Parkinson’s Disease: From Etiology to Treatment

Yoshikuni Mizuno, Hideo Mori and Tomoyoshi Kondo

We review the recent progress in the research of the etiology, pathogenesis and treatment of Parkinson’s disease. It has been postulated that mitochondrial respiratory failure and oxidative stress are two major contributors to nigral cell death in Parkinson’s disease. Loss of mitochondrial complex I and the α-ketoglutarate dehydrogenase complex in the substantia nigra has been reported. Evidence to indicate oxidative stress includes a high dopamine content, increase in superoxide dismutase activities, increase in iron, and decrease in glutathione in the substantia nigra. The question posed is which one occurs first. We believe mitochondrial respiratory failure occurs first, because slowing down of the electron transport induces an increase in the formation of activated oxygen species. The primary cause of Parkinson’s disease is still unknown, but we believe the interaction of environmental toxins and genetic predispositions is important. In this respect, molecular genetic studies on familial Parkinson’s disease are very important.

(Internal Medicine 34: 1045-1054, 1995)

Key words: pathogenesis, mitochondria, oxidative stress, familial parkinsonism, juvenile parkinsonism

Introduction

Parkinson’s disease was first described by James Parkinson in 1817 (1). The disease is characterized clinically by resting tremor, cogwheel rigidity, akinesia, and loss of righting reflex, and pathologically by selective degeneration of the pigmented nuclei of the brain stem, i.e., the substantia nigra and the locus coeruleus; although degeneration of the dorsal motor nucleus of the vagal nerve, the pedunculopontine nucleus (2), and the substantia innominata (3) has also been reported in Parkinson’s disease, degeneration of the substantia nigra and the locus coeruleus is the constant and the most severe finding. Another characteristic is the presence of Lewy bodies in the remaining neurons; Lewy bodies are the intracytoplasmic eosinophilic inclusions with a pale halo surrounding the core in hematoxylin-eosin staining.

Within the substantia nigra, ventrolateral part is usually most severely affected (4), and this part mainly projects to putamen. The medial substantia nigra mainly projecting the caudate nucleus is less involved and is believed to be related to cognitive functions (5). Severe lesion in the rostral dorso-medial part of the substantia nigra may be the cause of cognitive dysfunction and/or dementia (6).

The annual incidence rate of parkinsonism has not changed for many years; it was estimated to be approximately 20.5 per 100,000 population in Rochester, Minnesota; among them 86% had Parkinson’s disease (7). The prevalence of Parkinson’s disease among white people has been variously reported from 106 to 201 per 100,000 population (8). The prevalence rate in Japan is 80.6 per 100,000 population (9), and in China 57 per 100,000 population (10). Usually Parkinson’s disease has its onset in the fifth decade or later; the peak age of onset is between 55 and 65, but the age of onset ranges from 20 to 80 years. Patients with age of onset under 40 years have been grouped as juvenile parkinsonism (11) or young onset parkinsonism (12). Most of the late onset patients are sporadic; concordance rate among homozygotic twins is low (13). However, familial occurrence is not rare among patients with the onset of age under 40 years. Drug therapy of Parkinson’s disease has achieved a great success, and the life expectancy of patients with Parkinson’s disease has become very close to that of the general population (14), however, numerous problems may arise from the long-term drug treatment. To overcome those problems, elucidation of the etiology of Parkinson’s disease and development of drugs which can protect nigral neurons from degeneration are mandatory. Here, we review the etiology and pathogenesis of Parkinson’s disease and the recent progress in the treatment of Parkinson’s disease.

