6 Environmental Toxins and Parkinson's Disease

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INTRODUCTION

Studies suggest that genetic and environmental factors may interact to influence the progression of idiopathic Parkinson's disease (PD). Family history of PD is a risk factor for the disease. Genetic factors have been associated with early and late onset forms of PD. Exposure to certain chemicals has been associated with parkinsonism, but no consistent association has been made between exposure to any particular chemical and the prevalence or incidence of idiopathic PD. In this chapter, we review the research to date on the role of the environment in the normal aging of the nigrostrial pathway, parkinsonism, and idiopathic Parkinson's disease.

NORMAL AGING AND THE NIGROSTRIATAL PATHWAY AND PD

A review of the literature pertaining to the normal aging of the nigrostriatal pathway suggests that, if we all live long enough, we may all develop symptoms of parkinsonism, although we probably won't develop PD. Studies indicate that striatal dopamine concentrations decrease markedly after age 60 years. Nigrostriatal neuronal loss occurs at a rate of approximately 1.4% per decade from ages 15 to 65, but the rate is accelerated to about 10% per decade after age 65 years. These findings indicate that normal aging is associated with an age-related increase in nigrostriatal degeneration.[1]

Magnetic resonance imaging (MRI) studies of normal subjects reveals a negative correlation of age with estimated midbrain volume, anteroposterior diameter through the substantia nigra, and interpeduncular distance. The linear measurements for the right and left side were found to be almost identical demonstrating symmetry of normal age-related changes between the right and left side of the brain, a laterality finding that is in contrast to idiopathic PD.[2]

Normal aging has also been associated with an age-related increase in tissue damage due to free radicals.

The role of free radicals in apoptosis, and the aging process has received considerable attention.[3] Factors that decrease free radical damage, including limiting caloric intake and the use of antioxidants, have been associated with slowing of the normal aging process and with increasing longevity.[3,4,5–8]

Iron has been implicated in the formation of free radicals via the Fenton reaction and therefore may have a role in the normal age related effects of free radicals as well as in neurodegenerative disease. MRI studies were used to determine the relationship between age and basal ganglia iron content in 20 normal individuals ranging from 24 to 79 years of age. These authors analyzed paramagnetic centers sequestered inside cellular membranes to predict local brain iron content. A strong direct relationship between age and regional iron content was found in the putamen and caudate but not in the globus pallidus or thalamus. These findings indicate that striatal iron content increases with normal aging and may play a role in age related loss of function in this brain region.[115]

Ultrastructural analysis of neurons of the substantia nigra in four normal aged subjects revealed changes characteristic of apoptosis, including cell shrinkage and chromatin condensation in 2% of melanized neurons.[116] Although the endoplasmic reticulum appears normal, mitochrondria are markedly shrunken. Fragments of melanized neurons are found in glial cells. Evidence of autophagic degeneration or necrosis are not detected in melanized neurons. Signs of oxidative stress, such as vacuolation of mitochondria, are observed in melanized neurons devoid of apoptotic features. These findings suggest that apoptosis is involved in cell death of nigral dopaminergic neurons during normal aging. However, the morphological abnormalities found in this study, such as marked mitochondrial shrinkage in apoptotic neurons, are not characteristic of those observed in patients with Parkinson's disease, suggesting that the mechanisms underlying the apoptosis associated with PD differs from that associated with normal aging.

Collectively, these finding suggest that normal aging is associated with a loss of neurons and with a loss of function in the nigrostriatal pathway, which may be due to the cumulative effects of oxidative stress, and that at least one metal (iron) may play a role in this process. These findings also suggest that, although free radicals appear to have a role in normal aging and PD, the neuropathology of PD is also distinctly different from that of normal aging. These findings also provide evidence for a putative point of interaction (i.e., free radical generation and scavenging) between normal aging, the environment, and neurodegenerative disease, which may hasten the progression of idiopathic PD, possibly leading to a younger age of onset.

IDIOPATHIC PARKINSON'S DISEASE

Idiopathic Parkinson's disease is a progressive neurodegenerative movement disorder, the etiology of which remains unknown. The clinical manifestations of the disease result from the loss of pigmented dopaminergic neurons in the pars compacta of the substantia nigra. Symptoms of Parkinson's disease include tremor, bradykinesia, gait disturbances, cogwheel rigidity, postural instability, hypomimia, hypophonia, and micrographia. The symptoms of PD are alleviated by Levo-dopa, dopamine agonists, and anticholinergics.

