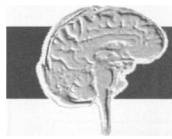

NEUROLOGY *Therapy*

Treatment of Parkinson's Disease

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Pharmacotherapy with levodopa for Parkinson's disease provides symptomatic benefit, but fluctuations in (or loss of) response may eventually occur. Dopamine agonists are also helpful and, when taken with low doses of levodopa, often provide sustained benefit with fewer side effects; novel agonists and new methods for their administration are therefore under study. Other therapeutic strategies are being explored, including the use of type B monoamine oxidase inhibitors to reduce the metabolic breakdown of dopamine, catechol-O-methyltransferase inhibitors to retard the breakdown of levodopa, norepinephrine precursors to compensate for deficiency of this neurotransmitter, glutamate antagonists to counteract the effects of the subthalamic nucleus, and various neurotrophic factors to influence dopaminergic nigrostriatal cells. Surgical procedures involving pallidotomy are sometimes helpful. Those involving cerebral transplantation of adrenal medullary or fetal mesencephalic tissue have yielded mixed results; benefits may relate to the presence of growth factors in the transplanted tissue. The transplantation of genetically engineered cell lines will probably become the optimal transplantation procedure.

The cause of Parkinson's disease may relate to oxidant stress and the generation of free radicals. It is not clear whether treatment with selegiline hydrochloride (a type B monoamine oxidase inhibitor) delays the progression of Parkinson's disease, because the drug also exerts a mild symptomatic effect. Daily treatment with vitamin E (a scavenger of free radicals) does not influence disease progression, perhaps because of limited penetration into the brain.

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Parkinson's disease is an idiopathic, chronic neurologic disorder characterized by some combination of tremor, rigidity, bradykinesia, and postural instability. It is generally progressive and leads to increasing disability with time. The disorder results from a disturbance of function of the basal ganglia that is due, in turn, to a loss of dopaminergic cells in the substantia nigra, a pigmented region of the midbrain.

Major advances have occurred during recent years in the treatment of Parkinson's disease, based in part on fresh insights into its pathophysiology gained from the development of animal models of parkinsonism. Parkinsonism may be induced in humans and nonhuman primates—and in certain other animals—by exposure to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a protoxin that is converted to *N*-methyl-4-phenylpyridinium (MPP^+), the active toxin, by monoamine oxidase B. The toxin is taken up selectively by dopaminergic neurons in the substantia nigra through an active transport system that is normally responsible for dopamine reuptake,[1,2] and MPP^+ then inhibits oxidative phosphorylation, probably by a specific inhibition of mitochondrial complex I in the respiratory chain.[3,4] This leads to the destruction of nigrostriatal neurons, to dopamine depletion in the basal ganglia, and thereby to parkinsonism. The neuronal death probably results from the generation of free radicals by the interaction of MPP^+ with complex I.[4] The MPTP model provides a useful framework for understanding the naturally occurring disease in humans, suggesting pathogenetic mechanisms and therapeutic approaches that can be tested experimentally.

This review is directed at therapy for Parkinson's disease and considers both symptomatic treatment and measures to influence the rate of disease progression. Attention is given not only to current therapeutic approaches but also to novel strategies that are being developed or tested. Contrary to popular belief, the treatment of neurologic disorders in general and of Parkinson's disease in particular is substantive, the response to treatment is often gratifying, and the recent development of new therapies has been based on rational scientific principles.

Symptomatic Pharmacologic Treatment

For many years, the only symptomatic therapy for Parkinson's disease was with nonselective muscarinic antagonists (anticholinergic drugs) that had been found empirically to help in some cases. These agents are of limited clinical use, however, and are often poorly toler-

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ABBREVIATIONS USED IN TEXT

COMT = catechol-*O*-methyltransferase
MPP^+ = *N*-methyl-4-phenylpyridinium
MPTP = 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
PHNO = 4-propyl-9-hydroxynaphthoxazine

ated, especially by older patients. The introduction in the 1960s of amantadine—an antiviral agent that was found by chance to have some antiparkinsonian action—led to disappointment when the drug failed to live up to initial expectations: many patients did not respond to it or had only short-lived benefit.

