PARKINSON'S DISEASE

A. VAN WIERINGEN, M.B., Ch.B., M.Med. (Int.) (Pret.)
Lecturer in Medicine, Karl Bremer Hospital, Bellville.

In 1817, James Parkinson, a general practitioner in Shoreditch, wrote "An Essay on the Shaking Palsy". He prefaced it with these remarks: "The disease is of long duration: to connect, therefore, the symptoms which occur in its later stages with those which mark its commencement, requires a continuance of observation of the same case, or at least a correct history of its symptoms, even for several years. Of both these advantages the writer has had the opportunities of availing himself." By his repeated observations he had come to certain conclusions regarding the "nature of the malady" and its probable relief or cure. He mentions that previously "the disease has escaped particular notice" and he considered it his "duty to submit his opinions to the examination of others, even in their present state of immaturity and imperfection".

We are still in a state of immaturity and imperfection regarding this fairly common disease. Much has been written from 1817 onward, many things are known about the Shaking Palsy, but its essential nature still escapes us.

DEFINITION

The words Parkinson's Disease, Parkinsonism, Parkinson's Syndrome are often used synonomously. Like many, James Parkinson had greatness thrust upon him: Jean-Martin Charcot applied the eponym Parkinson's disease to patients with this disease, thereby giving credit to James Parkinson's masterful description of the malady. Not that he was the first to describe it: in his essay Parkinson specifically refers to the writings of Galen (A.D. 129-199) and Sylvius de la Boë (1614-1672). Besides being a medical practitioner James Parkinson was also actively engaged in the politics of his day. It therefore seems inappropriate to apply the suffix "-ism" to his name when we consider his medical ideas and not his political ideology. The term Parkinsonism is inapt and, even when used, too vague: it covers a multitude of sins of commission! Parkinson's syndrome might be applied to that group of symptoms and signs which are collectively present under known etiological conditions e.g. post-encephalitic Parkinson's syndrome, arteriosclerotic Parkinson's syndrome, Parkinson's syndrome due to carbon-monoxide, or manganese poisoning, etc. In other words to apply the name "syndrome" to the symptomatic group of this disorder, and to call idiopathic that variety of the disease described by Parkinson. However, it is as well to point out now, as will be described again later, that the distinctions idiopathic, post-encephalitic and arteriosclerotic are probably not relevant and cannot truly be made. All the other varieties of the syndrome are examples of isolated symptoms of basal ganglion disease occurring simply or in combination with other unrelated symptoms and with a very different pathology e.g. necrosis of the globus pallidus following CO poisoning, the Parkinson-Dementia complex of Guam, and posttraumatic forms of the disease etc.

Parkinson's Disease can be defined clinically no better than James Parkinson's original description which stresses the point that "the submission of the limbs to the direction of the will can hardly ever be obtained in the performance of the most ordinary offices of life". It is this hypokinesia or akinesia that makes life so difficult for a patient with this disease.

Parkinson correctly starts his description of the disease by stating that "so slight and nearly imperceptible are the first inroads of this malady, and so extremely slow is its progress, that it rarely happens that the patient can form any recollection of the precise period of its commencement. The first symptoms perceived are a slight sense of weakness, with a proneness to trembling in some particular part . . . most commonly in one of the hands and arms." He then describes the progress of the disease: the inability "in preserving an upright posture"; "employments accomplised with considerable difficulty, the hand failing to answer with exactness to the dictates of the will"; walking becoming more difficult as the legs are not raised high enough or "with that promptitude which the will directs"; and finally "as the disease proceeds towards its last stage, the trunk is almost permanently bowed, the muscular power is more decidedly diminished, and the tremulous agitation becomes violent". All the difficulties the patient encounters in his daily activities are described fully till the final complete dependency on the services of his nearest relatives.

It is very strange that none of the six cases he describes showed that increase in tone throughout the somatic musculature, clinically most obvious in the limbs, which is known as rigidity. Whether Parkinson failed to appreciate this or did not distinguish it from the akinesia is not at all clear.

It is, however on this triad of symptoms, hypokinesia, rigidity and tremor, that the clinical diagnosis of Parkinson's disease depends. Other abnormalities were appreciated later and are present to a greater or lesser extent in many patients: spontaneous spasms of conjugate gaze (oculogyric crises), loss of involuntary blinking movements of the eyes, but a prolonged blinking response to tapping the bridge of the nose (glabellar reflex), loss of postural reflex mechanisms, seborrhoea, and hyperhydrosis. Loss of weight is a constant feature, reflecting both the heightened energy requirements to propel a rigid body mass and decreased food intake from lengthy meals, difficulty in chewing and swallowing. A not inconsiderable proportion of patients are constipated and a few have difficulty with micturition tending to residua after voiding.

