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Neuropathy Following Exposure to a Dimethylamine Salt of 2, 4-D

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A case of peripheral neuritis followed exposure to the dimethylamine salt of 2,4-dichlorophenoxyacetic acid. 2,4-D is widely used as a weed killer. In minute doses, plant growth is stimulated; but in concentrations employed in ordinary commercial herbicides, this chemical causes excessive stimulation resulting in death to the plant.

Although 2,4-D is usually nontoxic, in 1959, Goldstein, Jones, and Brown reported 3 cases of peripheral neuropathy following exposure to an ester of 2,4-D.[1] The neuropathy began shortly after the exposure to the skin; therefore, absorption seemed to be percutaneous. Disability was prolonged, and recovery was incomplete. Prior to this report there had been no evidence of serious toxic effect in humans. However, various toxic reactions had been reported in animals, including renal edema with tubular changes, liver damage, myotonia, stiffness of the extremities, ataxia, lethargy, paralysis, and coma.

Goldstein, Jones, and Brown did not describe details of manufacture or purity of the 2,4-D ester preparations. Therefore, it might be suggested that some other agent used in preparing or making a solution of the 2,4-D produced the neuritis and not the 2,4-D itself. It seems likely, however, that these authors were correct in assuming that the 2,4-D caused the neuritis. This report will include details of the preparation of the solution of 2,4-D.

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Report of a Case

A 39-year-old farmer was seen at the University of Michigan Medical Center during July, 1961; he complained of numbness and tingling of the hands and feet of 2 weeks' duration.

Four days before the onset of symptoms he was spraying weeds in his cornfield with a liquid solution of 2,4-D. He used an automatic sprayer behind his tractor and repeatedly used his bare hands to correct plugging-up of the sprayer. Exposure to the 2,4-D apparently was excessive, as he made no attempt to wash his hands after each exposure. He thought it possible that he inhaled some of the solution, as it was a windy day.

Initial symptoms were constant pricking of both fifth fingers and toes. Within a day, a similar sensation spread to all fingers and toes and also developed in areas in the midabdomen, the upper chest, and the anterior thighs. Despite numbness, he noted hypersensitivity to touch. He complained of aching in his arms and a feeling of stiffness in the hands and knees. During the second week of his illness, he developed difficulty buttoning his shirt and tying his shoes. He lost proper control of his hands; his handwriting deteriorated.

Past medical history disclosed one attack of low back pain with sciatic radiation and weakness of the right foot, occurring 5 years before his present illness and clearing within 1 year. A gastric ulcer developed one year before the present illness which responded to medical treatment. There was no history of exposure to any other toxin known to produce neuritis. Specifically, he had not used any heavy-metal sprays on his farm. There was no family history of neuritis or other nervous or mental disease.

Examination.—The general physical examination was normal. Mental status was normal. Neurological

examination disclosed normal cranial nerve function. Strength in all extremities was normal, and there was no atrophy. The biceps and triceps reflexes were hypoactive; the knee jerks were normal. The ankle jerks were hypoactive. There were no pathologic reflexes. Gait was normal. Fine movements of the hands were incoordinate: He had difficulty buttoning his shirt, tying his shoelaces, and his handwriting was unsteady. Position, motion, and vibratory sensation were impaired in the distal extremities; vibration was most severely affected. Light touch was decreased in the distal extremities in a neuritic pattern. There was a similar, mild decrease in distal perception of painful stimuli except that he was hyperalgesic over the fifth fingers.

Laboratory Studies.—Chest x-ray demonstrated a calcified lung scar and old calcified nodes. Skull x-rays were normal. Spine x-rays disclosed reduction of the L-5 S-1 disc space with sclerosis of the intervertebral margins. Blood studies disclosed hematocrit, 37.5%; hemoglobin, 16.5 gm.; leukocytes, initially 3,600 with a repeat of 4,900 and a normal differential count; blood urea nitrogen, 13 mg/100 cc; fasting blood sugar, 81 mg/100 cc with a normal glucose tolerance curve; serum calcium, 9.3 mg/100 cc; phosphorus, 3.3 mg/100 cc; blood Kahn, negative. Cerebrospinal fluid (CSF) examination disclosed 100 mm. CSF pressure; 2 cells; protein, 47 mg/100 cc; globulin, negative; colloidal gold, 0122100000; mastic, 0000000; serology, negative.

Electromyographic studies, including motor peroneal nerve conduction times were within normal limits; however, in view of the short duration of the illness, the results are of questionable significance.

Course of Illness.—A diagnosis of primarily sensory, peripheral polyneuropathy was made, and 2 multivitamin capsules (Zymacap, Upjohn) and 200 mg. of thiamine hydrochloride daily were prescribed. Several weeks later gradual improvement began and has continued. When last seen in April, 1962, he complained only of mild intermittent numbness of the hands after prolonged use. He handled tools and small objects normally. The deep tendon reflexes in the upper extremities remained hypoactive. Vibratory sensation was normal in the lower extremities and only slightly reduced in the fingers. Mild hypalgesia was evident only on the fourth and fifth fingers of the right hand. Otherwise the neurological examination was normal.

Comment

This farmer used an aqueous solution of the dimethylamine salt of 2,4-D. The 2,4-D was obtained as concentrated solutions of dimethylamine salts of 2,4-D or as 2,4-D acid, which was made into solution through interaction with dimethylamine and water. The result was a 40% solution of the dimethylamine salt of 2,4-D and water. Small percentages of antifreeze, isopropanol, were added; traces of a sequestering agent, citric acid, which formed the dimethylamine salt of citric acid were also added for hard water solubility. The 2,4-D acid is 98%-99% pure, and the other traces of impurities are probably the bis-form of 2,4-D; i.e., the interaction of dichloroacetic acid with 2,4-dichlorophenol to form a double-substituted acetic acid. Most 2,4-D acid is made from monochloroacetic acid and dichlorophenol, which are readily available in pure form; consequently most 2,4-D acid is very pure.

Conclusions

It is probable that 2,4-D dimethylamine salt produced a primary sensory neuropathy in this 39-year-old farmer. It is unlikely that a contaminant could be present in sufficient quantities to produce a neuropathy, but even admitting this possibility, it seems likely that preparations containing 2,4-D may produce neuropathy. Therefore, the recommendations of Goldstein, Jones, and Brown are emphasized: shorter periods of exposure, frequent washing of the skin after exposure, and changing of clothes when they become wet with the solution.

Despite the extensive use of 2,4-D preparations, resultant peripheral neuropathy is very rare, and an afflicted individual probably has some predisposition to neuropathy or susceptibility to the toxin. Nevertheless, as it cannot be determined who is predisposed or susceptible, and as no antidote to 2,4-D intoxication is known, prevention is simpler than treatment.

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