Parkinson's disease in 1984: an update

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This update reviews several important topics in the field of Parkinson's disease, including etiologic studies, the types and mechanisms of drug complications and their treatment, when and how to begin treatment, the association of dementia with Parkinson's disease, and the development of the newer research tools. The recent discovery of a highly selective neurotoxin (MPTP) that causes parkinsonism in humans and other primates and the use of positron emission tomography in living patients should improve our understanding of the cause of cell death in Parkinson's disease and assist in the development of more definitive treatment for this common, disabling neurologic condition.

Cet article passe en revue plusieurs facettes importantes de la maladie de Parkinson, y compris les études étiologiques, les complications médicamenteuses (types, pathogénèse et traitement), comment et quand instituer le traitement, la survenue d'états démentiels et les nouvelles techniques de recherche. Deux découvertes récentes, l'existence d'une neurotoxine hautement sélective (la MPTP) susceptible de déterminer un parkinsonisme chez l'homme et d'autres primates, et l'emploi de la tomographie à positons in vivo, vont sans doute éclairer les raisons de la mort cellulaire dans cette maladie neurologique qui rend tant de personnes infirmes, et montrer la route vers un traitement plus définitif que ceux qui existent déjà.

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Parkinson's disease remains one of the commonest causes of chronic neurologic disability, even though there have been major advances in our understanding of its pathogenesis and in the treatment of its signs and symptoms over the past two decades. As the average age of the general population increases and estimates of the prevalence of Parkinson's disease near 1 in 40 persons over the age of 65 years,[1] the need for improvements in management and for further research into the possible causes becomes all too obvious. There have been exciting developments in this field recently that may eventually allow us to realize our goals. It is timely, therefore, to review the state of the art of Parkinson's disease.

Etiology

The obvious hope in this area of study is that prevention may be possible if the cause is found. Even if the development of the disease is found to be unavoidable, the progression of symptoms related to degeneration of the substantia nigra might be prevented if the cause or mechanism of nigral cell death could be discovered. Calne and Langston[2] have categorized the possible etiologic factors as genetic, age-related and environmental.

Two familial subgroups of idiopathic Parkinson's disease have recently been reported.[3] The first has a more benign course, with tremor as the predominant symptom; here there is an autosomal-dominant family history of benign essential tremor. In the second group an akinetic–rigid form of parkinsonism is inherited via an autosomal-recessive trait. Other authors, however, have not found such familial subgroups in the course of their experience with idiopathic Parkinson's disease, excluding other disorders that present with similar signs and symptoms (e.g., "multisystem atrophies").[4] The strongest argument against a prominent genetic contribution comes from a recent study of twins in which one member, the "index case", had definite, typical, idiopathic Parkinson's disease. Of 43 monozygotic and 19 dizygotic twin pairs, only one monozygotic pair was concordant for Parkinson's disease.[5]

An alternative explanation holds that Parkinson's disease is simply a result of an exaggeration of the normal loss of substantia nigra neurons that takes place with ageing. Calne and Langston[2] counter this view by arguing that the central nervous systems of twins should age at similar rates. Thus, the results of study in this area do not support the ageing theory.[5] Also, the mild features of parkinsonism seen in normal elderly individuals are unaffected by treatment with levodopa[2] and, therefore, are probably not solely due to dopamine deficiency. Although it does seem that ageing is not primarily responsible for parkinsonism, the symptoms could still arise when the normal age-related loss of neurons is superimposed on pre-existing cell loss due to some previous insult.

The most exciting developments have been in the area of environmental factors. Aside from sporadic cases of postencephalitic parkinsonism similar to those that resulted from the epidemic of encephalitis lethargica earlier this century, there is no good evidence that any virus causes idiopathic Parkinson's disease.[4]

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In 1979 Davis and coworkers[6] reported the development of severe parkinsonism in a drug abuser who had been synthesizing meperidine. The abuser had taken a batch that had been hurriedly prepared, injecting the derivative 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Postmortem examination showed severe loss of dopaminergic substantia nigra neurons and a questionable Lewy body (the inclusion body seen in the damaged neurons of patients suffering from idiopathic Parkinson's disease). Langston and Ballard[7] subsequently reported on a number of drug abusers who took this toxin parenterally and subsequently suffered from severe parkinsonism. The condition also appeared in one patient who had "snorted" the drug.[8] In addition, parkinsonism developed at an unusually early age in a chemist involved in synthesizing MPTP, even though he had not taken it internally in any way.[9] Many of the features of parkinsonism develop in other primates given MPTP,[10] and both monkeys and human patients with disease induced by this chemical respond well to levodopa and other dopamine agonists. However, very early on they experience several of the complications common to this treatment that are ordinarily seen late in idiopathic Parkinson's disease, such as involuntary movements and the "on–off" phenomenon. Postmortem studies in the primates have shown a selective degeneration of the dopaminergic neurons of the substantia nigra compacta. In this respect, although this may be the best animal model of parkinsonism now available, the selective toxicity of MPTP does not completely mimic idiopathic Parkinson's disease, in which there is also involvement of other regions of the brain, including the ventral tegmental area, the locus ceruleus, the dorsal motor nucleus of the vagus and the intermediolateral nucleus of the spinal cord.

