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Hexachlorophene Poisoning

Hexachlorophene is an antibacterial agent widely used in soaps and antiseptic solutions because of its low toxicity and high bactericidal properties. It is used in agriculture as a fungicide on citrus fruits and a number of vegetables. Toxicity from either ingestion or topical application can occur, however. This paper will present four deaths related to hexachlorophene exposure, two acute and two chronic.

Materials and Methods

The files of the Armed Forces Institute of Pathology (AFIP) were searched for all cases of hexachlorophene poisoning. With the aid of the Institute's computer system, four fatal cases were located. Two deaths were cases of acute poisoning caused by ingestion of the drug, while the other two were chronic poisonings caused by repeated topical application of hexachlorophene. One of the deaths from ingestion has been previously reported [*1*].

Case Reports

Case 1

A 57-year-old white man accidentally ingested 240 cc of 3 percent hexachlorophene several hours prior to a routine right inguinal herniorrhaphy. The surgical procedure was done under spinal anesthesia and was uneventful. Postoperatively, the patient was unable to pass his urine. A catheter was inserted, but no urine was obtained. The following morning the patient was noted to be short of breath and cyanotic. He complained of being weak, extremely thirsty, and numb in his legs. On examination he was hypotensive, extremely restless, and had rapid deep respiration. He was pronounced dead approximately 30 h after the ingestion of 3 percent hexachlorophene.

At autopsy, there was severe congestion of the entire wall of the ileum, with mucosal hemorrhages. The brain weight was normal and showed no abnormalities grossly. On microscopic examination, severe congestion of blood vessels was seen.

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Case 2

A 46-year-old woman accidentally ingested 200 cc of 3 percent hexachlorophene [*1*] intended for preoperative skin cleaning. Shortly thereafter, she underwent an elective abdominal hysterectomy under spinal anesthesia. There were no problems during the course of the operation except for one episode of vomiting and a bowel movement. Soon after surgery the patient had another episode of vomiting and another bowel movement.

The day after surgery the patient was lethargic and confused. During the evening of this same day, she became febrile and later comatose. The patient was pronounced dead 44 h after the ingestion of hexachlorophene.

At autopsy there were bilateral pleural effusions as well as a peritoneal effusion. The lungs were edematous. The bronchial mucosa was hemorrhagic. There were fibrin thrombi in the lungs and the liver. The ileum was severely congested. The brain weight was normal. Sections of the brain revealed no pathologic abnormalities. Toxicologic analysis revealed a hexachlorophene blood level of 3.5 mg percent.

Case 3

A 3-year-old white girl was admitted to the hospital with 15 percent second-degree burns and 2–3 percent third-degree burns. She was treated with oral fluids, penicillin, and streptomycin plus 3 percent hexachlorophene baths several times a day.

Initially she did well. Several days after admission to the hospital, it was noted that the child was not behaving normally. She became extremely withdrawn, with absolute lack of communication with anyone, including her mother. She was very irritable, responding to contact with people by crying. She became anorectic and began to lose weight. There was no evidence of septicemia and her burns were improving. Several psychiatric consultations were obtained, since it was thought that her abnormal behavior was due to a pathologic relationship with her mother. Her feeding and behavior became a bigger problem than her burns.

She started to become lethargic, and during her third week of hospitalization she stopped breathing and became cyanotic. At this time the electrolytes and the complete blood cell count (CBC) were normal, there were no signs of septicemia, and the blood cultures were negative. Findings from urinalysis were within normal limits, as were roentgenograms of the chest. The patient was pronounced dead 22 h after this episode.

At autopsy, the first- and second-degree burns on both thighs were seen to be healed. On gross examination the brain showed flattening of the gyri and marked narrowing of the sulci, giving a completely smooth appearance to the surface of the cerebral hemispheres. There was uncal and cerebellar notching from herniation.

