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PORTAL HYPERTENSION AND BLEEDING ESOPHAGEAL VARICES*

Their Occurrence in the Absence of Both Intrahepatic and Extrahepatic Obstruction of the Portal Vein

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THERE are a few well documented cases of bleeding from ruptured esophageal varices in the absence of associated portal hypertension.[1-3] However, most patients with life-threatening hemorrhage from varices have portal hypertension, proved or assumed, as an underlying cause. Following the example of Whipple,[4] most authors emphasize the role of venous obstruction in the production of portal hypertension and its consequences, classifying their cases into "intrahepatic" and "extrahepatic" groups depending on the presumed site of obstruction. Although such a classification simplifies the clinical evaluation and management of variceal bleeding, it ignores other important, nonobstructive etiologic factors. Since the pressure within the portal system depends on the volume of blood flow as well as on the resistance to blood flow, it is reasonable to suppose that certain cases of otherwise unexplained portal hypertension may result from abnormalities of flow through the splenoportal axis.

Within the past eight years we have encountered at the Grace-New Haven Community Hospital 5 patients with bleeding esophageal varices and portal hypertension in the absence of demonstrable intrahepatic or extrahepatic venous obstruction. One of these did not have a satisfactory splenoportogram, but the other 4 underwent complete clinical, radiologic and surgical investigation and constitute the basis for this report. A total of 32 patients had portasystemic-shunt surgery for bleeding varices and portal hypertension in this hospital during the period 1950-1958. These cases are summarized according to etiology in Table 1. Many other patients with gastrointestinal hemorrhage and portal hypertension, usually caused by hepatic cirrhosis, were admitted to the hospital in this period, but were considered unsuitable for operation. For this reason, the true frequency of nonobstructive portal hypertension with bleeding varices cannot be estimated from our data.

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CASE REPORTS

CASE 1. S.S., a 23-year-old single man, was admitted to the Grace-New Haven Community Hospital on January 3, 1955, because of massive hematemesis of 2 hours' duration.

Aside from congenital mental retardation, the patient was well and active until June, 1950, when at the age of 18 years he experienced a sudden massive hematemesis followed by the passage of tarry stools. In another hospital physical examination was within normal limits except for moderate splenomegaly. Laboratory examinations at that time revealed a hemoglobin of 4 gm. per 100 ml., a white-cell count ranging between 3000 and 4900, a slight reduction in platelets and normal results on liver-function tests. A complete gastrointestinal x-ray series was considered to be within normal limits. The patient was treated with transfusions and discharged without a definite diagnosis. Two months later, in August, 1950, he had a similar episode of hematemesis and melena, physical examination and laboratory evaluation being basically as before and treatment being supportive. He returned to his normal activities feeling well, without further gastrointestinal bleeding, until August, 1954, when he again experienced massive hematemesis and melena. On hospitalization at this time splenomegaly was noted once more, and a gastrointestinal x-ray series was again interpreted as normal. He was seen in consultation at this hospital in November, 1954, when physical examination revealed moderate splenomegaly and a gastrointestinal x-ray series demonstrated large varices extending throughout the lower ⅔ of the esophagus and upper stomach. Liver-function tests were negative except for an elevation of the indirect-reacting serum bilirubin and a bromsulfalein retention of 9.4 per cent at 45 minutes. After a symptom-free interval of 2 months the patient suddenly experienced painless vomiting of about 2 liters of blood and was immediately admitted to this hospital for care and study.

His weight had been steady, and his diet had been adequate. There was no history of alcoholic intake or exposure to drugs or toxins. He had experienced transient jaundice immediately after a transfusion reaction during a previous admission to another hospital. There was no history of abdominal trauma, ascites or peripheral edema.

The family history was unremarkable except that 3 cousins were reported to have sickle-cell anemia.

Physical examination showed a pale, anxious, well nourished man, who was vomiting small amounts of blood. Significant physical findings included faint scleral icterus, slight cardiomegaly, with a Grade 2 apical systolic murmur, a normal-sized liver by percussion, the lower edge being palpable at the right costal margin, and a firm, nontender, rounded spleen palpable 6 fingerbreadths below the left

costal margin. No collateral veins were demonstrable over the abdomen, and there was no edema, clubbing, or spider angiomas.

The pulse was 140, and the respirations 20. The blood pressure was 110/70 in the recumbent position.

Initial laboratory studies revealed a hematocrit of 35 per cent, a white-cell count of 12,000, with a normal differential, and adequate platelets on smear. Urinalysis and a serologic test for syphilis were negative. The stools were guaiac positive and tarry in appearance. Liver-function tests at this time were within normal limits except for a total serum bilirubin of 10.08 mg. per 100 ml. (after many transfusions), with a 1-minute, direct-reacting fraction of 0.59 mg. per 100 ml. (Table 2).

TABLE 1. *Etiologic Factors in 32 Patients Undergoing Surgery for Bleeding Esophageal Varices and Portal Hypertension at the Grace-New Haven Community Hospital, 1950-1958.*

FACTOR		NO. OF CASES
Intrahepatic cause		24 (75.0%)
Laënnec's cirrhosis	18	
Postnecrotic cirrhosis	2	
Biliary cirrhosis	2	
Hemochromatosis	1	
Atypical cirrhosis	1	
Extrahepatic portal obstruction		3 (9.4%)
"Nonobstructive" portal hypertension		5 (15.6%)

The patient continued to vomit blood and to pass tarry stools, receiving 4500 ml. of whole blood, with maintenance of a normal blood pressure. A tamponade of the esophagus with the Sengstaken-Blakemore tube failed to control the bleeding satisfactorily, so that on January 4, ligation of the esophageal varices was carried out, 3 columns of large gastric and esophageal varices being plicated. After this he did fairly well, but continued to bleed slowly from the gastrointestinal tract. On January 27 a percutaneous splenoportogram demonstrated dilated, but patent, splenic and portal veins. The intrahepatic radicles were normal in appearance and emptied rapidly (Fig. 1). Immediately thereafter, a laparotomy was performed, demonstrating a greatly distended splenic vein and artery, a large spleen, and a portal-vein pressure of 315 mm. of saline solution. The liver was normal in size, felt slightly granular and somewhat firmer than normal, but was otherwise unremarkable. At this time a splenectomy and splenorenal shunt were performed, after which the portal-vein pressure dropped to 165 mm. of saline solution.

An adequate surgical biopsy of the liver was obtained at operation. Microscopical examination of the tissue demonstrated preservation of general lobular architecture (Fig. 2). The parenchyma was intact throughout except for a few small periportal linear zones in which there was loss of parenchymal cells, sinusoidal congestion, reticulum collapse and small collections of mononuclear leukocytes and pigment-laden macrophages (Fig. 3). There was no increase in connective tissue, no distortion of the vascular pattern and no evidence of disease of the biliary tree. The removed spleen was firm and greatly enlarged, weighing 1400 gm. On microscopical examination the splenic capsule and trabeculae were of normal thickness and cellularity. There was evidence of generalized, but minimal, passive congestion of the sinusoids, with prominence of the sinusoidal endothelium and moderate thickening of the fibrillar reticulum. Scattered, small, perivascular hemorrhages with early organization were noted around some of the thin-walled vessels involved. No excess of iron-containing pigment was demonstrated, and there was no evidence of arteriovenous aneurysms in any portion of the specimen.

The patient recovered rapidly after operation, returning home to his normal activities. He experienced no further gastrointestinal bleeding, although serial esophagrams continued to demonstrate small residual varices. In August he was hospitalized briefly for weakness and malaise. Gastrointestinal x-ray series now demonstrated a medium-sized hiatus hernia and persistent, small esophageal varices. At this time the hemoglobin was 5.2 gm. per 100 ml., and the stools showed a ++++ guaiac test for blood. Symptoms abated after transfusion of 3 units of whole blood. Since that time the patient has felt generally well, has been active at home, but has been admitted to the hospital on several occasions with evidence of moderate recurrent gastrointestinal bleeding. Esophagrams have continued to demonstrate varices involving the lower ⅓ of the esophagus and an esophageal hiatus hernia. Treatment has included whole-blood transfusions as necessary, and transesophagoscopic injections of the varices with sclerosing solutions.

A transthoracic needle biopsy of the liver was performed on January 31, 1957. As before, the general hepatic architecture was intact. Scattered throughout the specimen, usually confined to the mid-zone portions of individual lobules, were several small, irregularly outlined areas of sinusoidal dilatation and congestion, without associated hepatocellular destruction. A few clusters of dark-staining mononuclear cells were present in some of the sinusoids, suggesting foci of extramedullary hematopoiesis. Masson and reticulum stains demonstrated normal connective-tissue structure and normal vascular elements.

When last seen in September, 1957, the patient seemed well and had no complaints.

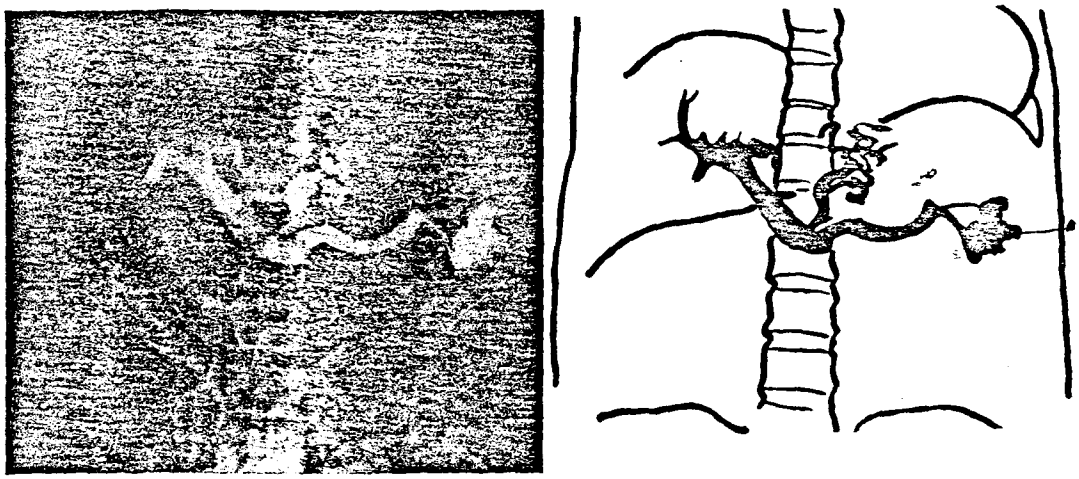
This young man with proved portal hypertension had experienced several bouts of massive gastrointestinal hemorrhage, presumably from large esophagogastric varices, in the five years before shunt surgery. The associated findings of mental retardation and

TABLE 2. *Admission Liver-Function Tests in Cases 1 to 4.*

CASE NO.	SERUM BILIRUBIN		BROMSULFALEIN RETENTION	CEPHALIN FLOCCULATION		THYMOL TURBIDITY	SERUM ALKALINE PHOSPHATASE	SERUM PROTEIN			TEST FOR BILE IN URINE	URINARY UROBILINOGEN	PROTHROMBIN
	1-MIN.	TOTAL	AT 45 MIN.					TOTAL	ALBUMIN	GLOBULIN			
	mg./100 ml.	*mg./100 ml.*	*%*	*in 24 hr.*	*in 48 hr.*	*units*	*S.J.R. units*	*gm./100 ml.*	*gm./100 ml.*	*gm./100 ml.*		*Ehrlich units*	*%*
1	0.59	10.08	9.4	0	0	1.1	4.6	7.05	3.68	3.37	0	0.45	—*
2	0.08	0.74	3.8	0	+	2.3	6.0	5.47	2.75	2.72	0	—*	100
3	0.13	0.72	20.3	—*	—*	3.6	4.4	6.07	3.02	3.05	0	0.18	90
4	0.09	0.44	1.4	0	0	2.0	7.4	7.10	4.40	2.70	0	—*	100

*Not determined.

congenital heart disease suggested that the hypertension was due to a developmental anomaly of the portal vein. However, both a splenoportogram and careful inspection at laparotomy demonstrated a patent, somewhat dilated, portal system with definite elevation of the portal pressure. Two generous liver-



A B

FIGURE 1. *Percutaneous Splenoportogram* (A) *and Tracing* (B) *in Case 1. Both splenic and portal veins are dilated but patent, and there is flow of dye into the coronary vein and large esophageal varices.*

biopsy specimens obtained two years apart demonstrated only small and inconstant zones of periportal congestion, with no apparent progression or alteration in the two-year interval. Serial liver-function tests have failed to indicate significant hepatic dysfunction. The transient icterus observed on two occasions was interpreted as being due to post-transfusion hemolysis. The changes in the spleen were simply those of mild chronic passive congestion.

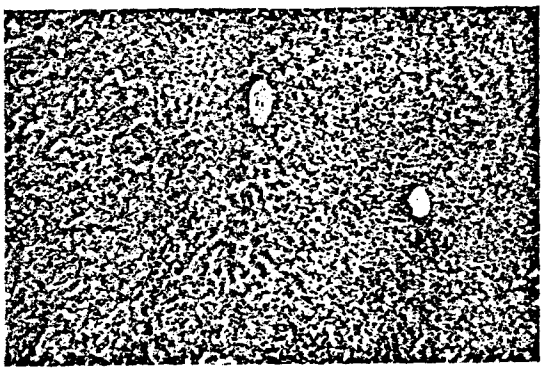


FIGURE 2. *Photomicrograph of the Operative Liver-Biopsy Specimen in Case 1, Showing Preservation of the Lobular Pattern, with a Normal Relation of the Portal Triad and Central Vein (Masson Stain — Original Magnification X20).*

Thus, definite portal-vein hypertension leading to rupture of esophageal varices occurred in the absence of any demonstrable obstruction to portal-blood flow.

CASE 2. E.D., a 58-year-old married male metal polisher, was admitted to the Grace-New Haven Community Hospital on April 22, 1955, because of massive hematemesis. He had apparently been well and active until 4 months previously, when he had an isolated episode of hematemesis of about 2 cupfuls of red blood, after which he recovered completely without treatment. Four days before entry, after drinking some beer, he experienced nausea, dizziness and faintness, followed by the vomiting of large amounts of red blood. He was admitted to another hospital, where x-ray studies revealed massive esophageal varices. He received 4 liters of whole blood and was transferred to this hospital for further evaluation and therapy.

He had drunk 5 or 6 glasses of beer daily for several years, but he reported a good dietary intake. His weight had been stable, and he recalled no exposure to drugs or toxins. He had experienced a brief bout of jaundice in 1914, while serving with the Army in the Philippines, but had had no recurrence. There was no history of abdominal pain or trauma.

The family history was unremarkable.

Physical examination showed a well nourished, somewhat pale and quite apprehensive man. There was no icterus,

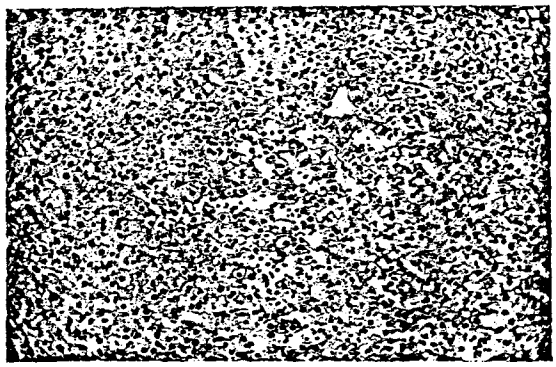


FIGURE 3. *Higher Magnification of the Specimen in Figure 2, Showing a Normal Parenchyma, with Dilatation of the Mid-Zonal Sinusoids and Moderate Intrasinusoidal Collections of Mononuclear Cells (Hematoxylin and Eosin Stain — Original Magnification X40).*

spider angiomas, hepatomegaly, palpable splenomegaly, ascites or evidence of collateral abdominal circulation.

The pulse was 64, and the respirations 20. The blood pressure was 110/58 in the recumbent position.

