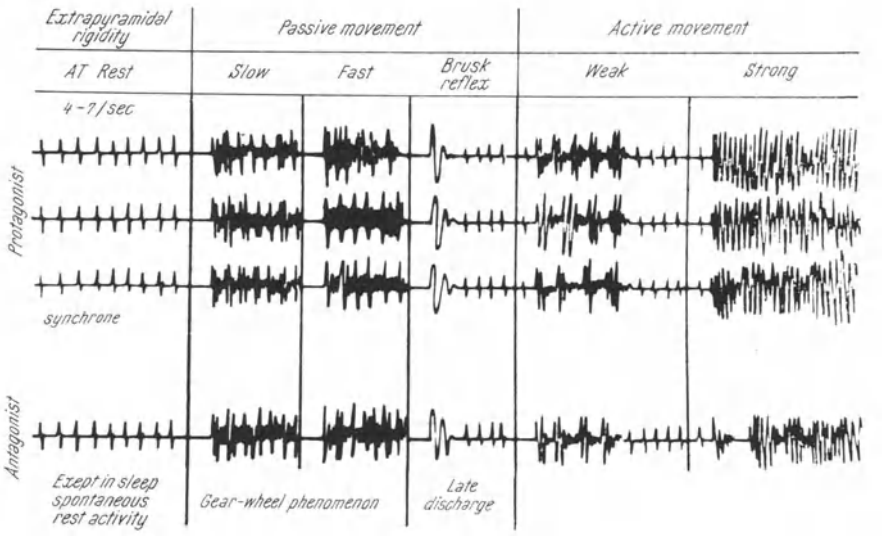


Fig. 14. Loss of reciprocal innervation (from *Pateisky* 1965; with permission)

Ventromedial tegmental lesions in monkeys result in hypokinesia and in a tremor of the contralateral side but do not produce rigidity (*Poirier* 1960). Reserpine- or phenothiazine-induced parkinsonism frequently exhibits rigidity (*Larochelle et al.* 1974). Since reserpine leads to a depletion of the monoamine neurotransmitter stores, and phenothiazines block dopamine receptors, one can regard rigidity as a result of depleted aminergic neurons.

In the striatum there are both small and large ganglia of which the smaller predominate. These degenerate in Huntington's chorea, the clinical outcome being choreic hyperkinesia. This symptom is accentuated by administration of L-dopa (*Gerstenbrand et al.* 1962). Since the larger ganglion cells predominate in chorea, it may be assumed that dopamine is synthesized from L-dopa in these cells. This tips the balance between ACh and dopamine towards the latter, resulting in hyperkinesia. In Parkinson's disease, on the other hand,

there is a loss of dopamine and hence a relative surfeit of cholinergic activity. In this case the result is rigidity. The fact that rigidity is the only major symptom of Parkinson's disease which can be treated successfully by anticholinergic medication strongly supports this argument. The increase in rigidity brought about by physostigmine emphasizes its cholinergic origin.

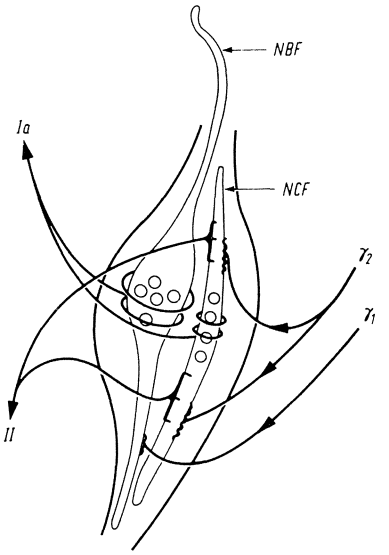


Fig. 15. Schematic diagram of the muscle spindle. *NBF* nuclear bundle fibres, *NCF* nuclear chain fibres, $\gamma 1$, $\gamma 2$ efferent fibres of the gamma cells of the anterior horn. *Ia* afferents stimulated by the NBF, *II* afferents stimulated by the NCF

Rigidity does not occur to the same extent in all groups of muscles. In Parkinson's disease there is a reduced activity of the gamma-loop (*Birkmayer* 1965). This is the major functional regulator of peripheral muscle tone, particularly in those muscles which act against gravity. Nerve fibres lead from the gamma cells to the nuclear bundle fibres (gamma-1) and to the nuclear chain fibres (gamma-2) of the muscle spindle (Fig. 15). Via I-a fibres of the lower-nerve roots, the gamma-1 fibres stimulate the dynamic postural tone. Correspondingly gamma-2 fibres regulate the static component of muscle tone. These stimuli reach the small alpha cells of the anterior horn, from which a tonic innervation of the trunk, shoulders and pelvic muscles is effected (Fig. 16).

This peripheral regulation of muscle tone is subject to a supraspinal inhibition from the pyramidal pathway. If there is a lesion of this

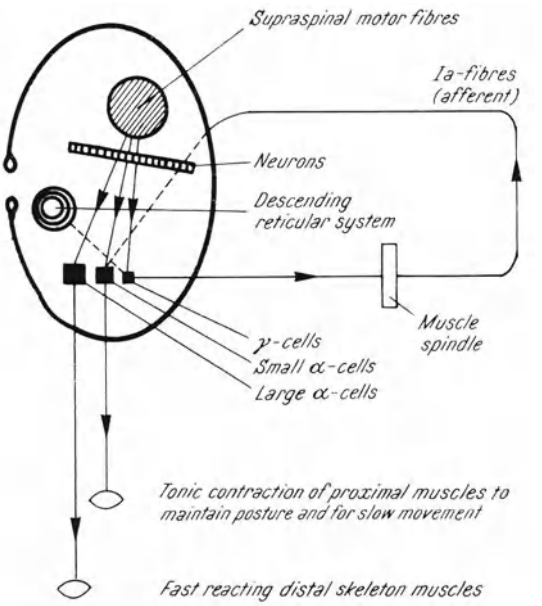


Fig. 16. Diagram of the gamma-loop. Supraspinal motor pathways have an inhibitory effect on gamma-cells while the reticular system has a stimulatory effect. Lesions of the pyramidal pathway increase the activity of the gamma-loop (gamma-spasticity). Loss of the reticular stimulation leads to an α-activation

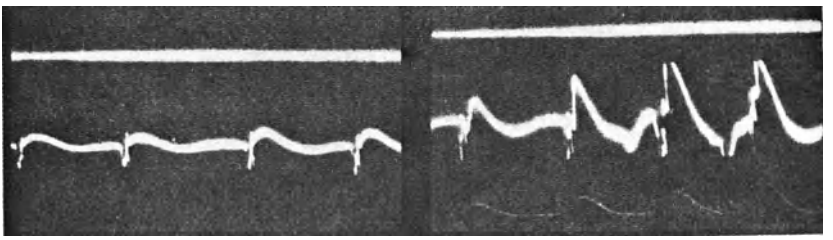


Fig. 17. T-reflex in a parkinsonian patient. Left: untreated, right: 30 min. after 50 mg L-dopa i.v. (from *Danielczyk;* with permission)

pathway (e.g. due to multiple sclerosis) then the loss of this inhibition leads to a reduction in the stimulatory threshold of the spindle and even minor stretch stimuli bring about an increase in tone. This is the basis of gamma-spasticity, elicited by hyperactivity of the gamma-loop.

Normally the gamma-loop is inhibited by the pyramidal system and stimulated by the reticulo-spinal pathways (*Granit* and *Kaada* 1952). Degeneration of the substantia nigra cells leads to a loss of stimulation of the descending nigro-reticulo-spinal pathways. This produces a

gamma-hypoactivity and an alpha-hyperactivity (*Steg* 1964). The consequence of this imbalance is rigidity (*Hassler* 1972). Function of the gamma-loop is tested by tendon reflexes. A defined stimulus of the patellar tendon will lead to a muscle extension and hence to an excitation of the spindles which, via the I-a fibre, effects a discharge in the quadriceps muscle and which can be measured by EMG. The frequency and amplitude of the response provide a measure of the activity of the gamma-loop and hence of the muscle tone. In Parkinson's disease the tendon reflex is reduced, while both frequency and amplitude increase after injection of L-dopa (Fig. 17; *Birkmayer* 1970).

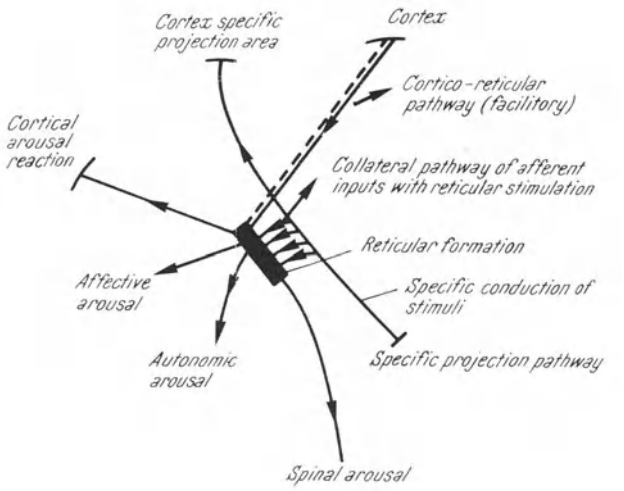


Fig. 18. Schematic representation of the reticular formation

There is evidence for a descending pathway from the posterior part of substantia nigra to the spinal cord. Stimulation of the substantia nigra brings about an action on spinal gamma-neurons (*Hassler et al.* 1980). A 50% decrease of spinal dopamine has been demonstrated after 6-hydroxydopamine lesions of substantia nigra (*Commissiong et al.* 1978). It remains to be established whether other brain areas are involved in the dopaminergic innervation of the spinal cord (*Jellinger et al.* 1981). Therefore descending dopaminergic and noradrenergic fibres might be involved in the motor disturbances of Parkinson's disease. Although a deficit of spinal dopamine has not been demonstrated so far in Parkinson's disease, drug treatment may also have effects here.

The reticular formation is stimulated by all the afferent innervations (from periphery to cortex) in the brain stem region (Fig. 18). These reticular stimuli elicit a cortical arousal reaction (*Moruzzi* and *Magoun*

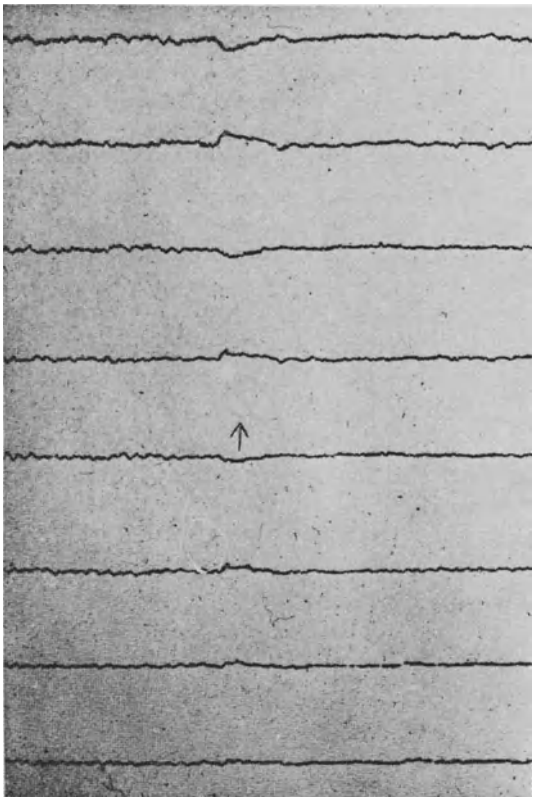


Fig. 19. Cortical arousal reaction: α-blockade, ↑ after opening the eyes, β-activity = arousal reaction

1949) which is paralleled by an increased clarity of consciousness/awareness and by an increase in EEG beta-activity (Fig. 19). Concurrently this reticular activation brings about a stimulation of affect (affective arousal reaction; Fig. 20): an autonomic stimulation (autonomic arousal reaction) and, via the reticulo-spinal pathways, a spinal arousal reaction (Fig. 21; *Birkmayer* and *Pilleri* 1965).

Let us picture a traveller passing through a forest at night. He hears a shot. The subsequent stimulation of the reticular formation in the brain stem elicits a cortical arousal (he is suddenly awake), an arousal of affect (he experiences fear), an autonomic arousal (his heart rate and blood pressure increase) as well as a spinal arousal reaction. This tenses his muscles and he is now capable of "fight or flight".

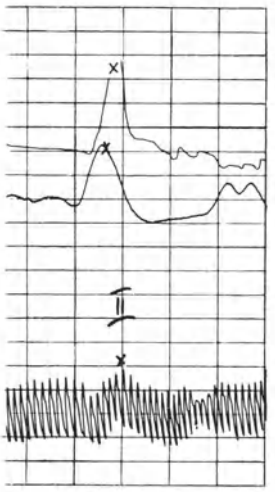


Fig. 20. Autonomic and affective arousal reaction. An acoustic stimulus induces increased breathing (upper curve), increased skin conductance (middle curve) and increased blood pressure and pulse rate (lower curve). Skin conductance demonstrates the affective arousal while the other parameters indicate autonomic arousal

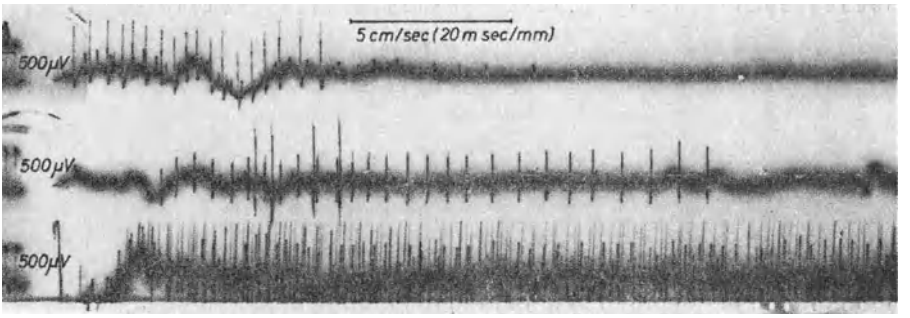


Fig. 21. Spinal arousal reaction. Increased activity in relaxed muscle in a control (above) and a spastic patient (below) after an acoustic stimulus

As shown above, the spinal arousal reaction of the parkinsonian patient is inadequate. The tendon reflex, as a measure of gamma-activity, is only weakly induced. Injection of L-dopa reverses this and thereby improves posture. Since biochemical analysis has shown a deficit of dopamine in the reticular formation and red nucleus, as well as in the striatum and substantia nigra (***Birkmayer et al.*** 1972), it may be assumed that a dopaminergic hypoactivity in the nigro-reticulo-rubral system prevents adequate stimulation of the gamma-loop by

the reticulo-spinal pathways. The clinical effect of the insufficient regulation of muscle tone which follows from this is the characteristic stoop of the parkinsonian patient (*Birkmayer* and *Neumayer* 1956).

It is very difficult for a patient with Parkinson's disease to hold himself upright. He stands bent forward with bent knees, bent hips and arms at an angle. In cases where there is an asymmetric disability, the trunk is bent to one side of the body, which, due to spondilogenic

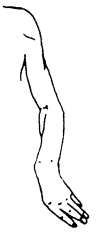


Fig. 22

dysfunction leads to neuralgia. While the stoop in the trunk can be interpreted as a loss of equilibrium between the muscles responsible for stretching and bending, abnormal tone in the muscles of the extremities is less frequent. When such symptoms appear they do not reflect an arthritic process (as can be seen by X-ray examination), but are an expression of a central neuronal dysfunction. We have described such abnormalities as "frozen athetosis" or "swimming attitude" (Fig. 22). They represent remnants of philogenetically old patterns of behaviour which are uncovered by the disease process (*Birkmayer* and *Neumayer* 1956).

If the weight of the body is relieved by immersion in warm water, these anomalies of muscle tone can be corrected, which is the merit of underwater treatment. The patient feels that his rigidity is a physical restriction, like being held in a plaster cast. It is important to distinguish between rigidity and akinesia. Rigidity can be relieved completely by anticholinergic drugs or neurosurgery, but this does not always lead to a return to normal mobility.

Akinesia

Akinesia was described by *Kleist* (1918) as a specific type of movement disorder due to Parkinson's disease. The defect consists of an inability to convert a potential for movement into actual motion. Using stroboscopic methods, we have recorded the motion of an arm being swung like a pendulum, and a hand being extended linearly. In the hand-punch, energy is liberated by the sudden development of a

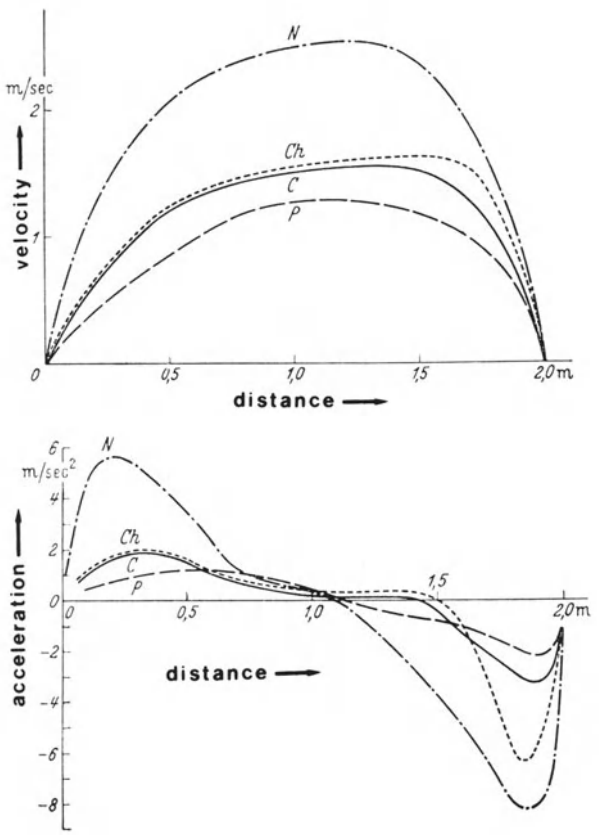


Fig. 23. Stroboscopic recording of a pendulum swing of the arm. *N* normal control, *C* cerebellar, *Ch* choreic, *P* parkinsonian

force in the upper arm. Velocity and acceleration can be calculated mathematically (*Birkmayer* and *Seemann* 1957; Figs. 23 and 24). Table 14 shows such a calculation with characteristic data and Fig. 25 illustrates the resultant criteria and their interpretation.

The distance travelled to reach maximum acceleration (l_1 in Table 14) and its duration are approximately equal in both controls and parkinsonian cases. However, this acceleration (b_{max}) is, on average, more than four times greater in the controls than in the parkinsonian patients. The punch requires a concerted effort in order to get a "rocket-like" effect. This explosive discharge of the stretch muscles is specifically reduced in Parkinson's disease. It is particularly difficult for the patient to stretch his hand upwards, or to jump using both legs. Neuronal stimulation of muscles acting against gravity is difficult due to the hypoactivity of the gamma system mentioned above.

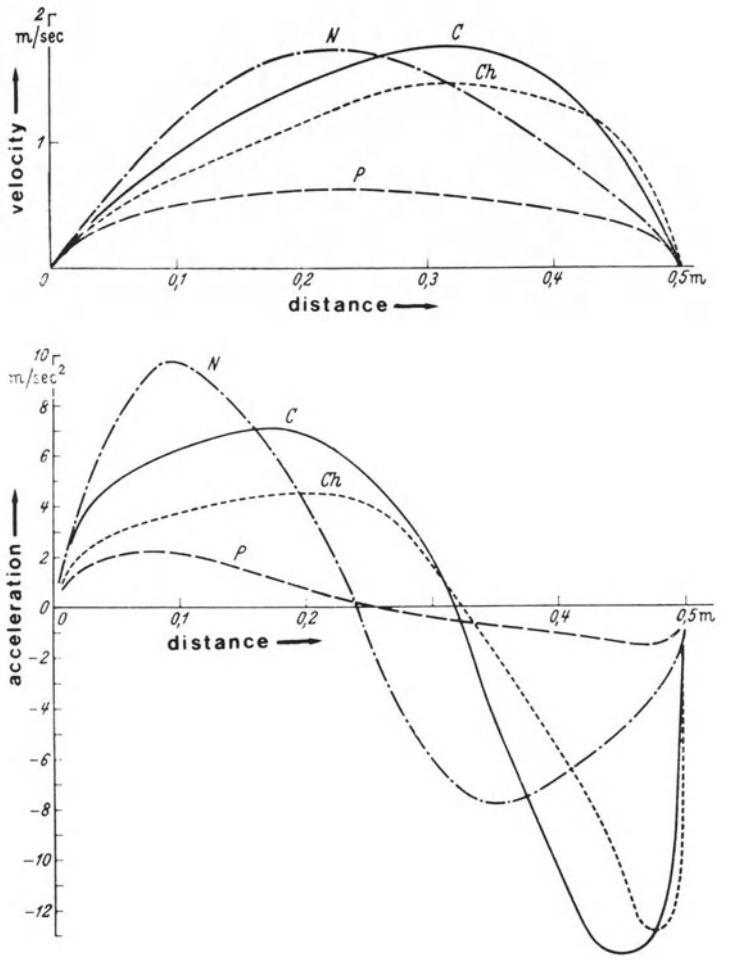


Fig. 24. Stroboscopic recording of a forward punch movement of the hand (see Fig. 23)

The pendulum arm swing requires not so much an input of force, more a relaxation to allow gravity and centrifugal force to produce the effect. The distance to maximum acceleration in parkinsonian patients is twice that for controls. This means that these patients cannot relax so quickly as to let the arm swing under the influence of gravity. This inability to relax is a characteristic feature of parkinsonian gait. The patient's legs will not swing forward freely, but have to be pulled along with an effort, dragging each foot on the ground. The greatest values for acceleration are 5,65 m/sec² and 1.2 m/sec² in controls and patients

Table 14. *Characteristic values from acceleration curves*

	Measure	l_1	l_0	K	b_{max}	b.dl	l'_1	l'_0	K′	b'_{max}	b′.dl′
	Dimension	m	m	–	m/sec.²	m/sec.²	m	m	–	m/sec.²	m/sec.²
Pendulum swing of the arm	Normal	0.21	1.1	0.417	5.65	3.11	0.16	0.9	0.4	8.2	3.79
	Choreic	0.34	1.0	0.641	2.0	1.46	0.17	0.5	0.642	6.3	1.60
	Cerebellar	0.33	1.0	0.625	1.9	1.18	0.12	0.58	0.44	3.3	1.17
	Parkinson	0.53	1.13	0.92	1.2	0.95	0.10	0.87	0.321	2.15	0.98
Punch movement of the hand	Normal	0.094	0.24	0.736	9.7	1.5	0.15	0.26	1.27	7.8	1.42
	Choreic	0.2	0.322	1.45	4.5	1.1	0.026	0.178	0.36	12.9	1.21
	Cerebellar	0.17	0.317	1.12	7.1	1.66	0.054	0.182	0.575	13.8	1.68
	Parkinson	0.077	0.256	0.575	2.2	0.24	0.034	0.244	0.353	1.5	0.22

l_1 = distance travelled from rest to maximum acceleration.
l_0 = total distance of acceleration movement.
b_{max} = maximum acceleration.
K = characteristic exponent of acceleration curves.
b.dl = integral of area.
Further abbreviations are mentioned in the legend to Fig. 25.

respectively. Hence this ability to respond to an external force with a swinging motion is severely restricted in Parkinson's disease.

Three criteria characterize the motor behaviour of Parkinson's disease:

1. The sudden application of a maximal neuromuscular impulse (e.g. a push or jump) is reduced or even completely blocked. Upper and lower extremities are not equally affected in this way. If a patient can thrust an arm out forwards quickly and energetically and yet can

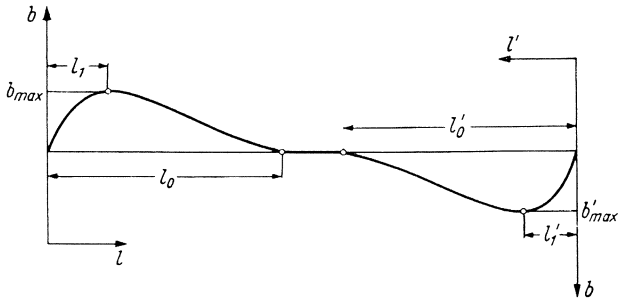


Fig. 25. Typical acceleration curve. b acceleration at the distance l, b_{max} maximum acceleration, b'_{max} maximum retardation, l_1 distance to b_{max}, b' retardation at the distance l', l_0 total distance of movement acceleration, l'_0 total distance of movement retardation, l'_1 distance to b'_{max}

hardly move from the ground when using both legs to jump, the therapeutic prognosis for L-dopa treatment is much better than in a patient who has a poor response in both upper and lower limbs. The speed at which this nerve response occurs is a measure of the integrity of dopaminergic neurons.

2. The inability to bring a movement gradually to a halt hinders the flexibility of movement of the parkinsonian patient.

3. The patient has great difficulty in moving against gravity, for example in standing up from a supine position without help. He is apparently rooted to the ground and cannot initiate a step. On the other hand, once started he finds it hard to stop the momentum and regular swing of walking, since he tends to fall forward. It is these two criteria which characterize akinesia. These movement abnormalities apparently have little in common with rigidity and tremor, although there is some comparison. When rigidity is at its highest, the patient cannot overcome the blockade and initiate active movement. However, even with no rigidity the patient may be unable to sit up after lying down, to stand after sitting, or to walk from a standing position. It is this difficulty in initiating motion which, as our analyses clearly show, is central to akinesia.

The freezing effect is well known to the clinician. Relatively normal movement can suddenly be arrested and the patient will hold himself stiff and still. If he is pushed on the chest he cannot compensate by an adjustment of balance and thus falls backwards.

This functional disturbance is due to an insufficient application of dynamic tone. If a parkinsonian is under pressure to carry out a particular task, such as crossing a busy road, it is likely that the stress would induce a release of noradrenaline. This would then induce a hyperactivity of the gamma-loop (in which noradrenaline functions as a neurotransmitter) and hence increase static tone. "Freezing" is the result. After some time the patient is able to overcome this particularly if, for example, he is told to lift up one leg. The initial movement permits the patient to start walking, which will continue until the action is again "frozen". This can occur when he reaches a step or an open door whereupon the "anxiety – noradrenaline – gamma-activation – stretch reflex" mechanism inhibits normal motion. The freezing effect is a frequent parkinsonian symptom unaffected by L-dopa treatment.

Although our interpretation of freezing is as yet unsupported by experimental or biochemical findings, the connection between affect and motor function is apparent. Emotional stimulus can lead to improvement in, for example, sport or even artistic performance. If, however, noradrenaline output is too great, the optimal effect on motor function is lost. "Scared stiff" is the popular expression for this. In parkinsonism there is a much finer division between optimum and inhibition.

Both clinical observation and theoretical considerations suggest that stress produces either excitatory or inhibitory noradrenergic modulation of the dopaminergic nigro-striatal system. The substantia nigra is innervated by two noradrenergic efferents from the locus coeruleus. The dorsal bundle acts synergistically, while the ventral bundle inhibits the dopamine system. Normally the activating effect predominates (viz. "fight-and-flight"). However the observed reduction in noradrenaline in parkinsonian brains perturbes this balance, in contrast to the losses of serotonin (in the inhibitory pathway from the dorsal raphe) and GABA (inhibitory striato-nigral pathway) which tend to minimize the effects of degeneration in the nigro-striatal dopamine system.

The short shuffling gait (festination) of the parkinsonian patient is an expression of akinesia. It reflects the inability to regulate rhythmic motion and results in the sort of stumbling movement that a healthy person would make in the dark. There is similarly a lack of the other movements accompanying normal gait.

Occasionally akinesia affects the respiratory muscles whereupon breathing becomes inadequate. This complicates the diagnosis of pneumonia since no rales can then be heard.

The characteristic aphonia is another manifestation of akinesia. Tension of the vocal chords is necessary for the modulation of speech tone, which is also reduced in Parkinson's disease. With inadequate vocal chord function and no pressure on expiration, speech is reduced to a whisper. The dysarthia of speech, palilalia, can be classified as "festination of speech".

Akinesia impares the writing of parkinsonian patients. The first words are often large and readable but the writing becomes progressively slower and smaller until the patient can write no further.

The mask-like face of the patient shows he is unable to transform affective and emotional function into facial expression. Amimia is a result of this inability. One of the most satisfying experiences for such a patient, as well as for his doctor, occurs after an L-dopa injection when this rigid mask drops to reveal a lively, expressive face. The afferent part of emotional feeling functions adequately in the parkinsonian, as is demonstrated by the increase in resting tremor in response to emotional stress. It is the projection of this into the physiognomy that is blocked.

There are several reasons for the many disturbances of posture and balance. As we have shown in our investigations, biochemical changes in the two halves of the brain are generally unequal. So if there is less dopamine in one red nucleus than in the other then there is inevitably a tendency to fall towards the side with the greater deficit. This means that the patient will, when walking, turn in the contralateral direction if at all possible since this movement will thus be freer and less hazardous. A one-sided rigidity can similarly lead to loss of balance, although this can be more easily compensated for than can the asymmetric akinesias.

It is instructive to observe how easily a patient can climb up a set of steps and yet has difficulty descending or walking on the level. This simple climbing represents a linear motion without the risks afforded by the other movements. Parkinsonian patients can even kick out, alternately shifting body weight from one leg to the other. But walking requires greater control and mistakes are more difficult to correct. The patient cannot make the continual tonic corrections necessary for normal movement. His gamma-1-system is unable to keep up the changes in dynamic tone. As we have described, the patient is unable to respond to a push on the chest by correcting his balance and thus he will fall over backwards. There are also patients who have an almost normal gait when out in the street, but who cannot pass through a doorway when they are at home. This reflects the akinetic effect on fast

motor control and which is responsible for the frequent falls. The patient falls heavily without trying to save himself or break the fall. If he falls backwards, he hits the back of his head. Falling forward, he makes no attempt to protect himself with his hands–he lands on his nose. However, relatively sportive parkinsonians are occasionally able to activate the slower tonic stimuli required for skiing (particularly during L-dopa treatment). On the other hand, playing tennis is not possible. The patient is able to drive a car even if he cannot really walk. Gamma-activity plays little part in being seated; while gamma-loop hypoactivity affects posture and gait, it does not interfere with driving. Attention and vigilance are generally increased in Parkinson's disease, and the responsiveness of the hands while sitting is adequate. Swimming, which is a philogenetically ancient pattern of behaviour, is often possible for many years. This reflects the relief of gravitational force, which in turn serves to diminish gamma-activity, and in warm water is an ideal treatment. Hemiparkinsonian symptoms make swimming much more difficult, since the patient will continually turn in one direction.

It is important to stress how akinesia varies with the weather and time of day. It diminishes in dry, cool, high pressure weather and the patient feels better. He can take longer steps and can walk faster and with more confidence. When the barometer falls he feels worse and his disability increases. Animal experiments have given some insight into the mechanisms involved. When negative ions predominate in the air (correlating with low pressure weather) an activation of the serotonergic system occurs, while positive ions (high pressure) stimulate catecholaminergic activity (*Krueger* 1968). Pharmacological data suggest a probable effect of sudden changes in the weather on a labile dopaminergic nigro-striatal system. The effect of these changes on the parkinsonian patient indicate that a dopamine deficit is followed by a general reduction in adaptability. This inability to adjust is not restricted to the weather, but includes all forms of stress (overexhaustion, mental distress, infections etc.).

