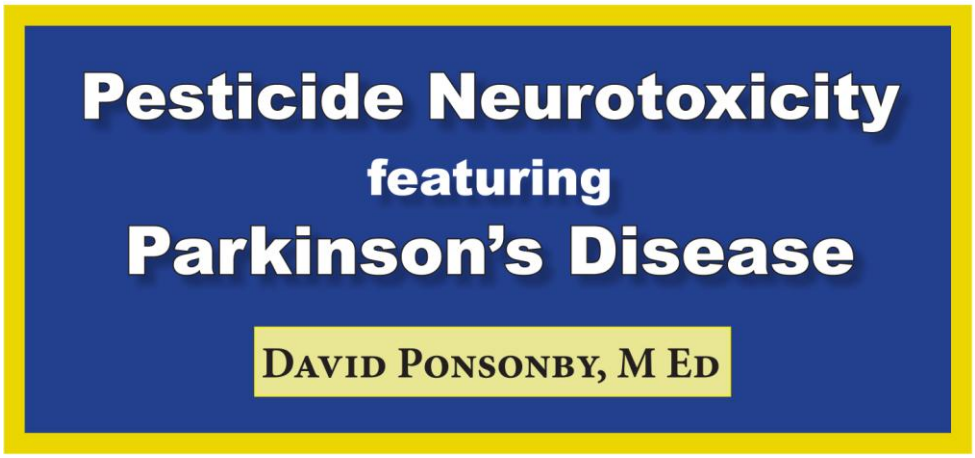

David Ponsonsby is a health educator residing in Carrollton, Texas. He developed a special interest in Parkinson's Disease (PD) after watching his late father struggle with the condition for 10 years. David felt helpless when prescription drug therapies did not reduce the tremors, or stop the progression of this degenerative disease. Fueled by the memory of his father's suffering, David has searched for answers on the cause of PD through a comprehensive review of the research. He offers a summary of one topic here. ***Note:*** *David's contact information is provided under "More Information" should you wish to follow-up.*

Foreword

We tend to think of pesticides (herbicides and insecticides, etc.) as modern solutions to age-old problems with weeds, insects, and other scourges that can impact farmers and, indeed, entire nations. Weiss has noted that almost every major pesticide acts by inducing neurotoxicity. (Weiss, 1983) Unfortunately, the weeds and insects have not been the only victims.

Many pesticides are watered-down versions of chemicals developed for use in wartime (e.g. sarin, soman, and tabun). DDT is a classic example; first introduced in 1942, it was banned, at least in the U.S., after 1987. Often the same companies that manufacture these chemicals also provide the pharmaceutical industry; indeed they may share the same corporate identity.

An association between chemicals and neurological symptoms has been recognized for some time. Carbon disulfide, a major component of fumigant mixtures, has been associated with neurologic symptoms in the rayon industry since the 1930s. (Peters, 1988) As a specific product of neurotoxicity, I am featuring Parkinson's disease in this paper. The condition has struck a number of public figures who have imprinted its symptoms on the public consciousness: Pope John, Muhammad Ali, Janet Reno, Billy Graham, and Michael J. Fox may spring readily to mind.

This is not to say that all neurotoxins are derived from pesticides, or that all neurotoxins produce PD. It is worth noting that toxins tend to produce irreversible Parkinsonism, whereas some drug-induced forms are reversible. (Langston, 1987) Several prescription drugs induce Parkinsonism. Drug-induced Parkinsonism is still common, under-recognized and treatable, examples being aripiprazole, metoclopramide, neuroleptics, olanzapine, risperidone and ziprasidone. (Esper, 2006*)* Reversible Parkinsonism has also been induced by prolonged (at least 4 years) treatment for seizures with valproate. Parkinsonism is sometimes reversible in less than 3 months after substitution of valproate with carbamazepine. (Onofrj, 1998)

Parkinsonian symptoms are sometimes seen during emergence from general anesthesia. (Muravchick, 1995) Anesthesiologists, themselves, have a significantly elevated risk for PD as an underlying cause of death. (Peretz)

PD holds a particular allure since, while it has been described for two centuries, its underlying cause (or causes?) still remain a mystery. It does run in some families but hereditary aspects have been summarized by Dr. Fernandez as simply: "about 5% of the general PD population is due to hereditary causes." (Fernandez, 2006) Also, the investigations into pesticides seem to be shedding some light on what lies behind the other 95%.

What is Parkinson's disease (PD)?

PD is a degenerative nervous system disorder that often starts with a barely noticeable tremor in a hand. The disorder can also cause a slowing or freezing of movement.

The two cardinal pathological features of PD are loss of dopaminergic neurons in the substantia nigra pars compacta and the presence of Lewy bodies in neurons in the substantia nigra and extranigral regions of the brain. So far as patients are concerned, there is a disadvantage to these features: they are only clearly evident at autopsy. The diagnosis is instead dependent upon the clinical skills of their neurologist. Yet from the perspective of a research scientist, these pathological features are wonderful because these cells can be visualized and quantified once the experimental animal models are sacrificed. The animals may also reflect changes in motor functions but parallels are limited.

Typically, Parkinson's disease (PD) is viewed as progressive, the product of many years of decline prior to becoming clinically evident.

Basically there is a threshold for the number of dopaminergic cells required for normal functioning. While some cell loss is normal, accelerated losses indicate an insult and/or dysfunction. It is said that we would all develop PD if we lived long enough. Thus, most people develop PD late in their lives, although some people are much younger: "Young Onset PD" (YOPD).

Victims may begin with fewer neurons or suffer a loss, or losses, through toxic insults, including pesticides or drugs etc.

The Historical Perspective of PD

In the West, a classic description of the *shaking palsy* was undertaken and published by Dr. James Parkinson just after the Napoleonic Wars. This has aroused a number of questions: When did PD first develop? Was it something that emerged with the Industrial Revolution in England? Why wasn't it described before?

Dr. Parkinson lived in London which was a teeming city even at that time. Even so, he only observed a handful of cases. Presumably, cases were so rare that no one had been able to tie together the common characteristics as a distinct disorder. Part of the scarcity may have been the lack of elderly people, especially out in the community once infirmity set-in.

Even up until the Great War few people developed PD. A major epidemiological study derives from the unique data set available at Massachusetts General Hospital from 1875. Between 1875 and 1915, a period of 40 years only 17 cases of Parkinson's syndrome were diagnosed (1 case every other year). By 1960 there had been 1,366 cases (c. 30 cases p.a.). (Poskanzer)

Postencephalitic Parkinsonism was identified after World War One in connection with several serious epidemics that initially produced *encephalitis lethargica* and eventually Parkinson-like symptoms in 40% of the survivors. It was this form of Parkinson's that Oliver Sacks dealt with during his pioneering efforts with Levodopa and captured for us in his book that was also made into a movie: "*Awakenings*."

