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HEPATO-TOXIC EFFECTS FOLLOWING OCCUPATIONAL EXPOSURE TO HALOWAX (CHLORINATED HYDROCARBONS)*

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On December 30, 1942, in many of the local newspapers the following headline appeared: "3 War Workers Dead, 511 Ill From Industrial Poison". The article went on to state that the poison was a hydrocarbon with a chlorine base. This probably would not have aroused the author's interest had he not been called in on consultation by an insurance company on the following case:

Case 1: The patient was a white male adult, 50 years of age, whose peacetime occupation was that of a painter and general laborer.

He started work in a defense plant on June 15th, 1942, as a wire cabler. He stated that a Halowax machine was directly in back of him while at work.

Approximately three months later he developed a Halowax Dermatitis of both arms. (This dermatitis, known in factory parlance as the "plant itch", is known to dermatologists as an acneform folliculitis, with lesions over the entire body, the exposed and nonexposed surfaces alike. No further references will be made to the dermatological aspects, as this condition is well described in the American literature and is beyond the scope of this paper.)

In December of 1942, six months after exposure to Halowax fumes and three months after development of the dermatitis, he became jaundiced.

His only other symptoms were loss of appetite and weight. He stated that his usual weight was 189 lbs. and he now weighed 173 lbs. There were no complaints of abdominal pain, gastric distress, or change of bowel hygiene.

On January 22nd, 1943, the plant physician sent him into a local hospital for study.

The patient appeared to be a well developed, well nourished, male adult, lying quietly in bed, in no apparent distress. There was apparent loss of weight.

The skin had an icteric tint. There was evidence of dermatitis of both arms, face, and back of neck.

The sclera of the eyes was jaundiced, the pupils were equal, regular, and reacted to light and accommodation. The nose was negative. There was evidence of a post-nasal drip in the throat. There was complete edentulation. The heart

*Read before the New York Chapter of the National Gastroenterological Association on Monday, November 15th, 1943.

**All names and initials of patients, attending physicians and hospitals have been purposely omitted in order to avoid any possible medico-legal complications.

rate was regular, the sounds were of good quality, with no murmurs, and the size was normal to percussion. The blood pressure was 102/60. The lungs were clear and resonant throughout.

The abdomen was soft, no masses palpable. The liver was not palpable. There seemed to be some diminution of the size of the liver to percussion. Spleen was not palpable.

The knees showed evidence of psoriasis. The reflexes were normal.

On January 22, the positive urine findings were bile 2 plus, few fine granular casts and occasional pus cells. On January 23, bile 1 plus, many fine granular casts.

A blood count revealed 4,730,000 red blood cells, hemoglobin 100 per cent, color index 1.05. Slight anisocytosis and slight poikilocytosis, few macrocytes and rare microcytes. White blood cells 3,800, segmented forms 68 per cent, stabs 5 per cent, lymphocytes 34 per cent, monocytes 1 per cent, eosinophils 1 per cent and basophils 1 per cent.

A radiograph of the abdomen showed a calcified shadow in the left side of the abdomen which resembled a calcified node. There was no evidence of shadows in the region of the gallbladder which would have suggested the presence of stones.

On January 22, fluoroscopic examination with barium meal showed a normal esophagus. The stomach was medium in size, situated high in the abdomen. The lesser and greater curvatures were smooth and regular. The cap was depressed and flattened and a very large loop was made by the duodenum which suggested an enlargement of the head of the pancreas. The multigraph showed a persistent crater on the medial aspect which might have been a crater of an old ulcer.

The two and six hour film showed the stomach to be completely empty, most of the barium was in the lower ileum. Twenty-four hour film showed the head of the barium to be in the splenic flexure. There was no evidence of pathology in the colon.

A barium enema was given and the barium entered readily and passed fairly quickly to the region of the cecum. There was definite spasticity of the descending colon and the appearance suggested the presence of colitis. There were no filling defects or diverticulae that suggested the presence of malignancy.

On February 2nd, the patient was referred by his family physician to a large medical center for further study. He remained in this institution until February 11th, 1943.

The additional data obtained was reported as follows:—

The history was essentially the same as reported above. The physical examination the same as reported above except that in addition, bilateral, small, indirect inguinal hernias were noted.

Red blood cells 7,520,000, hemoglobin 106 per cent, white blood cells 6,250, segments 60 per cent, lymphocytes 32 per cent, monocytes 4 per cent, eosinophils 2 per cent, basophils 2 per cent.

Urea nitrogen 9 mg., bilirubin 11.6, cholesterol 500 mg., serum protein 6.6 per cent, serum albumin 3.8 per cent, serum globulin 2.8 per cent, prothrombin time 19.3 seconds (normal 18-24), cephalin cholesterol flocculation test 2/3/43—2 plus, 2/8/43—3 plus.

X-ray of the chest showed no infiltration or consolidation in either lung fields.

The attending physician concluded that the chemistry pointed to obstructive etiology but the history was very suggestive of toxic jaundice. He believed this might have been an intrahepatic type of obstruction.

The discharge note by attending physician:—"Diffuse degeneration of the liver due to a derivative of Benzene i.e. Halowax." His chemical findings were suggestive of obstructive jaundice with a phosphatase of 15.6 and 14.2 Bodansky

units, a cholesterol of 500 and 480 mg., a normal protein and A.G. ratio and cephalin flocculation 2 plus. However, his cephalin flocculation increased to 3 plus and his stool remained dark. His history was suggestive of toxic hepatitis. It was felt that the jaundice was most likely on a toxic basis.

On March 9th, the patient was admitted to a third hospital with the chief complaints of weakness, itchy skin, dyspnea, epigastric pain, loss of appetite and insomnia.

