CASE REPORT

Karen S. Blisard,[1] *Ph.D., M.D.; Mario Kornfeld,*[2] *M.D.; Patricia J. McFeeley,*[3] *M.D.; and John E. Smialek,*[4] *M.D.*

The Investigation of Alleged Insecticide Toxicity: A Case Involving Chlordane Exposure, Multiple Sclerosis, and Peripheral Neuropathy

REFERENCE: Blisard, K. S., Kornfeld, M., McFeeley, P. J., and Smialek, J. E., **"The Investigation of Alleged Insecticide Toxicity: A Case Involving Chlordane Exposure, Multiple Sclerosis, and Peripheral Neuropathy,"** *Journal of Forensic Sciences*, JFSCA, Vol. 31, No. 4, Oct. 1986, pp. 1499-1504.

ABSTRACT: A man with no previous medical problems had two documented exposures to an insecticide containing the organophosphorous compounds chlordane and heptachlor. Six months to one year later, he began to experience neurological symptoms which progressed until his death. At autopsy, his brain showed classic findings of multiple sclerosis, and he had a severe peripheral neuropathy. Review of the literature indicates that the findings are not compatible with chlordane toxicity. Some of the factors to be used in determining the casual relationship between toxic exposure and disease processes are discussed.

KEYWORDS: pathology and biology, chlordane, multiple sclerosis, peripheral neuropathy

Exposure to toxic substances in the workplace resulting in serious or disabling disease is a matter of great public concern [*1*]. Several thousand chemicals are manufactured or used industrially in the United States; the majority of these could be capable of toxic effects in appropriate circumstances. Insecticides, because of their widespread use in industrial and domestic settings, are agents of particular concern [*2-6*]. Central and peripheral nervous system toxicity is frequently seen following insecticide exposure. Central neurotoxicity is manifested most often as hyperexcitability, convulsions, or coma and can be rapidly lethal. Peripheral neurotoxicity, on the other hand, is usually delayed in onset and can result in loss

Presented in part at the 37th Annual Meeting of the American Academy of Forensic Sciences, Las Vegas, NV, 12-16 Feb. 1985.

[1]Associate investigator, Research Service, Veteran's Administration Medical Center and research assistant professor, Department of Pathology, University of New Mexico, School of Medicine, Albuquerque, NM.

[2]Professor, Department of Pathology, University of New Mexico, School of Medicine, Albuquerque, NM.

[3]Medical investigator, Office of the Medical Investigator and assistant professor, Department of Pathology, University of New Mexico, School of Medicine, Albuquerque, NM.

[4]Former chief medical investigator, Office of the Medical Investigator and professor, Department of Pathology, University of New Mexico, School of Medicine, Albuquerque, NM.

of sensory or motor function. The question often arises of whether exposure to a toxic substance was causally related to development of a particular disease. Answering this question can be extremely difficult, demanding careful investigation and accurate documentation. An example of a man exposed to chlorinated hydrocarbon insecticides who later developed serious neurological disease is presented and discussed with respect to the problem of determining causal relatedness.

Case Report

A 51-year-old man with no previous medical problems experienced exposure to an insecticide containing chlordane and heptachlor, used for termites, on two separate occasions in August 1981. These exposures, each lasting 1 to 1½ h, occurred in a confined space under a house. He experienced no symptoms immediately after the exposures. However, approximately six months to one year later, he noted problems with equilibrium and diminished strength. He complained of visual impairment and double vision beginning approximately two years after the exposure. Neurologic examination in June 1983 revealed essentially unremarkable visual acuity, but constricted visual fields and nystagmus. He had intact sensation and motor strength in the face, but decreased motor strength, wasting, and loss of sensation in the lower extremities. He had mild to moderate ataxia. The patient's symptoms progressed. He was admitted to a nursing home for terminal care and died of pneumonia in June 1984.