Rajput[11] has recently presented data suggesting that patients from Saskatchewan with Parkinson's disease of early onset (before 40 years of age) may have been exposed to a common agent present in their well water. A number of environmental factors might serve as a "trigger" to eventual cell damage and death. Barbeau[1] has proposed that this could occur via the common mechanism of increasing turnover within catecholamine-producing cells, which results in the accumulation of toxic free radicals. When present in quantities that exceed the scavenging capacity of the cell, these radicals lead to cell death. The compensatory increase in catecholamine turnover in the remaining nigral cells (and other pigmented neurons) accelerates the process. If this proves to be the pathogenesis of cell death, then, in addition to identifying and preventing exposure to the triggering factors, there may be ways we could halt or slow the progression of the disease, perhaps by administering agents that would assist in the scavenging or trapping of toxic free radicals.

Interestingly, several epidemiologic studies have shown that patients with Parkinson's disease have smoked less than control populations. It is not clear whether smoking somehow protects against the later development of Parkinson's disease or whether those individuals in whom the disease eventually develops have a premorbid personality type that renders them less prone to take up the smoking habit.

Therapy: problems with levodopa

Before the advent of levodopa the mortality rate in Parkinson's disease was almost three times that expected for age.[12] Several studies since then have shown that the longevity of patients with the disease is now equivalent to that of age-matched controls.[13] However, there are a number of therapeutic problems, some of which persist or become increasingly common after 3 to 5 years of therapy.

Failure to respond to levodopa

Some 15% to 20% of patients fail to respond to treatment with levodopa.[14] Most of these patients also fail to respond to other antiparkinsonian agents, including the newer ergot derivatives. The reason for drug failure is not known. Although these patients are most often clinically indistinguishable from those who benefit from levodopa, there have been no large postmortem studies to show that all of them suffered from idiopathic Parkinson's disease. There are several other degenerative neurologic diseases that involve the substantia nigra and striatum (the caudate and putamen, to which the substantia nigra projects), such as striatonigral degeneration and the olivo pontocerebellar degenerations. Often these can mimic true Parkinson's disease, with little evidence (e.g., autonomic failure, eye-movement disturbances, cerebellar features or pyramidal tract dysfunction) for an alternative diagnosis early on.

Loss of response to levodopa

A large proportion of patients who initially respond to levodopa seem to gradually lose this benefit. Most of these patients, however, retain a so-called long-duration response,[15] which is recognized when the drug is withdrawn for several days (a "drug holiday"). At such a time the symptoms of their disease become much worse than they or their physicians ever thought possible, judging from the apparent poor response they had seen with the drug. This loss of response or declining efficacy probably has several causes. Continuing nigral cell death accounts for some of this change, but if this were the only cause, then these patients would be expected to do well with the addition of postsynaptic-acting dopamine agonists (e.g., pergolide or lisuride), which bypass the dying presynaptic nigral neurons. All too often, though, the response to these agents is not striking, if indeed it is seen at all.

When given for long periods levodopa and other dopamine agonists may desensitize or "down regulate" the patient's dopamine receptors, resulting in loss of response (although this is often not a true loss). Withdrawal of the drug might allow these receptors to be resensitized, and this is the theoretical basis for drug holidays.[16] Unfortunately, this approach does not improve responsiveness to the drug in many patients, and it is not without significant complications.[17]

Loss of striatal neurons, possibly because of transsynaptic degeneration, with subsequent reduction in the number of receptors for dopa-

mine, has been documented in some postmortem studies.[18] This could account for a loss of levodopa's efficacy and the failure of other dopamine agonists. Degeneration of other areas of the nervous system could also contribute to the loss of drug responsiveness in some unknown way.

