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COMMENTARY

PARKINSON'S DISEASE AND ITS CHEMOTHERAPY

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Parkinson's disease (Pd) is a chronic and progressive degenerative disease of the CNS [1]. As a clinical entity, it was described in England in 1817 by James Parkinson. Parkinson called the disease "shaking palsy"; this misnomer was later translated to the Latin "paralysis agitans". It was the French neurologist Charcot who gave it the name "Parkinson's disease".

In his masterly account on the clinical manifestations of the "shaking palsy", Parkinson was in a position to refer to several older medical sources, quoting among others the writings of the late-Roman physician Galen. Thus it seems that the disease to be eventually called "Parkinson's disease" has indeed been with our civilization for a long time.

Symptoms and course of Parkinson's disease

The fact that some of the clinical features of Pd were already known to the ancient physicians is not surprising; the cardinal symptoms of Parkinson's disease are obvious even to the untrained observer. As a matter of fact, three of James Parkinson's original cases described in "An Essay On Shaking Palsy" were not his patients but people Parkinson had observed in the street.

The rich variety of clinical signs of Pd of extrapyramidal origin can be reduced to three cardinal symptoms. These are: tremor ("shaking") which usually ceases when the affected limb is moved voluntarily but returns as soon as the movement comes to an end (= tremor at rest); "plastic" (cogwheel) rigidity or stiffness of the skeletal muscles; and akinesia, i.e. difficulty in initiating movements or modifying ongoing motor activity. Of this triad of symptoms, akinesia is considered to be the most disabling feature, and tremor, although being the most conspicuous sign, the least. In the final stages of the disease, the patient often appears quite immobile and "frozen", being unable to initiate (akinesia) and/or perform (rigidity) meaningful motor acts.

Pd sets in insidiously, most commonly in the middle period of life. Apart from being rare or unknown in equatorial regions, the disease does not otherwise discriminate between races, sexes, occupational groups or social classes. Usually the symptoms first appear on one side of the body (Hemiparkinsonism) but later spread to the other side. According to certain accepted clinical–morphological criteria, the patients are subdivided into three main categories: (1) idiopathic form (or paralysis agitans proper), etiology unknown; (2) postencephalitic form, a sequalae of Von Economo's encephalitis; and (3) arteriosclerotic form, as part of a generalized vascular encephalopathy. The most common form of Pd is the idiopathic variety for which hereditary factors have been demonstrated.

Pathophysiology

The seemingly simple question as to the main morphological lesion in the brain of patients afflicted with Pd has been a matter of considerable disagreement over the past hundred years. Clinically, however, Pd has long been regarded as a classical example of a dysfunction of the basal ganglia, that is the telencephalic subcortical nuclei, notably the striatum (= caudate nucleus and putamen) and pallidum (*globus pallidus*). At present, the lesion most specific for Pd is considered to be the degeneration of the melanin-containing neurons in the compact zone of the *substantia nigra* and, to a lesser degree, other melanin-containing brain stem nuclei, such as the *locus coeruleus*. Apart from speculations, nothing is known about the possible biochemical basis for this selective cell death.

The exact role of the *substantia nigra* for the functioning of the basal ganglia is not yet fully understood. It is known, however, that this midbrain region is interplaced in the subcortical neuronal circuits of the extrapyramidal motor system, being reciprocally connected with caudate nucleus, putamen and *globus pallidus*, as well as projecting to the ventral thalamus and receiving cortical inputs; nigral projections to the reticular formation of the lower brain stem and spinal cord have also been suspected. Thus, the *substantia nigra* may be regarded as a nodal point for the extrapyramidal motor system, probably exerting a modulating influence on the activity of the higher, striatal control centres. Lesions placed experimentally in the *substantia nigra* of laboratory animals will reproduce some of the main symptoms of Pd, notably akinesia [2]; under certain conditions, tremor and rigidity have also been produced.

