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THE SYSTEMIC EFFECTS RESULTING FROM EXPOSURE TO CERTAIN CHLORINATED HYDROCARBONS*

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CHLORINATED naphthalenes and diphenyls, because of their electrical, heat and moisture-resisting properties, and because they are non-inflammable, are used extensively for insulating wire and in the manufacture of electrical condensers. The chlorinated naphthalenes are naphthalenes in which one or more of the hydrogen atoms has been replaced by chlorine. There is, thus, a series of these substances beginning with monochlornaphthalene and going on to the octochlor derivative. In industry they usually occur in mixtures in which more than one chlorinated product is present. On the whole, the higher the chlorination, the more toxic this material becomes. In the manufacture of chlorinated diphenyls, C_6H_6 is converted into $C_{12}H_{10}$ which, in turn, is chlorinated to $C_{12}Cl_{10}$; the substitution products range from the monochlor to the decachlor diphenyl.

A rather characteristic acneform skin eruption resulting from exposure to these substances has been recognized for a great many years—indeed, ever since they began to be manufactured about 25 years ago. These skin eruptions came into some prominence in Germany during the war and have been attracting sporadic interest in this country ever since. An investigation of this condition, as it appeared among a group of young workers engaged in the manufacture of electrical condensers, was reported in a recent issue of this *Journal* (1).

Experience has shown that the medical practitioner is still somewhat unfamiliar with the skin eruptions, even

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The chlorinated naphthalenes are sometimes referred to as "Halowax" by purchasers and users. While the Halowax Corporation manufactures these substances, it also manufactures many others. Since the term "Halowax" is merely a trade name for substances manufactured by this Company, it should not be used indiscriminately. In all instances, substances should be designated by their chemical names only.

though they are by no means uncommon in the industries where the chlorinated naphthalenes and diphenyls are used. The reason for this is that any one physician is likely to see such cases only rarely, unless he happens to be practicing in the immediate vicinity of one of these factories where large numbers of workers are employed. That the relatively rare systemic effects resulting from such exposure almost invariably go unrecognised is not surprising under the circumstances. It is of the greatest importance however, that physicians become acquainted as promptly as possible with the clinical and pathological pictures presented by these patients, particularly as regards systemic effects, since failure to detect early clinical manifestations of toxicity, and to remove susceptible individuals promptly from further exposure, may, on occasion, result fatally.

Review of Literature on Systemic Effects*

Experimental studies.—The first mention in the literature of systemic effects from chlorinated naphthalenes is that of Lehmann in 1919 (2). He found that animals which were fed or which inhaled these substances lost appetite and at death showed "peculiar" lesions in the liver.

In 1936, Flinn and Jarvik (3) experimented on rabbits with three different compounds; (A) a mixture of tri- and tetrachlornaphthalene, (B) a mixture of tetra- and penta-chlornaphthalene and (C) a mixture of penta- and hexa-chlornaphthalene. They also used sublimates of (B) and (C) given off at 192°C and 172°C respectively. Large doses, approximately 15 mg. per kg, were injected subcutaneously each day.

Animals receiving compound (A) and the sublimate of compound (B) showed no lesions attributable to these substances when killed at the end of 2 months. The 30 animals, however, which had received the higher chlorinated compounds (B) and (C) and the sublimate of (C), all died in from 12 to 26 days. Autopsies uniformly showed extensive damage.

The next important study to be published was that of Drinker, Warren and Bennett (4). These investigators administered chlorinated hydrocarbons by inhalation, subcutaneously and by mouth, to white rats. Mixtures of (a) tri- and tetrachlornaphthalene; (b) penta- and hexachlornaphthalene alone, and (c) with 10% refined chlorinated diphenyl; and (d) chlorinated diphenyl were used.

Briefly, these experiments showed that the tri- and tetrachlornaphthalenes produced relatively unimportant pathological changes in the liver until extremely high concentrations were used. Animals exposed for 6 weeks to the higher chlorinations, however, in relatively low concentrations, regularly showed minor degrees of liver damage even though, as a group, they gave no clinical evidences of such toxicity while alive. Exposed to still higher concentrations, the rats lost weight and appetite, and began dying after days' exposure—many with severe jaundice. Examination of the livers of these animals at autopsy revealed marked central fatty degeneration with necrosis of liver cells.

