

PUBLIC HEALTH ASPECTS OF THE NEW INSECTICIDES

MORTON S. BISKIND, M.D. Westport, Connecticut

IN 1945, against the advice of investigators who had studied the pharmacology of the compound (70) and found it dangerous for all forms of life, DDT (chlorophenothane, dichlorodiphenyl-trichloroethane) was released in the United States and other countries for general use by the public as an insecticide. Contrary to popular opinion, DDT was not the first of the chlorinated cyclic hydrocarbons to be studied for its pesticidal properties, nor indeed is it the most potent compound of the group. In 1934, four years before DDT was introduced for this purpose in Switzerland, an American entomologist (17-19) reported on the insecticidal properties of the chlorinated naphthalenes, compounds shown shortly thereafter to be extremely toxic for man (53, 45).

Soon after the introduction of DDT for widespread use as a household, public health and agricultural insecticide, it became evident that virtually all forms of insects were propagating strains completely resistant to this compound. This led to a frantic search for more and more potent insecticides (which also turned out to be more and more toxic for animals and man). One after another new compounds were introduced, the total list being very long indeed. In addition to numerous variants of DDT itself, in widespread use appeared chlordane, toxaphene (chlorinated camphene), benzene hexachloride (hexachlorocyclohexane) and its gamma isomer, lindane (gammexane), heptachlor, and finally, going full circle, the incredibly deadly aldrin and dieldrin, both chlorinated naphthalenes (31, 33-37, 46, 52). In addition, the organic phosphorus compounds, closely related to the "nerve gases" of chemical warfare and lethal for man in minute doses, have also been widely used in agriculture—parathion, tetraethylpyrophosphate (TEPP), hexaethyltetraphosphate (HETP), malathion and others (22, 32).

In 1950, a year in which more than 200 million pounds of insecticides were used in agriculture alone in this country, investigators of the Federal Food and Drug Administration announced:

"The finding of hepatic cell alteration at dietary levels as low as 5 p. p. m. of DDT, and the considerable storage of the chemical at levels that might well occur in some human diets, makes it extremely likely that the potential hazard of DDT has been underestimated." (68)

In 1951, the United States Public Health Service (49) pointed out:

"DDT is a delayed-action poison. Due to the fact that it accumulates in the body tissues, especially in females, the repeated inhalation or ingestion of DDT constitutes a distinct health hazard. The deleterious effects are manifested principally in the liver, spleen, kidneys and spinal cord.

"DDT is excreted in the milk of cows and of nursing mothers after exposure to DDT sprays and after consuming food contaminated with this

poison. Children and infants especially are much more susceptible to poisoning than adults."

And the next year the U.S. Department of Agriculture (108) indicated that the chlorinated naphthalenes had been implicated as a cause of "X disease" (hyperkeratosis) in cattle, a usually fatal malady that has destroyed many thousands of animals in the United States in recent years (10,000 were reported from Texas alone in March 1953) (119). This represents not only a multimillion dollar loss to cattle-raisers but as will soon be evident, a serious hazard to the public that consumes meat, milk and animal fats. Just when chlorinated naphthalenes were first used in agriculture is not indicated in published reports (48), but it appears that they have been thus employed for some years and that they have been added to or have occurred as contaminants of other products used as insecticides. In addition they have been used for some time in lubricants (greases, cutting oils and crankcase oils)*—for what purpose is not made clear, and they have appeared in certain wood preservatives.

A number of remarkable features of the observations thus far reported on "X disease" deserve comment. The active agent has been found in wheat (59, 77, 87) (but the investigators say nothing about bread), and it is excreted in the milk. Calves fed on this milk develop the disease (nothing is said about babies** who drink such milk nor about those who eat the meat from these animals.) Cattle placed in a field in Indiana that had harbored others that previously had died of hyperkeratosis (1946 to 1949), developed the disease while cattle in an adjacent field were quite unaffected (114). All the investigators are extremely reticent about obvious and highly pertinent questions: Where did the wheat come from that contained the noxious agent? Was it sprayed or dusted in the field or exposed in storage to an insecticide, and if so, what? Were the cattle who originally developed hyperkeratosis on the farm in Indiana sprayed with insecticide, and if so, with what? Was the pasture likewise treated? The glaring omission of these data is not reassuring.

It is obvious from published material that the chlorinated naphthalenes are not the only chemical agents that can cause the disease. One such compound has tentatively been identified as trichlorobenzene (48). In view of the fact that in early studies on DDT in animals hyperkeratosis was observed (85), it seems very likely that this agent too is involved (9). And among the solvents used for DDT and related sub-

*The use of chlorinated naphthalenes in crankcase oils and other lubricants poses other public health problems: inhalation of these substances from motor exhaust on streets and highways and dermal absorption on the part of garage, service station and industrial workers.

**We have been accustomed for some time to a steadily declining infant mortality. But the over-all infant death rate increased in Metropolitan New York City in 1952 by 3 per cent. For economically less-favored groups the rise was 8 per cent. (Editorial: The City's Health in 1952, N.Y. Times, Jan. 14, 1953.)

stances are mixtures containing methylated naphthalenes. Since methyl groups may often be substituted for chlorine atoms in this variety of compounds, without loss of toxicity (16), these mixtures are at least suspect.

One insecticide solvent was indicated by W. C. Hueper (61) of the National Cancer Institute to have been found by other workers to be carcinogenic. One can only wonder why details of these findings have not been made available to the medical profession.