Parkinson's disease incidence rates of up to 190 per 100,000 persons have been reported.[9–14] A long preclinical or asymptomatic period may occur in PD. The presence of early-life risk factors is consistent with a long prodromal period. Marked degeneration of the substantia nigra and loss of striatal dopamine are necessary before clinical symptoms develop. Lewy bodies, the histological hallmark of PD, occur in 10% of normal individuals over age 50. Clinical symptoms develop slowly and are often unilateral and intermittent early in the clinical course of PD. Reduction of striatal dopamine can be detected with positron emission tomography (PET) scans in "at-risk" asymptomatic individuals. Biologic markers may eventually be able to detect subclinical PD and permit prophylactic therapeutic measures to prevent or at least forestall the onset of the disease.[15]

Although PD has been reported in relatively young persons, the likelihood of an individual developing PD increases as one ages. The mean age at death in PD patients increased from about 60 years in 1950 to 77 years in 1992 for both sexes living in Japan from 1950 to 1992.[16] In the United States, approximately 1% of the population over the age of 60 years is afflicted with PD.[17] The number of affected individuals and the cost associated with caring for affected individuals is likely to increase dramatically over the next several decades as the world's population becomes older and those individuals afflicted with PD live longer with the disease.[16,18] Projections indicate that therapies that delay disease onset will markedly reduce overall disease prevalence, whereas therapies to treat existing disease will alter the proportion of cases that are mild as opposed to moderate/severe. The public health impact of such changes would likely involve both the amount and type of health services needed.[19]

Most studies indicate that PD is a multifactorial disorder, which involves genetic and environmental factors acting together.[20,21] Evidence suggests that oxidative stress mediated by free radicals plays a central role in the pathogenesis of PD. This opinion is based in part on a decrease in the levels of glutathione found in the substantia nigra of patients with PD.

The evidence for a genetic risk factor includes reports of families presenting with a highly penetrant, ostensibly dominantly transmitted, form of PD.[22] Studies demonstrating an increased risk for PD among first degree relatives (i.e., siblings, parents, and/or children) of a patient with PD.[23] The incidence of PD in Blacks in is about one fourth of that found in Caucasians.[117,118] The greater similarity for age at onset than for year at onset among siblings with PD, together with increased risk among the subject's biological relatives compared with the subject's spouse, further supports a genetic component. However, no increase in risk was found among twins with an age of onset greater than 50 years old, suggesting that there may an interaction between environment and genetics in those PD cases with an age of onset greater than 50 years old.[24]

Genes that may be involved in the age of onset as well as the etiology of PD include α-synuclein on chromosome 4q21-23/PARK1. α-synuclein aggregation may be involved in Lewy body formation and in the pathogenesis of autosomal dominant forms of familial PD. The ubiquitin C-terminal hydrolase gene located on chromosome 4p14/PARK5 has been associated with autosomal dominant PD. The parkin gene on chromosome 6q25-27/PARK2 appears to be involved in autosomal recessive juvenile onset PD. Parkin mutations account for at least 15% (38 out of 246) of early-onset cases (≤45 years old) without family history, and this proportion decreases significantly with increasing age at onset. Loci on chromosome 1p35-36/PARK6 and 1p36/PARK7 have also been associated with autosomal recessive early-onset PD. Although the role of parkin, an E2-dependent ubiquitin protein ligase, in juvenile onset PD is well established, its role in the late-onset form of Parkinson's disease (PD) is not as clear. At least one study suggests that heterozygous mutations, especially those lying in exon 7, may act as susceptibility alleles for a later-onset form of PD.[25] Excluding exon 7 mutations, the mean age at onset among patients with parkin mutations is 31.5 years, but mutations in exon 7, are observed primarily in heterozygous PD patients with a mean age at onset of 49.2 years. Allele 174 of marker D2S1394 on chromosome 2p13/PARK3 has been associated with an older age at onset of PD (mean age: 69.8 years).[26]