It is of considerable interest that

* A review of the literature on skin manifestations appeared in the article by Mayers and Silverberg mentioned above (1).

the exposed rats, which gave no clinical evidences of disease, promptly died from acute yellow atrophy of the liver when given a very small dose of carbon tetrachloride—a dose well tolerated by control animals.

Two other points of interest were brought out by the study: (1) in the rats, which on autopsy showed even marked pathological lesions of the liver, no abnormalities were found in the other organs—a finding not uncommon in experiments on animals, but rather rare in humans who die from acute yellow atrophy of the liver; (2) even the less important pathological changes induced in the liver by these chlorinated hydrocarbons in the lower concentrations were found to be very persistent, being present even 2 months after cessation of exposure.

Clinical Reports.—Clinical reports of cases of systemic poisoning from the chlorinated naphthalenes are as yet rare in spite of the length of time that these substances have been in use. No doubt the infrequency of such reports has been, in part, due first, to the fact that cases of systemic poisoning are unusual occurrences—the element of individual susceptibility appearing to play an even more important rôle than usual in this situation—and second, to failure on the part of physicians to recognize cases of poisoning. Until recently there has been general lack of knowledge of the toxicological properties of these chlorinated hydrocarbons, and there is still relatively little information available regarding the clinical picture of industrial poisoning from them.

The danger that lies in such a lack of knowledge is exemplified in a situation that recently came to the attention of the Labor Department in New York State, in which a physician had been treating a severe case of jaundice in a young woman exposed to chlorinated naphthalenes. After a long and serious illness, when the girl was on her way to recovery, the physician expressed the opinion that within a few weeks she would be able to return to her former work. Whatever the cause of the jaundice in this case, there is good reason to believe, on the basis of the experimental work previously cited, that further exposure to such substances would have entailed a grave risk to the patient's life.

In 1934, Courtois-Suffit (5) reported on the work of Touraine who, with his associates, examined 60 workers exposed to trichlornaphthalene and found mild digestive disturbances and dizziness in 13, but nothing of a more serious nature.

In 1935, Schwartz suggested the possibility of systemic disease from exposure to these substances in a talk before the American Public Health Association (6).

In 1936, three fatal cases of jaundice in chlorinated naphthalene workers were recognised in this country. These were reported by Flinn (3) and Drinker (4) who summarised the cases briefly.

All three of the men were young and in none could any predisposing cause other than their industrial exposure be found to account for their illness. Two of the men who had worked side by side died within 2 months of each other. Both had been exposed to mixtures of penta- and hexachlornaphthalene, and one had been exposed to a mixture of tetra- and penta-chlornaphthalene with 10% chlorinated diphenyl. In both, the

diagnosis of acute yellow atrophy of the liver was made on autopsy. In the third case no autopsy was reported, but death occurred after an acute illness characterized by jaundice. In one case dermatitis characteristic of the effect of chlorinated naphthalenes had preceded the jaundice.

In addition to these fatal cases, Drinker (4) also mentions four cases of non-fatal jaundice among individuals with similar exposure. No details are given.

Case Histories

Because of the obvious need for more clinical data in regard to the effects of chlorinated naphthalene exposure, we are reporting 3 cases in persons who, after exposure in the course of their work to these known hepatoxic substances, died of acute yellow atrophy of the liver, and in whose cases no other etiological factors could be discovered even after very careful investigation. The first case was seen in consultation at the Lincoln Hospital in New York City by Adelaide Ross Smith. The second and third cases were seen in consultation at the New Haven Hospital by Dr. Leonard Greenburg, (now Executive Director of the Division of Industrial Hygiene of the New York State Department of Labor) when he was Commissioner of Health of New Haven, Conn. The plant conditions under which the patients had worked were carefully investigated.

