CURRENT AND EXPERIMENTAL THERAPEUTICS OF PARKINSON'S DISEASE

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Three decades after its introduction, levodopa remains the gold standard for the treatment of Parkinson's disease (PD). Levodopa is the most potent symptomatic antiparkinsonian agent, and it is associated with an increase in quality of life and longevity for patients with PD. Dopamine agonists are increasingly being used, not only as an adjunct to levodopa, but as early therapy aimed at reducing the risk of developing levodopa-induced motor complications. Catechol *O*-methyltransferase (COMT) inhibitors extend the elimination half-life of levodopa. They are useful as adjunctive treatment for patients with motor fluctuations to increase the time in which patients respond to the drug. There is now increasing interest in using these drugs from the start of levodopa therapy to deliver levodopa to the brain in a more continuous fashion and thereby, it is hoped, further reduce the risk of motor complications. In the advanced stages of the illness, surgical therapies are being performed with increasing frequency based on evidence that they can restore function when medications fail. Ablative, stimulation, and transplant procedures are all currently under investigation. Finally, there are a series of investigational drugs designed to provide neuroprotective effects and/or to block levodopa motor complications that are now being evaluated in the laboratory and in some instances in PD patients. Thus, therapies and investigational approaches to PD have been markedly expanded in the past several years and include treatments and treatment strategies aimed at restoring function to PD patients in the advanced stages of the illness, preventing the development of the motor complications that are the major source of disability for a large percentage of PD patients, and modifying the disease process so as to slow or halt disease progression.

Parkinson's disease is a progressive motor disorder caused by accelerated degeneration of selected populations of brain cells, primarily including the melanized neurons of the substantia nigra pars compacta (SNc) in the midbrain. It affects approximately 4% of the population over 65 years of age and there are 60,000 new cases each year in the United States (1). With the increasing numbers of elderly individual in modern society, the prevalence of PD is likely to increase in developed countries in generations to come. The classic clinical syndrome is composed of four cardinal features: bradykinesia (slowness of movement), rigidity (increased resistance to passive limb movement), resting tremor (i.e., tremor that is most prominent at rest and tends to abate during voluntary movement), and impairment of gait and posture. The impairment of movement in PD primarily affects "automatic" movements such as those involved during walking, speech articulation and phonation, handwriting, or swallowing. Postmortem studies indicate that approximately 25% of patients who present with a parkinsonian syndrome do not have pathologic changes of PD, but rather of an atypical parkinsonism such as multiple system atrophy (MSA), progressive supranuclear palsy (PSP), or corticobasal ganglionic degeneration (CBGD) (2–4). The clinical features that best predict parkinsonian pathology are resting tremor, asymmetry of motor findings, and a good response to levodopa (see below) (5).

The pathologic hallmark of PD is the loss of pigmented, dopaminergic neurons of the SNc, coupled with intracellular inclusion bodies known as Lewy bodies (6). Pathologic changes frequently including Lewy bodies can also be detected in the locus coeruleus, the nucleus basalis of Meynert, cerebral cortical regions, autonomic regions of the brainstem, the pedunculopontine nucleus, intermediolateral columns of the spinal cord, and peripheral autonomic nerves innervating the cardiovascular system and gastrointestinal tract (7). Without treatment, PD evolves over 5 to 10 years into an akinetic and rigid state in which patients are unable to care for themselves. Death commonly results from aspira-

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tion pneumonia due to swallowing impairment, or complications of immobility such as pulmonary embolism. The introduction of levodopa over 30 years ago (8) represented a revolution in the treatment of PD as it radically altered its prognosis. Under levodopa treatment, good functional mobility can be maintained for a number of years, and the life expectancy of levodopa-treated patients is markedly increased (9,10). However, it soon became apparent that levodopa therapy is associated with a series of motor complications that themselves are a major source of disability to PD patients (11). In recent years there have been dramatic advances in the therapeutics of PD with the development of new medical and surgical treatments that restore function to patients with advanced disease and prevent the development of levodopa-related motor complications. The final challenge involves the development of neuroprotective or disease-modifying therapies that slow or stop disease progression and herald the end of this devastating disorder. Here, too, enormous progress has been made, and several putative neuroprotective drugs and restorative therapies are currently being tested. This chapter reviews the major therapies for PD and describes present advances and future directions in the therapeutics of PD.

MEDICAL THERAPIES FOR PARKINSON'S DISEASE

Levodopa

Since its introduction in the late 1960s (8), levodopa (L-3,4-dihydroxyphenylalanine) has remained the single most effective antiparkinsonian agent, providing benefit to virtually all patients with PD. Levodopa use is associated with improved mobility, reduced disability, and prolonged survival (9,10,12). The involvement of dopaminergic systems in PD was first suspected in the late 1950s, following the observation that patients treated with the then newly available dopamine-blocking agents (antipsychotics) developed clinical signs of parkinsonism. In the same period, an animal study showed that movement slowness in rats, due to the catecholamine depletor reserpine, could be reversed with levodopa (13). The discovery that dopamine is depleted in the striatum of PD patients soon followed (14). This in turn gave rise to the notion that a dopamine replacement strategy might be useful in PD, and the therapeutic role of levodopa in patients with PD was subsequently established in 1967 (8,15). Levodopa is itself largely inert, and its therapeutic and adverse effects result from the decarboxylation of the prodrug levodopa into the active product dopamine (16). After oral administration, levodopa absorption occurs in the small bowel by way of the active transport system for large neutral amino acids. Thus, it is possible that other large neutral amino acids such as lysine and phenylalanine that are present in protein-rich foods can compete with and interfere with levodopa absorption. Levodopa is used in the place of dopamine as dopamine itself cannot penetrate the blood–brain barrier and enter the central nervous system (CNS). CNS entry is also an active process mediated by the large neutral amino acid transport system, and again there may be competition for brain access between levodopa and dietary amino acids (16).

Levodopa is normally metabolized in the periphery by two enzymatic systems: amino-acid decarboxylase (AADC) and COMT. This transformation occurs in the intestinal and gastric mucosa as well as in the liver. The peripheral metabolism of levodopa is so effective that the plasma half-life is approximately 60 minutes, and only 1% of an administered oral dose reaches the CNS (16). Further, accumulating concentrations of plasma dopamine secondary to decarboxylase-mediated metabolism of levodopa can activate dopamine receptors in the area postrema that are not protected by a blood–brain barrier and cause nausea and vomiting. Indeed, nausea and vomiting are limiting side effects in as many as 50% of patients when levodopa is administered alone. To defend against this complication, levodopa is now routinely administered in combination with a peripherally acting inhibitor of AADC. In the United States, levodopa is combined with the AADC inhibitor carbidopa and marketed as Sinemet. In other parts of the world, the AADC inhibitor benserazide is also frequently used with levodopa and sold as Madopar. The combination of levodopa with an AADC inhibitor permits the use of lower doses of levodopa (by doubling its bioavailability) and reduces the incidence of peripheral dopaminergic side effects such as nausea, vomiting, and hypotension. In most patients, a daily dose of 75 mg of carbidopa is sufficient to inhibit AADC and prevent these side effects. Interestingly, even in the presence of an AADC inhibitor, 90% of levodopa is still metabolized by COMT (17). This has led to the recent introduction of COMT inhibitors (see section below).

In the CNS, dopamine is synthesized from levodopa in dopaminergic terminals, transported into storage vesicles, and released in a spike-dependent manner in association with depolarization of the presynaptic neuron. The released dopamine acts on postsynaptic dopamine receptors (possibly in a volumetric manner). Its action is terminated primarily by a very rapid presynaptic reuptake system that is antagonized by cocaine. It can be degraded either intracellularly or extracellularly by monoamine oxidase (MAO) and COMT enzymes to yield homovanillic acid (HVA)(9). MAO has two subtypes; A, which is primarily intracellular, and B, which is primarily extracellular (18).