PARKINSONISM

Parkinsonism is a movement disorder that clinically resembles idiopathic PD. Although parkinsonism shares many of the features of PD, the underlying pathologies as well as the etiologies are different. Parkinsonism has been associated with vascular disease, head trauma, encephalitis, and exposure to pharmaceuticals (metachlopramide), illicit drugs (MPTP), pesticides, and industrial toxins.[27,28]

Neurodegenerative Parkinsonism versus Parkinson's Disease: The Role of Oxidative Stress

Several neurodegenerative diseases resemble idiopathic PD, including progressive supranuclear palsy (PSP), multiple system atrophy (MSA), Machado-Joseph disease, and Wilson's disease. These disorders are manifested clinically by symptoms, which may include tremors, dystonic posture, gait disturbances, and cognitive disturbances. The specific clinical manifestations seen in each of these parkinsonisms reflects the specific differences in the underlying pathologies (e.g., involvement of cerebellar pathways as well as neurons in the basal ganglia). These disorders are differentiated clinically from idiopathic PD by the findings on neuroimaging studies, rates of progression, and by the therapeutic responses to levodopa and/or dopamine agonist therapy.

The consistent findings of decreased levels of the major antioxidant glutathione in the substantia nigra of patients with idiopathic PD has provided the basis for the oxidative stress hypothesis of the etiology of this neurodegenerative disease. Recent studies have explored whether the nigral glutathione deficiency seen in idiopathic PD is present in patients with parkinsonism associated with nigral damage (PSP and MSA). These studies reveal decreased nigral levels of reduced glutathione in postmortem brain of patients with PD and PSP. A similar decrease was seen in the MSA patient group, but this did not reach statistical significance. Levels of reduced glutathione were within normal limits in all unaffected brain regions and in degenerating extranigral brain areas in PSP and MSA. A trend for decreased levels of uric acid (antioxidant and product of purine catabolism) also was observed in nigra of all patient groups (–19 to –30%). These data suggest that glutathione depletion, possibly consequent to over utilization in oxidative stress reactions, could play a causal role in nigral degeneration in all nigrostriatal dopamine deficiency disorders and that minimizing oxidative stress may be relevant to slowing the progression of these diseases as well.[119]

Chemical Exposure-Induced Parkinsonism: The Role of Oxidative Stress

There is evidence to suggest that oxidative stress in involved in the in the neuronal loss seen in the substantia nigra of patients with PD and other forms of parkinsonism. Free radicals and other metabolites, which are conjugated with glutathione are formed during the metabolism of many industrial chemicals and thus exposure to these compounds may contribute to the progression of nigral degeneration.

There are many published reports suggesting that exposure to industrial chemicals including manganese, paraquat, carbon monoxide, carbon disulfide, *n*-haxane,

and ethylene oxide, and pharmaceuticals such as metoclopramide and the neuroleptics (e.g., chlorpromazine) can induce extrapyramidal syndromes resembling PD (i.e., parkinsonism).[29–32] Exposures to organophosphate insecticides have also been reported to induce parkinsonism. While the specific mechanisms by which these compounds induce neuronal loss leading to parkinsonism may differ, the net result is a loss of viable neurons in the extrapyramidal system.

In some patients, parkinsonian symptoms arise for the first time immediately following a severe acute chemical exposure,[29] while in others, the onset of symptoms is insidious and associated with chronic chemical exposures.[28,30] The differential diagnosis of PD versus parkinsonism is complex and requires a review of the history of occupational and environmental exposure, on whether the onset of symptoms was unilateral or bilateral, the constellations of symptoms observed, and the response of the patient to levodopa and/or dopamine agonist therapy. Patients with idiopathic PD typically have a unilateral onset of symptoms and respond well to levodopa and/or dopamine agonist therapy while the symptoms seen among patients with chemically induced parkinsonism often develop bilaterally and show limited if any improvement with levodopa and/or dopamine agonist therapy. Patients with idiopathic PD and chemical induced parkinsonism can also be differentiated by the presence of associated symptoms. For example, patients exposed to carbon disulfide will exhibit symptoms consistent with idiopathic PD but also typically present with peripheral neuropathy as well.[33,34]