Laboratory studies on admission revealed a hematocrit of 42 per cent and a white-cell count of 6300, with a normal differential. Urinalysis and a serologic test for syphilis were negative. The stools were reported as tarry in appearance, and a guaiac test was positive. Complete liver-function studies (Table 2) and serum electrolytes were within normal limits. A transthoracic needle biopsy of the liver

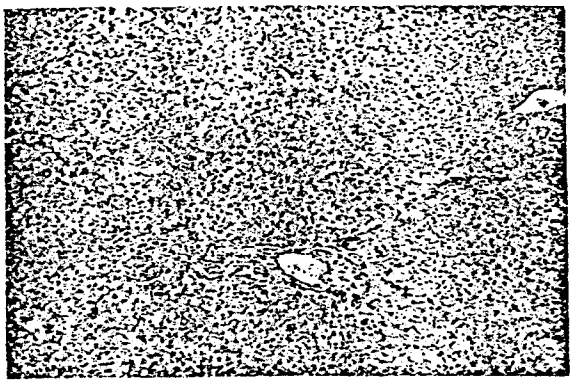


FIGURE 4. *Needle-Biopsy Specimen of the Liver in Case 2, Showing a Normal Lobular Pattern, with an Intact Central Vein and a Portal Triad with Slight Stellate Scarring (Hematoxylin and Eosin Stain — Original Magnification X20).*

was performed on April 25. Examination of the biopsy specimen revealed a well preserved architecture with intact parenchymal and portal triad elements. A few of the lobules contained tiny, poorly defined areas of sinusoidal dilatation without consistent zonal localization. Serial sections of the specimen demonstrated a single, elongated, poorly circumscribed, noncaseating granulomatous lesion composed of monocytes, epithelioid cells and necrotic liver cells; no giant cells or inclusion bodies were present, and no acid-fast bacilli were found on special staining. There was no increase in connective tissue on Masson and reticulum stains (Fig. 4).

On April 26 a percutaneous splenoportogram revealed normal splenic and portal veins, with reflux filling of the coronary vein and large esophageal varices; 3 major intrahepatic venous radicles were demonstrated that showed delayed emptying in 12 to 14 seconds. On that day, under general endotracheal anesthesia, an end-to-side portacaval anastomosis was performed, the portal venous pressure falling from 320 to 190 mm. of saline solution after establishment of the anastomosis. At the time of laparotomy 3 generous biopsy specimens of the liver were obtained. Although the over-all hepatic architecture and parenchymal plates were well preserved on microscopical examination, some of the portal triads appeared slightly expanded by collagen fibers, with fine strands of fibrous tissue extending irregularly into the periphery of adjacent lobules. Many of these triads contained large, dilated, thin-walled blood vessels, assumed to be portal-vein radicles. There was no evidence of bile-duct proliferation or of unusual inflammatory reaction. No granulomatous lesions were present.

The patient recovered promptly without postoperative complications. A follow-up esophagram taken on June 6 demonstrated persistence of the esophageal varices. He was well at this time and had returned to his former occupation.

This elderly man had two hematemeses in the four months before hospitalization, large esophageal varices being the only potential bleeding site found in the upper gastrointestinal tract on radiologic examination. The mild episode of jaundice forty years previously may have represented viral hepatitis, and the patient admitted to a moderate alcoholic intake. However, no evidence of either postnecrotic or Laënnec's cirrhosis was found on serial liver-function tests, two liver biopsies or gross inspection at laparotomy. The single, noncaseating granuloma seen in the first liver-biopsy specimen raised the question of an underlying sarcoidal or infectious process, but the later, more generous, surgical biopsies revealed only minimal, patchy and nonspecific periportal fibrosis and sinusoidal congestion. Although the passage of the contrast medium through the liver at splenoportography was retarded, no gross distortion of the intrahepatic portal or hepatic-vein radicles was noted, and the extrahepatic portal tributaries were patent.

As in Case 1, definite portal hypertension was demonstrated in the absence of both intrahepatic and extrahepatic portal-vein block. Factors other than obstruction to portal blood flow must have initiated and perpetuated the hypertension that ultimately led to rupture of esophageal varices.

CASE 3. C.W., a 72-year old single, retired male office worker, was admitted to Grace–New Haven Community Hospital on May 23, 1956, because of massive hematemesis. He had been generally well and active until about two months previously, when he experienced an episode of nausea and dizziness, followed by the passage of tarry stools. He sought no medical advice until 1 month before admission, when he entered this hospital for extraction of bilateral cataracts. At this time laboratory studies revealed a hematocrit of 23 per cent, a white-cell count of 5400, guaiac-negative stools and negative liver-function tests except for a bromsulfalein retention of 14.7 per cent at 45 minutes. Gastrointestinal films demonstrated large esophageal varices, with a normal stomach and duodenum. After receiving 3 liters of whole blood the patient had 1 of his cataracts removed and subsequently was discharged home asymptomatic. He did well except for mild weakness until the afternoon of entry, when he passed a large, tarry stool and suddenly vomited half a basin of black, partially clotted blood.

He had always been a hearty eater and had taken only a rare drink of alcoholic beverage. He reported no antecedent trauma, jaundice or exposure to drugs or toxins.

The family history was noncontributory.

Physical examination showed a sturdy, alert man in no distress. There was no icterus, spider angiomas, hepatosplenomegaly, evidence of collateral circulation or signs of fluid retention.

The pulse was 100, and the respirations 20. The blood pressure was 140/20.

Admission laboratory examination showed a hematocrit of 33 per cent, a white-cell count of 5400, with a normal differential, and slightly diminished platelets on smear. Urinalysis was negative except for a + test for albumin. A serologic test for syphilis was negative. Stools were tarry and gave a ++++ guaiac test. Complete liver-function tests were within normal limits except for a bromsulfalein retention of 20.3 per cent at 45 minutes (Table 2).

A percutaneous needle biopsy of the liver was carried out on May 31. Microscopically, the specimen revealed a normal lobular pattern, with intact parenchymal plates. Scattered throughout the sections were small areas of moderate sinusoidal distention, without distortion of the surrounding parenchyma or definite zonal localization. Several of the portal triads were slightly expanded by acellular collagenous connective tissue, thin strands of fibrous tissue often extending from the triads into neighboring lobules. Blood vessels and bile ducts appeared normal.

On June 4, a percutaneous splenoportogram revealed rapid opacification of the splenic and portal veins, with some filling of the major intrahepatic branches. In addition, dye refluxed into the coronary vein, with partial filling of large esophageal varices. The vessels were of normal caliber, and there was no evidence of occlusion or stenosis at any point.

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An end-to-side portacaval shunt was performed at this time, the pressure in an omental vein falling from 230 to 160 mm. of saline solution. At operation the liver was thought to be "slightly hobnailed," but microscopically it showed a normal lobular architecture with intact parenchyma throughout. Scattered throughout the specimen were small, ill defined, intralobular areas of sinusoidal dilatation. Many of the portal triads, especially those located immediately beneath Glisson's capsule, appeared enlarged by collagen fibers, which often extended in a stellate fashion into adjacent lobules. Some of these strands of connective tissue fused with the overlying capsule, and others reached adjoining triads to produce a "bridging" effect. This periportal fibrosis was minimal in degree and inconstant in distribution. The bile ducts and blood vessels were normal (Fig. 5).

The patient seemed to do well immediately after operation, but on the 3d postoperative day he became slightly drowsy and confused, and 2 days later signs of congestive heart failure developed. Despite vigorous treatment with digitalis, neomycin given by mouth and glutamic acid intravenously, he continued to fail and became comatose. The hematocrit fell, and gastric aspiration revealed blood in the stomach. In spite of several blood transfusions and placement of a Sengstaken–Blakemore tube, he failed and died on the 14th postoperative day.

Post-mortem examination demonstrated marked dilatation of the entire portal venous bed, with no evidence of thrombosis at any point. The portacaval anastomosis was patent. Perfusion of the portal vein with a plastic medium revealed a free flow of fluid throughout the liver. The liver weighed 1900 gm., was light brown and had a finely granular surface. Although the post-mortem specimen showed moderate autolysis, a normal underlying lobular pattern was evident. Glisson's capsule was thickened, edematous and lightly infiltrated with mononuclear inflammatory cells. Many of the portal triads appeared expanded by edema and fibrous tissue, small strands of connective tissue ramifying from the triads into the surrounding parenchyma. In a few periportal areas there were irregular patches of intense sinusoidal congestion, with atrophy and actual necrosis of the intervening parenchymal cells. Inflammatory reaction was minimal in the triads and lobules. Radicles of the portal vein were distended with perfusion solution, and the central veins appeared intact throughout.

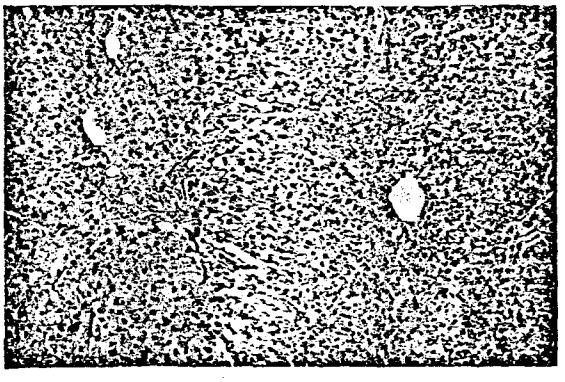


FIGURE 5. *Photomicrograph of the Operative Liver-Biopsy Specimen in Case 3, Demonstrating a Normal Lobular Pattern, Moderate Stellate Scarring of a Triad and Minimal Round-Cell Infiltration (Hematoxylin and Eosin Stain — Original Magnification X20).*

The spleen weighed 400 gm., and demonstrated slight capsular thickening, with scattered areas of subcapsular hemorrhage and necrosis. Microscopically, it showed slight sinusoidal congestion, with rare periarterial hemorrhages, definite thickening of the supporting reticulum fibers and a patchy, minimal increase in stainable iron pigment. Deep within the spleen were large, irregular areas of hemorrhagic necrosis, thought to represent recent infarction after injection of contrast medium.

Without previous known or symptomatic liver disease, this elderly man bled suddenly and massively from large esophageal varices. An abnormal retention of bromsulfalein dye, shortly after the most severe bleeding episode, suggested intrinsic liver disease. However, two ante-mortem and the autopsy specimens of the liver showed only inconstant, focal sinusoidal dilatation and a mild degree of periportal and subcapsular fibrosis. At operation the portal pressure was moderately elevated, and on splenoportography there was reflux of dye into the coronary and periesophageal plexus of veins, confirming the diagnosis of portal hypertension with the development of portasystemic collateral vessels. Yet neither the splenoportogram nor the examination of the liver gave any evidence of obstruction to the outflow of portal venous blood.

In summary, neither clinical studies nor post-mortem examination indicated a cause of increased resistance to flow within the portal bed. The minimal periportal hepatic fibrosis did not seem extensive enough to distort intrahepatic portal radicles and may have been secondary to the increased portal tension itself.

CASE 4. M.R., a 10-year-old Negro girl, was admitted to the Grace–New Haven Community Hospital on May 10, 1954, because of hematemesis.

She was said to have been well at birth, but at 10 days of age fever and chills had developed and she was noted to have an enlarged spleen. No diagnosis was established at this time, and she recovered completely without treatment, though palpable splenomegaly was recorded on a routine physical examination 6 years later. She had been well and active without gastrointestinal complaints until 4 days before admission, when she experienced a mild headache and transient abdominal cramps. On the day of admission she awoke feeling dizzy and weak, and had a transient fainting episode, followed by the gushing of about 0.5 liter of liquid blood from the nose and mouth.

The past history was unremarkable; she had experienced no jaundice, previous abdominal pain or trauma. She maintained a weight of 34.5 kg. (76 pounds).

Her mother, father and 6 siblings were all living and well.

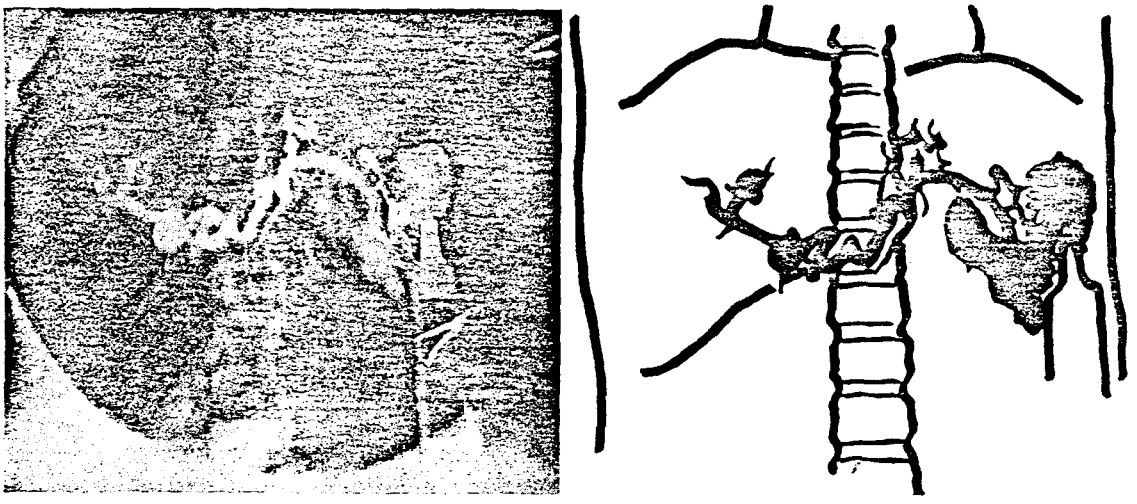
Physical examination showed a thin, muscular, rather restless girl in no acute distress. There was no jaundice, and, aside from pallor, the skin was within normal limits. The abdomen was flat and relaxed, without evidence of ascites or venous distention. The liver margin was soft and sharp, 1 fingerbreadth below the right costal margin. The spleen was rounded and firm, descending 2 fingerbreadths below the left costal margin. There was no edema or clubbing.

The pulse was 80, and the respirations 18. The blood pressure was 80/30 in the recumbent position.

On entry the hematocrit was 20 per cent, and the white-cell count 13,500, with a normal differential, and platelets were adequate on smear. A serologic test for syphilis was negative, and the nonprotein nitrogen was 43 mg. per 100 ml. The stools were tar colored and gave a ++++ guaiac test. Complete liver-function tests were within normal limits (Table 2).

A gastrointestinal x-ray series on May 15 demonstrated large esophageal and probable gastric varices, without evidence of gastric or duodenal ulceration. Esophagoscopy 5 days later revealed many large varices in the lower ⅓ of the esophagus, without evidence of active bleeding. After receiving 5.5 liters of whole blood the patient was asymptomatic, the hematocrit remaining between 22 and 28 per cent.

On June 8 a laparotomy was performed. The liver looked normal except for mild subcapsular stellate scarring, but the spleen was described as twice the normal size. An operative splenoportogram demonstrated patent, tortuous splenic and portal veins of normal caliber and rapid flow of dye into the coronary vein and into large esophageal varices, with partial filling of the inferior mesenteric and of several splenic collateral vessels (Fig. 6). Fine and regular serial branching of the intrahepatic veins was clearly demonstrated. The pressure in the gastroepiploic vein was 375 mm. of saline solution. After the performance of a splenorenal shunt and splenectomy, the pressure in this vein fell to 210 mm. of saline solution.



A B

FIGURE 6. *Operative Splenoportogram* (A) *and Tracing* (B) *in Case 4. The splenic and portal veins are tortuous but patent, and there is filling of several collateral vessels, including esophageal varices.*

A generous biopsy specimen of the liver was obtained at operation. Microscopically, the hepatic architecture was well preserved throughout, and the parenchymal cells were everywhere normal. The portal triads were small and contained normal vessels and bile ducts. Radiating from a few of the triads and central veins were thin strands of fibrous tissue that showed no tendency to join one another or to distort the normal lobular architecture. The sinusoids, central veins and portal-vein radicles appeared normal.

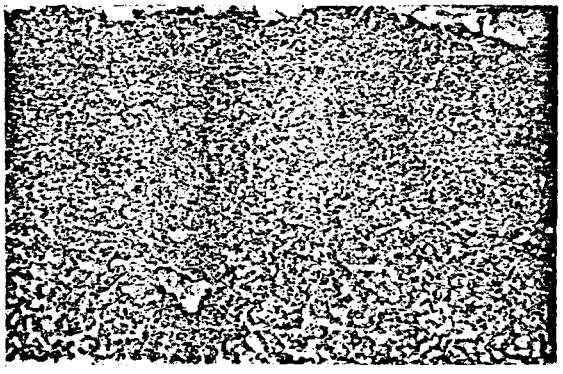


FIGURE 7. *Needle-Biopsy Specimen of the Liver in Case 4 Obtained Four Years after Splenorenal Shunt, Demonstrating a Normal Lobular Architecture, with an Intact Central Vein and Moderate Dilatation of the Mid-Zonal Sinusoids (Masson Stain — Original Magnification X20).*

The spleen, which measured 5 by 7 by 13 cm., appeared grossly nodular, with a few deep, contracted scars over its anterior border. On microscopical examination its architecture was obscured by fresh hemorrhage, thought to be related to the injection of dye at the time of splenoportography. Otherwise, the splenic architecture was considered to be within normal limits.