Microscopic examination revealed pathologic changes only in the brain. Severe vacuolation or spongiosis of the white matter was present. These vacuoles did not appear to contain any substance in their lumen. Swelling of oligodendroglia seemed to be forming some of these vacuoles, but in some instances no relationship with the latter was seen (Fig. 1).

Case 4

A 2-year-old white girl was admitted with the diagnosis of second-degree burns over less than 10 percent of the body area. Because she appeared to be in good condition, it was decided not to give her intravenous fluids or antibiotics. Her treatment consisted entirely of warm 3 percent hexachlorophene baths three times a day. These were increased to four times a day on the sixth hospital day. The first week in the hospital she appeared to be

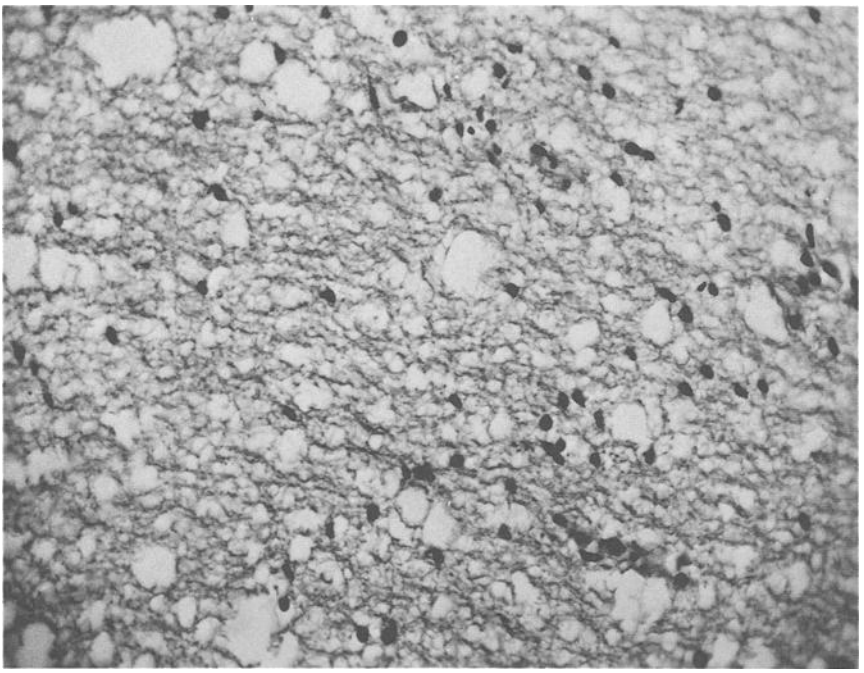

FIG. 1—*Section of the brain (Case 3) showing spongiosis of white matter and swelling of oligodendroglia (H and E stain, X305; AFIP Neg 72-3675).*

entirely normal, the burns appeared clean, and the patient was having adequate urinary output and appeared hydrated.

On the tenth hospital day, the patient became somewhat lethargic and less interested in her surroundings. She cried in response to any procedure and became severely anorectic and significantly withdrawn. The burns at this time had healed almost completely. She started on a downhill course, developing vomiting and dehydration. On the 18th hospital day, she sustained a grand mal seizure and lost consciousness. A spinal tap revealed an opening pressure of 500 mm H_2O. Examination of the fluid revealed no cells and a protein level of 40 mg/100 ml. Shortly after the lumbar puncture, she had a respiratory arrest. She was resuscitated and placed on a Bird respirator, but died four days later.

At autopsy, the pertinent positive findings were limited to the brain. The brain showed the same type of spongiotic appearance of the white matter (Fig. 2) as in Case 3. Focal areas of necrosis were also seen. These areas were interpreted as a recent change resulting from hypoxia superimposed on the original toxic insult.