MPTP

The most widely studied chemical that can induce parkinsonism in humans is 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP). MPTP is formed as a by-product of the synthesis of 1-methyl-4-phenyl-4-propionoxypiperidine (MPPP), a potent meperidine-analog. The occurrence of parkinsonism following exposure to MPTP was first reported in users of illicit "synthetic heroin" or MPPP that was contaminated with MPTP.[35] The clinical picture and neuropathology of MPTP poisoning is very similar to PD. Exposure to the MPTP, has been associated with damage to cells in the pars compacta of the substantia nigra.[35,36] Although cell loss is also seen in the pars compacta of the substantia nigra in patients with PD, other neuropathological features of PD, most notably the presence of Lewy inclusion bodies in the substantia nigra and locus ceruleus, are not seen in patients exposed to MPTP.[37,38]

Administration of either pargyline, a nonselective monoamine oxidase (MAO) inhibitor, or deprenil (selegiline), which specifically inhibits MAO-B, has been shown to the prevent both the clinical and pathological effects of MPTP exposure.[36,39] These findings led to the conclusion that the formation of a charged metabolite, specifically 1-methyl-4-phenyl pyridine (MPP^+), was dependent on the actions of MAO-B and that the production of free radicals from a redox reaction might be involved in the pathogenesis of the MPTP-induced parkinsonism.[39] This hypothesis is further supported by studies showing that the administration of diethyldithiocarbamate, a potent inhibitor of superoxide dismutase (i.e., an enzyme which scavenges free radicals) can potentiate the effects of exposure to MPTP.[40,41] Nontoxic doses of MPTP produced neuronal loss when given simultaneously with diethyldithiocarbamate. These findings indicate that chemicals that deplete the activity of neuroprotective enzymes such as superoxide dismutase may put certain susceptible individuals at an increased risk for developing PD especially if they are simultaneously exposed to more than one neurotoxicant.[41]

The discovery of a chemical that could induce parkinsonism led to the hypothesis that an environmental toxin or protoxin (a compound that is metabolized to a toxin) might cause Parkinson's disease. That MAO-B inhibitors do not have as profound an effect on preventing the progression of idiopathic PD attests to the subtle differences in the underlying pathogenesis of these two and suggests that Parkinson's disease is not the result of a simple toxic effect. Nevertheless, due to the theoretical practicality of interfering with the production of free radicals, the potential effectiveness of selegiline and/or antioxidants such as vitamin E and coenzyme Q_{10} for slowing the progression of PD continue to be studied and debated.[42]

Research has also demonstrated that MPP^+ inhibits activity of Complex I of the mitochondrial electron transport chain.[43,44] MPP+ is transported into dopaminergic neurons by the dopamine transporter.[45] Once inside the cell, MPP+ accumulates within mitochondria and inhibits the activity of Complex-I of the electron-transport chain.[46,47,41] Although iron-induced oxidative stress has been associated with reduced Complex-I activity in the substantia nigra, the relationship of this finding to the onset or progression of idiopathic PD has yet to be elucidated.[48–52] These findings have led to recent research into the therapeutic benefit of coenzyme Q_{10}, which is an endogenous electron acceptor for Complex-I and a powerful antioxidant. The level of coenzyme Q_{10} is reduced in the platelet mitochondria of patients with PD. Oral administration of coenzyme Q_{10} has been shown to increase Complex-I activity, but the therapeutic benefit of oral coenzyme Q_{10} has not yet been established.[42]

Paraquat

The pesticide paraquat is a bipyridyl herbicide that is metabolized by NADPH-dependent reduction to yield a free radical that reacts with molecular oxygen to form a superoxide anion, which is then converted to hydrogen

peroxide by superoxide dismutase. Both the superoxide anion and hydrogen peroxide are capable of reacting with lipids to induce lipid peroxidation, thereby altering membrane permeability and disrupting cellular functioning.[53] The toxic effects of paraquat are attenuated by the conjugation of the free radicals metabolites with glutathione-*S*-transferases.[54]

Paraquat has been shown cross the blood-brain barrier and to induce a loss of dopaminergic neurons in the substantia nigra of rats.[55] Exposure of humans to paraquat, which is structurally similar to 1-methyl-4-phenyl-1,2-5,6-tetrahydropyridine (MPTP), has been associated with an increased risk for PD.[9,31,56] Possible synergistic effects of paraquat and iron have been proposed. Recent studies in animals suggest that paraquat potentiates the toxicity of Maneb (manganese ethylene bisdithiocarbamate).[120]