Akinesia is generally less pronounced in the morning. Many patients have a near normal mobility from the morning medication until noon. Then there is a phase when mobility is more or less blocked–an end-of-dose "off" phase. In most cases this off phase cannot be overcome, despite L-dopa administration. On the other hand, an off phase in the morning responds to L-dopa (and hence is not a real "off") in 30–60 minutes. A genuine off phase is most often seen after the midday meal. The strength of the effect can be correlated to the degree of neuronal degeneration and in general it affects the lower extremities (*Damasio* and *Castero-Caldas* 1973).

Originally the L-dopa concentration in plasma was thought to be responsible for the off effect. However, later investigations showed the effect to be independent of blood L-dopa (*Muenter* and *Tyce* 1971, *Birkmayer et al.* 1973a). A peak of plasma L-dopa has been demonstrated during an off phase (*McDowell* and *Sweet* 1976). *Hornykiewicz* (1973) proposed that an inadequate availability of dopamine at the receptor was due to a receptor blockade by false transmitters such as tetrahydropapaveroline. If this were correct, one might expect that L-dopa administration during the off phase would lead to an increase in, or prolongation of, the akinesia. However this does not occur.

We have found that an addition of deprenyl can overcome initial off phases (*Birkmayer et al.* 1975), an observation which has been confirmed by several other groups (*Rinne et al.* 1978, *Csanda et al.* 1978). Inhibition of MAO type B blocks the breakdown of neuronal dopamine and thus brings about an increase in dopamine stores and the removal of the off effect. This evidence leads us to take the view that the cause of this off effect lies in a temporary drop in tyrosine hydroxylase or in an increase in MAO activity. *McDowell* and *Sweet* (1976) observed that the off phenomenon could appear after only two years of L-dopa therapy, whereupon the lower extremities were more severely affected. After five years, 50% of patients were affected. In our patients, 8.5% exhibited the off phenomenon after five years treatment. As we have said, the effect is most severe after lunch, implicating the involvement of increased protein intake (*Cotzias et al.* 1969). Investigations of striatal MAO have shown that this enzyme exhibits a circadian rhythmicity with its highest activity in the afternoon (*Birkmayer et al.* 1976). There is no doubt that this increased MAO activity results in a drop in intraneuronal dopamine. The blockade of movement in the lower extremities appears to result from this paucity of available dopamine. In the less affected upper extremities, hyperkinesias may be observed at the beginning of the off phase. This would seem to suggest that hyperkinesia is a side effect resulting from more of the administered L-dopa being converted to dopamine in the intact neurons.

This "on-off" phenomenon may be a symptom of the insufficient synthesis of neuronal dopamine, a result of inadequate storage or release, or possibly due to blockade of the receptor. The latter explanation is unlikely since medication with a receptor agonist such as bromocriptine has little effect. *McDowell* and *Sweet* (1976) also discussed a possible deficiency in the intestinal absorption of L-dopa. But this is unlikely since tryptophan inhibits L-dopa absorption and yet its administration does not increase the on-off effect. In addition one can

overcome peripheral side effects by increasing the dosage of decarboxylase inhibiting drugs. However, an addition of 100 mg benzerazide to the usual L-dopa medication does not influence the intensity and duration of the on-off phenomenon. Thus these effects are unlikely to be of peripheral origin.

An increase and intensification of the on-off phases occurs with increasing therapeutic dose as the disease progresses (see also *Marsden* and *Parkes* 1981). Thus the off phases turn with increasing frequency into akinetic crises–longer-lasting periods of akinesia. Hence these off phases can be regarded as reflecting a transmitter deficit in dopaminergic neurons, when the supply of L-dopa can no longer be utilized. The progressive degeneration increases the intensity of the akinetic phases. So the first clinical signs of a progressive disease process are the off phases, while akinetic crises follow as an indication of terminal symptoms (*Danielczyk* 1973). Inhibition of the intraneuronal dopamine metabolism by MAO type B can, in the initial stages, overcome the akinesia of the off phases.

Stereotactic operations, decarboxylase inhibitors, anticholinergic drugs, reduction in dietary protein, apomorphine and piribedil medication are all ineffective against on-off phases (*McDowell* and *Sweet* 1976). What is certain is that these effects appear prematurely if too much L-dopa is being taken. Since the mean L-dopa dosage in Europe is generally lower than that used by the Americans, it is no accident that *Yahr* (1971) first described the on-off effect. *Chase et al.* (1976) demonstrated that akinesia of the off effect to be present in 72% of patients on oral L-dopa, but in only 5% of patients taking the drug by intravenous infusion. The induction of off phases by high doses of L-dopa enforces the use of the lowest possible doses which can be optimised by employing decarboxylase inhibitors or MAO inhibitors (i.e. deprenyl).

Besides the akinetic crisis, another terminal symptom mentioned in the literature is paradoxical kinesia (*Jarkowski* 1925). A normally immobile parkinsonian patient can, under exceptional stressful situations, walk normally for a short time (from a few minutes up to over an hour). *Ajuriaguerra* (1971) observed this phenomenon in 7% of his patients. We occasionally hear from patients that they can walk normally for a short period at night. As we have mentioned, there can be a release of noradrenaline under particular conditions of emotional stress. This may in turn release the "movement transmitter" from dopaminergic neurons. However, this paradoxical effect is only transient. It is not difficult to make an objective record of tremor or rigidity. It is, however, impossible to do the same with akinesia in its many facets which include disturbances of speech, gait, mimicry etc.

Since the initiation of motion is most clearly abnormal in parkinsonian akinesia, we have measured the forces involved in movement by employing a physiological acceleration transducer (Philips). A sensor (2 g in weight) is attached to a particular part of the body (e.g. the back of the hand). It registers physical changes and converts them into electrical impulses which can be continuously recorded on an oscillograph. Acceleration due to gravity (G) can be read directly from the chart. A simple hand push in a normal person has a value of 8.5 G while a parkinsonian patient can produce only 1 G (see Fig. 26).

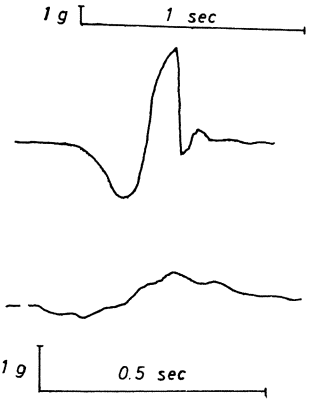


Fig. 26. Recording with a physiological acceleration transducer. Above = normal movement of the right hand extended forwards. Acceleration = 8.5 g in 0.2 sec., below = same movement in a parkinsonian patient. Acceleration = 1 g in 0.2 sec (g = acceleration due to gravity)

Thus this acceleration, as a measure of kinetic energy, is much smaller than normal in Parkinson's disease (*Birkmayer* 1967a). As well as being able to measure objectively the energetic development of a linear movement, this method is also invaluable in the assessment of therapeutic effects on this aspect of akinesia.

It is impossible to obtain an objective evaluation of total motor function in man. How should one assess the lack of facial expression, for example? Hence in the assessment of therapeutic results many methods of investigation are used. There is no single method which is employed generally; each investigation has his own approaches and interests. However, one of the most widely used is the Webster rating scale. There is no doubt that it is suitable for global comparative investigations, particularly when combined with further clinical parameters (p. 68).

Various Terms

The "Freezing" Effect

Emotional stimulus may suddenly induce a blockade of all movement. Fear of crossing a busy road, or the trivial worry in passing an open door can block further motion. This freezing effect often occurs on starting to move or on turning. We would suggest that emotional excitation effects a gamma-overactivity (the stretch reflex) by an increased noradrenergic output, and this in turn inhibits normal freedom of movement.

Kinesia Paradoxica (Jarkowski 1925)

A particular emotional stress may produce an amelioration of akinesia. Patients who are normally unable to walk and run are suddenly able to do so. This improvement is, however, only transient. We propose that stress can effect a release of neuronal dopamine, thereby restoring motor function. The phenomenon whereby the patient walks well when being examined by the doctor while his wife says "If only he did so well at home . . ." is an example of this paradoxical kinesia. An exceptionally anxious situation such as a doctor's examination, or a meeting with a particularly dear friend, can bring about this temporary effect on movement via dopamine release.

The On-off Phenomenon (Yahr 1971)

A sudden inability to move (complete akinesia) can occur independent of emotional or other environmental stimuli. This effect is most frequent after the midday meal. It is not completely clear whether this "off" is a side effect or a symptom of the advancing disease i.e. a precursor of the akinetic crisis. *Yahr* (personal communication) suggests it to be a side effect, since he has never observed it independent of L-dopa medication. That is indeed correct, but we feel that we can only refer to a side effect if the effect disappears (along with the hyperkinesias and L-dopa psychoses) when L-dopa treatment is interrupted. In our experience, the fact that the initial off effect can be overcome by deprenyl suggests that it derives from a neuronal dopamine deficit. We have suggested this to be due, in turn, to a depletion of tyrosine hydroxylase (*Birkmayer et al.* 1979a, b), since α-methyltyrosine (i.v.) increases the duration of the off phase. The recovery in the ability to move after a period of rest without any medication is also consistent with this explanation.

Animal experiments have shown that in the perfused rat brain there is an "autoinhibition" of L-dopa uptake. While this does not explain the appearance of the on-off phenomenon after several years treatment

with L-dopa, it does show that, in vitro at least, L-dopa uptake and hence dopamine synthesis does not always follow saturation kinetics. So in the case of a major depletion of endogenous dopamine in the CNS, changes in L-dopa and dopamine concentrations due, for example, to the circadian variation of MAO, may well be reflected by pathological changes (*Horse et al.* 1974).

Akinetic Crises (Danielczyk 1973)

These are longer-lasting phases of akinesia. As in the on-off effect there is no correlation with emotional states. We regard the akinetic crisis as a protracted off phase. Table 1 demonstrates that hardly any dopamine is present in the striatal regions of patients who died during akinesia. Thus with no available transmitter there can be no movement. While amantadine infusions including L-dopa and deprenyl can be useful in treating initial akinetic phases, at present there is no successful therapy for the later akinetic crises.

Yo-Yoing (Calne 1976)

This is a graphic description of fluctuations in akinesia. These variations in motor activity, which can frequently be very great, are independent of drug treatment. They may correlate with a circadian rhythm (better in the morning, worse in the afternoon) or with the weather. Yo-yoing is also dependent on the psychological state of the patient: if he is upset, the activity gets worse. Thus we should only refer to this phenomenon if it appears independently of the administered drug. Morning akinesia is an end-of-dose akinesia. If these fluctuations in akinesia occur regularly in the day or in the dosage schedule, a prophylactic administration of L-dopa, or bromocriptine in later stages of the disease, can be given an hour before the expected akinesia.

Assessment of Parkinsonian Disability

We have developed a disability score which we have applied to some 4000 cases (*Birkmayer* and *Neumayer* 1972a). Ten different functions are investigated: gait, pushing, jumping, speech, writing, posture, facial expression, swinging of the arms in walking, initiation of movement and tremor. Normal function is given 0 and total disability 10 points. Thus a score of 100 signifies a complete immobility which is incompatible with life. Parkinsonian patients can be classified approximately as being mild (up to 30), moderate (30–60) and severe (60–90) cases.

In gait we assess the length of stride, how much the foot is dragged along the ground, the force of propulsion, turning and balance.

In assessing pushing, both arms must be thrust out forwards and upwards. The velocity and length of the upward push are characteristically restricted in Parkinson's disease. All movement against gravity is made more difficult, and in severe cases a push is impossible and only a slow and slight movement can occur. Rigidity is, however, not responsible for this immobility.

In jumping, the patient is asked to jump into the air with both feet. This is particularly difficult for the parkinsonian, and there is hardly a patient who can jump higher than 20 cm.

Speech is assessed according to loudness and articulation. There has been a rigorous study of speech disorders in Parkinson's disease performed by *Logemann et al.* (1973). He distinguished several stages in the deterioration of speech. The first stage is a dysfunction of the larynx, while in the next phase there is a loss of function of the tongue in articulation. Then the lips are affected with a similar loss of coordination. In the most severe cases there is a loss of volume as well as a lack of coordination in the lip and tongue movements. Pronunciation of consonants is particularly affected.

Writing is assessed with a standard sentence (such as "Vienna is a beautiful city") in order to facilitate comparison. We look at speed of writing, rhythm, size of lettering and legibility.

The degree of stoop is used to determine postural abnormality. This can vary from a slight stoop to a situation in which the trunk is bent almost at a right angle. Interestingly this bent posture is generally lost on lying down; the patient can lie straight on his back. This suggests that the gamma-hypoactivity normally leads to a loss of upright posture, but permits the removal of the stooping contraction on lying down.

Facial expression is naturally dependent on subjective assessment. It can be only slightly affected; the face may be rigid and expressionless at rest and yet normal expressive response can occur in conversation or on being made to laugh. A much more severe amimia can also be observed, whereupon neither joy nor unhappiness induce an emotional expression.

Normal movement of the arms in walking is completely inhibited in severe cases. The patient holds his arms bent and pressed to his body. He struggles along in this way, dragging his feet. In less severe cases, one arm may swing along while the other is held stiff.

The assessment of ability to initiate movement is not difficult. In the worst cases the patient is "stuck" to the floor and is unable to take the first step. However, if the patient is asked to step over a stick on the floor, this voluntary movement can overcome the motor blockade. The overactivity of the gamma-2 fibres, which contribute to the control of

upright posture, is described on p. 49. Thus the patient stands as if rooted to the ground, and yet on sitting can move his legs freely. Even when he is on a fixed bicycle the patient can pedal without difficulty. Walking involves the function of two systems:

1. Carrying the body weight using the static tone of the musculature which acts against gravity,
2. forward movement using the dynamically acting muscles.

The change from the tonic function of the standing leg to the forward swing of the moving leg is more difficult, if not impossible, for the parkinsonian patient. In all situations where the effect of gravity is removed, e.g. in water or on lying down, or even while crawling, the dynamic action of propulsion is more easily effected than when the patient is upright. This inhibition of starting off, due to insufficient gamma-activity, occurs with each change in direction as well as on taking a first step. Every tonic change from static to dynamic function can block the course of movement. Thus many patients find it easier to walk outside on level ground than indoors, since moving around at home requires continual small changes of direction. Falls also occur more frequently indoors than outside. Walking out-of-doors can be aided by a stick, providing an additional gamma-activation.

Tremor is also easy to evaluate. The most severe cases generally have less tremor than moderately affected patients. The milder cases exhibit an enormous increase in the amplitude of resting tremor through emotional stimulus such as starting a conversation or entering a room.

Although this disability rating scale is a subjective evaluation, one can obtain consistent results within any one group of workers. We have made comparative investigations into the effects of Madopar and Sinemet in a single group of patients. These were assessed by three neurologists independently; their ratings varied by no more than five points on the disability score. Although in any one case this may be a relatively large difference, in a large number of investigated patients the variation is insignificant and the results are comparable (*Podiwinsky et al.* 1979).

Since all clinical research into Parkinson's disease involves assessing more or less the same parameters, one can obtain useful data despite variable results. However, as with all rating scales, the problems lie in the number of items that are to be included. If too few parameters are chosen, the investigation can be completed quickly, but at the loss of possibly important details. Too many items means that the investigation is laborious and not easily completed in a clinical setting. A complete and comprehensive collection of data is particularly important to the pharmaceutical industry, but makes little contribution

to the advance of clinical research. Both precise clinical observation and contact with a basic scientist are essential for successful research.

Autonomic Dysfunction

In addition to the abnormalities of motor function are the autonomic symptoms. These include hypersalivation, seborrhoea, sweating, flushing, hyperthermia, oedema of the legs and the more negative symptoms of loss of appetite, loss of weight and obstipation (*Birkmayer* 1964, 1964/65, 1965). These symptoms predominantly reflect disturbances of the parasympathetic nervous system. Furthermore, they can appear very suddenly. The greasy complexion and the seborrhoea oleosa of the head can vary from day to day and reflect the state of the patient. Circadian variations in the occurrence of the symptoms are very apparent. For example, salivation is generally greater at night, and can result in the bedding and pillows being soaked through. Acute attacks of profuse sweating are more frequent at night and are almost a specific symptom of Parkinson's disease. The period of sweating lasts 30–60 minutes, after which the unmedicated patient will stay completely dry. These sudden attacks of autonomic dysfunction suggested to us the possible involvement of an uncontrolled release of neurotransmitters. This was the initial stimulus for our biochemical studies of these compounds in Parkinson's disease. Our first investigations into the substance P content of the brain stem, studies performed by *Lembeck* and, later still, *Hornykiewicz*, showed no differences between post-mortem samples from parkinsonian patients and controls. However, *Bernheimer et al.* (1961) demonstrated that serotonin was decreased in various regions of the brain stem, although the deficit was not as great as with dopamine. Thus there is a general biochemical disturbance in the brain stem of the parkinsonian patient. This loss of biochemical balance leads to autonomic and affective disturbances as well as the defects of motor function.

In the hot sommer months we used to notice frequently patients who had a high fever for days on end. Body temperatures up to 40 °C were not uncommon. All attempts to reduce these high temperatures using drugs were unsuccessful; the only successful approaches were to wrap the patients in cool, damp sheets or to immerse them in lukewarm water. We assumed that these hyperthermias were due to a "blockade" of heat loss, since they only occurred in warm weather. This symptom was originally noted by *Parkinson* himself. According to *Aschoff* (1947), it is the vasomotor function of skin which is the critical factor in heat loss. The ability to vary this is a prerequisite for the maintenance of body temperature. The dilation of the vessels of the skin increases heat loss which will, however, vary between different regions of the body.

It is dependent on the amount of blood flow through the capillaries of the outer skin layers. There is an increased heat loss at the ends of the fingers and toes on opening of the arteriovenous anastomoses. Thus measurement of the skin temperature provides a measure of the rate of heat loss. We have investigated the skin surface temperature of the thigh and the big toe of parkinsonian patients and healthy control subjects. When the experimental subjects are naked, the skin temperature of the toe is invariably lower (Fig. 27). If the trunk and

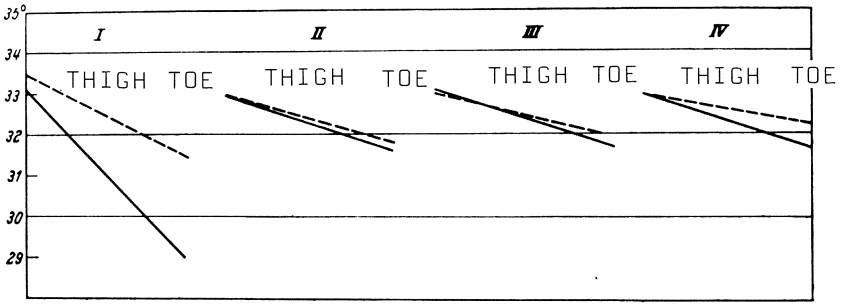


Fig. 27. Changes in skin temperature in 10 controls *(I)* and 16 parkinsonian patients: unmedicated *(II)*, 30 min. after 50 mg L-dopa i.v. *(IIIK)*, 30 min after 50 mg 5-hydroxy-tryptophan i.v. *(IV)*. —— naked, ----- trunk and upper extremities covered. I t score 3.24 ($p < 0.05$), IV t score 5.08 ($p < 0.05$). Tryptophan tends to restore normal control of heat loss

upper extremities are covered with a blanket, the temperature of the big toe increases considerably. This means that blocking the heat loss of these regions stimulates a feedback mechanism which increases the heat from other, uncovered areas. The temperature at the toes thereby increases in order to maintain the heat balance of the organism. In patients there was no such increase in temperature, showing that this feedback regulation of heat loss does not function properly in Parkinson's disease. This can, in extreme situations, lead to fatal hyperthermia.

Abnormal heat regulation can be observed to some extent in all parkinsonian patients. They all feel much worse in the heat and better in a cool climate. The frequent symptom of flushing also represents an attempt to increase heat loss by dilation of the vessels of the skin. L-dopa injection has no effect on this blockade of heat loss. However, 5-hydroxytryptophan (50 mg i.v.) does lead to an increase in temperature of the toes in response to covering the upper body. This indicates that serotonin is a transmitter involved in the control of body heat (*Birkmayer* and *Neumayer* 1963). This finding has resulted in the

prophylactic administration of L-tryptophan during the hotter parts of the year. Since this treatment was introduced hyperthermias have not been observed and during the summer months the patients feel substantially better.

Acute attacks of sweating, which often mean a patient having to change his shirt three times a night, can also be due to abnormal serotonin metabolism. These attacks can similarly be relieved by L-tryptophan treatment.

However, the increase in salivation does not respond to either tryptophan or L-dopa. Anticholinergic medication is the only effective treatment, suggesting that an imbalance of the ACh-dopamine systems is responsible for hypersalivation. On the other hand, the constipation which tends to occur is increased on treatment with L-dopa. Since serotonin is present in high concentrations in the intestines, the administration of L-dopa may produce a depletion of serotonin. *Bartholini et al.* (1968) first described how, after injection of L-dopa, experimental animals had a reduction in serotonin as well as an increase in dopamine in the brain. This competitive effect can also occur in the periphery. L-tryptophan medication can reverse this effect and leads to the repletion of the serotonergic ganglion cells of the intestinal wall, thereby restoring the dopamine-serotonin balance. In the same way the frequent oedema in the legs as a disturbance of serotonin metabolism can be explained. Again additional administration of L-tryptophan or 5-hydroxytryptophan can often eliminate, or at least improve, this oedema.

Patients in whom the disease is well advanced may exhibit a pronounced wasting. It can be as dramatic as that at puberty; but in children there is usually a loss of appetite (anorexia nervosa), while the parkinsonian patient has an increased appetite and can even be quite voracious. Increase in weight is brought about by a parasympathetic stimulation. In general the administration of L-tryptophan is ineffective in reducing weight loss in Parkinson's disease. The most successful treatment is with tricyclic antidepressants, indicating a disorder of central control mechanisms.

The hypothalamic-pituitary system seems to be disturbed in Parkinson's disease (Table 2, 3) and possibly in anorexia nervosa (for review see *Riederer et al.* 1982 c). Stimulation of dopamine receptors (D-4 receptors according to *Seeman* 1980) by L-dopa treatment suppresses prolactin secretion. Therefore loss of dopaminergic activity as well as an overactivity might account for disturbances in eating behaviour, which seems to be connected with hypothalamic subareas (*Pozo* and *Re* 1972, *Chase et al.* 1974b, *Eisler et al.* 1981b, *Lavin et al.* 1981, *Lancranjan* 1981 for review).

Galea-Debono et al. (1977) and *Agnoli et al.* (1981) have shown that there is an increase in growth hormone in plasma after L-dopa treatment. This effect has not been confirmed with bromocriptine (*Shaw et al.* 1978). The emaciation can be regarded as reflecting a disturbance in the dopamine-serotonin balance resulting from long-term L-dopa therapy. However, it is an extrastriatal neurotransmitter imbalance which is involved in these autonomic disturbances (*Birkmayer* and *Riederer* 1975a).

Many other complaints of parkinsonian patients are similarly due to autonomic disturbances. Patients complain of burning sensations in the extremities, itches, tickling, painful cramps (without rigidity of spasm), restless legs, burning feet and hot feelings in the chest, head or in the extremities. Characteristic of these symptoms is the inconsistency between the relatively objective findings and the affective component of the symptom which may include genuine pain. This connection between autonomic and affective disturbances implicates the involvement of a biochemical disorder within the limbic system (the visceral brain). Hemilateral feelings of heat in the lower extremities can be related to objective increases in skin temperature. Our biochemical analyses of the limbic system suggest such autonomic symptoms to be due to transmitter imbalance in particular brain regions. We would not agree with *Snider et al.* (1976b) in classifying such symptoms as sensory. Genuine sensory defects are invariably associated with objective findings (such as hypoesthesia, hyperpathia). Furthermore, these imprecise and vague complaints are typical of disorders of autonomic function. Since the imbalance of biogenic amines in the brain stem is responsible for the many motoric, autonomic and affective disorders (*Birkmayer et al.* 1972), it is obvious that these complaints relate to biochemical abnormalities in the same region.

The parkinsonian patient frequently complains of pain in the shoulder, hip and knee joints, as well as in the lumbar region. They have been reported by both *Parkinson* (1817) and *Charcot* (1877), but are not primarily due to the disease. The pains are not rheumatic, but are caused by nutritional disturbances in the tissues of the joint as we have already described. These autonomic disturbances occur more often in the evening or at night and are very unpleasant for the patient.

The clinician must find it remarkable that the patient with severe movement disabilities will not mention them, but complains of these disorders of autonomic function to the exclusion of all else. This shows that the affective component accompanying these symptoms is in the forefront of the patients' awareness. Thus between these

organic-vegetative symptoms of Parkinson's disease and the so-called masked depressions (*Walcher* 1969) is a substantial area of overlap.

Psychiatric Disturbances

In the brain stem in Parkinson's disease there appear to be disorders of the balance between individual neurotransmitters–as we mentioned above. We have proposed that a dynamic equilibrium between these biogenic amines is a prerequisite for normal behaviour (*Birkmayer et al.* 1972). It is apparent that there are psychopathological phenomena in addition to the disorders of motor and autonomic function. In fact there is hardly any psychiatric disorder which is not associated with the disease. Modern treatment with L-dopa leads to a whole range of psychopathological side effects. Such side effects are also produced by anticholinergics, amantadine and dopaminergic agonists. Moreover psychiatric symptoms can occur spontaneously in the course of the disease.

Without doubt the most frequent psychopathological disorder in Parkinson's disease is depression. Reports of its frequency vary between 30% and 90% (*Ajuriaguerra* 1971). In our own patients we found depressive states in 27%. Periods of depression appeared in 11% before the onset of parkinsonian symptoms. *Mendlewicz et al.* (1976) found 14 out of 30 parkinsonian patients who had had depressive phases before the appearance of disease symptoms.

This relationship between Parkinson's disease and depression is not surprising considering our biochemical findings. Fig. 28 demonstrates that dopamine is reduced below control values in the caudate nucleus, putamen and red nucleus taken post-mortem from depressive patients, although this decrease does not reach that found in Parkinson's disease. Furthermore, the deficit is reversible since a hospitalized patient, diagnosed as having "chronic retarded depression" and who died in remission, exhibited values close to normal (Fig. 9). These findings, along with others which will be discussed below, lead to the conclusion that depression is due to a reversible functional disorder of neuronal systems. Here lies a major difference from Parkinson's disease, in which the progressive degeneration cannot be held back. Functional disturbances may, however, be found in neuronal systems other than dopamine, which is particularly related to retarded depression.

Before proceeding further we should like to summarize the advances in research into depression. As we have described, L-dopa treatment of parkinsonian patients was a consequence of biochemical analyses of the brain, which showed a deficit of striatal dopamine (*Ehringer* and *Hornykiewicz* 1960). This order of discovery was reversed in

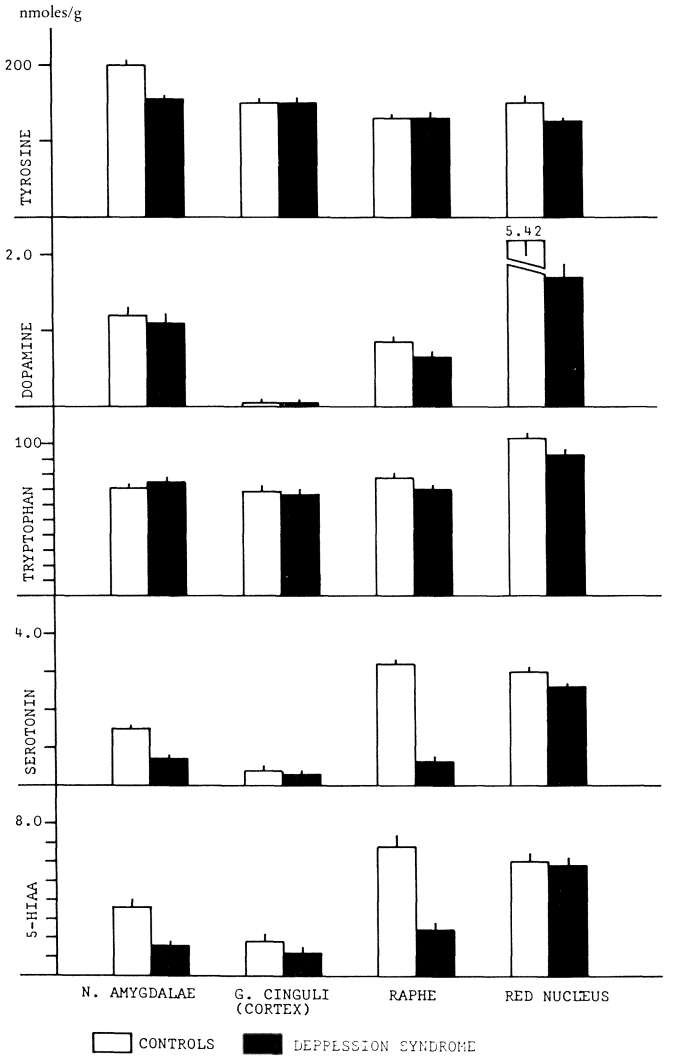


Fig. 28

Figs. 28 and 29. Changes of human brain precursor amino acids, neurotransmitters and metabolites in endogenous depression (*Birkmayer* and *Riederer* 1975 b)

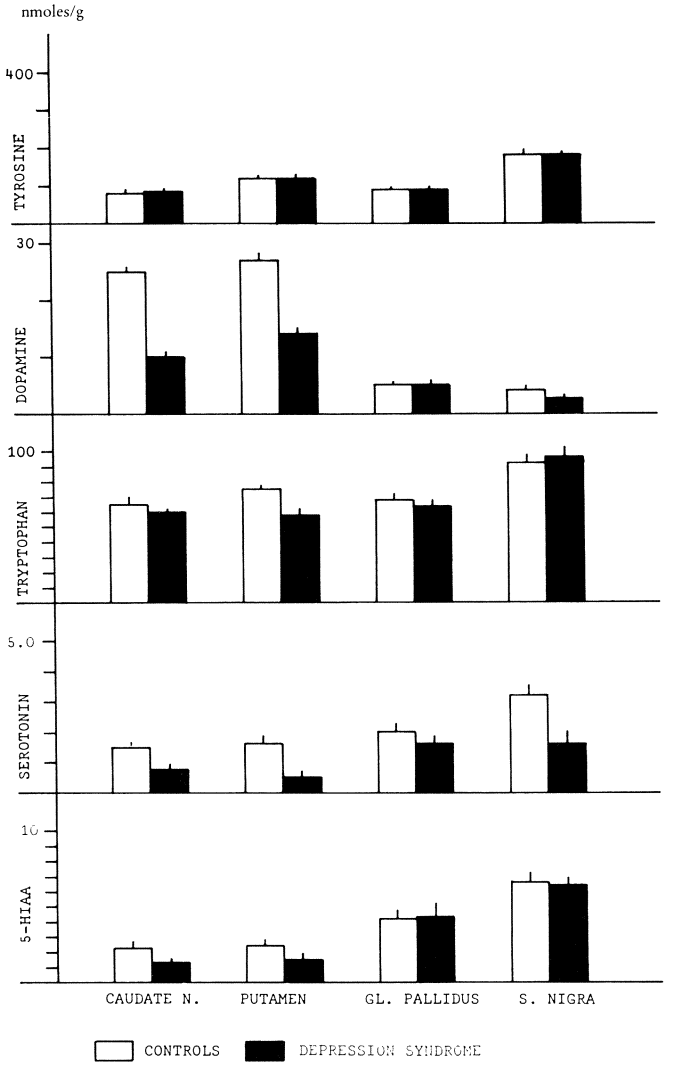

nmoles/g
400
TYROSINE
30
DOPAMINE
100
TRYPTOPHAN
5.0
SEROTONIN
10
5-HIAA
CAUDATE N.
PUTAMEN
GL. PALLIDUS
S. NIGRA
CONTROLS
DEPRESSION SYNDROME

Fig. 29

psychiatry. Pathophysiological research was activated out of stagnation by the discovery and application of psychiatric drugs. *Brodie, Carlsson* and their colleagues showed how reserpine effects a release of transmitter in the ganglion cells. Thus reserpine medication brings about a depletion of noradrenaline, dopamine and serotonin in these cells. The depletion of noradrenaline explains the antihypertensive action of reserpine. Reserpine and related compounds also induce depression in some 10% of treated patients. If the treatment is stopped, the depression disappears. These findings are consistent with the view that a deficit of the biogenic amine transmitters in particular ganglion cells correlates with the psychiatric state known as depression.