Levodopa metabolism produces several compounds that can interfere with the subsequent response to the parent compound. One example is 3-O-methyldopa, which competes with levodopa for the blood–brain-barrier transport mechanism for neutral amino acids.[19] Levodopa may also increase the production of free radicals or other toxins (e.g., dopa quinones and 6-hydroxydopamine), which might speed the progression of the disease through further cell damage.[2] The possibility that levodopa actually speeds disease progression and the development of other long-term complications is leading investigators to question the early use of the drug.

Involuntary movements (dyskinesias)

Long-term levodopa therapy is associated with a number of other complications. In over 80% of patients treated for longer than 5 years a wide range of involuntary movements or dyskinesias develop, ranging from orofacial chewing movements to wild ballistic flinging movements of the limbs. Some prolonged dystonic spasms (frequently in the foot) may be painful and quite disabling.[20,21] Dyskinesias most frequently occur at the time of the drug's peak action, but after many years of treatment some patients have involuntary movements throughout the entire period in which they respond ("square-wave response") or whenever they are excited or concentrating. Patients who fail to improve with each dose (so called short- or medium-duration responses)[15] may still have dyskinesias that develop without any associated change in their mobility. In some patients, especially those in whom the onset of disease was early, dyskinesias occur both a short time after the drug is taken (before any benefit is seen) and again as the effect of the drug begins to wane; these are often called diphasic or "beginning and end-of-dose" dyskinesias.[22,23] Unlike the "peak-dose" dyskinesias, which abate when the dose of levodopa is lowered, dysphasic movements are often aggravated by this maneuver. Shortening the interval between doses or using a longer-acting drug, such as bromocriptine or the dopamine agonist pergolide, may reduce the incidence or the severity of this type of dyskinesia.

Freezing

A sudden, short-lived (lasting seconds to minutes) inability to carry out certain actions, known as "freezing", may develop, usually later in the course of the disease. This is most commonly seen when the patient tries to walk ("start hesitation") or while walking, but it may also occur while speaking or using the hands (e.g., in writing). This is the phenomenologic converse of "kinesia paradoxica", the well known situation in which very disabled, apparently chair-bound patients may be able to rise and move quickly for a short time when faced with an emotionally charged situation. The pharmacologic basis of these spontaneous fluctuations is not known, but norepinephrine deficiency has been proposed as a factor in freezing, and one group of investigators has reported improvement with a norepinephrine precursor, DL-3,4-dihydroxyphenylserine (DL-threo-DOPS).[24] However, others have not had success with this compound.[25] On the whole, freezing tends to be extremely resistant to all forms of therapy; indeed, in some patients it may even be aggravated by the newer ergot-derived dopamine agonists.

Fluctuations

Clinical features and mechanisms: In addition to involuntary movements and freezing accounting for fluctuations in a patient's condition, the parkinsonian state itself may change several times per day. The transition between normal mobility, or the "on" state (frequently with superimposed dyskinesias), to a chair- or bed-bound state due to severe parkinsonism ("off") may occur with frightening speed, taking only seconds or minutes.* Usually these fluctuations are predictable because they are related to the drug's wearing off ("end-of-dose deterioration"). However, several factors that influence the pharmacokinetics of levodopa can make these fluctuations less predictable. Eating may slow or prevent the drug's absorption,[26] and proteins containing large, neutral amino acids (e.g., leucine, isoleucine or phenylalanine) will interfere with the transport of levodopa across the blood–brain barrier.[26] Metabolites such as 3-O-methyldopa may also interfere with a "smooth" response. It has also been postulated that the dopamine receptors can become excessively depolarized and unresponsive to dopamine stimulation ("depolarization block"),[27] but this hypothesis has been disproven with intravenous infusions of levodopa[26,28] and the parenteral administration of dopamine agonists, such as apomorphine.[29] These studies have shown that patients retain their responsiveness to dopamine stimulation during the "off" period. Another factor many patients and their families recognize as precipitating an unexpected "off" period is a change in emotional state, such as an increase in anxiety. Aside from the fluctuations that are precipitated by amino-acid competition for blood–brain barrier transport, many "off" periods are eliminated by the intravenous infusion of levodopa, which maintains steady blood levels. However, those that are precipitated by anxiety or emotions are not.[26] This factor will probably be a major stumbling block to the development of new strategies for managing patients with severe fluctuations.

