Chapter 8

Environmental Factors in the Development of Parkinson's Disease

Parkinson's disease is a neurodegenerative disorder first formally described in medical literature by James Parkinson in 1817. It usually begins slowly and becomes progressively more severe. The best known clinical symptom is rhythmic tremor of the limbs, which subsides with intentional movement (sometimes called a "resting tremor"), muscular stiffness, slow movement, and stooped posture. Sleep disorders are common. The earliest stages of Parkinson's disease may begin years or even decades before tremor and stiffness become apparent.[1] Constipation, impaired smell discrimination, and excessive sleepiness are sometimes early manifestations of Parkinson's.[2 3 4] In later stages, depression, psychosis, and dementia may appear, although depression may also be an early sign of the disorder.

The earliest stages of Parkinson's disease may begin years or even decades before tremor and stiffness become apparent.

Parkinson's disease typically begins in a person's 50s or 60s and slowly progresses with age. Early onset of Parkinson's disease before age 30 is rare, but up to 10 percent of cases begin by age 40. Descriptions of people with symptoms consistent with Parkinson's disease appeared in ancient time and periodically thereafter.[5] Lack of patient registries, however, makes it difficult to estimate incidence and trends of the disease even in recent times. The range of reported incidence varies from 4.5 to 21 per 100,000 people annually.

Historically, most attention has focused on degeneration of dopamine-producing cells in a portion of the midbrain called the substantia nigra.[a] When they can no longer produce adequate dopamine, neurons elsewhere in the brain are less well regulated and do not behave normally. Then the familiar clinical symptoms begin. But early Parkinson's disease pathology can involve nerves in the autonomic nervous system in the gastrointestinal tract and heart, even

The crane symbolizes health & protection in Asian cultures

[a] *Several neural pathways in the brain use dopamine as the major neurotransmitter. One of those is the pathway from the substantia nigra to the nearby striatum and is sometimes referred to as the nigrostriatal pathway or region. Degeneration of dopamine-producing cells results in lower levels of dopamine along this pathway. Studies described in this chapter variously refer to the substantia nigra, the striatum, or the nigrostriatum.*

before cells in the brain are affected.[6 7] Parkinson's disease may therefore be a more systemic condition.

In classic Parkinson's disease, affected neurons contain Lewy bodies. A major constituent of these cellular inclusions is a naturally occurring protein called alpha-synuclein (AS) that is misfolded and becomes insoluble.[8] Although the normal functions of AS in the brain are not well understood, it is likely to support synaptic nerve transmission via neurotransmitters. Normally, AS does not accumulate in the brain as it does in Parkinson's disease. Some genetic mutations can cause AS to misfold and become insoluble, but there are almost certain to be environmental factors that play a role in cases where genetic influences are not particularly strong.

The mechanism(s) leading to dopaminergic neuron degeneration, including the role of Lewy bodies, are not well understood. Whereas Lewy bodies may represent an initial attempt to sequester misfolded proteins, they may at some point become a trigger for an inflammatory response, which, in turn, damages dopaminergic neurons.

In addition to Lewy bodies, activated microglia are also present in the brains of people with Parkinson's disease and in various laboratory animal models.[9-11] As discussed in chapter 3, microglia are essential to immune function in the brain. When microglia are activated in response to pathologic stimuli, including infectious agents, chemical toxicants, or trauma, they release a variety of inflammatory substances and growth factors that can be both harmful and beneficial, depending on the nature of the stimulus and the degree and duration of the response. If not self-limited or ultimately reversed, microglial activation can be a source of ongoing, chronic inflammation, generating reactive oxygen species (ROS) and causing persistent oxidative stress. In animal models of Parkinson's disease microglial activation persists long after the initiating stimulus is gone. Imaging studies in people with Parkinson's disease show fairly widespread microglial activation in many areas of the brain, consistent with the now generally accepted conclusion that the pathology of Parkinson's disease is not confined to the substantia nigra.[12]

We now know that classic Parkinson's disease is one of a group of disorders with similar clinical symptoms but variations in areas of the brain affected or microscopic findings. People with symptoms resembling classic Parkinson's disease but with certain different features are sometimes said to suffer from "parkinsonism." Some people with parkinsonism lack Lewy bodies in affected areas

of the brain, but their symptoms may be indistinguishable from classic Parkinson's disease.[13] Some forms of parkinsonism may involve more extensive areas of brain injury than classic Parkinson's disease. In fact, boundaries between classic Parkinson's disease and parkinsonism are evolving concepts around which there is no clear consensus at this time.[14] Multiple pathologic mechanisms are likely to converge to cause a common clinical syndrome. Studies attempting to identify underlying causal factors, therefore, need to grapple with what appears to be considerable heterogeneity in the pathways leading to Parkinson's disease or parkinsonism.

People with symptoms resembling classic Parkinson's disease but with certain different features are sometimes said to suffer from "parkinsonism."

The Causes of Parkinson's Disease

Genetic Contributors

The origins of Parkinson's disease have been debated for decades. In the early 20th century, a small percentage of cases were noted to have affected family members, suggesting a genetic predisposition, but the overwhelming remainder appeared to be sporadic. In the 1990s, a large study of thousands of white male twins enrolled in a World War II veteran database attempted to estimate the extent to which genetic factors play a role in causing Parkinson's disease. The authors concluded that genetic predisposition was a strong determinant of risk in early-onset Parkinson's disease (before age 50) but that genetic factors do not play a major role in causing typical Parkinson's.[15]

More recent studies have identified a number of susceptibility genes that may play a role alone or in various combinations even in later-onset Parkinson's.[16] [17] [b] These candidate genes influence many different biologic processes including levels of neurotransmitters such as dopamine and their receptors, metabolism and excretion of potentially toxic compounds, and protein aggregation. Most investigators conclude that a number of susceptibility genes help to create the conditions in which environmental factors further influence events leading to clinical Parkinson's disease. Strong genetic influences are more important in early-onset Parkinson's than in more typical Parkinson's disease, where perhaps more numerous but weaker susceptibility genes play a less prominent role.

[b] *Several genes are associated with increases in Parkinson's disease risk, including parkin, alpha-synuclein, DJ-1, PINK-1, MAO-B, LRRK2, and UCHL-1, but they account for only a small number of Parkinson's disease cases.*

Environmental Contributors

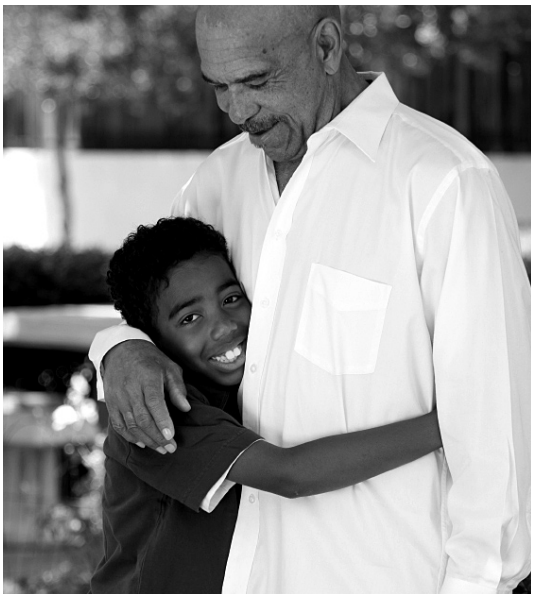
In the 1980s case reports of several individuals who acutely developed Parkinson-like symptoms after injecting a "new synthetic heroin" sparked interest in finding environmental agents that might cause the disorder.[18] MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) contaminated a batch of illicit meperidine (demerol) distributed to a small number of IV-drug users in northern California. Four people developed persistent Parkinson-like symptoms soon after injecting the drug. Two years later, after the death of one of the patients due to a drug overdose, autopsy revealed marked degeneration of cells in the substantia nigra of the brain, similar to what is seen in Parkinson's disease. However, Lewy bodies were not identified in this patient or in several others who later were examined at autopsy after MPTP-induced parkinsonism. Laboratory animals, including nonhuman primates, treated with MPTP also develop Parkinson-like symptoms, and this has been used as a toxicant-induced animal model for studying the disease. Lewy bodies are missing in MPTP-treated animals as well, although degeneration of dopaminergic neurons in the substantia nigra is a universal finding.[19]