Physical examination of March 9, 1943, showed the entire body had a deep orange discoloration, conjunctiva had a deep yellow discoloration and also evidence in both eyeballs of conjunctival hemorrhages. The entire body was covered with an elevated puckered dermatitis which was not uniformly spread out about the body, but in most parts, it appeared clustered. The skin rash was especially noticed about the cheeks, chin, neck and both lower and upper extremities. Other areas on the trunk of the body were also covered with the rash; a few of these were bleeding, especially on the trunk and forearms.

Tongue was dry and fissured.

The abdomen was extremely distended with some evidence of free fluid. Liver margin could not be palpated nor could spleen be palpated. There was no evidence of any masses or tenderness except a slight tenderness in the upper epigastrium on pressure.

Remainder of the physical examination was the same as previously reported.

Impression—"It appeared from the rash as seen on the body and extremities, together with the marked jaundice, and together with the history of exposure to toxic fumes, that an occupational toxic hepatitis must be strongly considered. There was no evidence at any time of any malignancy although this could not be ruled out except by postmortem examination. Acute carcinoma of the pancreas must be considered although there was no evidence of this condition at the time."

On March 15, 1943, the red blood count was 5,030,000, hemoglobin 97 per cent, white blood cells 9,300,000, segmented forms 74 per cent, lymphocytes 24 per cent, eosinophils 1 per cent, monocytes 1 per cent.

The bleeding time on the same date was 2 minutes, 15 seconds; coagulation time 7 minutes, icteric index 100, van den Bergh, positive immediate direct reaction, cholesterol 384 mgms. (normal 140-180).

On March 18, 1943, the bile findings were positive. No tumor cells were seen. Specific gravity, 1.010. Direct smear, no organisms found. Cultures were made on March 24, and were sterile after seven days.

Treatment consisted of high protein diet and intravenous glucose.

On March 18, 1943, an abdominal paracentesis was performed and 5,000 c.c. of orange colored fluid obtained. March 24 the patient went into coma and died on March 25.

On postmortem examination, the peritoneal cavity contained estimated 2500 c.c. of dark orange and lightly cloudy fluid. The peritoneal surface was smooth and glistening. Beneath the peritoneum of the lateral walls of the abdomen and the diaphragm were extensive, prominent networks of turtuous venules. The deep veins of the abdominal walls were dilated. There were no adhesions.

Grossly, the esophagus did not show any prominent varices. The stomach contained about 500 c.c. of turbid grayish chyme. The pancreas was hard and rather nodular, but lobulation was well defined with occasional pin-head size foci of opaque yellowish material between the lobules.

The liver weighed 1020 gms. The organ was very small. It measured 21 cm. in width, 16 cm. in length, and 6 cm. in depth through the right lobe. It was generally dull pale yellow in color. The surface was characterized by soft irregular rounded elevations exhibiting prominent lobular markings contrasting with extensive depressed areas, finely granular and wrinkled and without lobular markings. These portions of the liver were rather flabby in consistency and on cut surface contrasted sharply with the nodular elevations above described. The consistency

of the liver as a whole was increased. The edge varied from thin and sharp to rounded. The left lobe and spigelian lobe were relatively more reduced in size than the right lobe.

The diagnosis was cirrhosis of the liver: subacute necrotizing hepatitis (acute yellow atrophy of liver); ascites; fat necrosis of the pancreas; subacute vegetative endocarditis with mitral insufficiency; chronic acneform dermatitis.

Cause of death was cirrhosis of the liver due to subacute necrotizing hepatitis (acute yellow atrophy of the liver).

A careful review of the autopsy findings revealed no explanation for the x-ray findings to wit: "The duodenal cap is depressed and flatttened and a very large loop is made by the duodenum which suggests an enlargement of the head of the pancreas."

Following our experience with this case, the author was commissioned by the insurance company to study all the available literature and data relevant to the possible toxic effects of exposure to the various chlorinated hydrocarbons, and the following report is the result of my studies and subsequent experience in this field.

Systemic Effect of Exposure to Chlorinated Hydrocarbons

Chemistry of Halowax:—One of the most important hydrocarbons in the coal tar distillate is Naphthalene. It is a colorless, crystalline solid which melts at 79° Fahr. and boils at 218° Fahr. It has an empiric formula of $C_{10}H_8$. It consists essentially of 2 Benzene rings with 2 Carbon atoms in common.

Chlorinated Naphthalenes:—are naphthalenes in which one or more hydrogen atoms have been replaced by chlorine. The substitution begins with one chlorine replacement (monochlor) and may go all the way to eight chlorine replacements (octochloronaphthalene). Commercially, usually several chlorinated compounds are employed together.

Chlorinated Diphenyls:—(Occupational Disease-Johnstone-1941) in the manufacture of the chlorinated diphenyls, benzene (C_6H_6) is converted into $C_{12}CL_{10}$. The higher the chlorination, the greater the toxicity.

Industrial Use:—These substances are non-inflammable and are resistant to a high degree of heat, moisture and electricity. Because of these properties they are extensively used as wire insulation and in the manufacture of electrical condensers.

The chlorinated naphthalenes are often dissolved in carbon tetrachloride ($C\ CL_4$) and toluene $C_6H_5(CH_3)$. The use of carbon tetrachloride as a solvent increases the hazard of the chlorinated naphthalenes from the point of view of occupational diseases.

Animal Experimental Data:—In 1936 Flinn and Jarvik[2] of the School of Public Health, Columbia University, published the first report of animal experimentation in an effort to determine the toxicity of chlorinated hydrocarbons. This is the earliest reference in American medical literature on this subject.