*Case 1. H. F.**

A 17 year old girl was admitted to the Lincoln Hospital, New York City, on the service of Drs. Kenneth Taylor Hauser and Scott Johnson on Apri in a semi-comatose condition. intensely jaundiced on admission

Her past medical history, obtai members of the family, was entir tive with the exception of a tonsill 1930. Until the onset of the pres she had been unusually healthy from symptoms of any kind.

The occupational history was After being graduated from gramm she attended high school for 1 yea obtained a job, her only one, with manufacturing electrical condens in radios. She worked at this on 7 months and stopped working th before her admission to the hos

Her work consisted of sold labelling condensers. It is poss the information given, that she have assisted in the sealing oper this could not be definitely a In any event, in the soldering densers she was exposed to the fu and tetrachlornaphthalene with condensers were originally im At the same time she was expose of the higher chlorinated naphth the sealing operations conducte proximity to the tables at which ing was done.

The present illness began abou before admission to the hospit proximately 2 months after start the plant—at which time she noti pigmented areas on her face. tinued to increase in severity and caused her to visit the out partment of the Lincoln Hospi sugar was found in her urine referred to the skin clinic where of acute catarrhal jaundice was rectal temperature, at that tim A diffuse papulo-pustular erupt present on her face. On being about it, the patient stated that present to her knowledge f months.† From then on she

* Grateful acknowledgement is made of the courtesy extended by the staff of Lincoln Hospital and the Medical Examiner's Office in granting permission to use the records in this case.

† Investigation revealed th some of her co-workers were a from a similar acneform erupti girl discontinued her work be None of these other girls s systemic disease.

increasing weakness and nausea. Her appetite was poor; her skin became progressively more jaundiced, and the pigmentation increased.

About 6 weeks before admission her mother noticed that her eyes were yellow. About 3 weeks later she began to complain of severe headaches which continued unabated. This was followed in a few days by a puffiness and swelling of the face, hands, feet and abdomen.

She continued at her regular work until 1 week before admission. On the morning of admission she began to have convulsive movements of the abdomen with involuntary bobbing of her head, unassociated with any pain. At the same time there seemed to develop memory defects and a change in mental status. On the way to the hospital in the ambulance she vomited. This was the first time vomiting had occurred. She arrived in the hospital in a state of prostration.

Summary of physical examination.—The patient gave the impression of being a colored girl although she was, in reality, white. She looked well nourished and well developed for her age. There was general puffiness of the face, hands, feet and abdomen. She was hiccoughing, and was frequently disturbed by a series of tetanic contractions of the abdominal muscles associated with involuntary bobbing of the head. The temperature was 100°, pulse 114, respiration 26.

The first admission note stated, "patient is so jaundiced her face is black." More careful examination of the face and neck revealed a negroid type of pigmentation beginning at the hair line and extending down to, and including, the neck. Besides this general pigmentation there were three areas somewhat darker than the rest, appearing very much like dabs of charcoal—one on each cheek below the eyes and one on the chin. On close examination these black spots appeared to be the result of aggregations of comedones. The scalp did not share in the general dark pigmentation. It was of a yellowish color characteristic of jaundice.

The skin of the thorax and the lower part of the body was dark brown with a yellowish subtinge. Over the skin of the abdomen there was a girdle-like area of di pigmentation beginning at the level of umbilicus and extending to the pe There was also a line of deeper pigmental in the garter region on the posterior sur of the left thigh about 1 inch above popliteal fold.

Examination of the eyes revealed d jaundice of the sclerae and the conju tivae. The pupils were equal and regul and reacted to light and accommodati There was no nystagmus or strabism The blephoral conjunctivae were red than normal. The discs were somewh pale, though well defined. There was exophthalmus. The normal ratio in wid of artery to vein was preserved. The ve sels were not contracted, and did not pr sent the hair-line appearance believed be associated with arsenic or quinine po soning.

Other positive physical findings were slight injection of the throat; slight edem of the feet and hands; an apical systoli murmur; abdomen distended and tympani tic; liver on percussion small, with tympany extending to the very costal edge.

Laboratory findings: These were as follows:

Blood count on admission—White cells, 9,100; Red cells, 4,200,000; Polys., 80%; Lymphs, 20% Hemoglobin, 87%; Bleeding time, 4.5 minutes; Clotting time, 2.5 minutes; Platelets, 220,000.