A "Risk Factor" Approach to PD

As a result of the MPTP observations, many epidemiologic studies have looked for influences of other environmental agents on Parkinson's disease risk. At the same time, studies in laboratory animals have validated findings of some of the epidemiologic investigations and clarified underlying mechanisms whereby environmental agents may cause Parkinson's disease

Here we review and summarize the results of investigations into the role of individual risk factors for Parkinson's disease but caution that it is highly unlikely that a single "smoking gun" will ever be identified as causing most cases of Parkinson's disease. The picture that emerges is one of multiple genetic and environmental variables in differing combinations that collectively influence risk. This means that, within any group of people with Parkinson's disease, the underlying collection of factors ultimately leading to their symptoms, diagnosis, and progression will vary considerably. That is, multiple different pathways and mechanisms can ultimately lead to Parkinson's disease or parkinsonism. It means that in most affected individuals there are multiple determinants of Parkinson's disease

risk, and within populations the causes of Parkinson's disease are heterogeneous. We will discuss the implications of this conclusion for individuals and public policy decision-making in chapter 9.



Potentially Protective Factors (Decreased Risk)

The single factor that is most consistently associated with a reduced risk of Parkinson's disease is cigarette smoking. A meta-analysis of case-control and cohort studies reported an approximate 60 percent reduction of Parkinson's disease risk in smokers, including a dose-response relationship (higher cigarette consumption over a longer time associated with lower risk).[20] Decreased risk is greater in current compared to former smokers. Pipe and cigar smoking and chewing tobacco also seem to be associated with lower risk although they have not been studied as thoroughly as cigarette smoking.[21]

Various biological mechanisms have been proposed to explain an apparent protective effect of smoking. In animal studies, nicotine seems to partially protect against pesticide-induced damage to dopaminergic neurons in the nigrostriatal region of the brain involved in Parkinson's disease.[22] But cigarette smoke contains hundreds of chemicals and others may be involved. Therapeutic trials of nicotine in patients with Parkinson's disease are underway. An early pilot study shows promising results but larger, randomized clinical trials will be necessary.[23]

The picture that emerges is one of multiple genetic and environmental variables in differing combinations that collectively influence risk.

Caffeine consumption is also associated with a reduced incidence of Parkinson's disease in many studies.[24] [25] A proposed mechanism involves the capacity of caffeine and related chemicals to block the activity of a neuromodulator, adenosine, in the brain.[26] In clinical trials, blocking adenosine has resulted in less severe muscle rigidity in people with Parkinson's disease as well as improved responsiveness to other therapies.

Hormone replacement therapy is inconsistently associated with a reduced incidence of Parkinson's disease in women.[27] [28] As with Alzheimer disease, the timing of hormone replacement therapy in relation to the timing of onset of menopause may influence impacts on Parkinson's disease risk.

Factors that Increase Parkinson's Disease Risk

Age, Gender

The single biggest risk factor for Parkinson's disease is advancing age. Incidence increases from about 17 cases per 100,000 person years between ages 50 and 59 to over 90 per 100,000 person years between ages 70 and 79.[29] Men have a significantly higher risk than women, although it remains unclear if this difference is due to inherent gender differences or differential exposure to environmental risk factors.[30] [31]

Pesticides

In the 1990s, two converging lines of evidence began to point toward the likelihood that exposure to pesticides could increase the risk of Parkinson's disease. First, a number of case-control epidemiologic studies concluded that rural living and drinking well water increased the risk of Parkinson's disease, but the evidence was inconsistent and its quality varied.[32] [33] In over 20 studies, when occupation was taken into account, farmers and other agricultural workers appeared to have an increased risk of Parkinson's disease. Those reports, of course, sparked concerns that agricultural chemicals might be responsible.

Epidemiologic Studies

A recent review of the peer-reviewed literature found that 24 of 31 studies, primarily of case-control design, reported an increased risk of Parkinson's disease associated with pesticide use.[34] In 12 of the 24 positive studies, the increased risk was statistically significant, with odds ratios ranging from 1.6 to 7.0. Only two of the 31 studies reported an odds ratio of less than 1.0. In the studies that attempted to distinguish among categories of pesticides, herbicides and insecticides were most likely to be associated with an increased risk. Of the 31 reviewed, all of the studies (6 of 6) that attempted to determine whether the risk of Parkinson's disease increased as pesticide exposure increased found a trend in that direction, and it was statistically significant in 4 of the 6.

As is often true of epidemiologic investigations, many of these studies have some limits. For example, most of them rely on participants' estimates of past pesticide use or exposure, which may or may not be valid. One study concludes, however, that this is unlikely to be a major issue for licensed pesticide applicators, who are generally able to recall and report valid information.[35] Many of the studies address pesticides as a class of chemicals and fail to identify individ-

ual chemical agents that may increase Parkinson's disease risk. This may not be a weakness. It is entirely plausible that different pesticides from different classes could increase risk through different as well as common mechanisms of toxicity.

Laboratory Animal Studies

A second line of evidence linking pesticides to Parkinson's disease risk comes from experimental laboratory work. After the MPTP discovery, further investigations showed that MPTP caused neurodegeneration in the substantia nigra at least in part through mitochondrial toxicity and free radical damage to dopaminergic neurons that seemed particularly vulnerable to this kind of insult. Some investigators turned their attention to the pesticides rotenone and paraquat because of their propensity to damage mitochondria and structural similarities to MPTP or its toxic metabolite, MPP+. This work provided a new model for studying cellular mechanisms that damage dopaminergic neurons.

Studies in rats showed that chronic intravenous administration of rotenone caused a Parkinson-like syndrome, damage to dopaminergic neurons in the substantia nigra, and cellular inclusions that look like Lewy bodies microscopically.[36] Studies also showed that paraquat caused a loss of dopaminergic neurons in laboratory animals.[37 38]

Maneb, a widely used dithiocarbamate fungicide, is another agricultural chemical also linked to Parkinson's-like symptoms in humans exposed during agricultural work,[39 40] in laboratory animals[41] and in cultures of dopaminergic cells from the brain.[42] A 1991 study reported that pre-treatment with a dithiocarbamate markedly boosted the adverse impacts of MPTP on locomotor activity and increased dopaminergic neuron damage in laboratory rodents.[43] This stimulated more research into the impacts of mixtures of agricultural chemicals.