The patient made a rapid and complete recovery postoperatively and had no recurrent bleeding or jaundice. A repeat esophagram in July demonstrated persistence of the varices, but on a subsequent gastrointestinal x-ray study in September, these were no longer evident. She was readmitted to the hospital for evaluation of crampy left-upper-quadrant pain in February, 1958, when physical examination was within normal limits, the hemogram was completely normal, and complete liver-function tests were unremarkable. A barium swallow at this time was reported within normal limits, and a liver biopsy was performed percutaneously with a Vim–Silverman needle. The specimen obtained demonstrated a normal lobular pattern in all areas (Fig. 7). In the mid-zonal areas of about half the lobules visualized, there was considerable sinusoidal congestion and distention, without, however, appreciable atrophy or dis-

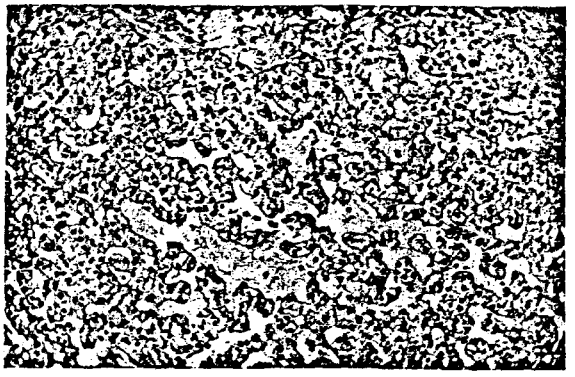


FIGURE 8. *Higher Magnification of the Biopsy Specimen Presented in Figure 7, Showing a Normal Parenchyma and Focal Dilatation of the Sinusoids (Masson Stain — Original Magnification X40).*

ruption of the adjacent liver-cell plates (Fig. 8). Adjoining a portal triad was a single, ill defined collection of small, uniform, mononuclear cells that seemed to compress and partially destroy several parenchymal cells; serial sections revealed no similar lesions. The connective-tissue framework and blood vessels were normal throughout.

On her last follow-up visit, the patient was sturdy, active and without complaints.

When this young Negro girl presented with massive hematemesis and palpable splenomegaly, the past history of a febrile neonatal illness, associated with splenomegaly, suggested that septic inflammation of the portal vein, perhaps from omphalitis, had led to subsequent portal thrombosis, portal hypertension, congestive splenomegaly and the development of varices. Although portal hypertension was confirmed by direct measurement at operation, a beautifully detailed splenoportogram and careful surgical exploration failed to demonstrate any obstruction to the portal outflow, either outside or within the liver. Biopsy on two occasions in a four-year period confirmed the impression that there was no intrinsic liver disease.

Observations

Of the 4 patients described in detail above, 3 were white adult males, and 1 was a young Negro female. Their ages at the onset of symptoms ranged from ten to seventy-two years.

Massive upper gastrointestinal hemorrhage from esophageal varices was the initial manifestation of illness in each case. In none was there any history indicative of antecedent hepatic, portal-system or gastrointestinal disease. The liver was normal in size and consistence, and there were no other manifestations of liver disease. Jaundice appeared after transfusions in Case 1, but this proved to be of hemolytic origin. Except for significant splenomegaly in 2 of the 4 patients, there were no clinical signs of portal hypertension, such as ascites, prominent abdominal-wall collateral veins and periumbilical venous hums.

Except in Case 1, there was no hematologic evidence of "hypersplenism," the blood studies being consistent with recent acute blood loss. Two months before the onset of esophageal bleeding, Case 1 was found to have an elevation of the indirect-reacting fraction of the serum bilirubin, which was interpreted as evidence of a mild hemolytic process.

Results of complete liver-function studies were within the limits of normal, with two exceptions (Table 2): the marked increase in total serum bilirubin, predominantly of the indirect-reacting type, in Case 1, which was compatible with acute hemolysis after recent massive blood replacement and mild hemolytic anemia; and the bromsulfalein retention of 20.3 per cent in Case 3, which in retrospect was probably secondary to massive hemorrhage.

The presence of varices was confirmed radiographically in all 4 cases. In 3, they were demonstrated in both the esophagus and stomach and in one, were limited to the esophagus. No other potential bleeding site, such as peptic ulcer or hiatus hernia, was demonstrated on the initial films.

Satisfactory radiographic visualization of the splenoportal axis was achieved in all patients, by percutaneous route in Cases 1, 2 and 3, and by cannulation of a mesenteric vein at laparotomy in Case 4. In none was there evidence of narrowing, occlusion or cavernomatous transformation of the splenic or portal vein. However, all patients had one or more abnormalities of the venous bed suggestive of portal hypertension[5]: marked dilatation of the portal vein was seen in Case 1; abnormal reflux of dye into coronary veins, esophageal varices, splenic collateral vessels, or inferior mesenteric branches was seen in Cases 2, 3 and 4; and delayed emptying of major intrahepatic portal radicles was noted in Case 2. At operation no gross arteriovenous fistulas or mechanical distortions involving the portal vein or its tributaries were found.

Portal hypertension was demonstrated by direct measurement at the time of surgery in all patients, the pressures ranging between 230 and 375 mm. of saline solution preoperatively. After establishment of the portasystemic anastomoses, all pressures fell to normal levels.

Although the livers of Cases 1, 3 and 4 were described as slightly scarred or firm at the time of operation, careful microscopical examination of both needle and surgical liver-biopsy specimens failed to confirm the presence of significant scarring or cirrhosis. The most constant lesion demonstrated in all patients was a poorly circumscribed distention of the sinusoids, with occasional compression atrophy of the intervening parenchymal plates, usually localized to the periportal or mid-zonal areas. Sparing of the central zones made it highly unlikely that these changes were due to passive congestion of cardiac disease or of hepatic venous obstructive origin. A second commonly observed pathological finding consisted of occasional thin strands of collagen that projected from slightly thickened portal triads into the adjacent parenchyma. This periportal fibrosis was absent in Cases 1 and 4, minimal in Case 2 and most striking in all the specimens obtained from Case 3. In the last, a few of the fibrous strands connected adjacent portal triads in the subcapsular area, but there was no consistent pattern of scarring, evidence of regenerative activity or pseudolobule formation. Aside from the sinusoidal dilatation described above, there was no distortion of the intrahepatic blood vessels by either connective-tissue bands or parenchymal nodules. None of the liver cells contained fat vacuoles, or gave signs of degeneration, such as "alcoholic" hyaline or acidophilic necrosis. The small zones of extramedullary hematopoiesis in the follow-up biopsy specimen in Case 1, and the single noncaseating granuloma seen in the first of the two specimens ob-

tained in Case 2, are of unknown significance. Liver-biopsy specimens two and four years after splenorenal shunting and splenectomy in Cases 1 and 4, respectively, demonstrated no progression of the previously found hepatic changes.

Microscopically, the spleen in Cases 1 and 3 showed the diffuse sinusoidal congestion, reticulum thickening and early perivascular fibrosis and hemorrhage considered characteristic of the chronic passive congestion of portal hypertension.[6] The fibrosis and hemorrhage surrounding the malpighian arteries, termed "fibroadénie" by Banti, and later shown to be nonspecific manifestations of passive congestion of portal hypertension by other workers,[7] were minimal in Case 1. No abnormal intrasplenic arteriovenous anastomoses were found in any of the spleens.

Discussion

The 4 patients described had clinical and pathological evidence of portal hypertension and bleeding esophageal varices in the absence of either hepatic disease or portal venous obstruction. That this experience is not unique is indicated by several reports in the medical literature. Sir William Osler,[8] in discussing the syndrome of "splenic anemia," described several patients with chronic splenomegaly and recurrent gastrointestinal hemorrhage in the absence of cirrhosis or gross disease of the portal vein, with apparent cure following splenectomy. Although Rousselot[9] attributed the portal hypertension of his 15 noncirrhotic patients with "Banti's syndrome" to splenoportal obstruction, he was unable to demonstrate the site of venous block in seven instances. In Whipple's[4] impressive survey of splenomegaly, 35 cases, or 20 per cent of his patients with "Banti's syndrome," remained with the assumed "obstructive factor" undetermined. Experience at the Mayo Clinic[10] indicated that some patients with the picture of "splenic anemia" and portal hypertension had neither intrahepatic nor extrahepatic venous block. More recently, several similar cases have been reported.[11-14] Of interest is the fact that 3 of the patients in the series of Hallenbeck and Shocket[14] had periportal fibrosis and venous distention similar to those described in the present study.

Cases of this type lead necessarily to an examination of the elements that affect portal pressure. Of these, vascular resistance and volume of blood flow appear to be of paramount importance. Partial or total obstruction of the portal vein, in either its extrahepatic or its intrahepatic course, may produce an elevation of portal pressure provided other factors remain constant. Similarly, an increase in the volume of blood traversing the portal vein may raise portal pressure if there is no accompanying change in vascular resistance. Obviously, the effect of either of these factors on portal pressure may be abolished by reciprocal changes in the other. Thus, the effect of increased blood flow on portal venous pressure may be minimized by dilatation of the portal trunk and the opening of collateral vessels. Similarly, diversion of blood into newly expanded channels may prevent the development of sustained hypertension in portal-vein obstruction.

Most clinical and pathological studies concerned with the pathogenesis of portal hypertension have emphasized the importance of factors that increase resistance to blood flow. Partial or complete obstruction of the portal system in its extrahepatic course by thromboses,[15] scars,[4] tumor masses[16] or cysts[4] is known to produce portal hypertension. Within the liver, the constrictive scars[17] and expanding regenerative parenchymal nodules[18] of cirrhosis and invasive tumors[19] commonly raise portal pressure. Finally, the increased intra-abdominal tension accompanying large abdominal cysts[20] and exaggerated respiratory movements[21] may elevate portal pressure.

In contrast to the many reports stressing venous obstruction as a cause of portal hypertension, few studies have dealt with the effect of increased portal blood flow on portal pressure. Theoretically, as stated previously, an increase in the volume of blood entering the portal system may lead to sustained portal hypertension. Practically, this concept is proved by the demonstration of portal hypertension and its consequences in some patients with arteriovenous aneurysms involving the splenoportal axis.[22]

Since the blood flow and *vis a tergo* of the portal system are determined largely by the capillary beds and arteriovenous channels of the pancreas, gastrointestinal tract and spleen, functional or structural derangements of their vasculature might permit increased portal blood flow and result in portal hypertension. Little is known about the contribution of the pancreatic circulation to portal blood flow. However, so far as the gastrointestinal tract is concerned, Womack and Peters[23] have demonstrated in the wall of the bowel humorally controlled arteriovenous anastomoses that help determine the degree of oxygenation of portal blood. Conceivably, these might permit the influx of sufficiently large volumes of blood to raise portal pressure, but further studies are required to establish the importance of this factor in the pathogenesis of portal hypertension.

Both experimental and clinical studies indicate that portal blood flow may be affected dramatically by alterations in splenic circulation. There is evidence that "capillary shunts" exist within the spleen that may permit rapid inflow of blood into the portal bed.[24] Ravenna,[25] in investigating the pathogenesis of "Banti's syndrome," concluded that primary lesions of the small splenic arteries are responsible for the splenomegaly and portal hypertension characteristic of this syndrome. Clinically, cases of "tropical splenomegaly" of undetermined cause may be associated with

dilatation of the portal and splen veins and border- line hypertension.[26] Hunt[16] has r orded portal pres- sures of up to 390 mm. of saline olution in patients with the splenomegaly of myelos rosis and primary splenic anemia. Although simple lenectomy is rare- ly considered the operation of c oice in cases with splenomegaly and portal hyperte ion, dramatic low- ering of portal pressure and c sation of variceal bleeding may follow this procedu ,[16] suggesting that the venous return from the splee affects the portal pressure directly.

Finally, in considering possible auses of increased portal blood flow that may result n portal hyperten- sion, disturbances of the intrah atic arteriovenous circulation must be evaluated. hat distorted vas- cular channels within the livers patients with cir- rhosis may produce increased pc al blood flow was demonstrated by Herrick.[27] Doc [28] on the basis of perfusion studies of normal and rrhotic livers, con- cluded that increased blood flow rough the hepatic artery accounts in large part for e portal hyperten- sion frequently observed in pat nts with alcoholic cirrhosis. Ligation of the hepati artery of cirrhotic patients has been performed to d rease intrahepatic blood flow and thus to lower po l pressure.[29] It is possible that similar abnormal teriovenous anas- tomoses, perhaps accompanied increased blood flow through the portal vein or patic artery, were present in the livers of the 4 pa nts under discus- sion. If such vascular lesions re small and er- ratically distributed, they could ve escaped detec- tion by both splenoportographic udies and micro- scopical examination of liver-bio y specimens.

We were unable in this study demonstrate the factors responsible for portal hy rtension in our 4 patients. Gross and microscopic structural lesions capable of producing increased esistance to flow within the portal vein and its i rahepatic radicles appear to have been excluded. lowever, the pos- sibility of increased vascular resi nce due to func- tional changes, such as increased enous tone of the portal trunk and its intrahepatic branches, has not been ruled out. Such vasomoto reactions seem to maintain portal venous pressur at normal levels after acute experimental alterati s in portal blood flow,[30] but their role in clinical c ease of the portal system has yet to be elucidated.

Increased portal blood flow se is the most likely cause of the venous hypertensic observed in the cases under discussion. Although ross arteriovenous anastomoses involving the spleni and portal veins were not found, functional or stru ural alterations of the vessels of the gastrointestinal t ct, spleen and the liver may have permitted increa d flow of blood into the portal vein, with a result t rise in pressure. Despite the compensatory dilat on of the main portal vessels and the opening o numerous venous collaterals, portal pressures rema ed elevated, with the eventual production and rupture of esophageal varices.

What is needed is careful study of the nonobstructive factors that may produce portal hypertension. Clinically, the combination of a normal or near normal liver-biopsy specimen and an unobstructed portal vein in a patient with bleeding esophageal varices secondary to portal hypertension should lead to investigation of the factors affecting portal blood flow. Of considerable help would be the direct measurement of blood flow through the portal-vein tributaries at the time of laparotomy. Such critical determinations have been carried out in laboratory animals by means of a square-wave electromagnetic flowmeter.[30] Another approach might be the differential temporary occlusion of arteries supplying organs drained by the portal vein, thereby localizing any abnormal arteriovenous unions. Finally, careful post-mortem perfusion studies of the liver, spleen and gastrointestinal tracts of such patients might well reveal important alterations in the structure and function of these blood vessels.

Summary and Conclusions

In 4 cases with portal hypertension and massive bleeding from esophageal varices morphologic examinations of the liver and splenoportograms revealed neither intrahepatic nor extrahepatic portal-vein obstruction. The possible etiologic role of functional or undetected structural obstructive alterations of the vessels of the liver remains uncertain.

It is suggested that portal hypertension in the absence of significant venous obstruction may be caused by increased blood flow through the portal vein.

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PATHOGENESIS OF HYPOFIBRINOGENEMIA IN PLACENTAL ABRUPTION*

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THE pathogenesis of hypofibrinogenemia associated with placental abruption continues to be a subject of much conjecture. The most commonly proposed explanation has been intravascular coagulation due to the escape of thromboplastin from the products of gestation into the maternal circulation.[1-6] Fibrinogen destruction resulting from the activation of circulating plasminogen has also been proposed to account for the fall in circulating fibrinogen.[7-9] Recently, Stefanini and Turpini[10] reported hypofibrinogenemia to follow massive hemorrhage in laboratory animals.

Dieckmann,[11] who in 1936 first clearly demonstrated that a coagulation defect with severe hypofibrinogenemia occurred with some cases of premature separation of the placenta, suggested that the fibrinogen was lost through hemorrhage and therefore utilized at the site of placental separation. In 1956 Ashworth and Stouffer[12] described in the blood clots from patients with placental abruption a great abundance of material that had the histologic characteristics of fibrin. They too believed that the hypofibrinogenemia resulted from the local deposition of fibrin at the site of placental separation. Very recently, while the present study was in progress, Nilsen,[13] in Norway, reported his observations on the fibrin content of blood clots from the uterus in cases of placental abruption. He recovered from the blood clots as much as 11.4 gm. of hemoglobin-free, water-insoluble material, which he considered to be fibrin. He concluded that factors other than intravascular coagulation may be concerned in defibrination.

Impressed by the large volumes of blood clots within the uterus of patients with this syndrome and by the observations of Ashworth and Stouffer that these appear histologically to be quite rich in fibrin, we undertook studies to quantitate the amount of fibrin that might be lost from the circulation owing to coagulation within the cavity of the uterus. Presented are the results of these studies.

