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Blood dyscrasias and childhood tumors and exposure to chlordane and heptachlor

by PETER F. INFANTE, D.D.S., Dr.P.H.,[1] SAMUEL S. EPSTEIN, M.D.,[2] and WILLIAM A. NEWTON, Jr., M.D.[3]

INFANTE, P. F., EPSTEIN, S. S. and NEWTON, W. A. Jr. Blood dyscrasias and childhood tumors and exposure to chlordane and heptachlor. *Scand. j. work environ. & health* 4 (1978) 137—150. In the United States, chlordane and heptachlor are commonly used in pesticide formulations for agricultural purposes and for termite eradication in the home. Pathological conditions possibly associated with prior exposure to such formulations are presented in this report. Five recently diagnosed cases of neuroblastoma associated with chlordane exposure during prenatal and postnatal development have been identified. Three cases of aplastic anemia and three cases of acute leukemia are also reported in association with chlordane formulations. The cases suggesting association between chlordane exposure and neuroblastoma are of interest in view of recent data on the carcinogenicity and mutagenicity of chlordane and heptachlor and in view of data on environmental distributions and body burdens. The cases of aplastic anemia and leukemia are of interest in view of previous literature reports on associations between chlordane and similar chlorinated hydrocarbon pesticides and blood dyscrasias, and in view of reports indicating that some subjects with aplastic anemia convert to leukemia. As previous studies are too limited to allow the development of valid inferences regarding the neoplastic risk of chlordane, there is need for formal epidemiologic study to evaluate health risks associated with chlordane through home exposure and through occupational exposure for termite exterminators, lawn care operators, and for workers in the agricultural setting.

Key words: acute leukemia, aplastic anemia, chlordane, neuroblastoma.

Chlordane is an active ingredient in many household and garden pesticides that have been in common use for about 25 years (48). The total usage of chlordane in the United States for 1975 is estimated at 25 million pounds. About 70 % was applied around the home, while the remainder was used for agricultural purposes, primarily corn crops (20). There have been various reports on the possible association between exposure to chlordane-based formulations, and to related chlorinated hydrocarbon pesticides, and blood dyscrasias in humans (5, 8, 25, 26, 36, 39, 40, 45, 52, 58, 60, 61, 63). Evidence also indicates that chlordane and heptachlor, as well as other chlorinated hydrocarbon pesticides, are carcinogenic in experimental animals (14, 18, 19, 20 54). Following the administration of chlordane, both hepatic and extrahepatic tumors have been induced in mice and rats (48). Perinatal administration of small doses of heptachlor have induced

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rare "lipomatous" renal tumors similar to those reported to have appeared in rats after treatment with pyrrolizidine alkaloid carcinogens (46). Heptachlor epoxide residues have been detected in the cord blood and organs of stillborn human infants, and this finding indicates transplacental passage (11). Technical grade chlordane is also mutagenic in *S. typhimurium,* strain TA 100, without metabolic activation (V. Simmon, personal communication). To date, no epidemiologic studies have been undertaken to negate the laboratory studies that demonstrate the carcinogenicity and mutagenicity of chlordane. Nor is there currently a reporting mechanism to gather pesticide-related pathological conditions in our population.

For these reasons, five cases of childhood tumors associated with pre- and postnatal exposure to chlordane, plus six additional cases of aplastic anemia and acute leukemia, are presented.

NEUROBLASTOMA

The children with neuroblastoma were diagnosed at a single pediatric hospital between December 1974 and February 1976. During this period, a total of 14 cases of neuroblastoma were admitted. A history of exposure to toxic agents indicates that five cases had prior exposure to chlordane formulations. These cases are summarized in table 1.

Case 1

A two-year-and-eight-month-old girl was diagnosed in December 1974 as having neuroblastoma. Excisional biopsy and tissue examination indicated a poorly differentiated (stage III) neuroblastoma of the right adrenal gland involving the kidney. Both organs were removed. The child was given radiation treatment and chemotherapy. She expired in September 1976. This case has been reported elsewhere (32).

