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TREATMENT OF CHLORDECONE (KEPONE) TOXICITY WITH CHOLESTYRAMINE

Results of a Controlled Clinical Trial

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Abstract Industrial workers exposed to the organochlorine pesticide, chlordecone (Kepone), had signs of toxicity in several organs. The extent of toxicity was proportional to the levels of this chemical in the tissues. In 22 patients, chlordecone was eliminated slowly from blood (half time of 165 ± 27 days — mean \pm S.E.M.) and fat (half time of 125 days, with a range of 97 to 177), chiefly in the stool. Output of chlordecone in bile was 10 to 20 times greater than in stool, suggesting that chlordecone is reabsorbed in the intes-

tine. Cholestyramine, an anion-exchange resin that binds chlordecone, increased its fecal excretion by seven times. In a five-month trial, cholestyramine significantly accelerated elimination of chlordecone from blood, with a half life of 80 ± 4 days (S.E.M.) ($P < 0.005$) and fat (half life of 64 days, with a range of 52 to 85) ($P < 0.05$). Cholestyramine offers a practical means for detoxification of persons exposed to chlordecone and possibly to other lipophilic toxins. (N Engl J Med 298:243-248, 1978)

WORKERS in a small factory that manufactured chlordecone (Kepone)* were exposed to large quantities of this organochlorine pesticide for many months. Some workers had high blood concentrations of chlordecone and evidence of sustained toxicity involving the nervous system, liver and testes.¹ Signs of neurologic impairment included appendicular tremor, stuttering speech, opsoclonus (chaotic eye movements), exaggerated startle response, pseudotumor cerebri and, in one case, visual and auditory hallucinations. Also evident were such neuropsychiatric findings as anxiety, irritability, short-term memory loss and headaches. In most patients the liver was enlarged, liver-function tests gave normal results, and nonspecific evidence of damage was present on light and electron microscopy of liver biopsies. Testicular function was impaired as judged by oligospermia and hypomotile sperm.

There are no antidotes capable of reversing the biochemical lesions resulting from intoxication with chlordecone or with other organochlorine pesticides,

and treatment is usually directed to symptomatic relief.² One approach to therapy is to devise methods for accelerating the excretion of these substances by the body, the assumption being that their continued presence in tissues is the proximate cause of toxicity and carries with it a potential for carcinogenesis.³ We therefore studied the distribution, storage and excretion of chlordecone in these patients and found that it is excreted chiefly in bile and is eliminated in the stools.⁴ However, a substantial enterohepatic recirculation of chlordecone exists that curtails its excretion. We tested the hypothesis that cholestyramine, an anion-exchange resin that binds bile salts and other substances in the lumen of the intestine, might also bind chlordecone and hasten its excretion. Cholestyramine was found to bind chlordecone effectively in vitro and to increase its excretion in rats.⁵ In this study we show that cholestyramine increases the excretion of chlordecone in human beings.

METHODS

Patient Population

A group of 32 male workers, 18 to 47 years of age, previously employed by Life Science Products Corporation, Hopewell, Virginia, were studied. The only product manufactured by this corporation was chlordecone. These men were heavily exposed to this single pesticide during a period of employment that ranged from three to 16 months. The interval between the last date of employment at the factory and the first medical evaluation at our hospital varied from two weeks to 13 months. On first presentation, each patient had signs or symptoms (or both) consistent with toxicity associated with chlordecone exposure, with blood chlordecone concentrations higher than 600 ng per milliliter. All clinical studies were approved by the Medical College of Virginia Committee for the Conduct of Clinical Research and were carried out with the informed consent of each participant.

Control Observations

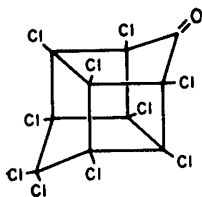
Before the start of the clinical trial of cholestyramine, patients were examined at least bimonthly. Samples were taken for measurement of chlordecone in blood, urine and adipose tissue (biopsied by aspiration of fat through an 18-gauge needle inserted subcutaneously in the abdominal wall without anesthesia).⁶ Liver biopsies were obtained with a Klatzkin needle. The entire sample of fat (10 to 15 mg) or portions of the liver biopsy (5 to 25 mg) were weighed wet and promptly analyzed for chlordecone.

