Recent Advances in Pharmacotherapy

Parkinson's disease

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In Parkinson's disease there is degeneration of neurons in the substantia nigra, with consequent depletion of the neurotransmitter dopamine. The triad of tremor, rigidity and bradykinesia is the clinical hallmark. Drugs currently used for palliative therapy fall into three categories: anticholinergic agents, dopamine precursors (levodopa combined with extracerebral decarboxylase inhibitors) and artificial dopamine agonists. It has been argued, on theoretical grounds, that some drugs slow the progress of Parkinson's disease, although no firm evidence has supported this. Treatment must be individualized, and more than one type of drug can be given concurrently after a careful build-up in dosage. We review the adverse effects of various drugs and consider new developments such as slow-release preparations, selective D-1 and D-2 agonists and transplants of dopaminergic cells into the brain. The treatment of Parkinson's disease can be demanding, rewarding and sometimes frustrating, but it remains a most challenging exercise in pharmacotherapy.

La maladie de Parkinson, dont les signes cardinaux sont le tremblement, la bradycinésie et la rigidité, résulte de la perte progressive des neurones du locus niger sécréteurs de dopamine. La pharmacothérapie palliative actuelle comprend trois catégories: anticholinergiques, précurseurs de la dopamine (lévodopa en association avec les inhibiteurs de la décarboxylase extra-cérébrale), agonistes synthétiques de la dopamine. Pour des raisons théoriques, mais sans preuve à l'appui, on a prétendu que certains médicaments ralentissent l'évolution de la maladie. Il faut adapter le traitement à chaque malade; il est loisible de prescrire simultanément plusieurs types de médicaments dont on augmente les doses avec soin. On passe ici en revue les divers médicaments et leurs effets secondaires. On évoque les nouveaux moyens thérapeutiques, soit les produits à libération lente, les agonistes spécifiques des récepteurs D-1 et D-2, la greffe cérébrale de tissu dopaminergique. Le traitement de la maladie de Parkinson exige beaucoup de doigté; souvent satisfaisant, il déçoit parfois. Dans tous les cas, il taxe au plus haut point la sagacité du pharmacothérapeute.

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Clinical hallmarks of Parkinson's disease are tremor, bradykinesia and rigidity. However, the onset symptoms are usually mild and vague: clumsiness of the hands, fatigue and sensory discomfort. As the disease evolves the most prominent signs appear: tremor, usually a coarse resting tremor but one that is sometimes prominent when the patient holds a posture or performs a voluntary movement; rigidity, especially during activation of the contralateral limb; bradykinesia, associated with a disrupted pattern of fine and rapid repetitive movements (e.g., tapping and writing), lack of facial expression, diminished blinking, dysarthria, dysphagia and a slow, hesitant gait accompanied by decreased arm swing; and postural instability. Other symptoms include constipation, impotence, sialorrhea, impaired cognitive function and depression.

Dopamine is a neurotransmitter that regulates many physiologic functions in the brain, the vascular system, the kidney and the gastrointestinal tract. It is produced in nerve-cell bodies and in the axons of certain neurons that are "dopaminergic". Dopamine is synthesized from tyrosine via levodopa. In the central nervous system several pathways involving dopaminergic neurons have been identified, the main pathways being nigrostriatal, mesocorticolimbic and hypothalamic. There is a reciprocal interaction between dopamine and acetylcholine in the striatum to increase dopaminergic activity.

Parkinsonism, the result of decreased nigrostriatal dopamine function, is most commonly caused by idiopathic degeneration of dopaminergic nigral neurons, which is also seen in progressive

supranuclear palsy and Shy-Drager syndrome. The cause of dopaminergic cell loss from the substantia nigra in Parkinson's disease remains unknown, although a toxic effect or infection from exposure to an environmental risk factor many years before the onset of symptoms has been suggested.[1,2] In Parkinson's disease the nigrostriatal system is the most affected: the substantia nigra shows loss of pigmented dopaminergic neurons, and the levels of dopamine, its metabolites and tyrosine hydroxylase (the rate-limiting enzyme necessary for the formation of dopamine) are all reduced in the striatum.

Drugs that deplete dopamine, such as reserpine and tetrabenazine, can cause parkinsonism, as can agents that block dopamine receptors, such as chlorpromazine, haloperidol and metoclopramide. Other, rarer causes include metal deposition in the striatum and globus pallidus (as in Wilson's disease and Hallervorden-Spatz syndrome), viral infection (as in encephalitis lethargica) and intoxication (from methylphenyltetrahydropyridine [MPTP] or manganese). Disorders that display some of the parkinsonian features are normal-pressure hydrocephalus, Creutzfeldt-Jakob disease, Segawa disease (hereditary progressive dystonia with diurnal fluctuations) and neuroacanthocytosis.