Therapeutic approaches: At present we have only a few treatment options when faced with these problems. Shortening the interval between doses of levodopa in those patients with the "wearing–off" phenomenon usually helps. However, the duration of the drug's clinical action will continue to shorten. This

*The term "on–off" phenomenon is best reserved for the rapid and unpredictable fluctuations from the "on" to the "off" state, and frequently vice versa, that occur without an intervening dose of levodopa.

may reflect the decrease in the capacity for storage of dopamine as the disease progresses and nigral cells degenerate. Dopamine synthesized from levodopa may then be released or utilized immediately; this would account for the shorter duration of benefit. (As mentioned earlier, there is often a less noticeable "long-duration response", which probably does not rely on the conventional intraneuronal storage of dopamine.)

Drugs with a longer duration of action than levodopa are being investigated. Most of these are ergoline derivatives that act directly on postsynaptic dopamine receptors. At present bromocriptine is the only one of these available for general use. Unlike many of the more recently developed ergot derivatives, bromocriptine seems to require the intact presynaptic dopaminergic neuron (i.e., the nigral neuron, which is degenerating in Parkinson's disease) for some of its action.[30] Bromocriptine treatment may help reduce the frequency of fluctuations but is often unsuccessful or results in troublesome side effects, such as gastrointestinal upset, orthostatic hypotension and psychiatric disturbances.

Lisuride, another ergoline, has the distinct advantage of being soluble in water. It can be given intravenously for infusional studies or in the perioperative period, when patients are unable to take drugs by mouth.[31] Unfortunately, it is short acting and highly metabolized on its first pass through the liver; although some investigators have reported a benefit,[32] its effectiveness when given orally to patients with fluctuations in the parkinsonian state may be limited.[33] It may be possible to administer such drugs with an ambulatory infusional pump system similar to that under trial with insulin in diabetic patients.

Pergolide is a long-acting, potent dopamine agonist, and it seems to be the most useful of the newer agents. Although striking improvements in the duration of the "on" state may be seen with this drug, up to half of the patients subject to fluctuations and resistant to other treatments fail to obtain much benefit.[34]

One dopamine receptor antagonist, domperidone, can also play a role in treatment. Domperidone does not (for the most part) cross the blood–brain barrier but may improve or prevent the "peripheral" side effects caused by dopamine agonists, such as nausea and vomiting[35] and cardiac arrhythmias.[34] Some patients who have persistent gastrointestinal side effects from levodopa that do not lessen with the substitution of a 4:1 preparation of levodopa and a peripheral dopa decarboxylase inhibitor (e.g., Sinemet 100/25 or Prolopa) may benefit from domperidone. Domperidone also has been found to reduce the delay in response seen with oral doses of levodopa, which occasionally presents a therapeutic problem. This action may be mediated by blockade of the gastric dopamine receptors, which would normally delay stomach emptying and thus retard the absorption of levodopa from the small bowel.[36]

Another way to prolong the clinical effect of levodopa and alleviate the problem of fluctuations in some patients would be to limit the rate at which dopamine is metabolized. Since monoamine oxidase (MAO) figures largely in this process, standard MAO inhibitors should prove useful, but when they were first given with levodopa hypertensive crises resulted (the "cheese effect").[37] It is now known that MAO is present in two subtypes, A and B, and that dopamine is metabolized by the B form. Deprenyl is a selective MAO-B inhibitor, but its effects are complicated and cannot be explained solely on that basis.[38] Variable results have been reported when this drug is used in combination with levodopa in Parkinson's disease. The most consistent improvement is seen in the fluctuations that occur predictably, when the effects of levodopa are wearing off.[39,40] The unpredictable "on–off" phenomenon may even be aggravated.[40] Birkmayer and colleagues[41] have also claimed that patients who are losing their initial benefit from levodopa have improved, but this effect has yet to be substantiated.

Psychiatric disturbances

In addition to the loss of response to levodopa, the involuntary movements and the fluctuations, a further "central" side effect of long-term levodopa therapy has been the development of psychiatric disturbances. These may occur on a continuum, beginning with the reversal of the patient's sleep pattern and the occurrence of vivid dreams or nightmares.[42] The patient's spouse may report a disturbed sleep pattern, with motor restlessness and calling out, for which the patient has no recollection. (Spouses frequently comment that during these episodes the patient's speech is strikingly normal in volume and clarity, whereas in the waking state severe dysarthria and dysphonia may be present.) Illusions and, later, hallucinations with a clear sensorium may develop. Initially these are often a carry-over from dreams upon awakening, but later they may be present while the patient is awake and be unassociated with drowsiness or sleep. Later still, a full-blown psychotic state with paranoia or vivid hallucinations may develop. All of these effects are much more common in patients suffering from additional dementia.