Combinations of paraquat and maneb have been studied using a variety of dosing regimens. Scientists at the University of Rochester administered saline, maneb, paraquat, or maneb plus paraquat to mice. They showed that the combined exposure to paraquat and maneb caused synergistic decreases in motor activity and dopamine and increased damage to dopaminergic neurons in the striatal region of the brain.[44 45]

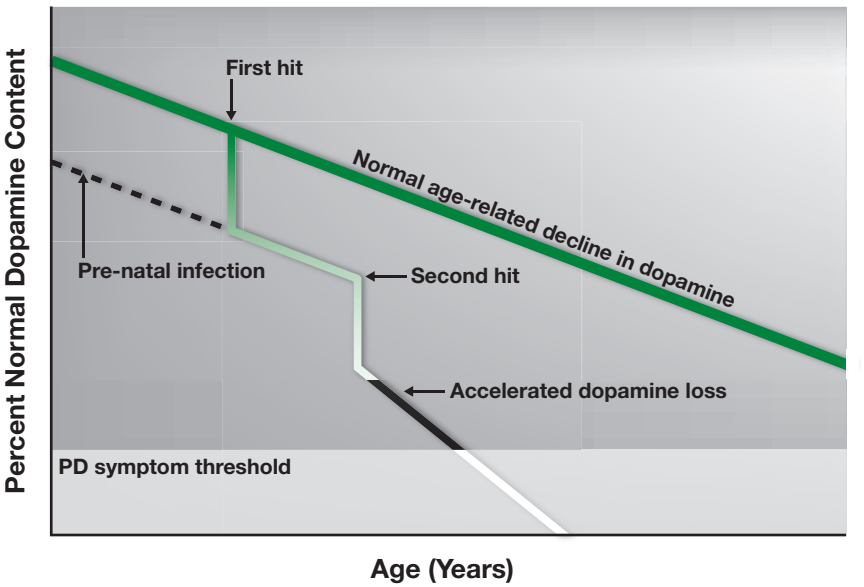
This team then explored the hypothesis that exposure to one or two of these chemicals during early development would increase susceptibility to exposures later in life. In one experiment, combined exposure to maneb and paraquat soon after birth produced loss of

dopamine and reduced numbers of dopamine neurons in the substantia nigra. Effects were greater than those produced by adult-only exposures. Moreover, combined exposures in infancy enhanced vulnerability to the same chemicals after exposure in adulthood.

In a second experiment, maneb exposures during fetal development markedly increased vulnerability to paraquat in adulthood, as measured by reductions in dopamine and numbers of dopaminergic neurons in the substantia nigra. Males were more vulnerable than females in both cases.[46] Other work in cell cultures had shown that paraquat caused oxidative damage by generating reactive oxygen species, while maneb interfered with regeneration of antioxidant defenses.[47]

In summary, these experiments showed the following: 1) Chemicals combined can act synergistically. That is, they can cause an enhanced effect that is greater than the sum of the effects of the individual chemicals. 2) Chemicals that cause toxicity through different mechanisms within the same system can have additive or synergistic effects. 3) Developmental exposures can "prime" the brain so that it is more susceptible to exposures that occur later in life. This is consistent with the concept of "multiple hits" that collectively, over time, result in clinical disease.

Multiple Hit Hypothesis



Early-onset or accelerated loss of dopaminergic cells caused by "hits" that may occur during fetal development and/or at any point throughout life ultimately result in sufficient loss of dopamine to cause clinical symptoms.

The herbicide paraquat and fungicide maneb are heavily used in large and often overlapping geographical areas with considerable likelihood of human exposures. Although investigators used intravenous exposures in the studies described above, follow-up studies in which paraquat was given to laboratory mice orally showed that the chemical was absorbed and transported to the brain with a half-life of one month.[48] Paraquat and maneb are absorbed after ingestion or inhalation and to some extent through dermal absorption in humans.[49] [50]

Additional Pesticides

Dieldrin is an organochlorine pesticide that is no longer manufactured or used in the U.S.. But traces of the chemical are still present in many humans and wildlife because it is persistent and bioaccumulative. An autopsy study found higher levels of dieldrin in the substantia nigra of ten Parkinson's disease patients compared to people without dementia and people with Alzheimer's disease.[51] The same study also found higher levels of lindane in the substantia nigra of people with Parkinson's disease. Lindane is another persistent, bioaccumulative pesticide that is still authorized for use in treating lice and scabies although alternatives exist. An earlier study detected dieldrin in 6 of 20 brains of people with Parkinson's disease, in 1 of 7 brains from people with Alzheimer's disease, and in none of 14 control samples. Since then, a number of in vitro and laboratory animal studies have attempted to elucidate mechanisms whereby dieldrin may increase the risk of Parkinson's.

In in vitro studies, dieldrin added to a preparation of alpha-synuclein protein markedly accelerates the development of protein aggregates similar to those seen in Lewy bodies.[52] Rotenone and paraquat have the same effect.

The ubiquitin-proteosome system (UPS) is another potential target for environmental agents associated with Parkinson's disease. The UPS is an intracellular mechanism that normally destroys proteins after they have served their purposes within the cell by shredding them into their component amino acids, which can then be recycled into new proteins.[53] Agents that impair the UPS may allow proteins such as alpha-synuclein, amyloid-beta, or others to inappropriately accumulate, increasing the risk of diseases associated with accumulation of those proteins. In in vitro experiments, rotenone, dieldrin, and two dithiocarbamate fungicides each impaired UPS functions at low concentrations.[54]

At low concentrations in cell culture systems, dieldrin also induces mitochondrial damage and microglial activation with release of reactive oxygen species causing oxidative stress, rapid release of dopamine, and apoptotic cell death.[55] [56] These effects also occur in intact laboratory animals at environmentally relevant levels of exposure.[57]

In another study, similar in design to those reported above with maneb, scientists fed dieldrin to female mice for three weeks at levels resulting in tissue concentrations similar to those found in people. The mice were then mated and their offspring studied after weaning. Male offspring that had been exposed to low-level dieldrin had a much larger decrease in nigrostriatal dopamine levels after MPTP exposure in adulthood than control animals. This once again demonstrates that perinatal exposures to toxic agents can prime the brain, making it more susceptible to further damage when challenged again in adulthood.[58] Female mice did not show the same dramatic drop in dopamine levels following MPTP, but perinatal dieldrin altered dopamine transport systems in both genders. The authors concluded that dieldrin had altered gene transcription activity at the DNA level, accounting for observed changes in levels of dopamine transport and packaging proteins.[c]

Finally, pyrethroids are another class of neurotoxic pesticides that deserve mention. They are usually divided into type I and type II based on their chemical structures. Pyrethroids are in widespread use, and their residues are commonly present in biomonitoring studies in the general population.[59] Several rodent studies have examined the impact of pyrethroids on dopaminergic systems in adults but few have examined developmental impacts. In one study, neonatal rats were given either pyrethrin (type I) or cypermethrin (type II) orally at 1/10 the LD50[d] daily from postnatal day 6 to 15.[60] They showed no gross evidence of toxicity or behavior changes. Activity levels were not different from controls at day 21 but by day 35, treated animals had increased levels of spontaneous activity. At day 35, dopamine content of the striatum was also significantly lower and evidence of oxidative stress was higher in treated animals compared to controls. Although no human data are available, this rodent study suggests that pyre-

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[c] *When the neurotransmitter dopamine is released into the synapse, it triggers a neuronal response. Dopamine is then transported back into the neuron by the dopamine transporter where it is repackaged into vesicles for subsequent use. If dopamine is not properly transported into the neuron or if transport into the neuron exceeds the rate of repackaging, excessive free dopamine may damage the neuron through oxidative stress. The concern is that perinatal exposures to certain chemicals, like dieldrin or PCBs, will permanently alter the dopamine regulatory system, making this part of the brain more vulnerable to additional challenges later in life.*

[d] *The LD50 is the dose that is lethal to 50% of the animals receiving that dose.*

throids, to which humans are commonly exposed, could be among the chemicals increasing the risk of Parkinson's disease by permanently down-regulating dopamine levels after developmental exposures.

In summary, despite remaining uncertainties and data gaps, the body of evidence linking pesticide exposure to Parkinson's disease fulfills generally accepted criteria for establishing causation. Epidemiologic studies show a fairly consistent association between pesticide exposure and increased Parkinson's disease risk, with an apparent dose-response pattern wherein larger exposures are associated with higher risk. These studies are consistent with extensive laboratory animal data, which also includes descriptions of underlying mechanisms of toxicity. Collectively, this evidence supports the conclusion that pesticide exposures can cause Parkinson's disease in some people.