The animals used in these experiments were rabbits. They employed 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 hexachlornaphthalene. They also used sublimates of (b) and (c) given off at

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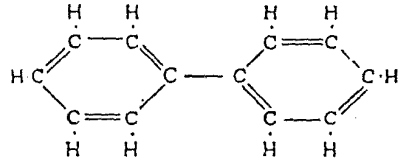
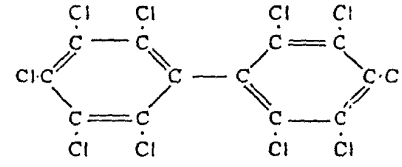
162°C and 172°C respectively. Large doses, approximately 15 mg. per kg. were injected subcutaneously each day.

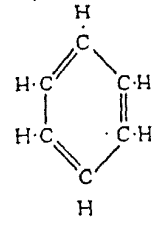
Animals receiving compound (a) and the sublimate of compound (b) showed no lesions attributable to these substances when killed at the end of two months. The 30 animals, however, which had received the higher chlorinated compounds (b) and (c) and the sublimate of (c), all died in from 12 to 26 days.

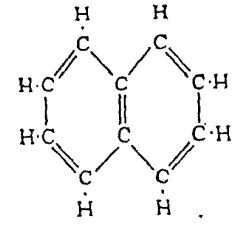




The autopsy findings were uniform, and strikingly limited to the liver. The detailed report of liver damage is quoted as follows:

Liver—"Very large, dark red with many opaque yellow areas. Capsule smooth, cuts with resistance, cut surface smooth. In many parts of the organ are yellow, opaque areas with dull surface, that involve groups of lobules. In between, the liver parenchyma in places is dark red, and the lobules are clearly visible. In other places, the lobulations cannot be seen, and the parenchyma has apparently disappeared and stroma is collapsed; these portions are greyish red. The gall-bladder is distended. In the peritoneal cavity there is a moderate excess of bloody fluid."





Histological findings present a most striking change. Beneath the capsule on one of the sections is a wide zone of necrosis, in which portal areas are seen surrounded by a single row of well preserved cells, or none at all. In other places in the section, efferent veins are surrounded by wide zones in which the liver cells have undergone necrosis. There are numerous other places where liver cells have completely disappeared and only the collapsed stroma remains. In many places calcification of the stroma is well advanced and larger masses of calcium are frequently seen. Multinucleated giant cells of huge dimensions are often clustered about masses of calcium or are found in the areas of collapsed stroma.

Liver cells remain but the regular normal architecture is not retained. Rounded groups of liver cells are numerous or only narrow bands of these cells surround portal areas. The liver cells also present a peculiar arrangement in many places. A double column of the cells will open up leaving a considerable space surrounded by cells. The space contains granular precipitate or large plugs of bile. Necrosis of individual liver cells is also taking place. Cirrhosis is negative. Flinn and Jarvik concluded:

"From the evidence obtained from 30 rabbits, all showing the same pathological picture, we feel that certain chlorinated naphthalenes or impurities contained in them are capable of producing yellow atrophy of the liver in the rabbit. This, with the history of the industrial cases, points to its being a possible etiological agent in the factory cases."

In the Spring of 1936 the Halowax Corporation, a division of the Bakalite Corporation, found that three of their workers died of jaundice following exposure to Halowax. They requested Dr. Cecil Drinker[3], of the Department of Physiology, Harvard School of Public Health, to investigate this problem from a research angle. In 1937, in the Journal of Industrial Hygiene and Toxicology, Dr. Drinker and his co-workers published the results of their experiments with rats exposed to the several chlorinated naphthalenes in varying concentrations in the air.

The conclusions drawn from these exhaustive studies from a practical point of view may be summarized as follows:

1—The degree of chlorination seems to determine the degree of toxicity.

2—All the compounds tested attack the liver and the liver alone.

3—A determination of the organically combined chloride in the livers of animals very severely poisoned by penta- and hexa-chlornaphthalenes showed no increase over normal figures, though the livers, as determined histologically, were very severely affected.

4—Ventilation should be so arranged that the air breathed does not contain more than 0.5 mg. per cubic meter of any compound above tri-chlornaphthalenes.

5—Carbon tetrachloride adds to the toxicity of the chlorinated naphthalenes and allied compounds, and if there is a possibility of inhaling these compounds in other parts of the factory, then inhalation of carbon tetrachloride adds a decided hazard. Under such circumstances, a solvent such as toluene should be used.

Reports of Toxic Effects on Humans:—Dr. Drinker reported the first three deaths, recorded in American literature, of patients who developed jaundice after exposure to Halowax. These three cases are briefly summarized as follows: *Case* 1—Age 21—Had an attack of jaundice six weeks before his fatal illness. Autopsy revealed a cirrhosis of the liver with acute yellow atrophy superimposed upon it. *Case* 2—Died after an acute illness characterized by jaundice. (No autopsy reported). *Case* 3—Became jaundiced and died after two weeks illness. There was no record of preceding attack of jaundice. Autopsy revealed an acute yellow atrophy of the liver.

Dr. Drinker mentions, in addition to the above three fatal cases, "we have learned of four other possible cases, none of them fatal". He gives no description of them, however.

In 1939, Greenburg, Mayers, and Smith[4] reported three additional cases dying of acute yellow atrophy following occupational exposure to the chlorinated naphthalenes. It is of interest to note that all three cases were exceptionally young adults, 17, 22, and 24 years of age. One constant laboratory finding is a drop in the serum albumin and total serum protein.

Report of One Non-Fatal Case:—In January 1942, in the Industrial Bulletin, Division of Industrial Hygiene, Department of Labor, State of New York, Mayers and Smith[5] reported one non-fatal case of poisoning by chlorinated naphthalene.

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This was a case report of an 18 year old girl who became exposed to the fumes by virtue of her occupation viz: soldering electrical condensers; as heat was applied to the condensers, fumes would come off; air tests showed the presence of 3.4 mg. Halowax vapor per cubic meter of air.