Iron

Studies on postmortem brains from patients with PD reveal elevated iron in the substantia nigra. Studies have demonstrated that iron chelation via either transgenic expression of the iron binding protein ferritin or oral administration of the bioavailable metal chelator clioquinol reduces susceptibility to the effects of MPTP in animals suggesting that iron is involved in parkinsonism induced by MPTP and that this metal may have a role in the progression of parkinsonism associated with exposures to other chemicals that are metabolized to free radicals and/or contribute to the adverse effects of oxidative stress by depleting stores of glutathione.[121,122]

Accumulation of iron within the brain is associated with specific disorders of iron metabolism and transport. The mutations responsible for hemochromatosis, a hereditary iron overload disorder, led to intracellular sequestration of iron. Studies comparing subjects with PD and parkinsonism suggest that subjects with PD are significantly more likely to be homozygous for the highly penetrant C282Y mutation associated with hemochromatosis than are healthy controls. Furthermore, subjects with parkinsonism are more often carriers of the C282Y mutation than are controls suggesting that the C282Y mutation increases the risk of PD and parkinsonism.[123]

Increased levels of iron within the brain can lead to an increase in oxidative stress mediated via the Fenton reaction. The vulnerability of the dopaminergic neurons of the substantia nigra has been related to the presence of neuromelanin in these neurons. It is hypothesized that neuromelanin may act as an endogenous storage molecule for iron, an interaction suggested to influence free-radical production.[124]

Recent studies have looked at the redox activity of neuromelanin-aggregates in parkinsonian patients who presented with a statistically significant reduction (–70%) in the number of melanized-neurones and an increased non-heme (Fe3+) iron content as compared with a group of matched-control subjects.[125] The level of redox activity detected in neuromelanin-aggregates was significantly increased (+69%) in parkinsonian patients and was highest in patients with the most severe neuronal loss. This change was not observed in tissue in the immediate vicinity of melanized-neurones. A possible consequence of an overloading of neuromelanin with redox-active elements is an increased contribution to oxidative stress and intraneuronal damage in patients with Parkinson's disease and parkinsonism.

Manganese

Manganese (Mn) is an essential trace element necessary for normal development and normal biological functioning.[57,58] Occupational exposures to manganese typically occur among miners, welders and during the manufacture and application of Maneb.[58–62] Food is the main source of nonoccupational intake of manganese.[63,64] Dietary intake of manganese alone has not associated with toxic effects except in those individuals with decreased excretion due to liver failure.[65,64] Recent studies suggest that high dietary intakes of manganese plus iron may contribute to the risk for PD.[64]

The valence state (i.e., the number of electrons in the outermost or valence orbital) of manganese is a factor in its effect on living tissues.[66] Divalent manganese (Mn^{2+}) acts as a powerful antioxidant, while trivalent manganese (Mn^{3+}) appears to have a high affinity for those brain regions with high concentrations of neuromelanin (e.g., substantiate nigra).[27,67–79] The capacity of manganese to induce selective lesions in the substantia nigra and basal ganglia appears to be related to the neuromelanin content in these brain regions, where divalent manganese is readily oxidized to the cytotoxic trivalent species.[37,77,80] Trivalent manganese potentiates the autooxidation of catecholamines (e.g., dopamine), thereby generating toxic free radicals.[71,76] The death of the dopaminergic cells results in a concurrent release of neuromelanin and accompanying depigmentation of the affected region.[71,81–83] Loss of neuromelanin, which is also a scavenger of free radicals, may further potentiate the toxic effects of manganese poisoning.[77,84] Studies indicate that neuromelanin has a high affinity for iron, lipids, pesticides, and MPP+ as well as manganese. The affinity of neuromelanin for a variety of inorganic and organic toxicants suggests that it normally acts to protect cells from the neurotoxic effects of these compounds. The synthesis and accumulation of neuromelanin associated with normal aging are also consistent with a putative protective role which could be exceeded during conditions of neurotoxicant overload such as may occur with occupational exposures to manganese.