METHODS AND MATERIALS

At the time of delivery as much as possible of the clotted and liquid blood contained within the uterine cavity was collected from 7 patients with placental abruption and varying degrees of hypofibrinogenemia. In each there was total placental abruption, and the fetus had very recently died. The interval from the onset of any symptoms suggesting placental abruption until delivery ranged from four to ten hours. Six patients were delivered vaginally, and 1 by cesarean section. They had received whole blood in a volume not in excess of 250 ml. and no fibrinogen before delivery. Serial measurements were made of the plasma fibrinogen level with the use of the method of Ratnoff and Menzie.[14] Plasma fibrinolytic activity was estimated by determination of the time for complete lysis of oxalated plasma that had been clotted by the addition of an equal volume of 0.025-molar calcium chloride solution and incubated under toluene at 37°C. When the plasma fibrinogen concentration was below 100 mg. per 100 ml., an equal volume of normal plasma was first added to supply fibrinogen. The time for complete lysis normally is longer than two days.

The material was frozen to lyse the erythrocytes, thawed at 37°C. and ground in a Waring blendor. It was then centrifuged at room temperature in an

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The Toxicity of Vinyl Chloride as Determined by Repeated Exposure of Laboratory Animals

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Groups of laboratory animals were exposed repeatedly for up to six months to either 500, 200, 100 or 50 ppm vinyl chloride in air. Detectable changes occurred at all but the lowest concentration. The results are discussed and handling precautions suggested.

Introduction

VINYL chloride (CH_2=CHCl) is a chemical of great industrial importance. It is used in the preparation of polyvinyl chloride resin, as a copolymer in saran and other plastics, as a chemical intermediate and as a solvent. Because of the flammability of vinyl chloride, it has been generally assumed that the greatest hazard associated with vinyl chloride is that due to its flammability rather than its toxicity.[1]

The toxicity of vinyl chloride has been reviewed by von Oettingen[2] and more recently by Mastromatteo *et al.*[3] von Oettingen concluded that the gas was anesthetic in high concentrations and that considerable interest had been shown in the use of vinyl chloride as a surgical anesthetic. However, its effect on the circulatory system has discouraged exploitation of this property. No doubt the hazard from flammability has also hindered this use. Only limited repeated exposures which were reported by Schaumann[4] were discussed by von Oettingen. These repeated exposures indicated little or no chronic effects even from anesthetic concentrations.

Mastromatteo *et al.*[3] also discussed the published data and reported the results of single exposures of mice, rats and guinea pigs which confirmed the low acute toxicity of vinyl chloride. Mastromatteo reported that only two human fatalities due to vinyl chloride had been reported.

It can be concluded from the published toxicological data that anesthesia is the only significant effect of acute exposure. Sufficient repeated exposures have not been reported to draw conclusions about chronic toxicity. The Threshold Limit Value of 500 ppm suggested by the American Conference of Governmental Industrial Hygienists (ACGIH)[5] is reported by Smyth[6] to be based on single animal exposures and human experience.

The following report summarizes the results of repeated exposures of laboratory animals to either 500, 200, 100 or 50 ppm of vinyl chloride. The significance of the results is discussed and recommendations for a threshold limit value are made.

Experimental Procedures

Materials Tested

Vinyl chloride, CH_2=CHCl, is a colorless gas. It has a boiling point of −13.35°C (+7.93°F) and a freezing point of −154°C (−244.82°F). The material polymerizes readily and hence is sometimes inhibited with phenol or tertiary butylcatechol. Vinyl chloride is very flammable, its flashpoint being −78°C (−108°F). The explosive limits are from 4% to 22% by volume. It has little odor although high concentrations may smell faintly sweet.

A single, uninhibited sample was used in these studies. It was shown by mass spectrographic analysis to be essentially pure CH_2=CHCl, air being the only impurity detected in gas phase samples.

Source and Feeding of Animals

The rats and rabbits used in this study were obtained from the stock colony of this laboratory, the guinea pigs were obtained from a commercial grower[7] and the dogs were purebred beagles obtained from a local kennel. The rats and dogs were fed Purina Laboratory Chow[8] or Famo Laboratory Ration.[9] The rabbits and guinea pigs received Famo Rabbit Breeder Ration. The guinea pig diet was supplemented with carrots.

Experimental Protocol

The experiments were conducted in three phases. In the first phase, groups of 10 male and 10 female rats were exposed seven d day five days per week to 500 ppm months. Exposures were given in a chamber previously described.[10] Morta growth records were kept. Final organ were obtained and tissues were saved f scopic examination. Five male and fiv rats served as unexposed controls.

The second phase consisted of rep hour daily exposures of 20–24 male an male rats, ten male and eight female gu three male and three female rabbits male and one female dog to either or 100 ppm of vinyl chloride. These an two groups of controls were carefully and matched on the basis of age, cond weight. The first group of controls no exposure and served as unexposed The second group received repeated hour exposures to room air in a chamb to the one used for exposures to the This group is referred to as the air-exp trol group. In addition to the animals 7-hour daily exposures, eight separate five male rats each were exposed to c or 100 ppm for 4, 2, 1 or 0.5 hours p

The procedures and equipment used ically the same as reported previously. and mortality records were kept on a The livers of the dogs were biopsied pr posure and after 3½ months of exposu the liver of each dog served as its ow Pre-exposure and terminal hematologi minations were made on all dogs and determinations on representative group Urine samples were collected from the representative groups of rats. At the te of the experiment, part of the rats wer overnight and then these and all the gu and rabbits were killed by decapitatio day after their last exposure. The c killed by exsanguination after anesth thiopental, sodium (Pentothal, Abbott) of blood were taken of representative animals for determination of alkaline tase, serum-urea-nitrogen (SUN), s tamic-pyruvic-transaminase (SGPT), rum-glutamic-oxalacetic-transaminase The organs were weighed and tissues histopathological examination. The r were not killed the day after expos stopped were pastured for eight weeks sacrificed in the previously described

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e of this experiment consisted
7-hour exposures of 24 male
, 12 male and 12 female guinea
3 female rabbits and one male
and one female dog to 50 ppm vinyl chloride. Equal matched groups served as unexposed and air-exposed controls. Three additional groups of 10 male rats each were exposed for 4, 2 or 1 hour per day to 50 ppm.

The procedures followed were essentially the same as used for exposures to 200 and 100 ppm except that hematological examinations were made on the dogs after three months and liver biopsies were made only prior to exposure. Urine was collected from the rabbits as well as the rats and dogs. The rats which were not sacrificed at the end of the exposures were pastured for six weeks and then sacrificed.

Equipment Used

The exposure equipment used has been described previously.[11] However, in order to gain additional data about the results of repeated short daily exposures, it was necessary to devise a method of introducing additional groups of rats. This was done without opening the doors of the chamber by dropping the rats through chutes made of 3.25-inch stainless steel tubing. These chutes were closed with a rubber stopper except during the brief time it took to insert the rats. The chutes, which were sloped at a 45° angle, ended in covered, screened cages inside the chamber. The additional groups were started 3, 5, 6 and 6.5 hours after the 7-hour exposures started. Since all animals were removed after the 7-hour exposure was completed, this routine resulted in exposures lasting 4, 2, 1 or 0.5 hours.

The vinyl chloride was metered from a saran plastic bag which served as a reservoir for the gas. Metering of the gas was done by Dual Syringe Pumps.[12] Total air flow through the chambers was measured by means of calibrated flow meters.

Analysis of the Chamber Atmospheres

Analyses of the air were made by direct combustion of a known volume of air in a heated quartz tube. The resulting chloride was trapped in 1% sodium formate—1% sodium carbonate solution and subsequently titrated by a micro-Volhard technique. The results of the individual analyses were within 15% of the theoretical concentrations during the exposures to 200, 100 and 50 ppm. The average concentrations recovered were 197, 100.5 and 48.7 ppm respectively.

Results of Repeated Exposures

Exposure to 500 ppm Vinyl Chloride

The rats exposed repeatedly at 500 ppm for 4.5 months, grew normally and no changes were

TABLE I

Summary of Terminal Average Body and Organ Weights of Male Rats Receiving Repeated Exposures to Vinyl Chloride 5 Days per Week

Concentration in ppm	Months on Exposure	Duration of Daily Exposure, hours	Ratio of Survival	Final Average Body Weight, g	Organ Weights, g/100 g Body Weight					
					Lung	Heart	Liver	Kidney	Spleen	Testes
Unexposed control	0	0	1 5	301	0.51	0.33	2.52	0.71	0.15	0.89
500	4.5	7	7 10	312	0.56	0.33	3.00[a]	0.73	0.17	0.95
Unexposed control	0	0	11 12	343	0.53	0.32	2.45	0.69	0.14	0.80
Air exposed control	6	7	10 12	356	0.52	0.32	2.52	0.70	0.15	0.76
200	6	7	9 12	341	0.52	0.32	2.85[b]	0.68	0.17	0.94
200	6	4	4 5	319	0.47	0.29	2.66[c]	0.61	0.16	0.85
200	6	2	4 5	341	0.56	0.30	2.62[d]	0.61	0.16	0.89
200	6	1	3 5	350	0.48	0.28	2.46	0.61	0.13	0.78
200	6	0.5	4 5	339	0.51	0.29	2.38	0.67	0.14	0.95
100	6	7	7 12	352	0.51	0.29	2.61[e]	0.63	0.15	0.85
100	6	4	3/5	360	0.51	0.28	2.62	0.65	0.15	0.74
100	6	2	4 5	331	0.53	0.31	2.64	0.67	0.16	0.93
100	6	1	3 5	387	0.49	0.28	2.52	0.64	0.15	0.78
100	6	0.5	5/5	363	0.45	0.30	2.42	0.64	0.16	0.78
Unexposed* control	0	0	10/12	351	0.49	0.31	2.43	0.64	0.14	0.84
Air exposed* control	6	7	8 12	393	0.59	0.30	2.41	0.63	0.15	0.78
200*	6	7	8 8	385	0.47	0.29	2.59[f]	0.61	0.15	0.71
100*	6	7	6 7	376	0.47	0.31	2.53[f]	0.65	0.14	0.76

* Pastured for 8 weeks after exposures ceased.
(a) P = 0.001
(b) P = <0.001
(c) P = 0.07
(d) P = 0.1
(e) P = 0.02
(f) P = 0.13

apparent grossly at autopsy. Microscopically their livers showed increased central lobular granular degeneration and the kidneys showed interstitial and tubular changes. The average weight increase of the livers of the male rats was statistically significant (P = 0.001), Table I. The average weight of the livers of the female rats was above that of the controls but not statistically significant, Table II. SUN, SGPT, S-GOT, and alkaline phosphatase determinations were within normal limits (Table III).

Exposure to 200 ppm Vinyl Chloride

All groups exposed seven hours per day 138–144 times in 204 days were normal in appearance, mortality and growth. Hematological, SUN, S-GOT, SGPT and alkaline phosphatase values (Table III) and the results of the urinalysis were within normal limits. Gross pathology was normal in all species. Micropathology was normal in the rats, guinea pigs and dogs, however, adverse effects were noted in the livers of rabbits of both sexes. In the male rabbits this was characterized by central lobular granular degeneration and necrosis with some foamy vacuolation. In the female rabbits the changes noted were central lobular granular degeneration and necrosis with periportal cellular infiltration. All organ weights were normal except for the livers of the male and female rats which were increased significantly after repeated daily 7-hour exposures (Tables I, II, IV, V, VI, and VII). In the males this increase was still apparent eight weeks after exposure ceased, although the liver weights appeared to be decreasing and returning to normal.

The male rats exposed to 200 ppm of vinyl chloride for either four or two hours per day for six months had elevated average liver weights (Table I). However, the small size of the experimental groups made the finding statistically insignificant (P = 0.07 and 0.1). The groups exposed for either 1 or 0.5 hours per day were entirely normal.

TABLE II

Summary of Average Body and Or
Female Rats Receiving Repeate
posures to Vinyl Chloride 5 Da

Concentration in ppm	Months on Exposure	Ratio of Survival	Final Average Body Weight, g	Or g	
				Lung	Heart
Unexposed control	0	5 5	194	0.82	0.4
500	4.5	9 10	195	0.68	0.3
Unexposed control	0	10 12	202	0.63	0.3
Air exposed control	6	9 12	223	0.66	0.3
200	6	10 12	208	0.63	0.3
100	6	11 12	221	0.59	0.3
Unexposed* control	0	8 12	223	0.61	0.3
Air exposed* control	6	9 12	210	0.58	0.3
200*	6	12 12	233	0.61	0.3
100*	6	12 12	235	0.63	0.4
Unexposed control	0	11 12	211	0.58	0.3
Air exposed control	6	12 12	202	0.59	0.3
50	6	9 12	206	0.61	0.3
Unexposed** control	0	11 12	195	0.66	0.4
Air exposed control**	6	9 12	221	0.63	0.4
50**	6	11 12	233	0.63	0.3

* Pastured for 8 weeks after exposures ce
** Pastured for 6 weeks after exposures ce
(a) P = 0.17
(b) P = 0.03
(c) P = 0.01
(d) P = 0.05

Exposure to 100 ppm Vinyl Chlo

All species exposed to 100 ppm ride, seven hours per day, 138–14 days, were judged normal on the l lowing criteria: appearance, mor hematological examination, SU GPT, alkaline phosphatase dete nalysis and gross and microscopic tissue. However, slight increases

tece ..g Repeated Exposures

Weights, g/100 g Body Weight

t	Liver	Kidney	Spleen	Testes
	2.52	0.71	0.15	0.89
	3.00[a]	0.73	0.17	0.95
	2.45	0.69	0.14	0.80
	2.52	0.70	0.15	0.76
	2.85[b]	0.68	0.17	0.94
	2.66[c]	0.64	0.16	0.85
	2.62[d]	0.64	0.16	0.89
	2.46	0.61	0.13	0.78
	2.38	0.67	0.14	0.95
	2.61[e]	0.63	0.15	0.85
	2.62	0.65	0.15	0.74
	2.64	0.67	0.16	0.93
	2.52	0.64	0.15	0.78
	2.42	0.64	0.16	0.78
	2.43	0.64	0.14	0.84
	2.41	0.63	0.15	0.78
	2.59[e]	0.64	0.15	0.71
	2.53[f]	0.65	0.14	0.76

xes. In the male rabbits this
by central lobular granular de-
rosis with some foamy vacuo-
ale rabbits the changes noted
ar granular degeneration and
portal cellular infiltration. All
e normal except for the livers
female rats which were in-
dy after repeated daily 7-
Tables I, II, IV, V, VI, and
this increase was still appar-
ter exposure ceased, although
ppeared to be decreasing and
l.

exposed to 200 ppm of vinyl
four or two hours per day for
evated average liver weights
er, the small size of the ex-
made the finding statistically
0.07 and 0.1). The groups ex-
or 0.5 hours per day were en-

TABLE II

Summary of Average Body and Organ Weights of Female Rats Receiving Repeated 7-Hour Exposures to Vinyl Chloride 5 Days per Week

Concentration in ppm	Months on Exposure	Ratio of Survival	Final Average Body Weight, g	Organ Weights, g/100 g Body Weight				
				Lung	Heart	Liver	Kidney	Spleen
Unexposed control	0	5/5	191	0.82	0.41	3.06	0.80	0.19
500	4.5	9/10	195	0.68	0.38	3.22[a]	0.81	0.20
Unexposed control	0	10/12	202	0.65	0.38	2.92	0.82	0.17
Air exposed control	6	9/12	223	0.66	0.39	2.99	0.81	0.18
200	6	10/12	208	0.63	0.38	3.39[b]	0.84	0.18
100	6	11/12	221	0.59	0.39	3.35[c]	0.79	0.20
Unexposed* control	0	8/12	223	0.61	0.37	2.67	0.82	0.18
Air exposed* control	6	9/12	240	0.58	0.37	2.97	0.83	0.18
200*	6	12/12	233	0.61	0.38	3.06	0.81	0.20
100*	6	12/12	235	0.63	0.40	3.17	0.83	0.21
Unexposed control	0	11/12	211	0.58	0.39	3.02	0.83	0.20
Air exposed control	6	12/12	202	0.59	0.38	2.93	0.84	0.20
50	6	9/12	206	0.61	0.37	3.02	0.81	0.20
Unexposed** control	0	11/12	195	0.66	0.40	2.88	0.91	0.22
Air exposed control**	6	9/12	221	0.63	0.40	3.01	0.87	0.19
50**	6	11/12	233	0.63	0.38	2.83	0.82[d]	0.20

* Pastured for 8 weeks after exposures ceased.
** Pastured for 6 weeks after exposures ceased.
(a) P = 0.17
(b) P = 0.03
(c) P = 0.01
(d) P = 0.05

Exposure to 100 ppm Vinyl Chloride

All species exposed to 100 ppm of vinyl chloride, seven hours per day, 138–144 times in 204 days, were judged normal on the basis of the following criteria: appearance, mortality, growth, hematological examination, SUN, SGOT, SGPT, alkaline phosphatase determination, urinalysis and gross and microscopic examination of tissue. However, slight increases were found in the average weights of the livers of male and female rats (Tables I and II). Although not significant statistically, an increase was also seen in the average weight of the livers of the male rats exposed to 100 ppm for either four or two hours per day. The groups exposed for either 1.0 or 0.5 hour per day were entirely normal.