This patient presented the usual symptoms of jaundice, loss of appetite, nausea, vomiting and abdominal pain. In addition her ankles, legs, face and abdomen began to swell. She showed definite evidence of liver damage as evidenced by her jaundice, increased icterus index (42 to 52) and the Levulose tolerance test—after two hours her blood sugar level was 105 mg. per 100 c.c. blood. Her serum albumin was also low 2.4 per cent. and fell further to 1.7 per cent. Her total protein was 4.5 per cent.

In the light of the findings of the previous cases, (diminution in serum albumin and total protein) the patient was placed upon a high protein diet and given several small transfusions. The edema subsided after a period of five weeks in which no progress had been made. The patient recovered.

The additional cases, all having a history of exposure to the fumes of the chlorinated hydrocarbons, were added in order to help complete the literature in this important industrial field.

Case 2—Admitted May 25, 1941, died on May 26, 1941. The patient was a white male, 43 years of age, born in the United States, of Irish descent, whose occupation was that of a laborer. His condition on admission was serious. The tentative diagnosis was obstructive jaundice? The final diagnosis was: Acute toxic hepatitis, pulmonary congestion with infarcts.

The patient, ill for two weeks, had complained of nausea and severe epigastric pain and had begun to turn yellow. Stools had been white for a week and urine was "dark as molasses." He had several bouts of vomiting in the past week with hematemesis for the past few days. He had gone steadily downhill, had become irrational and comatose.

Additional history obtained from brother-in-law via telephone, showed that he had been "employed as machinist in factory" (was exposed to fumes of chlorinated hydrocarbons—author's note). "Had burn on leg in April which healed. Complained of increasing weakness and fatigue for two weeks and stopped work one week ago. Jaundice was noticed four days ago. There was no history of alcoholism or drugs."

His wife died two months ago of sarcoma of hip. His father died of septicemia, his mother of pneumonia. One sister died at the age of seventeen of Bright's disease, two sisters died of kidney trouble after childbirth.

Physical examination showed the patient to be deeply jaundiced, but comatose, well developed and well nourished with no apparent loss of weight. There was involuntary nystagmus of eyeballs to and fro and an acidotis odor to the breath. Blood pressure 184/56, temperature 99°, pulse 108, respiration 24. The liver was enlarged two fingers below costal margin.

The blood count was: red blood cells 5,070,000; hemoglobin 15 gms.; white blood cells 11,200; eosinophils 1%, juveniles 1%, stabs 1%, segments 79% and lymphocytes 14%. The urinalysis showed a specific gravity of 1.028, albumin of 1 plus and a trace of sugar. There were a few granular casts, very occasional red blood cells and there was bile present.

Blood Chemistry:

Cholesterol	75	Normal	140-180 mg.
Icteric Index	143	"	4-6
Sugar	61	"	80-120 mg.
N.P.N.	44	"	25-45 mg.
Creatinine	1.8	"	1-2.5 mg.
CO_2 Combining Power	36%	"	53-78%
Albumin	3.3%	"	4.5-6.5%
Globulin	2.9%	"	1.0-3%
Total Protein	6.2%	"	6-9%

The death certificate read: Acute toxic hepatitis, duration two weeks, cause undetermined at this time.

The postmortem performed on May 27, 1941 read as follows: The liver weighed 750 gms., its surface was smooth and the capsule showed some shrinking. There were no subcapsular hemorrhages. Parenchyma did not bulge on section. The parenchyma was yellow-brown in color and showed atrophy and degeneration. The gallbladder wall was somewhat edematous. The gallbladder contained 15-20 c.c. of dark, cloudy, green bile; no stones were present, ducts were patent. The spleen weighed 225 grams. Capsule was smooth and gray. The parenchyma was deep red, soft and bulged slightly on section. On the head of the pancreas and extending down towards the tail was a dark gray area 6-7 cm. in length. The tissue beneath this area appeared somewhat necrotic. The microscopic report of the liver showed universal necrosis of the parenchymal cells with recovery manifest in the biliary ducts and healing in the stoma. There was no evidence of inflammation.

The gross summary was as follows: Jaundice; acute yellow atrophy, etiology unknown; Pulmonary congestion and infarcts; Arteriosclerotic congestion and heart disease; Pancreatitis; Toxic nephrosis; Generalized petechiae.

The results of the chemist's report, on May 27th, 1941, were: Urine—negative for arsenic; Kidney—negative for mercury, antimony and bismuth; Liver—negative for volatile poisons. Acid ether soluble poisons—negative. Alkaline ether soluble poisons—negative. Ammonia chloroform soluble poisons—negative. Negative for cinchophen.

The summary: A frank case of poisoning with destruction of the liver and kidney parenchyma and hemorrhagic diathesis. The toxicological examination was completely negative.

Case 3: This patient was admitted on July 19, 1942, and died on July 25, the final diagnosis being acute yellow atrophy of the liver with icterus and ascites.

He was a white male, 36 years old, born in the United States, married, Catholic. He was employed in a war plant as an electrician. On admission the chief complaint was diffuse abdominal pain from which he obtained greater relief on standing than by sitting. The sensation was described as sharp, cutting—one which "took the breath away"—and the patient stated that it began in the epigastrium and moved to the hypogastrium. Attacks of pain began at 9 a.m. that day. There was no nausea, but he vomited orange juice and coughed up phlegm. He felt lethargic. For two weeks before admission he had had "gas." No one had noticed the strange color of his eyes.

Eight years ago appendectomy had been performed, and twenty-seven years ago laparotomy had been done for intestinal obstruction. Since the appendectomy

there had been no abdominal symptoms. He had had measles, chicken pox, mumps and whooping cough in childhood.

His habit was to smoke one pack of cigarettes a day. He drank very little, only an occasional glass of beer.