Blood chemistry: Non-protein nitrogen, 35, later 45, mg./100 cc.; Protein, 6.9 mg./100 cc.; Urea N. 20.83 mg./100 cc., Creatinin, 2 mg./100 cc.; Glucose, 88 mg./100 cc.; Cholesterol, 145 mg./100 cc.; Calcium, 8 mg./100 cc.; CO combining power, 52; Albumin, 2.5 mg./100 cc.; Icteric index, 230; Van den Berg, immediate direct reaction; Wasserman, negative.

Urine—Sp. gr. 1.008: Alkaline. Albumin negative. Sugar, a trace. Acetone, 1+. Bile pigment present. Urobilinogen a trace. Few red and white cells.

Stools—Urobilin present.

Spinal fluid—Pressure normal. Cells: 10, Lymphocytes. Clear. Glucose present. Globulin absent.

X-ray examination—No evidences of lesions of the heart and lungs; bones of skull, ribs, shoulder joints, clavicles, tibia and fibula. The gastric contents, and later,

at autopsy, the organs were analyzed for arsenic, phosphate, lead, tin and antimony. A trace of phosphate was reported, probably from inorganic phosphates ingested before admission.

Diagnosis—The patient presented a picture which was distinctly puzzling to all physicians who saw her and no conclusive diagnosis was reached at the time. The various diagnoses suggested included: obstruction of the common bile duct, toxic jaundice possibly due to some dye, obstruction of the inferior Vena Cava, blood dyscrasia, Addison's diabetes, hemochromatosis, industrial poisoning of unknown origin possibly due to arsenic, causing acute glomerular nephritis and acute hepatitis; and finally acute yellow atrophy of the liver and pancreas possibly due to an unknown industrial poison.

Course—The clinical course was steadily down-hill. At 11 p.m. on April 27th the patient became unconscious and went into a coma. There was Cheyne-Stokes breathing. A peculiar odor was present which was variously identified by hospital physicians as ethylene or garlic. The pupils were immobile to light. Deep reflexes were greatly depressed. There was no Babinski. Abdominal reflexes disappeared. The skin became dusky throughout. The liver dullness seemed to diminish. On April 28th the temperature rose to 106°; the pulse to 140, and the patient died.

Anatomical diagnosis—An autopsy was performed at the Medical Examiner's office on April 29, by Dr. Chas. H. Hochman, Assistant Medical Examiner. The report in full was as follows:

Body is that of a white adult female, well developed and nourished. Cyanosis of lips, ears and fingernails. Marked pigmentation about eyes, lower lips, neck and abdomen. General icteric tinge to entire body. No evidence of violence. Some edema about ankles. Hair is black. Eyebrows black. Brown iris. Conjunctivae and sclerae icteric. Rigor mortis present. Postmortem lividity of dependent parts. Scalp incised and reflected, calvarium removed. Brain found congested. Meninges bile tinged. On section, no evidence of intracranial injury or hemorrhage. Dura stripped and reveals no evidence of fracture.

Body opened in usual midline incision. Sternum removed. Some remnants of thymus still present. Lungs are free. Bronchi contain a bloody mucous. Mucosa injected, has yellowish tinge. Hemorrhagic infarct about size of hen's egg in left lower lobe. This is airless and dark red in color, firm. There are also similar smaller areas in other lobes. Heart is small and shows some sub-epicardial hemorrhages. Some hypertrophy of left ventricle. Valves thinned. Arteries natural. All are bile stained. No significant findings in myocardium or coronary arteries.

Esophagus is natural. Stomach is distended, contains some dark material. The rugae are somewhat hypertrophied. The duodenum contains green chyme. The ampulla is patent. The jejunum, ileum and large gut are natural. Many petechial hemorrhagic areas noted in the mesentery with some enlargement of mesenteric lymph nodes.

Liver is small, weight 720 gm. Capsule wrinkled. Right lobe on section shows areas of yellow surrounded by red areas.

Left lobe much firmer although liver cuts firmly throughout. All ducts patent. Gall bladder small. Wall thickened throughout.