Exposures to 50 ppm Vinyl Chloride

The increase in weight of the rat livers, the only significant finding in animals exposed to 100 ppm, did not occur in rats exposed repeatedly to 50 ppm of vinyl chloride, 130 times in 189 days. All groups of animals were judged normal in all other respects. See Tables II, V, VI, VII, VIII and IX. A statistically significant decrease in kidney weight which was seen in the female rats (Table II) was considered to be an artifact since it was not seen at higher concentrations.

Discussion

Repeated exposure to vinyl chloride at concentrations considerably below the level that has been considered safe for human exposure has been shown to have an effect on the liver and kidney of laboratory animals. Histopathological changes and increased liver weights in male and female rats were noted after repeated exposure at 500 ppm. Repeated exposure at 200 ppm for six months resulted in an increase in the average weight of the livers of male and female rats and micropathological changes in the livers of the male and female rabbits. The only effect noted after repeated daily 7-hour exposures to 100 ppm for six months was a slight increase in the average weight of the rat livers. Repeated 7-hour exposures to 50 ppm for six months had no effect on any species studied. Hence, the highest concentration without detectable effect on any species was 50 ppm.

It is interesting to speculate on the apparent discrepancy between the effects observed at 100 ppm in this experiment and the lack of reported injury in humans using a threshold limit of 500 ppm. Several factors may be contributory. First, the effects noted in animals at 500 ppm were only slight to moderate; growth, mortality, and general appearance were unaffected. Hence, it is possible that if humans were exposed repeatedly at 500 ppm slight injury might occur but due to the lack of subjective symptoms the injury would escape detection. Secondly, the injury was apparently reversible. The liver weights of both male and female rats which had shown definite increases after exposures at 200 and 100 ppm were normal or approaching normal after 6–8 weeks of recovery (Tables I, II and VIII).

Table III

Summary of Average Biochemical Values Determined for Animals Receiving Repeated Exposures to Vinyl Chloride 5 Days per Week

Species and Dog No.	Sex	Concentration in ppm	Months on Exposure	Duration of Daily Exposure, hours	Number of Animals	Alkaline Phosphatase King-Armstrong Units	Blood Urea Nitrogen, mg/100 ml	SGPT	SGOT
								Sigma-Frankel Unit	
Dog #101	M	Unexposed control	0	0	1	12.2	24	18	43
#113		Air exposed control	6	7	1	4.1	19	19	17
#41		200	6	7	1	8.6	11	18	48
#98		100	6	7	1	4.5	16	21	19
Dog #106	F	Unexposed control	0	0	1	5.1	11	10	26
#107		Air exposed control	6	7	1	7.1	20	11	17
#103		200	6	7	1	7.9	14	16	26
#110		100	6	7	1	5.6	10	10	14
Rat	M	Unexposed control	0	0	5	32.9*	20.6*	30	
		500	4.5	7	4	18.9	13.8	35	
		200	6	7	5	17.7	16.2	36	
		200	6	4	4	18.4	16.2	32	
		200	6	1	3	20.2	17.7	42	
		100	6	7	4	19.4	15.0	27	
		100	6	4	3	14.7	16.3	36	
		100	6	1	3	19.0	15.3	30	
Rat	F	Unexposed control	0	0	4	12.1	20.5	38	
		500	6	7	3	16.1	22.3	26	
		200	6	7	5	13.6	22.2	21	
		100	6	7	6	9.5	22.8	23	
Rabbit	M	Control	6	0	5	4.0	25	36	
		200	6	7	3	5.3	21	23	
		100	6	7	2	5.9	26	26	
Rabbit	F	Control	6	0	6	4.9	33	38	
		200	6	7	2	5.6	27	35	
		100	6	7	3	4.0	26	35	

* Because of two unusually high individual values in this group these average values are elevated and do not correspond with the values obtained on similar control groups in our laboratory. Normal control values are in the same ranges as those of the experimental groups listed in this table.

Table IV

Summary of Average Hematological Values for Animals Receiving Repeated 7-Hour Exposures to Vinyl Chloride

Species or Dog #	Sex	Concentration in ppm	Months on Experiment	No. of Animals	Hemoglobin g/100 g	Hematocrit	WBC × 10^3	Neutrophils	Lymphocytes	Monocytes	Eosinophils
Rat	M	Air exposed control	6	4	14.5	51	15.8	26.5	71.2	1.5	0.8
Rat	M	200	6	5	14.4	50	16.7	19	77.8	0.2	3
Rat	F	Air exposed control	6	4	14.0	49.5	13.5	22.5	74.5	0.2	2.8
Rat	F	200	6	5	13.5	47.4	12.8	24.8	70.2	1.0	4
Dog #101	M	Unexposed control	0	1	—	—	—	—	—	—	—
Dog #101	M	Unexposed control	6	1	15	53	14.2	46	51	0	3
Dog #113	M	Air exposed control	0	1	14.5	50	13.5	61	23	5	11
Dog #113	M	Air exposed control	6	1	14.5	52	13.2	58	34	4	4
Dog #111	M	200	0	1	13	47	16.2	56	28	3	13
Dog #111	M	200	6	1	16.5	58	15.8	56	41	2	1
Dog #98	M	100	0	1	15.5	52	19.8	46	46	4	4
Dog #98	M	100	6	1	16	54	18.6	61	39	0	0
Dog #106	F	Unexposed control	0	1	14.5	51	21.8	42	37	3	18
Dog #106	F	Unexposed control	6	1	15.5	51	16.5	54	41	1	4
Dog #107	F	Air exposed control	0	1	15	53	14.4	55	33	4	8
Dog #107	F	Air exposed control	6	1	16	57	11.7	66	23	4	7
Dog #103	F	200	0	1	14	50	17.5	44	48	3	5
Dog #103	F	200	6	1	16	54	17.3	46	51	0	3
Dog #110	F	100	0	1	12.5	44	16.3	61	37	2	0
Dog #110	F	100	6	1	15.5	54	14.4	49	50	1	0

Table V

Summary of Terminal Average B
Weights of Guinea Pigs Recei
Daily 7-Hour Exposures to Vi
Days per Week for 6 Months

Sex	Concentration in ppm	Ratio of Survival	Final Average Body Weight, g	Organ W Bo	
				Lung	Heart
M	Unexposed control	8/10	927	0.61	0.28
M	Air exposed control	5/10	1030	0.52	0.28
M	200	7/10	1011	0.53	0.27
M	100	7/10	1089	0.52	0.25
M	Unexposed control	8/12	918	0.60	0.29
M	Air exposed control	11/12	936	0.61	0.27
M	50	10/12	1001	0.63	0.26
F	Unexposed control	6/8	899	0.62	0.27
F	Air exposed control	7/8	867	0.60	0.25
F	200	7/8	897	0.70	0.27
F	100	7/8	949	0.58	0.26
F	Unexposed control	9/12	728	0.78	0.34
F	Air exposed control	8/12	881	0.65	0.26
F	50	11/12	986	0.69	0.28

(a) P = 0.05
(b) P = 0.21
(c) P = 0.23

Table VI

Summary of Terminal Average B
Weights of Rabbits Receiving
7-Hour Exposures to Vinyl Chlo
Week for 6 Months

Sex	Concentration in ppm	Ratio of Survival	Final Average Body Weight, kg	Orga	
				Lung	Heart
M	Unexposed	3/3	3.61	0.39	0.
M	Air exposed control	2/3	3.90	0.31	0.
M	200	3/3	3.48	0.32	0.
M	100	3/3	3.65	0.33	0.
M	Unexposed control	2/3	3.80	0.32	0.
M	Air exposed control	1/3	3.87	0.37	0.
M	50	3/3	3.70	0.36	0.
F	Unexposed	3/3	4.13	0.31	0.
F	Air exposed control	3/3	3.91	0.30	0.
F	200	2/3	4.10	0.32	0.
F	100	3/3	4.12	0.29	0.
F	Unexposed control	3/3	4.31	0.30	0.
F	Air exposed control	2/3	3.95	0.30	0.
F	50	3/3	4.31	0.32	0.

...ing Repeated Exposures to

...lkal. Phos-...hatase King-Arm-...strong Units	Blood Urea Nitrogen, mg/100 ml	SGPT	SGOT
		Sigma-Frankel Unit	
12.2	24	18	43
4.1	19	19	17
8.6	11	18	48
4.5	16	21	19
5.1	11	10	26
7.1	20	11	17
7.9	14	16	26
5.6	10	10	14
32.9*	20.6*	30	
18.9	13.8	35	
17.7	16.2	36	
18.4	16.2	32	
20.2	17.7	42	
19.4	15.0	27	
14.7	16.3	36	
19.0	15.3	30	
12.1	20.5	38	
16.1	22.3	26	
13.6	22.2	21	
9.5	22.8	23	
4.0	25	36	
5.3	21	23	
5.9	26	26	
4.9	33	38	
5.6	27	35	
4.0	26	35	

...ited, ... o not correspond with the ... ranges as those of the experimental

Receiving

...×	Neutrophils	Lymphocytes	Monocytes	Eosinophils
	26.5	71.2	1.5	0.8
	19	77.8	0.2	3
	22.5	74.5	0.2	2.8
	24.8	70.2	1.0	4
	46	51	0	3
	61	23	5	11
	58	34	4	4
	56	28	3	13
	56	41	2	1
	46	46	4	4
	61	39	0	0
	42	37	3	18
	54	41	1	4
	55	33	4	8
	66	23	4	7
	44	48	3	5
	46	51	0	3
	61	37	2	0
	49	50	1	0

TABLE V

Summary of Terminal Average Body and Organ Weights of Guinea Pigs Receiving Repeated Daily 7-Hour Exposures to Vinyl Chloride 5 Days per Week for 6 Months

Sex	Concentration in ppm	Ratio of Survival	Final Average Body Weight, g	Organ Weights, g/100 g Body Weight: Lung	Heart	Liver	Kidney	Spleen	Testes
M	Unexposed control	8/10	927	0.61	0.28	3.32	0.70	0.16	0.18
M	Air exposed control	5/10	1039	0.52	0.28	3.36	0.61	0.10	0.18
M	200	7/10	1044	0.53	0.27	3.01	0.60	0.09	0.41
M	100	7/10	1089	0.52	0.25	2.79[a]	0.58	0.11	0.47
M	Unexposed control	8/12	918	0.60	0.29	3.21	0.68	0.12	0.52
M	Air exposed control	11/12	936	0.61	0.27	3.31	0.64	0.12	0.50
M	50	10/12	1001	0.63	0.26	3.11	0.61	0.12	0.48
F	Unexposed control	6/8	899	0.62	0.27	3.20	0.63	0.12	
F	Air exposed control	7/8	867	0.66	0.25	3.28	0.67	0.11	
F	200	7/8	897	0.71[b]	0.27	3.60[c]	0.66	0.13	
F	100	7/8	949	0.58	0.26	3.50	0.61	0.12	
F	Unexposed control	9/12	728	0.78	0.31	3.41	0.69	0.15	
F	Air exposed control	8/12	884	0.65	0.26	3.84	0.65	0.14	
F	50	11/12	906	0.69	0.28	3.11	0.61	0.14	

(a) P = 0.05
(b) P = 0.24
(c) P = 0.23

TABLE VI

Summary of Terminal Average Body and Organ Weights of Rabbits Receiving Repeated Daily 7-Hour Exposures to Vinyl Chloride 5 Days per Week for 6 Months

Sex	Concentration in ppm	Ratio of Survival	Final Average Body Weight, kg	Organ Weights, g/100 g Body Weight: Lung	Heart	Liver	Kidney	Spleen	Testes
M	Unexposed	3/3	3.61	0.39	0.21	2.27	0.43	0.03	0.16
M	Air exposed control	2/3	3.90	0.31	0.18	2.41	0.46	0.02	0.16
M	200	3/3	3.18	0.32	0.19	2.31	0.51	0.02	0.15
M	100	3/3	3.65	0.33	0.18	2.61	0.49	0.02	0.15
M	Unexposed control	2/3	3.80	0.32	0.17	2.33	0.45	0.02	0.15
M	Air exposed control	1/3	3.87	0.37	0.18	3.18	0.53	0.03	0.14
M	50	3/3	3.70	0.36	0.20	2.46	0.47	0.03	0.17
F	Unexposed	3/3	4.13	0.31	0.17	2.22	0.49	0.03	
F	Air exposed control	3/3	3.91	0.30	0.18	2.18	0.41	0.01	
F	200	2/3	4.10	0.32	0.16	2.26	0.42	0.05	
F	100	3/3	4.12	0.29	0.18	1.87	0.38	0.05	
F	Unexposed control	3/3	4.31	0.30	0.17	1.91	0.46	0.01	
F	Air exposed control	2/3	3.95	0.30	0.17	1.88	0.39	0.01	
F	50	3/3	4.31	0.32	0.17	2.19	0.38	0.01	

TABLE VII

Summary of Final Body and Organ Weights of Dogs Receiving Repeated Daily 7-Hour Exposures to Vinyl Chloride 5 Days per Week for 6 Months

Sex	Dog. No.	Concentration in ppm	Ratio of Survival	Final Body Weight, kg	Organ Weights, g/100 g Body Weight: Lung	Heart	Liver	Kidney	Spleen	Testes
M	101	Unexposed control	1/1	13.0	0.66	0.62	2.46	0.38	0.32	0.15
M	113	Air exposed control	1/1	8.5	0.68	0.77	2.63	0.47	0.19	0.14
M	111	200	1/1	10.2	1.03	0.96	2.50	0.52	0.25	0.13
M	98	100	1/1	12.0	0.86	0.80	2.50	0.12	0.26	0.15
M	152	Unexposed control	1/1	13.3	0.80	0.75	2.69	0.53	0.23	0.11
M	156	Air exposed control	1/1	10.6	0.77	0.87	3.05	0.15	0.36	0.14
M	162	50	1/1	9.6	0.89	0.78	2.40	0.15	0.23	0.12
F	106	Unexposed control	1/1	9.6	0.71	0.68	2.67	0.13	0.21	
F	107	Air exposed control	1/1	8.7	0.77	0.80	3.15	0.13	0.33	
F	103	200	1/1	10.5	0.78	0.71	1.88	0.15	0.28	
F	110	100	1/1	11.9	0.99	0.78	2.11	0.13	0.31	
F	151	Unexposed control	1/1	8.6	0.99	0.82	1.10	0.15	0.13	
F	155	Air exposed control	1/1	11.3	0.70	0.81	3.31	0.10	0.25	
F	161	50	1/1	7.4	0.87	0.76	2.48	0.47	0.33	

TABLE VIII

Summary of Terminal Average Body and Organ Weights of Male Rats Receiving Repeated Exposures to Vinyl Chloride 5 Days per Week

Concentration in ppm	Months on Exposure	Duration of Daily Exposure, hours	Ratio of Survival	Final Average Body Weight, g	Organ Weights, g/100g Body Weight: Lung	Heart	Liver	Kidney	Spleen	Testes
Unexposed control	0	0	8/8	319	0.50	0.33	2.67	0.75	0.18	0.98
Air exposed control	6	7	12/12	317	0.51	0.32	2.41	0.70	0.16	0.81
50	6	7	12/12	339	0.50	0.31	2.49	0.68	0.17	0.87
50	6	4	8/10	318	0.51	0.33	2.59	0.69	0.16	0.81
50	6	2	6/10	322	0.49	0.32	2.57	0.70	0.16	0.80
50	6	1	9/10	318	0.47	0.32	2.51	0.73	0.17	0.84
Unexposed* control	0	0	8/8	336	0.53	0.32	2.37	0.72	0.16	0.83
Air exposed* control	6	7	12/12	370	0.52	0.30	2.42	0.64	0.14	0.75
50*	6	7	12/12	360	0.49	0.33	2.51	0.68	0.15	0.82

* Pastured for 6 weeks after exposures ceased.