The family history was negative. His father died at 73 and his mother at 74, both of natural causes. One brother and two sisters were living and well.

No examination at the time of admission was recorded on the chart. At a consultation on July 24, moderate generalized jaundice, considered most probably of the obstructive type, was noted. There was moderate abdominal distention, with a soft tympanitic loop just beneath the xiphoid. The lower abdomen was flat with shifting dullness. Two scars on the right rectus, one from the appendectomy and the other from the laparotomy for intestinal obstruction, were noted. The edge of the liver was not palpable. No masses were found.

The diagnosis was incomplete obstructive jaundice with the following possible causes, in the order of their probability: (1) extensive abdominal adhesions, (2) atypical cirrhosis with ascites, (3) carcinoma of the head of the pancreas, (4) a stone in the common duct, or (5) catarrhal jaundice.

A blood count on the day of admission showed 3,600,000 red blood cells, hemoglobin 87 per cent, color index 1.2; 6,700 white blood cells, basophils 2 per cent, segmented forms 62 per cent, staff cells 6 per cent, juvenile forms 1 per cent, lymphocytes 25 per cent, monocytes 4 per cent. The icterus index, determined on the following day, was 57, and a van den Bergh test gave a biphasic direct reaction. On July 21 the urine had a specific gravity of 1.028, and was negative for albumin and sugar; bile was present, and urobilinogen was present in a dilution of 1.100. On the following day the specific gravity was 1.033; bile and urobilinogen were present, and a trace of albumin, but no sugar.

X-ray films of the abdomen from the anteroposterior and postero-anterior directions showed a considerable collection of gas in both the small and large intestines. The appearance was suggestive of partial intestinal obstruction or of peritonitis. A film made with the patient erect showed no evidence of air beneath either diaphragm.

A gastrointestinal series, in which films were made immediately after the ingestion of a barium meal, and two, six and twenty-four hours later, revealed no evidence of cancer or ulcer of the stomach. The gastric wall was pliable throughout. There was no evidence of a postpyloric ulcer, and the cap was not deformed.

The stomach began to empty immediately, but there were fairly definite changes in the mucosal pattern of the duodenum and jejunum, suggesting some physiological disturbance.

After two hours the stomach was completely empty. After six hours all the barium lay in the distal jejunum, and after twenty-four hours considerable barium had been eliminated. In both the two-hour and the six-hour films, the barium was seen scattered in sausage-like links in the coils of the small intestine; there was definite delay in the progress of the meal throughout the small intestine and into the colon. I suspect that the changes observed were due either to a deficiency state or to some disturbance of the physiology of the small intestine, such as might be caused by gastroenteritis.

There were no x-ray findings suggesting an obstruction.

The autopsy findings were as follows: The peritoneal cavity was distended by 4,000 c.c. of clear dark-yellow fluid, and the serous surfaces were stained dark yellow. The terminal ileum showed dense adhesions between individual loops and to the abdominal wall under the adhesions beneath the incision. The liver edge extended 4 cm. below the costal margin. The appendix was absent. The diaphragm extended up to the third interspace on either side, and on the right side between the diaphragm and the dome of liver considerable fluid was found, with

a little fibrous deposit on the peritoneal surface. The mesentery was fatty, and contained large, soft, reddened lymph nodes.

No abnormality was seen in the thoracic esophagus. The stomach was nearly empty, containing only a little gray thick fluid. The gastrointestinal wall was of normal appearance, though the serosa was considerably reddened. The mucosa was gray, and covered with deep rugae. The duodenum contained fluid which showed more bile stain, but the wall and the mucosa were normal. The entire small intestine showed a very thick edematous wall with much reddened serous membrane. The mucosa appeared normal. In the lumen, thin bile-stained fluid was found. The lower ileum had many loops firmly bound together by adhesions to the abdominal wall beneath the incisions. To some extent the large intestine shared the edema, and its serous surfaces were reddened.

The liver weighed about 900 gm., and showed a nodular yellowish and reddish-brown surface, with wrinkling of the capsule. It cut with slight difficulty, revealing swollen yellow lobules with dark red lobular centers, poorly outlined. In the lesser omentum were numerous enlarged soft reddish-gray lymph nodes. The hepatic artery showed calcification and narrowing, but was patent. The portal vein was distended by a loose clot of dark reddish-gray, apparently somewhat adherent to the tributary lienal vein. Although the superior mesenteric vein was widely patent, it contained fluid blood. There was considerable calcification of the wall of the lienal artery also, and of other branches of the superior mesenteric artery.

The gallbladder revealed a very edematous wall and congested serosa, but the mucosa was dark green and otherwise of normal appearance. The organ contained 40 c.c. of thick dark-green fluid bile. The ducts were patent, and there were no stones.

Microscopic examination of the liver showed areas of necrosis occupying an estimated half of the sections examined. Most of these areas were mid-zonal, but some lay next to the portal vessels or central veins. The remaining hepatic cords appeared as islands, with swollen cells showing indistinct boundaries and finely granular cytoplasm. Few were vacuolated. The necrotic areas showed a fine reticulo-endothelial framework enclosing finely granular, pale-staining debris, with a few indistinctly outlined cells containing yellow pigment. There was infiltration of lymphoid and plasma cells and a few polymorphonuclears and scattered fibroblasts. In the centers of many necrotic areas there was extravasation of red blood cells. Growing from the ducts in the portal spaces toward the remaining hepatic islands were numerous compressed and distorted small ducts, lined with low columnar or cuboidal epithelium, and showing dark-staining nuclei.

The anatomical diagnosis was subacute necrotic hepatitis (acute yellow atrophy of the liver), icterus, ascites, thrombophlebitis of the lienal vein, congestion and edema of the peritoneum, acute focal myocarditis, old adhesions of the ileum to abdominal scars, and old appendectomy. The cause of death was acute yellow atrophy of the liver.