Since the last war there have been a number of curious changes in the incidence of certain ailments and the development of new syndromes never before observed. *A most significant feature of this situation is that both man and all his domestic animals have simultaneously been affected.*

In man, the incidence of poliomyelitis has risen sharply; there has been a striking increase in cardiovascular diseases, in cancer, in atypical pneumonias and especially interstitial pneumonitis in babies and children (58), in retrolental fibroplasia among premature infants, in conditions involving excessive fatigability and muscular weakness, in hepatitis and in obscure gastrointestinal and neuropsychiatric disorders often attributed to a new "virus" (or "virus X").

In animals, cattle have developed hyperkeratosis (or "X disease"), and the incidence of hoof and mouth disease has risen; hogs have vesicular exanthemata; sheep have "blue tongue," "scrapie" and "overeating disease;" chickens have Newcastle disease and other ailments; dogs have developed the so-called "hard pad" disease and the highly fatal "hepatitis X," and so on (43). With the obvious exception of hoof and mouth disease, not one of these conditions is mentioned in the comprehensive U. S. Department of Agriculture Handbook, "Keeping Livestock Healthy," published in 1942. This coincidence alone should have been sufficient to rouse a suspicion that something new that is common both to man and his domestic animals, has been operating in their environment during the period these changes have occurred. This new factor is not far to seek.

When in 1945 DDT was released for use by the general public in the United States and other countries, an impressive background of toxicologic investigations had already shown beyond doubt that this compound was dangerous for all animal life from insects to mammals. In rats, mice, rabbits, guinea pigs, cats, dogs, chicks, goats, sheep, cattle, horses and monkeys, DDT produces functional disturbances and degenerative changes in the skin, liver, gall bladder, lungs, kidney, spleen, thyroid, adrenals, ovaries, testicles, heart muscle, blood vessels, voluntary muscles, the brain and spinal cord and peripheral nerves, gastrointestinal tract and blood. The compound is equally dangerous to birds, fish, crustaceans, lizards, frogs, toads and snakes.***

***H. R. Mills (Death in the Florida Marshes, Audubon Magazine, Sept-Oct., 1952) has reported incredible devastation to wildlife in the sanctuary of the National Audubon Society in Tampa Bay, Florida, following aerial spraying with DDT for the control of mosquitoes. With each successive spraying the destruction of wildlife increased several-fold until the beaches were literally covered with dead fish and crabs. The concentration of DDT in the tissues of crabs analyzed after spraying in 1950 averaged 2.18 p. p. m. The

Many of the beneficial predator insects like dragonflies, ladybugs and praying mantids may be even more susceptible to DDT than crop eating and other nuisance insects it is desired to kill. It was even known by 1945 that DDT is stored in the body fat of mammals and appears in the milk (106, 118). With this foreknowledge the series of catastrophic events that followed the most intensive campaign of mass poisoning in known human history, should not have surprised the experts. Yet, far from admitting a causal relationship so obvious that in any other field of biology it would be instantly accepted, virtually the entire apparatus of communication, lay and scientific alike, has been devoted to denying, concealing, suppressing, distorting and attempts to convert into its opposite, the overwhelming evidence. Libel, slander and economic boycott have not been overlooked in this campaign (21).—And a new principle of toxicology has, it seems, become firmly entrenched in the literature: no matter how lethal a poison may be for all other forms of animal life, if it doesn't kill human beings *instantly* it is safe. When nevertheless it unmistakably does kill a human, this was the victim's own fault—either he was "allergic" to it (the uncompensable sin!) or he didn't use it properly.

It is possible to consider in this article only a very small fraction of the total evidence as it has already filled many volumes and will undoubtedly fill many more.

It is not generally realized how vast are the quantities of the new poisons spread over the countryside in agriculture, used as sprays and aerosol fogs in mosquito control operations and applied in homes and gardens, in hospitals and other institutions, in food processing plants and retail establishments. In agriculture alone 232 million pounds were used in the United States in 1951 and 252 million pounds in 1952 (109); additional millions of pounds were of course used for the other applications. Herbicides of the chlorinated cyclic hydrocarbon group (e.g. 2, 4-D, 2, 4, 5-T) provide a further source of exposure. (In 1952, sale of pesticides in the United States amounted to 400 million dollars.)

Early in 1949, as a result of studies during the previous year, the author (9-11) published reports implicating DDT preparations in the syndrome widely attributed to a "virus - X" in man, in "X-disease" in cattle and in often fatal syndromes in dogs and cats. The relationship was promptly denied by government officials (12), who provided no evidence to contest the author's observations but relied solely on the prestige of government authority and sheer numbers of experts to bolster their position.

We had shown that exposure to DDT whether by inhalation, ingestion or absorption from the skin, leads to a bizarre syndrome which resembles other ailments in individual details but which had never been known to occur in its entirety prior to the introduction of the chlorinated cyclic hydrocarbon insecticides. This syndrome occurred repeatedly in hundreds of instances

next year after more sprayings the concentration of DDT in the crabs was 46 p. p. m. and the destruction of wildlife was proportionately faster and more extensive. Yet all this devastation was for naught, for, reports Mills, "None of the sprayings had any effect in mitigating the mosquito situation. Instead the mosquitoes increased until now they are more numerous than they were before the advent of DDT."

studied by the author following known exposure to DDT and related compounds and over and over again in the same patients, each time following known exposure. We have described the syndrome as follows (10-12):

The syndrome consists of a group of or all the following: Acute gastroenteritis occurs, with nausea, vomiting, abdominal pain, and diarrhea usually associated with extreme tenesmus. Coryza, cough and persistent sore throat are common, often followed by a persistent or recurrent feeling of constriction or a "lump" in the throat; occasionally the sensation of constriction extends subternally and to the back and may be associated with severe pain in either arm. In some cases the hyoid bone becomes acutely painful to pressure for a few days. Pain in the joints, generalized muscle weakness and exhausting fatigue are usual; the latter are often so severe in the acute stage as to be described by some patients as "paralysis." Sometimes the initial attack is ushered in by vertigo and syncope. Intractable headache and giddiness are not uncommon. Occasionally herpes zoster appears. Paresthesias of various kinds occur in most of the cases; areas of skin become exquisitely hypersensitive and after a few days this hyperesthesia disappears only to recur elsewhere, or irregular numbness, tingling sensations, pruritus or formication may occur. Erratic fibrillary twitching of voluntary muscles is common.