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*1,1a,3,3a,4,5,5a,5b,6-decachloro-octahydro-1,3,4-metheno-2H-cyclobuta[cd]pentalen-2-one:



Measurement of Chlordecone

The method developed for measurement of chlordecone in biologic samples is presented in detail elsewhere.⁷ In brief, samples were acidified with 60 per cent sulfuric acid, and the chlordecone was extracted with hexane/acetone 85:15. The extract was evaporated, and the chlordecone was redissolved in benzene for measurement by gas-liquid chromatography with electron-capture detector. Extracts of stool were alkalized, washed with hexane and reacidified to remove interfering substances.⁷ ¹⁴C-labeled chlordecone (Pathfinder Laboratories, St. Louis, Missouri, a gift of Allied Chemical Corporation) served as internal standard for recovery. Metabolites of chlordecone were not identified in blood, fat or urine. Sensitivity of the assay was limited primarily by sample size. In practice, the minimum detectable levels of chlordecone were 5 ng per gram in blood, bile and stool and 500 ng per gram in fat.

Biliary and Fecal Excretion of Chlordecone

Seven patients entered the Clinical Research Center for measurement of the rates of chlordecone excretion in stool, in duodenal fluid and, in one patient, in T-tube bile. The latter patient (Fig. 1, Patient 7) underwent cholecystectomy for multiple gallstones and agreed to implantation of a T-tube with an occludable distal balloon.⁸ The daily rate of excretion of chlordecone in T-tube bile was calculated from the volume of bile collected hourly for 24 hours, and the concentration of chlordecone in aliquots of each sample. The diverted biliary contents were continuously infused through a tube surgically implanted in the duodenum to maintain enterohepatic circulation of bile salts and chlordecone. When collection of bile was completed, the balloon was deflated, the T-tube was clamped, and stools were collected for 72 hours to measure the rate of fecal excretion of chlordecone. Six additional patients without evidence of biliary-tract diseases were placed on a diet rich in protein and fat, with frequent feedings (three-hour intervals) for 72 hours. Under these conditions tonic contraction of the gallbladder would be expected, and therefore, hepatic bile would flow into the duodenum at a steady rate. The rate of excretion of chlordecone in stool was determined during the next 72 hours. Then, the biliary excretion of chlordecone was measured with the marker-infusion technic of Grundy and Metzger.⁹ After an overnight fast, a double-lumen tube was placed in the duodenum and positioned fluoroscopically with the infusion port at the level of the ampulla of Vater, 15 cm proximal to the sampling port. A sample of "gallbladder bile" was obtained by aspiration of the duodenal contents after intravenous pulse administration of cholecystokinin, 40 Ivy dog units (Karolinska Institute, Stockholm, Sweden) to stimulate contraction of the gallbladder. Next, a liquid meal⁹ was infused into the duodenum at a rate (2 ml per minute) to stimulate release of endogenous cholecystokinin and thereby to cause tonic contraction of the gallbladder.¹⁰ This step permitted measurement of "hepatic-bile" flow under conditions simulating the frequent feeding diet. The infused solution also contained polyethylene glycol (molecular weight, 4000) (2 g per liter) with 4 μ Ci per liter of [1,2-¹⁴C-polyethylene glycol (New England Nuclear Corporation, Boston, Massachusetts) as a nonabsorbable water-soluble marker.¹¹ The duodenal contents were continuously sampled through the distal port of the tube for nine hours and were analyzed for chlordecone and radioactivity. Portions of the samples (0.3 ml) were digested in 2 ml of Soluene 350 and combined with 10 ml of Dimilume (Packard Instrument Company, Downer's Grove, Illinois) for liquid scintillation spectrometry. The rate of biliary excretion of chlordecone was calculated by standard dilution-marker principles.⁹ In two patients stigmasterol, a nonabsorbable lipophilic steroid, was included in the infusion mixture as a second marker.⁹ With use of stigmasterol, the apparent rate of bile production, and hence, for chlordecone excretion, exceeded by twofold the values obtained with [¹⁴C]-polyethylene glycol as marker for bile flow. This discrepancy probably reflects differences in partitioning of chlordecone and markers between the aqueous and lipid phases of intestinal contents.^{12,13} Since the solubility of chlordecone in the contents of the intestine is uncertain, the more conservative estimates for "biliary secretion" of chlordecone obtained with [¹⁴C]-polyethylene glycol as marker are presented.