Case 4. This patient, whose occupation was that of mechanic, was a white male 36 years old, born in England. He was admitted on January 10, 1943, and died on March 24, 1943. The provisional diagnosis on admission was toxic jaundice, the operative diagnosis biliary carcinoma.

The chief complaint was indigestion of three weeks' duration, noted especially at supper time: he felt as if his stomach were "tied in a knot", and vomited. He stated that lately he had been more run down than usual, and during the previous two weeks had noted a yellow tint in his skin and sclerae. The history given included itching at intervals from asbestos, and sensitivity to rubber dust.

On physical examination the positive findings were an icteric tint of the sclerae and skin, and enlargement of the liver (three fingers). There were no abdominal masses or tenderness. The examiner's impression was that this was a case of toxic jaundice.

Several urinalyses were essentially negative except for the presence of bile and finely granular and coarse casts. A blood count on February 10 showed 4,490,000 red blood cells, hemoglobin 87 per cent, color index 0.96; 8,600 white blood cells, eosinophils 2 per cent, staff cells 3 per cent, segmented forms 71 per cent, lymphocytes 21 per cent, basophils 1 per cent. Two weeks later there were 3,730,000 red blood cells, with the hemoglobin 71 per cent, 6,700 white blood cells, eosinophils 3 per cent, staff cells 3 per cent, segmented from 71 per cent and lymphocytes 23 per cent. The coagulation time was 4¼ minutes. The icteric index on February 17 was 75, and the van den Bergh test gave a prompt direct reaction. The fragility test o February 25, the reaction began with 0.38 per cent and ended with 0.16 per cent.

In a series of gastric analyses the findings were as follows:

Free HCl	Total HCl	Lactic acid	Occult blood
0	6%	2 plus	Very faint trace
0	8%	Trace	0
0	4%	2 plus	0
0	13%	2 plus	0
0	20%	2 plus	Very faint trace

X-ray examination (flat film) revealed no stones.

The operative procedure was not recorded on the chart, but according to the postmortem records, a cholecystogastrostomy was performed.

Postmortem examination showed the liver to be shrunken, weighing 900 gm. The capsule was slightly thickened. The entire outer surface was irregular, with numerous slightly raised nodules on all borders and surfaces, and the lower border of the right lobe was bent upward. The resistance to cutting was somewhat greater than usual, the organ consisting mostly of firm tissue showing green dots lying in gray material, both of the same consistency. These areas seemed to be partially circumscribed, and lying between them was soft brown homogenous tissue resembling that of a normal liver. This brown tissue, however, occupied very little of the total volume. The larger bile ducts running through the hepatic tissue were not conspicuous.

Microscopic examination revealed the absence of hepatic cords, with replacement by cellular fibrous tissue, in rather large areas throughout the liver. Most of these areas were found around the portal structures, but some occurred near the central vein and in the mid-zone. The remaining hepatic lobules showed swollen cells with cloudy cytoplasm and indistinct boundaries. Masses of dark greenish cytoplasm were seen in the cytoplasm and the biliary canaliculi, and the reticular-endothelial cells of the sinusoids frequently contained this pigment also. In the fibrous zones there was a little eosinophilic, finely-granular necrotic material lying in the tissue spaces between the numerous fibroblasts. These areas also showed considerable infiltration of polymorphonuclear neutrophiles, lymphocytes and endothelial leukocytes. A few eosinophils were present. There were foci of dilated and congested capilaries, and numerous distorted and apparently new bile ducts were seen growing toward the hepatic lobules. Within the lobules were a few small foci of neutrophiles.

Case 5: This patient when admitted to a hospital was deeply jaundiced and in coma, and died within a few hours. The case, therefore, was referred to the medical examiner. Chemical examination of the vital organs revealed traces of arsenic, and the cause of death was stated as acute yellow atrophy of the liver, probably due to arsenical poisoning.

Since I knew that this patient had been exposed to the fumes of chlorinated hydrocarbons, I arranged an interview with the medical examiner. He had not seen any of the livers affected by these fumes. He stated that the quantity of

arsenic found in this case was very minute—a quantity usually not sufficient to produce such fulminating acute yellow atrophy. Our conclusion was that either the patient had been exposed to an unsually heavy concentration of the fumes, or the liver had been rendered unusually susceptible by the presence of arsenic.

Under the microscope, sections of the liver showed an exceedingly small amount of normal liver tissue. Occasional strands of normal liver cells were seen, but most of the hepatic cells were undergoing degeneration. The nuclei had become pale, stained poorly, and had lost their granular cytoplasm. In many areas the cells had undergone complete autolysis, only the basic supporting stroma being retained. In other areas, infiltration of numerous small round cells, and an occasional plasma cell, were seen. These areas of degeneration chiefly centered about the central vein, but some were seen around the bile canals also and in the mid-zonal areas.

The diagnosis was acute yellow atrophy of the liver.

Case 6: This patient, who was 42 years old, had begun work in a war plant about six months ago. His work was varied, involving handling many compounds, including halowax. After about two months he developed a halowax dermatitis involving his face, hands, arms, chest, back and legs. In another two months his skin began to itch, and he became progressively weaker, with failing appetite and loss of weight. His ankles began to swell, and he became jaundiced. Shortly before admission to the hospital, his abdomen began to swell.

He stated that his usual weight was about 185 pounds, but that his present weight was about 160 pounds. He used alcohol in moderation.

On physical examination, he appeared well developed and moderatedly well nourished. The skin over practically the entire body showed a follicular dermatitis consisting of papules, many of which were secondarily infected, and cystic nodules varying in size from that of a pin head to that of a pea.

