



Essential Tremor (ET)

# Neurotoxins & tremor

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A neurotoxin is an agent capable of eliciting irreversible dysfunction and damage to the nervous system due to death of nerve cells. Sometimes exposure is so severe and damage so great death is the result. Toxic exposure may be divided into that occurring with acute high-level exposure and chronic low-level exposure. If patients survive the acute form, chronic and permanent neurologic deficits commonly persist.

Symptoms of neurotoxic exposure are broad and sometimes nonspecific. There is often a question whether a particular individual has had sufficient exposure to a possible causative neurotoxin to result in neurologic dysfunction. This uncertainty causes conflicts in compensation or litigation procedures.

There has been increasing public awareness and concern regarding the potentially harmful effects of exposure to low levels of a number of environmental toxins, for example, those originating in industrial waste. Patients commonly express concerns that past exposure to a possible toxin contributed to the development of a neurodegenerative disorder such as Alzheimer's disease (AD), Parkinson's disease (PD) or motor neuron disease (Amyotrophic Lateral Sclerosis - ALS). However, it must be emphasized that the role of modern industrial pollution in the causation of such common neurologic diseases is currently not known.

More often, unequivocal toxic exposure occurs in workers involved in specific industries that utilize the potential toxin in a manufacturing process. Routes of exposure vary depending on the nature of the toxin and the type of work involved. Individuals may be exposed by inhalation, direct skin contact and accidental oral ingestion.

Not typically included in the category of "neurotoxins" are illicit chemicals utilized by drug abusers through various routes including intravenous injection. One exception, which will be mentioned later, is the neurotoxin MPTP that has caused permanent Parkinsonism in drug abusers. Neurotoxins can be subdivided under the classifications of metals, solvents, pesticides and other agents.

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**Metals:** Our discussion will be limited to the consequences of environmental exposure to excessive amounts of heavy metals. It is noted there is considerable interest in the role of metals in causing neurologic diseases due to the body's metabolism and handling of metals in the absence of overexposure. Examples of this include iron in Parkinson's disease and the rare disorder, Hallervorden-Spatz disease, and aluminum in Alzheimer's disease. Another well-known example is Wilson's disease, which is a genetic disorder of abnormal copper metabolism.

Most acute heavy-metal exposures result in a syndrome known as encephalopathy, which manifests confusion, poor memory, mood changes, headache and possibly coma and seizures. A non-specific fine postural tremor of the arms may be present in this acute stage. Chronic exposure to certain heavy metals, including lead and arsenic, results in damage to peripheral nerves usually causing weakness in the hands and feet and tingling and loss of sensation in these areas. A peripheral neuropathy (damage to the peripheral as opposed to central nerves) may also result in a postural tremor of the limbs, but typically this is not a prominent feature of the neuropathy of chronic metal exposure.

Manganese has a selective ability to damage the basal ganglia region of the brain causing a syndrome very much like Parkinson's disease. This may be accompanied by varying types of tremor, including a tremor at rest and/or postural tremor. This syndrome has been seen in manganese ore miners in Chile as well as those involved in manganese smelting and individuals exposed to manganese oxide in a selected number of occupations such as the manufacture of paints and fireworks.

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Acute exposure to mercury may result in kidney failure, bowel hemorrhaging and death. Neurologic problems typically occur in survivors over the next 24 hours. Acute exposure to inorganic mercury may occur in the manufacture of scientific and electronic instruments, and work with dental amalgam. Symptoms include clumsiness and tremor. Although this disorder is rare, insights into the mechanism of action of manganese and

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The results of acute exposure to methyl mercury were seen between 1953 and 1956 when inhabitants of the Minamata Bay region of Kyushu Island in Japan ingested fish tainted with large levels of this toxin ("Minamata disease"). Severe neurologic consequences included numbness of the limbs, lips and tongue followed by clumsiness, slurred speech, deafness, blindness, spasticity and intellectual impairment. In contrast, chronic, low-level mercury exposure is possible in a variety of occupations including workers exposed to mercury vapors or mercury in dental amalgam (it should be emphasized that there is no evidence to support the concern that neurologic disease may be caused by tooth fillings containing dental amalgam). Chronic exposure typically results in postural tremor, deterioration of intellect and changes in emotional state.

Historically, nitrates of mercury were used in felt making and hat makers were particularly at risk. This accounts for the Mad Hatter character in Lewis Carroll's *Through*

*the Looking Glass* as well as the term "Hatter's Shakes" to describe tremors seen in these individuals.

**Organic Solvents:** Organic solvents are volatile chemical compounds used industrially to extract, dissolve or suspend materials that are poorly soluble in water.

As with heavy metals, exposure to organic solvents may result in a variety of both systemic and neurologic signs and symptoms. Rarely is tremor a major or predominant component.