Subsequent therapeutic approaches have had a more scientific basis. One of the characteristic pathologic features of Parkinson's disease is degeneration of the substantia nigra (Figure 1), although other regions, such as the locus ceruleus, are also affected. A loss of dopaminergic neurons in the substantia nigra, with a resulting depletion in the striatal dopamine concentration, was recognized about 30 years ago to underlie many of the motor abnormalities of parkinsonism. This led to replacement therapy with levodopa (Figure 2), the metabolic precursor of dopamine, with resulting symptomatic benefit in most patients with true Parkinson's disease. As experience with levodopa accumulated, however, controversy developed about the optimal time of initiating levodopa therapy, based on concerns that levodopa may lose its effect with time or even exert a deleterious effect on the course of the disease. A recent study found that the timing of the introduction of levodopa influenced neither disease progression nor response to treatment, suggesting that treatment with this agent should be initiated in response to a patient's clinical state rather than delayed because of concern about possible long-term side effects.[5] The dose of levodopa should be kept to a minimum, however, to reduce the risk for the development of late side effects.

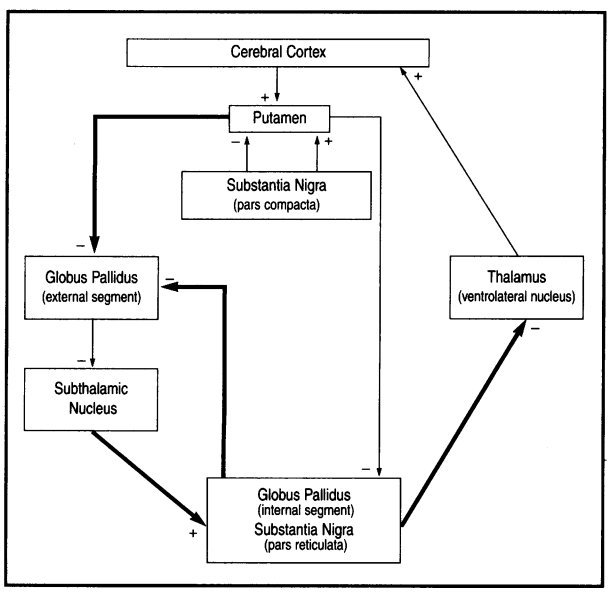

Figure 1.—Functional circuits are shown between selected cerebral structures involved in motor control. Excitatory circuits are indicated by + and inhibitory circuits by –. With the degeneration of the pars compacta of the substantia nigra that occurs in Parkinson's disease, there is increased activity in the projection pathways, indicated in the figure by bold lines.

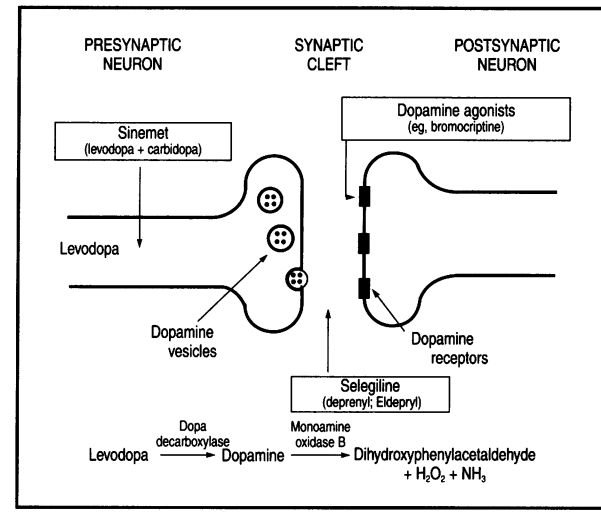

Figure 2.—The diagrammatic representation of dopaminergic therapy for Parkinson's disease shows the site of action of different therapeutic agents (given in boxes).