Polychlorinated Biphenyls (PCBs)

Polychlorinated biphenyls (PCBs) are members of a class of persistent, bioaccumulative organochlorine chemicals historically used for many purposes, including as electrical insulators in transformers, lubricants, and paint additives. The EPA banned PCB manufacture in the U.S. in 1977 because of concerns about potential carcinogenicity. Since then, numerous studies have documented other adverse impacts on the development and function of the thyroid and nervous and immune systems.[61]

PCBs continue to contaminate the general environment and food chain. Biomonitoring studies detect PCBs in the vast majority of the U.S. population and levels increase with age.[62] In general, however, since the ban environmental concentrations and serum levels have been declining, although highly contaminated "hot spots" and disproportionately exposed individuals still exist.

Epidemiological and laboratory studies suggest that exposure to PCBs may be a risk factor for Parkinson's disease. A retrospective mortality study of over 17,000 workers occupationally exposed to PCBs reported an excess of Parkinson's disease–related deaths (nearly three times as many as expected) and dementia-related deaths (twice as many) in the women most highly exposed to PCBs but not in men.[63] This gender difference finding is surprising since men are generally at higher risk of idiopathic Parkinson's disease. Another postmortem study found higher levels of PCBs in the brains of people with Parkinson's disease than in controls.[64]

Animal studies show that some PCBs can reduce dopamine levels in the substantia nigra of nonhuman primates and rodents.[65] [66]

One plausible mechanism whereby PCBs may reduce dopamine and increase the risk of Parkinson's disease involves the induction of prolonged oxidative stress in dopaminergic neurons.[67 68 69] In vitro studies show that PCBs facilitate prolonged up-regulation of heme oxygenase levels and release of iron, contributing to oxidative stress and cell damage.[70] In these studies, iron chelation and blocking the rise in heme oxygenase reduced the impacts of PCBs.

Another plausible mechanism whereby PCBs may increase Parkinson's disease risk involves changes to the dopamine transporter system. Mice exposed to PCBs at levels resulting in tissue levels similar to those in the post-mortem brains of people with Parkinson's disease showed a significant decrease in both the transporter protein and repackaging protein.[76] (See footnote c.) The authors propose that failure to repackage dopamine normally sets the stage for prolonged dopamine-related oxidative stress.

Solvents

Organic solvents are used in industry for cleaning, degreasing, extraction, surface coating, and laboratory work. They are components of paints, inks, glues, adhesives, and hydrocarbon fuels. The main route of exposure is through inhalation. Long-term exposures can be neurotoxic, causing peripheral neuropathies and central nervous system symptoms such as mood swings; depression; headache; and impaired cognition, concentration, and memory.[77]

Different solvents, including carbon disulfide, methanol, n-hexane, and trichloroethylene (TCE), have been reported associated with parkinsonism, although exposures to mixtures are more commonly identified in studies showing a significant relationship.[78-82] The central nervous system damage associated with solvent exposures includes the substantia nigra, but other areas of the brain are often involved.

A recent report of two cases of acute onset of parkinsonism after ingestion of ethylene glycol or methanol in suicide attempts described hemorrhagic necrosis in the basal ganglia of the brain.[83] The involved area is intimately interconnected with the nearby substantia nigra and plays a role in classic Parkinson's disease. The nature of the damage described in these two cases, however, differs from classic Parkinson's disease despite the similarities of neurological symptoms.

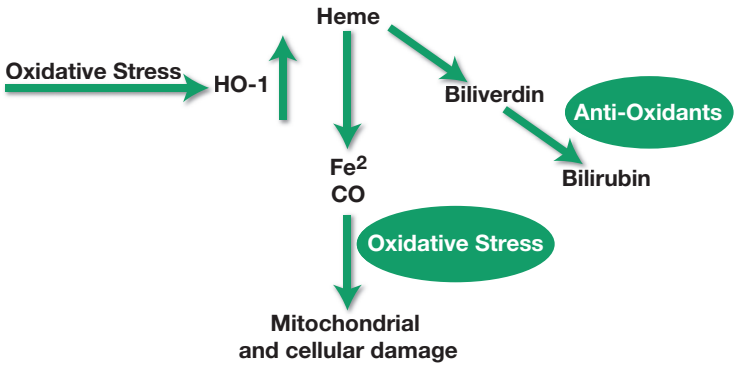
How *it* Works

Heme Oxygenase

Heme oxygenase 1 (HO-1) and heme oxygenase 2 (HO-2) are normally occurring enzymes that can be induced by oxidative stress and other noxious stimuli. Although present in many tissues, HO-1 is normally present in the brain at very low levels compared to HO-2. These enzymes facilitate the degradation of heme proteins (responsible for oxygen transport in red blood cells, among other functions), producing biliverdin, bilirubin, and low levels of carbon monoxide (CO).

At low levels, CO is neuroprotective*, and biliverdin and bilirubin have strong antioxidant properties. But free iron, which is also generated, combines with naturally occurring hydrogen peroxide to generate the highly reactive hydroxyl radical and is therefore a source of oxidative stress.

This system is generally thought to have protective effects by increasing the antioxidant capacity of cells. Recent data suggest, however, that chronic overproduction of HO-1 may actually increase rather than decrease oxidative stress by generating excessive iron.[71 72 73] HO-1 and iron are present in the substantia nigra at higher levels in people with Parkinson's disease than in controls. HO-1 is also present at higher levels in the hippocampus of people with Alzheimer's disease compared to controls.[74]



Some neuroscientists propose that the heme oxygenase system, which normally has a neuroprotective function, may, under certain circumstances, actually increase oxidative stress and cell death by generating excessive amounts of free iron, a powerful oxidant.

**High levels of CO exposure as may be caused by CO poisoning from an outside source may cause brain damage and symptoms of parkinsonism.[75] Brain imaging studies after CO poisoning show widespread damage of white matter and the basal ganglia.*

Another recent report describes parkinsonism in 30 workers associated with long-term occupational exposure to TCE.[84] In an accompanying study, adult male rats dosed orally with 1000 mg TCE/kg body weight five days a week for six weeks developed mitochondrial damage and dopaminergic neuron loss in the substantia nigra. Alpha-synuclein inclusions were present in the substantia nigra and dorsal motor nucleus of the vagus nerve in treated animals.

TCE is a particular concern not only because of frequent use as a degreasing agent in industry but also because it is a frequent surface- and groundwater contaminant resulting in widespread, low-level exposures in the general population.[85] One of the metabolites of TCE, chloral hydrate, can combine with tryptamine, a normally occurring chemical that serves as a backbone for a number of biologically active compounds, to form TaClo.[e] Structurally, TaClo resembles MPTP, easily crosses the blood-brain barrier, and causes neurodegeneration and Parkinson-like symptoms in animal tests.[86] [87] The clinical relevance of this mechanism and the influence of low-level exposures to TCE on Parkinson's disease risk in the general population are unknown.

Metals

Exposures to metals, such as lead, manganese, iron, copper, and others, have been of interest since some occupational studies identified them as potential risk factors for Parkinson's.[88] [89] [90] [91] Mechanisms whereby metals may influence Parkinson's disease risk include increased oxidative stress and facilitation of protein aggregation. Even without excessive exposures, however, abnormal transport of essential metals such as copper, zinc, or iron into the brain or mishandling of the metal within the brain may trigger these responses.[92] The following discussion will focus primarily on the potential influence of exogenous sources of metals on Parkinson's disease risk.