The adverse effects of trivalent manganese are also possible when protective scavenger enzymes such as manganese superoxide dismutase (Mn SOD) are unable to alter the oxidation potential of critical amounts of reactive oxygen species.[73,82,83,85] There is an increase in the levels of Mn SOD in patients with idiopathic PD, suggesting that synthesis of Mn SOD may be induced in response to free radical induced injury to cells.[86,87] Ironically, increased Mn SOD activity results in increased production of hydrogen peroxide, which can react with ferrous iron to yield hydroxyl radicals.[88] Mn SOD is also considered the point of contact between mitochondrial respiratory failure and oxidative stress. Experimental data have shown that treatment of dopaminergic neurons (PC 12 cells) with manganese chloride ($MnCl_2$) inhibits mitochondrial Complex I activity, while glial cells (C6) are not similarly affected. These findings suggest that environmental factors such as exposure to manganese, can induce oxidative stress and mitochondrial respiratory dysfunction and may also contribute to the pathogenesis of idiopathic PD (see Figure 6.1).[27,52,89]

Significant differences exist in the underlying neuropathology of manganese poisoning and idiopathic PD. Manganese damages cells in the basal ganglia as well as the substantia nigra, but the cell loss in the substantia nigra primarily involves the pars reticulata and is less marked than that which occurs in PD. Lewy inclusion bodies, which are found in the substantia nigra and locus ceruleus of idiopathic PD, further differentiate the two pathologically.[37,38] This difference in neuropathology is responsible for a remarkable difference in response to levodopa and/or dopamine agonist therapy, which is considerably less favorable the in those patients with manganese poisoning than it is in idiopathic PD.[58,90–96]

Aside from the reduced clinical response to dopaminergic therapy, there are other distinct differences in the clinical manifestations of manganese-induced parkinsonism that differentiate it from idiopathic PD.[38,52,81,84,89,95–99]

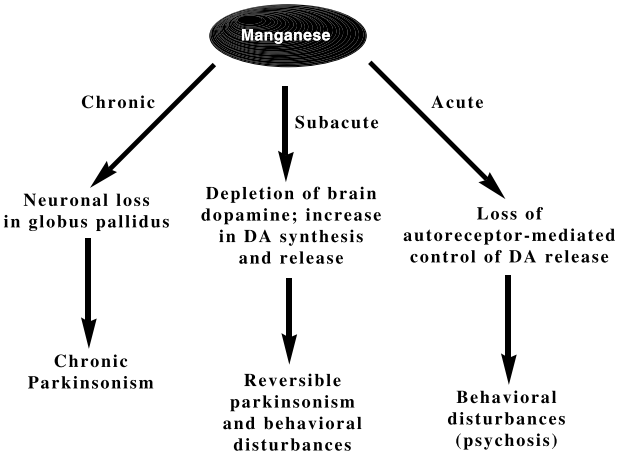

FIGURE 6.1 Effects of manganese exposure.

Perhaps the most overt clinical difference between idiopathic PD and manganese poisoning is that the extrapyramidal signs of manganese poisoning are frequently preceded or accompanied by an acute psychosis, which is not seen among patients with idiopathic PD. As manganese poisoning progresses, the acute psychosis gradually subsides, while dystonia, action tremor, and an awkward high-stepping dystonic gait appear.[58,100–103] The high-stepping dystonic gait of manganese poisoning is in stark contrast to the shuffling gait of patients with PD. Although the extrapyramidal symptoms of manganese poisoning may progress following cessation of exposure, the progression is slower than that seen in PD.[94,58]

ROLE OF ENVIRONMENTAL AND OCCUPATIONAL EXPOSURE TO CHEMICALS IN PARKINSON'S DISEASE

The possible role of environmental and occupational exposures to neurotoxicants (e.g., solvents, metals, and pesticides) in the development of idiopathic PD has received considerable attention from the medical community and public health researchers.[20,21,30,104–107] Environmental factors that have been associated with an increased risk for PD include home pesticide exposure, rural living, well-water consumption, and diet.[106,108–110] A rural predominance has been reported by several authors suggesting that environmental factors such as exposure to pesticides (e.g., organophosphates) may play a role in the etiology of PD.[13,31,110] Several researchers[84,111] have noted a correlation between living in a rural environment and drinking well water at an early age and the development of PD later in life. These authors have suggested that water is a likely vehicle for the causal agent, but that neither the concentrations of metals in the water nor any of the herbicides and pesticides used in agriculture in the areas where these studies were conducted are related to the cause. Tanner et al.[24] studied the role of environment in the development of PD in a Chinese population using a case-control method. These authors investigated the relationship between PD and place of residence, source of drinking water, and environmental and occupational exposure to various agricultural and industrial processes. Occupational or residential exposure to industrial chemicals, printing plants, or quarries was associated with an increased risk of developing PD while living in villages, and exposure to the common accompaniments of village life, wheat growing and pig raising, were associated with a decreased risk for PD. PD cases and controls did not differ with respect to other factors investigated. These findings were interpreted as consistent with the hypothesis that environmental exposure to certain industrial chemicals may be