As a result, two hypotheses have been formulated. *Schildkraut* (1965) proposed noradrenaline to be the transmitter responsible for depression, while *Coppen* (1974) and *Murphy et al.* (1978) postulated the involvement of serotonin. Either hypothesis is difficult to verify in a clinical setting. Thus the post-mortem investigations with brain tissue from depressives are all the more important. Such studies have been made by *Bourne et al.* (1968), *Pare et al.* (1969), *Shaw et al.* (1967), *Birkmayer* and *Neumayer* (1969), *Birkmayer et al.* (1969) and *Lloyd et al.* (1974). The problem with these studies lies in the fact that the material was mainly from depressive patients who had committed suicide. Although the results may have indicated a particular trend, individual values frequently exhibited relatively large scatter. This had its basis in the many variables which would include the immediate cause of death, whether it was sudden, the drugs (if any) used in the suicide and so on. We have reported several individual cases who had endogenous depression, but who had not committed suicide (*Birkmayer* and *Riederer* 1975b). The results are shown in Figs. 28, 29. There was no general consistent trend towards an overall decrease in any of the compounds of catecholamine or serotonin metabolism under study. Noradrenaline is far less affected than serotonin, which was found to be deficient in seven of nine brain regions. Cases in remission almost invariably exhibited normal values. Further investigations showed MHPG to be diminished in a whole range of brain regions, implying a reduced turnover of noradrenaline. So there is evidence for a disturbance of both catecholamine and indoleamine metabolism in depression.

Our findings from brain tissue are consistent with the results we have obtained from measurements of the amino acid precursors in blood and the metabolites in urine from patients with endogenous depression (*Birkmayer* and *Riederer* 1975b, *Ambrozi et al.* 1973). There is also agreement with the results of *Bourne et al.* (1968), *Shaw et al.* (1967), *Pare et al.* (1969) and *Lloyd et al.* (1974). We would agree with

the conclusion of *Pare et al.* (1969) that catecholamine metabolism is implicated to a lesser extent. Primarily our data demonstrate no unequivocal abnormality of either catecholamine or indoleamine metabolism; but there does appear to be an imbalance between the two aminergic systems. This supports our hypothesis, developed from peripheral investigations, that a disturbance of neurotransmitter balance is causal in disorders of affective behaviour. There are rhythmic changes in metabolite excretion which reflect normal circadian rhythms. The endogenous depressive does not, apparently, exhibit these metabolic variations, reflecting the presence of a central imbalance of transmitter function.

The results of brain analyses in depression demonstrate yet another point. There is a distinct difference from the results from brains of parkinsonian patients, whether or not they exhibited L-dopa-induced psychoses. It should be remembered that the L-dopa psychosis is also an example of a functional disturbance in biogenic amine metabolism, albeit one related to an organic brain lesion. A deficit of transmitter substances in particular brain stem regions is due to this lesion. However, no such genuine (i.e. morphologically defined) deficit is present in endogenous depression. The findings make it clear that only under particularly fortunate conditions could a therapeutic approach utilizing biogenic amine precursors ever be successful. Every attempt to correct a disturbance of catecholamine metabolism by administering precursors will effect a compensatory change in indoleamine metabolism, and vice versa. For example, while L-dopa treatment can correct the deficit in the striatum, it can lead to an excess of dopamine in other, unaffected brain regions.

Acetylcholine metabolism has yet to be considered; there is no doubt that it has a close functional connection with catecholamine and indoleamine metabolism. However, there are severe methodological problems in demonstrating abnormalities of ACh and its related compounds. From a purely clinical standpoint it is also interesting that practically all the brain stem nuclei which are affected by an imbalance of amine metabolism are those with the closest links to psychomotor function.

Hence it is important to consider whether the apparently disturbed transmitter balance within the brain stem is the biochemical correlate of the loss of drive in depression. These findings emphasize the intimate relationship between psyche and mood.

The determination of neurotransmitters in particular brain regions merely indicates their presence there and that they have some functional significance. These methods can only reveal general changes of functional importance; they do not indicate whether the site of the

disturbance is in the cell body, the synapse or the receptor. Nevertheless such work is not irrelevant. Certainly in our results we can conclude that there is a tendency to more normal amine metabolism in depressed patients in remission. This distinguishes a genuine amine deficit (Parkinson's disease) from an imbalance of transmitter function (depression).

The reduced noradrenaline turnover, as well as the abnormal indoleamine metabolism, may be responsible for the disturbances of autonomic function such as gastrointestinal disturbances, giddiness, headache, salivation and disturbances of the sleep-wake cycle. The notable loss of noradrenaline in the red nucleus, which can be regarded as the centre of motor integration (*Ward* 1968, *Olszewski* and *Baxter* 1954), may explain the typical posture of the depressed patient. This is related to the hypoactivity of the gamma-loop, which regulates noradrenaline (*Andén et al.* 1972). It is also plausible that the deficit of dopamine in the striatum leads to loss of drive and emotional activity while the serotonin deficit in the raphe nuclei correlates with the sleeplessness of many depressed patients. The obvious negative symptoms of these patients can be interpreted as an imbalance in neuronal systems (*Riederer* and *Birkmayer* 1980).

The question arises how antidepressant drugs can influence such varied systems. Animal experiments have shown that tri- and tetracyclic antidepressants are inhibitors of serotonin and noradrenaline uptake and, to a certain extent, dopamine uptake (*Carlsson* and *Lindquist* 1978). On the other hand, some effective antidepressants (e.g. mianserin and iprindole) have little, if any, effect on uptake (*Maj et al.* 1977, *Ross et al.* 1971). More recently it has been shown that mianserin increases the synthesis of dopamine and noradrenaline. Yet another effective drug, nomifensine, inhibits the synthesis of dopamine, noradrenaline and serotonin as well as blocking catecholamine uptake mechanisms (*Carlsson and Lindquist* 1978). Since most MAO inhibitors, such as tranylcypromine, also have good antidepressant properties, it would seem that more than one biochemical process is implicated in the dysfunction responsible for depression. As yet it is not known whether transmitter synthesis, release, reuptake, postsynaptic action or metabolism is involved. Our studies show no more than a neurotransmitter imbalance in depression. We have described this as a "brain area specific imbalance" in which functional disturbances are localized to particular brain regions, not necessarily affecting the whole brain.

Consequently it is proposed that, according to their physicochemical properties, drugs may exert their effects on different and specific parts of the brain involved in depression. Evidence for this

derives not only from the different pharmacological profiles of antidepressants, but also from the great variation in the clinically recognizable forms of depression. This hypothesis calls for the investigation and cross-comparison of:

1. the varied clinical symptomatology of depressed patients,
2. the disturbances of specific brain regions identifiable according to the symptoms,
3. the various biochemical disorders which correlate with particular symptoms,
4. the response of patients to medication which varies according to the symptom.

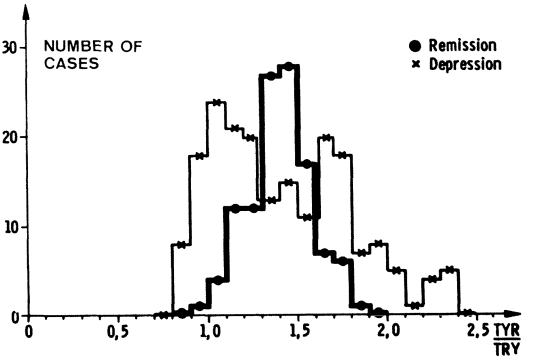


Fig. 30. The serum tyrosine/tryptophan ratio in depression and remission

Statistics	x	s	χ^2	p <
TYR/TRY (depression)	1.42	0.41	56.61	0.01
TYR/TRY (remission)	1.41	0.18	8.08	n.s.

Another important question is whether the disorder in depression is detectable in the periphery, which would mean it was accessible to biochemical analysis. At present, blood and urine analyses do not permit an exact differentiation between the various nosological forms of depression, although peripheral levels of catecholamine and indoleamine metabolites do differ from normal. The ratio of tyrosine to tryptophan, measured in fasting serum, yields values which differ in the same patients depending on whether they are in a depressive phase or in remission (Fig. 30). These fluctuations in the relative concentrations of precursors may contribute to changes in neurotransmitter function since they may influence uptake into the brain (*Fernstrom* and *Wurtman* 1971, *Baumann* 1979).

Urinary excretion of HVA, VMA and 5HIAA exhibit a circadian rhythm; significantly more of the catecholamine metabolites are excreted during the day than at night (*Riederer et al.* 1974). The patient with endogenous depression does not exhibit this effect (Fig. 31). HVA and VMA levels are significantly less during the morning, but are normal in the afternoon. This suggests to us that there is a biochemical correlate of the morning deterioration and evening remission. 5HIAA

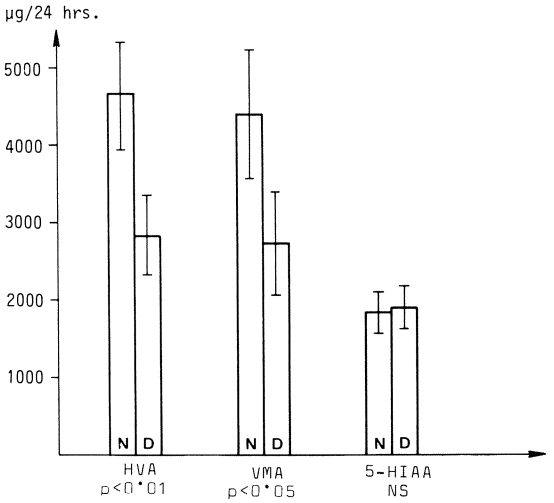


Fig. 31. Urinary excretion of HVA, VMA and 5-HIAA in depressive patients *(D)* compared to normal controls *(N)*. HVA and VMA excretion is significantly below normal

levels are not, however, abnormal. Further investigations are needed before one can conclude that these changes, or changes in other peripheral monitors like the dexamethasone suppression test, are characteristic of depression. Neither is it clear whether the differences are primary or secondary effects, nor whether parameters can be found which distinguish between different nosological forms.

The symptoms resulting from the biochemical changes of Parkinson's disease are essentially negative ones, as can be demonstrated by our rating scale (*Birkmayer et al.* 1973b). Prominent in the clinical picture are lassitude, anxiety and loss of drive. These psychiatric symptoms are particularly notable to the doctor when the parkinsonian patient moves easily, carries himself well and has only minor tremor, but yet has a large number of complaints. An obvious step was to try substitution therapy with tryptophan as well as L-dopa. There are reports of depression being produced in the course of L-dopa

treatment (*Klerman et al.* 1963, *Goodwin et al.* 1970). However, there are also reports of the successful treatment of depression with L-dopa (*Matussek et al.* 1966, 1970; *Knopp* 1970, *Murphy et al.* 1971). A combined treatment of tryptophan and benserazide, a decarboxylase inhibitor, was also partially successful (*Coppen et al.* 1965, *Birkmayer et al.* 1972). Understandably, the administration of tryptophan can reverse the depletion of serotonin in the reticular formation. In successful cases this leads to the relief of sleep disturbances. Similarly the increase of striatal dopamine by L-dopa treatment improves drive. The general dysphoria, the predominant symptom of depression, which we regard as a loss of affective equilibrium, responds neither to catecholamine nor indoleamine substitution therapy. Treatment with compounds such as p-chlorophenylalanine, an inhibitor of tryptophan hydroxylase and hence serotonin synthesis, or α-methyl-p-tyrosine, an inhibitor of tyrosine hydroxylase, are found to be ineffective in depression.

The uniquely successful treatments with the different antidepressant drugs, which act by blockade of transmitter reuptake, are in our opinion primarily due to the reestablishment of biochemical balance (*Ambrozi et al.* 1973). Table 15 shows some preliminary data on spiroperidol binding in putamen taken post-mortem from depressives who died from natural causes. No definite conclusion can be drawn from these results. It is, however, noteworthy that one patient (J. Z.) without any antidepressant therapy for more than three months before death did not show abnormal spiroperidol binding density. Nevertheless, symptoms of depressed patients might be correlated to changes in various neurotransmitter receptors (*Ögren et al.* 1979).

Pharmacotoxic Psychosis

Besides the disorders of affect in Parkinson's disease, exogenous reactive disturbances may be present. Psychopathological behaviour was described long before modern L-dopa therapy (*König* 1912, *Bostroem* 1922, *Ajuriaguerra* 1971). The most frequent symptom is confusion. This occurs in 21% of our patients; *Ajuriaguerra* (1971) reported the same frequency. There is a disorientation in time and space, a decreased awareness and a loss of critical thought faculties. We distinguish two forms: one being delirium with motor agitation similar to delirium tremens, this we describe as "agitated confusion". There are also confusional states without any of the accompanying affective or motor symptoms, as in senile dementia, which we call "inhibited confusion". Such behavioural forms are regularly found in patients presenting with abnormal EEG and brain atrophy detected by

Table 15. [^{3}H]*Spiroperidol-binding in post-mortem putamen of depressed patients*

	Age (yrs)	Diagnoses and therapy	B_{max} (pmol/g)	K_D (nM)
1. *Controls* (14 f/4 m)	73.6 ± 3.1	Cardiac decompensation, heart failure, broncho-pneumonia, no treatment with psychoactive drugs	23.3 ± 1.2	0.13 ± 0.016
2. Depression syndrome: A. W. (f)	69	Unipolar endogenous depression; Feighner neg.; ICD (8. rev.) 296.2/294.3; several suicide attempts; delirium from amitriptyline; hospitalization; treatment (last 3 months): 381 mg thioridazine, 384 mg dibenzepine, 50 mg levopromazine, 15 mg fluphenazine/day; last medication: 12 days before death	17.4	0.54
M. B. (f)	74	Bipolar manic-depression. Feighner neg., terminal pneumonia, cardiac decompensation, long-term treatment: lithiumcarbonate 562.5 mg, 128 mg amitriptyline, 91 mg clopenthixol, 242 mg dibenzepine, 40 mg fluphenazine/day; last medication: 40 mg fluphenazine/day; 400 mg meprobamate	26.7	0.48

M. J. (f)	67	Unipolar endogenous depression; Feighner neg., ICD (8. rev.) 296.2. oedema from lung; fat-liver; treatment: 100 mg thioridazine, 5.7 mg flupenthixol decanoate, 300 mg amantadine, 15 mg biperidene/day for 3 months; then 40 mg fluanxol-depot/week; last neuroleptic treatment 6 days before death: 50 mg thioridazine	18.2	0.17
E. J. (f)	55	Agitated depression; Feighner neg.; ICD (8. rev.) 296.8; pulmonary embolism; chlorprotixene 93 mg/day. Clopenthixol 106 mg/day. Duration of treatment: 12 days; last medication: 50 mg clopenthixol 12 hrs before death	17.5	1.81
J. Z. (m)	86	Unipolar depressed patient; died during a depression from acute cardiac failure; without any antidepressants before death	23.0	0.40

Means ± S.E.M.: post-mortem time: controls: 7.7 ± 1.2 hrs; depressed patients: 3.5 ± 0.3 hrs. From: *Riederer, P., Jellinger, K., Gabriel, E.* 1982 in preparation.

computer tomography. They occur spontaneously during anticholinergic therapy, but we observe them most frequently during treatment with L-dopa or bromocriptine. Hallucinations mostly appear in combination with delirious confusion (in 10% of our patients). However, these hallucinations are visual, rarely auditory, even occurring in patients with no clouding of consciousness. Such patients might think there is a relative in the room who doesn't reply when spoken to. Or an intruder is seen; this might disturb the patient, but rarely so much that it invokes an exceptional anxiety. The patient would not be afraid to force the "intruder" out from under the bed or behind the curtain with a stick or broom. Auditory hallucinations are less frequent and never have the emotional force of those experienced by paranoid schizophrenics. The patients do exhibit some anxiety, but are hardly ever aggressive. Although verbal contact is possible, they are not easily distracted. Agitation, incoherent confusion, hallucinations and deranged ideas are symptoms which are also seen in schizophreniform illness. But thought deprivation, autism and an absence of speech are not found in parkinsonian patients. There is a diurnal variation in these symptoms; together with anxiety they are more frequent at night. Such pseudoschizophrenic reaction can occur both spontaneously or as a side effect of drug treatment. We first described the psychotic side effects after administering L-dopa in combination with various MAO inhibitors (*Birkmayer* 1966). *Cotzias et al.* (1969) have also described psychotic episodes (toxic delirium) which occurred during high dose L-dopa treatment. Not surprisingly, a similar delirium can be seen after poisoning with Belladonna or amphetamine. Our biochemical analyses have indicated that the psychoses of Parkinson's disease are due to a displaced balance of individual biogenic amines in various brain nuclei: a "brain area specific imbalance" (*Birkmayer et al.* 1977).

Bradyphrenia describes changes in mental performance. It is recognized by a slowing of thought processes with accompanying losses in concentration and attention. A major question that is still under much investigation is whether there is a specific reduction in mental function in Parkinson's disease, or simply whether senile dementia occurs in the older patients (*Lewy* 1912). *Talland* and *Schwab* (1964) were unable to find any differences between organic dementia and dementia of Parkinson's disease. It is not surprising that cases of organic dementia in idiopathic parkinsonism are more frequent than in the postencephalitic form of the disease (*Talland* 1962) since the idiopathic form has a later age of onset. In an extensive series of tests, *Jacobi et al.* (1978) found that the intelligence of parkinsonian patients corresponds with age. There is a definite correlation between the

organic brain syndrome, atrophy (as shown by computer tomography), slower EEG and the motor abnormalities of akinesia and rigidity (*Schneider et al.* 1978).

In our experience organic dementia is to be distinguished from bradyphrenia. The latter only gives a superficial impression of dementia. It is the psychiatric correlate of akinesia. Thought processes are slowed down, but judgement and the handling of concepts are unchanged. The "input" of thought is more difficult, analogous to the difficulties experienced in starting to move. Understandably, the flow of words is slower, but a psychiatrist would not confuse this with dementia. Nor is memory capacity diminished (*Ajuriaguerra* 1971). There is no cognitive deficit in Parkinson's disease, merely a drop in the speed of recognition (*Jacobi et al.* 1978). The patient is more easily distracted and his mental performance is very dependent on mood. These bradyphrenic disturbances respond to L-dopa treatment, at least as far as the speed and impetus of mental processes are concerned. Of course, this will not ease the symptoms of genuine organic dementia. Nevertheless, we have tried L-dopa in the treatment of Alzheimer's disease and found an increase impulsive behaviour along with hectic, purposeless activity. *Bowen et al.* (1973) investigated parkinsonian patients treated with L-dopa for various lengths of time. Intelligence tests yielded IQ values of 114 for a control group and 113 for the patient group. Patients with two or three years L-dopa treatment had values of 114 and 115, respectively. These minimal differences show that L-dopa treatment does not increase the intellectual capacity of the parkinsonian, which is no lower than normal. L-dopa treatment cannot prevent the progression of senile dementia; nor is senile dementia without Parkinson's disease improved by L-dopa (*Woert et al.* 1970).

In Parkinson's disease there is a disturbance of all mental function that is normally associated with the brain stem (*Reichhardt* 1928). The adaptability of man to his surroundings, his social environment, demands a certain capacity of neurotransmitter function. A deficit of serotonin in the reticular formation leads to disturbances of sleep. A lack of dopamine in the red nucleus might bring about the well-known stoop of the parkinsonian patient. The dopamine loss in the striatum is responsible for the loss of drive, as well as for the akinesia, as is shown in our biochemical findings in Parkinson's disease and depression (p. 11, 22, 76, 77).

In Parkinson's disease it must not be forgotten that biochemical abnormalities are present in the limbic system and the whole of the mid-brain as well as in the striatum. The substantia nigra, as a biochemical "distribution centre", acts as a moderator of motor, autonomic and affective-emotional function. Delirium, whether or not

it is due to L-dopa treatment, originates in neuropathological changes of the mid-brain. So it is hardly surprising that the ability and function of the parkinsonian patient is influenced so much by mood, weather, infections, emotional stress etc. (*Schwab* and *Zieper* 1965). In addition to the disorder of affect, depression, there is hardly any form of abnormal behaviour which cannot be observed within the framework of Parkinson's disease. Consolidating the experience of 25 years, one can repeatedly recall the hysterical mechanisms and neurotic behaviour patterns which naturally suggest the brain stem as the site of the neurosis. But the most frequent disturbances are psychopathological. Particularly notable are the attacks of unwarranted aggression. One patient in our department had periods in which she would scratch the paint of the consultant's car. Afterwards she would be as good as gold for several weeks. Another patient would occasionally make nocturnal homosexual attacks on fellow patients. Others wandered off across Vienna while still in their hospital dress. It is notable that our patients hardly ever deviated into alcoholism; not even the depressive parkinsonians took to alcohol. Another point of some clinical note can only be observed after years of working with Parkinson's disease. While one can collect ten multiple sclerosis patients, or ten accident cases, together in one room, ten parkinsonians cannot get together without the appearance of psychopathological behaviour. The sclerotic patients would immediately establish a pecking order, with which a hierarchical structure in the room is created and maintained. Because of his phasic disabilities, both affective and autonomic, the adaptability of the parkinsonian patient to such a group is so poor that it is impossible for a hierarchy to be established. This malfunction of sociological adaptation is particularly notable in that it shows how man's ability to live successfully among others is related to biogenic amine function in the brain stem. When this ability is lost due to a biochemical defect, then disorders of the patient's judgement, behaviour and social interaction will appear. These social disabilities of Parkinson's disease, being an expression of brain stem disease, respond neither to L-dopa nor to tryptophan treatment. Antidepressant drugs may ameliorate the most severe disturbances, but cannot relieve them entirely. An improvement will follow on increasing the patient's biological "sphere of action". In other words, a parkinsonian patient should have a larger "territory" than is normal, so that this greater distance between patients will minimize the effect on their (hypersensitive) mood. These sociopathological behaviour traits are particularly important aspects of long-term in-patient care.

Treatment

Anticholinergic Drug Therapy

The aim of all treatment is to reestablish the equilibrium lost in the pathological process. This basic principle is circumscribed by present scientific knowledge and the availability of pharmaceutical substances. The excessive cholinergic activity caused by striatal dopamine loss could previously only be treated by anticholinergic drugs. Thereby it was possible to correct the positive symptoms of this imbalance, tremor and rigidity, with relative success. But the negative symptom of akinesia was unaffected. It was only the recognition of a deficit of dopamine in the striatum and the subsequent possibility of substitution with L-dopa which opened another pathway to the restoration of biochemical equilibrium. L-dopa passes across the blood-brain barrier and can be decarboxylated in dopaminergic neurons. Unfortunately, this process occurs in the periphery as well as in the brain. The peripheral dopamine synthesis is characterized clinically by a series of side effects in the gastrointestinal and cardiovascular systems in particular. It was the discovery of the inhibitory effect of benserazide on L-dopa decarboxylase (*Birkmayer* and *Mentasti* 1967) which permitted the almost complete elimination of these side effects and enabled optimal amounts of L-dopa to enter the nervous system.

An important feature of Parkinson's disease is that the patient is unable to regulate biochemical equilibrium by feedback mechanisms. While a healthy person has no central side effects resulting from L-dopa medication, the parkinsonian patient exhibits side effects with the smallest overdose of L-dopa. Medication with L-dopa and a decarboxylase inhibitor will initially increase striatal dopamine which, in the healthy person, will decrease tyrosine hydroxylase activity, and hence dopamine synthesis, by feedback inhibition and so restore equilibrium. However, the defective feedback function of the parkinsonian makes it difficult to achieve an optimal therapeutic effect.

An excess of L-dopa displaces the cholinergic-dopaminergic equilibrium in favour of the latter system. The clinical consequence is hyperkinesia. Furthermore, L-dopa may change the brain stem balance between dopamine and serotonin by so much that depression may appear. When the nigro-striatal degeneration is well

advanced, L-dopa administration can lead to a depletion of serotonin, resulting clinically in an exogenic-reactive psychosis. Finally, L-dopa may be displaced by an excessive administration of L-tryptophan, which can be effective in the treatment of L-dopa psychoses, whereupon the resulting loss of dopamine may bring about an increase in akinesia (*Riederer* 1980). Such inadequacies of feedback regulation are responsible for the side effects. However, it is unclear why these self-regulatory processes do not function. There may be a malfunction of a receptor which will consequently be unable to pass on information, or a defect in transmission to the regulatory centre may be responsible. Alternatively, the production of a chemical "correction factor" may be inadequate. The progressive degeneration of nigro-striatal neurons may be responsible for the insufficient feedback regulation. Neuroleptic therapy in schizophrenic patients blocks dopamine receptors on the one hand, and on the other stimulates tyrosine hydroxylase to increase dopamine synthesis. Extrapyramidal side effects are an indication of the resulting dopaminergic hyperactivity. However, a parkinsonian patient who receives haloperidol will experience a rapid increase in akinesia, never a hyperkinesia. This means that dopamine synthesis cannot be stimulated by feedback in the defective dopaminergic neurons. A further example: long-term neuroleptic treatment in schizophrenics can lead to the hyperkinetic movements of tardive dyskinesia. It is assumed that these side effects are due to a dopaminergic hyperactivity, and the therapeutic approach has been to restore the balance between ACh and dopamine. Infusions of choline have been found to suppress the movement of tardive dyskinesia. However, choline is ineffective against the hyperkinetic side effects in Parkinson's disease (*Yahr* 1979), which means that the structural lesions preclude any feedback regulation. So the treatment of Parkinson's disease must steer a course between the Scylla of dopaminergic hypoactivity and the Charybdis of hyperactivity due to (excessive) L-dopa medication.

The optimal therapeutic effect will depend on the number of intact neurons. The fewer functional dopaminergic neurons there are, the smaller the therapeutic effect and the greater the side effects will be. The rate of neuronal degeneration will vary with the individual; we have distinguished benign and malignant forms of the disease (see p. 152) which, on the basis of the number of remaining dopaminergic neurons, react with differing intensity and time to L-dopa medication. The basic rule of treatment in Vienna, independent of this division, is to commence L-dopa substitution therapy as quickly as possible, albeit with as low a dose as is effective. The high dosages of *Cotzias* certainly stimulated much initial enthusiasm. However, they undoubtedly lead to an accelerated degeneration with a range of side effects. The

Table 16. *Chronological table of the important advances in the treatment of Parkinson's disease*

1892	*Charcot*	Belladonna
1946	*Sigwald*	Synthetic anticholinergics
1961	*Birkmayer–Hornykiewicz*	Intravenous L-dopa
1961	*Barbeau–Sourkes*	Oral L-dopa
1962	*Birkmayer–Hornykiewicz*	Oral L-dopa, MAO-inhibitors
1962	*Gerstenbrand–Pateisky*	L-dopa, MAO-inhibitors
1967	*Birkmayer*	L-dopa combined with a peripheral decarboxylase inhibitor (benserazide)
1967	*Cotzias*	Large doses of oral L-dopa
1972	*Birkmayer–Neumayer*	L-tryptophan improves psychiatric side effects when given in addition to L-dopa
1974	*Calne*	Dopaminergic agonists (bromocriptine)
1975	*Birkmayer–Riederer–Youdim–Knoll*	Selective MAO-inhibitors (deprenyl)

Table 17. *Effects of anticholinergic drugs on rigidity and tremor*

Drug	Typical dose/day (mg)	Effect on:	
		Rigidity	Tremor
Benzhexol	5– 10	good	moderate
Benzatropine-methanesulphonate	4	good	moderate
Procyclidine	10– 20	good	moderate
Biperidine	4– 8	good	moderate
Orphenadrine	100–200	good	moderate
Ethylbenzhydramine	50– 75	good	moderate
Bornaprin	4– 12	moderate	good

appearance of side effects is an expression of a progressive disturbance of the nigro-striatal system. At higher doses these side effects appear earlier. In Vienna we use lower doses to avoid accelerating the course of the disease, while accepting that the therapeutic effect will be smaller.

Charcot (1892) introduced the first successful treatment using extracts of Belladonna. These extracts, like atropine, inhibit cholinergic hyperactivity and thus create a new equilibrium between ACh and dopamine, albeit at a lower level. As we have mentioned, this only improves the positive symptoms. Anticholinergic drugs are also indicated in the treatment of the autonomic symptoms of salivation, sweating attacks and seborrhoea as well as for tremor and rigidity. Today the treatment of these symptoms is made possible by all the

synthetic drugs that are available. *Sigwald et al.* (1946) first introduced a synthetic anticholinergic, orphenadrine. Such synthetic cholinolytic substances are preferable to atropine, since their central anticholinergic properties predominate over the unwanted peripheral effects. From the great range of available drugs we shall only mention a few that we have found useful (Table 17). *Yahr et al.* (1969) were able, with this conservative approach to treatment, to obtain a general improvement of 20%. There is a lack of agreement as to whether anticholinergics induce dementia in parkinsonian patients (*Drift* 1980).

L-Dopa Treatment

A crucial advance in therapy was brought about by the introduction of treatment with the precursor L-dopa (*Birkmayer* and *Hornykiewicz* 1961, *Barbeau et al.* 1961). The Viennese and Canadian groups independently initiated the administration of L-dopa. The Viennese approach was based on the deficit of dopamine found in the striatum, while the Canadians based their treatment on the observed reduction in urinary dopamine excretion in parkinsonian patients.

The first positive results stimulated tests of other compounds. Only L-dopa (administered i.v., orally or rectally), exhibited a strong kinetic response (Fig. 32); all other amino acids including tyrosine had no effect. However, more recent animal experiments have shown that large doses of phenylalanine and tyrosine can increase catecholamine synthesis in the brain (*Wurtman et al.* 1974). As expected, α-methyl-p-tyrosine increased parkinsonian akinesia since it is a specific inhibitor of tyrosine hydroxylase and inhibition of this rate-limiting enzyme will inevitably worsen Parkinson's disease symptoms (*Birkmayer* 1969a).