During the first trimester of gestation, the 28-year-old mother's home was treated for termite infestation with 528 l of a 1 % chlordane formulation, made by mixing 4.23 l of technical chlordane with 402 l of water. About equal amounts of chlordane were used inside and outside the house. On the outside of the house, the entire perimeter was treated with subsurface injection, and the ground surface also was sprayed in an area extending 30 to 60 cm from the house. On the inside of the house, holes were drilled into the cement blocks in the basement, chlordane was injected into the holes, and the holes were recemented. The mother states that the odor from the pesticide was offensive inside the house, and, since she was concerned about the possible effects on the developing fetus, she slept at a neigbor's home on the evening of the first day of application. On the second day of application, the spraying of chlordane was completed outside the house, and that evening the mother slept in her own home. The mother relates that the odor was very strong for only 3—4 days, but was noticeable for two weeks after the initial treatment. On the evening of the second day of treatment, the weather turned cold, the windows were closed, and the furnace was turned on. This situation created a particularly strong odor in the basement, where the mother spent 25—30 h a week typing. One year later, chlordane was again sprayed around the outside of the house. Other noteworthy information from the prenatal history is that the mother took two Valium tablets in early pregnancy and also had received a general anesthetic for a tonsillectomy during the first month of pregnancy. The general anesthesia was induced with thiopental sodium and was maintained with halothane and nitrous oxide.

Case 2

A four-year-old boy was presented in July 1975 with a two-week history of lethargy, decreased appetite, and right leg pain. Abdominal palpation and subsequent diagnostic radiographs demonstrated a mass in the right paravertebral area. Exploratory laparotomy revealed a tumor in the right paravertebral area with metastases to regional lymph nodes. Bone marrow biopsy showed malignant cells. The extent of the diseases and histopathologic evaluation indicated a metastatic neuroblastoma (stage IV).

Table 1. Cases of neuroblastoma associated with exposure to chlordane.

Case no.	Pathological condition	Sex	Age at chlordane exposure	Age at diagnosis	Chlordane use
1	Neuroblastoma (stage III)	Female	1st trimester of pregnancy	2 years 8 months	Termite infestation
2	Neuroblastoma (stage IV)	Male	1st trimester of pregnancy and every 6 months thereafter	4 years 5 months	Roach infestation
3	Neuroblastoma (stage IV)	Female	1 year 11 months	4 years 4 months	Termite infestation
4	Neuroblastoma (stage IV)	Male	2 years 5 months [a]	3 years 9 months	Termite infestation
5	Neuroblastoma (stage IV)	Female	3 years 8 months	6 years 5 months	Ant infestation

[a] House also treated with chlordane two years prior to child's birth.

A history of exposure to toxic substances revealed that the mother had been exposed to chlordane during her entire pregnancy. One year prior to conception, the house was treated with chlordane for roach infestation with the procedures presented in case 1. The operator returned every six months to spray under the sink and baseboards. Prior to and subsequent to birth, there was no history of exposure to other chemicals for the mother or child. Aspirin was the only medication taken during pregnancy.

Case 3

A four-year-old girl was diagnosed in November 1975 as having a neuroblastoma. Two weeks prior to admission, the child experienced abdominal pain. At the time of hospitalization, an upper left quadrant and flank mass was present. A radiograph of the chest revealed a mediastinal enlargement. An intravenous pyelogram showed an abnormal left kidney; bone marrow analysis showed no diagnostic abnormality. Exploratory laparotomy revealed an unresectable abdominal tumor arising from the left suprarenal area. Tumor biopsy and histopathological evaluation indicated a stage IV metastatic neuroblastoma.

When the child was 23 months old, the parents moved into a recently purchased house. Just prior to their moving, the newly acquired house was treated for termites by the spraying of chlordane around the baseboards and on the inside of the kitchen cupboards. Holes were drilled into the basement walls, and procedures were carried out as described in case 1. Additional exposure to other chemical agents known to induce tumors in either experimental animals or humans was not identified through interview with the parents.

A history of prior illness revealed that the child had a urinary infection at ages 18 and 24 months, at which time diagnostic radiographs were made. She was also X-rayed because of trauma to the head in May 1974.

Case 4

A three-year-and-nine-month-old boy began to limp, and changes were observed in his gait five weeks prior to admission in September 1975. Radiographs and bone scan showed involvement of several areas of the skeleton, particularly the skull and long bones. Bone marrow aspiration indicated an almost complete replacement of the marrow cells by clumps of tumor cells which were consistent with neuroblastoma (stage IV). A primary tumor site could not be identified.

Two years prior to the child's birth and also when he was two years old, the house was treated for termite infestation with chlordane, with the usual procedures for application. Between these two periods of

chlordane application, a commercial pesticide was used intermittently. Other noteworthy information is that the child was X-rayed to rule out a possible bowel obstruction within the first seven days of postnatal development. The remainder of the history was negative.