Etiology and Pathogenesis of Parkinson’s Disease

MPTP-induced parkinsonism

The recent progress on the etiology and pathogenesis of
Parkinson's disease has been greatly dependent upon the discovery of MPTP-induced parkinsonism. MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), a meperidine analog, was found as a contaminant of a home-made illicit narcotic (15, 16). People who injected MPTP-contaminated narcotic drugs developed severe parkinsonism with selective degeneration in the substantia nigra (15-17). Langston et al (16) identified MPTP as the most probable agent which induced parkinsonism in those patients. MPTP is taken up into cerebral astrocytes where MPTP is oxidized to MPP+ (1-methyl-4-phenylpyridinium ion) by monoamine oxidase B (18) (Fig. 1). MPTP itself is not toxic but MPP+ is toxic. Then MPP+ is actively taken up into dopaminergic nerve terminals (19, 20) through the dopamine transporter (21) leading to a marked concentration within dopaminergic neurons (22). Such concentration of MPP+ does not occur in neurons which do not possess dopamine transporters. Dopamine transporters are expressed only in dopaminergic neurons; this is the mechanism of selective degeneration of dopaminergic neurons in this model. Within nigral neurons, MPP+ is further concentrated in mitochondria (23, 24); as mitochondria respire, the inside of mitochondria becomes electrically charged negative because of proton translocation from the matrix to the intermembrane space. MPP+ is transported into mitochondria according to this electric potential gradient as many other cations are concentrated within mitochondria (25). In mitochondria, MPP+ inhibits mitochondrial state 3 respiration by inhibiting complex I of the electron transfer chain (26–28) and the α-ketoglutarate dehydrogenase complex of the tricarboxylic acid cycle (29) with resultant impairment of ATP synthesis. Thus energy crisis is induced within nigral neurons, and this has been considered as the most important mechanism of nigral neuronal death in this model. Recently, a lower concentration of MPP+ was found to induce apoptotic cell death (30, 31). This MPTP model has been considered as the best model of Parkinson's disease available.

Mitochondria in Parkinson's disease

Since the elucidation of the pathogenesis of MPTP-induced parkinsonism, we and other groups have been interested in mitochondria in Parkinson's disease. Schapira et al (32, 33) first reported a significant reduction in the biochemical activity of complex I in the substantia nigra of patients who died of Parkinson's disease. Using an immunohistochemical method, we found a decrease in the subunits of complex I in the striatal mitochondria (34) and immunoreactive complex I in the nigral melanized neurons (35). However, these decreases were of rather modest degree; the complex I activity in Parkinson's disease was only two-thirds of the control (32, 33), and in our immunohistochemical method, nigral neurons retaining immunostaining were also found. Thus loss of complex I alone does not appear to sufficiently account for nigral degeneration. Recently Przedborski et al (36) postulated that loss of complex I might be a secondary phenomenon to levodopa treatment, as chronic treatment of experimental animals with levodopa resulted in reversible loss of complex I activity (37). However, Cooper et al (38) are opposed to this notion because the complex I activity of the striatum where complex I is exposed to a high concentration of dopamine is not reduced in Parkinson's disease. Complex I activity was also measured in tissues other than the brain, however, a lot of controversies exist in the results.

Figure 1. Structure of MPTP and its oxidation to MPP+ by monoamine oxidase B. MPP+ has a structural similarity to NAD+; this may be a reason why MPP+ inhibits complex I.
Parkinson's disease, mitochondrial DNA does not appear to influence the disease. However, we could not reproduce their findings regarding the A to G mutation at nucleotide 4336 of tRNA^{gln} gene in Parkinson's disease. The effect of dual loss of complex I and the α-ketoglutarate dehydrogenase complex appears to be particularly vulnerable in Parkinson's disease. The decrease in the complex I activity is considered to be one of the most important risk factors of Parkinson's disease, and there was a rough correlation between the severity of degeneration and the loss of immunostaining intensity. Therefore, complex I and the α-ketoglutarate dehydrogenase complex appear to be particularly vulnerable in Parkinson's disease. The effect of dual loss of complex I and the α-ketoglutarate dehydrogenase complex on the electron transport and ATP synthesis would be enormous, because the α-ketoglutarate dehydrogenase complex provides succinate as a substrate for complex II. Unless succinate is sufficiently provided, alternate electron transfer via complex II cannot compensate for the reduced electron transfer via complex I of Parkinson's disease.

Mitochondrial DNA

Each mitochondrion has 2 to 10 copies of double-stranded circular DNA consisting of 16,569 base-pairs (41). Mitochondrial DNA encodes 13 subunits of the electron transport complexes, 22 transfer RNAs, and 2 ribosomal RNAs. Complex I consists of 41 subunits (42) and seven out of the 41 subunits are encoded by mitochondrial DNA (43, 44). Therefore, we considered that mutations in mitochondrial DNA might cause the decrease in the complex I activity. Thus we studied mitochondrial DNA for large deletions and point mutations (45, 46). From all five patients, by the PCR method, Ikebe et al (45) found mitochondria with a 5-kb deletion using striatal DNA preparation. This deletion was located between the 13 base-pair direct repeat sequences encompassing the ND 5 (NADH dehydrogenase subunit 5) gene and the ATPase 6/8 gene; between these two genes, genes for ND 2, ND 3, ND 4, ND4L, and CCO (cytochrome c oxidase) 3 are located. But subsequent studies revealed that those 5-kb deletions are frequently found in aged and aging tissues including the brain (47–49), the cardiac muscle (50, 51), the skeletal muscle (52, 53), and the liver (53, 54). This 5-kb deletion appears to represent the aging process rather than the disease-specific change, however, as aging is one of the most important risk factors of Parkinson's disease, this deletion may contribute to the progression of the degeneration in Parkinson's disease.