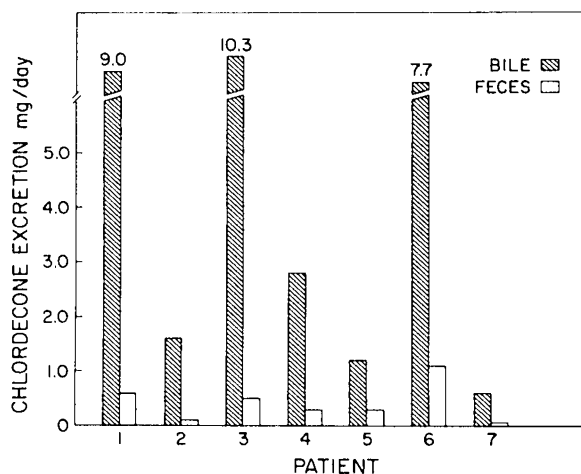


Figure 1. Rate of Excretion of Chlordecone in Bile and Feces in the Patients before Therapy.

Calculation of Total Chlordecone in the Body

We calculated total-body content of chlordecone (CD-T) from the concentration of chlordecone in blood (CD-B) as follows:

$$(\text{CD-T}) = 3.16 \times \text{body weight (kg)} \times (\text{CD-B}) (\mu\text{g/g}).$$

This equation assumes, first of all, that chlordecone is distributed in each patient according to the average values given in Table 1. This assumption is made because simultaneously obtained samples of various tissues in a given patient were not always available. It is also assumed that body weight is distributed equally in each patient as blood (7 per cent), liver (2.5 per cent), adipose tissue (25 per cent) and muscle (43 per cent)¹⁴ and that chlordecone is confined to these tissues. The final assumption, that the concentration of chlordecone in muscle is twice that in blood, is based on the low portion of the range of estimates from measurements of chlordecone in muscle in five patients (Table 1).

Controlled Trial of Cholestyramine Therapy

Randomization of patients. Approximately 12 months after their initial evaluation, 29 patients participated in the clinical study of cholestyramine therapy. The men were stratified into three groups according to their concentration of blood chlordecone upon entry into the study (greater than 1000 ng per milliliter, 10 men, 500 to 1000 ng per milliliter, 10 men, and 100 to 500 ng per milliliter, nine men) and, within each group, were randomly allocated to treatment with either cholestyramine or placebo. Neither the patients nor the investigators were aware of treatment assignments.

Experimental design. Patients were treated for five months with either cholestyramine (16 g per day) in the form of Questran (36 g per day) or Questran placebo in which cholestyramine was replaced by

Table 1. Distribution of Chlordecone in Man.

TISSUE	NO. OF PATIENTS	CHLORDECON CONCENTRATION	PARTITION	
			TISSUE BLOOD	RANGE
Whole blood	32	0.6-32.0	1.0	
Liver	10	13.3-173.0	15.0	4.6-31.0
Subcutaneous fat	29	1.7-62.1	6.7	3.8-12.2
Muscle	5	1.2-11.3	2.9	1.8-4.5
Gallbladder bile	6	2.5-30.0	2.5	1.4-4.1

cellulose and silica gel. The standard commercial preparation contained 75 per cent of the cholestyramine particles of size less than 75 μ m. Both drugs were purchased from Mead-Johnson Company, Evansville, Illinois. With the exception of vitamin K (5 mg per day) and multivitamins, the patients received no other medication regularly. The participants were examined biweekly, and samples were taken for measurement of chlordecone concentration in blood, subcutaneous fat, and urine. Compliance of the patients with treatment was judged by inquiry and need for resupply of medication. Seven patients (four assigned to placebo) failed to keep follow-up visits and were dropped from the study.