Case 5

A six-year-old girl was diagnosed in February 1976 as having neuroblastoma, stage IV. The child developed leg and hip pains two months prior to admission. Subsequently, bone marrow analysis indicated tumor cells. Histopathological evaluation indicated neuroblastoma.

Because of ant infestation, the father purchased a container of chlordane dust which he applied several times around the outside foundation of the house in the autumn of 1973, when the child was three years and eight months of age. The process was repeated in the spring of 1974. The parents could not recall having applied chlordane after the latter period. A history of prior illness was unremarkable.

Histories of pre- or postnatal exposure to additional toxic agents indicated that the mother of case 1 had had a halothane-nitrous oxide general anesthetic in the first month of pregnancy. Cases 3 and 4 had postnatal exposure to X rays. Thus 5 of 14 children diagnosed at the hospital during this period of time had a known home exposure to chlordane. Of the nine additional cases of neuroblastoma, history of exposure to chlordane is not known, because no formal study has yet been conducted.

APLASTIC ANEMIA AND LEUKEMIA

Cases of blood disease associated with chlordane exposure had been treated at several hospitals in the past several years. These cases are summarized in table 2.

Case 1 (aplastic anemia)

A 15-year-old boy had been well until February 1975 when he gradually developed pallor, bleeding gums, and fatigue and was diagnosed as having aplastic anemia. A history revealed that the boy sprayed Isotox[4] and chlordane on bushes and around the foundation outside the house with a garden hose attachment once a month between June and October of 1974. His clothing frequently became soaked with the formulation. Chlordane also was applied along door sills and in some kitchen cabinets where food staples were stored. There was no history of exposure to other substances which have been incriminated as possible etiologic agents for aplastic anemia.

On admission to the hospital in March 1975 the patient appeared pale; otherwise the physical examination was within normal limits. Examination of the peripheral blood showed: hemoglobin, 5.3 g %; reticulocyte count, 2.6 %; white cell count, 3,500, with a differential of banded cells, 20 %; segmented cells, 22 %; lymphocytes, 53 %; monocytes, 5 %; and a platelet count of 20,000. A bone marrow examination showed that all the normal cell types were present, but decreased in number, and the bone spicules were devoid of cells. The hematological findings were consistent with a diagnosis of aplastic anemia. The subject is currently being followed as an outpatient. On follow-up through December 1975 his blood count had remained the same, magakaryocytes were rare, and erythropoiesis and myelopoiesis were diminished. Symptoms of fatigue and, at times, headache and dizziness persisted.

Case 2 (aplastic anemia)

A 28-year-old man had been hospitalized in February 1975 with a two-month history of easily bruising, fatigue, and lightheadedness. One week prior to admission, he noticed bleeding from his gums and nose and black stools (generally indicative of upper gastrointestinal hemorrhage). The patient was diagnosed as having aplastic anemia. Upon admission, the initial hematologic evaluation of peripheral blood in-

[4] Active ingredients: Carbaryl (1-napthyl N-methyl-carbamate; S(2-(Ethyl-sulfinyl) ethyl) 0,0-dimethyl phosphorothioate; 1, 1-bis (p-chlorophenyl)-2, 2,2-trichloroethanol.

Table 2. Summary of new cases of blood dyscrasia associated with exposure to chlordane or heptachlor, either alone or in combination with other agents.

Case no.	Age at diagnosis (years)	Chlordane or heptachlor alone	Chlordane or heptachlor with other drugs	Blood dyscrasia
1	15	0	Isotox	Aplastic anemia
2	28	0	Diazinon, various paints	Aplastic anemia
3	68	0	Undetermined	Aplastic anemia
4	9	1	None	Acute stem cell leukemia
5	23	0	Banvel D, Diazinon, Dursban, 2,4-D, paints, strippers, thinners	Acute lymphoblastic leukemia
6	37	1	None	Acute myelo monocytic leukemia
All cases combined		2	4	

dicated: hemoglobin, 4.8 g %; red blood cells, 1.42 x 10^6; white cell count, 3,300, with a differential of polymorphonuclear cells, 10 % and banded cells 1 %; monocytes, 3 %; lymphocytes 86 %; platelets were 35,000. A bone marrow biopsy revealed absence of hematopoietic material; no megakaryocytes or hematologic precursors were present. The patient was given multiple platelet and red cell transfusions, and he became nearly refractory to these. He was given antigen therapy with no response and eventually a bone marrow transplant was performed. On 11 January 1976 the patient expired.

The subject was self-employed as a realtor and in the year prior to hospitalization he had used various insecticides, paints, thinners, and varnishes while restoring homes. In the six months prior to admission, he had used a 74 % chlordane formulation (Ortho-Klor 74) rather extensively, as well as Diazinon.