Nigral neurons synapse in the striatum with the two dopamine receptors, D-1 and D-2;[3] these receptors, especially D-2, appear to be involved in motor control[4] and may need to be stimulated for normal motor behaviour.[5] However, the evidence implicating the D-2 system in motor function is much more complete. A background of D-1 receptor tone may be required for D-2 agonists to act maximally.[6]

It has been estimated that the striatal dopamine level must decrease to 20% of normal (i.e., far below the level reached after normal aging) before the symptoms of Parkinson's disease will appear.[7] The neuronal counts in the substantia nigra of patients with Parkinson's disease have been reported to be 20% of those of healthy age-matched control subjects.[8] In patients whose levels are above this threshold the remaining dopaminergic neurons show augmented activity, as indicated by an increased ratio of homovanillic acid to dopamine in the striatum, and denervation hypersensitivity occurs (i.e., decreased transmission in a pathway increases the number of receptors postsynaptic to that pathway).

The severity of symptoms correlates with the degree of dopamine deficiency in the putamen,[9] and changes in mental function may be related to dopamine deficiency in the caudate nucleus and corticolimbic area.[10]

Therapeutic approaches

The treatment of Parkinson's disease is aimed at increasing dopaminergic function or decreasing cholinergic transmission. The antiparkinsonian drugs may be divided into four groups: anticholinergic agents, dopamine precursors, synthetic dopamine agonists and antioxidant drugs, whose role at present is only theoretical.

Anticholinergic agents

Amantadine has anticholinergic properties, but high tissue concentrations may also release dopamine from nigrostriatal nerve endings. The exact mode of action is still unknown. The plasma half-life is about 10 hours, and the side effects are mainly related to amantadine's anticholinergic activity. Other side effects are ankle edema, livedo reticularis (a red reticular discoloration of the extremities, usually the legs and feet [Fig. 1]), pruritus, headache, nausea and, rarely, cardiac arrhythmias.

Anticholinergic agents block muscarinic acetylcholine receptors. Some, such as benztropine, also increase striatal dopamine levels by blocking the synaptic reabsorption of dopamine. The effects last for 1 to 6 hours. Anticholinergic drugs also block parasympathetic transmission peripherally (outside the blood-brain barrier) and may cause blurred vision, urinary retention, narrow-angle glaucoma, dry mouth and constipation. Central side effects (those occurring inside the blood-brain barrier) include confusion, delirium, agitation and impairment of recent memory; these problems are due more to increased age than to peak serum levels and are prominent in the elderly and in patients who are already experiencing some degree of intellectual impairment.

Antihistamines share many of the properties of anticholinergic agents.

Dopamine precursors

Levodopa is effective in most patients with Parkinson's disease.[11] It crosses the blood-brain

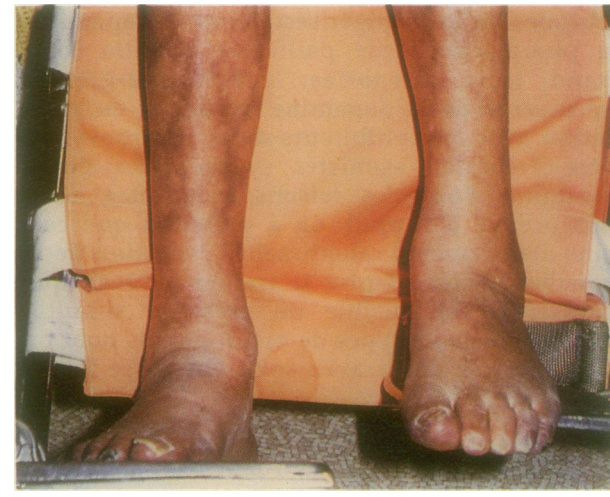

Fig. 1 — Livedo reticularis, commonly seen as adverse effect of amantadine therapy for Parkinson's disease.

barrier and, after decarboxylation, increases the striatal dopamine level. The plasma half-life is only about 1 hour. Decarboxylation by L-aromatic amino acid decarboxylase takes place inside and outside the brain. Dopamine formed outside the brain cannot cross the blood–brain barrier; extracerebral decarboxylase inhibitors block the conversion of levodopa to dopamine outside the brain and thus reduce the dopaminergic effect[12] and increase the serum concentration of levodopa for a given oral dose. Peripheral L-aromatic amino acid decarboxylase inhibitors, such as carbidopa and benserazide, have been combined with levodopa (Sinemet and Prolopa respectively) and are now used routinely. These preparations act within 1 hour after oral administration and maintain their effect for 4 to 6 hours.