The pharmacologic mechanisms for the development of these psychiatric disturbances are unknown. Several hypotheses relate to alterations in serotonergic, as well as dopaminergic, systems. These side effects remain a major cause of disability late in the course of Parkinson's disease. Since they are frequently precipitated by the addition of one of the dopamine agonists, such as bromocriptine, they are often the limiting factor in the use of these drugs or in increasing the dose of levodopa for disabling parkinsonian features. Drug holidays may relieve the psychiatric side effects, but in our experience most patients eventually require a return to the preholiday doses. The psychiatric features then frequently recur. Some patients who require higher doses of levodopa to maintain their mobility may benefit from regular, shorter drug holidays, carried out in supervised surroundings. Others may require small doses of a neuroleptic, such as thioridazine, which seems to induce less parkinsonism than other, more potent antipsychotic agents. Newer, more selective antipsychotic drugs now being studied in schizophrenia may prove useful for these difficult problems.

Dopamine receptors

It is possible that the various side effects of the dopamine agonists that we have outlined are related to differences in the actions of these drugs on different types of dopamine receptors. There may be more than one type of receptor for dopamine, as is the case for other transmitter substances, such as epinephrine and histamine. Up to five subclasses have been proposed, but most of the data favour there being two major classes of dopamine receptor.[43] At least one of these receptors can exist in two different states (high affinity and low).[44] The D_1 receptor is linked to the activation of adenylate cyclase, while the D_2 receptor is not. Stimulation of the D_2 receptor appears to be important for the relief of parkinsonism. Clinical study of the recently developed D_1 and D_2 antagonists[45] should help us understand the relations between these receptors and the antiparkinsonian and various side effects of these drugs. Such an understanding might allow us to develop antiparkinsonian agents that are free from serious complications or drugs that can counteract the side effects of these agents without increasing the symptoms of parkinsonism.

When and how to begin therapy

Because there are obviously a number of disabling long-term complications of levodopa therapy, and even reason to believe that it could speed the loss of cells, the controversial question of when to start giving levodopa has recently received much attention. Two opposing views have been voiced. Lesser and collaborators[46] and, more recently, Fahn and Bressman[47] have argued that the progression of disease and the development of levodopa-associated complications are correlated more with the duration of levodopa treatment than with the duration of the disease. These authors favour starting levodopa therapy only when parkinsonian symptoms are beginning to threaten the patient's employability or social life, and only after less potent drugs, such as amantadine and anticholinergics, have been found to be ineffective or contraindicated. On the other hand, Markham and Diamond[48] reported that the loss of levodopa's efficacy correlates better with the duration of the disease than with the duration of the therapy (Fahn and Bressman[47] criticized the Parkinson rating scale upon which this argument is based). Muenter,[49] in reviewing his extensive experience with fluctuations in the parkinsonian state, has argued that the development of many of these problems is related to the severity of the disease rather than to the duration of levodopa therapy.

MPTP causes severe nigral cell degeneration and, concomitantly, severe signs of parkinsonism at an early stage. Levodopa treatment of MPTP-induced parkinsonism in humans (and other primates) is associated with the very early development of dyskinesias and fluctuations.[7] This gives us further reason to believe that it is the severity of the disease rather than the duration of treatment that explains many of the late-stage problems seen in idiopathic Parkinson's disease. Those subscribing to this viewpoint favour the early use of levodopa, when the patient has become aware of mild but disabling symptoms. They argue that withholding levodopa at this time would deprive the patient of the drug's action during the very period of its maximum benefit.

At present no definitive answer can be given as to when levodopa therapy should be started. However, both camps agree that early, mild symptoms causing no disability do not warrant treatment. When treatment is instituted most physicians use the lowest dose needed to obtain the required reduction in disability without attempting to completely abolish all the signs of parkinsonism.

In a small number of studies of bromocriptine as the initial drug in previously untreated patients, fluctuations failed to develop and involuntary movements developed in only a small proportion of the patients in follow-up periods as long as 5 years.[50,51] Many of the patients treated in this way, however, did not maintain a useful response to the drug. Criticisms of these studies have suggested that the patients who took bromocriptine alone for 5 years were likely to have had milder cases of the disease; serious problems might not have developed had they been treated cautiously with levodopa. Only comparisons of ergot derivatives and levodopa in larger series of new patients will resolve this question. Teychenne and associates[52] advocated using bromocriptine in low doses (less than 20 mg). However, most investigators have found such low doses helpful in only a small minority of cases. Most patients require between 20 and 80 mg per day, depending on the severity of the disease. Because many patients fail to obtain as good a response with ergot derivatives as they might with levodopa, Calne and coworkers[53] recently proposed combining low doses of levodopa with bromocriptine in hopes of reducing the incidence of later complications.