Aromatic amino acid decarboxylase has little, if any, activity towards D-dopa, the corresponding stereoisomer. Thus after D-dopa administration hardly any extra dopamine will result and so no kinetic effect can be observed. The use of 3-methoxydopa similarly had no positive effect on parkinsonian akinesia. This substance is synthesized by COMT from L-dopa *in vivo*. Since it is increased in tissue after L-dopa treatment, it had been thought to be a possible storage form of L-dopa. Administration of 3,4-dihydroxyphenylserine (DOPS), which yields noradrenaline after *in vitro* decarboxylation, is also ineffective at low dosage (*Birkmayer* and *Hornykiewicz* 1962). Much higher dosage of DOPS, however, have been shown to be useful in the treatment of "freezing" (*Narabayashi,* personal communication). Even i.v. administered dopamine has no kinetic effect since it does not cross the

blood-brain barrier. Its peripheral effects on the cardiovascular system are severe and not tolerated.

Tryptophan and 5-hydroxytryptophan have a stimulatory action on the serotonergic system, but only when they are given in conjunction with an inhibitor of tryptophan 2,3-dioxygenase (e.g. nicotinamide) and/or an inhibitor of the decarboxylase (e.g. benserazide). In fact

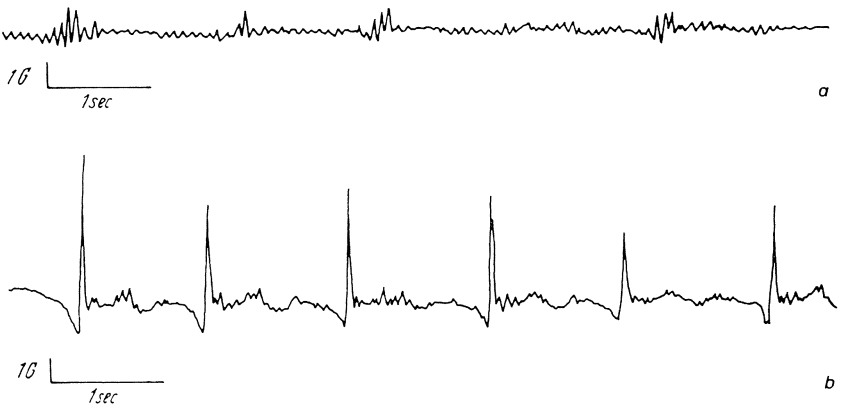


Fig. 32. Recording with a physiological acceleration transducer of a forward punch movement of the right hand in a 72 year old parkinsonian patient (disease duration 4 years). Upper curve: untreated. Kinetic energy 1 G, lower curve: 30 min. after 50 mg L-dopa i.v.; kinetic energy 5 G

benserazide also has an inhibitory effect on the former enzyme and has proved useful in minimizing the peripheral side effects of serotonin. 5-hydroxytryptophan has the distinct advantage of not being a substrate of tryptophan 2,3-dioxygenase. The disadvantage is, however, that it can be decarboxylated in all neurons with available aromatic amino acid decarboxylase, since this enzyme is unspecific. In this respect it is relevant that high doses of 5-hydroxytryptophan are found to increase dopamine metabolism (*Moir* 1971).

Stimulation of serotonergic activity in the brain could activate the serotonergic pathway from the dorsal raphe to the substantia nigra or striatum which would inhibit dopaminergic activity. Furthermore, a concurrent competition for transport sites across membranes (i.e. the blood-brain barrier and the neuronal membrane) would serve to restrict the availability of L-dopa and so decrease further the dopaminergic activity. The reverse is also true; high dose L-dopa treatment can restrict the transport of tryptophan into the brain and hence into serotonergic neurons. Dopamine is not easily formed from L-dopa in the degenerating dopamine neurons of advanced cases of Parkinson's

disease. So an excess of L-dopa may lead to an increased activity of extrastriatal dopaminergic neurons. Alternatively, the L-dopa may be metabolized in other neuronal systems, such as serotonergic neurons, leading to a release of serotonin and possible false dopamine release from serotonin systems. Tryptophan administration will displace this L-dopa from serotonergic neurons.

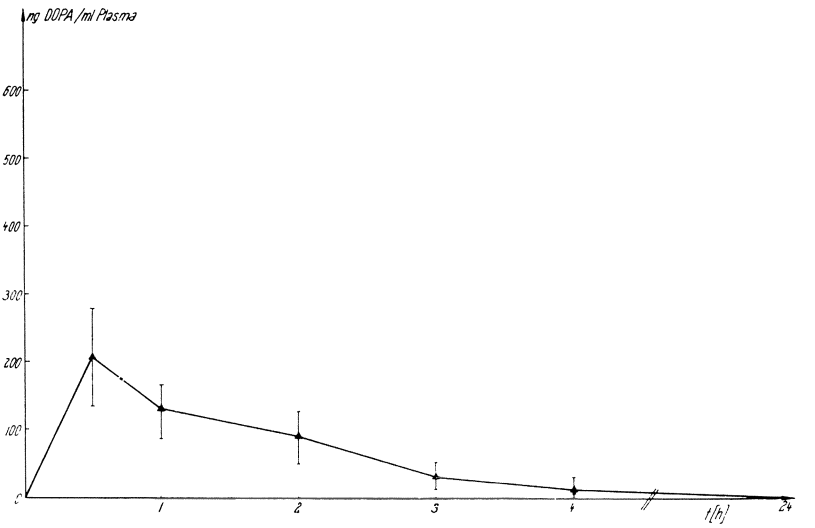


Fig. 33. Plasma dopa concentration after a single administration of 50 mg L-dopa i.v.; mean values ± s.d.; number of patients = 24 (*Birkmayer et al.* 1973a)

Kinetic effects deriving from a course of L-dopa treatment are only possible if a corresponding plasma level can be demonstrated. However, the L-dopa concentration in plasma need not necessarily correspond to the kinetic response. Plasma L-dopa is dependent on several factors: a) dose, b) body weight, c) resorption rate, and d) metabolism. It is apparent that a constant, optimal plasma level of the amino acid would be difficult to obtain in a straightforward L-dopa regimen. High doses must be used in order to overcome the fast metabolism of this "intermediate" amino acid, and these evoke strong peripheral side effects. Fig. 33 shows clearly how administration of 50 mg L-dopa leads to a maximum blood level of about 200 ng/ml, and that this concentration rapidly drops to ineffective levels. Hence multiple intravenous doses of L-dopa are required every day. While such a regimen is justified in certain critical states and may sometimes be the only choice, it is important to maximize the efficacy of the L-dopa.

Oral L-dopa has a similar effect on plasma levels (Fig. 34). *Cotzias et al.* (1970) and *Cotzias* (1971) have tried to overcome the limiting blood concentrations by administering extremely high L-dopa doses. While the therapeutic effects were excellent, side effects were intolerable.

Therefore other approaches were required. Soon after the discovery of L-dopa therapy, we in the neurology department of the Lainz

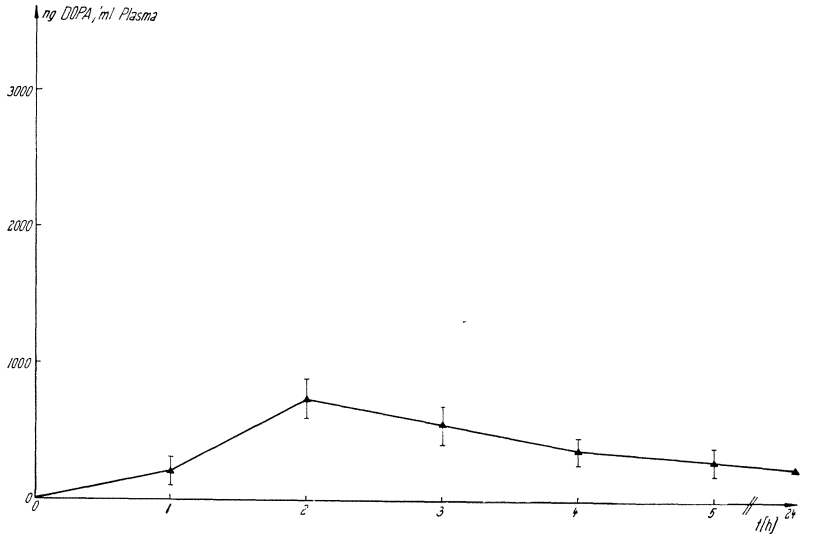


Fig. 34. Plasma dopa concentration after a single administration of 500 mg L-dopa orally; n = 4; mean values ± s.d. (*Birkmayer et al.* 1973a)

Geriatric Hospital, Vienna, tested some enzyme inhibitors. Various MAO inhibitors were investigated and showed positive effects on akinesia. They could not be used for long, however, without the appearance of peripheral and central (i.e. psychosis) side effects (*Birkmayer* and *Hornykiewicz* 1962). Later it was found that MAO inhibitors–when selective and hence "clean"– could indeed be used successfully in Parkinson's disease. So in principle our initial approach was correct. Another possible approach maximizing the L-dopa effect lay in the inhibition of aromatic amino acid decarboxylase.

Combination Treatment with L-Dopa and a Decarboxylase Inhibitor

In 1967, *Birkmayer* and *Mentasti* described the potentiation of L-dopa treatment by Ro4-4602 (N-Seryl-N-[2,3,4-trihydroxybenzyl]-hydrazine . HCl, benserazide). This substance was thought to be more

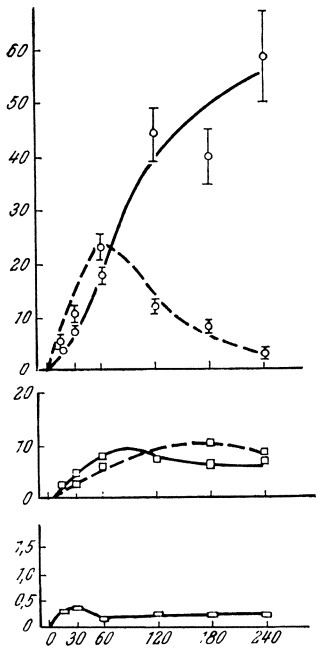


Fig. 35. Effect of benserazide on peripheral and central catecholamines. Change in ^{3}H dopa and ^{3}H catecholamines after i.p. administration of 50 mg/kg benserazide to rats 30 min. before 375 μg ^{3}H dopa i.p. (controls received ^{3}H dopa only. Upper curves: brain ^{3}H dopa only -----, brain ^{3}H catecholamines ——. Middle curves: plasma ^{3}H dopa -----, heart ^{3}H dopa ——. Lower curve: heart ^{3}H-catecholamines)

powerful than α-methyldopa and hence should be an effective antihypertensive. α-Methyldopa inhibits the decarboxylase, reduces the levels of dopamine and thereby has a sedative effect on patients with Huntington's chorea. However, benserazide was observed to have the opposite effect; these patients exhibited a severe increase in choreiform movements with the drug.

Correspondingly benserazide, in combination with L-dopa, not only brought about an improvement in parkinsonian patients, but also prolonged the kinetic effect. So a combination was found which met our original requirements and permitted the smallest possible L-dopa dose to have a relatively long efficacy (*Birkmayer* and *Mentasti* 1967). These findings were greeted with some scepticism; it was not at first clear how an inhibitor of the decarboxylase could improve parkinsonian akinesia when striatal dopamine had been shown to be significantly reduced. Subsequent investigations (*Bartholini et al.* 1967) showed that benserazide increases the amounts of L-dopa entering the brain

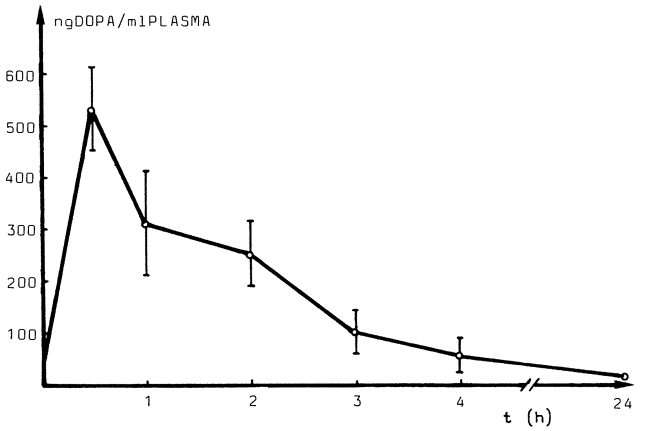


Fig. 36. Plasma dopa concentration after a single administration of 50 mg L-dopa i.v. plus 125 mg benserazide (oral 60 min. previous to L-dopa administration). n = 4; mean values ± s.d. (*Birkmayer et al.* 1973a)

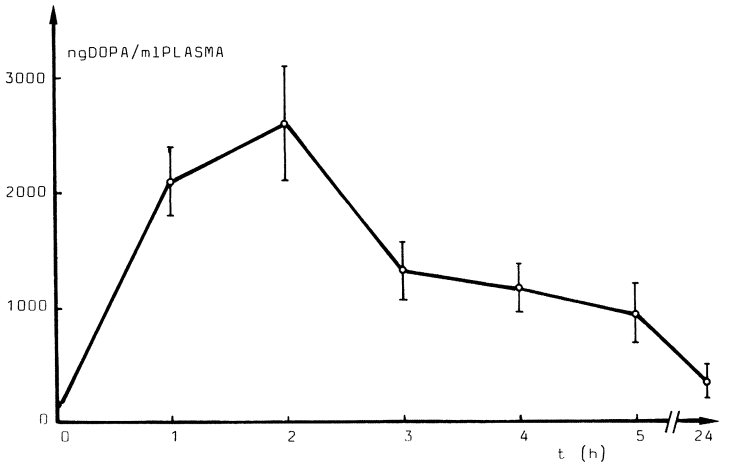


Fig. 37. Plasma dopa concentration after a single administration of 150 mg L-dopa plus 100 mg benserazide; n = 5; mean values ± s.d. (*Birkmayer et al.* 1973a)

(Fig. 35). Dopamine synthesis is also increased within the brain thus showing that benserazide is active peripherally, but not centrally. Fig. 36 shows plasma dopa after 50 mg L-dopa plus 125 mg benserazide. A prolonged increase in the concentration of dopa after oral administration of 150 mg L-dopa with 100 mg benserazide is demonstrated in Fig. 37. The L-dopa dosage can thus be kept low and yet be equally effective (*Birkmayer et al.* 1973a). In addition,

benserazide was found to have no effect on a range of important and routinely measured parameters in clinical biochemistry.

This therapeutic approach came of age in the appearance of "Madopar", a combination of L-dopa and benserazide. "Sinemet" is another combination using carbidopa as the decarboxylase inhibitor. Benserazide and L-dopa are mixed in the proportion 1 : 4, while the carbidopa : L-dopa ratio is 1 : 10. A clinical and biochemical comparison (*Podiwinsky et al.* 1979) was unable to show any difference between the two preparations in clinical efficacy, dopa plasma concentrations or in the biochemical parameters (*Birkmayer* and *Riederer* 1980). In pharmacological experiments carbidopa and benserazide can only be distinguished at doses far above those used clinically (*Lotti* 1973).

A different experimental approach enabled *Lieberman et al.* (1978) to demonstrate that in individual patients Madopar leads to earlier maxima in plasma dopa than does Sinemet. On the other hand, the half-life of dopa in Sinemet is significantly greater than with Madopar. These results indicate the equivalence of the two preparations, particularly when one considers all the various parameters, such as disease duration and progression etc.

At the beginning of the L-dopa era we chose primarily to administer 50–100 mg of the drug intravenously. Fortunately, in our first patients we were able to see an immediate improvement in akinesia which was unknown until then. The kinetic effect peaked at 2–3 hours after the application and was maintained for one to five days. Later we also gave oral L-dopa (100 mg three times daily) and saw an analogous effect, albeit with increased side effects (*Birkmayer* and *Hornykiewicz* 1962).

Some 30% of our patients had a very good response to L-dopa, while in 30% it had a moderate effect and 40% were non-responders. These results were confirmed by other european studies (*Gerstenbrand et al.* 1962, 1963, *Umbach* and *Baumann* 1964, *Hirschmann* and *Mayer* 1964, *Völler* 1968).

Our thoughts regarding the biochemical origin of the dopamine deficit lay in three main directions:

Firstly, the explanation that decreased dopamine reflected increased neuronal transmitter turnover was not consistent with the decrease of homovanillic acid in CSF and tissue samples (*Bernheimer et al.* 1962). Secondly, post-mortem investigations after treatment with L-dopa and various MAO inhibitors indicated increases in striatal noradrenaline and serotonin, but there was hardly any change in dopamine concentrations (*Bernheimer et al.* 1962, Fig. 38).

A third possibility was thought to be a blockade of dopamine synthesis. Phenylalanine administration (100 mg orally, 50 mg i.v.)

brought about improvement in mood, but had no effect on akinesia (*Birkmayer* 1965). p-Tyrosine similarly had no kinetic effect although a small effect could be seen when given in conjunction with NADH. Much higher dosage of L-tyrosine has shown mild effects in early stages of the disease (*Growdon et al.* 1982). In animal experiments,

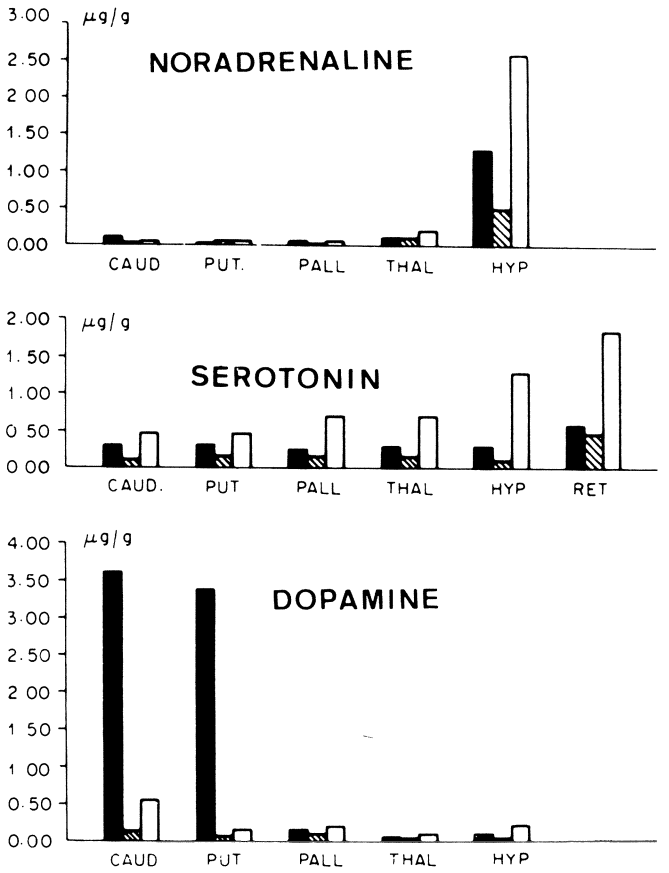


Fig. 38. Amine content of various brain regions in controls (1st column), parkinsonians (2nd column) and parkinsonians treated with L-dopa and an MAO inhibitor for several months before death (3rd column). (*Bernheimer et al.* 1962)

Spector et al. (1965) found that α-methyl-p-tyrosine inhibits the conversion of tyrosine to dopa by tyrosine hydroxylase. We found that 500 mg i.v. of this compound could inhibit hyperkinesia in five choreic patients for 24 hours (*Birkmayer* 1969a, Fig. 39). However, it diminished kinetic function in parkinsonian patients by over two-fold

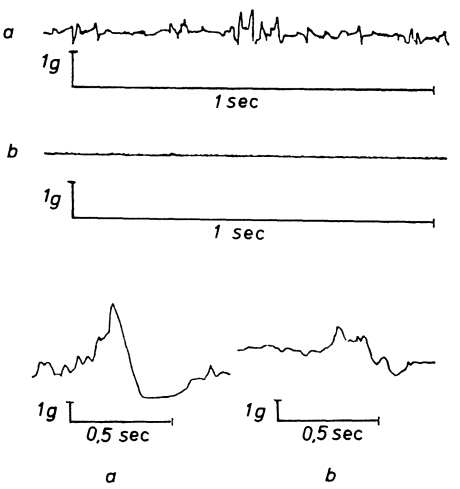


Fig. 39. The effect of α-methyl-p-tyrosine in a choreic and a parkinsonian. Upper traces: head movements in a choreic before *(a)* and 1 hour after *(b)* 500 mg α-methyl-p-tyrosine. Lower traces: left hand punch in a parkinsonian before *(a)* and 2 hours *(b)* 500 mg α-methyl-p-tyrosine. Kinetic energy is decreased from 3 G to 1.4 G

Table 18. *Comparison of L-dopa and Madopar treatment of parkinsonian patients*

Effect	L-dopa only (n = 108)	Madopar (n = 80)
None	11.0%	2.5%
Moderate	25.9%	13.5%
Good	40.7%	45.0%
Very good	22.4%	39.0%

(3 G to 1.4 G), as measured by a physiological acceleration transducer. These results led to our hypothesis that inadequate tyrosine hydroxylase activity was responsible for the dopamine deficiency. This has recently been verified by *Lloyd et al.* (1975), *Nagatsu et al.* (1977) and *Riederer et al.* (1978a).

With the introduction of the peripheral decarboxylase inhibitor, benserazide, we found that lower L-dopa doses were able to have the same antiakinetic effect. This resulted in a drop in peripheral side effects (*Birkmayer* and *Mentasti* 1967) and was confirmed by *Siegfried et al.* (1969), *Tissot et al.* (1969), *Barbeau et al.* (1971), *Barbeau* and *Roy* (1981) and *Yahr et al.* (1969). The results of a comparison of patients treated either with L-dopa alone or with L-dopa and

benserazide are shown in Tables 18 and 32a (*Birkmayer et al.* 1971). The combination therapy had a better success rate and decreased the number of non-responders.

There are two prerequisites for the successful treatment of Parkinson's disease with L-dopa:

1. The availability of the drug in the plasma must reach a certain level.

2. L-dopa in the brain must be utilized by dopaminergic neurons. The more these neurons degenerate the less effect L-dopa has, and it is particularly these presynaptic neurons which synthesize and store dopamine which are lacking (Fig. 40).

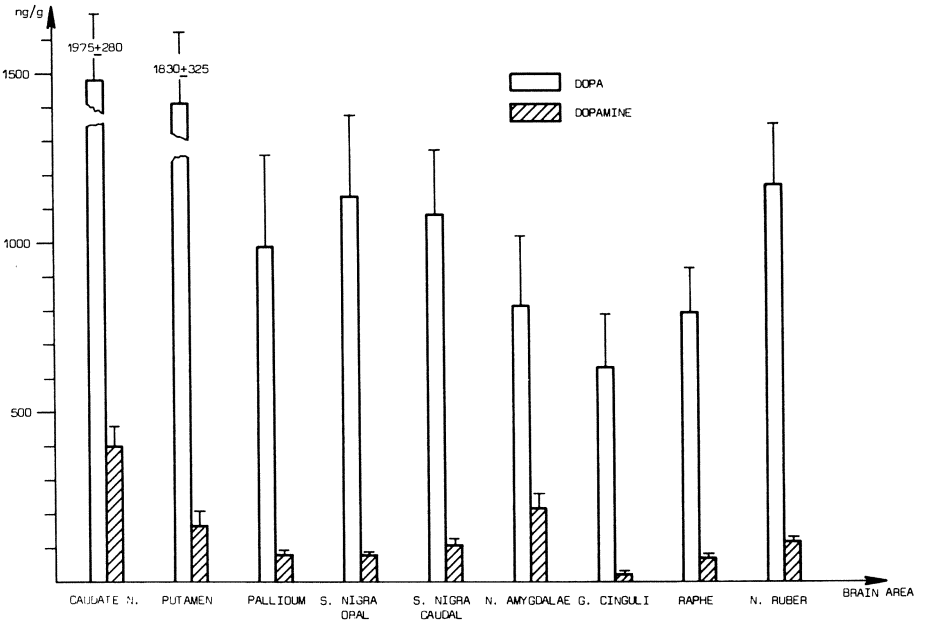


Fig. 40. Distribution of dopa/dopamine in various areas of post-mortem brains from 3 parkinsonian patients after L-dopa administration (750 mg L-dopa/benserazide), means ± s.e.

The first requirement is fulfilled best by combination treatment with decarboxylase inhibitors. L-dopa levels are higher and last longer (compare Figs. 34 and 37; *Birkmayer et al.* 1973a). A two year treatment shows that the improvement in all parkinsonian symptoms is a long-term one (Fig. 41).

In 1967 *Cotzias* first reported on the treatment of Parkinson's disease with very high doses of DL-dopa. Because of the toxic effects of

the D-isomer he later administered pure L-dopa: up to 10 g daily. The high doses exhibited especially good kinetic effects but inevitably produced correspondingly high side effects. Hyperkinesias, dopa psychoses and on-off effects were described (*Cotzias et al.* 1969, *Cotzias* 1971), although they were not novel observations. Fluctuations in motor ability and periods of akinesia have been seen by all neurologists. These akinetic crises (chronic off-phases) and their possible biochemical origins have already been discussed.

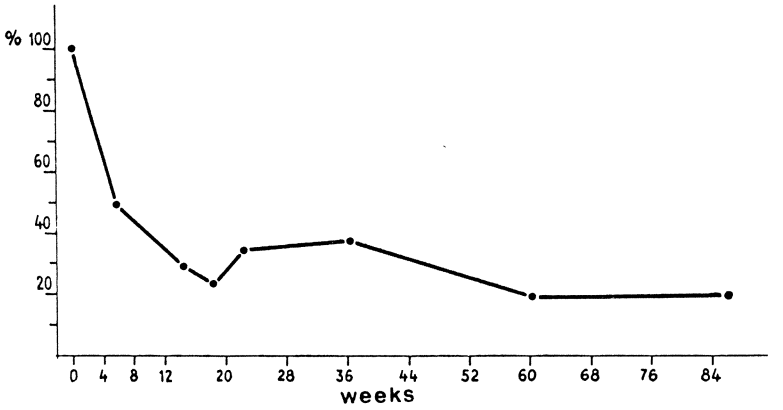


Fig. 41. Total score of akinesia, rigidity and tremor (on the Webster scale), indicating the long-lasting improvement due to combined dopa treatment

The combination of a peripheral decarboxylase inhibitor with L-dopa overcame many limitations of the latter drug. The improved kinetic effect permitted lower L-dopa doses to be used. One of our therapeutic principles, to use the lowest effective dose in chronic treatment, has been justified by many years' experience (*Birkmayer* 1971). Unnaturally high doses of L-dopa might accelerate the progressive neuronal disturbance through an unphysiologically accentuated pre- and postsynaptic dopaminergic stimulation (*Fahn* and *Barrett* 1979). L-dopa might then be a self-limiting drug (*Hornykiewicz* 1979).

So far Madopar and Sinemet are the only preparations of the combined treatment which are available. In our experience and that of others (*Markham* and *Diamond* 1981) low doses should be used as early as possible. Madopar is availabe in 250, 125 and 62.5 mg doses. These various dosages are very practical, since at the lower doses used initially there are essentially no side effects. Furthermore, the circadian variations in performance require individual dosage schedules. Depending on the clinical picture, 250 mg can be given in the morning

followed by midday and evening doses of one Madopar 125 or 62.5. There are numerous patients who, with only a single capsule of Madopar 125, can move normally all morning. The afternoon akinesia can be treated with 250 mg at midday followed by a late evening dose of Madopar 125. Other patients start with Madopar 250 and only need a dose of 62.5 mg in the afternoon and evening. Thus treatment can be optimized to the individual patient's needs with a minimal occurrence of side effects. Sinemet, based on 250 mg or 100 mg L-dopa doses, can be administered analogously and adjusted to the requirements of the individual. Positive reports have been published by *Calne et al.* (1971), *Papavasiliou et al.* (1972), *Marsden* (1973), *Mars* (1974), *Markham* and *Diamond* (1974), and *Yahr* (1978, 1981). While we have found no significant difference between the two preparations (*Podiwinsky et al.* 1979), the fact that there are two is advantageous since if one preparation loses its antiparkinsonian effect, transferring to the other may restore the effect. We have even used both Madopar and Sinemet concurrently. A personal impression (of W. B.) is that Sinemet is more frequently associated with side effects such as vomiting, nausea and dizziness. These can be avoided by the addition of carbidopa (25 mg) or benserazide (50 mg) which are unfortunately not commercially available. Madopar and Sinemet have brought about a therapeutic break-through in Parkinson's disease, since L-dopa treatment alone is limited by its side effects in a large percentage of patients (*Cotzias* 1971, *Fahn* and *Barrett* 1979).

Table 19 summarizes 15 years of experience with L-dopa treatment in 1,414 patients. A 10–20% improvement was found in 21.5% of

Table 19. *% Improvement of the disability after long-term combined L-dopa treatment*

Duration of treatment (yrs)	Number of parkinsonian patients	Disability score					
		10	20	30	40	50	60
1	147	3.0	5.0	2.0	0.5	–	–
3	455	0.5	6.0	11.5	8.0	3.5	1.5
5	315	–	4.5	6.0	6.5	3.5	2.0
7	210	–	1.5	3.0	7.5	2.5	0.5
9	210	–	–	3.0	8.5	2.0	0.5
11	42	–	–	0.5	1.5	1.0	–
13	21	–	–	–	1.0	0.5	–
15	14	0.5	0.5	–	–	–	–
Total		4.0	17.5	26.5	33.5	13.0	4.5

cases, a result typical of that found with the older anticholinergic drug treatment. However, this group represents the non-responders. A 30–40% improvement is found in 60%, while 17.5% of cases show a 50–60% improvement, representing near normal motor function. This summary clearly shows how the improvement due to L-dopa begins to diminish between approximately three and five years treatment. The

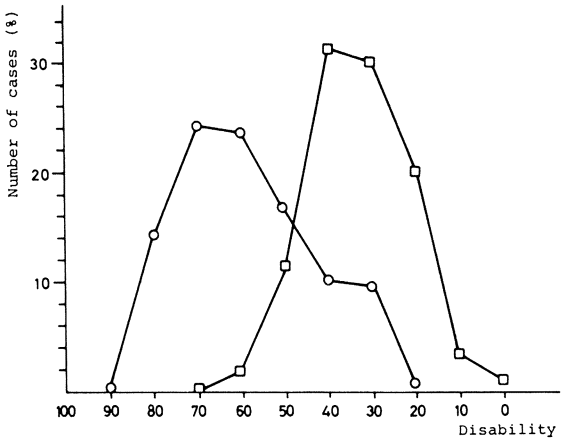


Fig. 42. Disability in Parkinson's disease before and after combined L-dopa treatment. ○ before combined L-dopa therapy, □ after combined L-dopa treatment

success of adjuvant deprenyl does not appear here since this treatment has only been employed for the last five years. Furthermore, it can be seen that the deterioration occurs earlier in those patients with only a small response to treatment. The patients with a 10% improvement deteriorate after the first year of treatment, while in patients with 40%, 50% and 60% improvement in disability score, the respective times are nine, seven and five years.