Statistical methods. The rate of disappearance of chlordecone from blood during the control and treatment periods appeared to follow first-order kinetics. Linear regression of the natural logarithm of the concentration of chlordecone in blood plotted against time was obtained by the method of least squares. All fitted lines showed a significant regression coefficient ($P < 0.005$). The slope of the regression line during the control period for each patient was compared with the slope during the treatment period (Fig. 3). The difference

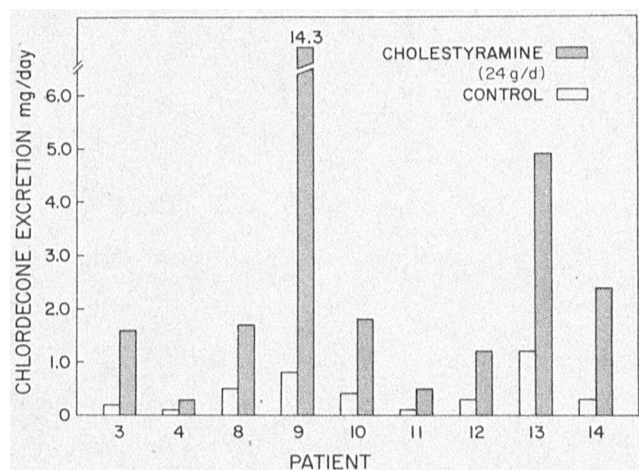


Figure 2. Stimulatory Effect of Cholestyramine on the Rate of Excretion of Chlordecone in the Stool.

Control collections of stool were obtained from each patient for at least 72 hours. Treatment with cholestyramine was started, and 48 hours later, stool was collected for a second 72-hour period.

between the slopes was tested for significance by the likelihood-ratio F-test.¹⁵ The half-life of chlordecone in blood was calculated from the slope of the regression line because exposure to chlordecone had ceased for all patients. Differences between the average half-lives of chlordecone in blood in the groups receiving cholestyramine and those given placebo were tested for significance by analysis of variance (Fig. 4). Sufficient samples of fat were not available during the control period to permit similar testing for statistical significance with data from adipose tissue. Therefore, we fitted a single regression line to the data pooled from the treatment period for each group,¹⁶ and tested the difference between the slopes for significance by the likelihood-ratio F-test. Because these calculations are based on pooled data, variation in the slope of the regression line for the rate of disappearance of chlordecone from fat is given as a 95 per cent confidence interval.

RESULTS

Distribution and Excretion of Chlordecone

High concentrations of pesticide were found in the blood, liver and body fat of the patients (Table 1). The distribution of chlordecone was unusual in that the ratio of the concentration of this substance in fat

as compared to blood (7.4 to 1) was lower than that reported for other organochlorine pesticides, which may be as high as 1400 to 1.^{6,17-19} In five samples of blood, chlordecone was confined to the plasma or serum fraction, with less than 15 per cent present in red cells.

In excretory fluids, chlordecone was undetectable in sweat and was present in minor quantities in urine, saliva and gastric juice. In contrast, "gallbladder bile" contained chlordecone at a concentration equivalent to that in the blood (Table 1). The rate of excretion of chlordecone in "hepatic bile" as estimated from aspirated duodenal contents (Fig. 1, Cases 1-6) or as collected directly from T-tube drainage (Fig. 1, Case 7) varied widely among the patients. However, daily biliary excretion represented a relatively constant proportion of the estimated total-body content of chlordecone (0.52 per cent, with a range of 0.29 to 0.85) in each patient. It was important that only 5 to 10 per cent of the "biliary" chlordecone entering the lumen of the duodenum appeared in the feces (Fig. 1, Cases 1-6). Similarly, the rate of chlordecone excretion in T-tube bile in two experiments was on the average 19 times greater than the rate of elimination of the pesticide in the stool (Fig. 1, Case 7).

Effect of Cholestyramine on Fecal Excretion of Chlordecone

Considering the possibility that biliary chlordecone would be reabsorbed, we administered cholestyramine, a nonabsorbable anion-exchange resin that binds chlordecone *in vitro*.⁵ In nine patients, cholestyramine (24 g per day) increased fecal excretion of chlordecone by 3.3-fold to 17.8-fold (Fig. 2). In contrast, oral administration of activated charcoal (40 g per day) to three patients produced less than a two-fold increase in fecal excretion of chlordecone. In three patients, a dose of cholestyramine of 16 to 24 g per day resulted in the maximum output of chlordecone. The lower of these doses was selected for long-term studies to lessen the chance of side effects and promote patient compliance.