Case 3 (aplastic anemia)

A 68-year-old man was hospitalized on 28 October 1969 because of increasing dyspnea, weakness and the development of a pallid complexion. An analysis of the peripheral blood indicated that the hemoglobin was 6.1 g % and that the white blood cell count was 1,000. Following administration of two units of packed cells, the hemoglobin rose to 10.2 g %, while the white blood cells remained at 1,200 with a cell differential of polymorphonuclear, 18 %; monocytes, 2 %; eosinophils, 4 %; and lymphocytes, 76 %. The platelet count was 70,000, and the reticulocyte count was 1.6 %. A bone marrow biopsy indicated aplasia for all cell elements, including megakaryocytes. The hematologic evaluation was consistent with aplastic anemia. Treatment with prednisone was started on 9 November 1969, and the patient was discharged a few days later in a greatly improved condition. The subject developed heart congestion and expired 30 January 1970.

A history of exposure to toxic agents ascertained from the surviving spouse revealed that the subject had purchased a bottle of chlordane which he had used for soil treatment around rose bushes, for crab grass control and for termite control in the basement of their house. The wife further stated that her husband had sprayed a 74 % chlordane formulation

(Ortho-Klor 74) in the basement more than once during a three-year period prior to the onset of symptoms.

Case 4 (acute stem cell leukemia)

A nine-year-old girl was diagnosed as having acute stem cell leukemia. Three weeks prior to admission the child developed symptoms of fatigue associated with a low grade fever. On admission to the hospital in December 1969, she appeared pale with a few scattered purpuric areas. Analyses of peripheral blood indicated: hemoglobin, 4.5 %; reticulocyte count, 0.1 %; white cell count, 6,250, with a differential of blast cells, 35 %; lymphocytes, 60 %; neutrophils, 5 %; and a platelet count of 2,500. A bone marrow aspirate showed that erythropoiesis was depressed, myelopoieses was replaced by stem cells, and megakaryocytes were absent. The patient expired in October 1973.

The child was born in November 1960. Beginning in the spring of 1961, the house was treated annually with chlordane for termite infestation. In 1967, floorboards were removed from the entire house, and 930 l of a 2 % chlordane formulation were poured over the ground inside the house. The father relates that the chlordane took about 10 days to soak into the ground. The floorboards were then replaced, and the family moved back into the house. Two years later, the child developed leukemia. The mother did not take any medication, nor did she receive any X rays during pregnancy. The remainder of the history was also negative.

Case 5 (acute lymphoblastic leukemia)

A 23-year-old man was diagnosed as having acute lymphoblastic leukemia in July 1973 and is currently in remission. Past history revealed that he had been in good health, except for a chronic ear infection, until two weeks prior to hospital admission, when he developed an external otitis and adjacent facial cellulitis, which did not respond to penicillin. At the time of admission in July 1973 the patient had had a temperature of 40.5°C; pancytopenia, with a white cell count of 1,800, consisting of 95 % lymphocytes; a hemoglobin of 10.0 g %; and a platelet count of 90,000. The bone marrow was consistent with a diagnosis of acute leukemia.

Before hospitalization, the only medication the patient had received was ear drops. He had been employed by a lawn care firm for a three-year period prior to hospitalization, during which he sprayed lawns with chlordane, Banvel D, Diazinon, and 2,4-D.[5] Also, a week before hospital admission, the patient removed the paint from his car and repainted it over a one-week period, using various paints, strippers and thinners.

The patient responded to antibiotic treatment for the acute infection and was treated with a regimen of predisone. One month later, his platelet count rose from 90,000 to 220,000, the white cell count rose from 1,800 to 6,000, and the hematocrit rose from 23 to 30 with two units of whole blood. Remission was induced with prednisone and vincristine. He was also treated with cranial irradiation and intrathecal methotrexate for the prevention of symptomatic central nervous system leukemia.

Case 6 (acute myelomonocytic leukemia)

A 37-year-old male was hospitalized for possible leukemia in August 1975. For two months prior to admission, he had been feeling weak and fatigued. Ten days prior to admission, he had his teeth cleaned by a dentist. He noticed that the gums did not stop bleeding until the second day after his visit. At the same time, he noticed bruise marks over his extremities.