Regarding point mutations of mitochondrial DNA, Ikebe et al (46) sequenced total mitochondrial DNA of five patients with Parkinson's disease and compared those sequences with those of more than 30 control subjects. Each of the five patients had at least one point mutation which would cause amino acid substitution in at least one of the subunits of complex I; however, the locations of the mutations were different from one patient to another. Shoffner et al (55) reported a higher incidence of A to G mutation at nucleotide 4336 of tRNA^{gln} gene in Parkinson's disease, however, we could not reproduce their results. Thus although the possibility that accumulation of mitochondria DNA mutations may constitute a risk factor for Parkinson's disease, mitochondrial DNA does not appear to play a primary role in the neurodegeneration in Parkinson's disease.

Consequence of mitochondrial respiratory failure

In acute mitochondrial respiratory failure, an energy crisis is induced due to the lack of ATP synthesis, and neurons may undergo necrotic death. But when mitochondrial respiratory failure progresses more slowly, numerous protean adverse effects are induced in neurons. One such effect is the disruption of calcium homeostasis.

When the cellular level of ATP goes down, the activity of Na-K ATPase decreases and Na⁺ transport from the inside to outside diminishes; then Na⁺ must be expelled by exchange with Ca²⁺ in the extracellular space (56). Thus the intracellular Ca²⁺ increases. An increase in intracellular Ca²⁺ induces activation of degradation enzymes such as neutral proteases (calpines), phospholipases, and endonucleases; the latter mediate cleavage of nuclear DNA in oligonucleosome-length fragments; activation of an endogenous endonuclease is involved in programmed cell death and apoptosis in many systems (57). Thus, the increase in the cellular Ca²⁺ level may induce apoptosis (58). Interestingly, mitochondrial respiratory inhibitors can induce apoptotic cell death (59, 60). Calcium homeostasis is also important for normal mitochondrial function. Another adverse effect of mitochondrial respiratory failure is the increase in the formation of cytotoxic activated oxygen species within mitochondria.

Oxidative stress in Parkinson's disease

Oxidative stress denotes the condition in which the formation of oxygen free radicals is increased. Oxygen free radicals include superoxide anions, hydrogen peroxide, hydroxyl radicals, and singlet oxygen. These species are produced in a small amount in every respiring cell; they are highly reactive and cytotoxic. In particular hydroxyl radicals are believed to mediate many cytotoxic reactions (61). Oxidative stress has been considered to be one of the most important contributors to nigral cell death in Parkinson’s disease in addition to mitochondrial respiratory failure. The oxidative stress hypothesis has been proposed based on four observations. First of all, a high content of dopamine in the nigral neurons predisposes those neurons to oxidative stress, as hydrogen peroxide is formed when dopamine is oxidized by monoamine oxidase. Secondly, superoxide dismutase (SOD) activities appear to be increased in the substantia nigra. In 1988, Marttila et al (62) reported a significant increase in Cu-Zn SOD but not in Mn SOD in the substantia nigra of Parkinson’s disease, while Saggu et al (63) reported an increase in Mn SOD but not Cu-Zn SOD. Although the results of these two studies did not agree, the increase in SOD activity was interpreted as a reaction to the increased formation of superoxide anions. Probably an increase in Mn SOD activity is more meaningful in Parkinson’s disease, because mitochondrial respiratory failure increases the formation of activated oxygen species (64). Hydroxyl radicals enhance lipid peroxidation, and as expected lipid peroxidation is reported to be increased in the substantia nigra of patients with Parkinson's disease.
reaction. Both reactions produce hydroxyl radicals in the presence of iron. Based on this assumption, many substances which accumulate in the substantia nigra of Parkinson’s disease (65). Thirdly, iron is increased in the substantia nigra of Parkinson’s disease (66-71). Most tissue iron exists in the ferric form (Fe³⁺), however, Fe³⁺ may be reduced to the ferrous form (Fe²⁺) in the presence of neuromelanin (67). Fe²⁺ is highly reactive and it may induce free radical reactions. Fe²⁺ catalyzes the Fenton reaction and Fe³⁺ mediates the iron-catalyzed Haber-Weiss reaction (Fig. 2) (72); both reactions produce hydroxyl radicals from hydrogen peroxide. Finally, glutathione is reduced in Parkinson’s disease (73-75). Glutathione is a natural antioxidant and it is a substrate for glutathione peroxidase.