Certain organic solvents may be more likely to cause tremor. Carbon disulfide used in insecticides, the rubber industry, the preparation of rayon viscose fibers, and in grain storage may selectively damage the basal ganglia as well as other regions of the brain. Parkinsonism's resting and postural tremors may occur as a result of toxic exposure to carbon disulfide. But, it is usually the slowness and stiffness of this disorder, which predominate rather than the tremor.

Toluene is an organic solvent used in the production of adhesives, glues, lacquers, paint thinners, rubbers and other substances. Toxic work-related exposure can be seen, for example, in rotogravure printers. It is more common now to see the consequences of acute and chronic exposure in glue sniffers. Tremor may be one syndrome component comprising mental changes, clumsiness, incoordination, unsteady gait and damage to peripheral nerves.

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**Pesticides:** There is considerable interest in the possible role of rural living and pesticide or fungicide exposure in causing Parkinson's disease. Support for this comes from several sources, including the chemical similarity between the pesticide paraquat and the neurotoxin MPTP. Despite intense research in this field, the role of environmental exposure in PD remains uncertain.

The largest group of pesticides is the organophosphate insecticides. These affect transmission between nerves and muscles as well as causing dysfunction in the autonomic nervous system (which controls such faculties and pupillary function, blood pressure, bowel and bladder control) and mental changes. There are numerous other types of pesticides, most with the same profile of toxicity. Carbaryl has been used commercially on growing cotton and corn to control grasshoppers and gypsy moths, and is also found in some household gardening sprays.

This is less toxic than the organophosphates; so much greater exposure is required to produce neurologic symptoms. Dermal (through the skin) and oral exposures have resulted in a variety of symptoms similar to those of the organophosphates. Interestingly, tremor may occur as a complication of chronic exposure. This may relate in part to central effects on the neurotransmitter dopamine.

Finally, chlordecone (Kepone®) used to control weevils, ants and roaches, has caused tremor ("Kepone shakes") along with a variety of other symptoms in heavily-exposed industrial workers in Virginia.

**Other Neurotoxins:** As mentioned earlier, this essay will not review the consequences of substance abuse. In addition to abusing chemicals that transiently affect neurologic function, drug addicts and alcoholics also may be exposed to toxins that permanently damage the nervous system. One example already discussed is toluene. Alcoholics may imbibe methyl alcohol (sometimes used by others in suicide attempts). Methyl alcohol exposure can also selectively damage the basal ganglia resulting in Parkinsonism, dystonia, and tremor.

In the early 1980's, a small number of heroin addicts in California developed acute, severe and permanent Parkinsonism after they injected a "bad batch" of homemade "heroin" which contained the neurotoxin MPTP. Both postural and resting tremors have been seen as part of this syndrome. The discovery of the selective ability of MPTP to damage the part of the brain most prominently affected in classic Parkinson's disease (the substantia nigra pars compacta) has revolutionized research in almost every aspect of PD, including the cause (possible environmental exposure), specific mechanisms of cell damage and death (e.g., mitochondrial dysfunction), the nature of symptoms (e.g., tremor as a manifestation of substantia nigra damage) and possible neuroprotective therapies (e.g., antioxidant drugs).

Research is extremely active in the area of one further category of neurotoxins, the excitatory amino acids. This is a large and important topic, which is beyond the scope of this discussion. With respect to disorders associated with tremor, it has been proposed (but far from proven) that exposure to the excitatory amino acid betamethylamino-L-alanine (BMAA) contained in the cycad plant may cause a form of Parkinsonism associated with dementia and motor neuron disease seen in the Chamorro inhabitants of Guam. Excitatory amino acids may cause neurologic damage through chronic exposure in the environment (most often via oral intake). They are also normal constituents of the brain, and there is increasing evidence that they play a role in acute neurologic dysfunction in disorders such as stroke, brain anoxia (the loss of sufficient oxygen for brain function) and seizures. Finally, excitatory amino acid toxicity may also play a role in slowly progressive neurodegenerative disorders such as Huntington's disease and PD.

As one can gather from this brief review, tremor is rarely a consequence of toxin exposure, and then it hardly ever occurs as an isolated symptom. More often than not, when an individual consults a physician complaining of tremor and claims an association with an environmental exposure, the association is no more than coincidental and the tremor is due to some other much more common neurologic problem.

However, each claim must be considered carefully, since there is still a great deal that we do not know about neurotoxins. On the other hand, we also see patients feigning neurologic diseases attempting to obtain compensation, and in these cases the tremor would relate to primary psychiatric factors such as malingering or "compensation neuroses".

A major challenge to industrialized nations in the 21st century will be the elimination of toxic waste. The importance of this goal to the preservation of our environment is well established. How low-level toxic exposure affects our health is still not certain. Further research is required to establish the possible roles of exogenous (coming from the environment) and endogenous (formed within the body) toxins in the causes of "naturally" occurring neurologic diseases such as essential tremor and Parkinson's disease.



**Our Mission:**

The IETF funds research to find the cause of essential tremor (ET) that leads to treatments and a cure, increases awareness, and provides educational materials, tools, and support for healthcare providers, the public, and those affected by ET.