Two classes of dopamine receptors (D1 family and D2 family) and five receptor subtypes (D1–D5) have been molecularly cloned to date (19). The D1 receptor family is characterized by positive coupling with adenylate cyclase formation, whereas D2 receptors have an affinity for neuroleptic agents and activation inhibits adenylate cyclase (20). Dopamine receptors are G-protein–coupled receptors, and activation of the different subtypes likely is associated with

a different signaling pattern and different gene and protein regulation (19). Indeed, it is becoming increasingly clear that activation of different receptors, the same receptor with different agents, and the same receptor with the same agent with a different pattern of stimulation can all lead to a different intracellular signaling cascade that potentially has different functional effects (19). Dopamine receptors are diffusely distributed throughout the CNS: motor striatum (D1, D2), hippocampus (D5), frontal cortex and amygdala (D4), hypothalamus (D3, D5), and mesolimbic system (D3). The precise role of each of these receptors in motor function remains unknown; however, it is likely that this wide distribution accounts for the diverse pattern of functional effects that can be obtained when exogenous levodopa is administered to PD patients. Although most attention has focused on the nigrostriatal dopaminergic system in PD, it is important to appreciate that there is also dopaminergic innervation of the cerebral cortex and numerous other basal ganglia regions including the substantia nigra pars reticularis (SNr), the subthalamic nucleus (STN), the globus pallidus pars interna (GPi), and the globus pallidus pars externa (GPe) (21). Activation of dopaminergic receptors in these regions might also contribute to the beneficial and adverse effects observed with levodopa administration to PD patients. Indeed, although levodopa dramatically improves the motor signs and symptoms of PD, it also has effects on vision, memory, mood, reward-related learning, and addiction (22–30).

Levodopa Benefits and Motor Complications

Levodopa is the most effective antiparkinsonian agent for the management of motor dysfunction in PD. Levodopa benefits can be dramatic, and improvement can be obtained in all of the cardinal signs and symptoms of PD. Levodopa has also been shown to provide a dose-dependent beneficial effect on mood and anxiety in PD patients that increases with the duration of therapy (27). These important nonmotor effects can contribute to the benefits associated with the levodopa response. Indeed, more than 30 years after its introduction, no other medication provides antiparkinsonian benefits that are superior to levodopa (30,31).

The acute administration of levodopa, even in the presence of a decarboxylase inhibitor can still be associated with nausea, vomiting, and orthostatic hypotension. These are usually seen during the titration phase and can be minimized by initiating levodopa at a low dose and titrating slowly to the desired clinical effect. Persistent nausea and vomiting can specifically be handled by adding supplemental doses of carbidopa (Lodosyn), or using the peripheral dopamine receptor antagonist domperidone (available in Canada and Europe) in doses of 10 mg 30 minutes before the levodopa dose. Postural hypotension can be managed by advising the patient to lie supine at night with the head of the bed elevated and rising slowly. If postural hypotension persists, pharmacologic agents such as fluorocortisone and midodrine may be helpful. If a parkinsonian patient experiences symptomatic orthostatic hypotension, the possibility that he or she suffers from MSA with autonomic involvement should be considered.

Motor complications that develop in association with chronic levodopa therapy are the most disabling side effect for most patients. In the early stages of PD, the duration of benefit following a single dose of levodopa is long lasting and far exceeds the plasma half-life of the drug (60 to 90 minutes) (32). This has been ascribed to the relatively preserved capacity of presynaptic dopaminergic terminals of nigrostriatal neurons to store dopamine and regulate its release. However, after a few years of levodopa therapy, there is further neuronal degeneration, and the duration of benefit following each dose of levodopa is shortened in duration. Thus, patients begin to fluctuate between periods of good motor function ("on" responses) and periods of poor motor function ("off" responses) (33). Further, the periods of good motor function that characterize "on" periods now becomes complicated by involuntary movements known as dyskinesia. These are usually choreiform in nature and occur in association with the peak plasma concentration of the drug. However, they may be dystonic or myoclonic in nature, and occur at the onset and termination of the "on" response. In this situation they are referred to as diphasic dyskinesia (34). Manipulating the dose and frequency of levodopa administration is the usual therapeutic approach to the onset of motor complications, but this can be difficult because doses high enough to induce a motor benefit may induce involuntary movements, and doses low enough to ameliorate dyskinesia may not be sufficient to provide antiparkinsonian benefit. Eventually, it may become virtually impossible to achieve a dose of levodopa that provides motor benefits without inducing dyskinesia, and patients may cycle between intolerable dyskinesia and intolerable parkinsonism.

In the early stages of motor fluctuation, increasing the half-life of levodopa by coadministration of a COMT inhibitor may be helpful (see COMT Inhibitors, below). Sustained-release formulations of levodopa (Sinemet CR, Madopar HBS) have been developed in the hope that they would better control motor fluctuations; however, the unpredictable intestinal absorption of these preparations makes them difficult to employ in routine practice, especially for patients with complex motor complications. Low-protein diets or redistribution diets with restriction of the protein intake until the later part of the day may provide some short-term benefits by facilitating levodopa absorption and thereby improving motor performance (36). Dyskinesias are difficult to treat medically, other than by lowering the dose of dopaminergic agent, and this in turn can be associated with worsening parkinsonism as described above. Amantadine has been reported to have an antidyskinetic effect (37) (see below). When motor complications are fully developed, medical therapies are for the most part ineffec-

tive and patients may be considered for surgical intervention (see below). Thus, despite the best of existing medical therapy, more than 75% of PD patients eventually experience intolerable disability (35,38).

It is currently thought that motor complications in PD are related to both presynaptic and postsynaptic mechanisms. Chase and his colleagues initially postulated that levodopa-related motor fluctuations develop because of the progressive loss of nigrostriatal neurons and a loss of their capacity to store dopamine and buffer fluctuations in plasma levodopa. Indeed, his group demonstrated a progressive shortening of the duration of the motor response following a dose of levodopa in patients with advancing disease, despite the fact that levodopa peripheral pharmacokinetics remain stable in all stages of PD (39,40). This "storage hypothesis" presumed that with the loss of dopamine terminals, central buffering capacity is lost, and striatal dopamine levels become dependent on the peripheral availability of levodopa. As a result, the patient's motor state begins to fluctuate in parallel with the fluctuating plasma levodopa levels that accompany intermittent administration of oral levodopa therapy. With increasing disease severity, there is progressive degeneration of dopamine terminals with further loss of their buffering capacity and consequent exposure of striatal dopamine terminals to alternating and pathologically high and low or "pulsatile" levels of dopamine. However, the storage hypothesis cannot account for the fact that apomorphine has similar pharmacokinetic and pharmacodynamic responses with advancing disease severity as does levodopa, even though apomorphine is not stored in dopaminergic terminals (41). This implies that postsynaptic mechanisms must play some role in the pathophysiology of levodopa-related motor complications.

Current evidence indicates that levodopa-induced motor complications are related to a sequence of events that include abnormal pulsatile stimulation of the dopamine receptor by dopaminergic agents with a short plasma half-life, dysregulation of downstream genes and proteins, and altered neuronal firing patterns (see ref. 42 for complete review of this topic; also see below). In support of this concept, it has been shown that motor complications in parkinsonian monkeys are induced by short-acting dopaminergic agents such as levodopa, which induce pulsatile simulation of receptors, but not by long-acting dopamine agonists, which more closely simulate the normal tonic activation of dopamine receptors (43). Indeed, intermittent administration of a short-acting dopamine agonist induces dyskinesia, whereas continuous administration of the same short-acting agonist does not (44). Further, altered expression of genes such as preproenkephalin (PPE) in striatal neurons have been recorded in association with the development of dyskinesia in N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated monkeys (45). Finally, levodopa-induced alterations in neuronal firing patterns have been described in dyskinetic monkeys, which include changes in firing bursts and pauses,

the degree of neuronal synchrony, and neuronal firing frequency (46).

These observations have led to the development of new therapeutic options and treatment strategies designed to reverse or prevent the development of levodopa-related motor complications. One such approach is based on lesioning the output neurons in the basal ganglia so as to disrupt their abnormal neuronal firing pattern and the communication of misinformation from basal ganglia to motor cortical regions. This concept likely underlies the antidyskinesia effects that have been observed with surgical therapies for PD (47,48) (see Surgical Therapies for Parkinson's Disease, below). A second approach has been directed at modulating dysregulated signaling pathways in striatal neurons leading to abnormal phosphorylation of *N*-methyl-D-aspartate (NMDA) receptors (49). This concept has led to studies of NMDA receptor antagonists and other agents that interfere with intracellular signals as a means of treating levodopa-induced motor complications in PD (37,49,50). Finally, and perhaps most importantly from the standpoint of the clinician, are the use of long-acting dopaminergic agents based on attempts to provide more physiologic continuous dopaminergic stimulation to striatal dopamine receptors and avoid pulsatile stimulation of striatal dopamine receptors (51). Indeed, prospective double-blind clinical trials have now demonstrated that PD patients randomized to initiate therapy with a dopamine agonist have significantly reduced risk of developing motor complications compared to those randomized to start with levodopa (30,31).