Upon hospitalization, his initial hemoglobin was 10.7 g %, reticulocyte count was 1.6 %, and platelets were 30,000. Bone marrow biopsy initially showed 100 % cellularity with markedly depressed erythrogenesis. Almost all of the recognized cells seemed to be immature. Granulocytic stem cells were 82 %. The impres-

[5] Banvel D: Dicamba or 3,6-dichloro-o-anisic acid or 2-methoxy-3,6-dichlorobenzoic acid; Diazinon: 0,0-diethyl 0-(2,isoprophyl-6-methyl-4-pyrimidinyl)phosphorothioate, Dursban: 0,0-diethyl 0-(3,5,6-trichloro-2-pyridyl)-phosphothicate; 2,4-D: 2,4-dichlorophenxyacetic acid.

sion was consistent with acute myelomonocytic leukemia. The patient was placed on acute leukemia protocol. He expired 24 October 1975.

A history of exposure to toxic agents revealed that the subject had frequently used chlordane around the house for insect control for the past 10 years prior to admission. He had often placed a full strength 44 % chlordane formulation (Ortho-Klor 44) in a paint pan and brushed it on all of the basement windows, both inside and outside the house several times a year. At times he complained of headache for a few hours after the application. Once a month, he also sprayed chlordane on the lawn and on the side of the house with a garden hose attachment apparatus for protection against grubs. His wife states that he purchased the chlordane in a pint bottle several times a year. A history of exposure to additional agents possibly associated with aplastic anemia or leukemia was negative.

A history of exposure to other toxic agents indicated that blood disease case 1 was exposed to Isotox; case 2 was exposed to Diazinon and various paints; case 5 was exposed to Banvel D, Diazinon, Dursban and 2,4-D and one week before hospital admission, he was exposed to paints and paint thinners.

REVIEW OF CASES IN THE LITERATURE

Table 3 summarizes 25 previously reported cases of blood dyscrasia associated with exposure to chlordane or heptachlor, either alone or in combination with other drugs. From these data, it can be seen that in six cases, chlordane or heptachlor alone was implicated; in 15 cases, chlordane exposure was accompanied with unspecified drugs, some indicated as "toxic" or as "not known to be associated with blood dyscrasias;" and in four other cases, chlordane was accompanied with other specified pesticides or drugs. Of the 25 cases shown in table 3, 19 were diagnosed as aplastic anemia, 2 as leukopenia, and 1 each as hypoplastic anemia, hemolytic anemia, megaloblastic anemia, and thrombocytopenia.

In addition to these previously documented cases, unspecified combinations of chlordane, lindane, and DDT were associated with 40 cases of pancytopenia, 10 cases of thrombocytopenia, and 10 cases of leukopenia reported in the United States between 1955—1961 as shown in table 4 (21). The data in table 4 are taken from a report by the American Medical Association's Study Group on Blood Dyscrasias. Through a voluntary reporting mechanism, the Study Group compiled cases of blood disease suspected as being etiologically related to drug or chemical exposure (21). The type of blood dyscrasia is presented either by pesticide alone or in combination with other unspecified "drugs not known to be toxic," plus those "known to be potentially toxic." In a majority of the cases, pesticide exposure was either alone or in combination with "drugs not known to be toxic." A maximum of eight cases in table 4 may have appeared in table 3, i.e., the cases reported by Conley (8), Muirhead et al. (40), and Huguley et al. (31), since the time period for the actual occurrence of these cases overlaps the period for the cases shown in table 3. The case reported by Moore (39) (table 3) occurred in 1953, which was prior to the existence of the Study Group, and is probably not represented in table 4. [During approximately the same period of time (1955—1963), 16 Mexican cases of aplastic anemia with a history of repeated contact with the pesticides lindane, dieldrin or DDVP were reported (45).]

Although chlordane and heptachlor have been suspended for major agricultural uses, no attention has been given to possible short- or long-term health risks involved with particular reference to carcinogenicity and blood dyscrasia through home application of chlordane, particularly for termite infestation. The five cases of blood dyscrasia in association with chlordane reported by Conley (8), Moore (39), Furie and Trubowitz (26), and Muirhead et al. (40), plus the 11 new cases of blood dyscrasia and childhood tumors reported in the present communication, total 16 cases available with detailed exposure

Table 3. Summary of cases of blood dyscrasia reported in U.S. literature, associated with exposure to chlordane or heptachlor, either alone or in combination with other agents.