Fig. 42 shows the disability range of patients in 1974, before deprenyl was introduced. L-dopa treatment in 255 patients provides a mean disability of 32.95, while prior to the treatment their score was 58.45, indicating improvement of 55% (*Birkmayer* 1974, *Birkmayer et al.* 1974 a, b).

Treatment with Tetrahydrobiopterin

The dramatic loss of tyrosine hydroxylase activity in the nigro-striatal pathway in Parkinson's disease is well established (*Lloyd et al.* 1975, *Nagatsu et al.* 1977, *Riederer et al.* 1978 a). The activity of this enzyme depends on the availability of a co-factor, presumably

tetrahydrobiopterin (BH_4). Recently a substantial loss of BH_4 has been found in parkinsonian striatum (*Nagatsu et al.* 1981a) and cerebrospinal fluid (*Lovenberg et al.* 1979). The loss in concentration of the co-factor was found to be less than in the activity of tyrosine hydroxylase. Administration of BH_4 or analogues to patients with Parkinson's disease was first described by *Birkmayer* and *Riederer* (1980). Low doses of BH_4 (25 mg i.v./day as single dose) have been found to be of therapeutical value only in early stages of the disease in mild to moderately affected patients, whereas no response to this treatment could be observed in advanced stages of the disease. More recent clinical findings by *Nagatsu et al.* (1982) and *Curtius et al.* (1982) confirm the therapeutic efficacy of BH_4, while *Le Witt et al.* (1982b) could not find any improvement in parkinsonian disability in patients who had not received previous Sinemet therapy.

Although only about 1–2% of BH_4 crosses blood-brain barrier, two reasons might explain its therapeutic efficacy.

1. More BH_4 crosses the blood-brain barrier in Parkinson's disease because of disturbances at this level.

2. BH_4 exerts its action at peripheral catecholaminergic sites. The latter assumption would be in line with findings showing a loss of tyrosine hydroxylase activity in the adrenal medulla of patients with Parkinson's disease (Table 3).

Although this type of treatment is as yet, little understood, it seems to be a promising new approach. Co-factors with higher lipophilic properties might give better therapeutic results.

Amantadine

In 1969 *Schwab et al.* reported the favourable kinetic effect of amantadine treatment. In our experience this effect, while useful, does not approach that of L-dopa.

The mechanism of action of 1-aminoadamantane (amantadine) and its derivative 1-amino-3,5-dimethyl adamantane is not completely understood. Amantadine may work by stimulating dopaminergic, noradrenergic and serotonergic neurons. The derivative is effective against rigidity and tremor (*Fünfgeld* 1976) and may act on dopamine receptors (*Svensson* 1973) or by increasing dopamine and serotonin release from nerve endings (see *Wesemann et al.* 1979, 1980).

The general practitioner frequently prescribes amantadine at the beginning of the disease, often in combination with an anticholinergic drug. This combination is certainly adequate for the minor symptoms of the initial stages, and has the great advantage of having practically no side effects. The side effects which can appear are primarily sleep disturbances, excited agitation and livedo reticularis. Generally

amantadine is given in doses of 300–500 mg daily. *Parkes* (1971) recommends amantadine in mildly-affected cases. *Danielczyk* and *Korten* (1971) prefer amantadine plus L-dopa in cases of moderate disability. In our experience it is a useful adjunct to L-dopa, but we have not observed any substantial improvement using amantadine alone. However, i.v. amantadine infusions are frequently very successful in treating initial akinetic crises (*Danielczyk* 1973, 1980); we employ daily amantadine infusions plus one or two 25 mg L-dopa ampules. Psychoses appear especially after oral amantadine; this suggests that there is a stimulation of (possibly limbic) dopamine receptors indicating that the pharmacological action of the drug includes a dopamine-potentiating effect.

In Madopar and Sinemet it seemed that we have an optimal treatment for Parkinson's disease. However, we shall describe how they lose efficacy after some five years and that there is then no response to increased doses of dopa-based medication.

Combined Treatment with MAO Inhibitors

Iproniazid, introduced by *Fox* (1952) for the treatment of patients with tuberculosis, was observed to improve their mental state. That year *Zeller* and *Barsky* (1952) showed iproniazid to be an inhibitor of mitochondrial MAO, and a few years later *Crane* (1956) reported its beneficial effects on psychiatric diseases. This led *Kline* (1958) to use the MAO inhibitor as a "mental energizer" to treat depression. The subsequent synthesis of other MAO inhibitors (*Pletscher et al.* 1961) helped provide a basis for our understanding of their pharmacological action. This opened the door to the application of MAO inhibitors to Parkinson's disease, where they could potentiate the kinetic effects of L-dopa (*Birkmayer* and *Hornykiewicz* 1962). The side effects, which included toxic psychosis, hypotension and gastrointestinal complaints, prevented the use of such a regimen in clinical practice.

A novel, irreversible MAO inhibitor, clorgyline, was described by *Johnston* in 1968. With this compound he demonstrated a substrate specificity in its inhibition of the enzyme. Serotonin oxidation was inhibited by very low concentrations, while tyramine and dopamine oxidation exhibited biphasic inhibition curves. These results were interpreted as indicating two forms of the enzyme which differed in their substrate specificity and their sensitivity towards clorgyline. They were classified as type A, active against serotonin, noradrenaline and tyramine, and type B, less sensitive to clorgyline and active against benzylamine, phenylethylamine, tryptamine and tyramine (*Houslay et al.* 1976, *Yang* and *Neff* 1973, *Youdim* and *Holzbauer* 1976, *Squires* 1972).

Deprenyl

Some years earlier *Knoll et al.* (1965) discovered a MAO inhibitor, deprenyl, which was later found to be a relatively specific inhibitor of the type B form of the enzyme. In vitro studies showed deprenyl to be more sensitive towards MAO in human brain than is clorgyline (*Youdim* and *Holzbauer* 1976) since some 80% of activity is of the B type. Certainly dopamine in rat brain (which has relatively less MAO B) increases after deprenyl treatment (*Neff et al.* 1974, *Dzoljic et al.* 1977). MAO activity of thrombocytes is almost exclusively of the B form (*Murphy* 1976) while intestinal MAO approaches 80% of the A type. Thus clorgyline has a greater effect here than does deprenyl.

We mentioned above that the use of unspecific MAO inhibitors is associated with severe side effects (*Hunter et al.* 1970). The most important is the hypertensive crisis. This occurs particularly in patients receiving foods containing large amounts of tyramine ("the cheese effect") and other neuroactive amines or amine precursors (*Youdim* 1976). In contrast to classical MAO inhibitors such as tranylcypromine and pargyline, deprenyl antagonizes this tyramine effect (*Knoll* 1976, *Knoll* and *Magyar* 1972, *Finberg et al.* 1981). This may reflect its inhibition of noradrenaline release. However, it has no action on noradrenaline stores, nor does it affect the sensitivity of noradrenergic (*Knoll* 1976) or dopaminergic D_1 receptors (*Riederer et al.* 1978b). For further details on the pharmacology of deprenyl see *Knoll* (1981, 1982).

Initial clinical trials of deprenyl showed it to have excellent effects on akinesia and mental state in Parkinson's disease (*Birkmayer et al.* 1975, 1977a, 1978; Tables 20 and 25), effects which will be described in detail later on. However, it should be mentioned that at the time of these first trials (we started using deprenyl at the end of 1974) there was little theoretical reason for the successful administration of the drug. Animal experiments had shown dopamine to be a substrate for both A and B forms of MAO. Only later was it shown that our clinical results had a theoretical basis; *Glover et al.* (1977) showed dopamine to be a MAO B substrate in human brain. This confirmed our supposition that deprenyl had a selective stimulatory action on the dopaminergic system (*Birkmayer et al.* 1975).

Why then did we decide to investigate deprenyl in Parkinson's disease? The following properties of the drug suggested that its clinical use might be worthwhile:

1. Its fast therapeutic action (20–30 mins i.v.; 1–2 hours orally). This was a great improvement on the slow onset of inhibition (approximately 2 weeks) brought about by the older, unselective MAO inhibitors.

Table 20. *Improvement of "on-off" periods in parkinsonian patients with previous L-dopa therapy after treatment with deprenyl. Results taken from Birkmayer et al. (1975)*

Cases	Sex	Age (yrs)	Duration (yrs)	L-dopa therapy before deprenyl (yrs)	% disability before deprenyl	% disability after deprenyl	Off-period before deprenyl (hrs)	Off-period after deprenyl
21	m	66.14	7.95	4.05	61.20 ($p<0.001$)	34.29	3 ± 1	Disappearance of severe off-periods
23	f	70.09	10.13	5.13	66.52 ($p<0.001$)	38.91	3 ± 6	

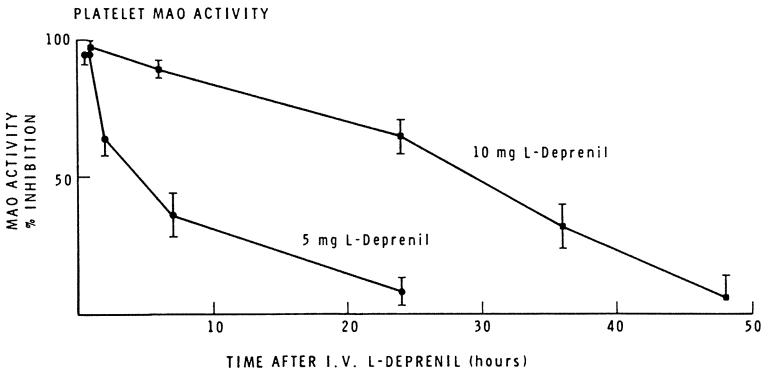


Fig. 43. MAO activity in platelets after (–)deprenyl treatment. Uninhibited platelet MAO activity was 5.62 ± 0.68 nmoles/min/10^9 platelets using kynuramine as a substrate. 5 or 10 mg of (–)deprenyl was given as a single i.v. dose at 8 a.m. to 10 volunteers (age 60 ± 2.5 years; sex: 6 males, 4 females). Values are the means ± standard error

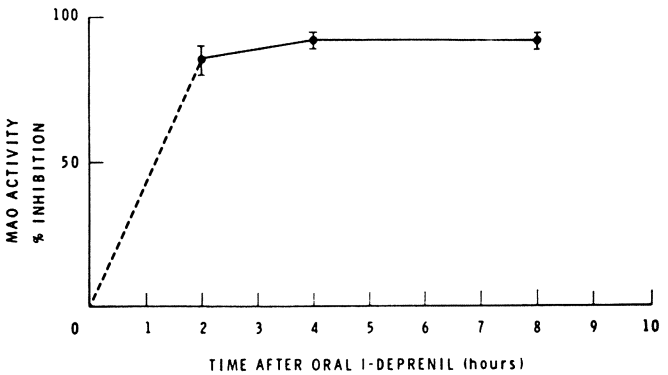


Fig. 44. Effect of oral L-deprenyl on platelet MAO activity. Each patient acted as his (her) own control and received 10 mg L-deprenyl orally at 7 a.m. Blood-samples were obtained before oral L-deprenyl and at intervals after ingestion of the drug. MAO activity was determined in the platelets using kynuramine as substrate. The results are the ± s.e.m. of 5 subjects

2. No dramatic side-effects at therapeutic doses. *Varga* and *Tringer* (1967) made no report of any hypertensive crises on administration of 40–60 mg deprenyl daily.

3. Deprenyl should have a specific action on brain MAO, while peripheral MAO (mainly type A) would probably not be inhibited. This is consistent with the lack of peripheral side-effects.

4. Our results relating to the diurnal rhythm of MAO suggested that off-periods might be due, to some extent, to the increased

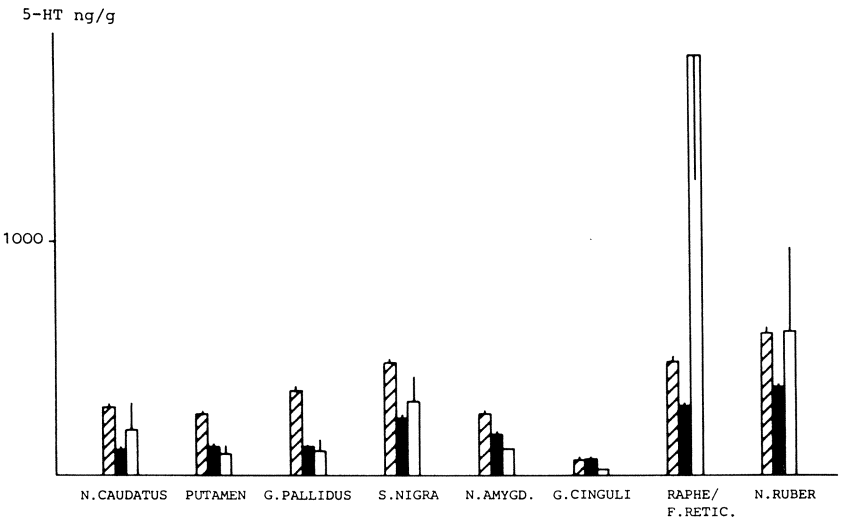


Fig. 45a

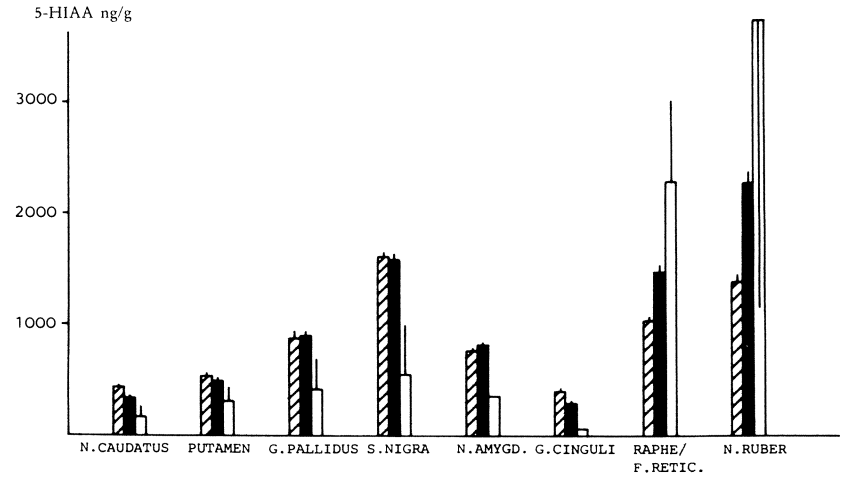


Fig. 45b

Fig. 45a and b. Serotonin and 5-hydroxyindole acetic acid (5-HIAA) in various areas of the human brain: □ 9 controls, ■ 6 patients with Parkinson's disease with usual therapy, □ 3 patients with Parkinson's disease [therapy: treatment of the akinetic, therapy resistant endstage with L-dopa (50 mg i.v.) plus (–)deprenyl (10 mg daily; duration of therapy about 6 days). All three groups are comparable regarding age (62–72 years) and post-mortem time (5–11 hours). Controls died by cardiac failure, heart infarction or bronchopneumonia]. (From *Birkmayer* and *Riederer* 1980)

metabolism of dopamine between 12 and 6 pm. Thus a MAO inhibitor might possibly diminish these short off-phases (*Birkmayer et al.* 1975).

A series of investigations were initiated in order to explain the clinical success of deprenyl. MAO activity in thrombocytes was used to monitor the action of the inhibitor. Intravenous administration of 10 mg can inhibit the enzyme by more than 90% in under 30 minutes (Fig. 43), while the same amount orally takes about two hours (Fig. 44). A single dose of deprenyl has a prolonged inhibitory effect. The much faster loss of inhibition after a 5 mg dose (Fig. 43) may be explained by the faster metabolic removal of lower deprenyl doses. The maximal inhibition of platelet MAO can be correlated with clinical improvement as measured by the disability score. Of course these peripheral investigations do not reveal anything about the inhibition of MAO in the brain. Post-mortem brain studies have provided evidence for an effective inhibition of this enzyme.

Parkinsonian patients who had received deprenyl as a treatment in the terminal stage of the disease showed an extensive inhibition of brain dopamine oxidation, while serotonin oxidation was substantially greater (Table 21). This selectivity towards dopamine as a substrate was

Table 21. *Inhibition (%) of human brain MAO after short-/long-term treatment with (–)deprenyl*

Substrate:	Dopamine		5-Hydroxytryptamine	
Treatment:	Short-term	Long-term	Short-term	Long-term
Brain regions				
Caudate nucleus	85.6 ± 1.8	89.0	65.7 ± 5.0	70.3
Putamen	83.4 ± 2.2	89.2	61.7 ± 5.7	66.1
G. pallidus	86.5 ± 1.9	90.5	70.8 ± 3.7	74.4
Thalamus	86.0 ± 4.2	77.3	50.0 ± 6.8	55.7
S. nigra	88.0 ± 2.2	88.7	74.5 ± 4.0	66.7
Raphe + Ret. form.	86.0 ± 2.6	85.4	70.6 ± 4.1	72.3
N. amygdalae	82.0 ± 2.8	85.6	70.3 ± 4.5	69.8

Means + S.D. Short-term treatment: 7 patients with idiopathic Parkinson's disease; age: 72.0 ± 1.3 yrs; duration of the disease: 9.8 ± 1.8 yrs; 2 males, 5 females; post-mortem time: 7.6 ± 2.3 hrs; storage of tissue at –70 °C. Treatment: long-term Madopar treatment (3 × 250 mg daily). To improve the severe akinetic crises (–)deprenyl (10 mg daily) was additionally given 6.0 ± 1.8 days before death.

Long-term treatment: one male patient with parkinsonism (age: 81 yrs) was treated over 4 years with 10 mg (–)deprenyl daily in addition to Madopar (625 mg daily). Duration of the disease: 5 yrs; post-mortem time: 3.0 hrs; last dosage before death: 8 hrs; storage of tissue at –70 °C.

upheld even after four years of deprenyl treatment (Table 21). Certainly it is this selectivity towards dopamine, without effecting an increase in brain serotonin (Figs. 45a and 45b), which is the basis of deprenyl's efficacy in potentiating dopa-based drugs (*Riederer et al.* 1978c). However, it is important to mention that deprenyl loses its selectivity at doses above 10 mg/day. In fact, 100 mg/day treatment of a terminal parkinsonian patient for seven days increased both dopamine and serotonin content of the brain (*Riederer et al.* 1978c; Table 22). Animal experiments by *Knoll* (1978) showed selectivity at doses up to 0.15 mg/kg, and *Waldmeier* and *Felner* (1978) found deprenyl to lose its selectivity at 1 mg/kg. The optimal dose in the clinic, which is at 1 mg/10 kg body weight (*Riederer et al.* 1978c), is consistent with these data; higher concentrations may lead to a loss of selectivity (*Riederer et al.* 1980, 1983a).

Deprenyl treatment is started at 10–15 mg with a subsequent drop, after one or two weeks, to 1 mg/10 kg body weight in order to retain selective inhibition (*Riederer* and *Reynolds* 1980, *Riederer et al.* 1981a). The deliberate use of 15 mg or more to obtain unspecific inhibition with deprenyl has other possible indications (see *Youdim et al.* 1979).

Table 22. *Changes in the concentration of biogenic amines (% of controls) in Parkinson's disease (n = 9) without (–)deprenyl compared to postencephalitic Parkinson's disease (n = 1) treated with 100 mg (–)deprenyl*

	% of controls			
	Dopamine		Serotonin	
	M. Parkinson without deprenyl (9)	Postenc. Park. with deprenyl (1)	M. Parkinson without deprenyl (9)	Postenc. Park. with deprenyl (1)
Caudate nucleus	12	2	42	68
Putamen	5	3	50	84
G. pallidus	17	79	35	91
S. nigra	20	18	58	152
N. amygdalae	100	155	65	114
G. cinguli (cortex)	100	238	100	247
Raphe + Ret. form.	35	86	60	178
Red nucleus	20	31	62	138

Means; MAO-activity (kynuramine as substrate) was inhibited between 95 and 100% in all brain areas; age of the postencephalitic Parkinson: 68 yrs; male; the patient died during an akinetic crisis; patients without (–)deprenyl were on an usual antiparkinsonian therapy consisting mainly of Madopar (3 × 125 mg up to 3 × 250 mg/day).

The dopaminergic action of deprenyl can, in some patients, be reflected by the acute appearance of a dopa psychosis. This psychosis cannot be prevented by the action of β-blockers (*Birkmayer et al.* 1974).

Knoll et al. (1965) showed behavioural changes in animals to occur with deprenyl. These changes include increased motor activity and stereotypy. Other workers have shown that these effects of deprenyl differ from those of other MAO inhibitors (*Christmas et al.* 1972, *Green* and *Youdim* 1975). Deprenyl more closely resembles (+)amphetamine in its effects, but a stimulation of dopamine release, as produced by (+)amphetamine, has been ruled out (*Knoll* 1978). However, it has recently been shown that deprenyl is metabolized to methamphetamine and amphetamine (*Reynolds et al.* 1978), this combination also having a central action including dopamine release (*Moore* 1977). *Reynolds et al.* (1978) have also demonstrated amphetamine in post-mortem brain tissue from deprenyl-treated patients (Table 23). However, none of these patients, nor any of the 400 or so who were treated with deprenyl, exhibited any amphetamine-like behaviour. It is also important to note that none of the patients had withdrawal symptoms. These have so far only been reported in four patients who had over 40 mg daily (*Lees et al.* 1977). There is no positive evidence that these metabolites of deprenyl are

Table 23. *Amphetamine* in deprenyl-treated parkinsonian brain (Reynolds et al. 1978)*

Patient	P1	P2	P3	P4
Last deprenyl before death (hours)	24	58	2	9
Post-mortem time (hours)	3	18	3	17
Deprenyl dose (mg/day)	10	5	10	10
Treatment period (days)	4	4	3	18
Amphetamine (ng/g):				
Putamen	35.0	3.3	–	–
G. pallidus	25.8	2.8	37.4	54.5
Caudate N.	30.6	3.3	–	52.5
Thalamus	26.2	5.9	35.5	56.3
Hypothalamus	22.0	1.4	–	–
Hippocampus	35.5	6.5	28.9	50.0
Raphe + ret. form.	32.4	–	29.0	38.1
Red nucleus	40.3	3.6	–	–
N. accumbens	23.1	1.3	26.5	–

– not estimated. * amphetamine could not be detected in controls.

Table 24. *2-Phenylethylamine in normal and deprenyl-treated parkinsonian brain (Reynolds et al. 1978)*

	Normal subjects				Parkinsonian
	N1	N2	N3	N4	P1
Post-mortem time (hrs.)	11	3	6	3	3
PE (ng/g):					
Putamen	–	0.7	0.3	–	4.4
G. pallidus	–	0	0.3	0.2	3.0
Caudate N.	0	1.5	1.0	1.0	6.4
Thalamus	0.3	0.5	1.0	1.0	4.2
Hypothalamus	0.8	–	0.5	–	2.2
Hippocampus	–	–	0.5	0.2	2.2
Raphe + ret. form.	0	–	0.3	–	4.1
Red nucleus	0	–	0.5	–	5.7

– not estimated. PE = 2-phenylethylamine.
0 below the limit of detection.

important for the therapeutic action of the drug (*Reynolds et al.* 1980c, *Elsworth et al.* 1982).

A further possibility for the mechanism of action of deprenyl is connected with phenylethylamine, a preferred substrate of MAO type B (*Yang* and *Neff* 1973). This compound is specifically increased in the brains of parkinsonian patients after deprenyl treatment (*Reynolds et al.* 1978; Table 24). Phenylethylamine has an amphetamine-like action (*Mantegazza* and *Riva* 1963), including a stimulation of dopamine release (*Baker et al.* 1976), and hence may contribute to deprenyl's potentiation of L-dopa.

Our first report on deprenyl indicated that it improved akinesia in patients who had received several years' Madopar treatment (*Birkmayer et al.* 1975; Table 20). The disability score was reduced from 64 to 36 on average, this corresponding to a 56% improvement in motor ability. The on-off effect was removed in 41 of 44 patients, although patients in a severe akinetic crisis, from which they do not recover, do not respond to deprenyl. The clinical results of a further study of Madopar treatment with and without additional deprenyl in 223 patients (*Birkmayer et al.* 1977a) are summarized in Table 25a, b and Fig. 46. The improvement in patients who had the disease for up to 6 years was 53%; in those with 7–15 years parkinsonism the improvement was 61%. Fig. 46 illustrates how Madopar plus deprenyl can give an even greater improvement than Madopar alone.

Table 25a. *Improvement of functional disability after oral treatment with Madopar alone or Madopar plus L-deprenyl in parkinsonian patients (Birkmayer et al. 1977a)*

Duration of Parkinson's disease (yr)	Age (yr)	Mean of duration of the disease (yr)	% disability before Madopar treatment	Madopar treatment (mo)	% disability after Madopar treatment	Madopar + L-deprenyl treatment (mo)	% disability after L-deprenyl + Madopar treatment
Group I:							
0–6	68.45 ±0.81	3.99 ±0.14	54.30 ±1.47*	18.47 ±1.53	36.50 ±1.39*†	6.33 ±0.28	25.31 ±1.34†
No.	115 (m = 60, f = 55)	115	115	115	110 (m = 58, f = 52)	115	110
Group II:							
7–15	69.39 ±0.70	10.90 ±0.38	60.05 ±1.33‡	48.35 ±2.51	37.23 ±1.39‡§	7.01 ±0.29	23.35 ±1.38§
No.	108 (m = 48, f = 60)	108	108	108	94 (m = 40, f = 54)	108	94

No. = number of cases. *–* correlation $t = 8.6605$, $p < 0.001$; †–†, $t = 5.8053$, $p < 0.001$; ‡–‡, $t = 11.5802$, $p < 0.001$; §–§, $t = 4.586$, $p < 0.001$.

Table 25b. *Side-effects during Madopar plus (–)deprenyl treatment of parkinsonian patients (from Birkmayer et al. 1977a)*

Side-effects	No. of cases*	
	Group I	Group II
Abnormal involuntary movements (dyskinesia)	0 (0)	14 *(13)*
Psychosis (vivid dreams, delirium, hallucination, delusion)	2 *(1.8)*	12 *(11)*
Nausea	5 *(4)*	3 *(3)*
Orthostatic hypotension	2 *(1.8)*	3 *(3)*

* number of Madopar + (–)deprenyl treated patients was 115 in group I and 108 in group II. Medication was 250 mg Madopar three times daily plus 10 mg (–)deprenyl once daily orally.

Figures in parentheses give percentage incidence of side-effects.

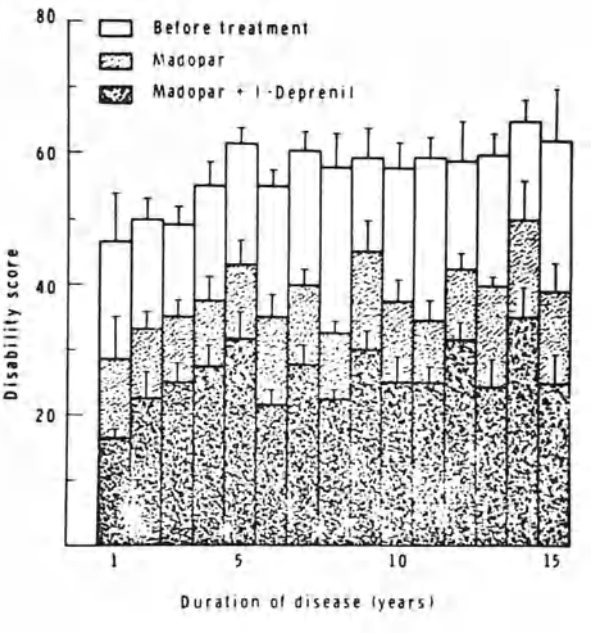


Fig. 46. Disability scores of same parkinsonian patients before and after treatment with Madopar alone and with Madopar plus L-deprenyl. Numbers of Madopar deprenyl-treated patients and Madopar-treated patients are the same

Table 26. *Duration of Parkinson's disease after long-term treatment with (–)deprenyl*

Duration of Parkinson's disease	Number of outpatients	
	without Deprenyl	with Deprenyl
5–10 years	238	89
–15 years	73	143
–20 years	11	41
–25 years	1	11
Average duration (yrs)	9.0 ± 2.7	12.0 ± 3.9[1]
	Number of deceased patients	
	without deprenyl	with deprenyl
5–10 years	125	30
–15 years	23	50
–20 years	2	15
–25 years	0	1
Average duration (x ± S.D.)	8.4 ± 2.1	11.8 ± 3.5[1]

[1] $p < 0.0005$

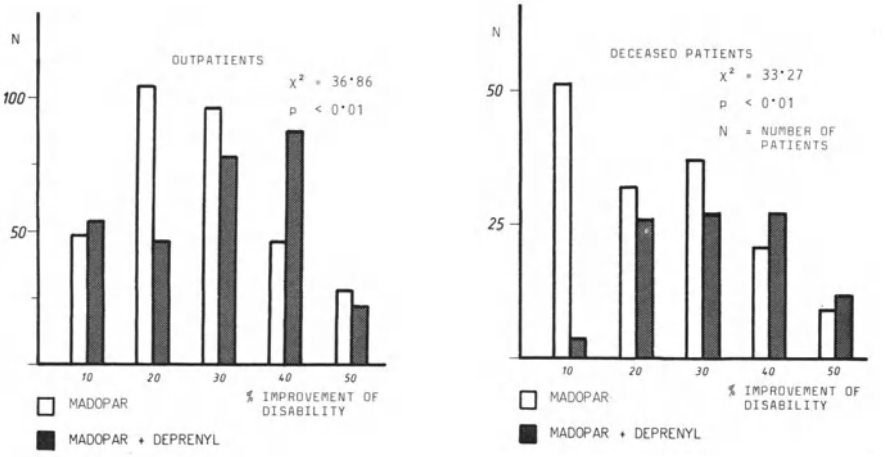


Fig. 47. Further improvement of the disability in parkinsonism by deprenyl

The disability of the parkinsonian patient increases as the disease progresses, whether the patient is untreated or receives L-dopa. On the other hand, however, motor function remains approximately constant over the years when deprenyl is given. This is certainly a result of the dopa-sparing effect of deprenyl, thereby minimizing or delaying the degenerative process. Furthermore, there are benign cases of Parkinson's disease which have a relatively long disease duration and later onset of side effects (see p. 152); these cases exhibit a good response to combined deprenyl-Madopar treatment while malignant and critically ill patients do not respond.