Levodopa can also be associated with dose-related sedation, and neuropsychiatric problems such as hallucinations and confusion. These are most likely to occur in the elderly and in patients with preexisting cognitive impairment. The initial hallucinatory episodes usually consist of benign visual hallucinations that are often a greater source of concern to the family than the patient, who retains insight into the nature of the problem. However, patients who experience levodopa-induced hallucinations are more likely to go on and develop dementia (52). An Alzheimer-type dementia can occur in as many as one-third of PD patients, particularly if they have onset after the age of 70 years. Managing hallucinations and confusion in a levodopa-treated patient (1) involves (a) ruling out other temporary causes of mental dysfunction, such as infection, electrolyte imbalance, other brain lesions; (b) elimination of nonparkinsonian medications that are not essential and can impair cognition, (c) elimination of antiparkinsonian drugs that are prone to causing delirium such as anticholinergics, amantadine, selegiline, and dopamine agonists; thereafter the levodopa dose should be reduced to the lowest dose that provides satisfactory control of mobility; and (d) finally, low-dose therapy with atypical neuroleptics can be considered. Clozapine is an atypical neuroleptic that has minimal parkinsonian effects and has been found to be useful in the treatment of psychotic symptoms in PD patients (53). Low doses are

frequently all that is required to provide benefit for PD patients. Accordingly, treatment is initiated with a dose of 12.5 to 25 mg at night and slowly and modestly increased to the desired effect. Hallucinations can usually be controlled with doses less than 25 mg daily. Clozapine is associated with a small risk of hematologic side effects and periodic monitoring is required. Respiradone (Respiradol), olanzapine (Xyprexa), and quietapine (Seroquel) are alternative atypical neuroleptics, but they have been less thoroughly studied than clozapine for PD psychosis, and anecdotal reports suggest that they are no more, and possibly less, effective.

Sudden withdrawal of levodopa can be associated with sudden deterioration in parkinsonian features and may precipitate a life-threatening neuroleptic malignant syndrome (54,55). Abrupt reduction of dopaminergic therapy is rarely indicated in the modern era and should be performed in a setting where appropriate monitoring can be performed. Diagnosis is based on altered consciousness, fever, increase in rigidity and other extrapyramidal signs, autonomic instability, elevated creatine kinase level, and leukocytosis. Treatment involves supportive measures (hydration and muscle relaxants) and reintroduction of dopaminergic therapy. PD can also be associated with features that do not respond to levodopa and can themselves be a major source of disability to the patient. These include dementia, autonomic dysfunction, sensory complaints, and freezing episodes in which patients experience arrests in mobility lasting seconds to minutes in duration.

Finally, there has been some concern that despite its many benefits, levodopa might accelerate neuronal degeneration through the oxidizing species generated through its oxidative metabolism. In particular, levodopa is oxidized by MAO to form peroxides, which can combine with iron to generate the cytotoxic hydroxyl radical (56). Levodopa has been shown to induce degeneration of cultured dopaminergic neurons (57). It is less clear that levodopa induces toxicity in animal models, where it has been shown to induce SNc damage in some studies (58) but not in others (59) where there is even the suggestion that it might be protective. Levodopa has not been shown to induce damage to dopamine neurons in normal animals or humans, but the situation may be different in PD, where the SNc is in a state of oxidant stress and defense mechanisms are compromised. A recent consensus conference concluded that although the possibility that levodopa might be toxic in PD has not been excluded, there was no reason to withhold the medication for this reason based on present evidence (60).

In the United States, levodopa is most frequently administered as Sinemet, which is available in dosages of 10/100, 25/100 and 25/250 (the first number represents the dose of carbidopa in mg and the second number the dose of levodopa in mg). Madopar is available in doses of 12.5/50 and 25/100. Long-acting formulations of both of these drugs are available: Sinemet CR in doses of 25/100 and

50/200 and Madopar HBS in a dose of 25/100. Liquid formulations of levodopa can be made by adding water and ascorbate to a Sinemet tablet, but these must be made fresh and offer little additional advantage for most PD patients. Rapidly absorbed methyl and ethyl ester formulations of levodopa are currently being assessed experimentally.

In summary, levodopa continues to be an important component of the therapeutic armamentarium for PD, but it is associated with troublesome complications and some parkinsonian features do not respond. Theoretically, levodopa could accelerate neuronal degeneration through oxidizing species generated by its oxidative metabolism, but there is little evidence to suggest that this is a concern in PD, and most physicians do not restrict the use of levodopa for this reason (60). On the other hand, current research suggests that if PD therapy is initiated with a dopamine agonist and levodopa is reserved until satisfactory benefits can no longer be controlled with the agonist alone, patients can enjoy comparable motor benefits and reduced motor complications in comparison to when levodopa is administered on its own (see Dopamine Agonists, below). There is also considerable interest in administering levodopa in conjunction with a COMT inhibitor to enhance its duration of effect and thereby improve motor response and reduce the risk of the drug inducing pulsatile stimulation of the dopamine receptor (see COMT Inhibitors, below).

Dopamine Agonists

Dopamine agonists are a group of drugs that act directly on dopaminergic receptors. Historically, they have been used as adjuncts to levodopa in the treatment of PD since the 1970s (61) and offer several theoretical advantages over levodopa (62): (a) They do not depend on enzymatic conversion for activity, i.e., they do not depend on the integrity of the nigrostriatal neurons, such that they should be active even in advanced stages of PD, at which time presynaptic dopamine neurons and terminals are largely degenerated. (b) They can be designed to stimulate specific subtypes of dopamine receptors, which may lead to selective functional responses. (c) Most marketed dopamine agonists have longer half-lives and longer durations of action than levodopa. This may permit more continuous (less pulsatile) stimulation of dopamine receptors than occurs with levodopa therapy. Therefore, there has been interest in the potential of this class of drug to reduce the risk of developing levodopa-related motor complications (62). (d) They do not undergo oxidative metabolism and do not generate free radicals that might promote degeneration of remaining nigrostriatal neurons. There are data now indicating that dopamine agonists can scavenge free radicals and protect dopamine neurons in *in vitro* and *in vivo* models of PD (63,64). Therefore, there has been interest in the potential of dopamine agonists to provide neuroprotective effects in PD (65).

Five dopamine agonists, bromocriptine (Parlodel), per-

golide (Permax), cabergoline (Cabsar, Dostinex), pramipexole (Mirapex) and ropinirole (Requip), are currently available for use in the United States and in many other countries throughout the world; cabergoline is approved for the treatment of PD in Japan and several European countries, but it has been exclusively marketed for suppression of lactation in the United States. Lisuride, piribedil, and apomorphine are other dopamine agonists that are available in some countries but not the United States. All dopamine agonists that are marketed for the treatment of PD stimulate the D2 receptor, which is thought to underlie their antiparkinsonian effects. Dopamine and apomorphine stimulate both D1 and D2 receptors. Pergolide is also a weak agonist and bromocriptine a weak antagonist of the D1 receptor. The role of D1 receptor activation or inhibition in PD is not known, although there is some suggestion that stimulation of both D1 and D2 receptors provides enhanced motor responses. Bromocriptine, pergolide, ropinirole, and pramipexole have plasma half-lives of 6 to 15 hours, whereas cabergoline has a much longer elimination half-life of 63 to 69 hours. This contrasts with the plasma half-life of levodopa, which is 60 to 90 minutes.

Dopamine Agonists in Patients with Advanced PD

Since their introduction in the mid-1970s, dopamine agonists have primarily been used as adjuncts to levodopa in PD patients with relatively advanced disease who have begun to experience motor complications (66). As an adjunct to levodopa, numerous prospective double-blind studies have demonstrated that dopamine agonists can significantly improve PD signs and symptoms, reduce dyskinesia and motor fluctuations, and reduce the need for levodopa therapy in comparison to placebo (67–73). Benefits have been observed with each of the currently approved dopamine agonists and they are of approximately equal magnitude. Apomorphine stimulates both D1 and D2 receptors. It has a very short latency to onset, but also a short duration of benefit. It has been used to provide a ''rescue effect'' for patients who turn ''off'' and do not respond to their next dose of levodopa (74). Some physicians have reported benefits in advanced patients with complex motor complications with the use of continuous apomorphine (75). However, apomorphine must be administered parenterally, is associated with cutaneous ulcerations at sites of entry, and is very difficult to manage for both the physician and the patient. It therefore has relatively little role in routine practice.

Despite the benefits obtained with dopamine agonists in patients with advanced disease, they generally do not provide satisfactory control of motor function or motor complications, and sooner or later alternate therapies must be sought.