Author and year	Number of cases reported				Blood dyscrasia
	Total cases	Chlordane or heptachlor alone	Chlordane or heptachlor with other drugs		
			Unspecified	Specified [a]	
Conley, 1955	1	0	0	Sulfonamide	Hypoplastic anemia
Conley, 1955	1	0	0	Toxaphene sulfonamide	Aplastic anemia
Moore, 1955	1	0	0	DDT and lindane	Aplastic anemia
Muirhead et al., 1959	1	0	0	Dieldrin toxaphene	Hemolytic anemia
Muirhead et al., 1961	5	2	3	0	Aplastic anemia
Loge, 1965	3	3	0	0	Aplastic anemia
Loge, 1965	9	0	9	0	Aplastic anemia
Loge, 1965	2	0	2	0	Leukopenia agranulocytosis
Loge, 1965	1	0	1	0	Thrombocytopenia
Furie & Trubowitz, 1976	1	1	0	0	Refractory megaloblastic anemia
Reports combined	25	6	15	4	

[a] Specified drugs are named.

Table 4. Number of cases of blood dyscrasias associated with pesticides (chlordane, lindane, and DDT) reported by the American Medical Association's Study Group on Blood Dyscrasias for the years 1955—1961 (21).[a]

Blood dyscrasias	Exposure history			
	Pesticides	Pesticides "with other nontoxic drugs"	Pesticides "with other potentially toxic drugs"	Exposures combined
Pancytopenia	10	19	11	40
Thrombocytopenia	8	2	0	10
Leukopenia	1	1	8	10
Dyscrasias combined	19	22	19	60 [b]

[a] In this report, exposure histories for chlordane were grouped together so that it is not possible to determine the number of exposures for the individual pesticide.

[b] Because the time periods for the cases reported by Conley (8), Murihead et al. (40) and Huguley et al. (31) (table 3) overlap with the cases reported in table 4, eight of the cases shown in table 3 might also be included in table 4.

histories. Of these 16 cases, 12 had exposure to chlordane through home application, 3 were involved with farm work and 1 worked for a lawn care firm. The greater number of cases associated with home use may be a reflection of a greater population at risk through home application. A second indication that health risks might be greater through home exposure can possibly be seen in the data for systemic chlordane poisoning presented by the American Medical Association's Committee on Pesticides (8). Excluding 1 suicide, 9 of 14 poisonings occurred through home use, 4 occurred through agricultural exposure, and only 1 case occurred trough industrial manufacturing.

In the absence of epidemiologic studies, the statistical demonstration that any chemical or drug has an etiologic relation to blood dyscrasias, such as aplastic anemia and leukemias, is difficult to make because of the relatively low incidence of these conditions (45). For example, chloramphenicol-induced aplastic anemia was observed sporadically soon after the drug was released in 1949, but so few case reports appeared in the literature that its potential toxicity was not apparent until several years later (21, 47). Because a large number of substances has been associated with blood dyscrasias (21) and the occurrence in the general population is rare, some type of idiosyncratic response might be involved. However, prior to exposure, the subpopulation that might have such a response as a result of normal pesticide usage would be virtually impossible to identify.

RELATION OF APLASTIC ANEMIA TO LEUKEMIA

In the United States, the mortality rate for leukemia is about seven deaths per 100,000 population, while mortality from aplastic anemia is about 0.5 deaths per 100,000 population. Whether aplastic anemia is a preleukemic process, or a potentially leukemic disease most likely depends upon the interaction of the etiologic agent with the host and the genetic make-up of the host's cells. The likely relation between aplastic anemia and leukemia may be a hereditary defect in the stem cells, which makes them susceptible to an agent which causes cell injury and leads to either aplastic anemia, leukemia, or both.

Several conditions and agents associated with aplastic anemia also have been associated with an increased incidence of acute leukemia. The aplasia may be a phase in the development of leukemia, or the absence of normal marrow cells might increase the susceptibility of the patient to leukemogenesis. Congenital conditions such as Down's and Faconi's syndromes and ataxia-telangiectasia that show either abnormal chromosomes and/or immune difficiencies show a high rate of leukemia (27, 29, 35). This finding suggests that instability of chromosomes and immune suppression predispose toward leukemia. In Faconi's anemia, increased chromosomal breaks, aplasia, and an increased incidence of leukemia are seen (28). Radiation is known to induce both aplastic anemia and leukemia (9, 10, 57), the latter peaking at about six to seven years after exposure (3). Chloramphenicol has also been associated with aplastic anemia (4). Some patients have later developed acute leukemia (6, 7, 41). The usual effect of this agent upon cells is to inhibit mitochondrial protein synthesis; however, in some people, because of a genetic biochemical defect, therapeutic concentrations of chloramphenicol inhibit DNA synthesis, which causes bone marrow aplasia (62). Bone marrow cells resistant to chloramphenicol have been shown to occur in some patients with aplasia (30), and this occurrence suggests the presence of at least two stem cell populations. Benzene has clearly induced aplastic anemia (23, 38, 56), and many times within a relatively short period after exposure. Benzene apparently acts by suppressing DNA synthesis of differentiated bone marrow cells and not by damaging stem cells. The subsequent development of acute myelogenous leukemia in some patients with benzene-induced aplastic anemia is well documented (15, 23, 56, 59).