Manganese

Manganese is a micronutrient required in a number of normal enzymatic processes, but excessive exposures can be harmful. Whereas dietary levels may vary considerably, in adults homeostatic mechanisms regulate manganese absorption and excretion, thereby maintaining optimal levels. Various mechanisms are responsible for transporting manganese across the blood-brain barrier.[93] For example, manganese can attach to an iron-transporter protein to

[e] *1-trichloromethyl-1,2,3,4-tetrahydro-β-carboline*

cross the blood-brain barrier, and when iron stores are deficient, brain levels of manganese increase. Unbound manganese can also gain access to the brain. Studies in rodents show that homeostatic mechanisms are not fully developed in infancy, and dietary manganese supplements result in elevated levels in the brain and decreased dopamine in the nigrostriatal system.[94]

Soy infant formula contains about 200–300 micrograms of manganese per liter. Cow's milk formula contains 50–100 micrograms of manganese per liter and human milk about 3–8 micrograms per liter.[95] Although in animals, manganese absorption is lower from soy formula than from milk formula or breast milk, manganese retention is quite high.[96] Studies in term and pre-term infants also show high retention of manganese.[97] Formula-fed infants have significantly higher manganese levels in their hair at four months than breastfed infants, indicating higher absorption and retention.[98] Initial studies of neurodevelopment in children exposed to high levels of manganese in drinking water (greater than 300 micrograms per liter) show impairments in intellectual function.[99] It is entirely plausible that excessive dietary manganese exposures in infant humans will result in higher brain levels of manganese and increase the risk of neurodegenerative diseases later in life, but this has never been studied.

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Occupational studies show that miners can be exposed to elevated levels of manganese, primarily by inhalation, and they are at risk for movement disorders resembling Parkinson's disease although other features of their illness differ.[100] [101] Despite some clinical similarities, pathologic studies of brain tissue after excessive manganese exposure in adulthood show that an important part of the basal ganglia known as the globus pallidus is the most prominently damaged, with relative sparing of the substantia nigra and an absence of Lewy bodies.[102]

Studies of metal welders who may also be exposed to manganese by inhalation have been inconsistent with respect to risk of Parkinson's disease. An extensive recent review concludes that many of the available studies are limited by methodologic issues such as lack of accurate exposure data, inadequate control groups, or case selection bias.[103] These limitations make it difficult to determine whether welders are at increased risk of neurological effects and if they are,

whether manganese is responsible. Although existing studies do not provide compelling evidence of increased risk of Parkinson's disease or parkinsonism among welders, the database is not sufficiently robust to justify dismissing the possibility, particularly in highly exposed or otherwise susceptible individuals.

Two additional potential sources of manganese exposure by inhalation in the general population deserve mention. Methylcyclopentadienyl manganese tricarbonyl (MMT) added to gasoline as an octane enhancer may cause elevated levels of manganese in particulate air pollution. The Ethyl Corporation, which manufactured tetraethyl lead as a gasoline additive until its use was banned in the U.S. and many other countries, is promoting MMT as an alternative. After Ethyl Corporation's legal challenges in response to proposed bans, MMT is permitted as a gasoline additive but is reportedly not being used by any major gasoline manufacturer in the U.S.[104]

In Canada, MMT use in gasoline has been common. Although environmental levels of manganese are higher in high-traffic than in low-traffic areas, blood levels of manganese in people do not significantly differ between the two.[105] Studies in rodents and fish, however, show that manganese can travel directly into the brain from the nose along the olfactory nerve.[106] Whether this occurs in people to any appreciable extent is unknown.

Emissions from steelmaking industries are a second potential source of population-wide manganese exposures. A study in the steelmaking city of Hamilton, Ontario, reported an increased risk of Parkinson's disease associated with increases in manganese content in particulate air pollution.[107] If the finding is valid, it may represent either an increase in manganese-related parkinsonism or acceleration of the onset of true Parkinson's disease, consistent with the theory that manganese further promotes the loss of dopaminergic neurons attributable to natural aging.[108]

Iron

Dietary iron is essential for a number of vital enzymatic processes throughout the body, including the brain, and as a component of hemoglobin in red blood cells. Normal myelination, neuron and synapse formation, and neurotransmission are highly dependent on normal iron availability. Excessive iron, however, can be toxic to cells. Iron increases levels of oxidative stress in the brain by contributing to

the formation of free radicals. It contributes to mitochondrial dysfunction, and in people with Parkinson's disease may promote the formation of Lewy bodies by enhancing alpha-synuclein aggregation.[109]

As a result of iron's essential but potentially toxic role in brain development, function, and aging, scientists investigating both neurodevelopment and neurodegeneration have extensively studied this metal. We do not intend to review this large literature here but rather to summarize findings related to potential neurodegenerative effects of excessive dietary iron, while explicitly recognizing the essential role of iron in normal brain development and function.

Dietary Iron—Infants and Children

Iron absorption, excretion, and metabolism are tightly regulated in most tissues, including the brain. It is well established that iron tends to accumulate in the substantia nigra and elsewhere in the basal ganglia in all people, beginning in childhood. An imaging study of normal children shows that brain iron accumulation begins sooner and is more extensive in some than in others, but the reasons are unknown.[110] Over time, people who develop Parkinson's disease tend to accumulate higher levels of iron in the substantia nigra for reasons also not well understood, although chronic oxidative stress may play a role.[111] (See the heme oxygenase sidebar.)

Most investigators believe that this iron comes primarily from endogenous sources and not from excessive iron exposure. One theory holds that excessive iron deposition in the substantia nigra of people with Parkinson's disease is the result of genetic variations in iron regulatory proteins.[112] Some evidence, however, suggests that this excess iron may not entirely result from endogenous sources. Studies in rodents, for example, demonstrate the following:

- Elevated dietary iron levels during the newborn period (up to three weeks) permanently increased brain iron levels and caused dopaminergic neurodegeneration in adulthood. Moreover, elevated dietary iron in newborn mice resulted in profoundly increased susceptibility to MPTP-induced neurodegeneration in adulthood. The dietary levels of iron used in this study (of mice) were comparable to the levels in fortified human infant formula.[113]
- Iron sequestered in the brain during infancy tends to stay there although it may be redistributed (according to a rat study).[114] Even an iron-deficient diet during adulthood does not mobilize previously deposited iron from the brain (rat).[115]

Taken together, these studies make a strong case that both too little and too much dietary iron during infant and child development can be harmful.

These results suggest that excessive dietary iron, beginning in infancy, could increase the risk of neurodegenerative diseases later in life.

Iron levels in human milk are fairly tightly regulated and largely independent of maternal iron status.[116 117] Breast milk iron levels are about 1 mg/L at birth and fall to about 0.3 mg/L at six months. Similarly, lactoferrin, a breast milk protein that plays a role in regulating the absorption of iron from the infant intestinal tract, is highest at birth and declines thereafter.

Infant formulas not fortified with iron contain about 2 mg iron/L. Fortified formulas in the U.S. can contain as much as 12 mg iron/L. Iron derived from infant formula is generally not accompanied by lactoferrin and is in a different form from iron in breast milk. As a result, iron in formula is not as well absorbed from the intestine as iron from breast milk. Nevertheless, absorption of iron supplements is not well regulated in the young infant and can be excessive if dietary levels are high.[118]

Excessive iron supplementation in the young infant can have adverse impacts on development if the child is iron replete.[119] Whether excessive dietary iron supplementation in human infants results in excessive brain deposition of iron is unknown. Recently, Betsy Lozoff from the University of Michigan reported for the first time that a group of children who had high hemoglobin levels at six months of age and were fed infant formula fortified with iron at 12 mg/L performed more poorly on tests of spatial memory, motor coordination, and overall visual-motor coordination.[120] This suggests that excessive iron may actually have adverse impacts on neurodevelopment in infants who already have adequate iron stores.