PATHOLOGY

Denny-Brown described the anatomical changes in Parkinson's disease as enigmatic. Again it might be said that the difficulty is in connecting the anatomical changes "which occur in its late stages with that which mark its commencement", such "continuance of observation" obviously not being possible.

What today is regarded as perhaps the most important feature, the loss of cells in the substantia nigra, with loss of the pigment melanin in these cells, was first described in 1925. Prior to this (1908) demyelinization of the ansa lenticularis and related efferent pathways of the pallidum was noted, as well as progressive loss of cells in the globus pallidus (1913). The other pigmented nuclei of the brainstem, the locus coeruleus and the dorsal (efferent) nucleus of the vagus also show loss of pigment. Furthermore, acidophilic cell inclusions have been noted: first by Lewy (1923) and subsequently by many others. The problem with these inclusion bodies is that some workers have described them as a constant feature, others have failed to find them, and to make matters worse they have been seen in specimens where the only clinical diagnosis was that of senility and no features of Parkinson's disease were present in life. However, their presence requires explanation. The image association of an inclusion body is always that of a virus disease, and Parkinson's disease has been closely associated to a presumed virus disease, encephalitis lethargica. Bethlem and Den Hartog Jager (1960) found Lewy bodies regularly in idiopathic paralysis agitans and not in known post-encephalitic cases. Denny-Brown on the other hand found numerous inclusion bodies in one post-encephalitic case. An electron-

microspic analysis has revealed the similarity of the fine filamentous structure of these inclusion bodies with the ultra-structural appearance of melanin granules. Is the Lewy body then perhaps an altered form of melanin?

These are the most important features of the pathology. Widespread changes have however been noted in the cerebral cortex, striatum, reticular formation of the brainstem, the inferior olives and the sympathetic chain ganglia: consistently however, the cortico-spinal tract appears to be spared.

From the material, the pathologist has difficulty in deciding whether the disease process is post-encephalitic, arteriosclerotic or idiopathic. The arteriosclerotic group are clinically those commencing at an age of approximately 60 years with the attitude and tremor of Parkinson's disease usually with a shuffling manner of walking ("marche à petits pas") and occasionally mild manifestations of pseudo-bulbar palsy. Other than the above-named pathological findings there is an association with small lacunar infarcts in the putamen. The arteries and arterioles show degrees of atherosclerosis compatible with the age of the patient and in all respects this group can be considered as "Parkinson's Disease with arteriosclerosis".

Where there is an evident antecedent history of the encephelitis lethargica which was epidemic throughout the world from approximately 1918 through 1926, and sporadically perhaps until 1930, the resulting Parkinson's disease may be labelled post-encephalitic. When all other etiological considerations are eliminated a group remains, which, for want of better, is labelled idiopathic. Poskanzer and Schwab have however even thrown some doubt on this approach by formulating their cohort group theory by which they imply a group of the population ageing together which were ages 5-59 in 1920. Their distribution curves show that with an increase in age the incidence of Parkinson's disease increases as well. They therefore regard most, if not all, cases of Parkinson's disease to be a late sequel of encephalitic lethargica. Important corollaries from this hypothesis are that forty years or more may elapse between an initial, presumably infectious insult and the development of a secondary neurological manifestation (such as Parkinson's syndrome), as well as that when this cohort ages and its members die off the disease should disappear. Here lies the difficulty: few patients under the age of 5 years were reported with encephalitis lethargica when it occurred: presuming a person was age 5 in 1926 he will only be 60 years of age in 1981, after which date the expected decrease in incidence could only become apparent.

There is no doubt that the incidence of Parkinson's disease is greater at the present time than in the previous century or even at the turn of this century. This might also be explained by the fact that the over-all life expectancy has greatly increased and since Parkinson's disease is usually a disease commencing in the late middle-years, more cases could be expected today than previously.