Clinical Trial of Cholestyramine Therapy

The effect of cholestyramine on levels of chlordecone in blood and adipose tissue was studied in a double-blind, randomized, controlled trial of the resin. Twenty-two men received either cholestyramine or placebo for five months. The drugs were well tolerated, and little change in weight occurred. In 11 of 12 patients, cholestyramine treatment accelerated the rate of disappearance of chlordecone from blood (by as much as five times in one patient) in comparison with the patient's rate during the pretreatment, control period (Fig. 3 and 4). The increase in disappearance rate achieved significance in seven patients ($P < 0.05$) for whom sufficient data were available for this type of comparison (Fig. 3 and 4). In contrast, the rate of disappearance of chlordecone in the blood remained unchanged in six of 10 patients given placebo

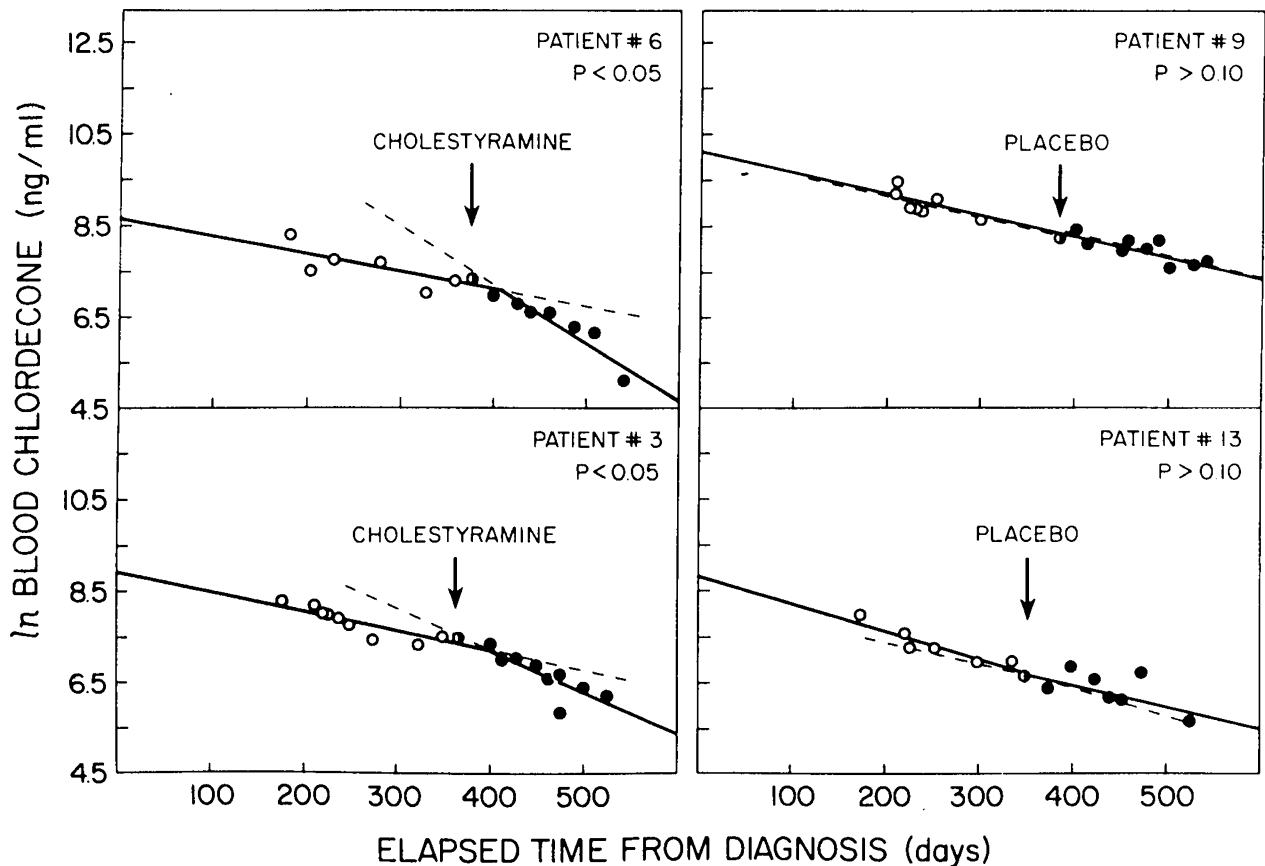


Figure 3. Effect of Cholestyramine or Placebo on the Rate of Disappearance of Chlordecone from the Blood in Four Patients. Linear regressions of the natural logarithm (ln) of the chlordecone concentration in blood during the control (O) or treatment (●) period were used for calculation of the half-lives, summarized in Figure 4.