Comment

Although hexachlorophene was introduced in 1948, case reports of morbidity or mortality from hexachlorophene preparations are few. There were only two deaths in the English-speaking literature up to 1972 [*2,3*]. The first death occurred in a 6-year-old mentally retarded child who ingested 120 to 150 cc of a 3 percent solution of hexachlorophene [2]. Even though gastric lavage was performed within 15 min of ingestion, the child became comatose in less than one h and died within nine h. The second death, mentioned

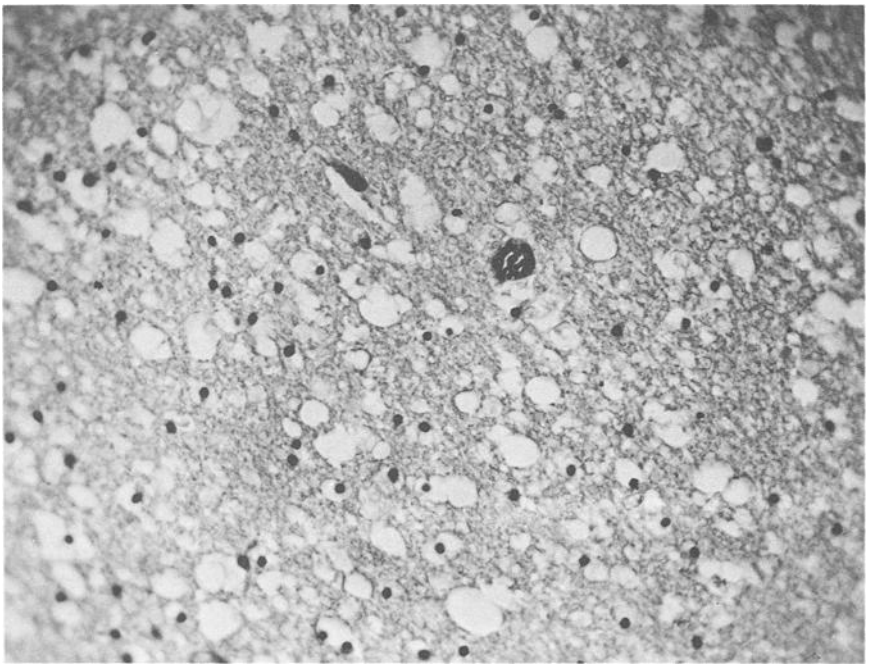

FIG. 2—*Section of the brain (Case 4) showing spongiosis of the white matter (H and E stain, X305; AFIP Neg 72-3676).*

briefly by Pilapil, was that of a newborn infant given a spoonful of 3 percent hexachlorophene solution in each feeding bottle for approximately two weeks, after which the infant "suddenly died" [3]. Wear et al [4] described ten cases of accidental ingestion of hexachlorophene preparations, four of which they had personally encountered. No deaths attributable to hexachlorophene occurred in their series.

While morbidity and mortality most often occur following oral ingestion of hexachlorophene, intoxication can occur following absorption through the skin. Herter [5] described an infant in whom convulsions occurred following four days of repeated external application of 3 percent hexachlorophene. The solution had been allowed to dry on the skin and was not rinsed off. The other cases of toxicity following absorption through the skin were reported by Larson [6]. He described six cases, three adults and three children, who developed signs of toxicity following repeated washing of burn wounds with 3 percent hexachlorophene solutions. One adult patient developed vomiting and extreme irritability after two weeks of washing. Hexachlorophene levels of 3.5 mg/100 ml in the serum were found, A second adult developed diplopia at serum levels of 2.9 mg/100 ml. Convulsive seizures occurred in the third person at a serum hexachlorophene level of 7.4 mg/100 ml. The three children in Larson's report were all burn patients admitted with a history of convulsive seizures. All had had daily washings with 3 percent hexachlorophene solutions prior to admission. Serum levels of hexachlorophene determined five to eight days following cessation of the washing varied from 0.4 to 0.8 mg/100 ml.