On the other hand, iron deficiency is the most common nutritional deficiency in the U.S. and throughout the world. It is associated with delayed neurological development including cognitive deficits. Iron deficiency in infancy may also increase the risk of neurodegenerative disease later in life. In a recent animal study, iron deficiency during development altered the expression of a number of genes in the developing hippocampus, including up-regulating several genes involved in Alzheimer's disease.[121]

Taken together, these studies make a strong case that both too little and too much dietary iron during infant and child development can be harmful. Excessive dietary iron from highly fortified infant formulas may not only adversely impact neurodevelopment in some children but also increase the risk of neurodegenerative diseases in adulthood, particularly in the context of additional sources of oxida-

tive stress. For non-breastfeeding children, the American Academy of Pediatrics strongly recommends the use of formula fortified with iron at levels between 4 and 12 mg/L. Within this range, however, there remains considerable uncertainty and debate about optimal levels.[122]

Dietary Iron—Adults:

Several case-control studies in adults, using dietary questionnaires to estimate exposure levels, have looked for links between dietary iron and Parkinson's disease risk. In a study of 250 people newly diagnosed with Parkinson's disease and 388 control subjects in which participants attempted to reconstruct dietary patterns over their lifetime, those with the highest dietary iron intake from supplements or multivitamins had a 70 percent increased risk of Parkinson's disease compared to those with the lowest intake.[123] A combined above-average intake of iron and manganese was associated with a doubling of Parkinson's disease risk.

In another study of 126 people with Parkinson's disease and 432 controls, in which a one-year retrospective history was used to estimate dietary patterns, those with the highest intake of iron had a near doubling of Parkinson's disease risk (OR 1.94; 95% CI 1.05-3.58).[124] A third study of 104 patients and 352 controls using dietary questionnaires found no association with dietary iron from food or supplements.[125]

In people with Parkinson's disease considerable uncertainty remains about whether iron deposition is an important contributor to dopaminergic neuron destruction or, rather, a manifestation of the disease. The most commonly held view emphasizes that iron deposition increases oxidative stress, contributing to dopaminergic neuron loss, and iron deposition increases as the disease progresses—creating a positive feedback loop. In summary, combinations of excessive iron intake, excessive deposition, and abnormal iron regulation are likely to influence the onset and progression of pathogenic processes in the areas of the brain affected in Parkinson's disease.

Lead

Many studies of lead exposure as a risk factor for Parkinson's disease have been limited by inadequate exposure assessment. Questionnaires, job histories, and blood lead levels are poor substitutes for quantifying actual exposure levels over time. A recent case-control study of 121 people with Parkinson's disease and 414 controls used bone lead measurements (via X-ray fluorescence technology), which

Particulate air pollution is likely to be a risk factor for both Alzheimer's disease and Parkinson's disease.

give an assessment of cumulative exposures over time. It found that the risk of Parkinson's disease was significantly elevated by more than two-fold in people in the highest quartile of lead exposure when compared to the lowest quartile.[126] The findings were modified to some degree when age was accounted for, but age did not fully explain the increased risk. The authors concluded that occupational lead exposure is a risk factor for Parkinson's disease. The mechanism(s) by which heavy metals, including lead, may increase Parkinson's disease risk include increasing oxidative stress, lipid peroxidation of cellular membranes, and abnormal folding of alpha-synuclein protein.[127] [128]

Air Pollution and Food Contaminants

Recent studies in laboratory animals and humans show that particulate air pollution increases markers of oxidative stress and inflammation in the brain and is associated with abnormal deposition of amyloid and alpha-synuclein.[129] [130] Particulate air pollution is likely to be a risk factor for both Alzheimer's disease and Parkinson's disease. This is discussed in more detail in chapter 7.

In recent years, indoor air pollution has also received much needed attention as a source of potentially harmful exposures. Depending on building design, operations, and furnishings, indoor air can be contaminated with a complex mixture of chemicals, which can, in turn, react with each other to form novel compounds.

No studies have specifically linked indoor air pollutants with Parkinson's disease or Alzheimer's disease. However, the type-2 alkenes, a group of chemicals to which people are commonly exposed occupationally, in indoor and outdoor air, and through dietary contamination, are receiving attention as potential sources of oxidative stress in the brain affecting large numbers of people.[131] Acrolein and 4-hydroxy-2-nonenal are two members of this class of chemicals that are also generated endogenously when lipids are damaged by oxidative stress. These two chemicals, in turn, add additional oxidative stress themselves and are hypothesized to damage synapses, ultimately resulting in neuronal death. Increasingly, neuroscientists are

considering their potential for playing a role in Alzheimer's disease and Parkinson's disease.

In addition to endogenous sources, however, some type-2 alkenes are used extensively in manufacturing, agriculture, and the chemical industry and are common environmental contaminants. Acrolein, for example, is present in both indoor and outdoor air, commonly at levels that exceed safety thresholds.[132] Outdoor sources of acrolein include incomplete products of fuel combustion and forest fires. Indoor sources include cigarette smoke, cooking fuels, and oxidation of emissions of volatile organic compounds from building materials and furnishings.

Acrylonitrile, also a type-2 alkene, is a high volume chemical used in the manufacture of textiles, nitrile rubbers, and plastics. It is also a chemical intermediate in the manufacture of dyes and pharmaceuticals. Type-2 alkenes acrylamide and methyl acrylate are common dietary contaminants.[133] Acrylamide, a carcinogen and neurotoxicant, is formed when carbohydrate-rich foods are cooked at high temperatures.

The concern is that widespread environmental exposures to type-2 alkenes will add significantly to the impacts of those produced endogenously, increasing oxidative stress in the brain and thereby, the risk of Alzheimer's disease and Parkinson's disease. At the moment, however, the public health implications of exposures to this class of chemicals are unknown.

Infectious Agents

In 1917, von Economo described a disease that emerged during and after pandemic influenza swept through Europe.[134] He named it encephalitis lethargica because many of its victims experienced extreme lethargy, often associated with abnormal eye movements. In some people rigidity was prominent, and von Economo remarked on the clinical resemblance to parkinsonism. Later, he began reporting cases with features of parkinsonism that suddenly appeared years after the initial illness of influenza had completely cleared, whether it had been accompanied by encephalitis or not.

Except for rare cases, searches for other infectious agents that may be responsible for parkinsonism have not been productive. Several more recent discoveries, however, rekindle interest in the possibility that infections may increase risk. They come from new models for studying Parkinson's disease and may help to explain variable susceptibility to environmental triggers.

Lipopolysaccharide (LPS) is the major component of the cell wall of gram negative bacteria. As discussed in chapter 6, LPS triggers the innate immune system by interacting with the Toll-like receptors (TLR), initiating a pro-inflammatory response cascade. Laboratory studies in rodents show that, compared to controls, exposure to LPS during pregnancy results in offspring with lower levels of brain dopamine, fewer dopaminergic neurons in the substantia nigra, Lewy body–like structures in the brain, increased levels of pro-inflammatory markers, and microglial activation.[135] [136] Prenatal LPS exposure also permanently lowers antioxidant levels in the brain and renders animals more susceptible to secondary challenges to neurotoxicants in adulthood.[137] For example, prenatal exposure to LPS followed by intravenous exposure to rotenone in adulthood causes a synergistic loss of dopaminergic cells and dopamine levels in the substantia nigra.[138] Even adult mice given a single injection of LPS develop prolonged activation of microglia and progressive loss of dopaminergic neurons in the substantia nigra that continues long after LPS exposure.[139] These studies support the idea that certain bacterial infections may increase the risk of Parkinson's disease through several mechanisms.

Finally, a recent study examined the impact of extremely low levels of formyl-methionyl-leucyl-phenylalanine (fMLP) on microglia and dopaminergic cells in tissue cultures from the brain of rodents.[140] fMLP is a chemical produced by bacteria as they invade and damage tissue. It is a chemo-attractor, guiding white blood cells and other cells involved in the inflammatory response to the site of an infection. The authors of the report decided to study fMLP because of its structural similarity to an endogenous compound in the brain that can activate microglia (substance P). They found that extremely low levels of fMLP activated microglia in the tissue culture and caused marked dopaminergic cell loss. This observation raises the interesting possibility that the body's response to a number of different infections could "prime" the substantia nigra by activating microglia. It will require confirmation and further study in intact laboratory animals in order to judge its relevance to Parkinson's disease risk in humans.