Dopamine Agonists in Patients with Early PD

As discussed in the section on levodopa-related motor complications (see above), there is growing evidence suggesting that pulsatile stimulation of dopamine receptors due to the use of short-acting dopaminergic agents contributes to the emergence of motor complications. Studies in MPTP-treated primates demonstrate that bromocriptine and ropinirole are associated with reduced frequency and severity of dyskinesia compared to levodopa, even though all groups provide comparable behavioral effects (76,77). These data suggest that starting treatment for PD patients with a long-acting dopamine agonist rather than levodopa might reduce the risk of developing motor complications. However, until recently dopamine agonists have not been well studied in early PD. There are now prospective double-blind controlled studies demonstrating that both pramipexole and ropinirole provide improvement in measures of motor functions and activities of daily living (ADL) in otherwise untreated PD patients that are superior to placebo (78,79), and almost as good as levodopa (30,31). Further, PD patients can be maintained on dopamine agonist monotherapy without supplemental levodopa for a mean of 3 years (80). More importantly, it has now been established in prospective double-blind long-term studies that PD patients randomized to initiate therapy with a dopamine agonist (ropinirole or pramipexole), supplemented with levodopa if necessary, have significantly fewer motor complications than patients randomized to begin therapy with levodopa alone (30,31). Reduced rates of both dyskinesia and motor fluctuations were observed in the agonist-treated patients. Measurements of motor function and ADL on the Unified Parkinson Disease Rating Scale (UPDRS) showed slight, but significant, benefits in favor of levodopa-treated patients in both studies. This is difficult to explain, as patients in both groups could have added open label levodopa to their blinded treatment regimen if either the physician or the patient thought it was necessary. This raises the question as to whether the UPDRS fully captures all factors that contribute to PD disability.

Based on these new studies and the concept of continuous dopaminergic stimulation, many authorities now recommend initiating symptomatic therapy for PD with a dopamine agonist, and reserving levodopa until such time as the agonist can no longer provide satisfactory clinical control (51,81–83). Others feel that the issue is still somewhat controversial and that physicians must choose between enhanced efficacy now versus delayed motor complications later. Our personal view is that the difference in motor and ADL scores between the agonist and levodopa groups is negligible, whereas the difference in the rate of developing motor complications is substantial and a much greater source of disability for the patient and frequently necessitates surgical intervention as the only means of providing satisfactory control. Accordingly, we favor initiating therapy

with a dopamine agonist in appropriate patients to diminish the risk that disabling motor complications will ensue. We still favor the use of levodopa as the initial agent in patients with cognitive impairment or who are elderly.

Adverse Effects of Dopamine Agonists

The acute side effects of dopamine agonists are similar to those observed with levodopa and include nausea, vomiting, and postural hypotension (84). These side effects tend to occur when treatment is initiated and abate over days or weeks as tolerance develops. Introducing the agonist at a low dose, and slowly titrating to the desired effect reduces the probability that they will occur. Dopamine agonists can acutely cause or intensify dyskinesias, but in the long term they have the potential to lessen dyskinesias and motor fluctuations because of their long duration of action (see above). Psychiatric complications (hallucinations, confusion) may occur and tend to be more pronounced than bioequivalent doses of levodopa (30,31). The ergot-derived dopamine agonists, bromocriptine, pergolide, and cabergoline, may have ergot-related side effects including pleuropulmonary and retroperitoneal fibrosis, erythromyalgia, and digital vasospasm, although these are rare (84). The newer non-ergot dopamine agonists are less likely to induce these problems, although there is anecdotal suggestion that they may still occur. Dose-related sedation may occur with dopamine agonists (69,78), as with other dopaminergic agents including levodopa. More recently, sudden episodes of unintended sleep while at the wheel of a motor vehicle have been described in PD patients and attributed to dopamine agonists (85). The episodes were termed "sleep attacks" because they occurred suddenly, although others have argued that there is no evidence to support the concept of a sleep attack even in narcolepsy. They have suggested that it is more likely that these patients have unintended sleep episodes as a manifestation of excess daytime sedation due to nocturnal sleep disturbances that occur in 80% to 90% of PD patients and to the sedative effect of dopaminergic medications (86). It is now apparent that these types of episodes can be associated with all dopaminergic agents including levodopa (87). Physicians should be aware of the potential of dopaminergic agents to induce sleepiness, and that patients themselves may not be aware that they are sleepy. To detect excess sleepiness and to thereby introduce appropriate management strategies, it is necessary to employ sleep questionnaires such as the Epworth sleepiness scale, which inquires into the propensity to fall asleep and does not rely upon subjective estimates of sleepiness (88).

Catechol *O*-Methyltransferase (COMT) Inhibitors

Orally ingested levodopa is massively transformed in the periphery by two enzymatic systems—AADC and COMT—such that only 1% of a levodopa gains access to the brain. To partially counter this effect, levodopa is routinely prescribed in combination with an inhibitor of AADC that does not cross the blood–brain barrier and blocks the peripheral decarboxylation of levodopa into dopamine. This combination reduces peripheral dopaminergic side effects associated with the administration of levodopa alone, and increases the amount of levodopa that is available to access the brain. However, even in the presence of a decarboxylase inhibitor, the bulk of levodopa is still metabolized by COMT and only 10% of a given dose is transported into the brain (17,89). Two new drugs that inhibit COMT, tolcapone (Tasmar) and entacapone (Comtan), have recently been introduced to the market as an adjunct to levodopa therapy. Both drugs inhibit COMT in the periphery, although tolcapone has mild central effects as well. Entacapone and tolcapone increase the elimination half-life of levodopa by approximately 40% without modifying the peak plasma concentration of levodopa (C_{max}) or the time to reach peak plasma concentration (*Tmax*) and effects are seen with both immediate and controlled release formulations (90–93). COMT inhibitors thus modulate peak and trough plasma levodopa concentrations, leading to a smoother plasma curve with reduced fluctuations in levodopa level (94). These pharmacokinetic effects have been shown to translate into enhanced levodopa entry into the brain on positron emission tomography (PET) (95) and clinical benefits particularly for patients experiencing mild to moderate motor fluctuations. Double-blind placebo-controlled clinical trials in fluctuating PD patients demonstrate that COMT inhibitors increase the duration of beneficial effect following a single levodopa dose (96). They also provide an increase daily "on" time of 15% to 25%, a decrease in "off" time of 25% to 40%, improvement in UPDRS motor scores, and a reduction in levodopa dose requirement of 15% to 30% (97–100). Benefits with COMT inhibitors have also been observed in nonfluctuating PD patients with a stable response to levodopa. Two placebo-controlled trials showed improved motor scores and reduced levodopa dose requirements in the group receiving the COMT inhibitor (101,102).

There has also been interest in using COMT inhibitors from the time levodopa is first initiated in order to reduce the risk of developing motor complications (103). As described in the section on motor complications, laboratory evidence supports the notion that treatment for PD patients should be employed in such a way as to try and avoid pulsatile stimulation of dopamine receptors (51). Indeed, there is now evidence indicating that initiating therapy with a long-acting dopamine agonist reduces the risk of dyskinesia and motor fluctuations (30,31). However, these patients eventually require levodopa, and when levodopa is administered the frequency of motor complications increases. It therefore has been postulated that administering levodopa from the time it is first introduced with a COMT inhibitor

to extend its half-life and deliver levodopa to the brain in a more continuous fashion might further reduce the risk of motor complications. Based on a similar hypothesis, studies comparing controlled-release levodopa to regular levodopa failed to demonstrate any difference between the two formulations (104,105). However, controlled-release formulations have variable absorption and do not provide stable plasma levels of levodopa. Further, the drug was prescribed twice daily in these studies, and that may not have been frequent enough to prevent fluctuations in plasma levodopa concentrations. Clinical trials to test this hypothesis using entacapone as an adjunct to levodopa are currently being planned.

Side effects associated with COMT inhibitors are primarily dopaminergic and reflect enhanced delivery of levodopa to the brain. Dyskinesia is the most common, but nausea, vomiting, and psychiatric complications may occasionally occur. Both the benefits and dopaminergic adverse effects develop within hours to days after initiating treatment. In general, they are easy to manage by simply reducing the dose of levodopa (by approximately 15% to 30%), not the dose of the COMT inhibitor. Dyskinesia is more likely to be a problem in patients who already experience dyskinesia, and the need for a levodopa dose reduction can be anticipated in these patients. An explosive diarrhea has been seen in 5% to 10% of tolcapone-treated and necessitates discontinuing the drug. This has been much less of a problem with entacapone and rarely requires stopping the drug. Brownish-orange urine discoloration may occur with either drug due to accumulation of a metabolite. This is a benign condition, but patients should be advised that it may occur.