The pupils were regular and equal, and reacted to light and the accommodation seemed normal. The conjunctiva was normal. The sclerae, however, were distinctly jaundiced. The ears, nose and throat were negative. The heart showed no enlargement, and the sounds were of good quality, with no murmurs. The pulse was regular, with 68 beats per minute. The blood pressure was 110/80. The chest clear and resonant throughout.

The abdomen was soft. The wound of a recent paracentesis was seen on the mid-line below the umbilicus. The liver was palpable, extending four fingers below the costal margin; it felt somewhat irregular, but was firm and not tender. The spleen was not palpable.

The prostate was moderately enlarged, but no nodules were felt. The ankles showed a very slight pitting edema. The reflexes were normal.

The report of the abdominal paracentesis performed two days previously, showed that two gallons of clear yellowish fluid had been obtained, and that at that time the liver had been hard, slightly nodular, and enlarged to five fingers below the costal margin.

A blood count revealed 5,000,000 red blood cells, hemoglobin 91 per cent, 12,700 white blood cells, staff cells 3 per cent, segmented forms 68 per cent, lymphocytes 24 per cent, monocytes 1 per cent and eosinophils 4 per cent. The urine was 3 plus for bile. The icterus index was 100 (normal 4 to 6), and a van den Bergh test gave a direct plus reaction.

The serum albumin was 2.93 and the globulin 3.09, with a ratio of 0.95 (normal 1.5 to 2.5). The blood chemistry showed sugar 139 mg., urea nitrogen 18.2, creatinine 1.6, nonprotein nitrogen 56.0 and chlorides 425 mg.

A Takata-Ara test, in which precipitation in any two of the first three tubes is a positive reaction and evidence of liver damage, gave the following results:

Tube	½ hour	24 hours
1	3 plus	0
2	3 plus	1 plus
3	3 plus	3 plus
4	2 plus	3 plus
5	1 plus	2 plus
6	Trace	1 plus
7	0	0
8	0	0

The patient gradually lost ground, and was tapped again. He became weaker and more apathetic, and finally died, approximately nine months after his first exposure to halowax fumes.

On postmortem examination, the peritoneal cavity contained more than six liters of clear, orange-yellow fluid. There were strong adhesions surrounding the pylorus, the duodenum and the head of the pancreas.

In the wall of the lower third of the esophagus were prominent dilated veins with varicosities, but the mucosa was intact. The stomach contained about 200 c.c. of coffee-ground fluid. The gastric mucosa was pale, but intact. In the duodenum were three ulcers. One on the duodenal side of the pylorus was small and shallow. Below this was a larger ulcer 2 by 0.7 by 1.5 cm., having a shelving edge, and showing a round perforation 8 mm. in diameter; the base of this perforation adhered to the common duct, but did not leak. Over the head of the pancreas was a large, deep, oval ulcer 3.8 by 2.7 by 1.3 cm., with a black base. The rest of the gastrointestinal tract was not remarkable.

The liver was notably reduced in size, measuring 20.5 by 15.5 by 5.0 cm.; its weight was 950 gm. The color was generally a light ochre brown. The surface was irregularly nodular and granular. Large smooth nodules up to 4.5 cm. in diameter, with the soft consistency of a normal liver, contrasted with small discrete coalescent firmer nodules, and with extensive depressed areas which were firm and had a pale brown color. The largest of these finely-granular depressed areas occupied a large part of the anterior surface of the right lobe, whereas the inferior portion of this lobe was generally smooth and soft. The cut surface showed reddish-brown depressed areas with indistinct lobulation, contrasting with softer areas in which the usual lobular structures of the liver were recognizable. On cut surface, the bile ducts were not remarkable.

The anatomical diagnosis was cirrhosis of the liver, due to sub-acute necrotic hepatitis (acute yellow atrophy); multiple perforating ulcers of the duodenum; chronic cholecystolithiasis; varices of the esophagus and dorsal retroperitoneal venules; ascites; hemorrhage into the stomach; aspiration of the gastric contents; icterus; acneform rash of the skin; lobar pneumonia, and chronic calcifying tuberculosis of the mesenteric lymph glands. The cause of death was the hepatitis, the consequent cirrhosis and the hemorrhage into the stomach and the duodenal ulcers being contributing factors.

Under the microscope, many specimens of the liver revealed essentially the same process. There were numerous islands of cellular connective tissue lying around the portals or in the mid-zone, and some were found about the central veins. These areas contained many spindle cells resembling fibroblasts, and also scattered lymphoid and plasma cells, a few endothelial leukocytes and rare polymorphonuclear neutrophiles. Usually there was a central zone of wide and congested capillaries, with some interstitial extravasation of red blood cells. In the portions of these connective-tissue areas near the portal vessels, there were many small distorted bile ducts lying in the tissue spaces. The remaining hepatic parenchyma consisted of lobular islands separated by the connective tissue. In these lobular islands the hepatic cords were slightly swollen, but had fairly well-outlined cells, and round nuclei showing the usual staining reaction. No mitotic figures were seen. The hepatic sinusoids in these areas showed some widening.

Sections of the duodenal areas of ulceration showed deep penetration of the wall. The floors of the ulcers were covered with necrotic material and fibrin, lying over a thick zone of cellular granulation which contained many spindle cells of the fibroblast type and scattered leukocytes. The adjoining muscular coat showed interstitial fibrosis and scattered leukocytes, and some fibrous thickening of the walls of the blood vessels.

The pancreatic acini, ducts and islands of Langerhans presented the usual appearance. There were a few scattered lymphoid cells, endothelial leukocytes and fibroblasts in the interlobular fat, and also in the connective tissue within the lobules.