The current question is which occurs earlier, mitochondrial respiratory failure or oxidative stress. Jenner et al (76) and Dexter et al (77) have attempted to answer this question by comparing the glutathione content and complex I activity in the substantia nigra of incidental Lewy body disease; the incidental Lewy body disease has been considered as a preclinical state of Parkinson’s disease (78). Jenner et al (76) found a significant loss of glutathione in the substantia nigra, however, complex I activity, although it was reduced, did not reach statistical significance, and the loss of complex I activity was slightly less than that of glutathione (75). Based on these findings, they concluded that oxidative stress occurs first in Parkinson’s disease, and that respiratory failure is secondary to oxidative stress.

We feel the reverse is true because not only complex I but also the α-ketoglutarate dehydrogenase complex is reduced in Parkinson’s disease (40). The reduction in state 3 respiration from the dual loss of complex I and α-ketoglutarate dehydrogenase complex is far greater than that from loss of complex I alone, and it may exceed the loss of glutathione. Furthermore, it has been shown that mitochondria produce free radicals such as superoxide anions (79), hydrogen peroxide (80), hydroxyl radicals, and semiubiquinone (81), and when mitochondrial electron transport slows down, a significant increase in the formation of oxygen free radicals occurs (64). Thus oxidative stress is induced as a result of mitochondrial respiratory failure.

**Primary cause of Parkinson’s disease**

This question has not been answered yet. It has been postulated that Parkinson’s disease may be caused by the chronic accumulation of substances toxic to mitochondria in the substantia nigra. Based on this assumption, many substances which have a structural similarity to MPTP and MPP⁺ have been tested for nigral as well as mitochondrial toxicity. Among these substances, tetrahydroisoquinolines and β-carbolines have most extensively been studied. Tetrahydroisoquinolines are a group of compounds that are formed by condensation of a phenylethylamine and an aldehyde (Fig. 3), and β-carbolines represent substances derived by condensation of tryptamine and an aldehyde. These compounds may be metabolized to the N-methylated form by an N-methyltransferase, and may be further oxidized by monoamine oxidase or by autoxidation (82, 83). Some of these substances are toxic to mitochondria respiration (84) and to the cultured nigral neurons (85, 86). However, compared to MPTP or MPP⁺, they are much weaker mitochondrial toxins. Typical parkinsonism has not yet been produced by these compounds, although striatal loss of dopamine was produced (87). β-carbolines are also toxic to mitochondria (88). It is interesting to note that some tetrahydroisoquinoline compounds are contained in foods (89), and they are easily transported into the brain (90).

Epidemiological studies offer another approach to determine environmental risk factors; subsequently rural living and well water use (91-93), and exposure to pesticides and herbicides (93, 94) and industrial chemicals (95) have been reported as risk factors for Parkinson’s disease, however, some controversies exist (92, 96). When those environmental neurotoxins are combined with poor metabolizing systems for those substances, such neurotoxins may become more toxic. Based on this concept, studies on genetic background are becoming more and more important. Genetic predisposition may be encoded in subtle difference in the base sequences of genes for proteins and enzymes as DNA polymorphisms. The first gene studied in this respect was CYP2D6 gene; its mutations which result in poor metabolizers of debrisoquine are associated with a higher risk for Parkinson’s disease (97, 98), which was estimated to be two-fold higher compared to those without mutations. The mutate gene frequency among Japanese patients with Parkinson disease, however, was not significantly different from the control population (99). Recently, Tsuneoka et al (100) found a new mutation in the CYP2D6 gene which results in poor metabolism of debrisoquine; 11.1% of Parkinson’s disease patients and 2.2% of control subjects had this mutation, and the risk factor for the mutant homozygote was estimated to be 5.56.

S-methylation is another detoxifying system for exogenous substances. Waring et al (101) reported reduced activity of erythrocyte S-methyltransferase in Parkinson disease, however, we could not reproduce their result in Japanese patients (102).