The search for a common virus has been a failure but remains an intriguing possibility. A recent Canadian survey brought to light an informal observation that school teachers (2.5 times normal) and healthcare professionals (3.2 times the risk) were disproportionately represented. They hypothesized that these occupations are exposed to viral respiratory tract infections circulating in schools and healthcare facilities. (Tsui, 1999)

The Environmental Hypothesis

Or, to look at it another way, how do most people in any population avoid developing PD?

Many more people are exposed to environmental toxins than develop PD. Somehow, they have more resources, or greater tolerance, or perhaps the vulnerable lack something most other people have. One hypothesis surrounds the ability of the liver to detoxify. (Steventon) Only persons with an impaired ability to detoxify a particular toxin will progress to PD. (Tanner, 1991)

Sherry Rogers, MD, (who has experienced chemical sensitivities herself) notes that patients with PD may often show up to a 60% deficiency in their ability to detoxify. Impaired detoxification, together with nutrient deficiencies are common precipitating factors for Parkinson's and other diseases. (Rogers)

It has been confirmed that those with PD do have defective liver enzyme systems. (Tanner, 1991) The first enzyme (P450) was proposed by Barbeau in 1986. (Barbeau, 1986a) More than one P450 enzyme abnormality may be involved. (Ferrari) An extraordinarily high percentage of PD patients have very low activity levels of cysteine dioxygenase (Steventon) and thiolmethyltransferase (Waring), which are key hepatic enzymes in detoxifying and eliminating environmental toxins and xenobiotics. (Shen, X-M; 1996a)

Glutathione transferases (GST) metabolize xenobiotics, including pesticides. Therefore, GST polymorphisms have been examined to see if they played a role in the pathogenesis of idiopathic PD.

GSTP1-1, which is expressed in the blood-brain barrier, may influence response to neurotoxins - an inability to detoxify them - and explain the susceptibility of some people to the Parkinsonism-inducing effects of pesticides. (Menegon, 1998) This defect may also explain why some people with PD also experience colon cancer. (Chenevix-Trench 1997)

GSH depletion, leading to oxidative damage and subsequent mitochondrial dysfunction, may serve as a trigger for neuronal cell death. (Tukov, 2004)

An association has been found in the CYP2D6 gene (this gene encodes for the enzyme debrisoquine hydroxylase which metabolizes several xenobiotics including MPTP, the herbicide atrazine and organophosphate pesticides).

The Toxic Connection

The present search is for a toxin (or toxins) that is toxic to some people, probably owing to a defect that may be inherited or acquired, which affects their ability to detoxify the substance(s).

Major exogenous toxins that affect us include: (After Stacy, 1996b)

- Alcohol withdrawal
- Amphetamines
- Bacteria: streptococcus, staphylococcus, salmonella (food poisoning)
- Carbon disulfide
- Carbon monoxide (Ringel)
- Coffee, tobacco, alcohol, sugar, food preservatives
- Cyanide
- Drinking water
- Heavy metals: mercury, aluminum, lead, cadmium
- Hydrocarbons
- Lithium
- Manganese (Mena)
- Mercury
- Heavy Metals
- Parasites
- Pesticides
- Smog and petrochemicals
- Viruses: Epstein-Barr, influenza, cytomegalovirus, herpes, HIV

A toxin model of PD has been propsed since the 1970s (Heikkila, 1971) but gained impetus from an infamous cluster of PD cases caused by intravenous injection of a compound (MPTP) by narcotics addicts. (Langston, 1983)

The neurotoxicity of MPTP was discovered in 1976 after Barry Kidston, a 23-year-old chemistry graduate student in Maryland, synthesized MPPP incorrectly and injected the result. It was contaminated with MPTP, and within three days he began exhibiting symptoms of PD. The National Institute of Mental Health found traces of MPTP in his lab and eventually discovered its effects by testing the chemical on rats.

The compound is often referred to as 1-methyl-1,2,4,6-tetrahydropyridine (MPTP). In fact, the toxic component is 1-methyl-4-phenylpyridinium ion (MPP+). Researchers have identified endogenous MPP+ analogs in the lumbar cerebrospinal fluid of patients with PD that mirrors MPP+ in mitochondrial toxicity.

We must not overlook that conjugates of dopamine itself (e.g. cysteinyldopamines and a number of dihydrobenzothiazines and benzothiazines) can be toxic (i.e. endotoxins) that

contribute to substantia nigral cell death and other neuronal damage that occurs in PD. (Shen, X, 1996a)

The dopaminergic neurotoxin, 1(R), 2(N)-dimethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline, N-methyl(R)salsolinol, and its oxidation product, 1,2(N)-dimethyl-6,7-dihydroxyisoquinolinium ion, accumulate in the nigro-striatal system of the human brain. (Maruyama*, 1997)*

A dopamine-derived neurotoxin, (R)-N-methylsalsolinol, was found to be increased significantly in the cerebrospinal fluid of untreated patients with PD. (R)-N-methylsalsolinol is selective to dopamine neurons and induces Parkinsonism in rats, (Maruyama, 1996)

Neurotoxic Plants

Epidemics of neurotoxic disease in developing regions of the world are often associated with dietary dependence on plant components with inherent toxic potential or which have spoiled and become contaminated with mycotoxins. (Spencer, 1993)

The neurotoxic cycad plant is thought to have a role in the etiology of western Pacific (e.g. Guam, New Guinea, Indonesia and Japan) amyotrophic lateral sclerosis (ALS) and Parkinsonism-dementia. (Spencer, 1993) Basically, most islanders (70% by 35 years of age) would have neurodegeneration equivalent to 75 year old Americans. Neurofibrillary tangles comparable to Alzheimer's disease are classic features of Guam Parkinson-Dementia/Amyotrophic Lateral Sclerosis. (Spencer, 1991) This was eventually linked to the diet, specifically, a flour made from cycad seed, from the false sago palm (Cycas circinalis). (Whiting) It was also used in folk medicine. Indeed, recent reports indicate that the toxin may have built up in another food source, flying foxes, which forage on cycad seeds. (Cox, 2002)

Other diseases triggered by plant toxins include lathyrism and cassavism, types of irreversible spastic parapareses associated with staple diets of grass pea and bitter cassava root, respectively. (Spencer, 1993)

Mildewed (i.e. a fungal toxin) sugarcane poisoning produces an encephalopathy and tardive dystonia. (Spencer, 1993)

Some "weak" neurotoxins are present in less exotic foods [e.g. harman and nonharman (Kuhn, 1996c) including: bananas, beef, cheese, cocoa, eggs, and milk].

Pesticides

Aside from toxic, or tainted, food supplies, in parts of the developing world, pesticide poisoning causes more deaths than infectious diseases. Use of pesticides is poorly regulated and often dangerous; their easy availability also makes them a popular method of self-harm. (Eddleston, 2002)

Pesticides are a broad range of substances most commonly used to control insects, weeds, and fungi (plant diseases). They are frequently classified by target organism, or mode of use, as: insecticides, herbicides, fungicides, or fumigants. (Kamel, 2004) There may also be pesticides and rodenticides; herbicides are also commonly known as "weedkillers". Fungicides may also be referred to as "biocides."