Neurochemical basis for a pharmacology of the basal ganglia

The most prominent biochemical feature of the basal ganglia is their conspicuously high content of putative neurotransmitters, notably dopamine (DA) and acetylcholine, which are both localized to synaptic terminals within the striatum, and gamma-aminobutyric acid (GABA). Acetylcholine may serve as transmitter in the rich intrinsic intraneuronal networks of the striatum [3]. The DA found in the striatal nuclei is confined within a well-defined pathway which originates in the compact zone of the

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substantia nigra and ends synaptically in the striatum [4]. Neuropharmacological observations suggest that in the striatum the cholinergic and dopaminergic systems are functionally interdependent; the exact nature of this interdependence is still under discussion [5]. In general, it seems that normal functioning of the striatum is determined by the proper balance between these two opposing systems. Dopaminergic overactivity or cholinergic hypoactivity results in increased locomotion, hyperkinetic behaviour and hypotonia of the skeletal muscles. In contrast, DA deficiency and/or cholinergic hyperactivity produce catalepsy (akinesia), rigidity of the skeletal muscles, and tremor [6].

Parkinson's disease as a striatal dopamine deficiency syndrome

Neurochemically, Pd is characterized by a severe deficiency of DA and its metabolic end product, homovanillic acid (HVA), in the basal ganglia, notably the caudate nucleus, putamen and *globus pallidus*, as well as the *substantia nigra* [7]. Concomitantly, there is also a decrease in activity of the enzymes synthesizing DA, namely L-tyrosine hydroxylase and L-dopa decarboxylase [8]. These changes are typical for Pd regardless of its etiology; they can be considered as a consequence of the degeneration of the melanin-containing neurons in the *substantia nigra*, which give rise to the dopaminergic nigro-striatal pathway [9].

The concept of Pd as a striatal DA deficiency syndrome is supported by the demonstration of a cause–effect type relationship between the striatal DA deficiency and the Parkinsonian symptomatology. Thus: (a) in Hemi-parkinsonism the neurochemical changes are more pronounced in the striatum contralateral to the affected side of the body [10]; and (b) the degree of striatal DA (and HVA) deficiency has been shown to be positively correlated with the severity of symptoms (notably akinesia and tremor) [9]. Accepting the concept of interdependence of striatal dopaminergic and cholinergic mechanisms, the striatal DA deficiency in Pd may be expected to result in a cholinergic preponderance; the latter may thus aggravate the symptoms due primarily to DA deficiency (see below).

Compensated and decompensated stages of Parkinson's disease

Important for the understanding of drug effectiveness in Pd is the observation that mild, clinically just detectable cases are accompanied by a disproportionately high degree of DA deficiency (70–80 per cent decrease) in the striatal nuclei [9]. This suggests that the striatum may be able to compensate functionally for lower degrees of DA deficiency. Based on this neurochemical–clinical correlation, Pd may be subdivided into two stages: (a) the compensated, clinically latent stage during which the remaining DA neurons can off-set functionally the decrease in striatal DA; and (b) the stage of decompensation, i.e. the clinically overt syndrome, which manifests itself when the degree of DA deficiency exceeds the compensatory capacity of the affected striatum. In support of the above considerations, one can refer to observations showing that: (a) in the Parkinsonian striatum, the ratio "DA:HVA" is shifted in favour of HVA; this suggests that in Pd the still functioning DA neurons are in a state of overactivity, synthesizing and releasing more DA per unit time than normally [11]; and (b) loss of DA neurons, if not too excessive, is not necessarily synonymous with impaired function; this can be inferred from the high degree of divergence characteristic of the dopaminergic innervation of the striatum [12].

From the above, it can be concluded that the main goal of an efficient chemotherapy of Pd will be to revert the decompensated stage of the striatal DA deficiency to the stage of functional compensation. Depending on the severity of the clinical condition, this may be achieved by different drugs or combinations of drugs, affecting either the dopaminergic or the cholinergic systems, or both.