Adverse reactions to levodopa are either peripheral or central. The most frequent peripheral reactions — nausea and vomiting — result from stimulation of dopamine receptors in the chemoreceptor trigger zone within the area postrema in the fourth ventricle (outside the blood–brain barrier). Central reactions comprise psychiatric disorders and dyskinesia. Orthostatic hypotension results from a combination of central and peripheral actions of dopamine. Dopamine can stimulate the adrenergic receptors of the vascular system and thus increase cardiac output and vascular resistance; in lower concentrations it can cause vasodilatation and diuresis.[13,14]

Levodopa, alone or with carbidopa or benserazide, is contraindicated in patients with psychosis and in those with decompensated cardiac disorders. In addition, it may activate melanoma. Levodopa diminishes the secretion of prolactin, and it may cause slight increases in the levels of transaminases, alkaline phosphatase and protein-bound iodine and mild transient decreases in the leukocyte and platelet counts.

Synthetic dopamine agonists

Synthetic dopamine agonists, such as dopaminomimetic ergot derivatives, act directly on both D-1 and D-2 receptors (e.g., pergolide) or just D-2 receptors (e.g., bromocriptine and lisuride) in the striatum. They have replaced the more toxic apomorphine and *N*-propylnoraporphine. The plasma half-life of bromocriptine is about 3 hours.

The most severe side effects are psychologic and cardiac problems. Dopamine agonists should be avoided in patients with dementia or psychosis, in those who have had a recent myocardial infarction and in those with uncontrolled cardiac arrhythmias. Other potential problems are pulmonary infiltration and pleural effusion (Fig. 2), erythromelalgia (Fig. 3), nausea, headache, dizziness and postural hypotension.

Antioxidant drugs

The reason nigral dopaminergic cells are lost in patients with Parkinson's disease is not understood; it has been suggested that free radicals, such as superoxide and peroxide, may contribute to neuronal death.[15]

Vitamin E and selective type B monoamine oxidase inhibitors, such as selegiline (Deprenyl), may protect against endogenous nigral degeneration mediated by free radicals by impeding dopamine oxidation.[16] They may also protect against

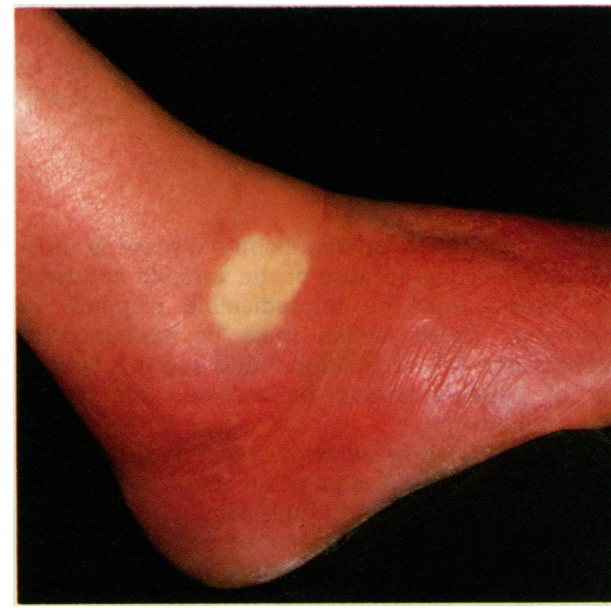

Fig. 3 — Erythromelalgia, rarely seen in association with bromocriptine therapy.