The other causes which are frequently listed as causing Parkinson's disease are however different. Acute anoxia, such as with CO-poisoning, results in necrosis of the globus pallidus and clinically these patients resemble an akinetic mutism with rigidity of all four limbs or a decerebrate rigidity. Clinically it is not truly Parkinson's disease. Manganese mine workers are reported to show Parkinson's disease indistinguishable from the idiopathic variety. The pathological changes in cases with manganese poisoning and idiopathic Parkinson's disease also do not differ. Poisoning is the result of inhalation, followed by coughing up of the dust which is then swallowed. In 1924 Mella experimentally produced basal ganglia changes in the Rhesus monkey by poisoning it with manganese. I think that the role of manganese has not been elucidated. Merritt states that the occurrence of symptoms of Parkinson's disease in a middle-aged or elderly male who is exposed to manganese raises a difficult medico-legal problem.

The dystonias produced by certain drugs, particularly of the phenothiazine group, may superficially resemble that of Parkinson's disease, but the course is benign, resolving on cessation of drug intake, except in the elderly where the clinical manifestations may be irreversible. Akinesia and dystonia are the hallmarks of the toxic effects of these drugs and it only confuses the issue to consider these as examples of Parkinson's disease.

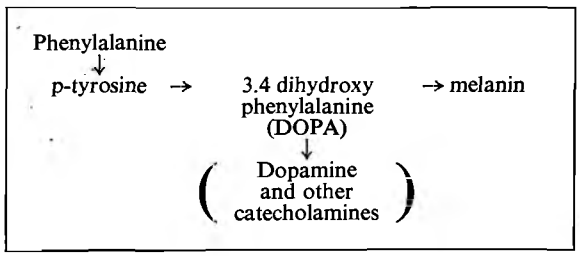
BIOCHEMICAL CHANGES

Latterly, it has become obvious that biochemical aberrations form part of Parkinson's disease and the persuance of these findings has led to the newest advance in the treatment of this disease and to better understanding of past treatment.

In 1957 Weil-Malherbe and Bone detected dopamine in the brain; its restricted distribution in the striatum, globus pallidus and substantia nigra, was appreciated in 1959. At this time it was proposed that dopamine was a transmitter substance of the central nervous system, specifically of the basal ganglia and associated structures. In 1960 Ehringer and Hornykiewicz demonstrated that the level of dopamine in these areas was greatly depressed or absent in patients dying of Parkinson's disease. Barbeau *et al* (1961) found that the urinary excretion of dopamine, strangely enough, was also decreased and that this finding correlated particularly well with the akinetic-rigid patient or with a very far advanced stage of the disease. It is not found when tremor or other dyskinesias are the main symptoms. The drop in dopamine excretion in the urine from the normal is some 30-40 per cent which cannot be due only to a decrease in dopamine production in the brain: basal ganglia dopamine accounts for only 1 per cent of the total body dopamine. It is acceptable therefore to believe that there may be a more generalized defect in Parkinson's disease. Other evidence to support this concept have been the frequent abnormal glucose tolerance curves, diffuse fibrotic changes in the liver, abnormal bromsulphtalein tests and a slightly elevated serum ceruloplasmin. Transferrin has been found to be significantly increased where tremor was the dominant symptom: the serum iron and serum iron binding capacity remain within normal limits.

To fit all these findings together we shall have to regard Parkinson's disease not as a disorder uniquely confined to the brain, but as a generalized defect and that the disease may be a systemic disorder. Whether these effects are secondary to the pathological change found in the dorsal nucleus of the vagus which is the control-tower of the autonomic parasympathetic system to the thoracic and abdominal viscera, or whether Parkinson's disease represents a primary enzyme defect cannot be said. Indirect evidence favouring the first is that there appears to be a diurnal variation in the rhythm of activity of tyrosine transaminase in the liver due to variation in the activity of adrenergic control pathways.

One apparent link ties some of these findings together. The metabolic pathways for the formation of the catecholamines and the formation of melanin have a common source in phenylalanine, an essential amino-acid.



The decrease in melanin in the pigmented neurones of the brain and the decreased content of dopamine in basal ganglia might therefore be considered as derangements of one single biological system.

Some aspects of melanin should therefore be considered. A great deal is known about cutaneous melanin, very little about neuromelanin and on histochemical ground they could be considered separate substances. Melanogenesis in the melanocytes of the epidermis is under control of M.S.H. (melanocyte stimulating hormone of the anterior hypophysis). An attempt to treat patients with Parkinson's disease with M.S.H., however, led to an aggravation of the symptoms.