PD is progressive, even after occupational exposure has ceased. (Hageman, 1998)

Some mycotoxins have been developed as biological and chemical warfare agents and have probably been deployed by Iraq during the first Gulf War. Ochratoxin-A (OTA) is a common mycotoxin, similar to that of the aflatoxins. It is possible that low dose exposure to OTA will result in an earlier onset of Parkinsonism when normal age-dependent decline in striatal dopamine levels are superimposed on the mycotoxin-induced lesion. (Sava, 2006)

PD is progressive, even after occupational exposure has ceased. (Hageman, 1998)

Insecticides are often subclassified by chemical type as: organophosphates (OPs), organochlorines, carbamates, and pyrethroids. (Kamel, 2004) From a list of a couple of dozen major pesticides, 19 have been classified as neurotoxins. Atrazine, for example, affects dopamine. (Das, 2001)

Airborne chlorinated pesticides are now ubiquitous, resulting in a broad public exposure to potentially hazardous materials. By 1980, over 400 synthetic chemicals had been identified in human tissue. The main involvements were blood, breast milk, liver, and nervous tissue. (US Environmental Protection Agency [EPA], Washington, DC. Chemicals Identified in Human Biological Media, EPA 560113-80-036B, PB81-161-176, 1980.)

In the U.S., more than 18,000 products are licensed for use, and each year more than 2 billion pounds of pesticides are applied to crops, homes, schools, parks, and forests (EPA Office of Pesticide Programs 2002). Such widespread use results in pervasive human exposure. (Kamel, 2004) California growers use approximately 250 million pounds of pesticides annually, about a quarter of all pesticides used in the US. (Ritz, 2000) In fact, there is increased PD mortality in California counties using agricultural pesticides. (Ritz, 2000)

One elusive aspect of neurotoxicity has been catching the process in the early stages, or recognizing that neurotoxicity has occurred. There have been some promising developments.

The measurement of prolactin may provide early identification of excess exposure to neurotoxic chemicals affecting dopaminergic control of pituitary secretion. (Mutti, 1988a)

Increased serum prolactin is a common finding among subjects exposed to styrene, perchloroethylene, lead (Pb), and manganese (Mn) at levels below the current threshold limit values. (Mutti, 1988a) [Perchloroethylene - is used at dry cleaners; styrene exposure is associated with the plastics industries.] Plasma prolactin appears to be a sensitive marker of styrene-induced tubero-infundibular dopaminergic dysfunction in male subjects. (Bergamaschi, 1997)

Epidemiological risk factor analyses of typical PD cases have identified several neurotoxicants, including MPP(+) (the active metabolite of MPTP), paraquat, dieldrin, manganese and salsolinol. (Chun, 2001)

Carbon Disulfide

Chlorpyrifos and terbutaline

Dieldrin

Hydrocarbons

Solvents: Carbon disulfide; *n*-hexane; methanol (a constituent in formaldehyde and lacquer thinner); toluene (monomethylbenzene) (a constituent in lacquer thinner); xylene.

Lipopolysaccaride (LPS)

Maneb (Manganese)

Organochlorine insecticides E.g. :Aldrin; Chlordane; DDT; Heptachlor; Lindane; Methoxychlor; Mirex; Toxaphene.
Organophosphates

PCBs

Paraquat

Radon

Rotenone

Carbon Disulfide

Carbon disulfide is used in agriculture as a fumigant and fungicide. A recent report cites carbon disulfide used in grain storage for the high incidence of Parkinsonism among

agricultural workers. (Peters, 1986 and 1988) However, carbon disulfide's effects aren't sufficiently narrow to even provide a useful model of PD, never mind constituting a likely candidate as an etiologic agent for PD, in general. (Langston, 1987) return to top of list

Chlorpyrifos and **terbutaline**

Given the common use of terbutaline in the therapy of preterm labor and the nearly ubiquitous exposure of the human population to organophosphorus pesticides, the combined oxidative burden of exposure to both agents was examined in an animal model. Worsened neurodevelopmental outcomes were duly noted in the animals. (Slotkin, 2005) Once again, we see a sequence of events, including dual exposures to chemicals, working via their shared potential to elicit oxidative stress and culminating in neurotoxicity.

The text, itself, however, reveals a robust increase in oxidation from Chlorpyrifos was obtained in the forebrain and cerebellum, restricted to males. Males were also impacted differently with terbutaline. As he puts it: "There is a sex-selectivity for oxidative stress, males > females, which matches the consequent morphological, neurochemical and behavioral susceptibilities." (Slotkin, 2005)

It has been shown in an animal study that if the mother is exposed to pesticides (atrazine) while she is lactating, the male pups will develop prostatitis after they mature. (Stoker) Prostatitis involves infection and inflammation, two factors that have been postulated as contributory factors in the development of PD. return to top of list

Dieldrin

One particular degenerating pesticide is called dieldrin. Dieldrin was first synthesized in 1946 and sold widely in the United States between 1950 and the mid-1970s. The popular pesticide was used for the treatment of seeds and to control soil pests like termites, grasshoppers, locusts and beetles. It is a lipid-soluble, long-lasting mitochondrial poison. (Fleming, 1994)

The EPA restricted the use of Dieldrin in 1974 because of the harmful effects but permitted its use mainly for termite control until 1987.

Although Dieldrin is no longer produced in the United States, it is still used in several developing countries around the world, leaving people open to exposure. Dieldrin was found to be the most abundant pesticide in tested river sediments during an epidemiological study recently conducted in Taiwan.

The half-life of Dieldrin in the environment is more than 50 years, Kanthasamy said: "With such continued use in some countries and its ability to accumulate, there is no telling when, if ever, the pesticide will be gone from the Earth."

- Dieldrin may be ubiquitous in the environment. (Sanchez-Ramos, 1998)
- Dieldrin can be retained for decades in lipid-rich tissue and has been measured in some postmortem PD brains. (Sanchez-Ramos, 1998)
- Dieldrin is a relatively selective dopaminergic neurotoxin in mesencephalic cultures. (Sanchez-Ramos, 1998)
- Dieldrin can initiate and promote dopaminergic neurodegeneration in susceptible individuals. (Sanchez-Ramos, 1998)

Dieldrin ... should be investigated as a potential etiological agent of Parkinsonism. (Fleming, 1994) return to top of list

Hydrocarbons

Hydrocarbons are present in glue, paint, rubber and petroleum derivatives (gasoline, solvents etc.) The most important solvents with respect to Parkinsonism are: methanol, toluene, carbon disulfide and n-hexane. (Hageman, 1998) Anyone occupationally exposed to hydrocarbons might be at risk for PD. This connection has been studied in Italy. (Pezzoli, 2000)