Kurth et al (103) reported the association of a monoamine oxidase B allele with Parkinson’s disease, however, this finding was not confirmed by a subsequent study (104). Hotamisligil et al (105) reported association of Parkinson’s disease with a MAO A allele. Association between Parkinson’s disease and genes for glutathione peroxidase, tyrosine hydroxylase, brain derived neurotrophic factor, catalase, amyloid precursor protein, Cu-Zn superoxide dismutase have been ruled out in autosomal dominant familial Parkinson’s disease (106).
Etiology and Treatment of Parkinson’s Disease

Familial and Juvenile Parkinsonism

As the primary cause of Parkinson’s disease is still unknown, molecular genetic studies on familial patients with Parkinson’s disease are very important. Patients with parkinsonism with the age of onset before the age of 40 are usually grouped as juvenile parkinsonism (11, 107) or early onset parkinsonism (12); Quinn et al (12) proposed to reserve the term “juvenile” to those patients with the age of onset before 20 years. Familial incidence among early onset parkinsonism is much higher than that among late onset patients; the familial incidence may be as high as 40% (107). Early onset parkinsonism is not a single disease entity, but a group of disorders with different modes of inheritance; the following familial types have been reported.

Lewy body-positive familial Parkinson’s disease

This is the most common form of familial parkinsonism. The age of onset is usually between 30 and 40 years of age, however, onset before 30 years and after 40 years is also known. Autosomal dominant inheritance appears to be more common (108–110), but autosomal recessive forms also exist (111). Clinical manifestations do not differ much from those of sporadic late onset Parkinson’s disease; these patients tend to show a good response to a relatively small amount of levodopa with a tendency to develop severe motor fluctuations and dyskinesias.

Lewy body-negative autosomal recessive type

The age of onset tends to be younger (15 to 30 years of age) than Lewy body-positive autosomal recessive Parkinson’s disease (112). These patients respond quite well to a small amount of levodopa, better than the Lewy body-positive patients; they develop dyskinesia and motor fluctuations more easily. In addition, they may show spontaneous fluctuations in parkinsonian symptoms with improvement after sleep. Dystonic posture in feet are not uncommon. Postmortem examination shows simple atrophy of the substantia nigra without Lewy bodies (113).

This hereditary Lewy body-negative autosomal recessive parkinsonism has some similarity to Segawa’s disease (114) and dopa-responsive dystonia (115), in that both respond to levodopa very well; both have spontaneous motor fluctuations with improvement after sleep. But the differences are absence of rigidity and tremor in Segawa’s disease; the cardinal symptom of Segawa’s disease is dystonic posture induced in the upper and lower extremities. Furthermore, Segawa’s disease is inherited as an autosomal dominant trait with linkage to chromosome 14 (116); recently point mutations in the GTP cyclohydrolase gene have been reported (117).
Autosomal dominant Lewy body-negative type

Nukada et al (118) reported a large Japanese family with autosomal dominant parkinsonism; the age of onset was between 38 and 78; the clinical characteristics were essentially the same as those of adult onset sporadic parkinsonism. Recently the autopsy findings in one of the family members revealed extensive nigral degeneration without Lewy bodies (personal communication with Dr. Kowa). Recently Dwork et al (119) reported a large family with autosomal dominant form of parkinsonism; the age of onset of the propositus was 28 years; he responded to levodopa well, however, severe motor fluctuation developed.

The question of whether or not Lewy body-negative patients should be termed as Parkinson’s disease requires further research. Linkage studies on these families are very important in that the information obtained from familial patients would provide clues to the investigation of the pathogenesis of sporadic Parkinson’s disease.

Treatment of Parkinson’s Disease

Treatement of motor fluctuations

Levodopa is still the standard treatment for Parkinson’s disease. Recently, an algorithm for drug treatment of Parkinson’s disease was proposed by Koller et al (120). The question of whether or not the use of levodopa should be delayed until the advanced stage of Parkinson’s disease has long been debated, however, the current trend appears to be starting levodopa treatment whenever the patient starts to show difficulty in moving in ordinary daily living or there is threat of losing his jobs. In our opinion, the use of levodopa should not be delayed intentionally.

Motor fluctuations from long-term levodopa treatment is a big problem. Newer drugs have been developed to decrease the severity and the incidence of motor fluctuations. Among the newly developed dopamine agonists, cabergoline is a new D2 receptor agonist of an ergot compound with an extremely long half-life of about 65 hours (121), and it was reported to have reduced the mean percentage “off” time by 31% in one report (122). Taliprexol is a presynaptic dopamine agonist as well as a potent post-synaptic D2 receptor agonist when the dopaminergic terminals are degenerated (123); the incidence of gastrointestinal side effects tends to be lower with this than with the conventional dopamine agonists (124). Deprenyl, a selective monoamine oxidase B inhibitor, is also effective in reducing the “off” time of motor fluctuations; Golbe et al (125) reported 56% increase in hourly self-assessed gait disturbance of fluctuating Parkinson’s disease patients; levodopa dose was also reduced by 17% in their study.