A major barrier to the absorption of levodopa is the presence in the intestinal mucosa of dopa decarboxylase, which converts levodopa to dopamine; in consequence, the greater part of an ingested dose of levodopa fails even to reach the general circulation.[6] Administering an extracerebral dopa-decarboxylase inhibitor with levodopa reduces both this extracerebral breakdown and any side effects of levodopa resulting from its peripheral actions. Levodopa is therefore administered routinely in combination with a peripheral dopa-decarboxylase inhibitor (carbidopa or benserazide) to increase the amount of levodopa reaching the brain; in the United States the combination of levodopa and carbidopa is available commercially as Sinemet (DuPont Merck). Certain side effects, such as nausea and vomiting, are less common with the use of Sinemet than with levodopa taken alone. After a few years of treatment, however, many patients who initially responded well to levodopa begin to have adverse reactions characterized by a wearing-off effect or by response fluctuations that seemingly have no relation to the timing of medication ("on-off" phenomenon). These complications can be disabling and pose major management problems. The duration and severity of disease and the duration of levodopa therapy have been implicated in their cause; proposed pathophysiologic mechanisms include the pharmacokinetics of levodopa, the degeneration of presynaptic dopaminergic nerve terminals, altered sensitivity of dopamine receptors, and abnormalities of nondopaminergic neurotransmitter systems.

Gastric emptying, which is erratic, markedly affects the absorption of levodopa. Such erratic absorption may account in part for any fluctuations in clinical response that occur during the day.[7] Levodopa is absorbed from the small intestine and transported across the blood-brain bar-

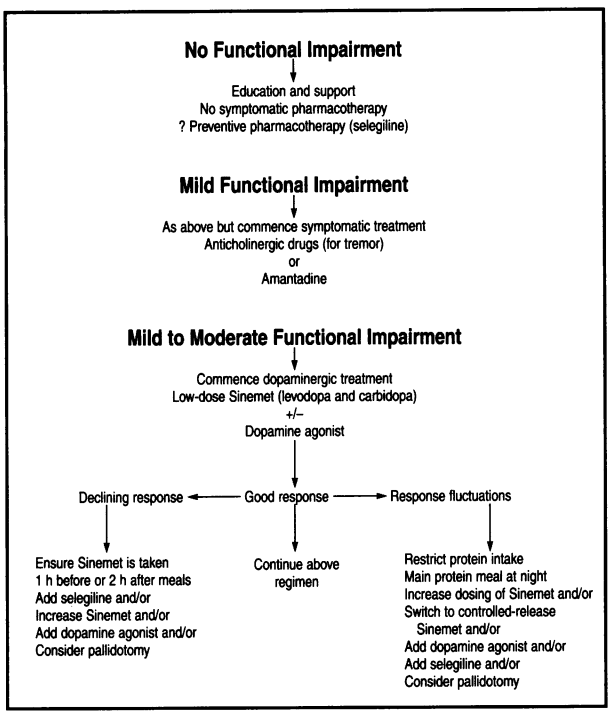

Figure 3.—The selection of treatment of Parkinson's disease is shown in this flow chart.

rier by an active carrier system that is also involved with the transport of certain other amino acids. Large protein meals reduce both the absorption of levodopa and its transport from the blood into the brain. In patients with the on-off phenomenon, then, restricting dietary protein intake to the minimum daily recommended allowance and scheduling the main protein intake to the last meal of the day are important management strategies to reduce response fluctuations (Figure 3). Fluctuations in response to oral levodopa can be overcome by continuous dopaminergic stimulation and are therefore reduced by a continuous infusion of levodopa intravenously, into the duodenum or, to a lesser extent, into the stomach.[8-10] A controlled-release formulation of Sinemet is now available and is sometimes helpful in reducing dosing frequency and maintaining steady blood concentrations of levodopa. It had been hoped that this would reduce the incidence of response fluctuations, but in many patients any benefit in this regard has been disappointing.

Abnormal involuntary movements may result from levodopa therapy, probably because of supersensitivity of postsynaptic dopamine receptors. Such dyskinesias may be present constantly, at times when plasma levodopa levels reach a peak, or at certain levels of plasma levodopa (and not at concentrations above or below this point). Correct management depends on determining the temporal pattern of the dyskinesia. When dyskinesias occur only at a certain submaximal blood concentration of levodopa, maintaining the concentration above this point by adjusting the dose may eliminate or greatly reduce them; by contrast, when dyskinesias coincide with peak blood concentrations of levodopa, a reduction in dose may be helpful.