Methylcyclopentadienyl manganese tricarbonyl (MMT) is an organic manganese (Mn) compound added to unleaded gasoline. The combustion products of MMT containing Mn, such as manganese phosphate, could cause neurological symptoms similar to PD in humans. Animal studies have confirmed that such inhalation results in manganese deposition in the following brain regions: olfactory bulb and caudate/putamen. (Normandin)

The organochlorine insecticide 1,2,3,4,5,6-hexachlorocyclohexane (lindane) but not 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane (DDT) augments the nocturnal increase in pineal Nacetyltransferase activity and pineal and serum melatonin levels. (Attia)

Hydrocarbon solvent exposure proved to be a risk factor for earlier onset of PD symptoms as well as for more severe disease progression. Confirmatory and further studies are recommended. (Pezzoli, 2000)

A pre-publication report in the Dalla Area Parkinsonism Society (DAPS, October, 2007) from Dr. German at UTSW notes that people with PD (or PWPs) have ten times more organochlorine pesticide levels than controls (beta-hexachlorocyclohexane). return to top of list

Solvents

At least three solvents have generally been implicated: carbon disulfide, *n*-hexane, and methanol, have neurotoxic properties that give rise to Parkinsonism with corticospinal signs. (Tanner, 1992b) The most important solvents have been listed: (Hageman)

- Carbon disulfide
- *n*-hexane
- methanol*
- toluene* (monomethylbenzene)
- xylene (neuropsychiatric symptoms but not Parkinsonism)

* Methanol and toluene, together with ethylacetate and methylethylketone constitute lacquer thinner. Methanol is also a constituent in formaldehyde. (Hageman)

Intriguingly, "I believe that tetanus vaccine is the most neurotoxic of ALL vaccines. Tetanus toxin (tetanospasmin) is made by deactivating it with formaldehyde and ammonium sulfate. It is filtered and adsorbed onto aluminum phosphate. Tetanospasmin is one of the strongest neurotoxins known to man." (Dr Sherri Tenpenny e-mail post, February 2008)

One case history was reported from Italy: a 55-year-old male Parkinsonian patient reported chronic exposure to *n*-hexane for 17 years. (Vanacore, 2000)

Toluene (or monomethylbenzene) is present in numerous adhesives, cleaners, gasoline, glues, inks, lacquers and paints. (Hageman) A specific toluene encephalopathy has been described. (Knox) Toluene is a very well known industrial chemical. In vivo it is oxidized to benzoic acid and was therefore regarded - back in the 50's and 60's - as far less toxic than benzene.

Specifically, after exposing rabbits to a variety of chemicals, ethylbenzene, styrene and vinyltoluene caused a marked depletion of striatal and tubero-infundibular dopamine. (Mutti, 1988a)

Styrene and toluene are common examples of aromatic hydrocarbons. Styrene exposure during the gestation-lactation period (200 mg/kg, orally) affected dopamine receptor binding, causing a significant increase in motor activity and stereotypy of rat pups. (Zaidi)

One case is on record for the development of Parkinsonism after daily exposure, for at least 9 months, to lacquer thinner. (Uitti, 1994)

A Dutch study reported 3 painters, who developed Parkinsonism after occupational exposure to various solvents for more than 20 years. (Hageman)

There are also several anecdotes on the *askthedoctor* PD forum concerning photographers who developed PD given exposure to developer, containing toluene. Specifically, in a reader's response, with regard to Polaroid's formula.

Another case report consisted of the accidental ingestion of a petroleum waste mixture. (Tetrud, 1994) return to top of list

Lipopolysaccaride (LPS)

Niehaus (2003) suggests that besides pesticides, endotoxin (lipopolysaccaride, LPS) may also be an environmental neurotoxin capable of producing PD. Endotoxin is a common airborne environmental and occupational contaminate in agricultural (Olenchock, 1990) and other industries. (Thorn, 2002; Enterline, 1985)

Endotoxins are part of the outer cell wall of Gram negative bacteria. (Rietschel, 1992)

The case event of PD is supported by animal experimentation. (Castano, 2002) Several animal studies (Herrera, 2000; Liu, 2000; and Castano, 2002) have shown that LPS causes damage to the substantia nigra, resulting in PD. These animal investigations support the hypothesis that LPS may be one of the environmental factors that trigger PD.

It is suggested that LPS is one of the causes for postencephalitic Parkinsonism after encephalitis from Gram negative bacteria. Further investigation of this potential environmental factor is warranted.

Pezzoli reported reported two cases of Parkinsonism from being exposed to n-hexane. N-Hexane, similar hydrocarbons and derivatives, are by-products of lipid peroxidation and may have a nigrotoxic effect like that of MPTP. (Pezzoli, 1995) return to top of list

Maneb

Fungicide / Biocide - Maneb (manganese ethylene-bis-dithiocarbamate)

Permanent Parkinsonism has been recorded in two men with chronic exposure to the fungicide maneb (manganese ethylene-bis-dithiocarbamate).

Manganese is a well-known Parkinson-igen toxin in humans. More recently, it has been shown that dithiocarbamates can also induce extrapyramidal syndromes. (Meco, 1994)

The major lesson from Maneb studies is that its combined effect with paraquat is much greater than either product, separately. A team, led by Dr. Deborah Cory-Slechta, (University of Rochester School of Medicine and Dentistry) studied the effects of a mixture of two very common agrichemicals, the herbicide paraquat and the fungicide maneb. Each is used by farmers on millions of acres in the United States: maneb is

applied widely on such crops as potatoes, tomatoes, lettuce, and corn, while paraquat is used on corn, soybeans, cotton, fruit, and a variety of other products. (Cory-Slechta, 2005)

In the experiment, mice exposed to either chemical had little or no brain damage but mice exposed to both mimic the very early stages of PD: though they appeared healthy, key brain cells known as dopamine neurons were dying. The mice exposed to the mixture carried nearly all of the molecular hallmarks of PD as seen in humans.

The environmental reality, Dr. Cory-Slechta points out, is that pesticides are not used in isolation from one another: “In the real world, we're exposed to mixtures of chemicals every day. There are thousands upon thousands of combinations; I think what we have found is the tip of the iceberg,” she said. “There are a dozen different fungicides related to maneb alone. I don't think we just happened to pick the right chemicals to see such an effect.”

Particulary potent may be the exposure to paraquat during the neonatal period. Combined environmental exposure to paraquat and neonatal iron, results in accelerated age-related degeneration of nigrostriatal dopaminergic neurons. (Peng, J) return to top of list

Organophosphates

Atrazine

Atrazine is one of the top two herbicides in the US. A member of the triazene family, it is primarily used on corn and fruits (citrus, pineapple). Atrazine is a neurotoxin and alters the production of dopamine and norepinephrine that, in turn, alters hormone levels (prolactin and luteinizing hormones). (Cox, C; 2001)

Diazinon

Diazinon should have been phased out during 2003 but since it is stored in fat, those who have been exposed will experience slow-release toxicity. (Reigart)

Dursban (chlorpyrifos) – toxic.
Malathion
Parathion - highly toxic.
Ronnel
TEPP (tetra-ethyl-pyro-phosphate) – most toxic.
Vapona

Organophosphates have replaced organochlorine insecticides to become the most common ingredient. The most notorious organochlorine is DDT. Organophosphates are now the most commonly used insecticides in the world.