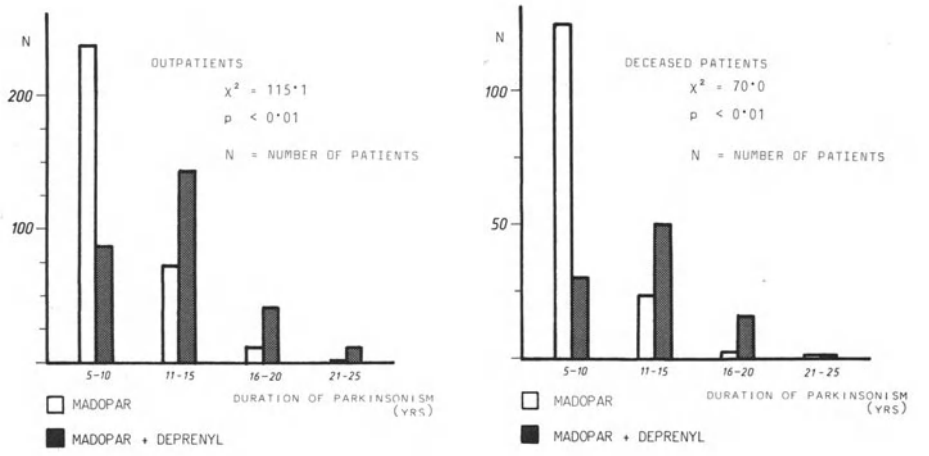


Fig.48. Deprenyl prolongs the therapeutic efficacy of combined L-dopa treatment in Parkinson's disease

In a more recent long-term study the clinical efficacy of deprenyl was studied in 285 outpatients and another group of 96 patients with Parkinson's disease, who died in the course of the disease (Table 26). Deprenyl was administered in addition to the basic treatment (anticholinergics, amantadine, and combined L-dopa treatment) in a dosage of 10 mg/day. The duration of deprenyl treatment ranged from two to eight years. Deprenyl shows antiakinetic efficacy (Fig. 47) resulting in the reduction of L-dopa doses, and has beneficial effects on on-off phases. Furthermore, it leads to a prolongation of the disease process (Fig. 48). Therefore, inclusion of deprenyl into therapy leads to a more physiological treatment of Parkinson's disease, and to improved therapeutical strategies in aged persons (*Birkmayer et al.* 1982b).

The studies on deprenyl have been generally confirmed by many others (for review *Yahr* 1981, *Birkmayer et al.* 1982a). Less

therapeutical efficacy has been noted by *Stern et al.* (1978, 1981) and *Eisler et al.* (1981a). The latter study has been performed with only a few critically ill patients without any homogeneity of the group and so introduces the problem of patient selection. However, we do agree that deprenyl is not effective in the late phase of Parkinson's disease.

Nevertheless, the concept of a selective inhibition of MAO B as adjuvant therapeutic strategy in this disorder is promising and a number of new selective, irreversible and reversible MAO A- and B-inhibitors are under preclinical study including *in vitro* studies on human brain tissue (*Riederer et al.* 1982b).

Tranylcypromine

The success of adjuvant deprenyl treatment prompted the closer investigation of another MAO inhibitor, tranylcypromine. Tranylcypromine is an effective antidepressant drug, although it is unclear whether this action is due to MAO inhibition since, like several other antidepressants it is also an inhibitor of neuronal catecholamine uptake.

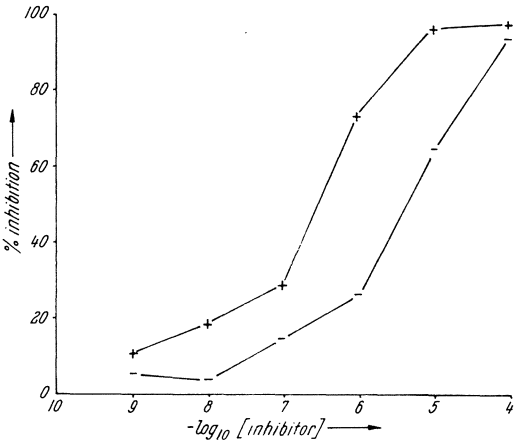


Fig. 49. In vitro inhibition of dopamine oxidation by tranylcypromine isomers in human caudate nucleus. + = (+)tranylcypromine, – = (–)tranylcypromine. %Inhibition of human caudate nucleus MAO by 10^{-6}M inhibitor

Inhibitor	Substrate	
	dopamine	5-HT
(–)Deprenyl	86	20
(+)Tranylcypromine	72	35
(–)Tranylcypromine	27	7

(*Reynolds et al.* 1980b)

Table 27a. *The effect of tranylcypromine isomers on motor-behaviour in Parkinson's disease*

	Basal level	Treatment	
		3 days	14 days
(−)TCP (6)	15.8 ± 1.47	14.5 ± 1.76	11.7 ± 2.56[1]
(+)TCP (6)	15.6 ± 1.75	13.5 ± 1.64[2]	9.7 ± 3.08[1]
(±)TCP (6)	15.5 ± 1.87	13.7 ± 2.16[3]	9.3 ± 1.97[1]

x ± S.D. (number of patients);
[1] $p < 0.005$ compared to basal level;
[2] $p < 0.05$ compared to basal level;
[3] $p > 0.05$ compared to basal level;
Items: Bradykinesia, rigidity, tremor, speech, selfcare, attitude, coordinative swinging of the upper extremities, gait, facial expression, seborrhoea.
Rating: 0 none
1 moderate disturbance
2 severe disturbance
Age: 77.3 ± 2.27 yrs
Sex: 1 m/5 f
Duration of Parkinson's disease: 6.2 ± 1.9 yrs

Table 27b. *Neuropsychiatric side-effects during tranylcypromine medication*

	Basal level	Days of treatment				Remarks
		5	8	10	12	
(−)TCP	2.8 ± 1.6	4.8 ± 2.7	4.5 ± 2.7	3.2 ± 1.9	2.5 ± 1.5	5 out of 6 patients
(+)TCP	3.0 ± 3.0	2.2 ± 2.9	2.0 ± 2.5	1.3 ± 1.9	0.8 ± 1.5	2–3 out of 6 patients
(±)TCP	1.2 ± 1.6	1.0 ± 1.2	4.2 ± 5.0	1.8 ± 3.5	1.2 ± 2.5	3 out of 6 patients

Means ± S.D.; n = 6.
Items: involuntary movements, sleeplessness, agitation, night mares, dizziness, delirium, delusions, hallucinations, increased or diminished libido.
Rating scale:
0 = no side-effects;
1 = slight irritation;
2 = moderate; reduction of dose not necessary;
3 = severe; reduction of dose required;
4 = severe; withdrawal of drug necessary or interruption of therapy.

Table 28. *Blood pressure response in tranylcypromine-treated parkinsonian patients (from Riederer et al. 1983b)*

Drug	MAO-I. (mg/day)	Days of treatment	Blood pressure Systolic		Diastolic		%MAO-inhibition in platelets[1]		
			before MAO-I.	after MAO-I.	before MAO-I.	after MAO-I.	5-HT	DA	PEA
(−)Deprenyl (10)	10.0	14	128 ± 10	129 ± 9	77 ± 3	78 ± 4	–		95.0 ± 4.1
Study 1									
(−)TCP (11)	5.0	3	125 ± 12	138 ± 6[4]	78 ± 3	78 ± 4	–	61.5 ± 7.2	63.0 ± 6.6
(+)TCP (11)	5.0	3	126 ± 12	143 ± 5[4]	79 ± 4	83 ± 4	–	94.3 ± 1.3	87.8 ± 1.7
Study 2									
(−)TCP (6)[3]	2.3	14	133 ± 9	140 ± 11	76 ± 2	72 ± 4	3.3[2]	–	26.8 ± 6.1
(+)TCP (6)[3]	4.0	14	135 ± 8	138 ± 6	77 ± 2	73 ± 3	57.0 ± 3.1	–	92.5 ± 2.9

Number of patients in parenthesis; values are means ± S.E.M.; – = not estimated;

[1] the activity of MAO in blood platelets was 0.12 ± 0.047 (6) with 5-HT and 6.23 ± 0.59 (6) with PEA as substrate (mean ± S.E.M.; nmol/min./mg protein; values in triplicate);

[2] one patient only;

[3] during the two week trial seven controlled determinations of the blood pressure were done on each of the 6 patients;

[4] $p < 0.05$ (two tailed t-test).

Commercially available is the racemic mixture (±)tranylcypromine; we have undertaken a series of studies with the individual stereoisomers to investigate their biochemical effects in man and to assess their effect in the treatment of Parkinson's disease.

Initial *in vitro* studies showed each isomer to be relatively selective towards inhibition of MAO type B (Fig. 49), although the (+)isomer is almost ten-fold more potent (*Reynolds et al.* 1980b, *Reynolds et al.* 1981b). This difference is upheld *in vivo* in man (*Reynolds et al.* 1980a).

Recently, an open study of the tranylcypromine isomers, and the racemic drug, was performed in six patients with Parkinson's disease. Drug dosage was increased from 1 mg/day to an optimal level for each patient. With the (–)isomer this was an average of 2.3 mg/day since the appearance of neuropsychiatric side effects prevented increasing the dose further. The (+)isomer was without this effect and, taken to 4 mg/day, had a substantial positive influence on motor function and behaviour (Table 27a, b; *Riederer et al.* 1981a, *Riederer et al.* 1983b). In addition to the specific improvement in parkinsonian symptoms shown by (+)tranylcypromine, it was found that this isomer induced over 90% inhibition of platelet MAO, and yet the dose was low enough to prevent any hypertensive crises despite the concurrent administration of L-dopa (Table 28). Therefore, it is not necessary to increase the doses of (+)tranylcypromine above 4 mg/day. Higher doses than 4 mg/day are not tolerated when combined with usual anti-parkinson therapy, particularly L-dopa treatment. It seems that the induction of the cheese effect is a second pharmacological property (independent of the MAO inhibition) which does not occur at this low dosage and with usual food intake (*Sandler* 1981, *Knoll* 1976).

The success of this treatment has led to continued use of (+)tranylcypromine in the clinic and further studies are at present underway.

Dopamine Agonists

So far we have described approaches to treatment directed at improving the dopamine availability in the presynaptic neuron. However, it is believed that the degenerative process of Parkinson's disease primarily involves the presynaptic dopamine neuron, while the postsynaptic cell remains relatively intact. This assumption has stimulated the search for compounds with a dopamine-like action at the postsynaptic receptor and yet which do not require intact presynaptic systems – the dopamine agonist drugs.

The first dopamine agonist found to be effective in animal models (*Corrodi et al.* 1973, *Miyamoto et al.* 1974) and in clinical practice (*Calne et al.* 1974) was the ergot derivative bromocriptine, although

Schwab et al. (1951) had already tried apomorphine in parkinsonism. *Hutt et al.* (1977) have indicated that the effects of this drug are not so straightforward: they find that low doses inhibit motor activity and higher doses are needed for a stimulation. This can be explained in terms of the presynaptically localized autoreceptors (*Carlsson* 1975, *Hjorth et al.* 1980), which may be activated at low doses and serve to inhibit dopamine synthesis. Higher doses will also stimulate the postsynaptic receptors and thereby increase motor activity. There are suggestions that bromocriptine requires some functional presynaptic dopamine since reserpine pretreatment reduces bromocriptine effects in animals.

The 200-odd publications on the clinical effects of bromocriptine in well over 2000 patients certainly provide enough data for an assessment of this drug. Large differences in dose are apparent (from 5 to 300 mg daily). *Teychenne et al.* (1981) report the beneficial effects of low doses (14 mg), at much the same level as our own dosages. Only a minority of patients require larger amounts. The improvements in particular symptoms are inconsistently reported. *Ludin et al.* (1976) and *Völler* and *Ulm* (1979) observed improvements in primarily rigidity and akinesia, while others noticed a greater effect on tremor. *Lieberman et al.* (1979) found all symptoms to be improved. There is also little concordance on the question of whether bromocriptine should be administered alone or with L-dopa. *Stern et al.* (1979) found that in a minority of patients monotherapy with bromocriptine can be as successful as L-dopa treatment. Of 40 patients who had not received L-dopa, 18 showed a 45% improvement in one year of bromocriptine treatment (mean of 70 mg daily). However, after two years only five patients still showed an improvement. The 22 patients who did not respond with bromocriptine first improved after combined bromocriptine and L-dopa.

There is general agreement on when to administer the drug (*Yahr* 1981, *Lieberman et al.* 1976, 1980a, b, *Gopinathan and Calne* 1981). Immediate administration is indicated in patients who do not respond to L-dopa. Combination treatment with L-dopa is indicated when ergot derivatives are ineffective (*Parkes* 1979, *Stern et al.* 1980, *Ulm* 1981, *Hoehn* 1981, *Godwin-Austen* 1981, *Schneider* and *Fischer* 1982). Since the kinetic effect of L-dopa is found to drop after 5–7 years, we would suggest that bromocriptine should be first given when an increase in L-dopa treatment cannot counteract the increase in symptoms.

A review of all publications has yielded an improvement of symptoms of 40–60% (*Ringwald et al.* 1982). The discrepancies are

undoubtedly due to the different methods of rating the disability. Such an improvement is similar to that with L-dopa-based treatment, a value which is higher than the 20% improvement we have observed with ergot-derived dopamine agonists. *Lieberman et al.* (1979) described an improvement in the on-off effect in 19 of 27 patients. There is also a positive action on the related akinetic crisis. It is notable that these symptoms do not respond to an increase in L-dopa treatment (see p. 92). On the other hand bromocriptine is generally not as successful as L-dopa in its action on motor function. Other dopamine agonists have been used clinically, although not as widely as has bromocriptine. Pergolide, lergotrile, lisuride, CU-32085 and bromocriptine have been compared; the latter was found to be the most beneficial. Akinesia, rigidity and tremor can all be significantly relieved in advanced parkinsonian cases. Pergolide has a greater effect on tremor, while lergotrile improves both tremor and akinesia. The action of bromocriptine most resembles that of L-dopa, although it is essentially weaker in its effect. One can easily be impressed by bromocriptine if it is given to a patient who has received L-dopa medication for seven years or more. Long periods of akinesia which are resistant to L-dopa frequently respond to bromocriptine treatment. It is in these later stages of the disease, when the remaining dopaminergic neurons cannot provide an adequate synthesis of transmitter, that the dopamine agonists show their strength. However, severe side effects limit the use of pergolide and lergotrile, while bromocriptine exhibits side effects similar to L-dopa. We find that hyperkinesias, toxic delirium, confusion, nausea and particularly orthostatic hypotension are the most serious problems. Most patients find dizziness and the likelyhood of falling to be so worrying that they stop taking the medication. As with L-dopa, a reduction in dose can keep the effects of bromocriptine at a tolerable level. Again like L-dopa, a gradual increase in dosage brings about a tolerance to these effects (*Schachter et al.* 1979, 1980; *Lees* and *Stern* 1981, *Lieberman et al.* 1980a, b, 1981, *Parkes et al.* 1981c, *LeWitt et al.* 1982a, *Tanner* and *Klawans* 1982, *Jellinger* 1982).

We first administer bromocriptine at 3×2.5 mg, increasing by 1.25 mg every third day. At the same time the L-dopa dose is decreased. The average dose we prescribe is approximately 3×5–10 mg, while *Calne* usually gives 50 mg bromocriptine daily. Where the patients can tolerate it, we find that 6×10 mg is more effective than any L-dopa regimen, although such patients are invariably pre-terminal cases. It is in these more severe cases that the best results with bromocriptine are obtained; the milder cases being more likely to respond better to L-dopa. However, the effects of L-dopa on movement and mobility cannot be matched by bromocriptine.

We have studied the effects of lisuride in 58 patients in the long term (*Birkmayer* and *Riederer* 1982). All patients had received Madopar for several years before lisuride was added to their treatment. All patients exhibited a significant improvement in disability score (ranging from 36 to 48%) except for a group exhibiting a malignant disease type (see p. 152) in whom the improvement was slight (~10%). At dosages between 0.6 and 1.2 mg/day lisuride had a particularly beneficial effect on motor function. Moreover, daily fluctuations and long-term oscillations were improved or disappeared completely. Side effects were typical of a potent antiparkinsonian drug with hyperkinesia, toxic delirium and orthostatic hypotension predominating. A few patients could not tolerate even 3 × 0.2 mg lisuride. Some patients in akinetic crisis respond dramatically to lisuride; this is perhaps best described by two case reports.

Case 1 (Fig. 50): a 76 year old woman who first developed parkinsonian symptoms (tremor) at 56 years. Originally she was hospitalized with a disability score of 60% and responded to Madopar treatment until aged 70. Her motor performance dropped, but disability improved by 15% with increased Madopar (3 × 250 mg) and addition of 10 mg deprenyl. After some two years her further deterioration did not respond to increased doses and for another two years her disability score was 70%. Eventually she went into an akinetic state which did not respond to L-dopa, deprenyl or amantadine infusions. After four days, lisuride (0.025 mg) was given i.v., whereupon she improved enough to take some food. Oral lisuride was continued for a day, but the following night she was restless, anxious and had vivid dreams. One night later she became totally deranged but 20 mg valium quietened her. The next morning she could eat, speak slowly, move her hands and walk with help. Treatment was continued with 2 × 62.5 mg Madopar and 0.2 mg lisuride p. d. and her disability score remains at 70%.

Case 2 (Fig. 51): a 78 year old male who developed akinetic signs of parkinsonism at 74 years. After treatment with Madopar (3 × 250 mg) and deprenyl (2 × 5 mg) his disability improved from 70 to 30%. At 77 years he again deteriorated and treatment was unsuccessful until 3 × 0.2 mg lisuride was given. One week later he became confused, emotional and aggressive, believing that the clinicians were making love with his wife. Anxiolytic drugs improved this and his disability score is now as low as 30% on Madopar (2 × 62.5 mg), deprenyl (5 mg) and lisuride (2 mg).

These reports exemplify the profound effect of lisuride on psychomotor function. They also illustrate the dopa-sparing effect, which is found to be typically 30–40% of the original L-dopa dose.

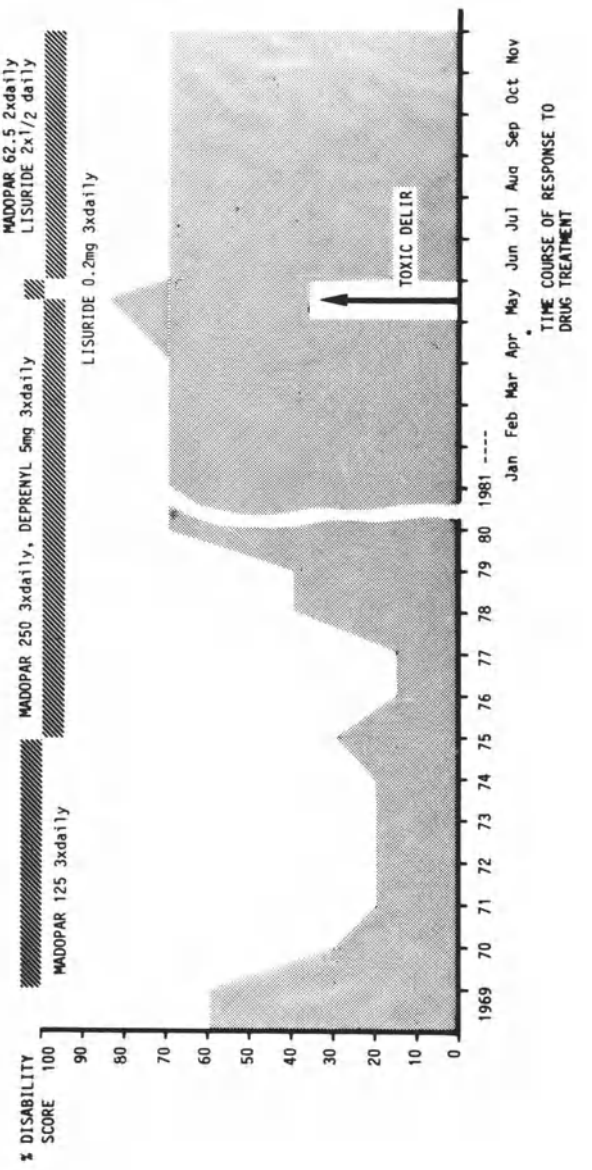


Fig. 50. Psychomotoric efficacy of lisuride in a parkinsonian

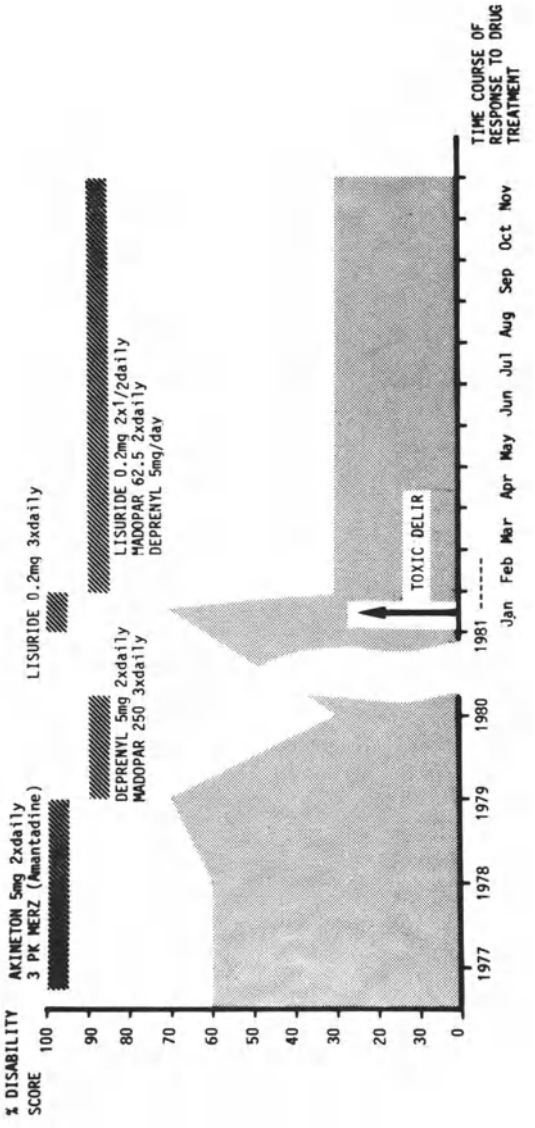


Fig. 51. Patient with "akinetic crises" (F. B. male, 78 a)

Table 29a. *Lisuride further improves parkinsonian patients on a steady state disability*

	Group I	Group II	Group III	Group IV
Duration of PD (yrs)	5–10	10–15	15–20	1–5
Type of PD[1]	B	B	B	M
N[2]	12	14	14	12
Sex (m/f)	7/5	9/5	8/6	8/4
Age range (yrs)	58–78	61–79	64–86	56–62
Duration of L-dopa + DI medication before lisuride (yrs)	6.5	9.5	7.4	3.0
% Improvement of total disability[3] in L-dopa + DI[4] treated PD	47.9	43.9	35.5	10.0
Total disability score[3] at start of lisuride medication (%)	68.5	53.5	68.5	60.0
Duration of lisuride medication[5] (months)	17 (7)	12 (8)	14 (10)	24 (12)
% Further improvement in lisuride treated Parkinson's disease	26 (7)	21 (8)	24 (10)	10 (12)

[1] According to *Birkmayer et al.* 1979a; B = benign, M = malignant.
[2] N or () = number of cases.
[3] According to *Birkmayer* and *Neumayer* 1972a.
[4] Madopar® (3 × 125 mg daily) in the mean.
[5] Lisuride hydrogen maleate 0.6–1.2 mg/day.

Table 29b. *Drop-out cases during lisuride medication (further clinical details see Table 29a and Birkmayer and Riederer 1982)*

	Number of patients with lisuride medication	Drop-outs due to		
		Hyperkinesia	Toxic delirium	Orthostatic hypotension
Group I	12	3	2	0
Group II	14	2	2	2
Group III	14	1	2	1
Group IV	12	0	0	0

As with bromocriptine, the improvement with lisuride is more pronounced in the advanced stages of Parkinson's disease. The drug is no more potent than others against symptoms of the malignant group of parkinsonian patients. The best results are obtained in those patients who respond well to L-dopa (Table 29a, b) (*Gopinathan et al.* 1980, *Lieberman et al.* 1981). We are fortunate in these timely developments in dopamine agonist drug treatment. The side effects found with these drugs are a problem, but side effects were similarly a hindrance in the early days of L-dopa treatment.

Influence of Bromocriptine and Lisuride on Plasma Catecholamines and Urinary Metabolites

Although changes in the turnover rate of biogenic amines have been reported for dopamine agonists like bromocriptine, these results are rather conflicting. *Fuxe et al.* (1978) find a decrease in dopamine turnover in the caudate nucleus and subcortical limbic areas, while serotonin turnover was not changed and noradrenaline turnover increased at high bromocriptine dose. Bromocriptine had no influence on the D_1-receptor (adenylate cyclase dependent), whereas changes in the affinity of D_2-receptors and a blockade of serotonin postsynaptic receptors have been observed *(Fuxe et al.* 1978). *Hutt et al.* (1977) and *Snider et al.* (1975, 1976a) have shown in animal experiments that serotonin increases and 5-hydroxyindole acetic acid decreases after bromocriptine. Dopamine exhibits slight changes. A combined treatment of the animals with bromocriptine plus L-dopa, however, led to increased 5-hydroxyindole acetic acid concentrations with no change in serotonin (*Hutt et al.* 1977). In patients with Parkinson's disease a significant reduction of dopamine-turnover as measured by homovanillic acid in the CSF (*Kartzinel et al.* 1976) while 5-hydroxyindole acetic acid increased after probenecid, thus showing an increase in the serotonin turnover, confirming earlier data by *Rinne et al.* (1975).

Data, however, are lacking regarding influences of dopamine agonists on peripheral neuronal systems. We add further evidence that the dopamine agonists bromocriptine and lisuride behave differently in influencing peripheral dopamine, serotonin and noradrenaline systems in Parkinson's disease. Table 29 indicates that noradrenaline and dopamine may be decreased during bromocriptine treatment. A decrease can be noted for urinary homovanillic acid, while 5-hydroxyindole acetic acid is higher after bromocriptine.

The plasma catecholamines show a tendency to decrease after lisuride treatment, and this is reflected by a drop in homovanillic acid and 5-hydroxyindole acetic acid in the urine (Table 30).

Table 30. *Plasma catecholamines and urinary metabolites in Parkinson's disease: influence of bromocriptine (from Riederer et al. 1983a)*

			Before bromocriptine	Bromocriptine
Plasma:	Dopa	(μg/ml)	0.70 ±0.068 (75)	0.65 ±0.15 (35)
	NA	(ng/ml)	0.84 ±0.129 (31)	0.67 ±0.09 (12)
	A	(ng/ml)	0.169 ±0.08 (18)	0.156 ±0.065 (12)
	DA	(ng/ml)	4.52 ±0.98 (31)	3.7 ±0.58 (12)
Urine:	VMA	(μg/ml)	6.48 ±0.53 (79)	5.91 ±0.5 (39)
	MHPG	(μg/ml)	1.48 ±0.18 (48)	1.96 ±0.258 (13)
	DOPAC	(μg/ml)	3.59 ±0.46 (47)	3.42 ±0.63 (13)
	HVA	(μg/ml)	5.80 ±0.79 (78)	2.58 ±0.38 (39)
	5-HIAA	(μg/ml)	2.09 ±0.17 (78)	2.72 ±0.43 (39)

Means ± S.E.M. (number of determinations); patients were on usual antiparkinson therapy including L-dopa plus decarboxylase inhibitors.

Table 31. *Plasma catecholamines and urinary metabolites in Parkinson's disease: influence of lisuride (from Riederer et al. 1983a)*

			Before lisuride	Lisuride
Plasma:	NA	(ng/ml)	0.46 ± 0.08	0.38 ±0.06
	A	(ng/ml)	0.039 ± 0.016	0.020 ±0.016
	DA	(ng/ml)	0.297 ± 0.16	0.226 ±0.15
Urine:	HVA	(μg/ml)	27.2 ±11.0	21.2 ±5.7
	5-HIAA	(μg/ml)	13.6 ± 3.5	2.8 ±0.6*

Means ± S.E.M. (n = 9). * $p < 0.01$; patients were on usual antiparkinson therapy including L-dopa plus decarboxylase inhibitors.

Thus we add further evidence that so-called dopamine agonists bromocriptine and lisuride also act on peripheral neuronal systems and that both drugs seem to behave differently particularly with regards to the serotonergic system. It seems likely that the peripheral effects of both drugs contribute to the side effects which include nausea, vomiting, gastrointestinal irritations and orthostatic hypotension.

Domperidone

Domperidone, a peripheral dopaminergic blocking agent, protects patients from dopamine-agonist induced nausea and vomiting (*Quinn et*

al. 1981, *Agnoli et al.* 1981a, *Agid et al.* 1981). We administer 3 × 10 mg domperidone/day and find this drug to be of particular benefit in orthostatic hypotension, cramps and dizziness.

MIF

Polypeptide therapy (L-propyl-l-leucyl-glycineamide) has been introduced by *Kastin* and *Barbeau* (1972).

Another approach has been that of *Gerstenbrand et al.* (1975, 1976, 1979) and *Barbeau* und *Kastin* (1976) who administered supplementary melanocyte inhibitory factor (MIF). As MIF can only be given by infusion any beneficial effect has little general application.

β-Blockers

The fact that tremor is increased by affective stimuli has led to the use of β-blockers (propranolol) in the treatment of tremor. *Marsden* (1973) found no positive effect on either tremor or akinesia while on the other hand *Gerstenbrand et al.* (1978) reported an improvement in tremor and also, to some extent, in akinesia.

Treatment of Autonomic Symptoms

Drooling, outbreaks of sweating and seborrhoea respond well to anticholinergic drugs. We prescribe biperiden (4–6 mg daily), phenglutarimide (15 mg/day) or 2-phenyl-norbornane-2-carboxylic acid-γ-diethylamino-propylester (4–12 mg/day). The latter substance is to be particularly recommended for nocturnal sweating. Dryness of the mouth can then be tolerated by the patient when he notices an improvement in his symptoms.

As has been mentioned, parkinsonian patients tolerate heat very badly. Overheating and flushing are detrimental to health and hyperthermia can sometimes be fatal. Since we assumed that disturbed serotonin metabolism was responsible, the administration of L-tryptophan (3 × 250 mg daily), or, in cases of fever, 5-HTP injection (50 mg) was found to be successful. Since L-tryptophan was introduced in our department, 3–8 hyperthermic deaths per 100 parkinsonian patients every summer have been completely eliminated. Tryptophan is used prophylactically in the summer at a dose of 3 × 125 mg; most patients find this very pleasant. The amino acid is also successful in treating ankle oedema provided it is not an old hard swelling. The drug treatment described above can be given in addition to L-dopa.

Treatment of Psychiatric Symptoms

Periods of depression, clinically indistinguishable from the classical syndrome, predominate among the mental disturbances of Parkinson's disease. However they are generally shorter, lasting from days to several weeks. The whole range of antidepressant drugs is available for treatment. We generally give a morning dose of an activating drug such as imipramine (10–25 mg), nomifensine (25–50 mg), orphenadrine (25 mg) or dibenzepine (80 mg). For evening medication we use amitriptyline (25 mg) or maprotiline (50–75 mg).

When the depressive symptoms are relieved we reduce the dose (to 25 mg nomifensine and 10 mg amitriptyline) which is maintained continually thereafter. In cases of unrest, anxiety or loss of sleep 1 mg lorazepam or a similar tranquillizer is used.