Pancreas is natural in size, somewhat congested. Spleen is natural in size. On section, firm, dark red in color. Follicles are somewhat indistinct. Kidneys show swollen cortex. Evidence of parenchymatous degeneration of epithelial cells. Capsule strips easily. No granulation. Degenerative changes in cells of glomeruli only. No glomerulitis. Uterus is small. Endometrium bile-stained. Ovaries are natural in size; right contains corpus luteum cyst. Bladder wall is somewhat thickened. Mucosa is injected.

Microscopic examination—Liver—From size of a through and through transverse section one suspects that the entire liver was about ½ normal size. Liver segment is very firm and composed of two distinct and peculiar types of tissue: (a) That constituting major portion of parenchyma is red in color, firm and elastic in consistency; (b) Other areas are light yellow in color and are scattered indiscriminately throughout reddish areas. Yellow areas vary from ½ to 2 in. in diameter. External surface

of liver, judging from this portion, was smooth.

A typical picture of clear subacute yellow atrophy is revealed. Slides show that red area is composed of so-called "red atrophy" in which all the liver cells have disappeared, their place being occupied by their normal supporting stroma, which seems to have been spared, great numbers of blood cells, early fibroblastic proliferation and older scar tissue. In these red areas, numerous bile ducts are seen. These also seem to have been spared destruction. The yellow areas are composed of actively regenerating islands of liver cells.

The toxin evidently has destroyed most of the liver cells, leaving intact their supporting stroma, blood vessels and bile ducts. The latter seem to be regenerated. Those liver cells spared destruction have regenerated and have formed yellow islands seen in the gross picture. *There evidently has been one or more attacks of hepatitis judging from the different ages of the pathological process in various parts of liver.**

Skin—Shows an increased density of corium which stains deeply with eosin. Some of the epidermal cells are slightly deeper in corium than normal.

Heart—Shows mild parenchymatous myocardial degeneration.

Kidneys—Show severe epithelial degeneration involving epithelium of tubules and glomeruli. No inflammatory reaction of glomeruli.

Adrenals—Show severe parenchymatous degeneration of cells.

Pancreas—Shows intense degeneration of cells of acini and of islets.

Summary—An unknown toxin has evidently caused a severe diffuse cytolysis involving most of organs, predominately the liver. *The latter has evidently undergone and recovered from previous attacks of a similar nature.**

Case 2—F. D.

A young man, 24 years of age, was admitted to the New Haven Hospital on May 2, 1934, complaining of jaundice. The history given was as follows:

He had worked in a wire factory coating wire with wax† from July to the middle of December, 1933. At that time he felt run down and became jaundiced. He was seen in the dispensary in January and found to have an enlarged palpable liver. He then spent several weeks in another hospital with slight improvement in the jaundice.

In March, 1934, he returned to the job in the wire factory. Following this, the jaundice became quite intense with increase in general malaise, anorexia, attacks of dizziness and loss of weight. Three days before admission vomiting had occurred. He had taken no drugs and there had been no exposure to carbon tetrachloride or chloroform.

Summary of physical examination—The temperature was 99°, pulse 74, respiration 20, blood pressure 130/74. The patient was a thin well-developed man who appeared moderately ill. There was bright yellow jaundice of the entire body. The pupils were widely dilated, the nasal septum deviated, causing obstruction on the right, the mucous membranes injected and the tongue moderately coated. The tonsils were enlarged and cryptic. Lungs were clear, heart normal, radial vessels soft, abdomen tympanitic, soft non-tender. The liver edge was felt at the costal margin. The organ was soft and non-tender. The upper edge of the liver dullness was in the 6th interspace.

Laboratory findings—These were as follows:

Urine—was dark yellow and was negative except for the presence of bile and urobilin.

Blood count—red cells, 4,380,000; hemoglobin, 85%; white cells, 6,800; Polys., 65%; Lympha, 29%; Large Monos., 4%; Eos., 2%. Subsequent examinations showed a slight rise in white cells to 10,000.

Stool—showed bile, considerable undigested food, small amount of fat.

Kahn test—negative.

Liver function tests—Icteric index +30 to 50. Bromsulfonphthalein showed marked

* Authors' italics.