Catechol-O-methyltransferase (COMT) inhibitors appear to be promising adjunctive treatment for symptom fluctuations of advanced Parkinson’s disease. A fair amount of levodopa is metabolized to 3-O-methylalpa by COMT in systemic organs, and 3-O-methylalpa may interfere with the transport of levodopa to brain. Concomitant use of a COMT inhibitor with levodopa increases the bioavailability of levodopa to the brain without increasing the peak height of the plasma levodopa level (126). The combined use of levodopa and tolcapone is reported to prolong the anti-parkinsonian response by 67% (127). Other COMT inhibitors such as nitcapone (128), entacapone (126), and CGP 28014 (129) are also effective in reducing the plasma 3-O-methylalpa level.

Levodopa is absorbed from the duodenum and the upper jejunum (130), and gastric acidity influences the absorption of levodopa; as the gastric pH goes up, absorption of levodopa is impaired. Therefore, concomitant use of an anti-acid or intake of a large volume of food may interfere with the absorption of levodopa with resultant poor improvement in motor symptoms. Avoidance of large meals and antacids is a simple way to improve the response to levodopa.

Peripheral dopamine receptor blockers may increase levodopa absorption by enhancing gastric mortality (131); recently cisapride, a prodrug of a metoclopramide-like peripheral dopamine receptor blocker, is reported to enhance levodopa absorption.

Future neuroprotective therapy

As the mechanism of nigral cell death has in part been elucidated, research on nigral neuroprotective therapy is a rapidly growing field. Deprenyl, a monoamine oxidase B inhibitor, is reported to slow the progression of disabilities of Parkinson’s disease by the DATATOP study (132, 133). The question of whether or not deprenyl has a truly neuroprotective effect on nigral cells has been debated. If MPTP-type bioactivated neurotoxins are involved in Parkinson’s disease, monoamine oxidase inhibitors may well be neuroprotective at least in part. Other potentially neuroprotective drugs include dopamine transporter blockers, anti-oxidants, iron-chelators, calcium antagonists, glutamate receptor blockers, and dopaminergic-neurotophins.

Stereotaxic surgery and thalamic stimulation

The effect of stereotaxic thalamotomy has been well established for tremor and rigidity. Drug-resistant tremor patients are good candidates for stereotaxic thalamotomy. The nucleus intermedius is the target for tremor and the nucleus ventralateralis the target for rigidity (134). Thalamic stimulation is also effective in alleviating tremor (135). Recently, posterolateral pallidotomy has been found to be effective for drug-resistant gait disturbance, akinesia, and motor fluctuations (136). This new finding is based on the recent progress in neurophysiology of the basal ganglia. Two pathways, the indirect and the direct, have been shown to exist between the striatum and the internal segment of the globus pallidus (137); the indirect pathway originates mainly in the GABA-ergic neurons in the striatum and they change neurons in the external segment of the globus pallidus and in the subthalamic nucleus ending in the internal segment of the globus pallidus. The loss of striatal dopamine ends up with a marked increase in the activity of glutamatergic neurons in the subthalamic nucleus, and this increased excitatory input to GABAergic neurons in the internal segment of the globus pallidus strongly inhibits thalamic neurons causing severe akinesia (136). The principle of the
postero-lateral pallidotomy is to remove this inhibitory input to the thalamus from the internal segment of the globus pallidus.

**Transplantation**

Transplantation procedures using the adrenal medulla, super-ciliary ganglion, or fetal mesencephalon have been performed only on a research basis. Transplantation of the adrenal tissue has rather limited effects and the operative morbidity is substantial (138), and, in our opinion, it should not be attempted any further. Transplantation of fetal mesencephalon appears to give better results (139) compared to adrenal transplantation, however, it may provoke ethical problems. Transplantation should be carried out only in centers specialized in the basic, clinical as well as technical aspects of transplantation.

**Acknowledgements:** This study was in part supported by Grant-in-Aid for Priority Areas and Grant-in-Aid for Neuroscience Research from Ministry of Education, Science, and Culture, Japan, Grant-in-Aid for Intractable Disorders from Ministry of Health and Welfare, Japan, and Center of Excellence-Grant from National Parkinson Foundation, Miami, Florida, U.S.A.

**References**

1052


Etiology and Treatment of Parkinson’s Disease