After subsidence of the acute attack, irregular spasm of smooth muscle throughout the gastrointestinal tract often persists for weeks or months, associated with increased fatigability, which only gradually regresses. Febrile reactions occur occasionally during the initial stages but are not the rule. Except for a tendency to anemia, and in some cases a relative lymphocytosis, no constant changes are observable in the blood. Many of the patients have an acute bout of apprehension associated with the foregoing symptom complex and rarely is this relieved by reassurance as to the absence of physical findings sufficient to account for the severity of the disturbance.

Most striking about the syndrome is the persistence of some of the symptoms, the tendency to repeated recurrence of others over a period of many months (some patients fail to show complete recovery even after a year) and the lack of detectable lesions sufficient to account for the severity of the subjective reaction.

By far the most disturbing of all the manifestations are the subjective reactions and the extreme muscular weakness. In the severe acute poisonings, patient after patient has used identical words, "I felt like I was going to die."

The sensation can perhaps best be described as one of unbearable emotional turbulence. There are at various times excitement, hyperirritability, anxiety, confusion, inability to concentrate, inattentiveness, forgetfulness and depression. Perhaps the one common phenomenon is extreme apprehensiveness. These episodes can easily be confused with anxiety attacks. The patients complain that they cannot keep their arms and legs still; they seem to "want to jump," and these phenomena may be accompanied by fine fibrillary twitchings. Disturbances of equilibrium may occur. Intractable headache and insomnia are frequent. Disturbances of the autonomic nervous system are likewise common; there may be attacks of tachycardia associated with dermal ischemia, sweating of the palms and a sense of impending syncope, followed by bradycardia, flushing of the skin, relaxation and cessation of palmar perspiration. (Whether or not disturbances of adrenal medullary function are associated with this phenomenon is a subject requiring further investigation.)

A characteristic of diagnostic importance, is the recurrence of the subjective reactions in "waves," as numerous patients have described it. Some have actually been able to clock the reaction with considerable precision from day to day. The reactions appear most likely to occur during periods of low blood sugar. Additionally, consumption of alcoholic beverages or acute emotional stress may provoke a severe exacerbation.

Often, patients with this disorder complain of a "hollow feeling" in the epigastrium which bears no constant chronological relation to the ingestion of food, and in fact may occur

immediately after a full meal. Attempts to eat further may provoke sharp repugnance for food and occasionally may lead to an attack of hiccups, or nausea. In other patients, actual overeating indistinguishable from the compulsive types seen in certain psychogenic disturbances may result.⁺

Hardly a single sensory nerve appears to be immune to involvement in this disorder: Paresthesias of every known variety, including disorders of vision, smell, taste, and hearing, may occur. Pain of varying intensity and duration may involve any area of the skin, may localize in a joint or even a tooth. Severe peripheral neuritis involving intense, protracted pain in one or more of the extremities is frequent. Pain in the inguinal region, usually bilateral, is also a frequent complaint; occasionally this may be referred to the genitalia. Virtually all these patients have striking diminution of vibratory sensation in the extremities. (This has repeatedly been observed in patients in whom readings had been taken on several occasions with the Collens vibrometer, prior to known exposure to DDT.) As already indicated, recurrent extreme fatigability is common. In acute exacerbations, mild clonic convulsions involving mainly the legs, have been observed. Several young children exposed to DDT developed a limp lasting from 2 or 3 days to a week or more.

Patients with this syndrome rarely show objective changes on physical examination sufficient to account for the severity of the subjective disorder and the actual amount of disability present. In addition to the change in vibratory sensation mentioned, enlargement and tenderness of the liver and palpable spasticity of the colon are the only findings which occur with any degree of constancy.

A characteristic history is that of a person (and in a number of cases, an entire family simultaneously involved) who, previously well and able to make a satisfactory emotional adjustment to his environment, suddenly is affected with the syndrome described and remains partially disabled for many months. In innumerable such cases it was possible to trace the onset of the illness to known exposure to DDT, usually from its use in the home.

Other investigators have also identified part or all of this syndrome with DDT poisoning. Wigglesworth (116), Case (28), Mobbs (82, 83), Pottenger and Krohn (91), Toomey (107), Arena (2), Stone and Gladstone (105), Knight (66, 67), Martin (80), Filkin (51), and numerous other observers have reported the occurrence of these cases following exposure to DDT and related pesticides. Pottenger and Krohn (91) have demonstrated the presence of DDT in the body fat of a large number of such patients, who showed in addition to the neuropsychiatric symptoms, hepatitis with low grade icterus and rise in blood cholesterol.

That this syndrome continues to be ascribed to a virus infection is indicated in a recent article by Dr. F. L. Mickle ("Connecticut Needs a New Virus Laboratory") (81):

"... virus diseases which appear to be increasing are coming to the foreground. They are of much greater importance in the State than formerly. For instance, almost every person you meet on the street or in the homes of your friends speaks at one time or another of having had the 'virus that's going around' . . . these viruses cause distressing and incapacitating upper respiratory symptoms often accompanied by diarrhea and vomiting."⁺⁺

⁺Note that, as already mentioned, there is now also an "overeating disease" of sheep.