related to the development of PD. A case-control study of 150 PD patients and 150 age- and sex-matched controls by Koller et al.,[15] which looked at residential histories, sources of drinking water, and occupations such as farming, revealed that rural living and drinking well water (which was dependent on rural living) were significantly more common among PD patients than controls, regardless of age at onset of PD. These data were interpreted to provide further evidence that an environmental factor such as exposure to a neurotoxic agent could be involved in the etiology of PD, but a putative toxic agent to account for this has not been identified.

Despite decades of research, exposure to a specific neurotoxicant has never been shown to induce idiopathic PD. Studies suggest that there has been an increase in the incidence of PD since the beginning of the industrial revolution. However, the existence of PD prior to the industrial revolution suggests that exposure to any of the synthetic neurotoxicants recently released into the environment is unlikely to be exclusively responsible for this neurodegenerative disease.

Review of the literature reveals many studies that have looked at the incidence and/or prevalence of PD among exposed and unexposed populations, although few studies that have stratified subjects by exposure history and age at onset.[15,20,24,84,112–114] The lack of consistent findings in the research performed to date that has looked at factors that increase the incidence and/or prevalence of PD suggest that this approach may need to be reconsidered. By contrast, the few studies that have looked at factors that influence age at onset have revealed interesting results which suggest that exposure to neurotoxic chemicals may unmask latent idiopathic PD by accelerating neuronal loss in the substantia nigra due to normal aging as well as that due to the neurodegenerative process.[113,114]

A study of 15 manganese-exposed welders with a mean of 47,144 welding hours revealed that welders were younger than controls at the time of PD symptom onset (46 years old versus 63 years old; $p < 0.0001$). There was no difference in frequency of tremor, bradykinesia, rigidity, asymmetric onset, postural instability, clinical depression, dementia, or drug-induced psychosis between the welders and the two control groups. Thirteen of the welders responded favorably to levodopa therapy, while one responded to pramipexole, and one did not yet require symptomatic treatment. Motor fluctuations and dyskinesias occurred at a similar frequency in welders and controls. PET with 6-[18F]fluorodopa obtained in two of the welders showed findings typical of idiopathic PD, with greatest loss in posterior putamen. Eight of the 15 welders (53%) included in this study had a positive family history for PD. Although these authors concluded that there was no significant difference between welders and controls subjects with regard to family history of PD, this was a small study, and cases and controls were not specifically matched for family history of PD.[114]

A similar study by Pezzoli et al.[113] looking at the role of hydrocarbon exposure also revealed a younger age at onset among exposed subjects with PD. The subjects worked in various industries where exposures to petroleum products, plastics, rubber, paints, paint thinners, lacquers, degreasing solvents, glues, pesticides, dyes, and refrigerants were likely to occur. The majority of subjects reported occupational exposure to hydrocarbons. Only 14 subjects reported occupational exposure to pesticides/herbicides. The most frequently encountered substances in this study were acetone, 2-di-methyl-ethyl-ketone (MEK), n-hexane and its isomers, cyclo-hexane and its isomers, hepthane and its isomers, ethyl-acetate, isobutylacetate, butyl-acetate, dichloropropane, trichloroethylene, trichloroethane, tetrachloroethylene, freon, toluene, and 1-methoxy-2-propanol. The exposed group ($n = 188$) had a mean age at onset of 55.2 years (± 9.8 years) compared with 58.6 years (±10 years) for unexposed subjects ($n = 188$) matched for duration of disease and gender. In addition to an earlier age at onset, the exposed subjects with PD were less responsive to treatment and required a higher mean dosage of levodopa than did the unexposed subjects. Although the diminished response to levodopa treatment in this group may be construed to be consistent with a diagnosis of multiple systems atrophy (MSA) rather than idiopathic PD, none of the subjects met all the clinical criteria for the diagnosis of MSA. Furthermore, among those subjects who had PET studies, these authors found no difference in striatal glucose metabolism, which is typically diminished in MSA. The exposed group was also composed primarily of men (76.4%) and was less educated and more disabled than the unexposed subjects. The severity of symptoms was directly proportional to the duration and the intensity of the exposure. These findings were interpreted to suggest that hydrocarbons may be involved in the etiopathogenesis of PD, which does not appear to have a major genetic component. There was no difference in the number of subjects in each group with a positive family history of PD.