Chemotherapeutic agents used in Parkinson's disease

Over the 150 years since its description as a clinical entity, there has been hardly a drug that has not been tried in patients suffering from Pd. This includes such oddities as ferrisulphate and barium chloride, but also strychnine, metrazole, diverse thyroid and parathyroid preparations and even "striaphorin", an extract from the striatal nuclei. (Outlandish as the latter attempt appears to us now, it is possible that "striaphorin" actually contained DA; thus, its failure as a remedy for Pd might have been due to such secondary factors as the impenetrability of the blood–brain barrier to DA.) However, it is interesting to note that during this period of pure empiricism three drugs had been discovered (belladonna alkaloids, amphetamine and apomorphine) which according to our present concepts can be regarded as representing the three main groups of anti-Parkinson agents. These three groups are:

Anticholinergic drugs. As early as 1867, Ordenstein recommended belladonna alkaloids as remedies in Pd. Newer, more effective compounds are: benztropine, trihexyphenidyl, procyclidine, biperidine, orphenadrine, and several compounds with both anticholinergic and strong antihistaminic activity, such as benadryl. The anti-Parkinson activity of such drugs is thought to be due to their ability to block the cholinergic (muscarinic) receptors in the CNS (see, however, below), based on the rationale that the cholinergic preponderance resulting from the decrease in striatal DA aggravates the main symptoms of Pd, adding to the over-all degree of decompensation. Thus, in mild cases with Pd, anticholinergic drugs can be expected to contribute significantly, though indirectly, to the re-compensation of the disturbance.

Indirectly acting dopaminomimetic drugs. The best known representative of this group is dexamphetamine, found to be effective in the treatment of Pd in 1937 by Prinzmetal. Newer drugs include the amphetamine-like methamphetamine and methylphenidate; amantadine, originally marketed as an antiviral agent, may also belong to this group. ("Indirectly acting" in the above definition means that the effectiveness of the compound is dependent on the intactness of the striatal DA stores.) These compounds produce a dopaminomimetic effect by releasing and/or blocking the reuptake of DA. The latter mechanism is probably the more important one, producing a "potentiation" of action of the synaptically

released DA at the receptor sites. Similar to the anticholinergics, indirectly acting dopaminomimetic drugs will also be effective mainly in cases in whom the DA deficiency, i.e. the degree of decompensation, has not yet reached too high proportions: in these cases inhibition of DA re-uptake into the synaptic terminals may be sufficient for functional re-compensation.

Directly acting dopaminomimetic drugs. Apomorphine is a good example of this group of drug. It was found to be effective in Pd in 1952 by Schwab. Piribedil is a newer drug possibly with direct dopaminomimetic activity (see below). From a clinical point of view, the most important drug in this group is L-dopa (levodopa), the immediate precursor in the biosynthesis of DA. ("Directly acting" in the above context means that the effectiveness of the drug is independent of the endogenous DA stores. However, in the case of L-dopa, the presence of a critical minimum of L-dopa-decarboxylating activity in the diseased striatum is a prerequisite.) In contrast to the other anti-Parkinson drugs, the directly acting dopaminomimetic compounds, notably L-dopa (via dopamine), are also effective in severely decompensated cases, that is, when the striatal DA deficiency has reached high degrees. In these cases, only an increase in direct dopaminergic activity in the affected striatum can be expected to be an effective means of producing a re-compensating effect, i.e. restoring function.

It should be emphasized, however, that the above classification represents, from a biochemical–pharmacological point of view, an over-simplification. Thus, anticholinergics and antihistaminics may, in fact, belong to the indirectly acting dopaminomimetic drugs, as it has been shown that they are potent inhibitors of the re-uptake of DA into the synaptic terminals [13]. Similarly, experimental results regarding amantadine are still controversial, with some observations suggesting that this drug may also have some direct dopaminomimetic activity. It is intriguing to note that, of all the above-mentioned drugs, only L-dopa has been introduced into the therapy of Pd on a clearly rational basis. This would be a discouraging circumstance if it were not for the fact that, of all anti-Parkinson drugs presently used, L-dopa is by far the most potent.