⁺⁺A factor that has led to considerable confusion in diagnosis is that DDT, for instance, produces mononuclear cell infiltration and splenic hyperplasia similar to that seen in genuine virus infections. This has been observed both in animals and in man.

Simultaneously with the occurrence of this disorder a number of related changes occurred in the incidence of known diseases. The most striking of these is poliomyelitis. In the United States the incidence of polio had been increasing prior to 1945 at a fairly constant rate, but its epidemiologic characteristics remained unchanged. Beginning in 1946 the *rate of increase more than doubled* (84). Since then remarkable changes in the character of the disease have been noted. Contrary to all past experience, the disease has remained epidemic year after year. It has largely lost its seasonal character, although still most prevalent in the Summer. More adults acquire the disorder than ever before. More cases of bulbar involvement are seen.

These changes have not been confined to the United States: For instance (54), "Until 1945, poliomyelitis was uncommon in Mexico. Since then, its incidence has been increasing; in 1950, nearly a thousand cases were observed in Mexico City . . . and the figures for the first half of 1951 seem to be higher."

In the Philippines and elsewhere in the Far East American troops, who used vast quantities of DDT as insecticides, had a high incidence of poliomyelitis, while it was extremely low in the surrounding native population (96).

In Israel (50), where the widespread use of DDT, especially in public health and agricultural applications, was delayed, "Prior to 1950 only one or two cases of poliomyelitis appeared monthly . . . During 1950, about sixteen hundred cases were listed, which is more than one case per thousand population. The epidemic was heralded by a rising number of isolated cases in the summer of 1950." It is recognized that a disturbed immunologic equilibrium as a result of mass immigration cannot explain this epidemic in Israel, any more than it can be a factor in Mexico or the United States. Curiously too in Israel (as in the case of the native populations in the Far East) the less technologically advanced Arabs have a much lower incidence of the disease.

McCormick (78), Scobey (100-101), and Goddard (57), in detailed studies, have all pointed out that factors other than infective agents are certainly involved in the etiology of polio, varying from nutritional defects to a variety of poisons which affect the nervous system.

Particularly relevant to recent aspects of this problem are neglected studies by Lillie and his collaborators (74, 75) of the National Institutes of Health, published in 1944 and 1947 respectively, which showed that DDT may produce degeneration of the anterior horn cells of the spinal cord in animals. These changes do not occur regularly in exposed animals any more than they do in human beings, but they do appear often enough to be significant. When the population is exposed to a chemical agent known to produce in animals lesions in the spinal cord resembling those in human polio, and thereafter the latter disease increases sharply in incidence and maintains its epidemic character year after year, is it unreasonable to suspect an etiologic relationship?

The mortality from cardiovascular diseases has also risen alarmingly since 1945. So serious is this problem that T. G. Klumpp (65) recently commented ". . . most

businessmen . . . work with mental brakes set against their work and in mortal terror of a heart attack. They are afraid to live for fear of dying."

Among its numerous effects, DDT is a liver poison, an observation made by innumerable investigators. Associated with the induced hepatitis, there is hypercholesterolemia and hyperlipemia with an enhanced tendency to coronary atherosclerosis (13). Myocardial lesions have been reported in animals exposed to DDT as well as lesions of the blood vessels resembling periarteritis nodosa. In addition to changes in cellular enzyme systems leading to increased oxygen uptake (62, 93) similar to that produced by dinitrophenol, DDT also interferes with lactic acid metabolism and inhibits heart cytochrome oxidase (63). Finally, according to Lehman (71) of the Federal Food and Drug Administration,

"DDT produces an excess excitability of the cardiac muscle so that any coincident sympathetic stimulation . . . can result in ventricular fibrillation."

In a recent publication purporting to disprove my contention that the insecticides are implicated in certain ailments, R. E. L. Fowler (55) of the U.S.P.H.S. Communicable Disease Center reported some statistics from the cotton belt of the Mississippi Delta, before and after the introduction of DDT. Mortality from "heart diseases" in this area rose from 141.3 before the use of DDT to 189.4 per 100,000 after its introduction (a rise of 34 percent!). But says Fowler, dismissing the subject, ". . . this was similar to the rise recorded for the state as a whole." Actually the figures he gives for the entire state are 170 per 100,000 before and 213.7 after DDT was used, an increase of 25.7 per cent! Surely this investigator could not have meant to imply that the population of Mississippi outside the Delta Area, was not significantly exposed to DDT. If the inhabitants of the Delta got an extra large dose, there is indeed an extra increase in cardiac mortality of 8.3 per cent to answer for it. The true difference is obviously even greater, for the comparison was not made between the Delta and the rest of the state but between the Delta and the whole state. (It is ironic that the statement by Klumpp already quoted appeared in the same issue of the same journal.)

With the known primary and secondary effects of DDT on the cardiovascular system, and the amazing increase in mortality from heart disease following widespread use of this agent, is it unreasonable to deduce an etiologic relationship?+++

+++W. J. McCormick in an excellent study (Clin. Med., 59:305, July, 1952) has recently implicated smoking of tobacco in the increasing incidence of coronary occlusion. Smoking has also been implicated in the rising incidence of cancer of the lung. Space does not permit an adequate discussion of the problem, but certain features of it appear to me to have been neglected. Despite the fact that prior to 1930 there were plenty of long-term intemperate smokers, cancer of the lung, for instance, was nevertheless a rare disease. Why was bronchiogenic carcinoma seen so rarely in chain smokers in the 1920's? Yet the evidence that smoking is today implicated in coronary thrombosis and in pulmonary cancer appears convincing. It is not generally realized that in growing tobacco, it is sprayed in the field with several of the DDT series of compounds, including the dangerous adrenal poison TDE (or "DDD"), chlordane, toxaphene and lindane and the

Fowler raises other issues but chooses not to discuss most of them—he gives no figures for the change in incidence of polio, nor in that of hepatitis. He does admit that absenteeism from school rose approximately 9 per cent during the period DDT was used, but he dismisses this as being possibly due to sociological factors. He also indicates an increase in “communicable diseases” in the Delta area over that in the State as a whole but this he dismisses as being due to a racial difference (obviously this racial difference existed prior to the use of DDT).