Patients who have marrow aplasia, and who later develop leukemia, show a persistent reduction in normal cells and the appearance of abnormal leukemic cells. Perhaps the few remaining cells in aplas-

tic anemia are either more susceptible to leukemogenic viruses or more susceptible to transformation to malignant blasts by the continuing efforts of the offending agent. The process appears to be similar in Fanconi's anemia, ionizing radiation, and chemically-induced aplasia. Although the type of leukemia may vary in all of these diseases, the incidence of acute myelogenous leukemia is increased the most markedly.

The association of paroxysmal nocturnal hemoglobinuria (PNH) with aplastic anemia (13, 24, 43) supports the presence of the development of two distinct cell populations. In PNH red cells from one of the populations are lysed by complement in the presence of acidified serum. In aplastic anemia, the marrow stem cell may be transformed to an abnormal cell which cannot replicate, or one of the cell clones may be susceptible to a cytotoxic effect of an offending agent (13, 27). Thus aplasia may be the result of either an abnormality of the pluri potential stem cell or an altered microenvironment due to defective stromal cells or both (53). An epidemiologic study to determine the proportion of patients with chemically-induced aplastic anemia who later develop acute leukemia would seem appropriate.

DISCUSSION OF NEW CASES OF BLOOD DYSCRASIA AND NEUROBLASTOMA IN RELATION TO REPORTS IN THE LITERATURE

It is apparent that our six blood disease cases are consistent with previous reports in the literature on the occurrence of various blood dyscrasias in association with the use of several chlorinated hydrocarbon pesticides. Since chlordane, heptachlor, toxaphene, lindane, DDT, dieldrin, and aldrin are similar in chemical structure (fig 1), chemical properties, and in toxicity to humans (51), findings that more than one of the aforementioned substances might be associated with blood dyscrasias in humans would not be entirely unexpected.

Although exposure to chlorinated hydrocarbon pesticides has been related to

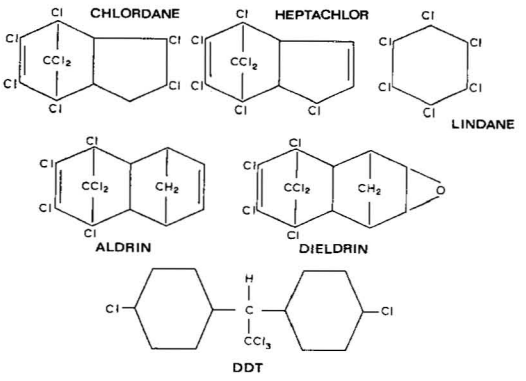

Fig. 1. Chemical structure of chlordane, heptachlor, and similar chlorinated hydrocarbon pesticides.

aplastic anemia, to our knowledge neither chlordane, heptachlor, nor other chlorinated hydrocarbon pesticides have been reported in association with acute leukemia. However, several reports have indicated that subjects with aplastic anemia associated with various agents have later developed acute leukemia (6, 7, 13, 15, 23, 41, 56). In some cases, the conversion from hypoplastic anemia to leukemia occurred within a relatively short period of time (16, 23). Although the leukemia is usually of the myeloblastic type, acute lymphatic leukemia has also been reported in association (44). Thus substances such as chlorinated hydrocarbon pesticides that might be capable of inducing bone marrow suppression might also be capable of inducing acute leukemia within a relatively short period of time.

In regard to our cases of childhood neuroblastoma, we are not aware of previous reports suggesting associations between perinatal pesticide exposure and childhood tumors. However, in view of the evidence of transplacental passage of chlordane metabolites (11) and experimental animal studies, which have indicated the carcinogenicity of chlordane, heptachlor (14, 20, 54), and heptachlor epoxide (55), the possibility of a transplacental carcinogenic mechanism should be experimentally investigated. [Another halogenated hydrocarbon, vinyl chloride, has been demonstrated to be a transplacental carcinogen in rats (37).] Because chlordane and the structurally similar

chlorinated hydrocarbon pesticides are known to be fat-soluble and neurotoxic (51), tissue of the sympathetic nervous system may be target sites for related tumors in humans. Epidemiologic study in this area of investigation also is needed.