Organophosphates, like Diazinon and methyl parathion, are indirect acting cholinomimetics, affecting the acetyl cholinesterase enzyme (AChE). Excess AChE at skeletal muscle junctions causes muscle twitching. Effector organs become over-stimulated. (Williams, MA, 2002)

Pesticides of the organophosphate and carbamate types act to paralyze and kill insects by inhibiting their acetylcholinesterase. [*N.B. Acetylcholinesterase:* Abbreviated AChE.]

Acetylcholinesterase is an enzyme that breaks down the neurotransmitter acetylcholine at the synaptic cleft (the space between two nerve cells) so the next nerve impulse can be transmitted across the synaptic gap. return to top of list

PCBs

Polychlorinated biphenyls (PCBs) and mercury together (as in fresh water fish) are much more potent in decreasing dopamine than if they were separate. (Seegal, 2000) There is an exception to every rule: In utero and lactational exposure to 3,4,3',4'-TCB resulted in significant elevations in concentrations of dopamine in the frontal cortex, and of dopamine and its metabolites in the substantia nigra that persisted into adulthood. (Seegal, 1997) Also, Females appear more sensitive than males to the neurochemical effects of PCB 28. (Chu et al, 1996)

Unfortunately, both increases and decreases in brain DA concentrations induce deficits in working memory. (Seegal et al, 1998)

How do PCB's affect dopamine metabolism?

PCBs inhibit two enzymes (tyrosine hydroxylase and L-aromatic amino acid decarboxylase) that are involved in dopamine synthesis. (Guarisco et al, 1999) One dose of modest PCB levels during pregnancy permanently effects dopamine regulation in the offspring. (Sauer et al, 1994)

Disappointiongly, once the changes are initiated, dopamine dysfunctions persist even when PCBs are no longer found in the brain – presumably, having been detoxified, or at least, reduced to a level beyond detection. Ortho-substituted PCBs are also neuroteratogens**.** (Seegal, 1992)

On a cautionary note, many animal studies of PCB toxicity used virgin commercial mixtures of PCBs called by their tradename: "Aroclor". These mixtures do not reflect the 209 kinds of individual PCB types. Also, they were usually purified of dioxin or furan contaminants. Thus, the researchers were testing a PCB mix very different from the highly toxic mixture in the real world that actually accumulates in fish. This could lead to serious underestimates of the true human health effects of PCBs, plus dioxins and furans.

PCBs were used between 1929 and 1971. The “Baby Boomers” of course, therefore were exposed throughout their critical *in utero* and childhood years. Many environmentalists are expecting a surge in PD as this group ages. The first wave has just turned 60.

[N.B. Children may be 10 times more vulnerable to chemical toxicities than adults. *Pesticides in Diets of Infants and Children.* National Research Council. Washington D.C.: National Academy Press, 1993.] return to top of list

Paraquat

Paraquat is the trade name for *N,N'-Dimethyl-4,4'-bipyridinium dichloride*, a quaternary ammonium herbicide. Other members of this class include diquat, cyperquat, diethamquat, difenzoquat and morfamquat. All of these are easily reduced to the radical anion, which in turn generates superoxide radical that reacts with unsaturated membrane lipids.

Paraquat (PQ; 1, 1'-dimethyl-4, 4'-bipyridinium), a widely used herbicide that is structurally similar to the known dopaminergic neurotoxicant MPTP (1-methyl-1, 2, 3, 6-tetrahydropyridine), has been suggested as a potential etiologic factor for the development of PD (PD). Paraquat has been one of the world’s most popular weed killers for decades.

Despite the apparent structural similarity to MPP+, paraquat exerts its deleterious effects on dopamine neurons differently than rotenone or MPTP. MPP+ is transported into dopamine neurons through the dopamine transporter, while rotenone is not. Rotenone produces complex I inhibition and oxidative damage. (Richardson, 2005) Thus, while their effects may be similar, their pathways are different.

Paraquat was introduced in 1962. In 1994 there were 175 recorded exposures and 4 deaths. It acts to interfere with the intracellular electron transfer systems in the plant. So, ingestion of paraquat leads to the formation of free radicals (superoxide, singlet oxygen, hydroxyl and peroxide radicals) which cause lipid peroxidation damaging cell membranes leading to cell death. It is rapidly taken up by the lungs and kidneys. Antidotes are listed as: vitamin E, selenium, thiosulfate and superoxide dismutase (SOD).

Focusing on paraquat, by itself, ignores the extensive geographical overlap of its use with other agrichemicals known to adversely impact dopamine systems, including ethylenebisdithiocarbamate fungicides such as maneb. (Thiruchelvam, 2000a)

The fact that combined exposures result in potentiated effects suggests that these combinations may be important environmental risk factors for Parkinsonism. (Thiruchelvam, 2000a) The nigrostriatal dopaminergic system is a preferential target of repeated exposures to combined paraquat and maneb that tend to occur seasonally on a perennial basis. (Thiruchelvam, 2000b)

When is the exposure critical? Spreading the fertilizer as an adult; breathing in overspray as a child; or being subjected to in utero or breastfeeding exposures with a toxic mother?

Thus, paraquat (PQ) and maneb (MB) exposure during critical periods of development could permanently change the nigrostriatal dopamine (DA) system and enhance its vulnerability to subsequent neurotoxicant challenges. (Thiruchelvam, 2002) Each insult would render the subject more vulnerable to each subsequent neurotoxicant challenge and ever closer to the threshold for Parkinsonism.

Findings indicated that exposure to pesticides during the post natal period can produce permanent and progressive lesions of the nigrostriatal dopamine system, as well as enhanced adult susceptibility to these pesticides. (Thiruchelvam, 2002)

Bentonite can absorb pathogenic viruses, aflatoxin (a mold), and pesticides and herbicides including Paraquat and Roundup. The clay is eventually eliminated from the body with the toxins bound to its multiple surfaces. [Lipson, *Canadian Journal of Microbiology* (31 [1985], 50-53.)

"While there are the caveats we discussed at the end of our paper such as chronic exposure, co-exposure with other chemicals, compromised BBB, etc., we found that paraquat is unable to enter the primate brain under the conditions of our acute study in middle-aged monkeys. We recently completed a similar study in pregnant monkeys and found the same minimal uptake in the brains of both mother and fetus." (Onofre T. DeJesus, Professor of Medical Physics; personal communication) return to top of list

Radon

Interestingly, in his consideration of possible causes, Charcot suggested damp cold in a badly ventilated apartment, or ground floor dwelling. This could be interpolated to refer to carbon monoxide (Mulhearn) or even radon.