Thirdly, it is doubtful whether it would be possible for humans to be exposed continuously at 500 ppm in production plants since this high a general concentration would indicate severe leaks in the equipment and extremely high concentrations

TABLE IX

Summary of Average Hematological Values for Dogs Receiving Repeated 7-Hour Exposures to Vinyl Chloride

Dog #	Sex	Concentration in ppm	Months on Experiment	No. of Animals	Hemoglobin g/100 g	Hematocrit	WBX $\times 10^3$	Neutrophils	Lymphocytes	Monocytes	Eosinophils
Dog #152	M	Unexposed control	0	1	11	43	12.9	51	41	1	4
Dog #152	M	Unexposed control	3	1	15	52	19.4	42	50	4	4
Dog #152	M	Unexposed control	6	1	15.5	51	15.4	52	40	5	3
Dog #156	M	Air exposed control	0	1	—	—	—	—	—	—	—
Dog #156	M	Air exposed control	3	1	14.5	50	13.4	45	50	2	3
Dog #156	M	Air exposed control	6	1	14	50	11.1	55	28	5	12
Dog #162	M	50	0	1	10.5	39	13.6	48	48	2	2
Dog #162	M	50	3	1	14.5	54	12.7	48	48	3	1
Dog #162	M	50	6	1	15.5	53	11.2	43	50	4	3
Dog #151	F	Unexposed control	0	1	11	48	13.3	59	30	3	9
Dog #151	F	Unexposed control	3	1	14.5	52	23.6	67	25	0	8
Dog #151	F	Unexposed control	6	1	15.5	58	15.5	46	42	3	9
Dog #155	F	Air exposed control	0	1	13	46	14	61	37	0	2
Dog #155	F	Air exposed control	3	1	16	59	18.2	60	33	5	2
Dog #155	F	Air exposed control	6	1	15.5	56	17.0	53	31	5	11
Dog #161	F	50	0	1	10.5	35	15.3	55	40	5	0
Dog #161	F	50	3	1	15.5	58	13.4	56	42	2	0
Dog #161	F	50	6	1	15.5	56	12.3	43	43	3	11

adjacent to the leaks. The flammability of vinyl chloride precludes such severe leaks if this hazard of vinyl chloride is to be controlled.

Industrial Hygiene Standard

The data presented indicate that little likelihood of injury would be expected if repeated daily 7- to 8-hour exposures are limited to 100 ppm or less.

Although the level of 100 ppm may not appear to offer any margin of safety since rats exposed repeatedly to this level were very slightly affected, the vast amount of human experience that is available while operating under an MAC of 500 ppm indicates that injury is not likely. Likewise the effects of even rather severe overexposure are not serious, hence this level seems reasonable.

A time-weighted average for all exposure should probably not exceed 50 ppm.

Summary

Vinyl chloride (CH_2=CHCl) is a monomer used in very large quantities in the production of plastics. Repeated exposures of laboratory animals to several concentrations of vinyl chloride in air were conducted to determine the chronic toxicity of this material towards animals in order to assess the hazard to humans. Vinyl chloride was found to have a slight capacity to cause liver and kidney injury on repeated exposures. Male and female rats showed micropathological changes after repeated daily 7-hour exposures at 500 ppm for 4.5 months. Repeated 7-hour exposures at 200 ppm for six months resulted in micropathological changes in the livers of rabbits and statistically significant increases in the average weight of the livers of male and female rats but no detectable changes in dogs and guinea pigs. Repeated 7-hour exposures at 100 ppm resulted in slight increases in the average weight of rat livers, the other species were not affected. All species studied tolerated repeated daily 7-hour exposures to 50 ppm for six months with no detectable injury.

Repeated daily 1-hour exposures at 200 and 100 ppm of vinyl chloride were without effect, longer exposures caused a slight increase in liver weight.

The standard for evaluating regular daily 7- to 8-hour exposures may be defined as the concentration below which practically all analytical results must fall. The value of 100 ppm is suggested as this standard for vinyl chloride, with a time-weighted average for all exposures not to exceed 50 ppm.

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8. Ralston Purina Company, St. Louis, M
9. Harris Milling Company, Mount Pleasa

Repeated 7-Hour

×	Neutrophils	Lymphocytes	Monocytes	Eosinophils
	54	41	1	4
	42	50	4	4
	52	40	5	3
	—	—	—	—
	45	50	2	3
	55	28	5	12
	48	48	2	2
	48	48	3	1
	43	50	4	3
	59	30	3	9
	67	25	0	8
	46	42	3	9
	61	37	0	2
	60	33	5	2
	53	31	5	11
	55	40	5	0
	56	42	2	0
	43	43	3	11

onths. Repeated 7-hour ex- for six months resulted in anges in the livers of rab- significant increases in the ie livers of male and female able changes in dogs and ed 7-hour exposures at 100 ght reases in the average th. ther species were not studied tolerated repeated es to 50 ppm for six months njury.

-hour exposures at 200 and hloride were without effect, sed a slight increase in liver

evaluating regular daily 7- may be defined as the con- ich practically all analytical ie value of 100 ppm is sug- ard for vinyl chloride, with rage for all exposures not to

Toxicol. u. Hyg. der technischen Losungsmittel, J. Springer, Berlin, 1938 p. 130. (From the translation, *Toxicology and Hygiene of Industrial Solvents* by E. King and H. F. Smyth, Jr., 1941).

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A. M. Fisher, H. Christie, and Inhalation Toxicity of Vinyl Chloimals. *Am. Ind. Hyg. Assoc. J. 21:*

by K. B. Lehman and F. Flury,

Industrial Hygiene Certification

THE AMERICAN BOARD OF INDUSTRIAL HYGIENE in es inquiries from those who are interested in applying for voluntary certificatic in the profession of industrial hygiene. Certificates will be issued on the basis of examination to those who have eight years of practice, following a suitable bacca reate degree. No examination will be required of those who have fifteen years of prac e with recognized contributions to the field, following acceptable education. Certai specialists within the field will be certified when one-fourth of their time has consist tly been devoted to application of their specialty to industrial hygiene. A broc e describing the certification program, and giving more details of eligibility will b ent to those who direct inquiries to Henry F. Smyth, Jr., Secretary-Treasurer, merican Board of Industrial Hygiene, 4400 Fifth Avenue, Pittsburgh 13, Pennsylvan

The Board was chartered as a non-profit corporation under the l s of the Commonwealth of Pennsylvania in September 1960. The incorporators w e selected by the American Conference of Governmental Industrial Hygienists an he American Industrial Hygiene Association from among their respective mem rships. They are John C. Soet, Chairman; Lester V. Cralley, Ph.D., Vice-Chairmar Henry F. Smyth, Jr., Ph.D., Secretary-Treasurer; and Edgar C. Barnes, William F Bradley, Allan L. Coleman, Hervey B. Elkins, Ph.D., Louis F. Garber, Thomas Maneuso, M.D., Kenneth M. Morse, James H. Sterner, M.D., and Charles D. Ya .

Industrial Hygiene Engineering and Chemis ry

THE DIVISION OF OCCUPATIONAL HEALTH, Public alth Service, will conduct two simultaneous courses January 8–19, 1962, at the upational Health Research and Training Facility, Cincinnati, Ohio. "Industrial Hygi e Engineering" is designed for industrial hygienists and engineers in the field of occu tional health who have a degree in engineering or in the physical sciences. "Industi l Hygiene Chemistry" is designed for chemists in this field who have a degree in ch istry or chemical engineering, or in the physical sciences with a minor in chemist During the first week, trainees for both courses meet together for instruction in inc strial hygiene and medicine, toxicology, and principles pertaining to evaluation of th environment. For the hygienists, the second week's work covers temperature and midity measurements, illumination, noise measurement and control, and industi l ventilation; for the chemists, laboratory analyses for lead, free silica, and solvents nd spectroscopy, polarography, x-ray diffraction, electron microscopy, and gas chro atography. Much time in both courses is spent in the laboratory.

It should be noted that applications for the course or reque for information should be addressed to the Chief, Training Program, Robert A. aft Sanitary Engineering Center, 4676 Columbia Parkway, Cincinnati 26, Ohi or to a DHEW Regional Office Director.

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Таблица 9. **Данные размера пылинок при различных способах бурения в процентах**

Производственный процесс	Размер пылинок	
	до 2 μ	от 2 до 5 μ
Бурение глубоких скважин	98,5	1,5
Перфораторное бурение по руде с промывкой	98,4	1,6

бокими скважинами есть все предпосылки для резкого снижения пылеобразования вследствие лучшего контакта буровой пыли с водой, что обусловливается длиной бурки, большой подачей воды без воздуха.

Несмотря на то что нами были приняты меры для изоляции блока, в котором велись наблюдения, от остальных выработок с целью исключения влияния общего запыления воздуха подземных выработок, все же нельзя быть уверенным в том, что общая запыленность выработок не повлияла на наши исследования. Необходимо повторить наблюдения при более тщательной изоляции от остальных выработок или при условии применения других мероприятий, исключающих влияние общей запыленности воздуха выработок на пылеобразование при бурении глубокими скважинами. Это тем более необходимо в связи с тем, что бурение глубокими скважинами является прогрессивным методом как в экономическом, так и в гигиеническом отношении (устранение вибрации, шума, статического компонента в работе, сокращение буровых работ).

Выводы

1. На основании проведенных исследований нужно сделать вывод о том, что ни один из методов, применяемых для борьбы с пылью при бурении, не дает еще вполне положительного гигиенического эффекта.
2. Необходимо продолжить работу по изысканию новых смачивателей или пенообразующих веществ для целей более эффективной борьбы с пылью при бурении.
3. Однако до изыскания новых средств борьбы с пылью следует широко применять воду, поскольку она дает значительное снижение запыленности воздуха, особенно с добавлением мылонафта в количестве 0,2%.

С. Л. Трибух, Н. П. Тихомирова, С. В. Левина и Л. А. Козлов

Условия труда и мероприятия по их оздоровлению при производстве и использовании хлорвиниловых пластических масс

Из лаборатории производственных исследований Института гигиены труда и профзаболеваний АМН СССР

Производство хлорвиниловых пластических масс, а также и различных изделий из них в течение последнего десятилетия получило значительное развитие. Между тем в гигиеническом отношении это производство мало изучено.

Основным сы
масс является хл
рида — бесцветно
с удельным весо
при взаимодейств
(винила) и газооб
руется с приме
в автоклавах. Та
дуктом полимери
щелочей, разбавл
полихлорвинилова
ных прокладок, т

При изготовл
пластифицируется
лат), фосфорной
(совол) или хлор
катора зависит от

Винилхлорид, со
Наркотические конц
до 250 мг/л. Согласн
щиеся при нагреве
у животных в услов
дующие явления: ра
поражения централь
и гибель при явлени

Совол и голова
лей, обладают общи
на организм совол
ряда. В основном о
отравление протекае
ратуре описаны слу
рированными нафтал
совола и голсвакса
тозно-везикулярных

Условия труда
изучались нами в
тов при примене
кожи и при прим

Производств
ных пластикатов хло
с дибутилфталатом
80—100°. Затем ком
лось до 130—160°.
В конце вальцев
ленты, которые в да

При гигиениче
производились исс
в нем паров сове
кислоты. Получен

В воздухе раб
это видно из дан
ческих соединени
отделении имело
и транспортировк
найденные в этом
могут быть отнес
хлорорганические
0,08 мг/л, а у раб

Основным сырьем при изготовлении хлорвиниловых пластических масс является хлорвиниловая смола, которая получается из винилхлорида — бесцветного газа, конденсирующегося при 12—14° в жидкость с удельным весом 0,86—0,90. Винилхлорид в свою очередь получается при взаимодействии газообразных продуктов разложения паров нефти (винила) и газообразного хлора. В дальнейшем винилхлорид конденсируется с применением дихлорэтана и подвергается полимеризации в автоклавах. Таким образом, полихлорвиниловая смола является продуктом полимеризации винилхлорида. Благодаря стойкости к действию щелочей, разбавленных кислот, спирта, бензина и смазочного масла полихлорвиниловая смола применяется для производства кислотоупорных прокладок, тканей для спецодежды, заменителей кожи и др.

При изготовлении различных изделий полихлорвиниловая смола пластифицируется сложными эфирами фталиевой кислоты (дибутилфталат), фосфорной кислоты (трикрезилфосфат), смесью хлордифенилов (совол) или хлорированных нафталинов (головакс). Выбор пластификатора зависит от назначения изготовляемой пластической массы.

Винилхлорид, согласно литературным данным, относится к слабым наркотикам. Наркотические концентрации его для человека находятся в пределах от 75 до 250 мг/л. Согласно данным Петропавловского (1942), летучие вещества, выделяющиеся при нагреве хлорвиниловой смолы и пластикатов до 130—165°, вызывают у животных в условиях однократной затравки в зависимости от концентрации следующие явления: раздражение видимых слизистых оболочек, нарушение дыхания, поражения центральной нервной системы, расстройство координации движений и гибель при явлениях асфиктических судорог.

Совол и головакс, вводимые в хлорвиниловые пластикаты в качестве мягчителей, обладают общим и местным токсическим действием. По общему воздействию на организм совол и головакс близки к хлорзамещенным углеводородам жирного ряда. В основном они оказывают действие на паренхиматозные органы. Тяжелое отравление протекает по типу острой или подострой желтой атрофии печени. В литературе описаны случаи смертельного исхода при отравлениях на производстве хлорированными нафталинами (головаксом) и дифенилами (соволом). Местное действие совола и головакса выражается в поражениях кожи типа акнеформных и эритематозно-везикулярных дерматитов.

Условия труда при работе с хлорвиниловыми пластическими массами изучались нами в заводских условиях в цехе хлорвиниловых пластикатов при применении хлорвинилового пластиката в качестве заменителя кожи и при применении его для изоляции электропроводов.

Производство хлорированных пластикатов. В цехе хлорированных пластикатов хлорвиниловая смола (белая порошкообразная масса) смешивалась с дибутилфталатом или с соволом в смесительных аппаратах при температуре 80—100°. Затем композицию передавали на вальцы, поверхность которых нагревалось до 130—160°.

В конце вальцевания хлорвиниловое полотно на вальцах разрезалось на узкие ленты, которые в дальнейшем сортировали и упаковывали в ящики.

При гигиеническом обследовании цеха хлорвиниловых пластикатов производились исследования воздуха рабочих помещений на содержание в нем паров совола, хлорорганических соединений и паров соляной кислоты. Полученные при этом результаты приведены в табл. 1.

В воздухе рабочих помещений цеха хлорвиниловых пластикатов, как это видно из данных, приведенных в табл. 1, концентрация хлорорганических соединений колебалась от 0,005 до 0,27 мг/л. В подготовительном отделении имело место выделение паров совола при нагреве, сливе и транспортировке его. Концентрации хлорорганических соединений, найденные в этом помещении (0,005 мг/л), с большой вероятностью могут быть отнесены главным образом за счет совола. У смесителей хлорорганические соединения были найдены в количестве от 0,01 до 0,08 мг/л, а у рабочего места вальцовщика—от 0,2 до 0,97 мг/л.

Таблица 1. Содержание хлорорганических соединений, совола и хлористого водорода в воздухе цеха хлорвиниловых пластикатов

Название отделения	Место взятия пробы	Концентрация в мг/л	
		хлорорганические соединения, в том числе совол [1]	хлористый водород
Подготовительное	В шкафу для подогрева совола	0,005	Не обнаружен
»	В середине помещения на уровне дыхания рабочего	0,003	» »
Смешения и вальцовки	У смесителя во время смешения компонентов . .	0,06—0,08	0,025
То же	У смесителя во время выгрузки композиций . . .	0,01—0,08	Не обнаружен
» »	На рабочем месте вальцовщика	0,2—0,97	0,002
» »	У стола для остывающего пластиката	0,27	Не обнаружен
Сверловочное	У рабочего места сверловщика	0,005	» »

В сортировочном отделении концентрации хлорорганических соединений обычно не превышали 0,05 мг/л. Хлористый водород мы находили лишь в отдельных пробах в количествах, не превышающих тысячных долей миллиграмма.

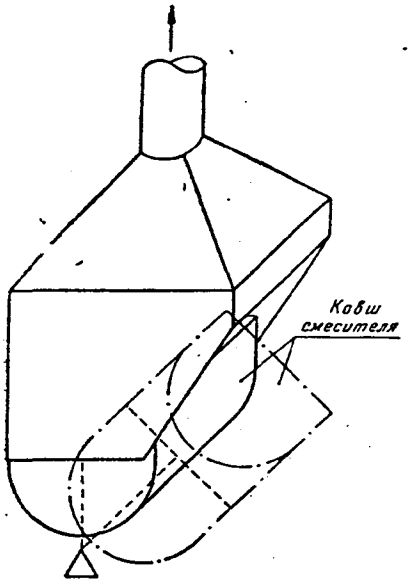

Схема шатрового укрытия смесителя

В связи с применением совола серьезную опасность представляет наличие условий для загрязнения кожи ингредиентами, входящими в состав композиции. На коже рук рабочих в конце рабочего дня мы находили хлорорганические соединения.