(Fig. 3 and 4) and decreased significantly in only one (Fig. 4). The average half-life of chlordecone in the blood of patients given cholestyramine was 80 ± 4 days (S.E.M.) — a significant reduction from the control period (165 ± 27 days) ($P < 0.005$). This reduced half-life was also significantly shorter ($P < 0.005$) than the average half-lives in the placebo-treated group during either the control (141 ± 10 days) or treatment (139 ± 20 days) periods (Fig. 4). The average half-life of chlordecone in the blood of patients treated with placebo was unchanged from the control values for either group ($P > 0.10$) (Fig. 4). The control values for each group did not differ significantly ($P > 0.10$).

The possibility that the effect of cholestyramine on blood levels of chlordecone represented redistribution of pesticide rather than depletion of total-body stores of chlordecone seemed unlikely because the concentration of chlordecone in blood was directly proportional to its concentration in fat over a wide range of values in both treatment groups. The regression equations were, for the placebo group, (blood) ng/ml = 0.140 (fat) ng/g + 236; $r = 0.97$ ($P < 0.001$), and for the cholestyramine group, (blood) ng/ml = 0.138 (fat) ng/g + 211; $r = 0.93$ ($P < 0.001$).

The regression coefficients for the two groups were not significantly different from each other. Moreover, in cholestyramine-treated patients, the average half-life of chlordecone in fat (64 days, 52 to 85, 95 per cent confidence interval) and blood (80 days) were similar. The half-life of chlordecone in fat in placebo-treated patients (125 days, 97 to 177, 95 per cent confidence interval) was significantly longer than that for the cholestyramine group ($P < 0.05$). These data indicate that cholestyramine depletes chlordecone from blood and adipose tissue at similar rates.

Relation between Toxic Manifestations and Chlordecone Levels

A decrease in severity of neurologic findings in the patients was evident while levels of chlordecone fell during 18 months of observation. At the time of diagnosis, 11 of 22 patients were unable to work because of tremor or other neurologic disorders, whereas only three remained severely impaired upon completion of the clinical trial. Because neurologic signs were difficult to quantify, we compared the sperm count, as a toxic manifestation of exposure to chlordecone, to the concentration of pesticide in the blood. We found less

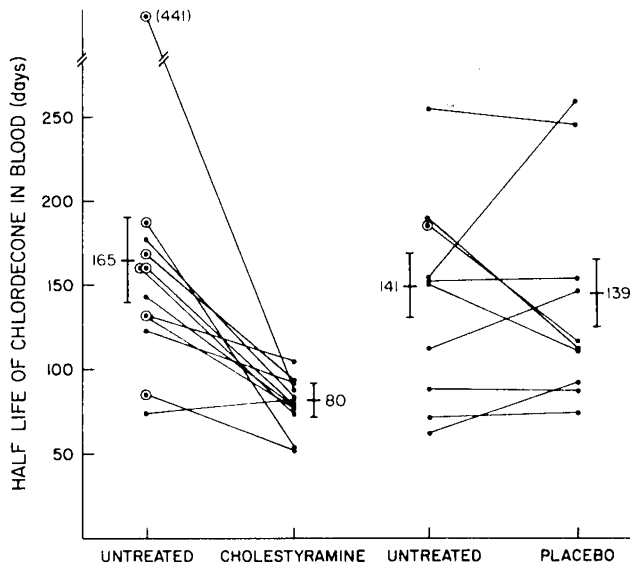


Figure 4. Effect of Cholestyramine or Placebo on the Half-life of Chlordecone in the Blood of Exposed Workers.

Open circles denote patients with statistically significant differences between the half-lives of chlordecone in the control period (untreated) and the treatment period ($P < 0.05$). Average half-lives are given as mean \pm S.E.M. (brackets). Differences are compared for statistical significance in the text.

than 25×10^6 motile sperm per milliliter, and thus assumed sterility, in 19 of 20 examinations of semen in patients whose blood chlordecone level was higher than 1000 ng per milliliter. Significantly fewer abnormal sperm counts were present (seven of 21 examinations) in patients with blood levels of chlordecone less than 1000 ng per milliliter ($P < 0.05$ by Fisher's exact test). Moreover, motile-sperm numbers increased as blood chlordecone concentration declined in 12 of 13 patients. The treatment period was too brief to determine whether accelerated elimination of chlordecone with cholestyramine was associated with a correspondingly rapid increase in sperm counts. After completion of the trial, all patients were given cholestyramine, and six months later, blood levels were undetectable in 12 of 22 and none were judged to have more than "mild" neurologic signs.