STUDIES OF OCCUPATIONAL EXPOSURE TO CHLORDANE

Although the need for field studies to determine the consequences of chlordane use by the general population was expressed over 20 years ago (42), little epidemiologic data from which to develop valid inferences are available. Because of the small sample sizes, high turnover rates, and poor response to health interviewing, the results of several studies on possible ill-health affects among pesticide workers exposed to chlordane appear to be inconclusive. In three studies (1, 22, 42), the sample sizes of the current work force on which conclusions were based ranged from 15 to 34 workers and are totally inadequate. For example, Alvarez and Hyman (1) reported no ill-health effects among 24 men who had worked in the manufacture of chlordane for periods of time ranging from two months to five years. Inspection of their data shows that eight workers had been employed a year or less and only 12 subjects had exposure periods ranging between three and five years. The data indicate a high turnover rate and an extremely small sample size on which to base conclusions. In another study, based on survey questionnaires (50), only 12 % of the companies responded and less than 20 % of the personnel at risk completed questionnaires. The latter study (50) indicates that the turnover rate of servicemen, the high exposure risk group, was 20 % annually. Thus, subject selection as well as the response may have biased the results. Also, no mention is made of any attempt to contact employees who had discontinued service in any of these studies.

It is also interesting to note that the relative risk for developing leukemia appears to be the greatest in farmers (47). One may question whether or not pesticide exposure, especially the chlorinated hydrocarbons, might be a contributing factor.

ENVIRONMENTAL DISTRIBUTION AND BODY BURDEN OF CHLORDANE AND HEPTACHLOR

Chlordane and heptachlor have a chemical structure similar to that of other chlorinated hydrocarbon pesticides such as dieldrin, lindane, and DDT. Technical chlordane consists of a complex mixture of compounds, with ratios that have been standardized since about 1950, and contains 38.48 % alpha- and gamma-chlordane, 7—3 % pure heptachlor, 5—11 % nonachlor, 17—25 % chlordane isomers, plus other compounds in lesser amounts (54). Technical chlordane is formulated in varying strengths in different pesticidal preparations. Exposure to chlordane can occur through the intact skin, by inhalation of dust or sprays, and by ingestion (2). Human poisonings and fatalities have been reported from dermal or oral exposure to chlordane (12, 17, 34).

Chlordane is one of the most widely used household and garden pesticides. In 1974, 9.5 million kilograms were used. Seventy per cent was applied for termite control and other household use, while the remainder was used for agricultural purposes (20). Chlordane and heptachlor, or their metabolites, are persistent in the environment long after use (54). Treated soil is subject to water erosion, which ultimately leads to aquatic contamination. Chlordane is also widely distributed in ambient air and in household dust (49). Although low in water solubility, their affinity for lipids make chlordane and heptachlor subject to possible bioaccumulation and transfer in the food chain (54). From market basket surveys, components of technical chlordane and its metabolites were found commonly in dairy, meat, fish, and poultry components of the diet (54).

As with other chlorinated hydrocarbon pesticides, metabolites of chlordane and heptachlor may accumulate in man (33). Oxychlordane and heptachlor epoxide residues have been detected in the adipose tissue in over 90 % of large samples of hospital patients studied in 1970—1972.

Heptachlor epoxide residues have been detected in the organs of stillborn infants (11) and also in samples of human milk (54). Because of this environmental accu-

mulation, humans may be exposed from the time of conception on throughout adult life.

SUMMARY

1. New cases of blood dycrasia and childhood tumors are reported following exposure to chlordane.

2. The cases of aplastic anemia are consistent with previous literature reports on associations between chlordane, similar chlorinated hydrocarbon pesticides and blood dyscrasias.

3. The cases suggesting association between chlordane exposure and leukemia are noteworthy in view of previous reports indicating that subjects with aplastic anemia convert to leukemia.

4. The cases suggesting association between chlordane exposure and neuroblastoma are of interest in view of recent data on the carcinogenicity and mutagenicity of chlordane and heptachlor and in view of data on environmental distribution and body burdens.

5. Previous epidemiologic studies are too limited to allow the development of valid inferences regarding the neoplastic risk of chlordane.

6. There is a need for epidemiologic studies to evaluate short- and long-term health risks associated with chlordane in home use and in occupational use for the agricultural setting, for termite exterminators, and for lawn care operators.

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