The rise in the incidence of hepatitis in the general population since 1945 is also without parallel and involves all age groups, including young infants. Information as to total morbidity from this disorder is obviously unavailable but even a cursory survey of recent medical literature shows that hepatitis is now one of the major medical problems. Most of the reported cases are considered “infectious,” although the virtual impossibility of diagnosing the “infectious” nature of a given case or of demonstrating the transmissibility of the disease must be obvious even to the casual observer, since human infectious hepatitis can be transmitted only to man. The most curious aspect of the rise in hepatitis is that simultaneously this has occurred for instance

organic phosphorus compounds as well. The residues of all these substances vaporize in the smoke.

Of course, still other factors may have operated even prior to the use of these compounds, such as changes in the composition of the tobacco plant from depletion of the soil, or use of certain fertilizers, or addition of certain substances in the final manufacturing process. Also, inhalation of other atmospheric contaminants which have increased in the last generation (e.g. lead, chlorinated naphthalenes and other products of combustion from motor exhaust), and the increased exposure to radiation (D. W. Moeller, et al.: Pub. Health Rep. 68:57, Jan., 1953) may well make the extra trauma of smoking the straw that breaks the camel's back. It is worth noting that a sharp rise in the rate of increase in carcinoma of the lung occurred about 1947, and this has persisted. It is interesting to compare charts showing the changes in the rates of increase of such diverse entities as poliomyelitis, retrolental fibroplasia, cardiovascular diseases and pulmonary carcinoma.

W. F. Enos et al. (J.A.M.A. 152:1090, July 18, 1953) have reported the startling observation that among 300 U. S. soldiers killed in action in Korea, average age approximately 22.1 years (range 18 to 48), 77.3 percent had “gross evidence of coronary arteriosclerosis” ranging “from ‘fibrous’ thickening to large atheromatous plaques causing complete occlusion of one or more of the major vessels.” Last year Army Surgeon General Armstrong (J.A.M.A. 148: ad. p. 17, March 8, 1952) reported that among conditions of major concern to the service was acute hepatitis and that the incidence of neuropsychiatric disturbances was 54.1 per 1000 troops a year. Can these remarkable coincidences have anything to do with the fact that DDT and lindane are used in Korea intensively?

As for retrolental fibroplasia among premature infants, in New Jersey for instance, “. . . new cases of preschool blindness had been coming in at a rate of around 100 a year for the last three years; before that for two years the rate was less than fifty a year; and earlier, less than ten a year . . . 75 per cent of the new cases were retrolental fibroplasia.” (G. Meyer: Proc. Am. Assoc. of Workers for the Blind, reported in the N. Y. Times, July 15, 1953.) It is noteworthy that cataract was among the unfortunate consequences of the use of dinitrophenol as a thyroid substitute for weight reduction, in the 1930's. Since, as already mentioned, DDT has been shown to produce an increase in oxygen uptake similar to dinitrophenol (93), and paradichlorobenzene has been reported also to produce cataract (4), is this phenomenon pure coincidence?

in cattle, in dogs and in other farm animals. In cattle “X-disease” (or hyperkeratosis) in which the chlorinated cyclic hydrocarbons are now etiologically implicated, involvement of the liver with a profound disturbance in vitamin A metabolism and storage is invariable. In dogs the highly fatal “infectious” hepatitis and hepatitis “X” have appeared.

It would be a most remarkable coincidence if several entirely different hepatic infective agents, each specific to a different animal species, arose simultaneously. Human infectious hepatitis is not transmissible to dogs or cattle or vice versa. How then account for this situation?

Without exception, every one of the chlorinated cyclic hydrocarbon insecticides is a liver poison. This is true of the entire series from the solvent monochlorobenzene and the mothicide paradichlorobenzene (4) to DDT and the chlorinated naphthalenes aldrin and dieldrin.† The chlorinated naphthalenes were shown to produce hepatitis (often with acute yellow atrophy) (45, 53) as long ago as 1936, and were responsible for much morbidity and many deaths among workers in industry (where they have been used in insulation for electric cable) long before these compounds were used in agriculture. Exposure to this whole group of compounds is now universal in the United States, and it appears that few persons escape storage of these toxic agents in the body fat.

The body fat has been termed a “biological magnifier” of DDT by investigators of the Federal Food and Drug Administration (68, 69). When amounts as low as 0.1 part per million dry weight (the average human diet contains very much more) are included in the diet, the body fat may reach concentrations up to 150 times as much. This has been confirmed by many workers on many species of animals. The significance and potential consequences of such storage in body fat have been reviewed in an excellent editorial in the Journal of the A.M.A., “Insecticide Storage in Adipose Tissue” (47). As pointed out in this editorial, body fat is not simply an inactive storage depot but is subject to continuous turnover and takes part in many metabolic processes. Further, “The influence of the stored insecticide may not be limited to adipose tissue. In fact, dichlorodiphenyltrichloroethane [DDT] is found in all other tissues in proportion to their fat content. Fats and lipids are constituents of cell membranes and are concerned with the phenomena of cell permeability and cell organization in every tissue of the body . . . Consequently storage of a toxicant in the fat of parenchymal cells is essentially storage in the cell itself, where such important enzymatic processes as oxidation, phosphorylation and cholesterol synthesis take place . . .”