Intriguingly, in rural India and industrialized England, poorly ventilated fires can also produce carbon monoxide. (Hutton)

Radon is one item that has existed prior to industrialization. Radon is an ubiquitous noble gas in the environment and a primary source of harmful radiation exposure for humans; it decays in a cascade of *daughters* by releasing the cell damaging high energy alpha particles. (Momcilovic, 2006) According to the WHO, there is approximately 39 Bq/m3 in the air we breathe.

210Po and 210Bi radioactivity increased tenfold in the cortical grey and subcortical white lipid fraction in patients with PD. (Momcilovic, 1999)

Paradoxically, smoking (which usually rates as negative, or inversely correlated with PD) strongly increases radon daughter retention in the central nervous system. (Momcilovic, 2001) return to top of list

Rotenone

Rotenone is frequently mentioned. It is a naturally occurring toxin and a commonly used pesticide, insecticide and piscicide (poisonous to fish). Rotenone is extracted from the dried roots, seeds and leaves of various tropical plants, including the Jewel vine, derris and hoary pea. It is highly toxic to birds and fish but conventional thought regards it as non-toxic to humans at normal doses.

Rotenone is found in 680 compounds marketed as organic garden pesticides and flea powders, said Dr. Caroline Tanner, director of clinical research at the Parkinson's Institute in California. It is often sold as a white powder that is dusted onto roses, tomatoes, pears, apples and African violets, and even on household pets.

Because rotenone is naturally occurring, it is advertised as being safer than synthetic pesticides. In addition, unlike many artificial pesticides, which linger in the environment, rotenone breaks down in five to six days of spring sunlight, or two to three days of summer sunlight.

Rotenone causes nigrostriatal degeneration similar to Parkinson disease pathology in a chronic, systemic, in vivo rodent model (Testa, 2005)

Data indicate that rotenone is not capable of causing overt dopaminergic toxicity. Rather, an increase in dopamine turnover, as indicated by a higher (DOPAC+HVA)/DA ratio, [dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA)] seems to be associated with rotenone-induced striatal energy impairment. (Thiffault, 2000) Rotenone is also a complex I inhibitor. (Testa, 2005)

Chronic systemic complex I inhibition caused by rotenone exposure induces features of PD (PD) in rats, including selective nigrostriatal dopaminergic degeneration and formation of ubiquitin- and alpha-synuclein-positive inclusions (Betarbet et al., 2000).

PD involves intracellular deposits of alpha-synuclein in the form of Lewy bodies and Lewy neurites. One study shows that several hydrophobic pesticides (including rotenone, dieldrin and paraquat) induce a conformational change in alpha-synuclein and significantly accelerate the rate of formation of alpha-synuclein fibrils in vitro. (Uversky, 2001)

A pharmacological model of reduced complex I activity can be created by prolonged treatment of neuroblastoma cells with low doses of rotenone, a selective inhibitor of complex I. (Sherer, 2001a)

Chronic low-grade complex I inhibition caused by in vitro rotenone exposure induced accumulation and aggregation of alpha-synuclein and ubiquitin, progressive oxidative damage and cell death, mechanisms that may be central to PD pathogenesis. (Sherer, 2002) In vitro this all took place within 4 weeks.

Folate deficiency has also been implicated in the vulnerability to rotenone and MPTP via elevated homocysteine levels. (Duan, 2002)

Exposure of rats to the pesticide and complex I inhibitor rotenone reproduces central features of PD, including: selective nigrostriatal dopaminergic degeneration and alpha-synuclein-positive cytoplasmic inclusions. (Betarbet et al., 2000; Sherer et al., 2003b)

A new protocol was recently established for chronic rotenone administration. Essentially, subcutaneous rotenone exposure caused alpha-synuclein-positive cytoplasmic aggregates in nigral neurons. (Sherer, 2003b)

Like MPTP, rotenone is highly lipophilic and thus readily gains access to all organs including the brain. However, because of its short half-life and that it does not readily leach from soil, it is not expected to be a groundwater pollutant. Consequently, the likelihood of PD being caused directly by an environmental exposure to rotenone is considered to be low, even null. (Bove, 2005)

Nevertheless, Dr. John Trojanowski, an expert on neurodegenerative diseases at the University of Pennsylvania School of Medicine, has called rotenone: “The best model we have ever had for this disease being associated with an environmental agent.”

Although these candidates have been treated under individual headings, the findings of synergy from certain combinations also raises questions about the adequacy of current risk assessment guidelines for these chemicals which are based on effect levels derived from exposures to single agents. (Thiruchelvam, 2000a) return to top of list

How much gets into our food?

In a recent report, the Pesticide Residues Committee said that 1.7 percent of 3,787 food items tested in the U.K. exceeded the legal limits for pesticide content, and 30.2 percent contained traces within the legal limits. (Pesticide Residues Committee Report)

A person can consume Dieldrin while eating meat, dairy products, or (as with PCBs and mercury) consuming fish or shellfish from contaminated waters. Dieldrin also accumulates in the body, storing itself in the body’s fat and leaving very slowly.

Milk intake is associated with an increased risk of Parkinson disease. It is not known whether this is due to neurotoxic contaminants in milk, and further study is warranted. (Park, 2005b)

See this chart for a database of select foods common pesticide levels from the Environmental Working Group.

Are legal limits also safe limits?

This is a debatable question.

In 1985, the UN Food and Agriculture Organisation (FAO) produced a voluntary code of conduct for the pesticide industry in an attempt to limit the harmful effects of pesticides. (Eddleston, 2002)

Exposure is usually occupational, or accidental. Either you are involved in spraying such chemicals, (Dvais, 1978) even as a home gardener; or you happen to be close by when such chemicals are sprayed. Typically, chemicals may drift a short distance on the wind, especially when sprayed from the air by planes or helicopters. (Ames, 1993) Many individuals are frequently exposed to many different pesticides, or mixtures of pesticides, either simultaneously, or serially. (Kamel, 2004)

Nine blue-collar occupations in Italy accounted for 91% of exposures to hydrocarbon solvents. (Pezzoli, 2000) Clinical expression is more severe in PD patients with previous high degree solvent exposure because of the associated post-synaptic damage of the nigro-striatal pathway. (Rango, 2006) Thus a specific physiological change has been identified in this group of Italian patients.