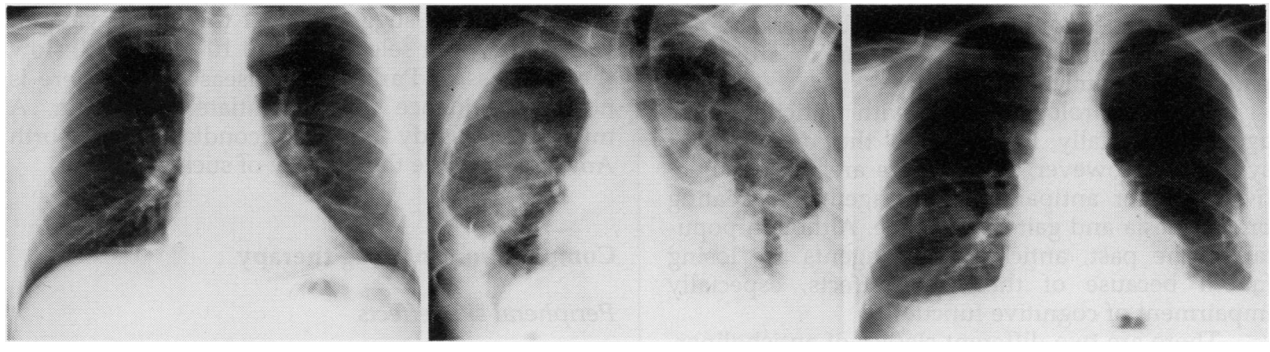

Fig. 2 — Chest x-ray films before, during and after bromocriptine therapy.

exogenous damage due to oxidation, which may play a role in the cause of Parkinson's disease,[17] especially because antioxidants such as catalase and peroxidase have been found to be decreased in the substantia nigra of patients with Parkinson's disease.[18] The use of selegiline also allows a reduction of 10% to 25% in the dose of levodopa.[19] Selective type B monoamine oxidase inhibitors can block dopamine reabsorption and may have an antidepressant effect.

Brain implantation

Recently adrenal medullary tissue has been stereotactically implanted into the neostriatum of four Swedish patients with Parkinson's disease.[20,21] In addition, adrenal medullary tissue was placed into a cavity excavated in the caudate nucleus in 10 Mexican patients.[22] There were no significant improvements in the Swedish group, whereas dramatic improvements were reported in several of the Mexican patients. Subsequently over 100 transplants of medullary tissue and a few of fetal nigral tissue have been performed, with generally disappointing and in some cases catastrophic results.[23] Questions concerning the optimal nature of the transplanted tissue, the choice of the implantation site, the long-term outcome and the ethical issue of using fetal tissue must be resolved.[23-25]

Practical treatment

The prognosis of Parkinson's disease is difficult to determine because of the variable nature of the disease and the unpredictable response to treatment. These factors must be explained to patients and the occupational and social functioning of patients should be assessed for proper management.

The decision of when to start pharmacotherapy and the choice of medication and dosage are all controversial issues. Although some experts argue that prolonged levodopa therapy is beneficial,[26-28] others believe that it contributes to management problems.[29,30] Because the severity of presenting symptoms and their impact on lifestyle vary, patients should be evaluated individually. We recommend that low doses of levodopa (200 to 400 mg/d combined with carbidopa or benserazide) be started as soon as symptoms begin to affect the patient's economic or social life.

Some neurologists start with anticholinergic agents, especially if tremor is the predominant symptom. However, these drugs are not as effective as other antiparkinsonian agents in treating bradykinesia and gait disturbance. Although popular in the past, anticholinergic agents are losing favour because of their side effects, especially impairment of cognitive function.[31]

There are two different classes of anticholinergic agents: piperidyl derivatives (e.g., trihexyphenidyl, 6 to 15 mg/d, biperiden, 6 to 30 mg/d, and procyclidine, 10 to 30 mg/d) and tropanol derivatives (e.g., benztropine, 2 to 6 mg/d). Orphenadrine, 150 to 250 mg/d, and diphenhydramine, 50 to 150 mg/d, have anticholinergic properties as well as sedative properties and may be useful in patients with insomnia.

Amantadine, 100 to 200 mg/d, is also used in early treatment. It tends to be well tolerated, but the doses should be decreased or therapy stopped if severe ankle edema or livedo reticularis develops. Amantadine is more effective against rigidity and bradykinesia than against tremor. In the elderly the dose should not exceed 100 mg/d. Because amantadine is almost entirely excreted, unchanged, in the urine, therapy should be stopped in patients with renal failure.

Now therapy is usually started with levodopa, which is invariably combined with a decarboxylase inhibitor. A daily dose of 300 mg of levodopa and at least 75 mg of carbidopa or benserazide may be reached in 3 weeks and can be increased further, if necessary, until the effect is satisfactory. For an optimal response levodopa should be taken after light meals during the day. Food produces a physical barrier to gastric emptying, and the large-molecule amino acids in meat, fish, eggs, milk products, seeds and nuts compete with levodopa for the active transport mechanism of the blood-brain barrier.[15] Taken without food, levodopa achieves a fast but brief therapeutic response and is likely to cause gastrointestinal side effects.[15] Levodopa may be combined with amantadine or anticholinergic agents, especially if there is prominent tremor.