Dopamine agonist drugs may alleviate symptoms by directly stimulating central dopamine receptors. Unlike levodopa, they do not require enzymatic conversion to an active metabolite, and their absorption and subsequent distribution to the brain are less erratic. The agents currently used in the United States are bromocriptine mesylate and pergolide mesylate; lisuride is in widespread use elsewhere, but is not approved by the Food and Drug Administration. Studies with bromocriptine, in particular, have shown that its early introduction in association with low-dose Sinemet therapy not only leads to sustained benefit but reduces the incidence of later complications such as response fluctuations and dyskinesias.[11,12]

New Approaches to Symptomatic Treatment

Recent work on the symptomatic treatment of Parkinson's disease has focused on the development of new dopamine receptor agonist drugs and of novel methods of administering them. Drugs to inhibit the breakdown of dopamine in the brain and of levodopa in the periphery are also being developed, as are various other pharmacologic strategies.

Dopaminergic Agents

Several new dopamine agonists are currently undergoing clinical trials. Some are more selective D-2 agonists and may therefore provide greater antiparkinsonian benefit with fewer side effects than the agonists currently in use.

New means of administering dopamine agonists may result in a steadier clinical response. Continuous dopaminergic stimulation by the subcutaneous administration of lisuride (a water-soluble D-2 receptor agonist) by a portable mini-infusion pump reduces fluctuations in response to oral levodopa,[13] but psychiatric complications have limited the long-term use of this approach.[14] The subcutaneous administration of apomorphine hydrochloride (a D-1 and D-2 agonist) similarly diminishes the incidence of response fluctuations,[15,16] in some patients for more than two years.[15] Administering dopamine agonists transdermally may also be helpful. For example, the transdermal administration of the D-2 agonist, 4-propyl-9-hydroxynaphthoxazine (PHNO), in conjunction with oral levodopa, leads to a more sustained response and less fluctuation than with levodopa taken alone,[17] but PHNO itself has had to be withdrawn for toxicologic reasons. In rats, the delivery of levodopa by subcutaneous implantation of a slow-release polymer matrix system leads to constant plasma concentrations of the drug for several months.[18] Such an approach may be helpful in humans in the future.

Monoamine Oxidase Inhibitors

Another novel approach to the symptomatic treatment of Parkinson's disease is by inhibiting the oxidative breakdown of dopamine by type B monoamine oxidase. Selegiline hydrochloride (deprenyl; Eldepryl, Somerset) inhibits this enzyme. It has therefore been used for some

years in Europe to augment the effect of dopamine by retarding its breakdown and thereby to treat patients in whom administered levodopa is either losing its effect or leading to response fluctuations. Such benefits are often minimal or transient, however, and selegiline is therefore usually prescribed for other purposes (discussed later under Preventive Treatment).

Catechol-O-Methyltransferase Inhibitors

The inhibition of dopa decarboxylase (by the carbidopa component of Sinemet) leads to a compensatory action of other pathways for the metabolism of levodopa, especially catechol-*O*-methyltransferase (COMT), and this leads to increased circulating levels of 3-*O*-methyldopa. The 3-*O*-methyldopa competes with levodopa for an active carrier mechanism involved in its transport across the intestinal mucosa and the blood-brain barrier. Selective COMT inhibitors may therefore enhance the benefits of levodopa therapy by reducing the conversion of levodopa to 3-*O*-methyldopa and increasing the availability of levodopa in the brain itself. Clinical studies are currently in progress to evaluate their therapeutic role.

Other Neurotransmitters

Other peptides and neurotransmitters present in the basal ganglia may also be affected in Parkinson's disease. For example, noradrenergic neurons of the locus ceruleus are known to be involved. The norepinephrine precursor, DL-threo-dihydroxyphenylserine has been given to certain parkinsonian patients with "freezing" or pronounced immobility that was unresponsive to dopaminergic therapy. Benefit was reported by some authors[19,20] but not others.[21]

There is evidence accumulating that increased activity of the subthalamic nucleus is important in producing parkinsonian deficits. This nucleus receives a glutamatergic input from the cortex and gives off glutamatergic efferent fibers to the substantia nigra and globus pallidus. Certain antiparkinsonian agents with known anticholinergic or antihistaminic properties are now recognized to be glutamate antagonists.[22] Other glutamate antagonists may therefore benefit patients with Parkinson's disease.[22] Experimentally induced parkinsonism is lessened by blocking excitatory amino acid transmission in the medial globus pallidus.[23] In rats and monkeys with pharmacologically induced parkinsonism, antagonists of certain glutamate receptors have antiparkinsonian effects and potentiate the effects of levodopa.[24] Therapeutic strategies based on glutamate antagonists may thus be rewarding, but await appropriate trials.