Для борьбы с загрязнением воздуха цех оборудован приточной и вытяжной вентиляцией с механическим побуждением. Вытяжная вентиляция устроена по принципу местной вытяжки от зонтов, установленных над основными источниками выделений газа.

Эффективность вентиляции, как показало санитарно-техническое обследование, была недостаточной вследствие того, что подача воздуха производилась со скоростью только 7—8 м/сек на уровне плеч рабочего. Неприятные ощущения, вызываемые подобным способом подачи воздуха, наряду с раздуванием и охлаждением композиции на вальцах, вынуждали рабочих перекрывать шибера душирующих патрубков и даже при этом струи воздуха, вырывающиеся через различные неплотности, сбивали работу вытяжных устройств, отклоняя конвекционные потоки, поднимающиеся от вальцов. Вместе с тем за-

крытие приточны
тяжкой и влекл
воздуха из сосе

Существенны
точная эффекти
для готовой пр
тивными оказал
смесителями в в
При производит
ностью локализ

Примене
стве замен
основным сыр
чается при по
Температура ра
катора здесь
стеарат кальция

Композиция дл
пропитанного дибу
композицию уклад
ном прессформу.
несколько минут, а

Композиция д
полихлорвиниловой
созревания на 12 ч
при температуре 1
вальцевания хлорви
ратуре 160°.

Анализы воз
хлорвиниловой

Таблица 2.

Место взятия проб	с
У вальцов . .	
У прессов . .	
В помещении сварочной	

Хлорорганич
обработке хлор
молекулы хлор
ных соединений
виниловой обув
0,14 до 1,2 мг/л
в концентрация
определении) о
до 0,022 мг/л.

[1] В связи с недостаточной разработанностью метода раздельного определения хлорорганических соединений производилось их суммарное определение.

крытие приточных патрубков нарушало баланс между притоком и вытяжкой и влекло за собой неорганизованное поступление загрязненного воздуха из соседних помещений.

Существенным дефектом вентиляционной системы являлась недостаточная эффективность малоемких зонтов, установленных над столами для готовой продукции и над смесителями. Значительно более эффективными оказались осуществленные по нашему проекту укрытия над смесителями в виде шатров с открытой передней стенкой (см. рисунок). При производительности в 1 000 м³/час эти укрытия практически полностью локализовали выделения вредностей.

Применение хлорвиниловых пластикатов в качестве заменителей кожи. В производстве хлорвиниловой обуви основным сырьем является полихлорвиниловая смола, которая получается при полимеризации хлорвинила водноэмульсионным способом. Температура разложения этой смолы 130—150°. В качестве пластификатора здесь применяется дибутилфталат, а стабилизатором служит стеарат кальция.

Композиция для подошвы приготовляется путем смешения текстильного лоскута, пропитанного дибутилфталатом, и хлорвиниловой смолы в смесителе. Полученную композицию укладывают на нагретую до 170—200° и протертую после этого вазелином прессформу. Заполненную таким образом прессформу закрывают, выдерживают несколько минут, а затем ставят на непродолжительное время под горячий пресс.

Композиция для верха обуви получается при смешении определенных количеств полихлорвиниловой смолы и дибутилфталата в мешателе. Массу оставляют здесь для созревания на 12 часов при температуре 70°. После созревания композицию вальцуют при температуре 120—140° с прибавлением стеарата кальция. Полученный после вальцевания хлорвиниловый пластикат перекладывают текстилем и прессуют при температуре 160°.

Анализы воздуха на содержание в нем вредных газов и паров в цехе хлорвиниловой обуви сведены нами в табл. 2.

Таблица 2. **Концентрация газов и паров в воздухе рабочих помещений производства хлорвиниловой обуви в мг/л**

Место взятия проб	Хлорорганические соединения			HCl			C (суммарно)			CO		
	концентрация в мг/л											
	минимальная	максимальная	средняя	минимальная	максимальная	средняя	минимальная	максимальная	средняя	минимальная	максимальная	средняя
У вальцов . .	0,14	0,48	0,35	0,028	0,036	0,032	0,07	0,35	0,21	—	—	0,022
У прессов . .	0,26	1,13	0,65	0,008	0,036	0,055	0,21	2,61	1,23	—	—	0,019
В помещении сварочной	0,53	1,2	0,92	0,03	0,17	0,23	0,10	0,68	0,23	—	—	0,01

Хлорорганические соединения, которые выделяются при термической обработке хлорвиниловой смолы, представляют собой отщепившиеся молекулы хлорвинила в различных количественных сочетаниях их цепных соединений. В воздухе рабочих помещений на производстве хлорвиниловой обуви эти соединения были найдены нами в количестве от 0,14 до 1,2 мг/л. Здесь были обнаружены также пары соляной кислоты в концентрациях от 0,008 до 0,17 мг/л, углеводороды (в суммарном их определении) от 0,21 до 2,61 мг/л и окись углерода в пределах от 0,01 до 0,022 мг/л.

Загрязнение воздушной среды хлорорганическими соединениями и парами соляной кислоты возрастало по мере повышения температуры нагрева при различных производственных операциях.

Вентиляция рабочих помещений осуществлялась с помощью нескольких вытяжных установок, первоначально предназначавшихся для местной вытяжки. Несмотря на сравнительно высокую кратность воздухообмена (10—20), эффективность вентиляции оказалась недостаточной. Основным дефектом ее было отсутствие местного удаления выделений, образующихся при обработке композиции на прессах, вальцах и при сварке обуви.

Установка зонтов над сварочными верстаками, обычно применяющихся в этом производстве, не эффективна и не может рассматриваться как местное вытяжное устройство, так как при сварке хлорвиниловой обуви газы выделяются на уровне колен сидящего сварщика в непосредственной близости от его лица. Наиболее радикальным устройством в данном случае является вертикальный вытяжной канал против каждого из рабочих мест. Удаление воздуха может производиться через отверстие в столе верстака, верхняя часть которого при этом должна быть использована как плоский вытяжной канал.

Удовлетворительный эффект наблюдался и в случае вытяжки через горизонтальные короба, располагаемые на поверхности верстака. Скорость отсоса через вытяжные отверстия должна быть не менее 6 м/сек.

Применение хлорвиниловых пластикатов для изоляции электропроводов. На заводе, где хлорвиниловый пластикат используется в качестве изоляционного материала для электропроводов, покрытие провода хлорвиниловой оболочкой производится на шприцмашинах.

Во время сушки хлорвинилового пластиката в сушильных шкафах, а также при плавке его и при выходе провода в горячей оболочке из головки шприцмашины в воздух рабочего помещения выделяются следующие летучие вещества (табл. 3).

Таблица 3

Место взятия проб	Хлорорганические соединения		HCl		C (суммарно)		CO	
	концентрация в мг/л							
	минимальная	максимальная	минимальная	максимальная	минимальная	максимальная	минимальная	максимальная
У шприцмашины в зоне дыхания рабочего . . .	0,003	0,1	0,001	0,06	0,3	0,6	—	—
Над проводом, покрытым горячей пластмассой . .	0,14	0,65	Не обнаружена	—	—	—	0,017	0,05
В середине помещения	0,004	0,088	То же	—	—	0,11	—	0,02
Над сушильным шкафом	0,10	0,14	—	0,016	0,08	0,24	—	—

В составе летучих веществ, выделяющихся при нагреве хлорвинилового пластиката до 120—140°, содержатся хлорорганические соединения в количестве от 0,003 до 0,6 мг/л, пары свободной соляной кислоты от

0,001 до 0,06 мг/л, углеводороды от 0,08 до 0,6 мг/л и окись углерода от 0,01 до 0,05 мг/л.

Вентиляция цеха осуществлялась с помощью вытяжных зонтов, установленных на телескопическом опуске над каждой головкой шприцмашины. Газы, выделявшиеся при сушке пластиката в сушильных шкафах и при остывании хлорвинилового провода после выхода из головки шприцмашины, поступали в воздух рабочего помещения, поддерживая в нем значительные концентрации токсических веществ.

Результаты медицинского обследования рабочих. Медицинскому освидетельствованию были подвергнуты выборочные группы рабочих обследованных предприятий. В цехе хлорвиниловых пластикатов было осмотрено 48 человек, преимущественно вальцовщики. При рино-ларингологическом исследовании у значительной части рабочих в верхних дыхательных путях (в носу, гортани и трахее) были обнаружены белого цвета пленки, образовавшиеся в результате смешения пыли со слизью. Эти пленки были плотны наощупь, и их трудно было удалить с поверхности слизистой оболочки. У 17 человек была установлена гиперемия слизистой оболочки верхних дыхательных путей. Явления хронического бронхита были найдены у 13 человек. Из изменений со стороны органов кровообращения должна быть отмечена сосудистая гипотония (90—100/45—50) у 13 человек, умеренная гипертония у одного, артерио-кардиосклероз — у 5 человек. Состояние желудочно-кишечного тракта характеризовалось у 10 обследованных явлениями хронического гастрита и у 2 — хронического колита. У 15 человек имелись изменения со стороны печени в форме более или менее выраженных гепатитов, сочетавшихся у 2 обследованных с явлениями холецистита.

Со стороны крови у 29 обследованных имели место низкие цифры гемоглобина: у одного — 46%, у 22—50—55%, у 6—56—60%. Формула крови и РОЭ без особенностей.

Обращает на себя внимание, что у обследованной группы отмечались заболевания кожи (акне, комедоны), в особенности на лице, шее, груди. Поражения кожи наблюдались не только у лиц, соприкасавшихся с соволом, но и у тех, кто прямого контакта с ним не имел, но работал в том же помещении. Видимо, заболевания кожи вызывались воздействием совола при сорбции его паров.

На химическом заводе было обследовано 25 женщин-работниц, преимущественно прессовщицы и сварщицы, с преобладающим стажем работы в данной профессии от 3 до 6 лет. У некоторых из них, осмотренных ото-ларинголом, оказалась различной степени гиперемия слизистых оболочек верхних дыхательных путей на всем их протяжении или только на ограниченных участках. Хронические бронхиты были выявлены у 5 человек, умеренно выраженная эмфизема легких у 3, остаточные явления плеврита у 2 человек.

Со стороны сердечно-сосудистой системы у 14 человек установлена сосудистая гипотония (R/R 90—110/55—65) и у 4 человек умеренно выраженная гипертония (R/R 140—165/80—85). Глухие тоны сердца, расширение его границ и данные электрокардиограммы: низкий зубец *T* не менее чем в 2 основных отведениях и закругленность интервала *S—T*. дали основание в нескольких случаях диагносцировать миокардиодистрофию.

В обследованной группе у 6 человек был диагносцирован гепатит. При этом у некоторых лиц отмечено одновременно заболевание печени и желудка. Ни в одном из случаев заболевания печени мы не могли констатировать в анамнезе или при осмотре признаков желтухи. В моче желчных пигментов также не было. У значительного числа осмотренных обнаружено небольшое увеличение печени без характерных жалоб и чувствительности при пальпации.

Анализируя результаты медицинского обследования, необходимо отметить, что у известной части рабочих были обнаружены изменения со стороны верхних и более глубоких дыхательных путей. Эти наблюдения подтверждаются и литературными данными.

Обращает на себя внимание высокий процент кожных поражений, что этиологически, несомненно, связано с воздействием совола.

Серьезного внимания заслуживает наличие гепатитов у некоторых рабочих, соприкасающихся с хлорвиниловой смолой и хлорвиниловыми пластикатами. Необходимы поэтому дальнейшие динамические наблюдения за состоянием здоровья рабочих, соприкасающихся с хлорвиниловой смолой и ее пластикатами, чтобы предупредить развитие серьезных поражений печени.

Выводы

1. В составе летучих веществ, образующихся при термической обработке хлорвиниловой смолы и пластикатов на производстве, входят хлорорганические соединения, углеводороды, пары свободной соляной кислоты и окись углерода.

2. Воздействие этих летучих веществ проявляется в раздражении слизистой оболочки преимущественно верхних дыхательных путей; длительное влияние высокодисперсной пыли и паров хлорвиниловой смолы вызывает, кроме того, сухость и атрофию слизистой оболочки верхних дыхательных путей, а также способствует развитию хронических бронхитов.

3. Значительное число гепатитов среди обследованных рабочих, а также изменения в верхних дыхательных путях ставят вопрос о необходимости дальнейших динамических наблюдений за состоянием здоровья рабочих и проведения ряда лечебно-профилактических мероприятий, в частности, организацию для рабочих тепловлажной (щелочной) ингаляции лекарственных веществ.

4. При применении в качестве пластификатора хлорвинилов совола у большинства рабочих наблюдались кожные поражения типа акне с преимущественной локализацией на лице и шее.

5. В целях профилактики кожных заболеваний при работе с соволом необходим следующий комплекс оздоровительных мероприятий: 1) обеспечение рабочих бельем и спецодеждой; 2) устройство душевой типа санитарного пропускника с отдельными раздевальными для домашней и рабочей одежды. При санитарном пропускнике должна быть оборудована паровая камера для пропарки белья и спецодежды при температуре 110—120° в течение часа. В цехе должны быть оборудованы умывальники с подведенной горячей и холодной водой.

6. Для оздоровления воздушной среды необходимо по возможности уменьшить степень разложения хлорвиниловой смолы при термической ее обработке. Этого можно достигнуть путем стандартизации ее термостойкости, а также путем регулирования температуры нагрева вальцов, прессов и другого оборудования, не допуская превышения ее сверх 120—130°.

Чрезвычайно важное значение имеет рационально оборудованная система вентиляции, рассчитанная на максимальное укрытие источников выделения газов, паров и пыли.

В связи с тем, что на некоторых производствах наблюдались случаи воспламенения конденсата, образующегося в вытяжных вентиляционных трубах при соприкосновении с открытым пламенем, вытяжные устройства должны проектироваться с соблюдением условий, принятых строительным законодательством для устройств, предназначенных к перемещению огнеопасных газовых смесей.

О способе ог

Из каф

Как известно
нию, получивше
в видимом пожс
витием специфи
страняется вглу

Многие авто
ния» рыбы с п
свободных непр
кислоты. Одна
«ржавлении», м
жирах. Можно
ния сложных ра
виях белковой
органического и

Обычно степ
органолептическ
ным дополнить
нами предлагае
стадии ржавлен

Первое, что
вещества «ржав
танных раствор
щим оказался
кислоты и в то
обладает и тем д
не требует какс

Второй проб
рыбы, была пр
рыбы. Альдегид
прогоркании жи
ления этот прод

Методика по
ривалась, и про
органолептическ
ной, с диффузно
ных покровов (
костей.

От каждой р
разных мест и
резали ножом н

Мелкую рыбу
скали целиком
части вырезали
а для получения
участки мяса, п

Для экстраги
щали в колбы и
этилового алкого
пробкой. Рыбы
встряхивании.
складчатый фил
каучуковой или

Donc le principal danger résulte de l'introduction de la main dans la zone dangereuse.

Sur les 42 accidents arrivés plus haut :

22 sont arrivés au moment de la fermeture du moule *mais* 10 presses n'avaient pas de sécurité, 5 insuffisamment protégées, 1 protection mal conçue, 4 mauvais fonctionnement de la sécurité, 2 ruptures du vérin de commande, 11 se sont produits à cause d'un autre organe mécanique, 9 furent causés par le montage du moule.

CONCLUSION

L'industrie des plastiques requiert des mesures de précaution qui lui sont propres, dont l'élaboration n'est nullement plus compliquée que celles qui concernent les autres industries, mais qui sont simplement adaptées au caractère particulier découlant du mode d'obtention de ces matériaux.

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2e PARTIE : TOXICOLOGIE

Aspects toxicologiques de l'industrie des matières plastiques.

Par M. Louis TRUFFERT.

Le problème toxicologique posé par l'industrie des matières plastiques est extrêmement complexe, aussi ne saurait-on le traiter complètement dans cet exposé.

On est amené à rencontrer, dans cette industrie, un nombre considérable de toxiques dont les actions peuvent se contrarier ou s'ajouter et l'on voit apparaître chaque jour de nouveaux produits dont on ignore la nocivité.

Au moment de la fabrication, on pense surtout aux dangers présentés par les matières premières utilisées, mais il faut également tenir compte des produits susceptibles de se former au cours de la réaction. Lors de l'utilisation, le dégagement de nouvelles substances peut être à craindre, du fait par exemple, d'une décomposition par la chaleur, nécessaire au moulage, ou de l'emploi de solvants pour une dissolution.

Le travail mécanique de la matière plastique peut, lui-même, être une source de poussières agressives.