What is the situation with regard to fat storage of insecticides in the human being? The difficulties involved in studying this problem are formidable. Quantitative chemical methods do not exist for all the com-

†Aldrin was recommended by the U. S. Department of Agriculture in 1953, for use on corn, wheat, oats, barley, rye, potatoes, peanuts, cotton, and on pastures. Dieldrin has likewise been recommended for corn, wheat, and other small grains, as well as for cotton and alfalfa. In the State of California dieldrin has been registered for use on alfalfa, apple, bean, cabbage, citrus fruit, corn, cotton, garlic, grape, melon, onion, peach, pear, and for treatment of wheat seed and outdoor use against house flies, mosquitoes, ants, chiggers, ticks and fleas.

pounds and the methods that are available, though accurate, are difficult, time consuming and laborious. Certain of the compounds are converted in the body to other substances before being stored. (Heptachlor, for instance, a constituent of chlordane which is also used separately, has been reported by F.D.A. investigators (40, 92) to be stored as heptachlor epoxide, *considerably more toxic* than the original heptachlor.) Obtaining sufficiently large fat specimens requires minor surgery, and only in lactating women can fat storage be estimated without surgery, since these compounds appear in the fat portion of the milk. In addition, numerous impediments of a nontechnical nature have been placed in the path of those who would pursue such studies on a sufficient scale. Nevertheless, the data that do exist, although limited thus far to studies on DDT, are the more alarming because they are derived from subjects in many widely separated parts of the country.

DDT has been demonstrated to occur in human body fat in all but a few of the cases examined (e.g., in sixty out of seventy-five in one series (69); in twenty-three out of twenty-five in another) (80) in concentrations from 0.1 to 34 p. p. m. (the highest result obtained—34 p. p. m.—came from an infant!). It has likewise been demonstrated in mother's milk (in seven out of seven cases in one series, in thirty out of thirty-two in another (11, 12, 69) in concentrations of from 0.01 to 116 p. p. m. In a study reported more recently from the U.S. Public Health Service (98), biopsy specimens were obtained from 113 volunteers from widely scattered sections of the United States. In 111 of these the range of DDT content was from 0 to 68 p. p. m., with an average concentration of 6.41 p. p. m. (The significance of this figure may perhaps be appreciated by the fact that as little as 3 p. p. m. has been found to inhibit heart cytochrome oxidase.) Two DDT handlers had 91 and 291 p. p. m. respectively! Even after prolonged rest from their occupations (in the first case, two years) the DDT levels in the fat were still 30 and 240 p. p. m., illustrating the tenacity with which this material is stored. A further study by workers at the United States Public Health Service (88) showed, in eight specimens of human fat, from 1.9 to 14 p. p. m. DDT and from 1.7 to 44.7 p. p. m. of a compound tentatively identified as DDE (an ethylene derivative of DDT). These investigators point out:

"Presumably the DDT occurring in the fat of individuals of the general population arises mainly through contamination of a number of common foodstuffs. It is not known whether the DDE evidently present is also a contaminant as a result of partial degradation of the DDT residues on plant products prior to ingestion, or whether degradation occurs during digestion or after deposition in the fat."

This study has unfortunately been used as propaganda for the alleged safety of DDT on the assumption that it shows that DDT is detoxified in the body, hence is virtually harmless (104). The observations, already cited, that the related compound heptachlor is converted in the body to a *more toxic* substance points up the inadvisability of drawing such far-reaching conclusions from inadequate data. Quantitative studies on the occurrence in human body fat of other insecticides to

which there is universal dietary and environmental exposure, such as technical benzene hexachloride and its individual isomers, toxaphene, methoxychlor, chlordane, heptachlor, aldrin and dieldrin are as yet not available, although qualitative evidence of human storage of benzene hexachloride has been obtained and evidence of fat storage of the other compounds is available from animal investigations.#

Contamination of foodstuffs (e.g., 3, 5, 6-8, 24-27, 31, 38, 42, 64, 79, 95, 103, 110, 117) provides probably the main source of the chlorinated hydrocarbons found in human body fat, although this is by no means the only source. These compounds are used as sprays, aerosols and fogs in inhabited areas in such manner that the finely dispersed particles are readily absorbable through the lungs and through the skin, they are vaporized by means of heating devices in homes, restaurants, food stores and other buildings; they are incorporated into paints, wallpaper and floor wax; they are used to mothproof virtually every variety of textile, including many that no moth larva could eat; they are sprayed and painted on every conceivable surface in homes and institutions. As the Canadian Department of National Health and Welfare (29) has pointed out, "Dangerous residues of these compounds may persist on treated surfaces for very long periods." Obviously, once used, finely dispersed vapors and dusts of so stable a character readily become resuspended in air, can be inhaled directly over long periods and can contaminate foods and food utensils. Contact with treated surfaces can lead to significant absorption through the skin. The amounts required to produce severe acute reactions in human beings are often extremely small. In one case investigated by the author, the syndrome described in detail earlier in this article was produced by the ingestion of only four micrograms of DDT in food.

Unfortunately, today contamination of food is virtually universal. Even if the farmer does not use the new insecticides (and few do not), it is a rare food that escapes contact with insecticides in storage, shipment, processing plants, warehouses and stores.

Dendy (44), for instance, bought milk and meat on the open market in Texas, from July through December. Every specimen of these staples was found to contain DDT, from less than 0.5 p. p. m. to 13.8 p. p. m. in milk and from 3.1 p. p. m. in lean meat to 68.5 p. p. m. in fat meat. Corn and sunflowers were sprayed in the field with DDT, toxaphene, chlordane, BHC, methoxychlor, or aldrin using less than standard agricultural practice. In every case the insecticide penetrated to the interior of the kernels or seeds and was present in concentrations of from 4 to 7.4 p. p. m.