At autopsy, the significant findings involved both the central and peripheral nervous systems. The predominant central nervous system findings were those characteristic of multiple sclerosis (Fig. 1). There were well circumscribed, punched out plaques of demyelination in numerous locations in both cerebral hemispheres, mostly in the white matter, but also in cortical gray matter and in the thalami. A predominant pattern of periventricular distribution was identified. Additional plaques were present in the cerebellum and in numerous locations in the brainstem and spinal cord. Some of these plaques appeared quite active,

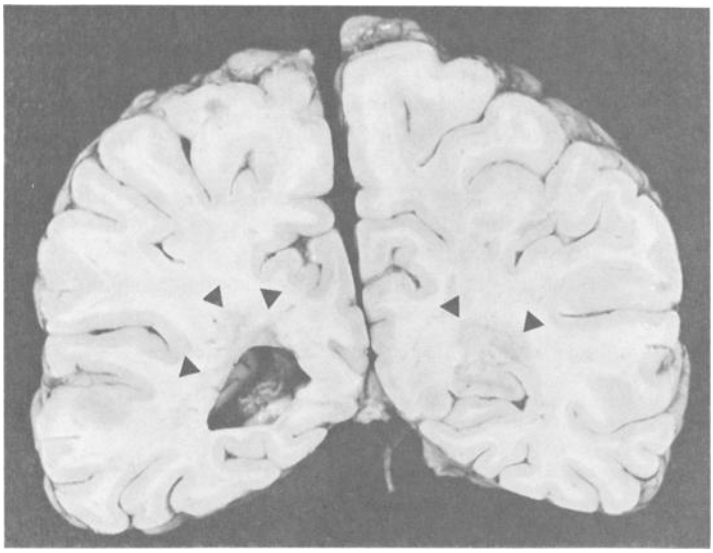

FIG. 1—*Plaques of demyelination* (arrows) *were present throughout the cerebral hemispheres. The predominantly periventricular pattern is characteristic of multiple sclerosis.*

with an intense perivascular infiltrate and foamy macrophage infiltration; other plaques were older, consisting only of residual glia. There was moderately good axonal preservation in the areas of the plaques.

Sections of peripheral nerve were examined at several levels. Except for the presence of a relatively large number of Renaut bodies, the sections from most of the nerves were essentially unremarkable with good preservation of large and small myelinated fibers. However, the distal tibial nerve showed a marked decrease in the number of large myelinated fibers (Fig. 2). Sections of nerve stained with Bodian's silver proteinate stain displayed marked axonal loss, but minimal signs of active degeneration. Teased nerve fiber preparations confirmed the loss of large axons, but again showed minimal signs of active degeneration. Electron microscopic evaluation of the distal tibial nerve again confirmed the marked diminution in the number of large myelinated fibers, with better preservation of the unmyelinated and small myelinated nerve fibers (Fig. 3). An occasional degenerating axon was observed. There was a marked increase in the amount of endoneurial collagen.

Discussion

In evaluating this man's case, the possible interaction of three processes, that is, his exposure to the insecticides chlordane and heptachlor, his multiple sclerosis, and his peripheral neuropathy, must be considered.

Multiple Sclerosis

Multiple sclerosis is a devastating disease resulting from demyelination in isolated foci (plaques) in the central nervous system [*7–10*]. Although these plaques can be located anywhere, a periventricular distribution is very characteristic. Microscopically, active plaques are characterized by perivascular inflammatory infiltrates and evidence of myelin breakdown. Chronic plaques are hypocellular with proliferation of astroglial cells. Although mye-