Dietary Risk Factors

Diet may play a role in the origins of Parkinson's disease by altering the oxidative balance in the brain, by otherwise increasing or decreasing susceptibility to neurotoxicants, or as a source of neurotoxic agents. But studying the impact of diet in people presents

several challenges. First, investigators commonly use dietary recall or food frequency questionnaires to identify eating habits of study participants. Even when the questionnaires are carefully designed, the risk of inaccurate recall is always a concern that grows with increasing length of time of interest. This is a significant limitation for Parkinson's disease, which usually has an insidious onset of symptoms and a long pre-clinical latency period. Recent dietary history may not be as relevant as eating habits long ago—even as far back as early development.

Recent dietary history may not be as relevant as eating habits long ago—even as far back as early development.

A second limitation comes from considering the diet be a collection of individual foods or nutrients rather than as an integrated whole. Single nutrient deficiencies (e.g. a vitamin) or excesses (e.g. saturated fat) may be relevant, but focusing entirely on specific foods ignores biologically relevant interactions among nutrients, increasing the likelihood of inconsistent, conflicting, or even misleading conclusions. Alternative approaches, such as dietary pattern analysis, can help to address this problem.[141 142]

Table 1 summarizes the findings of available epidemiologic studies examining the influences of diet on Parkinson's disease risk. Study sizes and designs differ, including methods for controlling for covariates, effect modifiers, and confounders.

Three large prospective cohort studies find an increased risk of Parkinson's disease with increased intake of milk. A meta-analysis of these three studies[156] found a 60 percent increased risk in people who consume the largest amount of milk when compared to those who consume the least (80% increased risk for men; 30% increased risk for women). The reason for this increased risk is not clear, but it does not appear to be related to dairy fat or calcium. Hypotheses include the potential presence of neurotoxic agents in the milk, for example, pesticides, [157 158] and decreased uric acid associated with increased dairy product intake.[159]

The studies also suggest reduced Parkinson's disease risk with higher intake of dietary vitamin E. Increases in dietary unsaturated fatty acids may also decrease risk. As mentioned previously, two of three case-control studies found an increased risk of Parkinson's disease with increased dietary iron.

The single study employing dietary pattern analysis found reduced risk with a diet rich in fruits, vegetables, nuts, legumes, and fish and low in saturated fat. Such a diet would contain abundant antioxidants and be less likely to stimulate a general inflammatory response. (See chapters 6 and 7.)

Table 1: Diet and Parkinsons's Disease Risk

Study	Study type	Sample size	Dietary features analyzed	Results
Etminan, 2005[143] (includes Zhang, 2002)	Meta-analysis of 6 case-control, 1 cohort, 1 cross-sectional studies		Vitamins E, C, beta-carotene	Dec. risk of Parkinson's disease with inc. dietary vitamin E
Chen, 2004[144]	Prospective cohort	47,341 men 88,716 women	Folate, vit B6, vit B12	No effect
Chen, 2002[145]	Prospective cohort	47,331 men 88,563 women	Food groups	Inc. risk of Parkinson's disease with higher intake of dairy products in men; not in women
Chen, 2007[146]	Prospective cohort	57,689 men 73,175 women	Dairy products	Inc. risk of Parkinson's disease with inc. intake of dairy products, mostly explained by milk intake
Zhang, 2002[147]	Prospective cohort	47,331 men 76,890 women	Foods rich in vitamins E, C, carotenoids; vitamin supplements	Dec. risk of Parkinson's disease with vit. E-rich foods but not supplements; dec. risk with nuts
Gao, 2007[148]	Prospective cohort	46,692 men 81,676 women	Principal component analysis to identify dietary patterns	Dec. risk of Parkinson's disease with diet rich in fruits, vegetables, legumes, nuts, fish; low in sat'd fat
De Lau, 2005[149]	Prospective cohort	7,983	Total energy, total fat, sat'd FA, trans FA, cholesterol, MUFA, PUFA, carbohydrates, dairy, alcohol, vit E, coffee (beginning one year prior to onset of study; 6 yr follow up)	Dec. risk of Parkinson's disease with higher intake of total fat, MUFA, PUFA; no assoc with sat'd FA, cholesterol, trans FA
De Lau, 2006[150]	Prospective cohort	5,289	Dietary folate, vit. B6, vit. B12	Dec. risk of Parkinson's disease with higher intake of B6; no assoc. with folate, B12
Park, 2005[151]	Prospective cohort	7,504 men	Milk; dietary calcium (at the time of study initiation; follow up over 30 yrs.)	Inc. risk of Parkinson's disease with inc. milk intake; no assoc. with calcium
Logroscino, 1998[152]	Case-control	104 cases 352 controls	Dietary iron, animal fat	No effect of dietary iron; inc. risk of Parkinson's disease with animal fat intake in people with low transferrin saturation*
Powers, 2003[153]	Case-control	250 cases 388 controls	Food freq. habits for most of adult life	Inc. risk of Parkinson's disease with high iron intake; higher risk with high iron and manganese intake; no assoc. with fat
Johnson, 1999[154]	Case-control	126 cases 432 controls	Estimates of foods eaten in past year	Inc. risk of Parkinson's disease with high intake of total fat, sat'd fat, cholesterol, lutein, iron
Gao, 2008[155]	Prospective cohort	47,406 men	Foods that influence blood uric acid level	Dec. risk of Parkinson's disease with inc. intake of foods that raise uric acid levels

**This suggested to the authors that dietary fat and abnormal iron metabolism might interact to increase Parkinson's disease risk*

Three large prospective studies and one case-control study found that lower plasma uric acid levels are associated with an increased risk of Parkinson's.[160] [161] [162] [163] A meta-analysis of the three prospective studies concluded that a 1.32 mg/dl increase in plasma urate was associated with an approximate 20 percent decreased risk of Parkinson's disease. This is plausibly a causal relationship since uric acid is a strong antioxidant, and oxidative stress in the brain is likely to play a major role in the etiology of Parkinson's disease.

A prospective cohort study of over 47,000 men concluded that higher intake of foods that increase blood levels of uric acid result in a decreased risk of Parkinson's disease.[164] [f] This relationship remained significant after controlling for smoking, coffee consumption, body mass index, and total caloric intake.

Finally, an animal study examining the impact of polyunsaturated fatty acids on susceptibility to MPTP-induced nigrostriatal damage deserves mention.[165] For ten months investigators fed one group of mice a diet enriched with omega-3 fatty acids so that the omega-6:omega-3 fatty acid ratio was 1.19. They fed a second group a diet with an omega-6:omega-3 fatty acid ratio of 101:1. Each diet contained equal calories per gram and equal percentages of proteins, fats, and carbohydrates. However, the high omega-6 fatty acid diet was completely devoid of the omega-3's eicosapentanoic acid (EPA) and docosahexanoic acid (DHA). After ten months some of the mice were given intraperitoneal injections of MPTP at doses known from previous studies to cause moderate damage to dopaminergic cells. When the brains were examined two weeks later, the omega-3 fatty acid–enriched diet had completely blunted the loss of dopaminergic neurons in the substantia nigra caused by MPTP. In the striatum, dopamine levels were significantly preserved in the group given the omega-3–enriched diet. This dramatic protective effect led the authors to conclude that low human consumption of omega-3 fatty acids might be an important modifiable risk factor for Parkinson's disease. It is worth noting that this is different from concluding that excessive omega-6 fatty acids are responsible for the increased susceptibility. Both omega-6 and omega-3 fatty acids are essential in the diet, but high levels of dietary omega-6s combined with inadequate levels of omega-3s can result in an excessive inflammatory response. (See chapter 6.)