Of greater seriousness is the problem of liver toxicity that has been reported in association with tolcapone (106). No evidence of liver dysfunction was detected in preclinical toxicity studies, but in clinical trials elevated liver transaminase levels were observed in 1% to 3% of patients. For this reason, liver monitoring was required. Following approval of the drug, there have been reports of four cases of severe liver dysfunction leading to the death of three of the individuals (106,107). These observations led to the drug being withdrawn from the market in Europe and Canada and to the issuance of a "black box" warning in the United States (108). This requires biweekly monitoring of liver enzymes for the first 12 weeks, monthly monitoring thereafter, and discontinuation of the drug if liver enzymes are elevated above normal on a single occasion. No preclinical toxicity, clinical trial, or postmarket reports of liver dysfunction have been described to date with entacapone, and no laboratory monitoring is required with its use (109).

Entacapone is typically administered in a dose of 200 mg with every scheduled dose of levodopa, whereas tolcapone is administered at a dose of 100 or 200 mg three times daily. No comparative studies between entacapone and tolcapone have been performed, but pharmacokinetic and clinical trial data indicate that tolcapone is the more potent agent. However, because of the greater risk of hepatotoxicity and diarrhea, entacapone has become the more widely employed COMT inhibitor. It should be emphasized that COMT inhibitors provide antiparkinsonian benefit only when used as an adjunct to levodopa. By themselves they have no effect.

In conclusion, COMT inhibitors represent an important advance in the medical treatment of PD and may be useful in all stages of the illness (110). Used in combination with levodopa, they extend the half-life of levodopa, smooth the plasma levodopa concentration curve, and enhance clinical dopaminergic benefits. They have been established to provide benefit in PD patients with motor fluctuations, although particular care must be taken in managing the more advanced patients with severe dyskinesia, and this is usually best left to the Parkinson specialist. There are preliminary data suggesting that they enhance motor function in the milder patient with a stable response to levodopa, and this is being further evaluated. Finally, there is good evidence to suggest that administering levodopa with a COMT inhibitor from the time it is first introduced may prevent pulsatile stimulation of dopamine receptors and minimize the risk of developing motor complications. The drugs are easy to use and require no titration. Dopaminergic side effects tend to occur within days and can be managed by tapering the levodopa dose. Because of the restrictions in the use of tolcapone due to liver toxicity, entacapone is now the COMT inhibitor of choice. It is likely that a single tablet will soon be developed that contains the combination of levodopa, an AADC inhibitor, and a COMT inhibitor.

Other Antiparkinson Agents

Anticholinergics

Anticholinergic drugs were first used as a treatment for PD in the 1860s, using extracts from the alkaloids *Atropa belladonna* and *Hyscyamus niger*, which contain hyosciamine and scopolamine (111,112). Synthetic anticholinergic drugs were developed in the 1940s, and they became the mainstay of PD treatment until the emergence of levodopa (113, 114). These drugs have largely been replaced by the newer antiparkinsonian drugs, but are still used occasionally in the modern era particularly for the treatment of tremor (115). The main anticholinergic agents currently in use are trihexyphenidyl (Artane), benztropine (Cogentin), biperiden (Akineton), orphenadrine (Disipal), and procyclidine (Kemadrin). An interaction between dopaminergic and cholinergic neurons in the basal ganglia has long been recognized, and classic experiments demonstrated the capacity of cholinergic agents to worsen and anticholinergic agents to improve parkinsonian features (116). Cholinergic agents have been shown to block dopamine reuptake into presynaptic dopaminergic terminals (117) and dopamine receptor activation has been shown to regulate acetylcholine release (118).

More recent work has demonstrated that dopamine-regulated neuropeptide (preproenkephalin) expression in striatal neurons is regulated by cholinergic interneurons (119). Despite these observations, the relationship between the cholinergic and dopaminergic systems is poorly understood, as is the basis for the clinical benefits that are seen with anticholinergic agents.

Clinical studies demonstrate that anticholinergic agents provide a 10% to 25% improvement in rest tremor, whereas akinesia and postural impairment are not affected (120). In practice, anticholinergic agents can be used in early PD patients to treat tremor when it is the predominant complaint and to delay the introduction of levodopa, provided that cognitive function is preserved and that the patient does not have narrow angle glaucoma or orthostatic hypotension (see General Adverse Effects of DBS, below). Trihexyphenidyl is the most widely used anticholinergic agent in PD, although head-to-head comparisons have not been performed. The usual trihexyphenidyl doses range from 0.5 to 1 mg b.i.d. initially, with gradual increase to 2 mg t.i.d. Benztropine is also commonly used, with doses ranging from 0.5 to 2 mg b.i.d.

Side effects are a major limiting factor with respect to the use of anticholinergic drugs in PD. The most important of these are central, and consist of memory impairment, confusion, hallucinations, sedation, and dysphoria (115). These tend to be most pronounced in older individuals with some preexisting cognitive impairment, but can affect young patients with seemingly intact mentation as well. Peripheral side effects include dry mouth, dysuria, constipation, dizziness due to orthostatic hypotension, tachycardia, nausea, blurred vision, and decreased sweating. Anticholinergic agents should be avoided in patients with narrow angle glaucoma, and caution is required in using them in patients with prostatic hypertrophy because of the risk of inducing acute urinary retention. Anticholinergic drugs can enhance levodopa-induced choreiform dyskinesias, and orobuccal dyskinesias have been reported with anticholinergic therapy alone (121). If the decision is made to discontinue anticholinergics, this should always be done gradually to avoid withdrawal effects and acute exacerbation of parkinsonism (122).

Peripherally active anticholinergic drugs are also used in PD. Anticholinergic agents that are relatively selective for bladder cholinergic receptors such as tolterodine tartrate (Detrol), and oxybutynin (Ditropan) can be used to treat bladder instability (123). Anticholinergic agents that are relatively selective for salivary gland receptors such as glycopyrrolate (Robinul) can be used to treat sialorrhea.

Because of their adversity profile, and particularly their tendency to induce cognitive impairment, anticholinergic agents are not commonly used in the treatment of PD. They are perhaps most frequently used in younger PD patients with tremor-dominant PD. However, there is evidence suggesting that levodopa and other dopaminergic agents provide antitremor effects that are just as good as or superior to anticholinergic agents (124). Certainly when these agents are employed, side effects should be sought and the drug discontinued when they occur.

Amantadine

The discovery of the antiparkinson properties of the antiviral agent amantadine (Symmetrel) was fortuitous (125). The primary mechanism of action of amantadine in PD is not established with certainty. The drug has been described to increase dopamine release, block dopamine reuptake, and stimulate dopamine receptors. It has also been shown to have anticholinergic effects and weak NMDA receptor antagonist properties (126–128). Improvement in akinesia, rigidity, and tremor, as well as reduction in choice reaction time, have been described in uncontrolled studies, particularly in mildly affected PD patients (125,129–131). In comparison to anticholinergic drugs, amantadine was found to have a greater effect on akinesia and rigidity but lesser benefit for tremor (132).

With the recognition that amantadine provides NMDA receptor antagonism (128), there has been interest in the notion that it might have antidyskinetic and even neuroprotective effects. The potential of the drug to interfere with dyskinesia is based on the notion that dyskinesias are related to excessive phosphorylation of NMDA receptors on striatal neurons due to loss of dopamine-mediated modulatory effects (49). Studies in monkeys show that NMDA receptor antagonists can improve dyskinesia (50). Preliminary clinical trials suggest that the same is true in some PD patients (37,134), and this has now been confirmed in a double-blind controlled study (135). The potential of amantadine to provide neuroprotective effects is based on evidence suggesting that excitotoxicity contributes to neuronal degeneration in PD (136,137). Indeed, one retrospective study did suggest that there was an increase in the survival of PD patients that had been treated with amantadine (138).

The elimination half-life of amantadine is 10 to 30 hours, and the medication is typically administered in dosages of 100 mg two to three times per day. Unfortunately, amantadine is frequently associated with dose-related cognitive problems including confusion, hallucinations, insomnia, and nightmares that limit its usefulness. Amantadine has also been associated with livedo reticularis, ankle edema, and peripheral neuropathy. If amantadine must be withdrawn, it should be done gradually as some patients may experience dramatic worsening of PD on withdrawal.

In conclusion, amantadine can be used in the initial stages of PD to provide some symptomatic benefit and to delay the need for levodopa. It can also be used as an adjunct to levodopa to try to control levodopa-induced dyskinesia. Cognitive side effects limit the usefulness of this drug, and mental status must be closely monitored particularly in patients with advanced disease or preexisting cognitive impair-

ment. As it is difficult to withdraw in many instances, many physicians do not use this drug as a first-line therapy.