Neurotrophic or Growth Factors

Another new approach to the treatment of Parkinson's disease is with neurotrophic factors. A possible role in this regard for GM_1 ganglioside has recently been suggested.[25] Primates with MPTP-induced parkinsonism show a partial restoration of striatal dopamine levels following treatment with GM_1 ganglioside.[25] Whether this effect is mediated by the trophic support of degenerating dopaminergic cells or through the stimulation of fiber growth in the striatum is not clear. Again, muscle-derived differentiation factor (MDF) increases dopamine synthesis in damaged (but not intact) nigrostriatal dopaminergic cells.[26] Brain-derived neurotrophic factor (BDNF) is of especial interest because it protects dopaminergic neurons from the toxic effects of MPP^+ and 6-hydroxydopamine.[27,28] Other neurotrophic factors may also influence dopaminergic nigrostriatal cells.[27]

Surgical and Transplantation Procedures

Destructive surgical procedures have been in use for the treatment of parkinsonism for 40 years, but fell into disfavor with the introduction of levodopa. There has been a recent resurgence of interest in such procedures, however, for patients responding poorly to pharmacologic maneuvers. In particular, posteroventral pallidotomy may be especially effective in relieving tremor, rigidity, and bradykinesia in such circumstances.[29] The procedure is best reserved for patients with advanced disease that has become unresponsive to medical treatment or patients with intolerable side effects of medication.

A novel surgical approach involves cerebral transplantation procedures. In a pharmacologically induced rodent model of Parkinson's disease, grafting of adrenal medullary tissue—which is rich in dopamine—into the lateral ventricles and striatum leads to a reduction in abnormal motor activity.[30] The mechanism involved is unclear; the grafted tissue may act as a source of catecholamines and other neurotransmitters or of some neurotrophic factor. Sprouting of endogenous nerve terminals in the striatum has been observed after the transplantation of adrenal medullary tissue in animals, regardless of the survival of the grafted tissue,[31,32] and the importance of nerve growth factor has been illustrated more directly.[33]

Grafting adrenal medullary tissue into nonhuman primates also leads to a reduction of parkinsonian deficits. In humans with Parkinson's disease, however, the results of grafting portions of the patients' adrenal medulla (autografts) into the caudate nucleus have generally been disappointing despite dramatic early reports of benefit.[34-36] Nevertheless, some studies have yielded encouraging data that medication could be reduced, "on" time increased, or quality of life improved by the procedure, at least temporarily.[37,38] In fact, the grafted tissue often fails to survive.[39] The reason for the disparate results is unknown. It has been suggested that the addition of nerve growth factor to the transplanted tissue may improve the clinical response, but this awaits adequate demonstration. In experimental studies in monkeys, however, grafted adrenal medullary tissue has been shown to survive longer if myelinated peripheral nerve tissue (a source of nerve growth factor) is transplanted into the striatum with it.[40,41]

The use of transplantation procedures involving mesencephalic fetal tissue is another therapeutic approach that is under investigation.[42] Pronounced improvement has been reported in two American patients with MPTP-induced parkinsonism,[43] and more moderate benefit has followed such procedures performed in the United States in

patients with typical Parkinson's disease.[44,45] The experience in other countries has been summarized elsewhere by Ahlskog,[46] who emphasized the difficulty in comparing outcomes in different series because of the heterogeneity of patients, the varied rating procedures, and differences in follow-up. In no case was there complete reversal of parkinsonian symptoms, although in some patients disability was reduced. Most patients received unilateral grafts, but clinical improvement was often bilateral, with benefit typically beginning several weeks after transplantation. There have been concerns about ethical aspects of this approach and the limited amount of fetal tissue available for use. Many other issues remain to be resolved, including the optimal amount of graft tissue and the site of its deposition, the necessity for immunosuppressant therapy, and the need for growth factors.

