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PERIPHERAL NEUROPATHY AFTER EXPOSURE TO AN ESTER OF DICHLOROPHENOXYACETIC ACID

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Severe sensory and motor symptoms necessitated hospitalization of three patients, a 52-year-old man, a 50-year-old woman, and a 65-year-old man. In each case the disorder began some hours after the use of preparations of dichlorophenoxyacetic acid (2,4-D) to kill weeds; the symptoms progressed through a period of days until pain, paresthesias, and paralysis were severe. Disability was protracted, and recovery was incomplete even after the lapse of years. There was little doubt that the neurological damage was done by the percutaneous absorption of spilled 2,4-D. The electromyographic examination supported the diagnosis of peripheral neuropathy. Since there is no antidote or other specific treatment for 2,4-D poisoning, this herbicide should be used with caution.

Disease of the peripheral nerves has been shown in the past to follow exposure to various heavy metals, organic solvents, and medicaments.[1] These substances are often used in industry and in the practice of medicine. With the synthesis of new compounds for both industrial and clinical use, it is likely that additional compounds will be shown to produce disease of the peripheral nervous system.

In three cases of polyneuritis the history indicated that exposure to the herbicide dichlorophenoxyacetic acid (2,4-D) preceded the development of the neuritis. The time relationship was such that it seemed reasonable that the herbicide caused the neurological disease.

Report of Cases

CASE 1.—A 52-year-old farmer registered at the Mayo Clinic on Oct. 10, 1955, with the chief complaints of weakness, paresthesia, and aching in all four extremities. Five months prior to our examination, he had spilled about 2 fl. oz. (60 cc.) of a 10% solution of an ester of 2,4-D on his forearms. He had failed to wash it off, and that evening he had felt unduly fatigued. A few days later, nausea and vomiting had developed. These symptoms had lasted for 10 days, and during this time the patient had lost 20 lb. (9.1 kg.) in body weight.

About two months later, while again using the same concentration of this herbicide, the patient accidentally had wetted his legs with it. Over the next five days nausea and vomiting had developed and also diarrhea. A week after this second exposure to the herbicide, the patient had noted numbness and aching in the fingers and toes of both right and left extremities. He had been hospitalized. The sensations of numbness and aching gradually had extended proximally from the fingers to involve the hands, and in the lower extremities they had reached the lower part of the thighs. During the next four weeks, the fingers and toes had become more numb, and shooting pains had developed in both feet, the right foot being more painful than the left. The pain had been severe enough to require the use of narcotics. In addition, there had been desquamation of the skin of the palms and soles.

Approximately six weeks after the second exposure to 2,4-D, the condition had progressed so far that the patient was unable to walk because of the pain and weakness in both legs. He had lost sensation in both intestine and bladder but was able to urinate and control his bowel movements. An examination of cerebrospinal fluid was said to have shown an increased concentration of protein.

At the time of his admission to the Mayo Clinic, the findings on the patient's general examination were satisfactory. The neurological examination disclosed the presence of a flaccid quadriparesis that was more severe in the lower extremities. There was a sensory deficit of the hands and forearms, with moderate impairment in perception of pain, light touch, and temperature. In the lower extremities there was a similar sensory disturbance from the mid-thigh downward. Joint sensation in the fingers and toes was absent, as was appreciation of vibratory stimulation at the ankles. The muscle stretch reflexes were absent. Testing for the Babinski sign elicited no response on either side.

The hemoglobin concentration, leukocyte count, and erythrocyte count, the results from urinalysis, and the serologic test for syphilis were normal, as was the result from a sulfobromophthalein (Brom-

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sulphalein) test of liver function. Examinations of the urine for porphyrins and for arsenic disclosed none; the lead concentration per liter of urine measured 0.03 mg.

This patient returned for reexamination on Sept. 18, 1957, stating that his condition had improved gradually in the two intervening years. By January, 1956, he had progressed sufficiently to be able to walk with the aid of crutches. In the spring of 1956 he had returned to part-time farm work. Approximately one year later he had been doing full-time work on the farm "except for heavy lifting." His complaints in September, 1957, included (1) "numbness" of the feet and fingers, (2) inability to move his toes, and (3) aching of the feet.

The neurological examination revealed marked improvement. The patient had only slight difficulty in walking on his toes and heels, although he was unable to hop on either foot. The muscle stretch reflexes were slightly hypoactive in the upper extremities; the quadriceps reflex was moderately decreased bilaterally, and the ankle reflexes were absent. Muscular strength was normal, except for slight weakness of the muscles of the lower parts of the legs and inability to move the toes. Findings on the sensory examination were normal, except for subjective hypesthesia and hypalgesia of the feet; joint sensation was normal in the feet, but vibratory sensation was moderately diminished at the ankles. An electromyogram showed only minimal denervation in the right gastrocnemius and decreased motor unit activity in the left extensor digitorum longus.

The patient wrote to us on Oct. 30, 1958, informing us that his legs had become stronger, although he still could not move his toes, and that the paresthesia of his feet and fingers had lessened.