In the gallbladder, the thick plaque of the serosa was composed of loose granulation tissue with wide capillaries, many spindle cells, and scattered polymorphonuclear cells, lymphocytes and endothelial leukocytes. The wall proper showed fibrous thickening, especially of the subserosa and submucosa, with focal lymphoid infiltration. The mucosa showed fibrous thickening of the rugae with distortion and adhesion, and consequent formation of enclosed crypt lines with columnar epithelium.

Several lymph nodes were present, and showed the same process. The nodules were not distinct, and there was diffuse hyperplasia of lymphoid cells, and the sinuses were wide.

The histologic diagnosis was subacute necrotic hepatitis in a late stage, peptic ulcers of the duodenum, mild subacute interstitial pancreatitis, subacute focal peritonitis, serositis of the gallbladder, chronic cholecystitis, and recent infarction of the right kidney.

The lesion found in the liver was one which has followed exposure to halogenated hydrocarbons, and although the process was in a later stage than in the cases which I had seen previously and in those recorded in recent literature[3, 6], I have no doubt that the hepatic lesion in this case illustrates the effects of halowax poisoning. The pancreatic inflammatory reaction and the lesion in the serosa of the gallbladder appeared to be secondary to the hepatic disease, and the renal infarction may have been secondary also, although this was not certain. The duodenal ulcers were of some duration, and I cannot be sure whether they preceded or followed the onset of the liver disease, and therefore their relation to the latter is not clear.

Treatment

1. If a worker develops jaundice or Halowax dermatitis he should be immediately removed from any possible contact with the vapors of the chlorinated hydrocarbons.

2. He should be placed on a high protein diet and given several transfusions of either whole blood or plasma.

3. He should never be permitted to return to the same occupation or to any one that subjects him to the inhalation of carbon tetrachloride or its allied compounds.

Recommendations For Control

Dr. Greenburg offers the following recommendations for control of this occupational hazard:

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

2. 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, gallstones or other diseases known to affect the liver adversely.

3. 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.

4. 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.

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

6. 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.

In addition to the above recommendations for control as suggested by the Division of Industrial Hygiene, Department of Labor, State of New York, the author would like to add the following safeguards which have been instituted at the plant where this case and the cases described below have occured.

Every new employee, in addition to his routine pre-employment physical examination, urine and Wassermann, was given the "I-V-C" Routine—an icterus index, van den Bergh and cephalin-cholesterol flocculation test, and, if any of the three tests deviated from the normal, the applicant was refused employment in any part of the plant where he was liable to be exposed to the fumes of the chlorinated hydrocarbons. Furthermore, all workers, exposed in any way to the fumes, were examined every six months with the "I-V-C" routine, and were immediately removed if any of the three tests deviated from the normal. Since this added safeguard has been instituted, no new cases of toxic hepatitis have occured in the past seven months.

Conclusions

1. The animal experimental data of Flinn and Jarvik (1936), and Drinker, Warren and Bennett (1937) clearly showed that the chlorinated Naphthalenes produce acute yellow atrophy of the liver.

2. Drinker further demonstrated that animals exposed to low concentrations of vapor of the chlorinated hydrocarbons developed acute yellow atrophy of the liver promptly upon being fed sublethal doses of carbon tetrachloride.

3. Dr. Leonard Greenburg et al. presented three fatal cases of acute yellow atrophy following occupational exposure to the chlorinated hydrocarbons. Careful investigation ruled out any other possible etiology.

4. Mayers and Smith reported one non-fatal case of jaundice following exposure to the vapors of chlorinated naphthalenes.

5. All cases showed a drop in the serum albumin, and the total proteins.

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Discussion

Dr. Alfred Angrist, Jamaica, N. Y.: The increasing use of some of the more heavily halogenated hydrocarbons as insulation and for other industrial purposes has intensified our interest in the hazards involved. Dr. Strauss has stressed the most common effect of halowax in chronic minimal exposure.

As with so many toxic industrial substances, the problem is very complex, often hinging upon the variations in individual cases. This is at least partly understandable, for we cannot expect an individual who has previously suffered damage to the kidney or liver to react to the same dosage in the same way as a normal, healthy person. This indicates one form of preventive medicine which should be undertaken by the industry or employer. In my opinion, failure to make a routine examination to detect basic deficiencies justifies liability for compensation, regardless of all other circumstances. In addition, the employer should require routine check-ups to detect the earliest manifestation of toxic injury. Neglect of this precaution should bear weight in favor of full compensation.

Halowax consists of a group of halogenated hydrocarbons whose toxic action in a way is similar to that of carbon tetrachloride and allied compounds. The latter agents tend predominantly to involve the kidney and liver in cases of chronic exposure, and the cerebrum and kidney in the more acute forms of toxicity. In addition, the blood-forming tissues and other tissues undoubtedly are affected.

The physiological explanation for the acne occurring in chronic cases of halowax poisoning remains a mystery. The variations in the response of normal human beings to identical exposure also is not understood. It is my opinion that the vitamin content and other variations in the diet may account for some of the discrepancies in the pharmacologic action of these substances. In an unpublished work, I found a report of bizarre changes in the mitochondria in chloroform poisening; since the mitochondria are thought to be lipoid elements in the cells, one might expect them to show some morphological changes in the presence of agents known to be lipoid solvents.

The effect of halowax compounds on the parenchymal organs still deserves careful morphological study in both acute and chronic cases of poisoning.

There is another aspect of the subject which is of considerable significance—namely, the synergistic action of the toxic agents with other commonly used chemicals. It is my opinion that an individual exposed to any of the agents of this nature should not ingest alcohol at all, and certainly should not use it to excess. The work of Bennett, Drinker and Weiner* demonstrates such synergism experimentally, and confirms the clinical experience in this respect. Certainly no alcoholics should be employed for duties exposing them to such toxic agents.

*Bennett, Drinker and Weiner: J. Indust. Hyg., 20:97, 1938.