The four deaths in our series fall into two groups. One group represents acute poisoning from oral ingestion, while the other group represents probable chronic poisoning caused by absorption through the skin. Our two cases of acute poisoning were adults who acci-

dentally ingested 7.2 and 6 g of hexachlorophene, respectively. The lethal dose as determined by animal studies has been estimated as from 2 to 10 g [*4*,*7*]. The clinical courses in our cases were relatively short, with death occurring 30 h and 44 h after ingestion. In both cases depression of the central nervous system had occurred. Both victims had a hemorrhagic enteropathy associated in Case 2 with a terminal septicemia and diffuse intervascular coagulation. Postmortem toxicologic studies on this victim disclosed a level of hexachlorophene in the blood of 3.5 mg/100 ml. Examination of the brain in both cases did not reveal the edema of the white matter seen in the two children.

The probable chronic poisonings were in two children who had suffered thermal burns, involving less than 18 percent of the skin surface in one case and less than 10 percent in the other. Both patients had a clear sensorium prior to the institution of multiple daily bathing of their burns with hexachlorophene. Several days later the onset of withdrawal from the environment was noted. The children became lethargic, cried at the slightest provocation, and did not eat. Although the burns responded excellently to therapy, the children experienced cardiorespiratory arrest and died 28 and 22 days after admission, respectively. At autopsy, in both cases, there was severe cerebral edema of the white matter. Similar findings have been reported in two recent animal studies of chronic hexachlorophene poisoning [*8*,*9*]. Kimbrough and Gaines [*8*] fed rats doses of hexachlorophene. Subsequently, the rats developed paralysis and at autopsy were found to have cerebral edema of the white matter. In a second study, six newborn monkeys were washed daily with a 3 percent hexachlorophene solution for 90 days [*9*]. No symptoms developed, but two monkeys had papilledema. At autopsy, all animals had edema of the white matter of the brain and spinal cord.

Although toxicity from hexachlorophene is related to multiple exposures of raw skin surfaces, as in burns, or the bathing of large areas of intact skin surfaces for a number of months, routine whole-body bathing as performed in nurseries for the newborn followed by rinsing off the hexachlorophene is not associated with toxicity [*6*,*9*,*10*]. The serum levels of hexachlorophene detected in the latter cases are nontoxic [*10*]. Multiple exposures to hexachlorophene of small areas of intact skin over long periods of time does not produce toxicity [*6*]. Larson did not find significant levels of hexachlorophene in the sera of physicians and nurses who washed their hands frequently throughout the day with 3 percent hexachlorophene solutions [*6*]. Although the bathing of burn wounds has been associated with toxicity, specific details concerning the final concentration of hexachlorophene in the bath water, the frequency of bathing, and the total skin area bathed have not been reported [*6*].

Even though in our two burned patients, the hexachlorophene probably was a neurotoxic agent, before it can be definitely established as such, much closer observation and more extensive recordings must be made on burned patients bathed in a hexachlorophene solution.

It is suggested that with each bathing of the burned victim records be maintained that include: (1) the final hexachlorophene concentration in the bathing solution, (2) the percentage of the body surface bathed, (3) the percentage of bathed body surface that is raw, (4) the bathing time, and (5) the extent of rinsing. In addition, levels of hexachlorophene in the serum should be determined at regular intervals, and patients should be observed for signs of toxicity.

Summary

Four deaths related to hexachlorophene exposure are reported. Two deaths were acute and were caused by the ingestion of fatal amounts of 3 percent hexachlorophene. In both

cases the victims expired in less than 44 h. At autopsy both had hemorrhagic enteropathy. In one there were diffuse microthrombi in the lungs and liver. Neither victim had edema in the cerebral white matter. The other two deaths were related to numerous repeated exposures to hexachlorophene. These deaths occurred in two children, despite healing of their burns, 22 and 28 days, respectively, after the institution of multilpe daily bathing of the burns with hexachlorophene solutions. The course was characterized by a gradual mental deterioration. At autopsy there was extensive cerebral edema of the white matter similar to that previously reported in experimental animals with chronic hexachlorophene poisoning.

Acknowledgments

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