Dementia

Dementia is one important feature associated with Parkinson's disease that seems independent of drug therapy. However, the psychiatric side effects of antiparkinsonian drugs, particularly the anticholinergics, are much more frequent in patients with pre-existing cognitive disturbances. Although it was infrequently discussed before levodopa came into use, dementia is now said to be present in 30% to 90% of patients, depending on the population studied and the criteria used.[54] Disturbances of higher mental function are probably multifactorial.

The mental state of some patients with dementia associated with Parkinson's disease is indistinguishable from that seen in Alzheimer's disease: there are prominent apraxias and language difficulties, in addition to generalized cognitive disturbances. These patients may, in fact, be suffering from both Alzheimer's disease and idiopathic Parkinson's disease. Hakim and Mathieson[55] have reported that the changes of Alzheimer's disease are more frequent in the brains of patients with Parkinson's disease than in those of controls. Many of the clinical features of dementia in this group and even in those without the changes of Alzheimer's disease[56] may be explained by degeneration of acetylcholine-containing neurons in a region of the brain known as the nucleus basalis of Maynert,[57] which

is the main source of widespread cholinergic innervation to the cerebral cortex. Cortical acetylcholine deficiency might account for some of the disturbances in mentation, particularly memory. On the other hand, most patients with Parkinson's disease and dementia are much less severely affected than are those with Alzheimer's disease,[58] and they may show a different pattern of neuropsychologic deficit.[59]

Two other neurochemical disturbances present in parkinsonian brains might account for some of these features. First, norepinephrine may be important to memory,[60] and degeneration of the locus ceruleus of the pons in Parkinson's disease substantially reduces its levels in the brain. Second, dopaminergic neurons in the ventral tegmental area of the midbrain project to the frontal and limbic regions (forming the mesocortical and mesolimbic dopaminergic pathways). The cells of the ventral tegmental area also degenerate in Parkinson's disease,[61] and the reduction of the dopamine content in these projections could account for some of the neuropsychologic abnormalities seen in this disease.

Finally, the substantia nigra projects to both the putamen and the caudate nucleus. The putamen is closely linked to the motor system,[62] but the caudate projects (via the thalamus) to association areas, particularly the prefrontal and parietal cortex, and receives most of its cortical projections from these same regions.[63] The caudate seems to be more involved in the behavioural and cognitive realm than in the control of movement. Using fluorine-18-labelled levodopa Garnett and colleagues[64] studied cerebral dopamine activity with positron emission tomography (PET). In our patients with clinical hemiparkinsonism they found that the contralateral putamen showed markedly abnormal fluorodopa activity, and the opposite putamen was also often abnormal, but to a lesser extent, presumably owing to subclinical disease; on the other hand, in these neuropsychologically intact patients caudate dopamine activity could not be distinguished from that of normal controls (personal communication, 1984). Further study concentrating on caudate activity in cognitively impaired patients and comparing it with that in mentally intact patients matched for duration of disease and severity of motor signs may help us understand the contribution of caudate dysfunction to the neuropsychologic deficits seen in Parkinson's disease. This technique also shows widespread dopamine uptake in the cerebral cortex, and this may provide another avenue of investigation. In addition, PET scanning may allow us to study dopamine receptors.[65] This, too, may further our understanding of a variety of problems, including declining drug efficacy and certain side effects of treatment.

Conclusions

In this review we have attempted to touch on a number of important aspects of this complicated and fascinating condition. In emphasizing the more controversial and pivotal developments we have omitted several other areas. For example, a great deal of work has been done on the physiologic aspects of rigidity and tremor in Parkinson's disease.[66–69] In addition, a large number of pharmacologic approaches have been used to treat Parkinson's disease or the complications of levodopa treatment,[70] and experimental surgical therapy has recently been extended to include the cerebral implantation of catecholamine-producing cells.[71] Newer technologies may provide better methods of delivering dopamine to the brain and of promoting the regeneration of damaged neurons.[36]

The last two decades have seen exciting developments in the field of Parkinson's disease research. However, there are still more questions than answers. With careful clinical study of new agents and further research into the causes and mechanisms of cell death, the next two decades may see us move much closer to the solution of the "Parkinson puzzle".

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