Selegiline

Selegiline (Deprenyl, Eldepryl) is a relatively selective inhibitor of monoamine oxidase-B (MAO-B). It was approved in PD as an adjunct to levodopa that provides a modest increase in "on" time in fluctuating patients with advanced PD (139). However, it is primarily used in the treatment of early PD patients as a putative neuroprotective agent. This was based on two important observations that suggested that an MAO-B inhibitor might alter the natural course of PD. First, the neurotoxin MPTP causes parkinsonism (140) by way of an MAO-B–catalyzed oxidation reaction forming the toxin MPP^+ (141), and second, dopamine is oxidized by MAO-B to generate peroxides and other potentially cytotoxic oxidizing species (56). In the laboratory, selegiline has been shown to protect nigral dopaminergic neurons in cell cultures and in MPTP-treated animals (142,143). Prospective double-blind clinical trials in previously untreated PD patients have demonstrated that selegiline delays the emergence of clinical dysfunction as determined by the need for levodopa and the progression of parkinsonian signs and symptoms (144,145). However, post hoc analyses have demonstrated that selegiline has symptomatic effects that might account for these benefits. These confound interpretation of these studies (146). In addition, the disease continues to progress, and initial benefits do not appear to persist (147,148).

Although there remains equipoise with respect to the possible beneficial effects of selegiline, it is now clear that the drug has clear neuroprotective effects for dopaminergic neurons in both *in vitro* and *in vivo* laboratory models (see ref. 149 for review). Further, it is now clear that neuroprotection with selegiline does not depend on MAO-B inhibition (150,151), and is mediated by the drug's metabolite desmethyl selegiline (DMS) (152). Work by Tatton's group (153–155) has now shown that DMS and other propargylamines provide neuroprotective effects by binding to the protein glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and preventing its translocation to the nucleus. GAPDH accumulation in the nucleus inhibits BCL-2 expression and promotes apoptosis (153,154). These findings, indicating that selegiline is an antiapoptotic drug, are particularly relevant to PD, where there is evidence that cell death occurs by way of an apoptotic process (155).

Selegiline is administered in a dose of 5 mg b.i.d. and is generally well tolerated. In levodopa-treated patients it has the potential to increase dopaminergic side effects and to possibly induce cardiovascular problems. Its amphetamine metabolite can also cause insomnia, and for this reason the second dose is usually not administered after 12 noon. The adversity profile of selegiline has been somewhat clouded by the findings of a 5-year open label study reporting increased

mortality in patients receiving the combination of levodopa-carbidopa/selegiline as opposed to those treated with levodopa-carbidopa alone (156,157). However, the statistical methods used in this study were questioned (158), and increased mortality has not been confirmed in a metaanalysis evaluating mortality in all other prospective trials of selegiline (159).

In summary, there is theoretical evidence suggesting that selegiline might provide neuroprotective benefits in PD. Clinical trials are consistent with this notion, but might be explained by the drug's symptomatic effects. The drug is generally well tolerated, and claims of increased mortality have not been substantiated. It remains a matter of judgment and personal philosophy as to whether or not to use selegiline as a putative neuroprotective drug.

SURGICAL THERAPIES FOR PARKINSON'S DISEASE

In the past few years, the renaissance of functional neurosurgery has transformed our vision of PD therapy. Functional neurosurgery for movement disorders dates back to the beginning of the 20th century, with the introduction of pyramidal tract lesions or dorsal root sections (160–162). These were unfortunately characterized by their unacceptable morbidity. Lesions of the basal ganglia as a treatment for PD were introduced by Meyers in the early 1940s (163,164). These procedures provided some benefits for tremor and rigidity, but adverse events were common and there was an unacceptably high mortality rate ranging from 8% to 41% (162–168). Surgery therapies for PD became more widely accepted with the introduction of stereotactic techniques (169) and the determination that lesions of the thalamus could provide benefits with fewer adverse events (170). With the introduction of levodopa, surgery for PD was almost abandoned. However, the shortcomings of classic levodopa therapy (as discussed above), the tremendous advances in brain imaging and intraoperative monitoring techniques for target localization, and insights into the pathophysiology of the basal ganglia (171,172) have catalyzed a dramatic resurgence of interest in surgical procedures for PD. However, most current information is based on open trials that do not control for placebo effects and physician bias, and may thus have overstated the benefits that can be achieved (173). There is little doubt that surgical techniques offer the potential to provide benefit to PD patients with advanced disease who cannot be controlled with medical therapies, but well-designed placebo-controlled double-blind studies are required in order to determine their true value (174).

Ablative Procedures

Thalamotomy

Current knowledge of basal ganglia physiology in the normal and PD state suggest several targets for ablative proce-

dures, one of which is the ventral intermediate nucleus (VIM) of the thalamus. Metabolic and physiologic studies consistently indicate that the ventral anterior and ventral lateral thalamic nuclei, the STN and the GPi, are overactive in PD (175,176), probably reflecting increased inhibitory output from the GPi. Cooper (170) and Hassler and Riechert (177) noted in the 1950s that thalamic lesions could relieve contralateral tremor. Their experience led to thalamotomy becoming the preferred surgical procedure for the treatment of tremor-predominant forms of PD. Their choice of target was facilitated and supported by electrophysiologic studies demonstrating abnormal tremor synchronous electrical activity in this region (178–180). Ohye and Narabayashi (181,182) subsequently used these techniques to conclude that lesions in the VIM nucleus of the thalamus were most effective in reducing contralateral tremor. Studies reported a consistent reduction in contralateral tremor, but it is less certain that there are benefits with regard to rigidity, and there is virtually no benefit for more disabling features such as bradykinesia or postural impairment (183–186). These studies also suggested that thalamotomy has the potential to reduce or prevent the development of levodopa-induced dyskinesia (183,184,187–189). In recent studies, persistent morbidity associated with unilateral thalamotomy occurs in less than 10% of patients. Complications includes dysarthria, dysequilibrium, contralateral hemiparesis or hemiataxia, cognitive impairment, and personality changes (185,190). Bilateral thalamotomy is associated with a further increase in morbidity including dysarthria, dysphagia, and cognitive impairment, and is usually avoided (185,190).

In conclusion, for a select group of PD patients with disabling tremor that cannot be controlled with medications and marked unilateral predominance, thalamotomy can still be considered; however, this technique has now been largely replaced by a different surgical procedure (deep brain stimulation) and alternate targets (STN or GPi) (see below).

Pallidotomy

Despite the early encouraging reports (163,164), lesioning the pallidum or its efferent fibers fell out of favor and was replaced by thalamotomy. However, Leksell persisted in developing this surgery and was able to determine that lesions placed in the posteroventral portion of the globus pallidus pars interna (GPi) were the most beneficial in relieving PD signs and symptoms (191). A generation later, his pupil Laitinen performed Leksell's technique using more modern stereotactic techniques, and described benefits with respect to bradykinesia, rigidity, and levodopa-induced dyskinesias (192,193). Complications were observed in 14% of patients and included partial homonymous hemianopsia, transient dysphasia, and facial weakness. These results followed shortly after neurophysiologic studies demonstrating that the pallidum was hyperactive in PD (171,194). These re-

sults prompted a renaissance in pallidotomy as a surgical option for PD. Using the posterolateral pallidum as a target, several surgical groups have now reported benefits in PD patients (195–197). The most dramatic finding is a consistent long-lasting abolition of contralateral dyskinesia; antiparkinsonian benefits are more modest (198,199). Complications occur in 3% to 10% of patients and are primarily visual in nature, although cognitive impairment, sensory deficits, and motor weakness may all occur. Bilateral pallidotomy is associated with increased risk of disabling dysphagia, dysarthria, and cognitive impairment (200,201), and has largely been abandoned with the availability of stimulation procedures. Current pathophysiologic models of PD explain the improvement in parkinsonism, but do not explain the striking antidyskinetic effect of pallidotomy (202). It has been proposed that the antidyskinetic effect of pallidotomy may be due to elimination of an abnormal firing pattern in pallidal output neurons that are providing misinformation to cortical motor regions that result in the emergence of dyskinesia (42).

In summary, unilateral pallidotomy provides consistent and dramatic improvement in contralateral levodopa-induced dyskinesia. However, improvement in parkinsonian features is modest and the procedure is associated with lesion-related side effects, especially when it is performed bilaterally. Here, too, it is being replaced by stimulation procedures in many centers (173).

Subthalamotomy

Physiologic and metabolic studies demonstrate that the subthalamic nucleus (STN), similar to the GPi, is overactive in parkinsonian syndromes (171,175,202,203). This has led to the notion that lesions of the STN might provide benefits in PD. Indeed, subthalamotomy has been shown to improve parkinsonian features in MPTP-treated monkeys (204, 205). However, lesions of the STN are associated with hemiballismus, and accordingly physicians have been reluctant to perform this procedure in PD patients. Deep brain stimulation procedures avoid the need to make lesions in target structures (see below), and stimulation of STN is associated with marked improvement in parkinsonian features. Preliminary studies of subthalamotomy have been performed and indicate that it also can provide excellent benefits in PD with minimal adversity (206). Nevertheless, until further experience has been gained with respect to the long-term safety and efficacy of this procedure, it must be considered experimental.