Each of these two studies independently concluded that exposure to a specific chemical or a type of chemicals (i.e., manganese or hydrocarbons) could influence age at onset of PD. Because the findings in these studies are complementary, these findings can be interpreted to suggest that neither manganese nor hydrocarbon exposure is responsible for the younger age at onset of PD but, rather, that a common mechanism of neurotoxic action (e.g., free radicals induced neuronal loss in the substantia nigra) may hasten the progression of idiopathic PD. Assuming this hypothesis to be true, then it could further be expected that any factor that induces neuronal loss in the substantia nigra could hasten the neuropathological process that underlies PD by contributing to the total number

of neurons lost per unit time. If the loss of a critical percentage of neurons in the substantia nigra is associated with the onset of parkinsonian symptoms, then it logically follows that any factor that hastens the loss of neurons in the substantia nigra will lead to a younger age at onset of PD.

CONCLUSIONS

The material presented in this review suggests that PD can interact with environmental factors to affect age at onset of the disease and that this interaction could possibly increase the incidence of PD in an exposed population, but these data do not provide evidence for a causal relationship between the environment and prevalence of PD. However, this does provide a foundation upon which to base future research. In addition, it appears that higher levels of exposure that occur in occupational settings are more likely to significantly affect age at onset of PD, but whether subtle changes in age at onset occur at lower levels of exposure has not been determined. Large-scale epidemiological studies could provide the statistical power needed to answer this enduring question. The need remains for large retrospective studies that stratify subjects based on exposure history and genetic risk factors that can plausibly interact with exposure (e.g., glutathione-S-transferase polymorphisms). Prospective studies to ascertain the role of exposure and therapeutic measures such as antioxidants at onset and disease progression are also needed. As a our understanding of genetic modulation of enzyme activity and neurotransmitter receptor assembly and function, as well as genetic control of apoptosis and other factors that modulator neuronal viability, increases, our understanding of many of the interactions between environment and disease will likely grow as well.

Few therapeutic strategies to slow PD progression have been tested in clinical trials, but pharmaceuticals with antioxidant properties including ropinirole and pramipexole may slow PD progression. Neutraceuticals that scavenge free radicals, including antioxidant vitamins (e.g., vitamin E) and co-enzyme Q10, have also gained attention for their potential ability to slow the progression of PD.[10] Although the effects of minimizing lifetime exposure to free radicals via use of antioxidant vitamins and limiting cumulative lifetime exposure to neurotoxic chemicals have not yet been fully elucidated by prospective human studies, emerging evidence from retrospective studies suggests that these measures may slow the progression of PD and delay its onset until later in life.[10,21,27,113,114] For the time being, its seems prudent to conclude that minimizing exposure to free radicals, which appears to be the single common factor involved in normal aging of the nigrostriatal pathway, parkinsonism, and PD, is a reasonable first step in reducing the risk for developing PD.

A LOVING TRIBUTE TO ROBERT G. FELDMAN, M.D.

Robert G. Feldman, M.D., unfortunately passed away before this chapter was completed. Dr. Feldman was a dedicated physician, researcher, and mentor. He was world renowned for his work in both Parkinson's disease and neurotoxicology. His interest in these two distinct areas afforded him the unique level of understanding necessary to not only recognize but to logically investigate potential interactions between the environment and neurodegenerative disease. Although the role of the environment in the etiology of Parkinson's disease was not fully elucidated during his lifetime, his unique perspective and the contributions he made through his research and publications will undoubtedly facilitate future research in this area for years to come.

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