L-Dopa as an example of rational approach to drug therapy of Parkinson's disease

The discovery of diminished DA concentrations in the basal ganglia of patients suffering from Pd led directly to the attempt at replenishing the missing amine with its precursor substance, L-dopa [14, 15]. (DA itself does not penetrate the blood–brain barrier.) At present, therapy with L-dopa represents the most efficacious form of drug treatment of Pd [16]. Of the three cardinal symptoms, akinesia reacts the most sensitively to L-dopa and tremor the least.

All available evidence justifies the original expectation that, in patients with Pd, L-dopa acts, in principle, as a DA-replenishing drug. Thus, it could be shown in post-mortem analyses that patients, who were on chronic oral L-dopa (2–6 g daily) until death, had 9 to 15-fold higher levels of DA and HVA in the caudate nucleus and putamen than non-dopa-treated patients [17]. The biochemical basis for the metabolic transformation of L-dopa in the striatum of patients with Pd is provided by the observation that, although markedly reduced, enough L-dopa-decarboxylating enzyme activity remains in the Parkinsonian striatum to account for the formation of DA in these nuclei [18]. In this context, it is significant that patients with a good response to L-dopa therapy achieved striatal DA levels several-fold higher than those of poor responders [8]. This observation is not unexpected in view of the cause–effect relationship between the striatal DA deficiency and the main symptomatology of Pd. Particularly noteworthy is the possibility (see above) that the clinically manifest Pd may represent a (late) decompensated stage of a progressive DA deficiency which in earlier stages can be functionally compensated by the affected striatum. Thus, the fact that therapeutically administered L-dopa is converted to DA in the Parkinsonian striatum suggests that the main pharmacological property of L-dopa as a specific anti-Parkinson drug may be its ability to revert the decompensated stage of the striatal DA deficiency syndrome to that of functional re-compensation.

Possible neurophysiological mechanisms for L-dopa's effectiveness in Parkinson's disease

The fact that L-dopa is effective also in severe cases of Pd invites a special comment. Obviously, in such cases a rather marked degeneration can be presumed of those neural elements which contain the enzymatic machinery necessary for formation of DA. Here, the same two factors which may be responsible for the "compensated stage" of Pd (see above), seem to be at work: (a) because the still functioning DA neurons are in a state of over-activity, the rate of synthesis and release of the DA derived from the therapeutically administered L-dopa will be considerably above normal; and (b) the high degree of divergence of the dopaminergic innervation of the striatum is a safety factor which tends to preserve the "critical minimum" of innervation indispensible for functional re-compensation by L-dopa. Thus, the combination of these two factors may ensure that: (a) there will be high amounts of DA formed from L-dopa, and (b) this DA will reach a wide enough area of the diseased basal ganglia so as to restore the dopaminergic control of striatal function. An additional important factor is the possibility that, because of degeneration of the nigro-striatal DA neurons, the Parkinsonian striatum becomes supersensitive to DA. This "denervation supersensitivity" can be assumed to increase with the degree of the denervation of the striatum, that is to say with the severity of the clinical condition. This possibility is supported by observations showing that: (a) severe cases react more sensitively to a test dose of L-dopa than milder cases [9], and (b) L-dopa-induced hyperkinetic reactions can be easily provoked in Parkinsonian patients but not in control subjects [19]. From the above comments, it is obvious that some Pd cases with a complete or near complete degeneration of the nigro-striatal DA pathway will have lost the most essential prerequisites for re-compensation; these might, in fact, be those cases that, despite achieving sufficient blood

levels of the drug, consistently show little or no response to L-dopa.