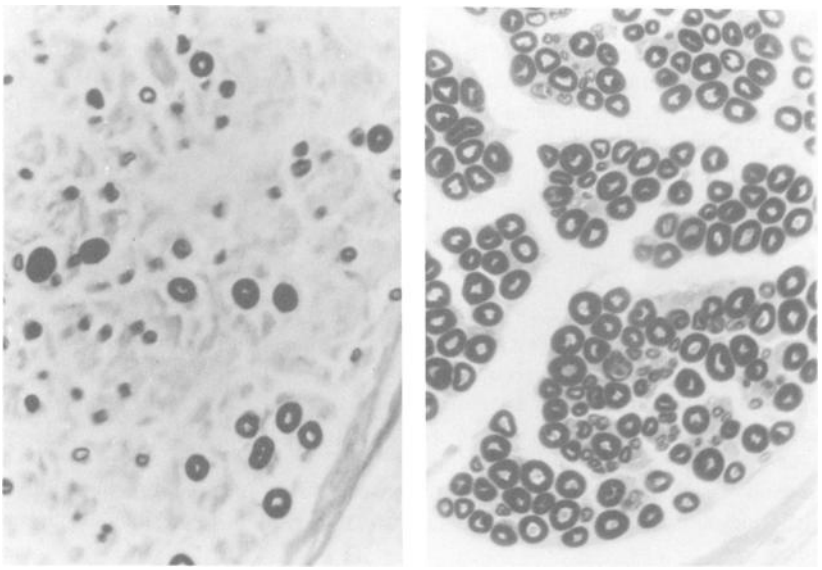

FIG. 2—*Section from distal tibial nerve* (left) *shows marked decrease in large myelinated fibers, compared with section from more proximal nerve* (right), *which appears essentially normal (osmium tetroxide postfixation, original magnification* × *400).*

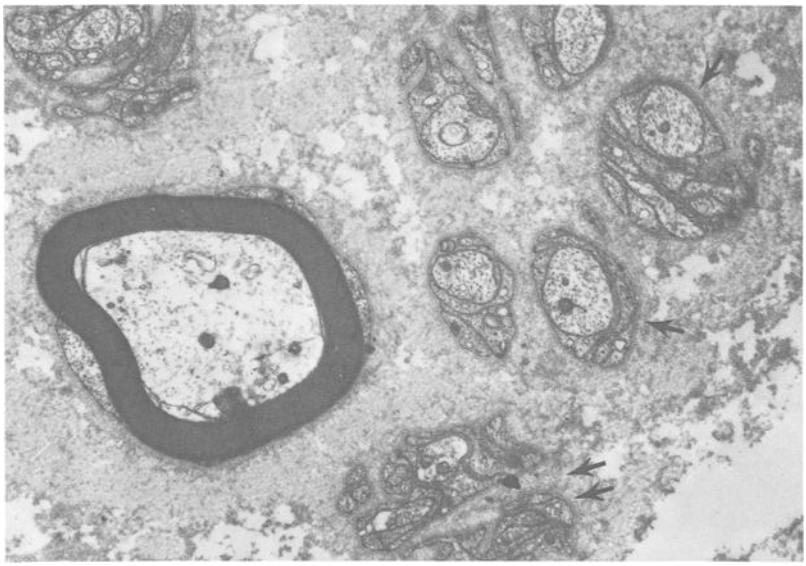

FIG. 3—*Electron micrograph from distal tibial nerve shows loss of large myelinated fibers, with better preservation of unmyelinated fibers* (arrow). *Complementary bands of Schwann cells are proliferating about small axons* (double arrows) *(original magnification* × *7500).*

lin may be almost entirely lacking, axons are relatively well preserved. The clinical picture is one of remitting and relapsing symptoms, with residual deficits increasing with time. In this case, the patient's symptoms were atypical, and the disease was not diagnosed premortem. The etiology of multiple sclerosis is unknown, but is speculated to be related to an autoimmune phenomenon possibly activated by a latent viral infection. Rare patients with multiple sclerosis have been documented to have a peripheral neuropathy as well. Some patients had an inflammatory polyneuritis similar to Guillain-Barré syndrome, which may also be mediated by an autoimmune-type mechanism [*11,12*]. Other authors who reported peripheral demyelination attribute the disease to malnutrition in multiple sclerosis patients [*13*]. Although this patient was malnourished terminally, malnutrition occurred *after* the onset of his neuropathy. In general, peripheral neuropathy developing in multiple sclerosis patients is very uncommon, and it is not highly probable that these two processes are related in this patient.

Organic Insecticides

Organic insecticides are divided into three classes, each with characteristic toxic effects [*2-6*]. The organophosphorus insecticides cause acute poisoning by inhibition of acetylcholinesterase, resulting in autonomic nervous system symptoms. Central nervous system effects include anxiety, convulsions, and coma. A delayed peripheral neuropathy involving large diameter fibers can occur [*14*].

A second class encompasses the carbamate insecticides, which are reversible inhibitors of acetylcholinesterase [*2-6*]. Toxicity is similar to that caused by organophosphorus compounds.