The most effective surgical procedure for treating Parkinson's disease may ultimately involve the transplantation of genetically engineered cell lines, and work along these lines is already proceeding.[47]

Preventive Treatment

The cause of the degeneration of nigral dopaminergic neurons that occurs in Parkinson's disease is unknown. With the recognition of the selective neurotoxicity of MPTP, a likely cause seemed to be exposure to some ubiquitous environmental toxin, perhaps structurally similar to MPTP. Such exposure would not necessarily have had to occur immediately before the clinical onset of the disease, but may have occurred years earlier. Symptoms would not be expected to occur until the cumulative cell loss from exposure to such a toxin and to natural aging exceeded about 80% of the original cell population. No such toxins have been identified, however.

A widely held but not universal view currently relates the development of Parkinson's disease to endogenous toxins, such as free radicals, resulting from oxidation reactions (perhaps as a consequence of exposure to some exogenous environmental toxin).[48,49] More specifically, superoxide or hydroxyl radical formation from hydrogen peroxide may be important pathogenetically. In support of this hypothesis are the findings that the substantia nigra of patients with Parkinson's disease contains increased amounts of total and ferric iron, increased monoamine oxidase B activity, reduced glutathione levels, and diminished activity of enzymes involved in the breakdown of hydrogen peroxide and free radicals.[50] Exposure to free radicals leads to cell death by interaction with various cellular constituents. Their formation is promoted by the reduced form of iron, whereas glutathione is involved in the clearance of hydrogen peroxide from the brain. With age there is an increase in the presence and activity of striatal monoamine oxidase type B, the enzyme that leads to the oxidative deamination of dopamine.[51] An increased breakdown of dopamine enhances the formation of hydrogen peroxide, which may exceed the capacity of glutathione to clear it. The observations discussed earlier concerning the inhibition of mitochondrial complex I in MPTP-induced parkinsonism are of especial interest because mitochondrial complex I deficiency has also been reported in the substantia nigra of patients with Parkinson's disease.[52,53] Such mitochondrial abnormalities can be interpreted as a cause or product of oxidant stress.[48] At present, the evidence relating the pathogenesis of Parkinson's disease to damage by free radicals is circumstantial and compelling, but not conclusive.

Type B monoamine oxidase inhibitors or antioxidants such as vitamin E may protect against oxidative damage and thereby slow the progression of the disease. The role of selegiline in this regard has been examined in several studies, but especially in a large multicenter study in the United States.[54,55] This study showed that treatment with selegiline delayed the need to introduce levodopa as symptomatic therapy in patients with untreated parkinsonism. This was interpreted initially as evidence that the natural history of the disease had been altered, but it subsequently became apparent that selegiline itself exerted a mild symptomatic effect; accordingly, there remains some ambiguity about the basis of the effect that was observed.[56] Under these circumstances, it is difficult to formulate rational guidelines concerning its use, but it is my practice to prescribe selegiline to all patients making an informed decision to take the medication, unless they have end-stage disease or are of advanced age. It is taken in a standard dose of 5 mg with breakfast and 5 mg with lunch; such a regimen is not associated with the hypertensive or "cheese" effect of the nonselective monoamine oxidase inhibitors. It is important for patients to understand that the medication is not being taken for symptomatic benefit, that there is no way of knowing whether they are deriving any other benefit from it, that the medication will probably need to be continued indefinitely, and that its usefulness cannot be determined with certainty from the published studies. The evaluation of other inhibitors of monoamine oxidase type B, such as lazabemide, may be revealing.[57]

The multicenter study referred to earlier failed to find any protective benefit of vitamin E, 2,000 units daily, although tocopherol is an important scavenger of free radicals.[55] The extent to which this agent penetrates the brain is unclear, however.

Iron chelation therapy—to maintain iron in a relatively nonreactive state—has yet to be explored, but is another promising treatment avenue under study.

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