Numerous other studies both on market samples of foods bought at retail, and on specimens obtained by duplicating standard agricultural practice, show that

#It has been claimed that certain compounds, like methoxychlor (an analog of DDT containing methoxy groups in place of two chlorine atoms), are less toxic and less likely to be stored in body fat than DDT. But if the liver is first damaged by another toxic agent, methoxychlor produces symptoms similar to those of DDT and stores in the body fat from 10 to 100 times as much as in control animals. (Laug, E. P., and Kunze, F. M.: *Fed. Proc.*, 10:318, March, 1951.) (Cf. also, Haag, H. B., et al.: *Arch. int. de Pharmacodyn. et de Therap.*, 83:491, Sept., 1950.)

it is a rare food that escapes contamination with amounts often greatly in excess of that known to produce liver damage in animals.

It has been claimed that without the use of newer insecticides, there would not be enough food to go around and that even though these substances are toxic, their use involves a "calculated risk." But as a number of agricultural and public health workers have now recognized, even disregarding toxic effects on the human population, the use of the newer insecticides is not only not helpful, but in the long run actually detrimental, both for the growth of crops and the prevention of disease carried by insect vectors. Everywhere that DDT has been used for any length of time, strains of insects, both those that attack crops, as well as flies, mosquitoes and lice, have become resistant not only to DDT but to related compounds as well. This has been shown to be caused by the long persistence of the toxicity of these compounds. The phenomenon never occurred so long as only short-acting insecticides like pyrethrum and rotenone were employed (30).

A. D. Pickett (89, 90) in Nova Scotia, and Paul DeBach (41), in California have both pointed out that the use of preparations like DDT in orchards, for instance, by creating insecticide resistance and by destroying natural predators of the noxious insects, *actually perpetuates the emergency* for which these compounds were used in the first place.

As many workers have now shown, by maintaining proper fertility of the soil, it is possible without the use of insecticides to raise crops showing little or no damage from insects (1, 20, 115). It must be remembered that agriculture flourished for thousands of years without the use of insecticides and that even today the average yields per acre for many crops grown without these chemicals in other countries greatly exceed the average yields in the United States.

Owing to the insoluble problems created by insecticide resistance in public health applications, A. D. Hess (60) of the U.S. Public Health Service Communicable Disease Center, has advocated a return to biologic methods and the older technics of sanitation for the control of insect vectors. The futility of the chemical approach to the insect problem is perhaps no better illustrated than by the fact that after seven or eight years of the most intensive imaginable poison campaign, virtually the entire "bread basket" area of the United States was blanketed in 1953 with army worms, that destroyed vast areas of food crops, over many states. It was admitted by the U.S. Department of Agriculture that further chemical attack on these insects was fruitless, although this same Department then released the extremely toxic dieldrin for use against them! (112).

The extremely stable nature of the DDT group of insecticides poses another problem. In amounts normally used for growing of crops, severe poisoning of the soil (39, 76, 99, 102, 111, 113) has persisted for the entire duration of reported observations (seven years) and as no means are available to destroy these compounds, millions of acres of farmland may ultimately have to be withdrawn from cultivation, since these substances not only inhibit the growth of many plants but may be absorbed into the food portions in dangerous concentrations.

Two widespread practices deserve special comment: the use of chlordane in homes (73), institutions and food establishments (94) and the similar use of electric vaporizers for DDT or lindane (the gamma isomer of benzene hexachloride) or a mixture of the two.

Chlordane is probably the most commonly used for roach control in buildings of all the available insecticides. It is routinely used even in hospitals. Chlordane, a technical mixture with a musty odor, consisting mainly of chlorinated indanes (heptachlor, already mentioned, is one of the constituents), is an extremely dangerous nerve and liver poison. Although very persistent when applied, it is nevertheless slowly volatilized. Frings and O'Tousa (56) report in studies on animals:

"The first system affected is the nervous system, and nervous symptoms predominate in acute toxicity. In chronic intoxication, however, the liver seems to be most affected . . . Because of the widespread use of chlordane in structural pest control, the rather striking toxicity of the vapor is significant . . ."

Lehman (72) recently reported experience with chlordane at the Federal Food and Drug Administration:

"In my opinion, chlordane is one of the most toxic of insecticides we have to deal with . . . it penetrates the skin very readily. Therefore, anyone handling it could be poisoned. Or if it is used as a household spray, the potential hazard of living in these houses is quite great because of the ability of chlordane to penetrate the skin and because of the volatility of the insecticide and the possibility of poisoning by inhalation. More to the point is that it is very toxic to the liver and kidneys . . . I would put chlordane four to five times more poisonous than DDT . . . I would hesitate to eat food that had any chlordane on it whatsoever . . . It is our opinion that chlordane has no place in the food industry where even the remotest opportunity for contamination exists.** We feel that its use as a household spray*** or in floor waxes is out of place . . . we have not been able to maintain pigeons in a small room that was treated with chlordane, even after a thorough scrubbing with strong alkali and subsequent airing for several weeks."

Exposure to chlordane leads to rapid, high and tenacious storage in body fat. Heptachlor, one of its components, as already mentioned, is converted in the body to a more toxic substance, heptachlor epoxide, and stored as such.

The use of chlordane against termites in the foundation of a house, in a case brought to my attention, re-

**As an example of the use of these materials in the food industry, Holmes and Salathe (Proc. Am. Chem. Soc. 115th meeting, 1949, p. 18A) state: "Experience has shown within the baking industry that DDT and chlordane can be applied safely in 5 & 2 per cent solutions respectively . . . the application must be so general that there are few if any areas that insects might travel over, which have not been treated." (!)