The third group includes the organochlorine compounds [*2-6*]. Although they can also be divided into several different subgroups, they are commonly considered to act by a single mechanism. This group contains such insecticides as 2,2-*bis* (*p*-chlorophenyl)-1,1,1-tri-

chloroethane (DDT), chlordane, heptachlor, chlordecone, dieldrin, and lindane. Acute neurotoxicity is often seen after a toxic exposure, resulting in paresthesias, hyperstimulation, convulsions, and tremors [*2–6*]. Liver changes in the form of hepatomegaly and centrilobular necrosis are also very common. The most extensively studied member of this group is chlordecone (Kepone), which was implicated in the Hopewell, Virginia incident in 1975 [*15–18*]. Several factory workers, with an average exposure to chlordecone of four to eight months, developed a peripheral neuropathy and central nervous system toxicity. The clinical symptoms consisted predominantly of tremor, irritability, and decreased short-term memory. Levels of chlordecone in their blood and fat were very high, and as the chlordecone levels declined, the symptoms abated, resulting in substantial recovery in most individuals. The morphological evaluation of peripheral nerve biopsies in these patients showed a predominant involvement of small myelinated and unmyelinated axons. Electron microscopic studies showed reduplicated cytoplasmic folds in Schwann cells, as well as cytoplasmic Schwann cell inclusions. There was an increase in endoneurial collagen, and signs of axonal degeneration were seen. The mechanism of organochlorine insecticide toxicity is poorly understood. It is speculated that they act at the synapse to increase synaptic activity and enhance transmitter release, resulting in central nervous system effects [*19,20*]. The mechanism of insecticide-induced peripheral neurotoxicity is completely unknown.

Possible Relationship of Neurologic Disease to Insecticide Exposure

Given this background, can the findings in this case, that is, multiple sclerosis and peripheral neuropathy, be related to exposure to insecticides? Guidelines for points to consider in the determination of causal relatedness are given in Table 1 [*3,4*]. Once exposure to a particular compound is documented, attention must be paid to the specific details of the exposure. If possible, the actual dosage of the chemical should be known, either by documenting the amount ingested or absorbed, or by determination of blood or tissue levels. In the case presented here, quantitation of dosage is not possible. However, since the duration of exposure was very short, the dosage would likely be relatively small. Most workers who develop symptoms secondary to chronic exposure have worked with the offending agent for months and have a large cumulative dosage. Another way of expressing this concept is Haber's Rule [*3*], which says that dosage multiplied by time of exposure is important in determining toxicity. This expression may be modified by route of exposure, metabolism, excretion, or storage of the toxin.

Time from exposure to onset of symptoms can be very helpful. In this case, no acute symptoms were observed, and indeed symptoms did not appear until six months to one year later. Thus, none of the exposure history factors are consistent with insecticide-induced toxicity.

Another consideration is the clinical symptomatology known to be caused by a toxin compared to those experienced by the patient. Again, in this case, acute findings often seen with organochlorine insecticides were *not* present. Peripheral neuropathy has, however, been described with chronic exposure to organochlorine compounds.

TABLE 1—*Factors influencing causal relatedness.*

I. Specific agent(s)
II. Details of exposure
Dosage
Duration
Route
III. Clinical symptoms
IV. Morphological findings

The final factor to consider is the morphologic findings in the patient compared to those reported in the literature. To our knowledge, multiple sclerosis has never been reported to be associated with exposure to insecticides of any kind. Peripheral neuropathy was seen in some of the workers in the chlordecone (Kepone) incident. However, the morphologic appearance of the affected nerves are quite different. Patients with chlordecone poisoning show loss of unmyelinated and small myelinated fibers. In this case, the loss is predominantly confined to the large myelinated fibers. For chlordane, reports of neurotoxic effects are rather sparse. Only rare cases of peripheral neuropathy have been described and none have been biopsied [*4*]. No cases of human poisoning with heptachlor have been described. Thus, comparison of the history, symptoms, and morphology for this case with what has been reported in the literature leads to the conclusion that neither the central nor the peripheral neuropathy in this case were caused by exposure to insecticides. The etiologies of this man's illnesses remain enigmatic.

References

[*1*] Landrigan, L. J., Kriess, K., Xintaras, C., Feldman, R. G., and Heath, C. W., "Clinical Epidemiology of Occupational Neurotoxic Disease," *Neurobehavioral Toxicology*, Vol. 2, 1980, pp. 43-48.