Deep Brain Stimulation Procedures

High-frequency deep brain stimulation (DBS) was introduced by Benabid and his group (207) alternate to ablative procedures. Benabid et al. noted that high-frequency stimulation of selected brain targets simulates the effects of a

lesion without the necessity of making a destructive brain lesion. In this procedure, an electrode is implanted into the desired brain target and connected to a stimulator placed subcutaneously over the chest wall. DBS has several advantages over ablative procedures: (a) It avoids the need to make a destructive brain lesion. Side effects due to stimulation can be reversed by changing the stimulator settings. (b) Bilateral procedures can be performed with relative safety. (c) Stimulator settings can be adjusted as with the doses of a medication to maximize benefit and minimize adversity. The precise mechanism of action of DBS is unknown, but it may involve jamming abnormal firing patterns of nerve cell populations within the stimulated area. Other possible mechanisms include depolarization blockade, release of inhibitory neurotransmitters, and indirect effects due to backfiring with stimulation of distant cell populations through orthodromic or antidromic firing.

Deep Brain Stimulation of the VIM of the Thalamus (DBS-VIM)

The initial trials of DBS were performed in the VIM nucleus of the thalamus. The procedure provided prominent antitremor effects in the vast majority (80% to 90%) of patients with tremor predominant PD and essential tremor (208). Tremor arrest occurs within seconds following the onset of stimulation, and the effect is lost within seconds of its cessation. These results were confirmed in a double-blind crossover study (209) that led to the approval of unilateral DBS-VIM as a treatment for essential or parkinsonian tremor by the Food and Drug Administration (FDA) in the United States. Interestingly, stimulation slightly posterior and medial to the VIM—close to the centromedian and parafascicular complex of the thalamus—also induced reduction in levodopa-induced dyskinesias (210). Unfortunately, DBS-VIM does not meaningfully improve the more disabling features of PD such as bradykinesia and gait impairment. This shortcoming has led to consideration of other targets for DBS, such as the GPi and the STN (see below). DBS-VIM remains a very valuable procedure for PD patients for whom tremor is the main handicap.

Deep Brain Stimulation of the Subthalamic Nucleus (DBS-STN)

A large body of experimental evidence has pointed toward targeting the STN as a treatment for PD: (a) neurons in the STN are hyperactive in PD (203,211); (b) lesions of the STN provide benefit to MPTP-treated primates (204, 205); (c) improvement in contralateral parkinsonism following a spontaneous hemorrhage into the STN of a PD patient (212); and (d) improvement in MPTP-treated monkeys following stimulation of the STN (213). Based on these findings, DBS-STN was introduced as a treatment for PD patients (214–216). Significant benefits of stimulation have

been reported for all of the cardinal features of parkinsonism; these have been confirmed in a double-blind crossover study (217). Improvements in motor function range from 40% to 80%. Highly significant benefits have also been observed in home diary assessments of percent "on" time without dyskinesia, leading to a dramatic reduction in patient disability. This is all the more remarkable when one considers that these benefits have been obtained in a population of patients that could not be further improved with medical therapy. Interestingly, dyskinesias have not been a problem, which may be related to disruption of the abnormal firing pattern in STN neurons. Finally, it has recently been proposed that DBS-STN might provide neuroprotective effects by inhibiting STN-mediated excitotoxic damage in its target structures (137). Indeed, lesions of the STN have been shown to protect SNc neurons in 6-hydroxydopamine lesioned rodents (218). It is currently thought that stimulation of the STN is the most effective surgical procedure, but prospective double-blind placebo-controlled studies directly comparing stimulation of the STN to other target structures such as GPi (see below) remain to be performed (173).

Deep Brain Stimulation of the Globus Pallidus Pars Interna (DBS-Gpi)

The experimental rationale for performing stimulation of the GPi is similar to that for STN. As is the case with the STN, the GPi is also overactive in PD (203,211), and lesions of the GPi provide benefits in MPTP monkeys (219). Several studies have now reported that DBS-GPi can improve all of the cardinal features of parkinsonism and reduce the severity of levodopa motor complications (220–222). Benefits do not appear to be as potent as with DBS-STN, but a prospective controlled trial has yet to be performed to objectively compare these two targets.

General Adverse Effects of DBS

Adverse effects of DBS can be related to the surgical procedure, the device, and the stimulation itself. Surgical complications involve hemorrhage and infarction and occur in less than 3% of cases. The electrode itself does not seem to be toxic to local tissues, as in the only postmortem pathologic study available, gliosis around the electrode tip was less than 1 mm in diameter (223). Problems associated with the implanted material (infection, dislodgment, mechanical dysfunction) occur in 1% to 3% of cases and may lead to the need to replace the electrode. Stimulation-related side effects include paresthesiae, motor twitch, dysarthria, and eye movement disorders. They are usually transient and controllable by stimulator adjustment. Finally, the battery has limited longevity, ranging from 6 months to 5 years or more, depending on the electrical consumption of the stimulator

settings chosen. The battery in the chest wall can be easily replaced under local anesthesia in most cases.

Despite the potential side effects of the DBS procedure, the risk of permanent side effects is less than with ablative procedures, particularly when bilateral with procedures (224).

Management of DBS

Optimization of stimulator settings is necessary to achieve maximal benefit with DBS procedures. This is not an easy task because of the large number of stimulation variables. These include electrode configuration, amplitude, pulse width, and frequency. Determination of the optimal stimulation settings may be complicated and time consuming (hours) and may require multiple visits. Validation of a rapid and simple method for determining stimulator adjustment will enhance the utilization of these techniques.

In conclusion, DBS of selected brain targets offers PD patients the potential of experiencing clinical benefit when this cannot otherwise be attained with medical therapy. Further, this can be accomplished without the need to make a destructive brain lesion with its accompanying side effects. Studies to determine the long-term safety and efficacy of DBS and the optimal target site for individual patients remain to be performed. Nevertheless, studies performed to date indicate that this procedure has much to offer patients with advanced PD. Based on existing information, DBS-STN appears to provide the best clinical effects and is presently considered to be the stimulation target of choice. It is possible that other brain targets such as the globus pallidus pars externa and selected cortical motor regions will prove superior in the future.

Transplantation Procedures

Yet another approach to the treatment of patients with advanced PD is transplantation of dopaminergic neurons aimed at replacing host neurons that degenerate during the course of the disorder. Transplantation is a rational strategy for treating PD because (a) PD is due to specific degeneration of dopaminergic nigrostriatal neurons and its symptoms are dramatically relieved by dopaminergic treatment; and (b) the striatum, which is denervated in PD, is a well-defined target for transplantation (225). In animal models, fetal nigral neurons have been shown to survive, reinnervate the striatum, produce dopamine, and improve motor dysfunction in rodent and primate models of PD (226–229).

The first clinical trials in PD patients involved implantation of adrenal medullary cells into the caudate nucleus, but despite the initial encouraging reports (230), the inconsistent outcomes and the associated adverse events led to this procedure being abandoned (231,232). Human fetal nigral grafts provide more potent results in animal models (225), and led to the initiation of clinical trials in PD patients

(233–238). Results were somewhat inconsistent among the different groups, but some studies noted consistent and clinically meaningful benefit. In one study using a predetermined transplant protocol, six PD patients who could not be improved with medical management experienced significant improvement over baseline in motor scores when "off" (mean of 31%) and in percent "on" time without dyskinesia (mean of approximately 250%) (238). The variability in clinical response in the different centers may have related to the use of different transplant variables (e.g., donor age, method of tissue storage, target site for transplant, volume of distribution within target site, amount of implanted tissue, use of cyclosporine). In trials documenting clinical benefit, striatal fluorodopa uptake on PET demonstrated a significant and progressive increase in striatal fluorodopa uptake (237–240). Benefits on PET correlated with improvement in motor scores (238,241). Postmortem studies have been performed on some patients who have received transplants and expired for reasons not related to the transplant procedure (242,243). These studies demonstrated robust survival of implanted neurons and reinnervation of the striatum in an organotypic fashion (242). In this study, there were strong correlates between the number of surviving cells and UPDRS motor scores and striatal fluorodopa uptake on PET.