Occupations that account for 91% of hydrocarbon exposures. (After Pezzoli, 2000)

- Chemists;
- Farmers;
- Leather workers;
- Motor mechanics;
- Petroleum, plastic, or rubber workers;
- Painters, lacquerers, furniture workers;
- Refrigeration workers;
- Textile workers, weavers;
- Typographers, lithographers;

Genetic or acquired defects

PD patients may be unusually susceptible to exogenous, or even endogenous, toxins. Most PD patients (70%) excrete less than 5% of an acetaminophen dose as the sulfate conjugate; the corresponding figure for controls is 84%. This suggests a deficiency in detoxication pathways involving sulfur metabolism. (Steventon, 1989)

A 'significant minority' of patients express problems in sulphur biotransformation pathways. (Steventon, 2003)

- 40% of patients with Parkinson's have a defect in the S-oxidation of S-carboxymethyl-L-cysteine (4% of controls)
- 35-40% of patients with Parkinson's have a defect in the sulphation of paracetamol (4% of controls)
- 38% of patients with PD have a low capacity for the S-methylation of 2-mercaptoethanol (4% of controls)
- The relation between *GSTP1* and onset age is modified by herbicide exposure. (Wilk)
- Three single-nucleotide polymorphisms (SNPs) were associated with PD onset age in the group of men occupationally exposed to herbicides. Three additional SNPs had significant trends for the association of PD onset age across the herbicide exposure groups. (Wilk)
- genetic variation in the CYP2D6 gene (for the enzyme debrisoquine hydroxylase which metabolizes several xenobiotics including MPTP)

Thiolmethyltransferase activity is indicative of S-Methylation. In Parkinsonian patients, mean thiolmethyltransferase activity was low (300 U/mg protein) compared with that in controls (947 U/mg protein). (Waring, 1989)

A progressive impairment of mitochondrial function has been suggested to play a critical role in the pathogenesis of several neurodegenerative diseases, including PD, Alzheimer's disease and Huntington's disease. Including:

- impaired calcium buffering, (Albers)
- generation of free radicals, (Albers)
- activation of the mitochondrial permeability transition pore (Albers)
- secondary excitotoxicity (Albers)

Probable etiological factors in the disease require: (Head/Kidd)

- genetic susceptibility,
- acute toxic exposure (e.g. MPTP)
- chronic toxic exposure (e.g. pesticides like Rotenone and mercury),
- a deficiency in detoxication pathways (Steventon, 1989)
- oxidation overload
- an inadequate antioxidant defense system, and
- lack of dietary/supplemental antioxidant nutrients (e.g. glutathione, lipoic acid and NAC).

Rural Environment?

Attention has re-focused on environmental toxicants in the disease etiology, particularly agrichemicals. (Barlow) Unfortunately, while numerous toxins have been proposed as a cause of PD few have been confirmed. Those that have been identified only cause a PD-like disorder in a minority of the people exposed. So there appears to be interdependence as well. Interactions between genetic susceptibilities and environmental exposures are the focus of current research regarding the cause of idiopathic PD. (Firestone)

The first observation of a correlation between early age exposure to rural environment (and drinking well water) and development of idiopathic PD dates back to 1984. These findings were subsequently confirmed elsewhere (Barbeau, 1985; 25 Tanner, 1985).

Unfortunately, while well water is probably a vehicle for the agent responsible, neither water metal concentration nor any of the herbicides and pesticides used in Saskatchewan agriculture could be confirmed. (Rajput, 1986) In a follow-up study, there was no discernible difference in the metal composition of the well water for any of 23 metals evaluated, including 7 elements implicated in the etiology of PD. (Rajput, 1987a)

Patients with early-onset Parkinson's are likely to have drunk well water and lived in a rural environment. (Rajput, 1987) In a study of kibbutzim in Israel, the incidence of PD quintupled (500%) in relation to communities using a different aquifer. (Goldsmith)

Living in a rural environment and drinking well water are risk factors for PD. (Wong, 1991)

In another Canadian study, heavy pesticide use raised the incidence of PD seven-fold (700%). (Barbeau, 1986a) Pesticide and herbicide users ranged up to 3.2 times more susceptible. [Kanthasamy, 2002]

Farming, together with herbicide and pesticide use may be the key factors. (Koller, 1990) Specifically, farmers ranged up to 5.2 times more susceptible to PD. A consistent pattern of high PD morbidity is found among occupational groups employed in agriculture and horticulture. (Tüchsen, 2000)

PD appears to be less common in countries more recently industrialized. Studies using antiparkinsonian drug sales to estimate prevalence found vegetable farming, wood pulp mills, and steel alloy industries in areas with the highest disease prevalence. (Tanner, 1996)

While diesel fuel has not been identified, specifically, compounds capable of causing Parkinsonism may exist in commonly used petroleum products. (Tetrud, 1994)

There also exists a paradox between the studies in the West and those in China. Epidemiologists are turning to China, where industrialization is relatively recent and the

population is geographically stable. (Tanner, 1989d) In North America and Europe, early onset PD appears to be associated with rural residence. Factors associated with this include vegetable farming, well water drinking, wood pulp, paper and steel industries. (Tanner, 1989c)

Living in Chinese villages and exposure to wheat growing and pig raising, were associated with a decreased risk for PD. (Tanner, 1989c) Living in industrialized urban areas of China increased the risk of developing PD. (Tanner, 1989d)

Similar differences can be noted between American Black populations and in Africa. The age-adjusted prevalence rate of PD in blacks living in Copiah County, Mississippi (341 per 100,000 or 3.4 per 1,000), is slightly more than five times higher than that of blacks living in Igbo-Ora, Nigeria (67 per 100,000 or 0.67 per 1,000), suggesting a role of environment, rather than race, in the pathogenesis of PD. (Muthane)

Comment:

"I think it is important to remember that if pesticides have a role in Parkinson's, it may not be a predominant one. By that, I believe that many underlying genetic factors play a major role and exposure to various chemicals may accelerate the disease process. People with minimal pesticide exposure still get the disease." (Gary W. Miller, personal correspondence q.v. Hatcher, 2008)

Hatcher JM, Pennell KD, Miller GW: Parkinson's disease and pesticides: a toxicological perspective. Trends Pharmacol Sci. 2008 Jun; 29(6):322-9. Epub 2008 Apr 29.

Gary W. Miller, Ph.D., Associate Professor, Center for Neurodegenerative Disease. Emory University

Ecological and case-control studies support the association of PD with: [Ascherio, 2006)

- Rural residence (Barbeau, 1987; Svenson, 1993; Rajput, 1986; Tanner, 1986; Ho, 1989; Golbe, 1990; Koller, 1990; Wong, 1991; Butterfield, 1993)
- Use of private wells (Rajput, 1986; Tanner, 1986; Koller, 1990; Wong, 1991; Goldsmith, 1990)
- Farming (Barbeau, 1987; Ho, 1989; Semchuk, 1992; Ross, 2001)
- Exposure to pesticide products (Ho, 1989; Golbe, 1990; Semchuk, 1992; Butterfield, 1993; Hubble, 1993; Hertzman, 1994; Seidler, 1996; Liou, 1997; Chan, 1998; Gorell, 1998; Menegon, 1998; Ritz, 2000)

Farming communities had more than double the proportion of Parkinsonians as control populations. (Stern, 1991; Wechsler, 1991)

Farming as an occupation and well water use had a significant positive association with PD in north-east Italy. (Zorzon, 2002)

Microcosm – a farming community, Fairfield MT

In rural Fairfield, Montana, PD occurrences are much higher than the national aver age (1 in 10,000 people under the age of 60 or 1 in 1,000 people over the age of 60).At least 12 people living around Fairfield have developed Parkinson's (with a population of 650 i.e. 1:50 or 200 times what might normally be expected). (Pfohman, 1992) Fairfield is known as the world capital for malt barley.