Parkinson's disease is extremely rare among the Bantu whilst schizophrenia is common. Patients with schizophrenia excrete 3.4 dimethoxyphenylethyl-amine (DMPEA), a dimethylated derivative of dopamine which gives a characteristic "pink spot" on paper chromatograms; this same substance has been found in the urine of patients with Parkinson's disease. The hypokinesia of Parkinson's disease and the catatonia of schizophrenia may therefore be related clinical manifestations due to the same underlying defect in dopamine metabolism. Furthermore, the phenothiazine drugs are effective in the treatment of schizophrenia, but, as already mentioned, produce a dystonic syndrome, occasionally with a marked akinesia resembling Parkinson's disease. To complete this circle, chronic schizophrenics on long-term phenothiazine therapy develop a peculiar pigmentation of the skin. Finally, the ultrastructural resemblance between the Lewy inclusion-body and normal melanin is an interesting recent finding.

Melanin is a strong electron acceptor and the question arises whether it may be concerned in dopamine synthesis.

Following the discovery of the lowered dopamine content of the basal ganglia in Parkinson's disease an attempt at a therapeutic approach was made by trying to substitute this substance. Dopamine does not cross the blood-brain barrier, but its precursor, dopa, does. Through trial and error it was finally found that the L-isomer was the physiologically active principle and that large doses were required to be therapeutically effective. George Cotzias' results in 1967 were repeated in many centres in Europe and America with the same promising results.

Although the premise was rational and the results in keeping with it, the explanation of the action of this drug is not quite so facile. What does L-dopa do?

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It would appear as if less than half of the oral dose (capsule or tablet) is absorbed from the gut. The lion's share of the absorbed quantity has first of all to saturate the decarboxylating enzyme (which converts it to dopamine) and which is present in the blood and other extra-cerebral tissues. Only then can the remainder pass over the blood-brain barrier into the brain where it selectively accumulates in the basal ganglia as shown by isotope-tagged L-dopa autoradiographic studies. In the brain it is presumably immediately decarboxylated to dopamine. A promising new development is the use of a decarboxylase inhibitor which selectively inhibits extra-cerebral decarboxylase, thus increasing the L-dopa available for transfer across the blood-brain barrier and leading to a reduction of the dose to be taken by the patient.

A minute amount of the L-dopa taken by mouth is therefore finally used for its specific therapeutic response and this represents a gross wastage of a very expensive drug.

What does the newly-formed dopamine then do? As already stated dopamine is considered a central nervous system transmitter substance and (one of ?) its normal anatomical site is an ascending nigra-striatal pathway. It is not conceivable that the newly-formed dopamine can influence the degenerated neurones in the substantia nigra: these cells are dead and as neurones are considered to be non-mitotic cells, cannot regenerate. However, a sick but not dead neurone's function could conceivably be restored and this could explain the common observation in patients with Parkinson's disease that increasing improvement occurs with steady doses of the drug. This makes a strong point to give L-dopa to early mild cases of the disease as a prophylactic measure in order to prevent progression of the disease. On the other hand it may be that non-dopaminergic neurones are converted to dopaminergic ones during prolonged treatment which could explain the late development of involuntary movement of a choreiform nature.

A practical, although extremely simplified, view is that there appears to be a delicate balance between the concentrations of the various central transmittor substances, the most important being acetylcholine and the catecholamines, particularly dopamine. The scale is tipped in favour of the former in Parkinson's disease owing to the decrease in dopamine. Correction of this imbalance in the past has been by lowering the effectiveness of acetylcholine through the administration of anticholinergic drugs such as benztropine, orphenadrine, trihexyphenidyl, procyclidine, etc., as well as the naturally occurring belladonna alkaloids. The scale is then balanced again, albeit at a lower level. Dopamine now lifts the scale in its own favour and should therefore restore the balance at a more physiological level.

SUMMARY

An attempt has been made to define Parkinson's disease in terms of its clinical, anatomical and biochemical aberrations. The apparent link between the anatomical (melanin) and biochemical (dopamine) aspects is the common metabolic pathway from phenylalamine through 3.4 dehydroxyphenylalamine (DOPA). A tenuous link between the clinical (catatonia; akinesia), anatomical (melanin: race, and pigmentation effects of phenothiazine) and biochemical (DMPEA) is provided by the comparison of schizophrenia with Parkinson's disease.

Finally, although the rationale for treating patients with Parkinson's disease with L-dopa would appear to be that of simple substitution of a deficiency state (of dopamine) the interpretation of the therapeutic effects is, as James Parkinson said, still in a state of immaturity and imperfection.