Early adjuvant thrapy with synthetic dopamine agonists supplements the benefit of levodopa therapy.[32] A useful approach is to add bromocriptine, in slow titration of 2.5 mg/wk up to 15 to 30 mg/d, when the dose of levodopa reaches 400 to 600 mg/d. This combination, in lower doses than initially advocated for either drug alone, seems to result in fewer long-term side effects.[33] Patients should be monitored carefully when the dosage of either drug is reduced abruptly or therapy stopped. A symptom complex that resembles the neuroleptic malignant syndrome can occur;[34] this involves muscular rigidity, elevated body temperature, increased plasma creatine phosphokinase level and coma.

It has been suggested that the use of vitamin E, 2400 IU/d, or selegiline, 5 to 10 mg/d, will slow the progress of Parkinson's disease,[27] but there is no firm evidence to substantiate this claim. A multicentre study is being conducted in North America to prove the efficacy of such treatment.

Complications of drug therapy

Peripheral side effects

The emetic action of dopaminomimetic drugs

is mediated through the chemoreceptor trigger zone of the area postrema in the medulla. Although this is anatomically a central effect it is functionally a peripheral mechanism because it occurs outside the blood–brain barrier. Nausea and vomiting are infrequent if a peripheral decarboxylase inhibitor is used in combination with levodopa. If necessary, a supplement of this inhibitor (up to 300 mg/d) or domperidone (10 to 80 mg/d) may be given in divided doses of 10 to 20 mg half an hour before each dose of levodopa or bromocriptine. Gastrointestinal side effects can be minimized through the administration of levodopa or bromocriptine with food.

Extracerebral inhibitors or antagonists can help to manage postural hypotension, as can an increased intake of salt and fluids. If hypotension persists fludrocortisone, 0.1 to 0.3 mg/d, may help; however, the patient must be monitored for supine hypertension.

If erythromelalgia develops because of bromocriptine therapy the drug's use must be stopped. Similar action must be taken if pleural effusions and pleuropulmonary fibrosis occur. A chest x-ray film taken before bromocriptine therapy is started can be useful for retrospective comparison if respiratory symptoms develop.

Central side effects

Psychiatric problems: Increased intracerebral dopaminergic transmission with the use of levodopa and bromocriptine can cause agitation, confusion, hypomania, hallucinations and delusions.[35] The last two side effects are most frequently observed in older patients after prolonged treatment with high daily doses.[36] Vivid dreams, nocturnal hallucinations and illusions may be relieved if the evening dose is reduced. More severe problems require drug withdrawal.

Loss of neurons from the nucleus basalis may contribute to the intellectual impairment often seen in Parkinson's disease. It has also been suggested that this slowed cognitive function results from deficient dopaminergic transmission in the caudate nucleus and corticolimbic area and that memory may be impaired because of degeneration of noradrenergic neurons.[37] Another theory involves central serotonergic dysfunction.[38] Depression, observed in about 50% of patients,[39] may be related to central noradrenergic deficiency;[37] tricyclic antidepressant drugs (e.g., amitriptyline, 25 to 100 mg/d or more) are usually beneficial.

Dyskinesia: An excess of dopaminomimetic agents can induce involuntary movements, such as chorea, dystonia and myoclonus,[37] which seem to be confined to patients with degeneration of the nigrostriatal dopaminergic system.[40] The movements are usually evident at peak plasma drug levels[41] and are often prominent in patients with severe akinesia who initially respond well to levodopa therapy.[42] Dyskinesia occurs far more frequently with levodopa than with bromocriptine and can be alleviated through the administration of dopamine receptor antagonists[43] or through dopamine-depleting agents; however, these drugs cannot be used therapeutically because they exacerbate parkinsonism.

It has been speculated that chorea, dystonia and ballismus result from selective dysfunction in the caudate nucleus, the putamen–globus pallidus complex and the subthalamic area respectively.[37] However, the mechanism of dyskinesia is not fully understood. Dyskinesia due to peak levodopa doses can be alleviated by diminution and fractioning of the daily dose; onset and end-of-dose dyskinesias can sometimes be avoided if the size of each dose is increased and the frequency is decreased.[44] Dopamine receptor antagonists can achieve the same results, but they have no advantage over reduction of the dopaminomimetic dosage.