Although motor symptoms may not be noticably improved by such treatment, the pseudoneurotic and psychopathological behaviour and all the hypochondriacal-depressive complaints of the parkinsonian patient can be kept within tolerable limits. There is only one contraindication in this antidepressant medication: cardiac arrhythmia. If this occurs another drug can be substituted; only if the side effects persist need the antidepressant treatment be stopped. The patient, and particularly his relatives and nursing staff, confirm that additional chronic antidepressant medication substantially stabilizes his mental state. While there is no direct kinetic effect, motor function and affect are linked to the extent that an elated mood brings about better motor performance. In the same way, posture and akinesia will worsen with depression. Thus the patient with Parkinson's disease exhibits a range of disorders associated with a degeneration of the phylogenetically old region of the brain, the brain stem.

Patients and their relatives frequently complain of forgetfulness, disorientation and periods of confusion. These are inherently senile defects which can nevertheless be found in younger patients in whom the disease is well advanced (see *Loranger et al.* 1972, *Mayeux et al.* 1981). The medication we use for these symptoms is 3–6 × 400 mg piracetam daily, pyritinol (400 mg) or an infusion of amantadine containing 50 mg L-dopa, 50 mg 5-HTP, piracetam and 25 mg nomifensine would be prepared. An improvement is apparent in affect, thought processes and attention.

The bradyprenic thought disturbances are improved with L-dopa, as is motor function. The psychoses associated with Parkinson's disease can generally be treated as side effects, since they are mostly produced by L-dopa treatment.

The Drug Treatment of Parkinson's Disease in Practice

Each patient who comes to us for initial treatment is started on medication with a dopa preparation. The patient with a disability of ~ 30 (i.e. mildly affected) would receive Madopar 62.5 (or 1/4 tablet of Sinemet) three or four times daily, plus 5 mg deprenyl in the morning. Since L-dopa can be successful (albeit less frequently) against rigidity and tremor, as well as akinesia, we would then wait 4–8 weeks for an improvement. If, after 2 months, akinesia and rigidity have improved but tremor has not, then we would administer an anticholinergic drug, e.g. phenglutarimide (1.5 mg), 2-phenyl-norbornane-2-carboxylic-acid-γ-diethylaminopropylester or benzhexol (2 mg thrice daily). Every four weeks the Madopar or Sinemet dose is increased, until an optimal response is obtained or until side effects appear. In many cases a medication of Madopar 125 or 1/2 tablet of Sinemet, thrice daily, is effective for up to seven years. If the patient feels depressed or complains of autonomic disturbances then we would prescribe nomifensine in the morning and amitriptyline (25 mg) at night. A patient complaining of hot flushes and restlessness would be given 125 mg L-tryptophan. Symptoms of depression are treated as above with an activating and a sedating antidepressant, taken morning and evening respectively.

Most patients have one or two years initial treatment with amantadine and an anticholinergics before coming to us. It is only when the response diminishes that they are seen in our clinic, whereupon we stop the anticholinergic therapy and introduce combined dopa treatment: Madopar 125 thrice daily or, for moderate disability (score 40–60), Madopar 250 or one tablet Sinemet three times daily, plus deprenyl (2 × 5 mg). After four weeks we increase the dose by 1 capsule Madopar. Only very rarely would we prescribe more then five Madopar 125 or Sinemet doses daily, because the increase in side effects overcomes any improvement. A further consideration is the accelerated progression of the disease which occurs at high L-dopa doses. In hot weather, our patients are given 3 × 125 mg tryptophan if they suffer from the heat. Morose patients, or those with pseudoneurotic symptoms are prescribed 3 × 10 mg amitriptyline daily. 1 mg lorazepam or 3 mg bromazepam are used in patients who have difficulty in sleeping.

As well as the diurnal variations in motor function and well-being of parkinsonian patients, they also have longer term changes in these parameters. To allow for these fluctuations, the patients are asked to vary the doses appropriately. For example, in the case of early morning inactivity with a pronounced akinesia, Madopar 250 with 50 mg

nomifensine and 5 mg deprenyl can be taken, while at midday and in the evening only one dose of Madopar 125 is required. If the patient is content with his daily dose schedule but complains of difficulties in turning over in bed or in micturition at night, then he should take an extra night dose of Madopar 125 or ½ tablet Sinemet.

As we have described, the greater the initial dosages of L-dopa, the earlier the fall-off in response to the drug. Patients who respond well to L-dopa tend to take higher doses than are prescribed in order to increase their motor abilities and for the emotional "high". This will bring about a premature loss in the efficacy of L-dopa. Against our advice, a 65 year old patient (disability 35) took 8 Madopar capsules daily for their sexually stimulating effect. His motor symptoms remitted completely, he was euphoric and very active sexually. After two years he was readmitted into our department with an unresponsive akinetic crisis, and after three years he was dead.

Patients who have received L-dopa for several years in whom the disease is well advanced (disability 70: walks with great difficulty, unable to dress, wash and eat without help) are given L-dopa injections (50 mg i.m. or i.v. twice weekly) additional to oral treatment. With this low dose we can improve the disability by 20% in about half our severely ill patients–particularly important for their self-care. If this has no effect then an infusion of amantadine with L-dopa (50 mg), 5-HTP (50 mg), nomifensine (10 mg) and deprenyl (10 mg) is tried. This is given thrice weekly to mildly affected out-patients and daily to severe in-patient cases. We have long found it surprising how the positive effects of our original L-dopa injection have only been confirmed in Europe and not in America. The discrepancy lies in differences in the disease severity. We first investigated L-dopa in a neurological hospital for chronic cases where 70% of patients had a disability of 60 or more. The i.v. or i.m. administration is successful in just such cases. Only later did we try oral L-dopa, which was given to mildly or moderately affected cases. These respond better to the oral dose, particularly because the effects last longer and because doses can be given more frequently.

Today we know that as the disease advances the number of functional dopaminergic neurons drop. A small i.v. L-dopa dose (25 mg) is sufficient for this small number of active neurons. An oral dose cannot be utilized to any greater extent; it only leads to increased side effects. This is presumably due to inhibition of dopaminergic function, already greatly diminished, caused by the unphysiologically high level of L-dopa. The first akinetic crisis or off period can, as a rule, be overcome by amantadine infusions, deprenyl or L-dopa, restoring mobility for weeks or months. We treat the appearance of

akinetic crises or a lasting deterioration in mobility as indications for the administration of a dopamine agonist. We start with a reduced maintenance dose of Madopar (on average 3 × 125 mg) and deprenyl (5 mg) to which is added 2.5 mg bromocriptine. Every three days the dose of bromocriptine is increased to reach a daily optimum of 15–30 mg. L-dopa treatment can be reduced slowly. The standard treatment for the patient with well advanced Parkinson's disease (but not so severe as to require hospitalization) contains bromocriptine (3 × 10 mg), deprenyl (5–10 mg in the morning), Madopar (3 × 62.5 mg), nomifensine (50 mg in the morning) and lorazepam (1–2.5 mg in the evening). Occasionally real miracles occur. Totally akinetic patients confined to bed for 2–3 months can suddenly become mobile and are even able to walk slightly. The improvement in motor function after such a long akinetic period is about 10–20%.

In the later stages of the disease the most frequent secondary symptoms include pain in the hip, knee and lumbar vertebrae, less often in the joints of the foot and in the shoulder. Muscular insufficiency leads to an overloading of the joints which results in symptoms of arthrotic abrasion. Treatment of the cause is impossible. For symptomatic treatment we prescribe indomethacin (100 mg, 2–3 times daily), diclofenac (3 tablets) or triamcinolon (i.m., monthly). Since these problems occur mainly while walking or standing, the mobility of the patients should be reduced in order to minimize the intake of these drugs and hence their toxic side effects.

Drug Prescription Guide

Two principles of drug prescription:

1. If one substance can provide an optimal effect, then a combination of drugs should not be given.

2. Drug dosages should be kept to a minimum. The more of a substance acting on the defective dopaminergic neurons, the greater will be the side effects due to inadequate feedback mechanisms.

1. *Mild parkinsonism (disability 30):*

Madopar (3 × 62.5–125 mg) or Sinemet (3 × 10/100 mg) with deprenyl (1–2 × 5 mg). If tremor is still present eight weeks later, then an anticholinergic should be administered. Oxprenolol (3 × 20 mg) is recommended for tremor of affective origin.

2. *Moderate parkinsonism (disability 30–60):*

Madopar (3 × 125–250 mg) with deprenyl (2 × 5 mg). Anticholinergic drugs for treatment of tremor. In addition: Nomifensine (25 mg) or imipramine (10 mg) in the morning and an evening dose of amitriptyline (10 mg) or maprotiline (10 mg). In

summer tryptophan (3 × 125–250 mg). For "non-responders" an additional i.v. dose of 10–30 mg tetrahydrobiopterin.

3. *Severe parkinsonism (disability 60–90):*

Bromocriptine (3 × 10 mg), deprenyl (2 × 5 mg), Madopar (3 × 62.5–125 mg) or Sinemet (3 × ½ tablet [25/250 mg] daily). Tryptophan (3 × 125 mg), nomifensine (2 × 50 mg). Akinetic crises, complete immobility: Daily infusions of amantadine with L-dopa (50 mg) plus 5-HTP (50 mg) and nomifensine (10–25 mg), in addition to the oral therapy.

Neurosurgery

We have mentioned that stereotactic ventrolateral thalamotomy is the only sure method of removing parkinsonian tremor (see *Mundinger* and *Wünsch* 1980). *Siegfried* and *Zumstein* (1976) reported a 78% improvement in tremor and *Krayenbühl* and *Yaşargil* (1961) reported 80% improvement after such operations. However, we, along with most neurologists, are of the opinion that the era of stereotactic surgery has passed. The method can improve one symptom but the course of the disease is unaltered. Worse still, additional problems may be encountered. Contralateral reappearance of the tremor, increase in akinesia after the operation and mental deterioration are all reasons for the return of the patient to the neurologist.

However, the future may see a role for the neurosurgeon in the treatment of Parkinson's disease. Animal experimentation with dopaminergic lesions of the substantia nigra after 6-hydroxydopamine application have shown that effects of the lesion can be overcome by implantation of embryonic nigral cells. These cells continue their in vivo development to send out new axonal and dendritic processes. Such a procedure has great potential in man (*Perlow et al.* 1979, *Schmidt et al.* 1982).

Physiotherapy

It is understandable that the patient and particularly his relatives want some form of physical treatment. Stroke victims or multiple sclerosis patients will calmly submit to an enthusiastic rehabilitation programme which is primarily aimed at patients with brain or spinal injuries. These patients are generally younger and have a greater capacity for rehabilitation. Stroke and MS patients have a lower capacity since energy is needed to participate in a rehabilitation programme, and this is what is lacking in such severely ill patients.

In Parkinson's disease it is even more problematic; the participation in any physical treatment programme requires some dopamine release, and of course it is just this transmitter which is lacking. It is a pity if a

patient, congratulated on how well he walks, replies: "Well, doctor, that's because I do exercises every morning". "Plenty of exercises and long walks" is useless advice. The patient and his family must understand that too much movement will quickly use up dopamine. L-dopa administration can to some extent compensate for the dopamine deficit, but the more the patient does senseless exercise, the less dopamine is available for the movements necessary to normal life.

Often the patient's partner shows a complete lack of understanding when it is necessary to rest every ten minutes or so. Most patients feel subjectively that too much movement is bad for their condition and so are pleased if the doctor explains this to the nurse or relatives. Of course a patient resident in a hospital clinic must be given something more to do than just take three capsules of Madopar each day. It is important to explain, however, that movement therapy will have no effect on the course of the disease (*Parkes* 1981b). While exercise is important in motor rehabilitation (*Birkmayer* 1951) in Parkinson's disease, this must be limited to such as the following:

1. Active and passive exercise in warm water. Since it is the muscles acting against gravity which are particularly affected, relief of these by exercise while floating in water is very advantageous. This treatment can reestablish the balance between extensor and flexor muscles. There is a substantial psychotherapeutic value in this exercise since the patients movement in warm water is easier and freer, and this relative freedom of movement continues for sometime after treatment.

2. Underwater massage is found to be very pleasant for the patient. This involves a moderately strong water jet which is played over the musculature of the back and on the shoulder and hip joints.

3. Movements of all the joints, particularly the shoulders and hips, should be performed slowly but thoroughly. This is especially important in severe cases of rigidity.

4. A dry massage is also beneficial. It relieves much of the secondary spondilogenic pain which is often followed by cramps.

5. For the mildly affected patient, the sole exercise which can be recommended is cycling. By neutralizing the body weight (i.e. static tone) it is much easier to use the legs for pedalling. If the locality makes cycling difficult, a fixed exercise cycle can be employed. However, it cannot be emphasized enough that movement therapy has no curative effect; it can only restore some balance to the postural abnormalities and rigidity. Patients with less severe symptoms can, of course, carry out gymnastic exercises, but this form of physiotherapy is only indicated when, after the exercise, they can move more easily for an extended period of time.

Side Effects

A drug without side effects generally has no therapeutic effects. An overdosage of drug in a normal person will invoke a series of regulatory functions which prevent the appearance of side effects. For example, hyperkinesia or psychosis is not produced in a healthy person receiving L-dopa or the dopaminergic agonist lisuride (*Schwibbe et al.* 1982). But in the parkinsonian patient these side effects are frequent and troublesome.

Drug dependence has not been observed in Parkinson's disease. Alcoholism is frequently observed in patients with depression syndrome. Alcohol dependence, however, has not been noted in Parkinson's disease. Similarly, amphetamine given to parkinsonians did not induce withdrawal symptoms or the wish to increase the dosage. Therefore, Parkinson's disease might provide a model for biochemical investigations into this problem. The biochemical imbalance at several neuronal levels might prevent drug dependence.

It is the progressive degeneration of dopaminergic neurons in Parkinson's disease which prevents the feedback control mechanisms restoring normal function. The more advanced the disease, the more side effects appear with L-dopa or dopamine agonist treatment. Thus these drugs induce striatal dopaminergic hyperactivity resulting in hyperkinesias. The appearance of such side effects is not dependent on the drug itself but on the degree of dopaminergic function and the amount of drug administered. Higher doses produce greater side effects with a faster appearance. However, the individual response is another

Table 32a. *Improvement of L-dopa treatment by benserazide*

Disability before treatment	200 mg L-dopa 50 mg Benserazide			150 mg L-dopa 100 mg Benserazide		
	disability	%impr.	n	disability	%impr.	n
100	–	–	–	–	–	–
90	–	–	–	–	–	–
80	50	38	4	–	–	–
70	40	43	7	–	–	–
60	32	48	48	21	65	32
50	29	42	52	15	70	58
40	26	35	23	20	52	24
30	14	54	18	15	51	36

Rating scale according to *Birkmayer* and *Neumayer* 1972a.
%impr. = %improvement; n = number of patients.

Table 32b. *Occurrence of side-effects in parkinsonian patients treated with two different regimes of L-dopa and benserazide (from Birkmayer and Neumayer 1972a)*

Side-effects	200 mg L-dopa 50 mg Benserazide (n = 150)	150 mg L-dopa 100 mg Benserazide (n = 150)
Hyperkinesia	57	14
Depression	19	0
Increased libido	6	0
Sleeplessness	24	3
Vivid dreams	18	0
Night mares	10	0
Alarm reaction	14	0
Agitation	21	0
Anxiety	18	2
Confusion	21	0
Delirium	8	0
Delusions	6	0
Hallucinations	7	0

important factor in the point at which the side effects occur. This will be discussed later on as a criterion to distinguish benign and malignant disease subtypes; both time of onset and intensity of side effects are fundamental to the prognosis for the course of the disease.

Table 32b shows the frequency of central side effects in two groups of 150 patients. The first group, receiving more L-dopa, has far more side effects than the second, suggesting that there is a dependence on the amount of L-dopa reaching the CNS.

Peripheral Side Effects

Previously nausea and sickness were the major peripheral side effects, followed by constipation and, less often, diarrhoea. Bleeding of the mouth and throat mucosa, stomach and intestinal ulcers, bloody stools and haematuria occurred only rarely. Retention of urine and occasional pollakisuria occurred frequently, particularly at night. These are caused via a parasympathetic mechanism, possibly through serotonin release. Since the introduction of dopa combination therapy, essentially no autonomic side effects occur apart from initial constipation and nausea. If nausea does occur we have found that additional medication with a decarboxylase inhibitor is effective, although unfortunately neither benserazide nor carbidopa are commercially available alone. Metoclopramide (20–30 mg), given

concurrently with the L-dopa preparation, also minimizes nausea, although these autonomic side effects disappear naturally after a few weeks. Bleeding of the mucosa or disturbances of micturition can be relieved by treatment with L-tryptophan (*Birkmayer* and *Neumayer* 1972, 1972a).

Table 33 summarizes the appearance of L-dopa side effects in the patient group of Table 19. Gastrointestinal side effects total only 2.5%.

Cardiac Side Effects

Cardiac side effects occur in 5% of patients, mainly in the first years of treatment, becoming less frequent later (Table 33). Essentially these amount to sinusoidal tachycardia and arrhythmias. Administration of β-blockers is the treatment of choice (*Goldberg* and *Whitsett* 1974); we employ oxprenolol at 3×40 mg since higher doses are poorly tolerated by parkinsonian patients.

Orthostatic hypotension only appears after some five years of treatment (Table 33), when the disease is well advanced. *Reid et al.* (1976) have studied the circulatory disturbances associated with L-dopa treatment in some detail. They have shown that the parkinsonian patient has no blood pressure abnormality while supine, but exhibits

Table 33. *Side-effects of Madopar treatment*

Length of L-dopa treatment (yrs)	1	3	5	7	9	11	13	15	
No. of cases	147	455	315	210	210	42	21	14	Σ 1414
Side effects (%)									% of total
Gastrointestinal		1.5			1.0				2.5
Cardiac		2.0	1.5	1.0	0.5				5.0
Orthostatic hypot.			1.5	2.5	1.0				5.0
Dizziness	0.5	1.0	2.0	1.0	1.0	0.5			6.0
Hyperkinesias		2.5	4.0	6.5	4.5	1.0			18.5
Cramps		1.0	2.0	1.5	2.0	0.5			7.0
Sleeplessness		1.5	2.5	1.5	2.0	1.0			8.5
Depression	1.5	7.5	3.0		2.5	0.5			15.0
Dopa-psychoses (ameliorated by L-tryptophan)		4.0	5.5	3.5	2.0		0.5		15.5
Non-responders		1.0	1.5	0.5	0.5				3.5

hypotension on standing. However, systolic and diastolic blood pressure are both reduced significantly by L-dopa medication. *Reid et al.* (1976) have suggested that since a peripheral decarboxylase inhibitor (benserazide) has no effect on orthostatic hypotension, it must have an origin within the CNS. The classification of orthostatic hypotension as a central side effect is supported by the fact that sodium administration (as recommended by *McDowell et al.* 1970), the wearing of elastic stockings or medication with peripheral hypertensive agents are all unsuccessful treatments. The positive effect of antidepressant drugs such as nomifensine (2 × 25 mg), imipramine (2 × 25 mg) and tranylcypromine (2 × 5 mg daily) also support the central localization of orthostatic hypotension. On the other hand, deprenyl has no effect, suggesting a hypofunction of noradrenergic systems is important since tranylcypromine, but not deprenyl, inhibits noradrenaline oxidation via MAO type A. Nevertheless deprenyl (5 mg) combined with phenylalanine (250 mg) can provide a very good treatment for orthostatic hypotension (see pp. 107–119). We feel that the progressive degeneration of the locus coeruleus may well be responsible for the later appearance of these side effects (*Riederer et al.* 1977).

Cerebral ischemia is a direct consequence of this side effect, and results in a vascular dizziness. Characteristic blackouts, feeling faint and short syncope with loss of consciousness are particularly worrying for the parkinsonian patient, since they frequently result in broken bones. Fear of these attacks of dizziness will inhibit the already reduced motor function. We find that a reduction in the L-dopa dose has hardly any effect.

A second type of dizziness in the parkinsonian patient is the typical "Menière attack". This can occur on rolling over in bed or on walking, particularly when turning the head sideways on changing direction. We would suggest that this vestibular symptom derives from a neck spondylopathy which may cause a constriction of the vertebral artery on turning the head, resulting in ischaemia of the vestibular nuclei. A pronounced unilateral rigidity of the neck muscles can also lead to syncope on turning. This can be effectively treated by dimenhydrinate or thiethylperazine.

A further symptom with similar effects on the patient is the balance disorder. This originates in the unequal neuronal degeneration; one side of the body will be more severely affected than the other. Parkinsonian patients always lean toward this side and attempts to correct this attitude can result in loss of balance. It is not to be confused with cerebellar ataxia. The treatment that we recommend is to use two walking sticks. Since the parkinsonian symptoms are generally less

severe in the upper extremities, the addition of two extra "legs" can generally overcome the problems of balance.

Motor Side Effects

Not only are the motor side effects of L-dopa treatment the most frequent (hyperkinesias occurring in 18.5%), they are also the most difficult to correct. ***Fischer et al.*** (1978) have observed some 20–30% of their patients with these side effects after only one or two years' treatment. A dopaminergic hyperactivity is assumed to be responsible since the hyperkinesias disappear on withdrawal of L-dopa. ***Duvoisin*** (1976) proposed this to be due to a stimulation of striatal dopamine receptors. ***Steg*** (1972) implicated a supersensitivity of striatal cells since hyperkinesias are not observed on the unaffected side of a hemilateral case. In Parkinson's disease the biochemical balance is disturbed, with a dopaminergic hypoactivity and a cholinergic hyperactivity. L-dopa ideally leads to a restoration of the balance between these two transmitters. Normally this balance is retained by feedback control mechanisms since L-dopa given to a healthy person cannot elicit hyperkinesia. However, the parkinsonian patient has lost this control (***Riederer et al.*** 1981b).

Hyperkinesias undoubtedly originate in the CNS; they are potentiated by L-dopa given with a peripheral decarboxylase inhibitor. As decreased values of GABA have been observed in both the substantia nigra and striatum of choreic patients (***Bird*** and ***Iversen*** 1974), it seems likely that GABA normally restricts the nigral dopamine output and a deficit of GABA results in dopaminergic hyperactivity. A reduction in L-dopa dose leads to a reduction in hyperkinesias but inevitably a return of akinesia. Plasma dopa levels may be important in that high levels correlate with the appearance of hyperkinesias, while at low levels there are no kinetic effects (***Mones*** 1973).

Understandably, many and various drugs have been investigated in respect of their action on this serious side effect. Dopamine receptor blockers such as haloperidol can be effective in preventing hyperkinesia (***Duvoisin*** 1976). Recently other dopaminergic antagonists (flupenthixol and tiapride) have been investigated (***Price et al.*** 1981). Dyskinesias were reduced in nine out of ten patients, although in seven patients the disability increased, an effect overcome by increasing the L-dopa dose. We have investigated tiapride and found an impressive effect on dyskinesias. However, most patients refuse this drug as they feel very lethargic, even at dosages as low as 10 mg.

The stimulation of the GABAergic system should theoretically lead to a decrease in nigro-striatal dopaminergic activity. However, so far there is no GABA precursor or agonist which has been used clinically in dyskinesia.

A precursor of ACh, deanol, has been employed in the treatment of hyperkinesia (*Miller* 1974). A daily dose of 500–900 mg brought about a complete improvement in eight of eleven patients. However *Klawans et al.* (1975) could not confirm these results. We have occasionally observed an improvement with 300 mg deanol, but have found that in the majority of patients the path between suppression of hyperkinesia and reappearance of akinesia is too narrow (*Birkmayer* 1976). *Duvoisin* (1976) showed that cholinergic activating drugs such as physostigmine (1 mg i.v.) reduce choreiform hyperkinesias but aggrevate parkinsonian symptoms.

α-methyl-p-tyrosine has a beneficial effect on choreas (*Birkmayer* 1969a) as well as on the tardive dyskinesias which follow neuroleptic drug treatment. However it is, not surprisingly, unsuccessful in treating the dopa-induced hyperkinesias (*Gerlach et al.* 1974). The fact that anticholinergic medication worsens hyperkinesia reinforces the suggestion that it derives from an inadequate cholinergic activity. Infusion of the physiological ACh precursor, choline, had a sedative effect in 10 of 20 patients with tardive dyskinesia (*Growdon et al.* 1977). *Yahr* (1979) did not observe any improvement in dopa-induced hyperkinesia. In recent years we have administered taurine (3 × 0.5–1.0 g daily) for this side effect (*Birkmayer et al.* 1979) and have found it beneficial in those patients who have only received L-dopa for a short time. But if too high a dose of taurine is used, akinesia reappears. Valproic acid increases CNS GABA levels and has been proposed for the treatment of hyperkinesias (*Rüther* and *Bindig* 1978). *Nittner* (1978) reported that hyperkinesia, including the L-dopa induced side effect, does not occur after a contralateral stereotactic operation. *Duvoisin* (1976) concludes that noradrenaline is not involved since fusaric acid, which blocks the conversion of dopamine to noradrenaline (being an inhibitor of DBH), does not improve hyperkinetic symptoms. In our experience the stimulation of noradrenergic systems accentuates both tremor and hyperkinesia. Antidepressant drugs, including the tricyclics and tranylcypromine, increase the symptoms of tremor and hyperkinesia as does excitation and we interpret this as being an effect of increased noradrenaline function.

The onset of hyperkinesia occurs much later in benign than in malignant Parkinson's disease (see pp. 152–153). This means that the early appearance of side effects reflects early neuronal degeneration. This

degeneration prevents the restoration of biochemical balance by feedback mechanisms. The structural lesions of the striatum (*Gross* and *Kaltenbeck* 1968) and the substantia nigra (*Christensen et al.* 1970) found in tardive dyskinesia can certainly be interpreted as being due to long-term neuroleptic treatment. While choline infusions or taurine medication are initially successful, in later stages after the occurrence of structural lesions a regulatory correction is no longer possible.

In Parkinson's disease the problem remains that each and every drug is active in a defective neuronal system. This is where the difference from depression and schizophrenia lies. In these cases there are biochemical dysfunctions within intact neurons. The treatment of Parkinson's disease will only be completely successful when it is possible to implant healthy melanin cells into the defective substantia nigra.

It is accepted that high L-dopa dosages might accelerate the progression of the disease and lead to an earlier onset of side effects. *Fischer et al.* (1978) have shown that hyperkinesias occur less often with Madopar 125 than with Madopar 250. Lower doses undoubtedly have a protective effect on the neurons. *Barbeau* (1976a) has reported that 50% of his patients develop hyperkinesias after six years. *Parkes* (1981a, b) has observed 50% of mild cases, and 80% of severe cases, with this side effect. There is a dose-dependence; only 33% of patients receiving less than 1 g L-dopa exhibit hyperkinesia, while the respective frequencies for more than 5 g L-dopa, combined anticholinergics and L-dopa, and without anticholinergics are: 88%, 86% and 75%. It is apparent that all the literature reports indicate higher percentages of hyperkinesias than are present in our patients (Table 33). This is certainly due to our lower dosages: Madopar (3 × 250 mg) is the highest dose received by 80% of our patients, albeit in conjunction with deprenyl and possibly bromocriptine or lisuride later.

Hyperkinesias in the shoulder or torsion dystonia cramps are often so painful that a reduction of the L-dopa dose or medication with taurine (3 × 1 g daily) is necessary. Similarly hyperkinesias of the respiratory musculature can be very painful. The patient's respiration loses its natural rhythm and a gasping, groaning breathing occurs, analogous to cardiac extrasystolic sounds. This induces great agitation and perspiration which can often only be controlled by neuroleptics (2 × 25 mg clozapine).

The emotional accentuation of hyperkinesias can be ameliorated by tranquillizers such as diazepam (3 × 2 mg daily), bromazepam (2 × 3 mg), lorazepam (3 × 1 mg) and γ-glutamyltaurine (3 × 5 μg). Akinesias will not normally reappear with this treatment except after an

overdose of tranquillizer. A preliminary study indicated a 60% improvement in hyperkinesia in 200 parkinsonian patients.

Most patients exhibit hyperkinesias when the L-dopa effect is at its highest. The few patients whose hyperkinesias appear as an end-of-dose symptome respond to a timely dose of L-dopa. The correct therapeutic course will depend on the tolerance of the patient. If he can accept oral dyskinesias in order to keep a functional mobility in the legs, then he should be maintained on a higher dosage. The ability of the patient to look after himself is often impaired by a reduction in dose. The earlier the onset of hyperkinesias, the more malignant is the disease and the lower the optimal dose of L-dopa.

Stretch Spasms

Painful stretch cramps occur mainly in the lower extremities and are particularly disturbing at night. They inhibit active movement; when the spasms reach the toes it is impossible to walk. They occur less frequently before the first morning dose. The large toe is often so severely distorted that orthopedic surgeons are induced into making a tendon transplant. This is, of course, futile since it cannot restore the tonic equilibrium. *Ward* (1968) and *Fahn* (1974) attribute these cramps to an imbalance between alpha- and gamma-activity. Too high a dose of L-dopa induces a gamma-hyperactivity, leading to stretch spasms. Night cramps can often be cured by spontaneous movement in bed or – when possible – by walking around. If they persist then the evening dose of L-dopa should be replaced by diazepam (5 mg), lorazepam (1 mg) or taurine (1 g). Morning cramps can be treated with a night-time dose of Madopar 125 or Sinemet 110. As with hyperkinesia, the cramps occur between the third and ninth years of L-dopa treatment. They are, however, less frequent (7%) and easier to remedy.

Sleep Disorders

These are some of the most frequent side effects of L-dopa treatment. They occur in 8.5% of our patients (Table 33), although one should also include the 15% with depression and 19% with dopa psychosis since sleep disturbances occur in both these phenomena. There is recent evidence that sleep disruption is an early feature of L-dopa psychosis (*Nausieda et al.* 1982). Disorders of sleep are accompanied by vivid dreams and anxiety, which correlate with an increase in REM phases. Treatment of this side effect is straightforward; usually omission of the evening dose of L-dopa is sufficient. Otherwise we administer 0.5–1.0 g of L-tryptophan in the evening. A hypnotic effect only occurs when benserazide is given

concurrently to inhibit the decarboxylase and tryptophan 2,3-dioxygenase. This combination has proven effective since the latter enzyme is normally responsible for the removal of more than 90% of tryptophan. Tryptophan given without benserazide improves digestion and lowers blood pressure. An addition of peripheral decarboxylase inhibitors prevents peripheral serotonin synthesis but increases the activity of serotonergic systems in the brain stem and hence has a tranquillizing and hypnotic effect. Older patients occasionally experience a slight "hangover" on the next day. In our experience classical hypnotics are contraindicated as they greatly reduce motor performance on the following day.

Depression

Depression can occur several years before the first appearance of parkinsonian symptoms. However, periods of depression continue to appear during the course of the disease, occasionally elicited by L-dopa treatment. They can be immediately recognized when the patient complains of loss of sleep, appetite, energy, interest, pleasure and so on, despite good motor performance. An evening remission with lightening of mood is accompanied by improved motor function. The drug treatment is straightforward and has been described and discussed on p. 132. The only complication in parkinsonian depression are the cardiac problems such as palpitations, pulse arrhythmias and nightmares. The response of depression to L-dopa and other substitution treatments have been discussed, concluding that depression in Parkinson's disease has a poor response to such treatment.