Directly acting dopaminomimetics other than L-dopa

Several attempts have been made to introduce directly acting dopaminomimetics other than L-dopa into the chemotherapy of Pd. Of these, apomorphine, a "rigid" analogue of DA, has been already mentioned. More recently, piribedil, a non-catechol analogue of DA [1-(2"-pyrimidyl)-piperonyl-piperazine] has been tested experimentally and clinically. It seems, however, that in regard to therapeutic potency none of these compounds comes close to L-dopa. This is not surprising because, when compared with DA, neither apomorphine nor piribedil has a full agonistic activity at the DA receptors. Apomorphine has been shown to be a partial agonist, that is a potential antagonist, of DA, both centrally [20] and peripherally [21–23]. The same seems to be the case for piribedil. Thus, similar to apomorphine, piribedil possesses only a fraction of DA's potency in activating the specific (DA-sensitive) striatal adenylate cyclase [24]; this cyclic-AMP-forming enzyme has been suggested to be the possible (immediate) DA receptor in the striatum [25]. Likewise, several complex L-dopa derivatives which may be formed in the body during prolonged L-dopa administration (such as various tetrahydroisoquinoline and tetrahydropapaveroline derivatives [26]) have been shown to be poor activators of the DA-activated striatal adenylate cyclase [27, 28]. This, among other evidence [29], makes speculations [30] that these L-dopa derivatives may be responsible for the drug's main therapeutic effectiveness in Pd rather unlikely.

Prospects for future research

L-Dopa, being the physiological precursor substance in the biosynthesis of DA in the mammalian organism, is obviously the most "natural" compound for replenishing the depleted brain DA of Pd patients. However, from a biochemical–pharmacological point of view, L-dopa is not "ideal" as a drug, because in the body L-dopa is extremely unstable. It is being quickly and extensively metabolized in the peripheral tissues so that rather high and frequent doses are necessary in order to obtain effective and sufficiently sustained brain levels of the drug. In addition, the metabolic transformations of L-dopa give rise not only to DA but also to a host of other compounds, some of them with known (norepinephrine) pharmacological properties, but most of them with as yet little known (tetrahydroisoquinolines, tetrahydropapaverolines, *O*-methylated and transamination products, etc.) properties. The numerous side-effects observed in patients treated chronically with L-dopa attest to the above. Although concomitant administration of an extracerebral decarboxylase inhibitor may obviate some (but not all) of L-dopa's disadvantages [31], this ingenious approach introduces new problems which are inherent in any potent "combination therapy."

At the present stage of our knowledge—which perforce is incomplete—the "ideal" chemotherapeutic agent in Pd should possess the following attributes: (a) directly acting dopaminomimetic agent, exerting (in contrast to apomorphine and piribedil) a full agonistic activity at the striatal DA receptors; (b) good penetrability through the blood–brain barrier; and (c) metabolic stability (in contrast to L-dopa and apomorphine), thus producing a prolonged effect on the DA receptors. Although apart from the striatum there may exist several other (peripheral and central) tissues which react specifically to DA, the supersensitivity of the DA receptors in the Parkinsonian striatum would appear to confer, quantitatively speaking, some degree of selectivity of action for such an "ideal" dopaminomimetic anti-Parkinson drug. The development of such a compound represents a challenge to medicinal–chemical as well as biochemical–pharmacological research.

In 1959, Schwab [32], a profound expert on Pd, wrote in reference to the drug therapy of this disabling disorder: "...Until this present day there has not been any specific remedy for Parkinson's disease, such as for instance insulin for diabetes.... This represents a challenge to the medical community...." With the discovery of L-dopa as a potent, though (like insulin) mainly symptomatically acting agent, we are now in possession of such a specific remedy for Pd. It is to be hoped that further development along these lines will eventually result in a more optimistic appraisal of the chemotherapeutic possibilities for Pd, in particular, and chronic degenerative brain diseases, in general.

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