Fluctuations in response

Sudden or gradual deteriorations in the response to levodopa are common, particularly after prolonged treatment. If they occur at the end of the interdose period they are termed wearing-off reactions.[45] If they are entirely unpredictable and erratic they are called on–off reactions.[46] Both types can last from minutes to hours and should be distinguished from "freezing attacks", which last only seconds and are a common finding in advanced-stage Parkinson's disease, regardless of treatment. Nothing is known of the mechanism underlying on–off reactions, although some may result from factors that modify pharmacokinetics;[47,48] these factors include the intake of protein and variations in the duration of gastric emptying.

Wearing-off reactions may be due to (a) accumulation in the plasma of 3-O-methyldopa, which competes with levodopa transport across the blood–brain barrier,[49] (b) progressive loss of dopaminergic nigrostriatal neurons, which causes a reduction in decarboxylase activity and thus dopamine formation, or (c) progressive reduction of presynaptic dopamine storage capacity. However, none of these explanations is entirely satisfactory.

Bromocriptine has a more prolonged effect than levodopa has and may be useful in patients with wearing-off reactions. Deprenyl has been reported to relieve wearing-off effects in more than 50% of patients.[50]

Future developments

Recently studies have been performed to determine the ability of sustained-release levodopa/carbidopa (200/50 mg) to achieve more stable plasma levodopa levels and to avoid wearing-off reactions;[51] however, only limited improvements have been reported so far.[52–54] Sustained-release

preparations that contain bromocriptine are also being developed.

D-1 agonists may have clinical potential, but the reported observations have been contradictory, inconsistent and controversial.[55] Synthetic dopamine agonists such as bromocriptine seem more effective in controlling symptoms when combined with levodopa;[56] this may be because bromocriptine releases dopamine from nerve endings in addition to direct D-2 agonism or because it increases D-1 receptor tone. One D-1 agonist has been reported to correct symptoms induced by MPTP in monkeys (Rudolph Markstein: personal communication, 1986). Another one, however, failed to improve the condition in either monkeys with MPTP-induced symptoms or patients with Parkinson's disease.[57-60] The possible role of antioxidants will become evident after the completion of the North American multicentre study.

Conclusions

A powerful array of antiparkinsonian drugs is available for palliative therapy. However, the most effective drugs tend to produce side effects. The most important recent trends are (a) the use of lower doses of levodopa (combined with carbidopa or benserazide) in conjunction with lower doses of a synthetic dopamine agonist (e.g., bromocriptine) and (b) the study of new D-1 and D-2 dopamine agonists, new sustained-release preparations and the possible role of vitamin E and deprenyl; the potential value of these approaches will take several years to determine, and at present there is no strong evidence that any of these agents has a place in routine treatment.

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Additional comments on Parkinson's disease

This is truly an exciting time in the field of Parkinson's disease. As Wolters and Calne indicate, there is increasing interest in the potential for preventing progression of the disease, and a large North American multicentre study of antioxidant drugs has begun within the last year.

When to begin therapy is controversial; most authorities would agree with Wolters and Calne that treatment must be individualized on the basis of the level of disability. Some of the later complications, such as dyskinesia, may relate to the pulsatile manner in which levodopa preparations have always been given. The earlier concomitant use of longer-acting dopamine agonists such as bromocriptine may help to prevent or delay some of these problems. Other similar approaches might include the initiation of controlled-release levodopa or levodopa in combination with deprenyl, which should sustain the central levels of dopamine.

Several newer dopamine agonists that have different receptor-stimulating properties are being investigated, as are new methods of administering antiparkinsonian drugs. These methods include subcutaneous infusion, parenteral injection as necessary, sublingual administration, intraduodenal infusion (to bypass gastric-emptying disturbances) and intracerebral ventricular infusion of dopaminergic drugs. One of the more exciting examples of new routes of administration is the transdermal delivery of the dopamine agonist (+)-4-propyl-9-hydroxynaphthoxazine (PHNO), in a fashion similar to that used to administer scopolamine for motion sickness. Another example is the use of subcutaneous injection of apomorphine, as needed, when the first symptoms of an "off" period begin to emerge.

During the last 2 years we have seen an explosion of interest in brain implantation. Possibly more than 200 patients around the world have undergone autologous adrenal medullary implantation, and a handful have received grafts of fetal mesencephalic cells. The results of adrenal medullary implantation have been quite varied, but some patients seem to benefit from this intervention. It is