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[f] *The authors derived a dietary urate index by assessing intake of the following foods and nutrients: meat, seafood, dairy protein, individual dairy foods and dairy products, alcohol, vitamin C, fructose, sucrose, vegetables, legumes and soybean products, flavonoids, folate, coffee, caffeine. Some of these tend to increase uric acid levels (e.g. meat, fructose, alcohol) and others tend to lower levels (dairy proteins, vitamin C).*

In summary, available epidemiologic and laboratory animal data indicate that the risk of Parkinson's disease can be influenced by diet. The weight of evidence points to an increased risk, primarily in men, with increased consumption of dairy products. Increased iron intake also appears to increase Parkinson's disease risk although the evidence is more limited. Foods rich in antioxidants and polyunsaturated fatty acids and foods that increase uric acid levels are likely to decrease risk. Among the polyunsaturated fatty acids, an increase in omega-3 fatty acids may be particularly useful.

Obesity, Body Mass Index as Risk Factors

Available epidemiologic and laboratory animal data indicate that the risk of Parkinson's disease can be influenced by diet.

The results of prospective studies of the influence of obesity or body mass index on Parkinson's disease risk are inconsistent. Table 2 summarizes the available data. Although it is tempting to hypothesize a connection among obesity, higher intake of dietary fat, and increased Parkinson's disease risk, it must also be noted that dopamine plays an important role in appetite regulation and energy metabolism. Obesity is also associated with decreased dopamine (2) receptors in the brain, which may in turn influence dopamine levels and turnover.

Obesity could also influence the effect of other Parkinson's disease risk factors. For example, in a study in mice, obesity was induced by adding beef tallow to the diet.[166] Obese and lean control animals were then exposed to low and high doses of MPTP. Obese

Table 2: Obesity/BMI and Parkinson's Disease Risk

Study	Study type	Sample size	Measurement	Results
Abbott, 2002[167]	Prospective cohort	7,990 Japanese-American men	Triceps skin fold thickness	Inc. Parkinson's disease risk with inc. triceps skin fold thickness
Chen, 2004[168]	Prospective cohort	47,700 men 117,062 women	Baseline BMI; waist circumference; waist-hip ratio	Parkinson's risk not assoc. with BMI; inc. risk of Parkinson's with inc. waist circumference and waist-hip ratio in never-smokers only
Hu, 2006[169]	Prospective cohort	22,367 men 23,439 women	Baseline BMI	Inc. Parkinson's disease risk with inc. BMI in men and women

animals had higher levels of oxidative stress and inflammatory markers than control animals. Obese animals experienced a much greater decline in dopamine levels in the striatum than lean animals after MPTP exposure, even though the toxic metabolite of MPTP, MPP+, was present in equal amounts in the striatum of both groups. The authors concluded that the neurodegenerative effects of MPTP were enhanced by obesity.

Head Trauma

Studies examining head trauma as a risk factor for Parkinson's disease have produced inconsistent results, but here again, long latencies and other study design issues are challenging to address. Case-control studies can be limited by recall bias; that is, people with Parkinson's disease may be more likely than controls to recall past head trauma. Other variables may confound the relationship. For example, genetic makeup could influence risk-taking behavior or personality type, which might be related to head trauma risk. Yet, Parkinson's disease as an outcome of repeated head trauma, as in boxers, is well known.

At least two mechanisms other than direct injury to neurons in the substantia nigra could plausibly increase risk. The blood-brain barrier could be disrupted by head injury, allowing neurotoxic agents to gain access to the brain. Or, trauma could initiate an inflammatory response that does not fully resolve, ultimately resulting in clinically significant loss of dopaminergic neurons decades later.

Of nine published retrospective case-control studies, five showed a significantly positive association between past head trauma and Parkinson's disease, two showed a positive association that was not statistically significant, and two were negative.[170] [171] One prospective nested case-control study, in which the history of head trauma was obtained before the onset of symptoms of Parkinson's disease, found a four-fold increased risk.[172] A study of twins in which one had Parkinson's disease and one did not found that previous head trauma was positively associated with the disease, and the risk was greater with more severe or repeated trauma.[173]

Summary

Various combinations of genetic and environmental factors are likely to explain most cases of Parkinson's disease. Distinctions between classic Parkinson's disease and other forms of parkinsonism are not always clear. Loss of dopaminergic neurons and their influences on other neuronal circuits are responsible for the most commonly recognized motor features of Parkinson's disease. But the pathology of Parkinson's disease is not confined to the brain and, in fact, some of the earliest changes may begin completely outside of the central nervous system, long before clinical symptoms appear. A range of timeframes may precede the development of clinical symptoms, including neurotoxic insults as far back as early development.

Different mechanisms may reduce dopaminergic function in Parkinson's disease. Oxidative stress is a common finding but whether it is essential early in the development of Parkinson's disease or a later phenomenon following other triggers is uncertain. Nevertheless, virtually all environmental factors associated with increased risk also increase oxidative stress, to which the substantia nigra and its dopaminergic system are particularly vulnerable. Other relevant mechanisms include combinations of abnormal alpha-synuclein deposition, mitochondrial dysfunction, proteosome dysfunction, inflammation, and DNA damage. These mechanisms are not independent and unrelated. Rather, interactive, evolving feedback loops consisting of combinations of mechanisms are likely to influence the onset and progression of disease. Each of these mechanisms can be set in motion by environmental factors.

Table 3 lists Parkinson's disease risk factors discussed in this chapter. But, they do not exist in isolation. Most people experience them in interactive combinations. Their timing varies and impacts may be additive or synergistic, as described in the "multiple hit" model. Together they create conditions in which susceptibility is increased or decreased. For example, animal studies show that diet-induced obesity increases susceptibility to MPTP-induced neurodegeneration whereas an omega-3 fatty-acid enriched diet is protective. Prenatal exposures to maneb or lipopolysaccharide prime the brain to be much more susceptible to neurodegenerative damage from pesticides in adulthood.

Given the growing list of risk factors for Parkinson's disease and long latency periods between relevant exposures and clinical symptoms, studying them collectively becomes a nearly insurmount-

Table 3: Environmental risk factors for Parkinson's disease or parkinsonism discussed in this chapter*

Increased risk potential:

- Pesticides
- PCBs
- Solvents
- Dietary iron
- Manganese
- Lead
- Carbon monoxide
- Diet rich in dairy products
- Obesity
- Lipopolysaccharide
- Head trauma
- Air pollution
- Type-2 alkenes
- Infections

Decreased risk potential:

- Diet rich in polyunsaturated fatty acids
- Diet rich in antioxidants
- Diet rich in foods that raise uric acid levels
- Coffee drinking
- Cigarette smoking

**strength of evidence varies*

The pathology of Parkinson's disease is not confined to the brain and, in fact, some of the earliest changes may begin completely outside of the central nervous system, long before clinical symptoms appear.

able challenge. Imagine the difficuties inherent in studying the combined impacts of lifelong diet—including excessive dietary iron in infancy and adulthood, dairy products, or manganese from infant formula—and exposures to pesticides and air pollution. Although studies that try to identify single risk factors in multifactorial diseases are valuable, we must not expect them to be able to provide definitive proof of the role of individual factors in complex causal networks in genetically diverse populations of people. Single risk factors act in a complicated sea of conditions that increase or decrease overall susceptibility to Parkinson's disease, Alzheimer's disease, and the Western disease cluster generally. In the final chapter, we explore the option of a more comprehensive model of health and disease within which to consider decision-making intended to prevent environmental threats to healthy aging and promote individual and community health.

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