***In 1952 a popular journal of immense circulation advised its readers to apply chlordane to floors, baseboards, sinks, under refrigerators and other appliances, to mattresses, wallpaper, rugs, clothes closets and clothing.

sulted in such a high vapor concentration that the house remained thereafter uninhabitable to the owner. All efforts to remove the offending agent failed.

In a hospital in which technical chlordane is applied routinely in the kitchen and food storeroom and less regularly elsewhere in the institution, for roach control, an epidemic of hepatitis has persisted among the resident nursing staff for three years. This disorder was considered "infectious,"** yet despite adequate epidemiologic precautions the cases continue to appear. The chlordane is still in use.

During the past two years or so an incredible profusion of devices for vaporizing insecticides in room air have appeared on the market. These vary from thermostatically controlled heating devices, to special electric light bulbs with a compartment for inserting a pellet or crystals of DDT or lindane, to metallic gadgets and even impregnated adhesive tape for application to ordinary light bulbs. The hazards of these devices have been pointed out repeatedly, yet newspapers and magazines promote them to the public as if they were the safest of all the new miracles. A newspaper of international repute even carried an article in which it was pointed out, referring to such a device, ". . . it is easy in using it to increase the rate of vaporization to the point where it is hazardous to humans . . . the experts advise that products containing lindane be used with the utmost precaution. One goes so far as to say that: 'Although they're advertised as safe, they are really not.'" Yet the same issue and succeeding Sunday issues carried numerous advertisements for them.

To quote the A. M. A. Council on Pharmacy and Chemistry (35),

" . . . it is not reasonable to expect that human beings can avoid injury if they are exposed . . . year after year to a toxic agent in atmospheric concentrations that kill insects in a few hours . . . the resultant injury may be cumulative or delayed, or simulate a chronic disease of other origin, thereby making identification and statistical comparison difficult or impossible."

It was found that, in an eight hour period an average person might inhale from 1.3 to 13 mg. of DDT or from 0.9 to 2 mg. of lindane, as ordinarily vaporized from one of these devices. In addition, the vaporized material ultimately recrystallizes on walls, ceilings, furniture, clothing, on food utensils and food.

The California State Board of Health (23) passed a resolution last year,

" . . . that electrical vaporizers dispensing lindane or other chlorinated hydrocarbons be not used in closed spaces where people sleep, work or where unpackaged*** food is exposed, and that

**Aside from the question of the nature of "viruses," which is too intricate to consider here (cf. reference 78 and 101, for instance), it should be pointed out that not only may a toxic agent which damages a particular organ simulate infectious disease, but the damaged organ is more susceptible to transmissible agents, if exposure occurs.

***It is unfortunate that the California Board did not also include packaged food. The U. S. Department of Agriculture has reported the following experience: "An unexpected find-

extreme caution be exercised in the indoor dispersion of such chemicals by any means . . ."

The Federal Interdepartmental Committee on Pest Control has also advised that insecticide vaporizers not be used for insect control in living quarters.

TREATMENT

Treatment of poisoning with the chlorinated cyclic hydrocarbons of the DDT group requires both elimination of further exposure from environment and food, and treatment of the associated nutritional defect which accompanies the hepatitis. Sprayed clothing, textiles and bedding must be cleaned with lipoid solvents, the particles of DDT must be removed from the room dust in places that have been treated with DDT aerosol, preferably by lacquering, painting or waxing (with wax that is insecticide-free, of course!) all affected surfaces. Wall paper impregnated with DDT has caused severe symptoms in a number of cases investigated. Persons sensitive to DDT and related compounds must avoid as much as possible visiting places known to have been treated with these agents. Foods or portions of foods in which DDT and the like are now known to occur must be avoided. This entails avoidance of butterfat in all its forms, careful peeling of all fruits and vegetables and avoidance of those that cannot be peeled, substitution of fish and seafood and skim milk products as much as possible for the usual sources of protein, and the medicinal grade of peanut oil (which we have found to be free of the DDT group of compounds) for the usual sources of fat.

Repeatedly, I have had patients who lost weight continuously to the extent of 20 or 30 pounds on a full diet containing large amounts of beef and butterfat, who promptly regained all or most of their weight on a diet lower in calories but restricted as indicated. Unless further exposure to the newer insecticides is avoided as stringently as possible, both from direct contact or inhalation and from food, no remedies I have tried give any except slight symptomatic relief. (Pentobarbital in small—30 mg.—doses often temporarily relieves the symptoms related to the nervous system.)

As Pottenger and Krohn, and we have found, administration of intensive, complete and persistent nutritional therapy is essential in these cases to repair the liver damage. A source of the available water-soluble and lipo-soluble vitamins, suitable oral liver products and lipotropic factors, together with a high protein diet, are all necessary to adequate tissue repair. The requisites for this type of therapy have been discussed in detail elsewhere (15).

ing was the contamination of raisins stored for one month in boxes treated with DDT on the outside only, which indicated that DDT could be spread by volatilizing. This idea was substantiated by analyzing grain samples that had been in storage three to four months in elevators that had been treated with DDT when empty." (A procedure incidentally which the Department of Agriculture still recommends!) (Toxicity of Insecticides, Fungicides and Herbicides, p. 45.) A similar experience was reported from Britain. When wheat flour, soya flour, ground nuts or coca beans were stored for from four to thirteen months in sacks treated with 1 per cent or 5 per cent DDT (the amounts found necessary to prevent insect penetration) all these products absorbed DDT in concentrations of from 5 to 645 p. p. m. (G.V.B. Herford: J. Roy. San. Inst., 70:666-673, Nov., 1950.)

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