CASE 2.—A 50-year-old bookkeeper and housewife registered at the Mayo Clinic in October, 1955, with the chief complaints of weakness and numbness of both legs. She had been well until the spring of 1954. Just prior to the onset of her illness she had sprayed dandelions with a solution of an ester of 2,4-D, kneeling on the ground to do so. In the process her hands and legs had become wet with the herbicide. Shortly after this, she had noted swelling and aching of her feet and legs that had persisted for about two and one-half weeks. Rest in bed had given complete relief. The patient had been well from then until May, 1955, when after a similar exposure to the herbicide similar symptoms had occurred. She had continued to work, and the swelling had progressed to involve the knees. Her legs had not changed color, but they had felt warm.

The patient had been hospitalized for one week for observation. On the night of her discharge from the hospital excruciating pains had developed in her legs and a painful swelling in the metacarpal joints of both hands, necessitating rehospitalization that same night. While in the hospital she had been affected considerably by anorexia and had lost 20 lb. (9.1 kg.) in body weight. No fever or jaundice had been noted.

Therapy with cortisone had been started but was discontinued when the patient became agitated and depressed and had frequent crying spells. After three weeks she had returned home but had been unable to walk.

In August, 1955, there had been an episode of diarrhea of unexplained origin. After admission to a hospital for physical therapy, she had noted a rash in the groin that had spread to the thighs. The rash had itched, and a few bullae filled with serous fluid had developed. After the beginning of physiotherapy the numbness of the extremities had lessened gradually, but stiffness of the legs and difficulty in walking had persisted.

At the Mayo Clinic, the findings on the general medical examination were normal. The neurological examination revealed a flaccid paraparesis, with marked weakness of the lower part of the legs. Sensory tests of touch, pain, and temperature disclosed a moderately severe sensory deficit. The sensory loss was more marked in the feet than in the legs. In the upper extremities were a sensory loss corresponding to the ulnar nerve distribution in the left hand, and a weakness of the intrinsic muscles of both hands. The Achilles reflexes were absent, but the other tendon reflexes were not unusual.

The hemoglobin level and the erythrocyte and leukocyte counts were normal. Albuminuria, with albumin content of grade 2, was the only unusual finding in urinalysis. The result of the serologic test for syphilis was negative. The fasting blood sugar level was normal. Findings from tests for lead, arsenic, and porphyrins in the urine were negative.

An electromyographic study showed denervation in several peripheral muscles, with typical fibrillation potentials. The proportion of polyphasic motor unit potentials was above normal. The velocity of conduction was slower than normal in the left ulnar nerve (37 meters per second).

On Nov. 21, 1958, we received information about this patient from her family physician. She had improved, although she still had some pain in the legs. She was able to walk but was clumsy on her feet. The paresthesia also had lessened. She was able to do her own housework, despite the fact that she had fallen and fractured one arm. In general, she was considered to be approximately two-thirds recovered from her worst stage in 1955.

CASE 3.—A 65-year-old farmer registered at the Mayo Clinic on Oct. 13, 1955, with the chief complaint that pain in the lower extremities and twitch-

ing of muscles had persisted for five months. Prior to the onset of this complaint, he had spent two days spraying a cornfield with a solution of an ester of 2,4-D. During this time his sleeves and trouser legs had been wetted with the herbicide. On the next day increasing malaise, headache, nausea, and finally vomiting had made him retire early. On the following day vertigo had prevented his standing, and vomiting had been frequent. After four or five days he had felt generally improved, but at this time he had noted paresthesia of the extremities and pain in the legs, as well as twitching of the muscles of the calves and arms. He described the paresthesia and muscle twitching as a "feeling of worms crawling beneath the skin." Gradually the fasciculations had become more pronounced, until all skeletal muscles were involved. No muscular weakness had been noted.

General examination revealed old healed pulmonary tuberculosis, chronic glomerulonephritis, and atrophy of the right testis. The blood pressure was 120 mm. Hg systolic and 80 mm. Hg diastolic. Neurological examination revealed generalized, extensive fasciculations that were fine to coarse. No objective sensory or motor deficit was found. No evidence of disturbance of the autonomic nervous system was noted. Funduscopic examination disclosed minimal changes of hypertensive sclerosis.

The concentration of hemoglobin and the counts of erythrocytes and leukocytes were within normal limits. The sedimentation rate was 41 mm. in one hour (Westergren method), and the blood urea level 40 mg. per 100 ml. In the urine no arsenic and only 0.04 mg. of lead per liter were found. Urinalysis showed persistent albuminuria and occasional casts. On examination of the cerebrospinal fluid, the findings from manometric studies were normal, as was the appearance. The concentration of protein was 65 mg. per 100 ml., one lymphocyte was present, the Wassermann reaction was negative, and the colloidal gold curve was 0000000000.

An electromyogram (made by Dr. E. H. Lambert) showed no evidence of denervation. The velocity of conduction of the left peroneal nerve was slightly slowed (38 meters per second). Motor unit potentials were normal. Fasciculations were of the grouped discharge type and similar to those that can be caused by drugs such as neostigmine.