[*2*] Cassarett, W. and Doull, J., *Toxicology*, 1st ed., MacMillan, New York, 1975, pp. 418-437.

[*3*] Hayes, W. J., Jr, *Toxicology of Pesticides*, Williams and Wilkins, Baltimore, 1975.

[*4*] Ecobichon, D. J. and Joy, R. M., *Pesticides and Neurological Diseases*, CRC Press, Boca Raton, FL, 1982.

[*5*] Hayes, W. J., Jr., *Pesticides Studied in Man*, Williams and Wilkins, Baltimore, 1982.

[*6*] Finkel, A. J., *Hamilton and Hardy's Industrial Toxicology*, 4th ed., John Wright, Boston, 1983.

[*7*] Allen, I. V., in *Greenfield's Neuropathology*, 4th ed., J. H. Adams, J. A. N. Corsellis, and L. W. Duchen, Eds., John Wiley and Sons, New York, 1984, pp. 349-368.

[*8*] Waxman, S. G. and Ritchie, J. M., *Demyelinating Disease: Basic and Clinical Electrophysiology, Advances in Neurology*, Vol. 31, Raven Press, New York, 1981.

[*9*] McFarlin, D. E. and McFarland, H. F., "Multiple Sclerosis" (two parts), *New England Journal of Medicine*, Vol. 307, Nos. 19 and 20, 1982, pp. 1183-1188 and 1246-1251.

[*10*] Rodriguez, M., Powell, H. C., and Lampert, P. W., in *Neuropathology*, R. N. Rosenberg and S. S. Schochet, Eds., Churchill Livingstone, New York, 1983, pp. 434-445.

[*11*] Forrester, C. and Lascelles, R. G., "Association between Polyneuritis and Multiple Sclerosis," *Journal of Neurology, Neurosurgery and Psychiatry*, Vol. 42, 1979, pp. 864-866.

[*12*] Lassmann, H., Budka, J., and Schnaberth, G., "Inflammatory Demyelinating Polyradiculitis in a Patient with Multiple Sclerosis," *Archives of Neurology*, Vol. 38, 1981, pp. 99-102.

[*13*] Hasson, J., Terry, R. D., and Zimmerman, H. M., "Peripheral Neuropathy in Multiple Sclerosis," *Neurology*, Vol. 8, No. 7, 1958, pp. 503-510.

[*14*] Lotti, Becker, C. E., and Aminoff, M. D., "Organophosphate Polyneuropathy: Pathogenesis and Prevention," *Neurology*, Vol. 34, No. 5, 1984, pp. 658-662.

[*15*] Martinez, A. J., Taylor, J. R., Houff, S. A., and Issacs, E. R., "Kepone Poisoning: Clinico-Neuropathological Study," *NeuroToxicology*, Vol. 1, 1977, pp. 443-456.

[*16*] Tilson, H. A. and Mactutus, C. F., "Chlordecone Neurotoxicity: A Brief Overview," *NeuroToxicology*, Vol. 3, No. 2, 1982, pp. 1-8.

[*17*] Taylor, J. R., "Neurological Manifestations in Humans Exposed to Chlordecone and Follow-up Results," *NeuroToxicology*, Vol. 3, No. 2, 1982, pp. 9-16.

[*18*] Phillips, D. E. and Eroschenko, V. P., "An Electron Microscopic Study of Chlordecone (Kepone) Induced Peripheral Nerve Damage in Adult Mice," *NeuroToxicology*, Vol. 3, No. 2, 1982, pp. 155-162.

[*19*] Shankland, D. L., "Neurotoxic Action of Chlorinated Hydrocarbon Insecticides," *Neurobehavioral Toxicology and Teratology*, Vol. 4, 1982, pp. 805-811.

[*20*] Joy, R. M., "Mode of Action of Lindane, Dieldrin and Related Insecticides in the Central Nervous System," *Neurobehavioral Toxicology and Teratology*, Vol. 4, 1982, pp. 813-823.

Address requests for reprints or additional information to
Karen Blisard, Ph.D., M.D.
Office of Medical Investigator
Department of Pathology
University of New Mexico School of Medicine
Albuquerque, NM 87131