DISCUSSION

The use of cholestyramine was based on the present studies of the pharmacodynamics of chlordecone in human beings. The patients were exposed to chlordecone in different quantities and for various lengths of time, resulting in a 20-fold range of chlordecone concentration in the blood. These concentrations were directly proportional to the amount of chlordecone in fat, a major depot in the body. This observation suggests that there is a rapid movement of chlordecone from fat to blood. This view is supported by unpublished studies showing that removal of 80 per cent of blood chlordecone by a four-hour plasmapheresis does not alter blood levels. Although it is commonly

assumed that polychlorinated hydrocarbon pesticides are inextricably retained in body fat, our findings suggest that mobilization of chlordecone from adipose tissue is not the rate-limiting process for the excretion of the pesticide. Similarly, Morgan and Roan have concluded that DDT in human body fat establishes a dynamic equilibrium with the blood en route to elimination via the gastrointestinal tract.¹⁹

Highly lipophilic substances are assumed to distribute among tissues in direct proportion to the lipid content of each tissue.²⁰ The unusually high concentration of chlordecone in blood as compared to fat stands in marked contrast to the partition of other organochlorine pesticides in human beings. A possible explanation is that in biologic systems, chlordecone may exist largely in the form of chlordecone hydrate,⁷ and this circumstance may increase its solubility in such an aqueous medium as blood. Alternatively, from the observations that chlordecone is found predominantly in the plasma fraction of blood, without detectable quantities of "free" chlordecone, and that only minor amounts of chlordecone are found in urine, it may be inferred that chlordecone is bound tightly to plasma proteins. If this postulate is correct, in contrast to the nonspecific hydrophobic interactions reported for other organochlorine compounds,²¹ selective binding of chlordecone by plasma proteins may account for the surprisingly high level of chlordecone in blood.

Approximately 0.075 per cent of the estimated total-body content of chlordecone was eliminated daily in the stool.⁴ On the basis of this fractional excretion rate of chlordecone, and with the knowledge that chlordecone is excreted almost exclusively by the gastrointestinal tract, the calculated half-life of the pesticide in the body is 924 days. In contrast, the observed half-life of chlordecone in blood and fat is about 20 per cent of this value. One explanation for this discrepancy could be that our estimates of total stores of chlordecone may be erroneously elevated. However, an error of five times would be necessary to reconcile the calculated and observed half-lives of chlordecone, and such an error seems unlikely. Another possibility is that chlordecone is sequestered in a "deep" compartment that does not readily equilibrate with the sampled tissues, fat and blood. This phenomenon was not observed in our studies in rats.⁵ An additional explanation could be that chlordecone is modified in the liver or intestine to a chemical form (or forms) that is not measured as chlordecone under the standard assay conditions. In pursuing this possibility, we have identified in human stool the presence of chlordecone alcohol,²² in concentrations apparently equal to or greater than those of chlordecone. Therefore, the discrepancy is best explained by an underestimate of chlordecone excretion in the stool.

The present studies establish that cholestyramine is a practical treatment for patients exposed to large quantities of chlordecone. They do not resolve the question of cholestyramine treatment in asympto-

matic patients with low levels of chlordecone in the body. If both the dose of chlordecone and the length of exposure of the tissues to this chemical are related to development of cancer, cholestyramine may have value in preventing this potential complication. Detection of small quantities of chlordecone in some residents of eastern Virginia and Maryland may be expected because the rivers and marine life of this region are extensively contaminated with the pesticide²³ and because chlordecone is degraded minimally, if at all, in the environment.²⁴ However, the magnitude of the hazard of environmental contact with chlordecone to human beings has not been established. Therefore, the indications for therapy remain speculative and warrant further investigation.

We are indebted to Drs. John Taylor and William Blackard and the staff of the Clinical Research Center for assistance in conducting these clinical studies, to Drs. Charles Schwartz and Z. Reno Vlahevic for supplying cholecystokinin and analyses of stigmastrol, to Dr. Lorne Garrettson for helpful suggestions and to Dr. Gabriel Makhoulouf for a review of the manuscript.

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