This patient returned for reexamination on Aug. 24, 1956. He stated that he had constant pain in the upper and lower extremities. He had stopped working in November, 1955, because of the pain. The fasciculations had persisted. Prednisone therapy for three months had not lessened the pain or fasciculations, and he was taking codeine to control the pain. Minimal paresthesia was present in all four extremities.

The findings from neurological examination were essentially unchanged, except for a slight decrease in perception of vibratory stimuli at the ankles. An electromyographic examination indicated no significant change from the status disclosed by the previous examination.

Comment

In all three of the cases reported above, symptoms and signs of a general toxic reaction as well as involvement of the peripheral nervous system developed after exposure to an ester of 2,4-D. So far as we know, there have been no other reports of a toxic reaction to this substance in humans. Hildebrand [2] mentioned that some investigators consumed unreported amounts of 2,4-D and suffered no ill-effect. He also stated that the 2,4-D solution is not irritating to the skin.

Hill and Carlisle,[3] however, in autopsies on animals subjected to chronic poisoning, found renal edema with tubular changes; in some dogs they also found evidence of damage to the liver. Bucher [4] noted the production of temporary myotonia in several species of laboratory animals after a single injection of 2,4-D. He did not find any striking change on histological examination of various organs, but he did note that parenteral administration in dogs caused sneezing, lacrimation, and rubbing of the eyes, as well as a gastrointestinal disturbance with vomiting and anorexia. In mice, besides the myotonia and other reactions found in dogs, there were diarrhea, sluggishness, reluctance to move, rigidity of the tail, and a coarse clonic tremor. Coma and death followed in some animals, while others recovered without residual neurological deficits.

Sollmann [5] has said that a syndrome of myotonia, stiffness of the extremities, ataxia, lethargy, paralysis, and coma may follow the parenteral administration of 2,4-D in experimental animals. Large doses may cause ventricular fibrillation also.

In plants, a concentration of 10 ppm of 2,4-D stimulates growth. When the concentration is increased to between 100 and 1,000 ppm, the excessive stimulation of growth kills the deep root system.[3] It has been postulated that the metabolism of phosphate is interrupted or inhibited.

In our patients the toxic substance entered through the skin and possibly also by way of the respiratory system. The 2,4-D had been diluted, but still, with wetting of the extremities and the clothing, the exposure apparently was greater than usual. The involvement of the peripheral nervous system could be a result of a direct toxic effect, or possibly a sensitivity reaction, such as that seen after the injection of a vaccine or an antitoxin. At present, the mechanism of toxicity that follows exposure of mammals to 2,4-D is not known.

In order to prevent further cases of neuropathy from this herbicide, it seems logical to recommend shorter periods of exposure, frequent washing of the skin, and changing of clothes when they be-

come wet with the solution. No antidote is known, and there seems to be no specific treatment for the neuropathy if it develops.

Summary

Three cases of polyneuritis occurred after heavy exposure to an ester of dichlorophenoxyacetic acid (2,4-D). The mechanism of the toxicity affecting the peripheral nervous system is unknown. There is no antidote and no specific treatment.

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THE PROCTOLOGIST AND THE PRACTICE OF MEDICINE

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There is evidence that proctology was practiced in ancient times and existed even then as a specialty. Nevertheless a proctologist should be a physician first and a specialist second. There are many conditions, such as pruritus ani and hemorrhoids, that should not be treated locally until there has been a general search for causative factors. Conversely there are many conditions that should not be treated systemically until the physical examination has included a proctologic survey for the diagnostic information it may yield. Specialties rise as their need arises and fall for lack of usefulness. Proctology is a much-needed specialty, but physicians must never forget that, whatever their regions of special interest, they are treating human beings and not just diseased parts of people.

While ours is called the "age of specialization," a look back through the centuries reveals that specialization had developed to a marked degree in the earliest times of which there is any record. Imhotep, an Egyptian of the third dynasty (about 3000 B. C.), the earliest known physician, was especially skilled in relieving pain by producing sleep. Herodotus of Halicarnassus, the Greek historian, reporting his travels in Egypt in the fifth century B. C., recorded the following statement (same meaning given by various translations):

> The art of medicine in Egypt is thus exercised: each physician is confined to the study and management of one disease only; there are of course a great number who practice this art: some attend the disorders of the eyes, others to those of the head, some take care of the teeth, others are conversant with all diseases of the bowels; whilst many attend to the cure of maladies which are less conspicuous.

As a general rule, however, practitioners who were especially skilled in a branch of medicine in ancient times were not necessarily "full specialists" as we define specialists today. They were apt to be men who were more proficient in one phase of practice and devoted more time to that phase in the course of their general practices.

Pioneers in Endoscopy

The means to inspect adequately and to explore visually the hollow viscera, such as the urinary bladder, trachea and bronchi, esophagus, and the large intestine, for diagnostic and therapeutic purposes, was made possible by ingenious men of vision with inquiring minds. The urologists were the pioneers in such work. It was Philip Bozini who in 1805 devised the first endoscope, which he called the *lichtleiter*, an illuminating tube with which to see inside the urinary bladder.

It was not until 1895 that the first proctoscope and sigmoidoscope were introduced, and it remained for Howard Atwood Kelly of Johns Hop-

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