Following these open studies, two prospective randomized double-blind placebo-controlled trials have been initiated. The first was a 1-year study involving 40 patients. Two donors per side were implanted into the caudate and putamen bilaterally, without immunosuppression (244). Quality of life was the primary endpoint and was not improved. However, significant improvement in UPDRS motor and ADL scores were observed in patients under 60 years. The second study is a 2-year study that compares bilateral transplantation into the postcommissural putamen with one versus four donors per side (174). Immunosuppression with cyclosporine was employed in this study. The study is still ongoing and will terminate in 2001.

Several hundreds PD patients have now undergone transplant procedures. In general, the procedure has been well tolerated, especially when performed in major university centers. There is one report of a death due to obstructive hydrocephalus caused by graft migration into the 4th ventricle. Postmortem study revealed that the migrated tissue was composed of nonneural tissue containing bone, cartilage, hair, and epithelium (243). This study illustrates the importance of developing experience in transplant biology and appropriate dissection techniques before embarking on this surgical adventure. There has also been a report in abstract form of new-onset disabling dyskinesia that persists even when levodopa is withdrawn for prolonged periods of time (245). The frequency, clinical significance, and basis for this problem remain unknown, but clearly warrant further investigation.

The role of fetal nigral transplantation in PD has not

yet been fully determined, but the only double-blind study completed so far has not shown satisfactory benefits, and there are concerning side effects that remain to be explained. Concomitant use of antioxidants, lazaroids, antiapoptotic agents, and trophic factors, or modifications in the type of donors, the amount of cells transplanted, and the site of transplantation may all enhance transplant benefits. Also, alternate sources of dopaminergic tissues will have to be found to avoid the societal and logistical problems associated with the use of fetal human tissue. Transplantation of fetal porcine nigral cells has been shown to provide some clinical benefit and postmortem cell survival (246), and a prospective double-blind clinical trial is ongoing. Other experimental approaches to repopulating the basal ganglia with dopaminergic cells include the use of stem cells and gene therapies. The concept of restoring dopaminergic innervation to the basal ganglia is appealing, and to some extent it is now clear that this can be accomplished. For the present, however, transplant therapies must still be considered experimental and not a practical option for PD patients outside of research trials.

FUTURE RESEARCH DIRECTIONS

Symptomatic Therapies: Nondopaminergic Agents

Despite the advances in the therapeutics of PD, patients continue to experience parkinsonian disability and disabling motor complications. New treatment strategies aimed at providing more continuous dopaminergic stimulation to prevent motor complications and surgical approaches to ameliorate them represent major advances. Nonetheless, many patients continue to experience disability despite these new treatment approaches. This has led to experimentation with other approaches to the symptomatic treatment of PD and its complications. Although most interest has focused on the motor aspects of PD, dementia is the greatest unmet medical need and the major reason for nursing home placement for patients with this condition (247). There are currently no treatments that are established to attenuate the decline in mental function that accompanies PD. Some physicians use central cholinergic medications such as donepezil or rivastigmine on an empiric basis, but there are no studies confirming their value in PD.

There has been increasing interest in developing new antidyskinetic therapies for PD based on activating the numerous nondopaminergic cell-surface receptor targets on basal ganglia neurons that modulate dopaminergic activity or other systems that are affected in PD (248). The development of an agent that blocks dyskinesia would permit levodopa to be used in larger doses and thereby eliminate motor fluctuations. Some possible antidyskinetic agents include drugs that are glutamate antagonists, adenosine A2A antag-

onists, opioid antagonists, serotoninergic 5-HT$_{2C}$ agonists, canabanoid CB1 agonists, α_2-antagonists, dopamine uptake inhibitors, selective muscarinic antagonists, and nicotinic agonists (249). Glutamate antagonists have already been shown to have antidyskinetic effects in some PD patients (133–135), but they are complicated by mental side effects that limit their utility in PD. However, other agents such as riluzole that inhibit sodium channels and impair glutamate release have also been reported to improve dyskinesia and are better tolerated (250). The adenosine A2A receptor is localized to striatal cholinergic interneurons, and antagonists to the adenosine A2A receptor have been shown to increase motor activity in rodent and primate models of PD, without provoking a dyskinetic response, even when administered to levodopa-primed animals (251,252). Clinical trials of this agent are currently under way. Nicotine receptors are present on terminals of nigrostriatal neurons, and their stimulation has been shown to increase dopamine release in the rat nucleus accumbens (253). This may account for why cigarette smoking is addictive, and why there is a seeming reduction in the frequency of PD in smokers (254). In MPTP-treated primates, nicotine has no effect on the basal motor disability or on levodopa-induced dyskinesia, but muscarinic agonists and antagonists did influence levodopa-induced dyskinesia (255,256).

Restorative Therapies

The threshold for developing levodopa-induced dyskinesias appears to depend on the degree of denervation of the SNc (42,257). This has led to the hypothesis that increasing the number of dopaminergic terminals might better regulate dopamine storage and release and control dyskinesia. Bjorklund et al. (258) have shown that dyskinesia can be prevented in a rodent model following transplantation of dopamine neurons with restoration of greater than 20% of striatal dopamine terminals as detected by staining for dopamine transporter protein. There is considerable interest in the potential of neurotrophic factors, such as brain-derived neurotrophic factor (BDNF) or glial-derived neurotrophic factor (GDNF), to provide restorative effects and increased numbers of dopamine terminals in PD. GDNF has been shown to promote functional and anatomic recovery in MPTP-treated monkeys (259,260). GDNF treatment in these animals was associated with improvement in motor behavior, a reduction in levodopa-induced dyskinesia, and increased dopamine production. This approach could provide combined symptomatic and neurorestorative benefits. Clinical trials of intraventricular GDNF administration in PD patients have been stopped, presumably because of lack of efficacy. This may relate to failure of GDNF to cross the blood–brain barrier. Further studies of direct intraparenchymal injections are warranted. Administration of GDNF by gene therapy using a lentivirus vector has been shown

to prevent motor deficits and nigral degeneration in MPTP monkeys (261). This provides another opportunity for introducing GDNF to PD patients, although such trials are not likely to be started until a number of regulatory concerns have been addressed. Stem cells have tropic properties and can migrate to sites of neuronal damage. They also have the potential to be converted to dopaminergic neurons. The question is, Can the two functions be merged? This too is a promising area of research, but clinical trials may be far in the future.

Neuroprotective Therapies

Neuroprotective therapies are designed to slow or stop disease progression by rescuing or protecting vulnerable neurons. To date, no therapy has been established to be neuroprotective in PD. When a neuroprotective treatment becomes available, it will be important to define at-risk subjects or patients with very early PD so that treatment can be initiated at the earliest time possible. An ideal neuroprotective therapy would eliminate the cause of the disease. Unfortunately, it is likely that both genetic and environmental factors contribute to the etiology of PD, and they may be different in different patients (262). The recent twin study indicates that genetic factors do not play a role in the etiology of PD in the majority of patients (263). A small number of familial cases are now known to be due to mutations in the genes that code for the proteins α-synuclein and parkin (264,265). Although they represent a small number of individuals, these findings may yield clues for understanding the pathogenesis of PD and permit the development of therapies that are of value for the majority of cases. α-Synuclein is a protein that accumulates even in sporadic PD (266). Parkin is now known to be a ubiquitin-protein ligase that is involved in protein degradation and reduced in activity in the mutant form (267). These observations suggest that protein clearance may be a fundamental problem in the origin of nigral degeneration in PD and a source of new therapeutic opportunities. Pathogenetic factors that have been implicated in PD include oxidative stress, excitotoxicity, mitochondrial dysfunction, and inflammation (268). It is unknown to what degree each of these contributes to the initiation of cell death, but each represents an opportunity for targeting a neuroprotective therapy. There is also a growing amount of evidence supporting the notion that cell death in PD occurs through an apoptotic process (155,269). Apoptosis is a gradual form of cell death that is associated with intracellular signaling mechanisms (270). The knowledge of these signals and the ability to manipulate them provide another opportunity for developing neuroprotective strategies.

Thus, there are numerous possible avenues for neuroprotective therapies (82): antioxidants (free radical scavengers, glutathione, ion chelators); glutamate inhibitors (excitatory aminoacids antagonists, glutamate release inhibitors, e.g., riluzole); calcium channel blockers; mitochondrial "energizers" (creatine, coenzyme Q10, nicotinamide, gingko biloba, carnitine); antiinflammatory agents (steroids); estrogens; trophic factors (GDNF, see above); transplant strategies (human, porcine, see above); antiapoptotic agents (desmethylselegiline, TCH 346, caspase inhibitors, cyclosporine); and agents that prevent intracellular protein accumulation. To date, none has been proven to be neuroprotective in PD. Indeed, the challenge is to find sufficient funding so as to be able to evaluate so many promising new therapies (271).

ACKNOWLEDGMENTS

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