† The waxes employed in this process are the higher chlorinated naphthalenes. These are used in a molten state in a bath through which the wire to be coated is passed. The process is partially but not entirely enclosed. Exhaust ventilation is in use.

impairment: 100% retention in 5 min., 85% retention in 30 min.

Blood chemistry: Non-protein nitrogen, 28 mg./100 cc.; Urea N, 11 mg./100 cc.; Serum total proteins, 6.15 mg./100 cc.; Serum total albumin, 2.66 mg./100 cc.; Serum total globulin, 3.49 mg./100 cc. A/G ratio, 0.76; Blood sugar, 68.0 mg./100 cc.; Blood calcium, 10.32 mg/100 cc.; Blood phosphorus, 4.12 mg./100 cc.; Serum fatty acids, 11.3 mg./100 cc.; Serum lipoid phosphorus, 7.5 mg./100 cc.; Serum total cholesterol, 10.5 mg./100 cc.; Serum free cholesterol, 63.0 mg./100.

Sugar tolerance test was within normal limits.

X-ray of abdomen showed hepatic flexure of colon unusually high.

Course. The patient was put on a high carbohydrate diet and his general condition improved but the jaundice persisted. He was discharged on May 16, 1934 with the diagnosis of toxic hepatitis.

He was admitted again on June 1, 1934 complaining of abdominal swelling of 3 days' duration, weakness, anorexia and edema of the legs which had developed soon after his discharge. The physical examination showed deep jaundice, systolic murmur, abdomen distended and tympanitic with dullness in the flanks, moderate pitting edema of the legs. Examinations of the urine, blood and stool showed no important variations from the original findings with the exception of a drop in white cell count to 6,400 with 74% polys., and a decrease in serum albumin to 1.88%. Serum CO_2 content was 54.54. Serum chloride was 98.0 mg./100 cc.

The patient's course after the second admission was rapidly downhill. The distention could not be controlled and he soon passed into complete coma. A convulsion occurred on June 8th and on June 10th he died.

*Anatomical diagnosis.** Extensive necrosis, fibrosis and regeneration of liver, acute entero-colitis with edema, fibrosis of pancreas, acute pancreatitis, jaundice, ascites, edema of lower extremities, focal pneumonia (bilateral), subpleural hemorrhages, cloudy swelling of kidneys.

Case 3 – C. C.

A young man 22 years of age was admitted to the New Haven Hospital on February 28, 1935 with the complaints of jaundice, abdominal pain, nausea and vomiting of bloody material. The history given was as follows:

He had worked in the same wire coating plant as the previous patient (F. D.). The present illness had begun with jaundice 2 months previously with no other symptoms. This continued for about 1½ months. Two weeks before admission he became more jaundiced and concomitantly developed upper abdominal pain, malaise, nausea and finally vomiting the vomitus becoming bloody in character. He was treated by his family doctor with no relief. His condition became worse and he finally became delirious and incoherent. Hospitalization was advised.

Summary of physical examination The patient was comatose, irrational and vomiting bloody material. Positive findings of significance were as follows: Temperature not elevated. Blood pressure 102/68. Generalized jaundice, petechiae over the extensor surfaces of the arms; tenderness over the upper quadrants of the abdomen. No liver dullness percussable.

Course—His condition became rapidly worse, coma setting in soon after admission. The vomiting continued. The patient died about 24 hours after admission.

Anatomical diagnosis—Extensive necrosis and regeneration of liver; jaundice, acute lymphadenitis of portal nodes; ascites; perienteritis of jejunum; cloudy swelling of heart and kidneys; acute pulmonary congestion; healing exanthematous rash of fore-arms.

DISCUSSION

These three cases show the occurrence of similar pathological changes in the liver in three young adults known to have been working with chlorinated naphthalenes and diphenyls--all were exposed directly or indirectly to the higher chlorinated hydrocarbons. In

* Autopsies on this and the following case were performed on the pathological service of the New Haven Hospital by Dr. H. M. Zimmerman. Grateful acknowledgement is made of his courtesy in permitting use of the records.

all three cases, a most careful investigation failed to reveal any other predisposing cause for the condition. In the first case in particular, that of a healthy young girl on her first job, the absence of any conditions predisposing to liver damage either preceding or following her exposure to the substances in question is especially clear.