Dopa Psychoses

The most problematic side effects at the beginning of the dopa era were undoubtedly the psychotic disturbances. They are classified phenomenologically as exogenous reactions. As mentioned, we first encountered this side effect in combined treatment with L-dopa and monoamine oxidase inhibitors (*Birkmayer* 1966). *Cotzias et al.* (1969) later described what he called "toxic delirium"; we find the term "dopa psychosis" more useful. It refers to a psychotic state brought about by dopa, and this trace amino acid cannot be regarded as a toxic substance since it will not induce psychoses in normals (*Rüther* and *Bindig* 1978).

Biochemical Aspects of the Dopa Psychosis

Table 33 shows that 19% of all patients exhibit dopa psychoses. Two vital questions pose themselves:

1. What biochemical mechanism is responsible for their appearance?

2. Which brain regions are involved?

L-dopa is the only natural amino acid known to elicit psychoses in particular circumstances. There is, of course, an inherent predisposition in the parkinsonian brain; the degeneration of the dopamine nigro-striatal pathway presumably causes the dopa psychosis. Other toxic psychoses, including those due to amphetamine, tricyclic

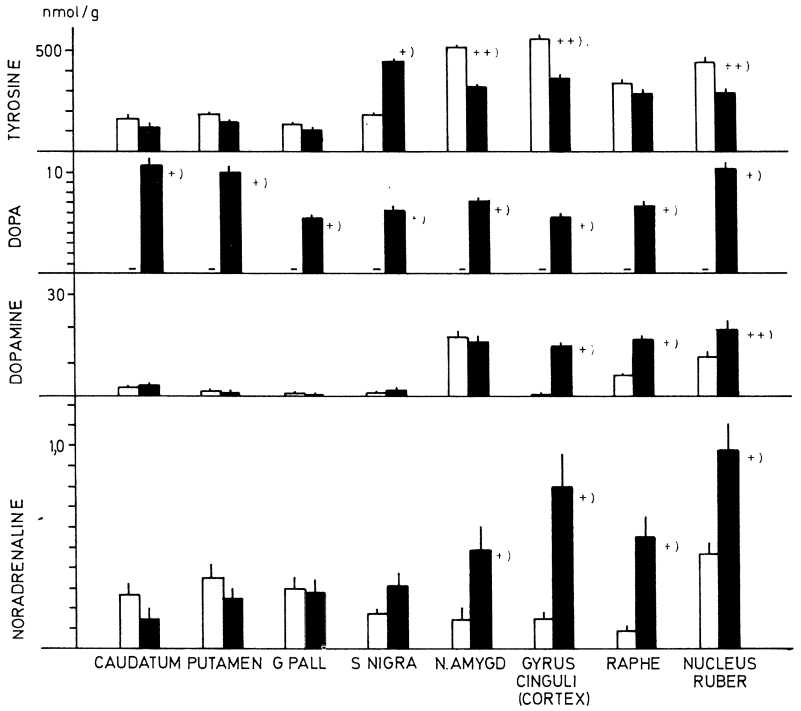


Fig. 52. Dopamine and noradrenaline and their precursors in various brain regions taken post-mortem from parkinsonian patients: relation to L-dopa psychosis. □ parkinsonism, ■ parkinsonism + L-dopa psychosis; * $p < 0.01$, ** $p < 0.05$

antidepressants, anticholinergics etc., also occur more readily in Parkinson's disease. It is noticeable that almost all antiparkinsonian drugs can induce psychoses in parkinsonian patients. Most susceptible are patients receiving dopaminergic agonists, followed by L-dopa and (–)deprenyl . Amantadine infusions are better tolerated, although even anticholinergics can occasionally induce psychoses.

In previous biochemical studies of CSF we found the serotonin metabolite 5-HIAA to be increased almost threefold during an acute

psychotic phase. Since the patients were treated with L-dopa, it would seem that a dopaminergic-serotonergic interaction occurs. Post-mortem studies (Figs. 52 and 53) have shown L-dopa treatment in these patients to induce an increase in brain dopa but a drop in brain tryptophan. Dopamine can only be formed from L-dopa in intact neurons; as dopaminergic cells degenerate a greater proportion of dopamine may be

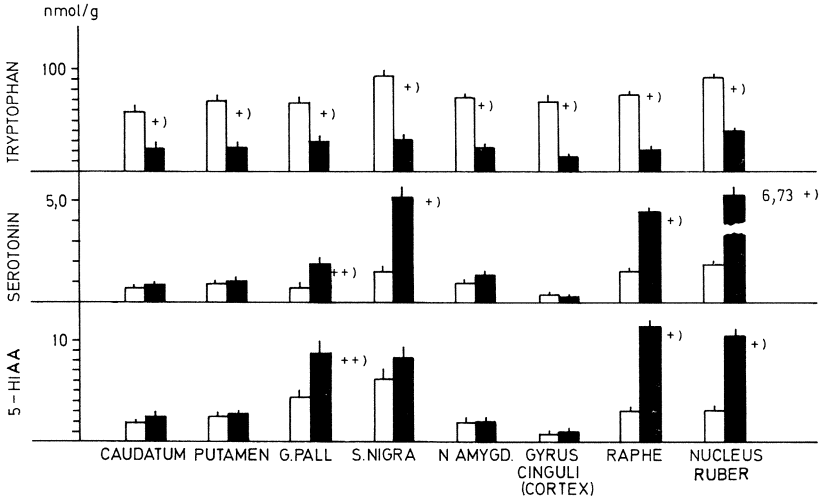


Fig. 53. Serotonin, its precursor and metabolite in various brain regions taken post-mortem from parkinsonian patients: relation to L-dopa psychosis. □ parkinsonism, ■ parkinsonism + L-dopa psychosis, * $p < 0.01$, ** $p < 0.05$

synthesized and stored in other systems. This could lead to a release of serotonin from serotonergic cells due to displacement by dopamine, leading in turn to increased serotonergic activity. It is also possible that the psychosis derives from the increase apparent in dopamine or noradrenaline (Fig. 52) and their subsequent action on respective receptors. The increase found in serotonin and 5-HIAA would then merely reflect a compensatory process. Certainly mild psychotic cases improve with tryptophan treatment (*Birkmayer* and *Neumayer* 1972, 1972a), although in more severe cases it has no effect. It is, however, unclear whether this is a central effect or is possibly due to competition of the amino acids at the blood-brain barrier.

Tryptophan medication had its basis in our observations of increased 5-HIAA in CSF. The dose varies with the intensity of psychotic symptoms (3 × 250 mg – 6 × 500 mg daily). Despite maintaining L-dopa treatment, these symptoms disappear. In severe cases of confusion with motor symptoms, an almost immediate effect is

obtained with 5-HTP (50 mg i.v.). Confusion without disturbed motor function, as in organic dementia, can very rarely be treated successfully. Such patients compose the 3.5% of non-responders (Table 32).

These non-responders represent patients with brain atrophy (Fig. 54), pathological EEG (*Danielczyk* 1978) or an organic brain syndrome (*Jörg* and *Kleine* 1979). Such neuronal lesions cannot be corrected biochemically. In these terminal states *Gehlen* and *Müller* (1974) have found clozapine and clopenthixol to be antipsychotics without increasing akinesia while haloperidol is not recommended. As there are no dopamine neurons to deplete, even reserpine does not accentuate akinesia in severe parkinsonian cases. However, clozapine and other neuroleptics cause reduced motor activity in mild to moderately affected patients (*Birkmayer* 1966).

Patients in remission continue on reduced tryptophan (3 × 125 mg). After the psychotic phase, CSF values normalize: HVA increases and 5-HIAA drops. It was these findings which led us to the hypothesis of "biogenic amine balance" as a prerequisite of normal behaviour.

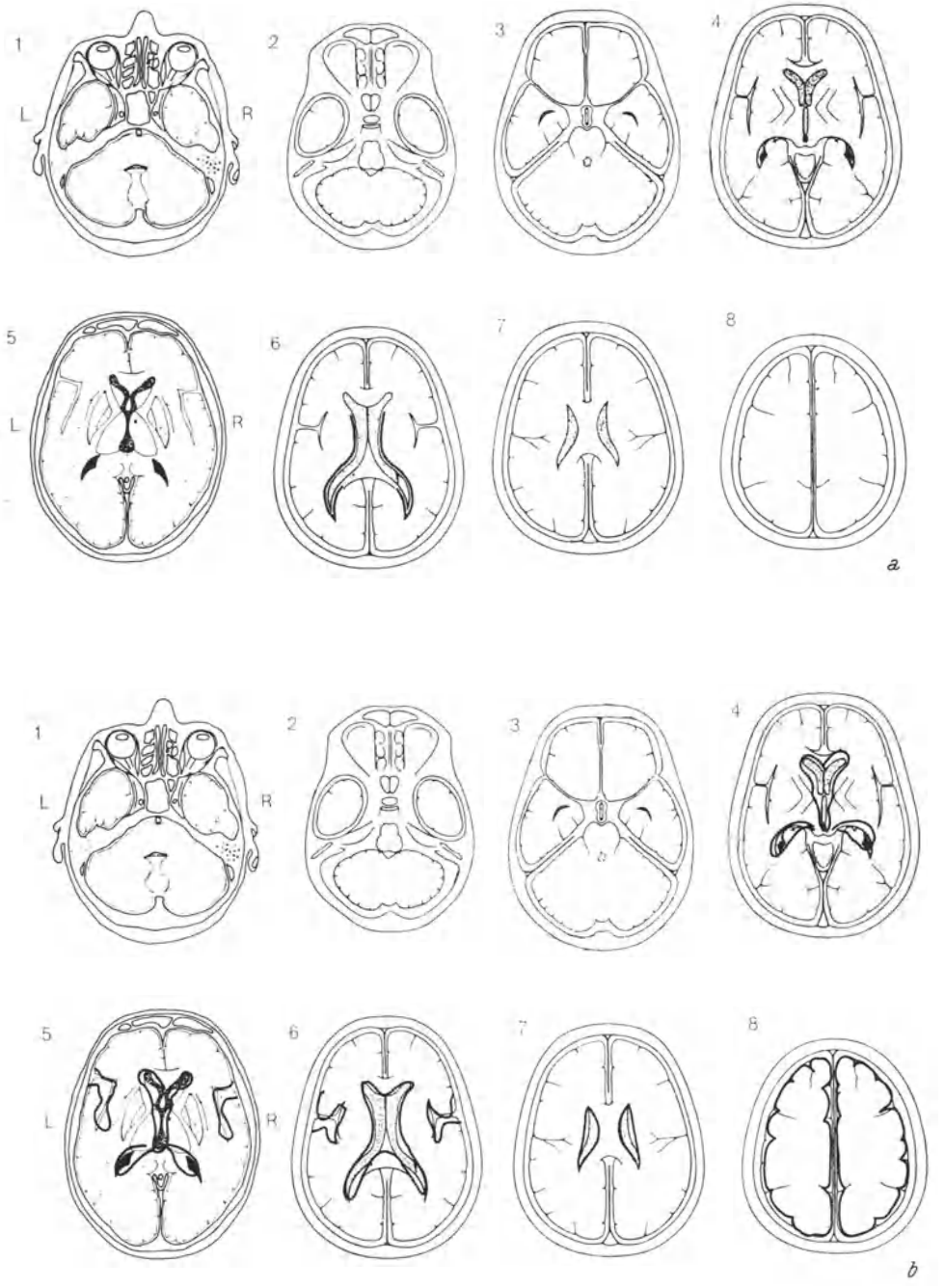


Fig. 54. Two characteristic CT-scans of parkinsonian patient. *a* R. H., female, 60 years diagnosed Parkinson's disease (benign form). Observations: moderately enlarged ventricles (index 3.9). Slight cortical atrophy, particularly in interhemispheric space (mean width 7 mm). *b* K. K., female, 78 years diagnosed Parkinson's disease (malignant form). Severe atrophy with a widening of the upper sulci, enlarged ventricles. (*Fochem* and *Seemann* 1979, with permission)

Treatment of Side Effects

		Daily dose	
Gastrointestinal side effects (Nausea, vomiting)	Metoctopramide	2 tablets	
	Benserazide*	2 × 50 mg	
	Carbidopa*	2 × 25 mg	
	Tryptophan	3 × 250 mg	
Extrasystolics	β-receptor blockers e.g. Oxprenolol	3 × 40 mg	
Orthostatic hypotension	Non-sedating antidepressants		
	Nomifensine	2 × 50 mg	
	Imipramine	2 × 25 mg	
	(Dibenzepine	2 × 80 mg)	
	Deprenyl	5 mg	
	plus Phenylalanine	250 mg	
Vertigo	Dimenhydrinate	3 × 50 mg	
	Thiethylperazine	3–5 × 6.5 mg	
Hyperkinesias	Haloperidol	3 × 2 mg	
	Valproic acid	50 mg	
Spasms	Diazepam	5 mg	
	Bromazepam	3 × 3 mg	
	Lorazepam	1–2.5 mg	
Sleep disturbances	Tryptophan	500 mg	
	Lorazepam	1–2.5 mg	
	Flunitrazepam	2 mg	
Depression	Imipramine	25 mg	Morning dose
	Nomifensine	50 mg	Morning dose
	Amitriptyline	25 mg	Evening dose
	Amitriptyline/ Chlordiazepoxide	12.5/5 mg	Evening dose
Dopa psychosis	Tryptophan	3 × 500 mg	
	5-HTP	50 mg i.v.	
	Clozapine*	3 × 25–50 mg	
	Haloperidol	6 × 2 mg	
	Clopenthixol	3 × 5–10 mg	

* Not commercially available.

Clinical Course of Parkinson's Disease

The progression of Parkinson's disease is more favourable for those patients in whom tremor predominates than for those whose major symptoms is akinesia. Patients presenting with a superimposed brain atrophy, who have a poorer response to L-dopa treatment, have a bad prognosis (*Birkmayer et al.* 1979a, *Danielczyk et al.* 1980).

The disease course can be divided into benign and malignant forms. Table 34 shows that this prognosis is independent of age. However, the severity of the disease is reflected by its duration. The milder cases have a mean duration of 12 years, reduced in the malignant form to four years. Thus in some patients the progressive degeneration is rapid while in others it advances slowly. Of course this parameter only provides a retrospective criterion for benign or malignant disease. There are, however, other criteria which provide an earlier indication. Fig. 55 shows that response to L-dopa treatment distinguishes two forms. Benign cases improve by 40% and return to the original disability score after nine years treatment, while the malignant form is characterized by a poor (14%) improvement, disappearing after about three years. This presumably reflects the rate of loss of functionally intact dopamine neurons, the non-responding malignant group having an inadequate number of neurons for a good L-dopa effect on mobility. The predictive value of this observation can be useful in mentally preparing the patient and his relatives.

A further criterion is the appearance of side effects (Table 35). Hyperkinesias appear between the fifth and tenth years of treatment of

Table 34. *Clinical differentiation between benign and malignant types of Parkinson's disease (from Birkmayer et al. 1979a)*

	Benign type (39)	Benign type (10)	Malignant type (20)
Age (yrs)	63.85 ± 1.38	77.7 ± 1.22	71.4 ± 1.19
Sex	17 f, 22 m	5 f, 5 m	12 f, 8 m
Onset of disease at age (yrs)	56.7 ± 1.25	67.0 ± 1.63	68.0 ± 1.11
Duration of disease (yrs)	12.5 ± 0.44	12.7 ± 0.45	4.0 ± 0.28

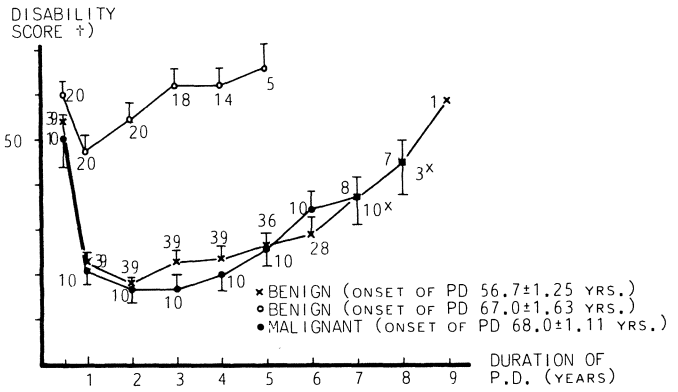


Fig. 55. Benign and malignant parkinsonian patients and their response to L-dopa treatment. (rating see p. 68)

Table 35. *Occurrence of side-effects in benign and malignant Parkinson's disease after the start of combined L-dopa treatment (yrs) (from Birkmayer et al. 1979a)*

Side-effects	Benign type (39)	%	Benign type (10)	%	Malignant type (20)	%
Akinetic crises	5.5 ± 0.51 (14)	36	10.0 ± 1.0 (3)	30	3.2 ± 0.28 (14)	70
On-off phases	5.3 ± 0.56 (17)	44	9.6 ± 0.7 (5)	50	2.7 ± 0.20 (11)	55
Hyperkinesias	4.1 ± 0.30 (22)	56	10.6 ± 0.9 (5)	50	2.5 ± 0.50 (2)	10
L-dopa psychoses	4.4 ± 0.70 (8)	21	5.3 ± 0.6 (3)	30	2.6 ± 0.37 (13)	65

Number of patients in parenthesis; means ± S.E.M.

benign cases, while malignant patients exhibit hyperkinesia after only 2.5 years of L-dopa. This reflects the earlier loss of feedback control between the dopaminergic and cholinergic systems due to the inability to reestablish the biochemical balance.

Similarly dopa psychoses, off-phases and akinetic crises occur earlier in the patients with the malignant disease form. Again these reflect dopaminergic neuronal degeneration with subsequent unspecific dopamine synthesis (psychosis) or inadequate specific synthesis (akinesia).

The specific enzyme defect in Parkinson's disease cannot be overcome by L-dopa substitution, MAO type-B inhibition, attempted restoration of the biochemical balance with antidepressant drugs nor by receptor stimulation with dopamine agonists. Thus it is hardly surprising that the duration of the disease is much the same whether or

not it is treated by L-dopa. This is indicated in Fig. 56, where disease duration is shown for 1256 patients who were treated with L-dopa and 188 who were not (*Birkmayer* 1974). A Finnish group has obtained essentially the same results (*Martilla et al.* 1977). A normal distribution can be seen with a maximum mortality after eight years. Here the only statistical effect of L-dopa on mortality is the relative decrease in the first year of the disease; the group without L-dopa exhibit a mortality peak in the first three years.

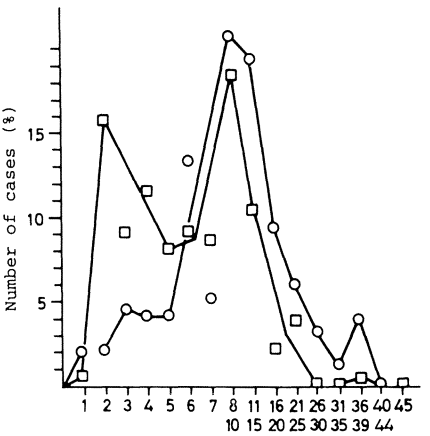


Fig. 56. Duration of Parkinson's disease with and without combined L-dopa therapy. □ patients without combined L-dopa treatment (n = 188), ○ patients with combined L-dopa treatment (n = 1256)

Hoehn and *Yahr* (1967) have calculated that before L-dopa the ratio of observed:expected deaths was 2.9. Put another way, the death rate in Parkinson's disease was almost three times higher than in a matched control group. A comparative study by *Diamond et al.* (1976) revealed the astonishing result that the life expectancy of an L-dopa treated parkinsonian patient was the same as in a normal control group. A multicentre study of some 29 investigators using the methods of *Hoehn* and *Yahr* (1967) obtained an observed:expected mortality ratio of 1.01 in males and 1.08 in females, indicating that with L-dopa treatment, patients with Parkinson's disease have effectively the same life expectancy as the average population (*Charsan* and *Koch* 1978). However, other workers have come up with life expectancy ratios of 2.4 (*Barbeau* 1976b) and 2.33 (*Fischer et al.* 1978), results which are closer to our own experience.

Causes of death in our patients were decubital sepsis in terminal akinesia (50%), circulatory failure (28%) and urinary tract infection

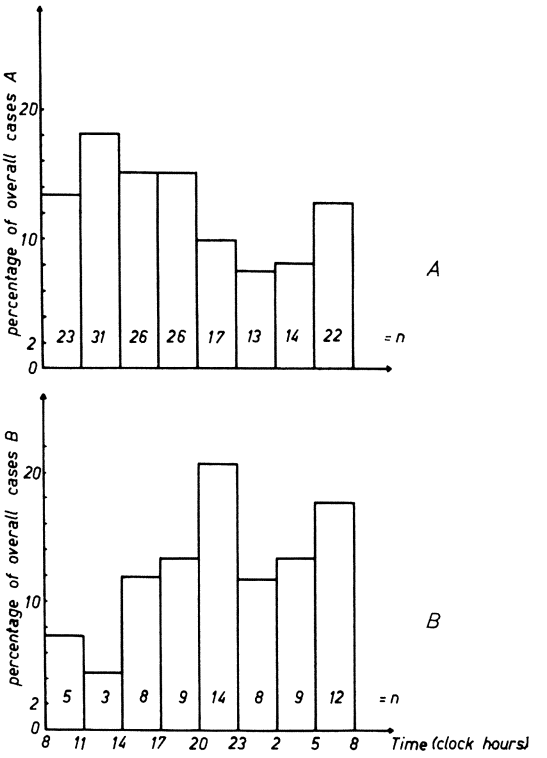


Fig. 57. Circadian rhythm of the time of death in Parkinson's disease compared to other neurological diseases

(8%), the remainder dying of pneumonia. Whatever the agent, the patient had lost all resistance to it. Pneumonia rarely induced fever and decubital ulcers never showed any tendency to heal, in spite of treatment. In most cases this represents an undramatic failure of life functions.

In contrast to other neurological diseases, the time of death of parkinsonian patients lies predominantly in the early hours of the morning (Fig. 57). This is a period of the circadian rhythm in which the parasympathetic system prevails and the action of L-dopa is diminished (*Riederer* and *Wuketich* 1976).

Observations on Human Behaviour

The term "behaviour" immediately invokes Konrad *Lorenz* and his work. Although his considerable observations and the conclusions he drew from them were restricted to the animal kingdom, the psychiatrist sees immediately how much of the behaviour of man is also instinctual. A chain of behavioural actions is initiated by a desire and leads to its satisfaction. Such fulfilment does not come from conscious thought but from territorial acquisition, oral satiation, sexual conquest and aggression. Man, too, is largely governed by instinct.

What then is instinct? Every experience is recorded as a chemical "memory matrix" in a particular part of the brain. Consequently the individual who can rapidly convert these records of experience into a course of action has better chances of survival. Thus instinct is a matrix of memory from previous human and animal experience. The chain of action is so strongly impressed that no behavioural choice is possible. The greater the effect of the original experience, the more readily the instinctual memories are invoked.

A child who has burnt his hand severely will, in later life, keep well away from any fire since his memory associates fire with pain and fear. As a young mountaineer one of us (W. B.) was struck by lightening while on a climbing expedition. Since then, even after 50 years, a thunderstorm provokes fear and an emergency reaction.

These brief sketches serve to indicate how "Lorenzian" behavioural research naturally leads to a consideration of brain stem function. Some important transmitters can be analyzed and their presence in the brain stem may be correlated with particular behavioural functions. Abnormalities in these transmitters produce clinical dysfunctions in motor behaviour, in affect and in the regulation of the autonomic system.

Goethe postulated that a single observation of a scientific phenomenon had an universal validity. Accepting this, it is tempting to view the biochemistry of the brain stem along with the biochemical abnormalities of specific syndromes such as Parkinson's disease and depression in terms of a general model for human behaviour. This has lead us to the following considerations.

If the poor function of motor systems and affect in Parkinson's disease follows from the dopamine deficit, an analogous defect, albeit

not so profound, should be responsible for similar behavioural abnormalities in otherwise healthy people. If one accepts that parkinsonian hyperkinesia is an expression of an imbalance between striatal dopaminergic and cholinergic activity, then it does not seem very far-fetched to us to include the behaviour of "fidgity Phil" (who can't keep still). Thus compulsive movement ranging from fidgiting to tics or Gilles de la Tourette's syndrome are apparently elicited by an analogous biochemical imbalance, a relative hyperfunction of dopamine. If particular neurotransmitter deficits in particular brain stem regions were responsible for single symptoms of depression (e.g. serotonin in the reticular formation for insomnia, noradrenaline in the red nucleus for the stooped posture, or dopamine in the striatum for loss of drive), then single psychosomatic disorders such as insomnia might reflect an imbalance between serotonin and noradrenaline, due perhaps to a stress-induced increase of noradrenaline. Certainly an increased release of this transmitter does occur in situations of stress, inducing the arousal reaction.

The dopa psychosis is another model of a particular type of madness. The L-dopa-induced displacement or depletion of serotonin or noradrenaline from neurons correlates with psychotic behaviour ranging from delirious confusion to hallucinations and delusions. The great increase in dopamine in the cingulate gyrus and the raphe suggests that disturbances of extrastriatal biochemical balance are involved. These observations led us to formulate a hypothesis for the balance of biogenic amine function as a requirement for normal human behaviour (*Birkmayer et al.* 1972).

There is also a reduction of the biogenic amine transmitter with age. This is due to a reduced enzyme activity. The characteristic complaints of old age (lack of drive, inability to make decisions, poverty of affect, reduced sleep, digestive troubles from loss of appetite to constipation) can all be easily related to reduced activity of these neurotransmitters. Nor is it difficult to interpret the decreased motor function of old age as a deficit of dopamine.

To what extent can the "thinking cap" of the human cortex overcome malfunction of the brain stem? Very little is the simple answer. The brain stem of both man and mouse need an increased noradrenergic activity in situations of danger in order to invoke the fight-and-flight reaction. Such archetypal, genetically-coded instinctual memories require the presence of monoamine stores in the appropriate nerve cells. On release the transmitter crosses the presynaptic membrane and the synaptic cleft to communicate with a specific receptor. Reuptake returns the biogenic amine to its specific presynaptic cell. Reduced activity of the synthesizing enzyme (i.e.

tyrosine or tryptophan hydroxylase) or an overactivity of the metabolizing enzymes (MAO or COMT) are biochemical defects which have characteristic behavioural disorders. Specific inhibitors of MAO and other enzymes are at present the most effective therapeutic tools for restoring biochemical balance.

The dynamic equilibrium of these regulatory transmitters is maintained by feedback mechanisms. These function in the autonomic as well as in the affective and extrapyramidal motor systems. For example, low blood sugar induces a noradrenaline output via central stimulation (positive feedback), a large emotional stimulus effects a release of noradrenaline. Blockade of dopaminergic receptors stimulates tyrosine hydroxylase which leads to increased dopamine synthesis to overcome the blockade (positive feedback). Stimulation of the presynaptic autonomic receptor inhibits the tyrosine hydroxylase (negative feedback) which restores the original equilibrium.

These feedback mechanisms do not always function adequately. Murderous instincts are normally suppressed, but in the uninhibited psychopath this feedback inhibition is lacking. The emotional equilibrium of such a person can only return after satisfaction of his desires, his "needs". The disturbed drive and weak will of the psychopath might illustrate the inadequacy of dopaminergic or noradrenergic regulatory activity which would otherwise overcome his pathological behaviour.

Neurotic behaviour can also be understood in these terms. We view the neurotic as having a genetically inadequate tolerance. The biochemical balance necessary for normal behaviour is difficult to maintain due to poor feedback regulation. Normal, "sub-threshold" stimuli repeatedly induce emotional and autonomic disturbances. Thus one can assume that the disorder is sited within the limbic system of the brain stem region. Certainly no peripheral pathology (of the heart, digestive system etc.) has been identified in these cases.

The fashionable psychosomatic diseases have a pathogenic correlation with biochemical abnormalities in the limbic system. Not that this rules out the role of infantile trauma or environmental factors in producing psychosomatic disorders. However, knowing the original cause does not bring us any closer to the mechanisms eliciting these effects.

How does this approach apply to alcoholism? Alcohol is undoubtedly one of the oldest psychoactive drugs. It frequently effects e.g. a serotonin release which leads to sedation, relaxation and sleep. Sweating, flushing and tiredness are clinical symptoms of an overdose. Alcoholism as an addiction is not inherently due to the drug itself, but is an effect of insufficient feedback regulation. Normally the

consumption of alcohol produces a release of tension. A feedback mechanism inhibits further drinking after satisfaction. This regulatory mechanism is lacking in the psychopathological drinker.

The same is true of addiction to amphetamine. This drug induces both a release of biogenic amines and a blockade of their reuptake. Consequently there is an increase in euphoric activity which, in extreme situations (e.g. mountaineering in the Himalayas), can save lives. However, where normal feedback systems are inadequate, this heightened sensation and genuine increase in performance lead to a continual rise in the dose taken in an attempt to overcome the depression which follows the amphetamine effect. Thus the addict is also characterized by poor feedback regulation which is unable to initiate an antagonistic transmitter activity after the need is fulfilled.

These few examples illustrate our view of the biochemical balance of the brain stem as a model for all human behaviour. Rational control via cortical function is unsuccessful; the religious approaches which attempt to reestablish biochemical equilibrium are no longer feasible. In today's society, faith (itself a brain stem phenomenon) possibly is no longer capable of creating harmony in man. The modern surrogate religion of psychoanalysis is based on two hypotheses: 1. The brilliant postulate of *Freud* that human behaviour is essentially controlled by brain stem instinct and that behavioural disturbances are due to a frustration or a childhood trauma. 2. The supposition that various methods can actually release the imprinted instinctual memory of the brain stem and that by reliving these memories behaviour can be normalized: an approach which we feel (after 40 years of experience–W. B.) to be therapeutically useless. Psychoanalysis has alienated itself from scientific research with the attitude found in the christian dogma "Nulla salus extra ecclesiam".

Our interpretations and suggestions, particularly those in this last section, aim to understand all human (pathological) behaviour in terms of the biochemical balance of the brain stem. This provides a basis for research into various neurotransmitters and modulators and their receptors and enzymes which should in turn provide us with a biochemical model for normal behavioural function and thereby enable us to assign biochemical disturbances to their corresponding clinical disorders.

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Subject Index

Journal of
Neural Transmission
Supplementum 16

Current Topics in Extrapyramidal Disorders

Edited by
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für Klinische Neurobiologie, Wien

1980. 1 portrait and 31 figures. X, 241 pages.
ISBN 3-211-81570-8

The pace of research into extrapyramidal disorders has greatly accelerated in recent years. This volume, dedicated to the 70th anniversary of Professor W. Birkmayer, one of the pioneers of research in Parkinsonism and other disorders of the nervous system, spans the range of basic and clinical research on the causes and treatment of disorders of the extrapyramidal system. It includes a series of important contributions on animal models, biochemistry, pathology, physiology, membranes, pharmacology, experimental and clinical therapy of extrapyramidal disorders, written by well-known specialists. The volume is intended to give a review of the current state of knowledge in this particular field of neurology and neurobiology, and will be of interest to research neuroscientists, clinical neurologists, neurochemists and other health care professionals and neurobiologists who deal with extrapyramidal disorders.

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