Other rural factors?

Farming is a risk factor for Parkinson's beyond herbicide and insecticide exposure. (Gorell, 1998)

Does the answer simply lie in the ground? An early announcement in the November, 2001 Parkinson brief newsletter from the National Parkinson Foundation of Miami, Florida poses the question of whether we can catch Parkinson's from dirt?

Microbiologist Blaine Beaman, from the University of California-Davis, is investigating a possible link between a bacterium that occurs in the soil (Nocardia asteroids) and PD. It is already identified as a cause of lung disease in humans but may also travel to a small part of the brain's basal ganglia to infect nerve cells that manufacture dopamine. The bacteria also deposits clumps of protein resembling the Lewy bodies that are a signature of PD.

What proof is required?

- Hypotheses of a link and pathways have been delineated
- In vitro experiments -
- Laboratory animals - replication
- Acute Cases
- Retrospective studies
- PET scan confirmation
- Meta-analysis

Treatment with Glutathione and Herbs

Glutathione is an antioxidant and free-radical scavenger, and is found in the brain. Research shows that in PD, the glutathione levels are reduced in critical dopamine neurons. David Perlmutter, MD, has led research in this area. He has indicated that glutathione allows dopamine in the brain to be more effective. Dr. Patricia Kane of the Haverford Wellness Center in Havertown, PA reports symptom improvement with the use of IV lipostabil, leucovorin, glutathione and phenylbutyrate; many other physicians now use this approach.

It is always heartening to find some good news, amidst the bad. Our primary focus has been on the neuro-toxins released in our efforts to control nature. In spite of this, Mother Nature provides some antidotes, including these relative to *n*-hexane:

The chemoprotective potential of two antioxidants, EGCG (Green Tea catechin) and Thymoquinone (from Black cumin or Nigella sativa) were assessed, against *n*-hexane (an important industrial solvent and ambient air pollutant) toxicity.

Treatment of cells with EGCG, at a concentration reached in plasma, reduced the reactive oxygen species formation caused by exposure to *n*-hexane and inhibited the decrease in cell proliferation. Similar effects were obtained with Thymoquinone. (McDermott)

Conclusion

In conclusion, there is mounting evidence that chronic, moderate pesticide exposure is neurotoxic, including specific risks for the development of PD. (Kamel, 2004) It has proven elusive to clarify exactly what these "risks" are. One possible answer was discussed recently by Gary Miller, Ph.D., an associate professor of environmental and occupational health at Emory University. "Our current study clearly shows that pesticides such as dieldrin appear to accelerate, or exacerbate, the already underlying disease."

Thus pesticides are a catalyst to a complex process, rather than being capable of initiating the process itself, or of making the culmination of the process into fully-fledged PD inevitable.

This leads us to the model in which environmental factors, in conjunction with genetic susceptibility, may form the underlying molecular basis for idiopathic PD. (Uversky, 2002)

More information:

For information on neuroprotection, and a comprehensive listing of research abstracts, contact the author: David Ponsonby [mailto:dponsonby1@aol.com]

Glossary of Pesticides

Aldrin - Organochlorine insecticide.

“Aroclor” – PCB used in animal testing.

Atrazine – pesticide

Carbon Disulfide – hydrocarbon solvent

Chlordane - Organochlorine insecticide

Chlorpyrifos (Dursban)

Cyperquat - a quaternary ammonium herbicide. (Paraquat)

DDT - Organochlorine insecticide

Diazinon - phased out during 2003.

Dieldrin – (Pesticide) It is a lipid-soluble, long-lasting mitochondrial poison.

No longer produced in the United States.

Diethamquat - a quaternary ammonium herbicide. (Paraquat)

Difenzoquat - a quaternary ammonium herbicide. (Paraquat)

Diquat - a quaternary ammonium herbicide. (Paraquat)

Heptachlor - Organochlorine insecticide

Hydrocarbons

Solvents: Carbon disulfide; *n*-hexane; methanol (a constituent in formaldehyde and lacquer thinner); toluene (monomethylbenzene) (a constituent in lacquer thinner); xylene.
Lindane - Organochlorine insecticide

Lipopolysaccaride (LPS) – endotoxin

MMT - Methylcyclopentadienyl manganese tricarbonyl (MMT) is an organic manganese

(Mn) compound added to unleaded gasoline.

MPTP (1-methyl-1, 2, 3, 6-tetrahydropyridine)

Malathion - organophosphate

Maneb (Fungicide / Biocide - Maneb (manganese ethylene-bis-dithiocarbamate) May combine with Paraquat.

Methanol (in formaldehyde and lacquer thinner) - hydrocarbon solvent

Methoxychlor - Organochlorine insecticide

Mirex - Organochlorine insecticide

Monomethylbenzene – see under Toluene

Morfamquat - a quaternary ammonium herbicide. (Paraquat)

n-hexane– hydrocarbon solvent [Case history]

Organochlorine insecticides E.g. :Aldrin; Chlordane; DDT; Heptachlor; Lindane;

Methoxychlor; Mirex; Toxaphene.

Organophosphates – see separately Dursban (chlorpyrifos); Malathion; Parathion;

Ronnel; TEPP (tetra-ethyl-pyro-phosphate); Vapona. [Cholinomimetics]

PCBs - Polychlorinated biphenyls combine with mercury (Hg). There are 209 kinds.

Paraquat - *N,N'-Dimethyl-4,4'-bipyridinium dichloride*, a quaternary ammonium herbicide. one of the world's most popular weed killers for decades. (Also: cyperquat, diethamquat, difenzoquat, diquat and morfamquat)
May combine with Maneb.

Parathion - highly toxic organophosphate

Radon - is an ubiquitous noble gas in the environment.

Ronnel – organophosphate

Rotenone is a naturally occurring toxin and a commonly used pesticide, insecticide and piscicide (for killing fish). Rotenone is extracted from the dried roots, seeds and leaves of various tropical plants, including the Jewel vine, derris and hoary pea. Rotenone is found in 680 compounds marketed as organic garden pesticides and flea powders. "The best model we have ever had for this disease being associated with an environmental agent." [Rotenone is not capable of causing overt dopaminergic toxicity.]

Styrene – aromatic hydrocarbon

TEPP (tetra-ethyl-pyro-phosphate) – most toxic organophosphate

Terbutaline – Labor drug

Toluene - (monomethylbenzene) - hydrocarbon solvent and a constituent in lacquer thinner [Case history]

Toxaphene - Organochlorine insecticide

Vapona – organophosphate

Vinyltoluene – aromatic hydrocarbon

Xylene - hydrocarbon solvent but not linked to PD.

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