It is of interest to note that two of the cases apparently had suffered from at least one previous attack of hepatitis followed by a certain degree of improvement before the onset of the fatal attack.

In view of the fact that Drinker, Warren and Bennett found no lesions in organs other than the liver in their experimental animals, it is noteworthy that such lesions were conspicuous in all three of the cases here reported. Such lesions, are, indeed, usual findings in cases of acute yellow atrophy of the liver in humans regardless of etiology. On the basis of present knowledge, it would be impossible to say whether they are the result of primary intoxication or are merely secondary to liver damage. In the light of the animal experiments, however, one would incline to the latter view and speculate as to the part played by length of exposure, in the final pathological picture.

It has been mentioned that in Drinker's (4) experiments, rats with no evidence of clinical disease while being exposed to the chlorinated naphthalenes, promptly died from acute yellow atrophy of the liver when given doses of carbon tetrachloride so small as to be harmless to control animals. This prompts speculation as to whether death from acute yellow atrophy of the liver in workers similarly exposed occurs only in those having some pre-existing substratum of liver damage—such as might follow an attack of catarrhal jaundice, for example—and that this might account, in part at least, for the fact that only a very occasional worker out of a large group will suffer from systemic effects of exposure to these substances. In the three cases reported however, no history was given suggesting that any hepatic disorder prior to exposure had occurred.

The presence of a papulo-pustular eruption in two cases is of interest. In one it antedated the systemic symptoms. This type of eruption is characteristic of the dermatitis caused by chlorinated naphthalenes, and until recently was the only disturbance attributed to them.

The presence of "aggregations of comedones" such as were found in Case I is also characteristic of the skin eruptions produced by these substances. The question as to whether or not the skin eruption in such a case is in any way connected with the onset of systemic effects cannot be answered, since thus far no correlation has been established between skin lesions and systemic disease (1).

It is interesting, therefore, that in Case I the skin eruption apparently antedated all evidences of systemic disease. Had the girl been promptly removed from further exposure, when it was first observed, it is possible that her life would have been saved; or had the physicians first called upon to treat the jaundice (of whatever origin) in her case, or in the second case here reported, recognized the danger of continuing exposure to the chlorinated naphthalenes, these deaths might possibly have been averted.

Recommendations for Medical Control

1. The authors wish to stress the need for the conscientious reporting by physicians of *all* illnesses occurring among workers exposed to the chlorinated naphthalenes and diphenyls, particularly cases which have been carefully worked up, so that the clinical disease entities resulting from such exposure can become further clarified and thus more readily recognized in the future. Fewer errors in the diagnosis and management of these cases would occur, and workers' lives could undoubtedly be saved in this way.

2. Persons suffering from the typical acneform eruptions should be removed from further exposure.

3. Persons who have, at any time in the past, had any liver disease—even a mild catarrhal jaundice—should not work with these substances; nor should workers with a history of typhoid fever, malaria, gall-stones or other diseases known to affect the liver adversely.

4. Persons receiving arsphenamine treatment for syphilis; or those who are taking drugs believed to be injurious to the liver in susceptible persons, should not be further exposed in their work to potential liver poisons.

5. Persons working with the chlorinated naphthalenes and diphenyls, if requiring a general anesthetic for an operation, should not be given chloroform or avertin, and vice versa, individuals who have recently received such anesthetics should not immediately thereafter go back to their former work or to work with other substances believed to be potentially toxic to the liver.

6. Pregnant women should not be exposed because the liver, in pregnancy, appears to be peculiarly susceptible to injury.

7. Experience seems to indicate that by proper attention to ventilation and medical supervision of workers the chlorinated naphthalenes and diphenyls can be used in industry with safety.

Summary

The systemic effects resulting from exposure to certain chlorinated naphthalenes are discussed, and the literature of the subject briefly summarized. Three liver deaths in workers handling these substances are presented in some detail, with autopsy findings. Recommendations for prevention are given.

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