Enfin, des traces d'impuretés peuvent avoir une action physiologique et, alors même qu'il n'y a aucun risque d'intoxication, des accidents allergiques peuvent se manifester.

Il importe donc d'être circonspect et d'admettre que l'on peut fort bien observer des troubles très différents de ceux auxquels l'étude toxicologique des substances mises en œuvre ou produites par les réactions, permettait de penser.

C'est ainsi par exemple que Devignevielle et Mlle Flucher [1], ont observé que le travail des résines polyvinyliques comportait une toxicité faible, mais certaine, ne s'expliquant pas par les données connues. Cette toxicité se manifestait par des troubles gastro-intestinaux, des dermites de type eczémateux et des troubles sanguins : altérations morphologiques des polynucléaires neutrophiles, éosinophilie et mononucléose.

Cette réserve étant faite, nous passerons rapidement en revue les produits finis et les matières premières utilisées, mais nous ne saurions les étudier tous et nous citerons seulement quelques exemples présentant actuellement de l'intérêt.

RÉSINES

Si les résines peuvent être considérées comme généralement inertes lorsqu'elles sont pures, il arrive cependant qu'on leur impute divers accidents du fait de la présence d'un excès d'un de leurs constituants, ou de la persistance d'un peu de monomère.

La nocivité des constituants des résines polycondensées, ou des monomères des hauts polymères, se manifeste d'ailleurs dès la fabrication et peut réapparaître lors de la décomposition du produit (sous l'influence de la chaleur par exemple).

C'est ainsi que le *polystyrène* est obtenu à partir du styrolène, dont la toxicité est notable (voir l'article de P. Dervillée, H. Desoille et L. Truffert dans l'Encyclopédie Médico-Chirurgicale).

On trouvera des renseignements à ce sujet dans un mémoire de R. Lefaux [2] qui traite également des produits suivantes : chloroprène, métacrylate de méthyle, α-chloracrylate de méthyle, nitrile acrylique, chlorure de vinyle, butadiène, héxaméthylène-diamine, di-isocryanates, polytétrafluoro-éthylène, solvants, plastifiants, etc...

La nocivité des poussières de *polyamides* a été mise en évidence par Massmann et Pilgrim [3] chez le Rat (pneumonie granuleuse par administration intratrachéale, mais rien par voie orale).

Mecheels [4] a étudié les effets physiologiques du perlon et son influence sur la flore de la peau humaine.

D'après Schultz et Hermann [5], les eczémas provoqués par les bas de perlon seraient dus à des colorants amino-azoïques ou anthraquinoniques.

Dans la fabrication des *polyuréthanes*, on utilise beaucoup les di-isocyanates, en particulier le di-isocyanate de toluylène ou Desmodur T, dont la toxicité a été signalée en France par Fuchs et Valade [6]. D'autres cas d'intoxication ont été signalés, en particulier par Swensson, Holmquist et Lundgren [7], par Johnstone [8], et par Hama [9]. Zapp [10] effectua une expérimentation animale qui montra le danger d'inhalations répétées pour des teneurs de 1 à 2 p.p.m., qui eurent des suites mortelles.

Pour les *résines époxy*, l'étude effectuée par Hine, Kodama, Anderson, Simonson et Wellington [11] a montré une toxicité relativement basse, mais des dermites peuvent être causées par des impuretés (notamment des amines).

PRODUITS D'ADDITION. — Ils sont très divers et nous ne pourrons qu'en citer quelques-uns.

Catalyseurs. — Ce sont souvent des acides (sulfurique, chlorhydrique), mais aussi des peroxydes d'aldéhydes ou de cétones. Ceux-ci ont une action très irritante sur la peau et causent des dermites. Rogers [12] a signalé le danger de combustion spontanée en présence de matières organiques, ce qui nécessite des mesures de prévention d'incendie.

Mallette et Haam [13] ont étudié divers *accélérateurs* dont la toxicité est très variable :

	Toxicité en g/kg
Dithiocarbamate de cyclopentaméthylène pyridinium (Pip-pip)	0,25
N-Isopropylbenzothiazolsulfonamide (Isocyclex)	0,25
Bis 2(benzothiazolylthio éthyl) urée (EL.60)	6
N-Cyclohexyl-N-diéthylthiocarbonyl sulfonamide (Thiopentex)	1,2

Il en est de même pour les *activateurs* étudiés également par ces auteurs :

	Toxicité en g/kg
Cyclohexylamine	0,2
Stéarate de cyclohexyl-ammonium	4
Formiate de cyclohexyl-ammonium	58

Tous irritent plus ou moins la peau et ils sont pour la plupart sensibilisants.

Parmi les *stabilisants*, on trouve à côté de sels inoffensifs (stéarates, ricinoléates, laurates, naphténates de sodium, de lithium ou de calcium), des sels de zinc, de cadmium, d'étain et surtout de plomb dont la toxicité est bien connue.

On utilise également des composés organiques d'étain tétravalent tels que dibutyl-dilaurate d'étain, ou dibutyl-étain-monopropylèneglycol-maléate-2-hydroxypropoxyde) toxiques nerveux pour lesquels il est difficile de transposer de l'animal à l'homme en ce qui concerne les déterminations de la toxicité, ce qui incite à se montrer très prudent.

Les *antioxygènes* sont très nombreux et leur toxicité est également très variable (Mallette et Haam [13] donnent les chiffres suivants :

	Toxicité en g/kg
Diamylphénol	0,62
2-6 dibutyl (tertiaire) paracrésol (Ionol)	8
Phosphite de triphényl (E.F.E.D)	0,25
Sulfure de di-4 butyl (tertiaire) métacrésol (Santowhite)	5
NN_1-di ; naphtyl-p-phénylènediamine (Agerite white)	4,5

Les *plastifiants* sont encore plus nombreux et extrêmement divers. Parmi eux, il faut noter dans les *esters phosphoriques*, le *phosphate de tri-orthocrésyle* qui est responsable d'un nombre considérable d'intoxications. Les *esters phtaliques*, sont beaucoup moins nocifs et l'on peut considérer les homologues supérieurs comme inoffensifs. J'ai administré jusqu'à 50 ml/kg de *phtalate d'heptyle* à des cobayes, sans parvenir à provoquer la mort.

L'emploi comme plastifiants de *caoutchoucs synthétiques* est très intéressant en raison de leur inocuité.

De même on peut utiliser des *esters époxy* qui sont en même temps des stabilisants du chlorure de polyvinyle et dont la toxicité paraît faible. Witnauer, Knight, Palm, Koos, Ault et Swern [14] ont étudié plus d'une vingtaine de ces produits.

Les *colorants et les charges* peuvent aussi présenter certains dangers. C'est ainsi que la question du pouvoir cancérigène du *Carbon-Black* s'est posée. Von Haam et Mallette [15] ont extrait du Carbon-Black des produits causant des cancers chez la souris, alors que d'autres auteurs affirmaient que cette matière était sans action sur les ouvriers qui l'employaient. Tout récemment Nau, Neal et Stembridge [16] ont montré que non seulement le Carbon-Black n'avait pas d'action cancérigène, mais encore que, grâce à son pouvoir absorbant, il empêchait celle d'un corps aussi actif que le méthylcholanthrène.

La présence dans les *pigments* d'éléments toxiques tels que plomb, cadmium, zinc, manganèse, chrome (à l'état de chromate), mercure, baryum, sélénium, peut constituer une source de danger. Mais celle-ci n'est pas toujours réelle, car si le pigment est pur et très insoluble, sa toxicité peut être très faible, ainsi que j'ai pu le constater pour le sulfure et le sulfo-séléniure de cadmium. C'est l'excès de sel de cadmium soluble utilisé pour la préparation, qui paraît être la cause de la toxicité de ces pigments et cet excès étant éliminé, j'ai pu administrer à des animaux, par voie orale, de fortes doses de ces deux pigments (plus de 1 g/kg) sans suite fâcheuse.

En ce qui concerne les solvants utilisés pour dissoudre les matières plastiques, je dois dire que leur nombre augmente tous les jours et que l'usage de nouveaux produits se répand de plus en plus. C'est notamment le cas des *dérivés furanniques*. Le furfural est connu depuis longtemps ; c'est un irritant, dont la concentration maximum tolérable a été fixée à 5 ppm (soit environ 20 mg/m³). Le tétrahydrofuranne paraît moins toxique (concentration maximum tolérable = 200 ppm ou 590 mg/m³). L'alcool tétrahydrofurfurylique est encore mal étudié et quant à l'alcool furfurylique, il joint à sa toxicité (concentration maximum tolérable = 50 ppm, soit 200 mg/m³) un danger d'explosion spontanée, en particulier dès qu'il se trouve en présence d'un acide, qui le résinifie (cette réaction permet d'ailleurs de fabriquer certaines matières plastiques).

PRODUITS DE DÉCOMPOSITION DES MATIÈRES PLASTIQUES

Les matières plastiques peuvent se décomposer sous l'influence de divers facteurs : lumière, chaleur, catalyseurs.

La décomposition peut donner naissance aux constituants d'origine, dont on retrouve la toxicité. C'est le cas de certaines résines formoliques qui résistent mal à la chaleur. Comme exemple de décomposition catalytique on peut citer celui du bioxyde de titane, pigment blanc très utilisé et qui incorporé dans une résine polyamide, considérée, avec raison, comme très résistante, provoquait sa dépolymérisation, avec l'action combinée des rayons solaires.

Des *produits nouveaux* peuvent se produire sous l'action de la chaleur.

Dans le cas des *thiokols*, il suffit d'une élévation de température relativement faible pour provoquer un dégagement de composés organiques soufrés : mercaptans, thioéthers, etc... La toxicité de ceux-ci, que j'ai pu mettre en évidence [17], et qui a été étudiée, notamment par Ljunggren et Norberg [18] n'a généralement pas l'occasion de se manifester, mais leur odeur très désagréable, même à des concentrations extrêmement minimes, est des plus incommodes.

Pour le *chlorure de polyvinyle*, d'après Coleman et Thomas [19], à 300° C, on a environ 30 p. 100 du chlore transformé en acide chlorhydrique, mais il ne se forme que des traces négligeables de phosgène. Au cours de la combustion il y a, en même temps, dégagement de gaz carbonique et d'oxyde de carbone.

Le *celluloïd*, lorsqu'il brûle donne naissance à de l'oxyde de carbone et surtout à des vapeurs nitreuses qui ont fait de nombreuses victimes.

Il suffit de rappeler l'accident d'une clinique de Cleveland, en 1929, où 126 personnes furent mortellement intoxiquées par les gaz résultant de la combustion de films radiographiques.

L'évolution était caractéristique des gaz suffocants du type phosgène avec ses trois périodes : suffocation, rémission, œdème pulmonaire aigu.

Mac Nally [20] a signalé que beaucoup de personnes avaient après l'accident, conduit leur voiture jusqu'à leur domicile pour succomber dans les 36 heures après l'inhalation des gaz toxiques. Il est à noter qu'en dehors de cette affaire, Mac Nally déclare avoir observé 48 cas d'intoxications par vapeurs nitreuses dont 3 mortels.

Easton [21] a relaté un cas d'incendie aux États-Unis ayant fait 492 morts et où des dérivés nitrés provenant de décors en pyroxyline avaient pu donner à la fumée leur effet toxique.

Nous avons eu personnellement connaissance, avec M. Moureu, de deux accidents :

En 1947, l'inflammation de quelques kilogrammes de paillettes de celluloïd, servant à la fabrication de couronnes funéraires, provoqua en 2 à 3 minutes la mort de 22 femmes occupant un atelier dortoir.

Les secours furent immédiats, mais sans effet, bien qu'aucune des victimes ne portât des traces de brûlures susceptibles d'entraîner la mort. Nous avons pu établir qu'un gramme de ces paillettes dégageait environ 6 mg d'oxyde de carbone et 37 mg de vapeurs nitreuses. C'était donc à ces dernières, plus toxiques, que l'on devait attribuer la mort.

En 1949, un incendie dans un studio de montage de films cinématographiques faisait trois victimes. Le cadavre de l'une d'elle était retiré intact, sans trace de brûlure, montrant que la mort était due au torrent gazeux produit par la combustion des films nitrocellulosiques.

Avec M. Moureu, nous avons constaté que l'arrosage de ces films, en masses compactes, ne fait qu'aggraver le danger, la combustion faisant place, sous l'eau, à une décomposition thermique dégageant des quantités beaucoup plus considérables de vapeurs nitreuses.

Le *polytétrafluoroéthylène* résiste beaucoup mieux à la chaleur et se décompose à une température élevée, d'une manière qui est encore très discutée.

Il provoque chez l'homme une *fièvre des fumées de polymère*, analogue à la « fièvre des fondeurs », qui a été décrite par divers auteurs (Harris, Sherwood, etc...)

La dégradation thermique du polytétrafluoroéthylène a été étudiée (dans le vide) par Madorsky, Hart et Sedlak [22]. Ils trouvèrent que la pyrolyse entre 423° C et 513° C conduit toujours à 100 p. 100 de tétrafluoroéthylène monomère.

Atkinson et Trenwith [23] ont fait passer un courant de tétrafluoroéthylène gazeux à des températures variant entre 300 et 800° C. Au-dessous de 550° C : dimérisation en octofluorocyclobutane. Entre 600 et 700° on obtient l'hexafluoropropène et deux octofluorobutènes. A 800° C se produit la décomposition des octofluorobutènes avec formation de radicaux libres, puis combinaison pour donner de l'hexafluoroéthane et des molécules non saturées, hautement polymérisées.

L'effet de ces corps est encore mal connu, mais certains peuvent présenter une toxicité assez élevée.

D. R. Hagemeyer et W. Stubblebine [24] ont fait des expériences en chauffant du polytétrafluoroéthylène et ont trouvé que lorsque la concentration de l'atmosphère en halogène ne dépassait pas 10 p.p.m. il n'y avait pratiquement pas d'effet sur la souris. Il fallait atteindre 100 p.p.m. pour provoquer la mort de cet animal et même 1 000 p.p.m. si l'exposition était très courte (30 secondes).

H. H. Schrenk [25] a relaté les expériences suivantes :

Des quantités pesées de Téflon enrobant des fils de cuivre ont été chauffées rapidemant dans un four à 800° (le téflon brûle au-dessus de 400° C). Les chats et les chiens, qui se sont montrés les plus résistants, survivaient quand 6,4 g de Téflon étaient consumés dans un courant d'air de 31,8 l/mn, mais mouraient quand 14,8 g étaient brûlés. Les morts, chez les rats et les souris, apparaissaient lorsque seulement 0,92 g de Téflon était consumé et il fallait atteindre 3,7 g pour les cobayes.

Il considère que les produits de décomposition du Téflon entre 500° et 800° sont apparemment de même toxicité. Cependant les fumées produites aux températures n'excédant pas 375° ou 390° C sont beaucoup moins toxiques que celles formées aux hautes températures.

Les fumées formées au-dessous de 300° C ne causent la mort d'aucun des animaux.

TABLEAU

EXPÉRIMENTATION SUR L'ANIMAL PAR INHALATION DES PRODUITS DE DÉCOMPOSITION THERMIQUE DU POLYTÉTRAFLUOROÉTHYLÈNE UTILISÉ COMME REVÊTEMENT D'USTENSILES DE CUISINE

ANIMAUX		TENEUR EN TÉFLON EN MG/M³	DURÉE DE CHAUFFAGE EN MN	DURÉE DE L'EXPOSITION EN MN	OBSERVATIONS
ESPÈCE	POIDS moyen EN G				
COBAYE	452	179	6	30	Aucun symptôme.
	450	330	6	60	—
	587	525	6	60	—
	550	970	8	60	Légère irritation. Rémission rapide.
	545	3 340	8	60	Irritation des muqueuses, larmoiement, suffocation.
LAPIN	3 355	515	8	60	Aucun symptôme.
	3 150	974	9	60	Légère irritation, Rémission rapide.
RAT	272	1 023	9	60	Légère irritation. Rémission rapide.
SOURIS	34	978	10	60	Légère irritation. Rémission rapide.

Un animal (sur 4) est mort dans les 36 heures suivantes On a trouvé à l'autopsie une une congestion pulmonaire presque totale et des lésions gastriques.

Les produits de décomposition ont provoqué une irritation des voies respiratoires et des dégénérescences du foie, des reins, et du cerveau des animaux. Les tissus des animaux survivants étaient normaux, sauf pour l'irritation résiduelle des poumons et une dégénérescence occasionnelle du foie. La spectrométrie infra rouge des produits de décomposition a montré la présence des bandes du perfluoro-isobutène et du difluorure d'oxygène.

Nous avons effectué des essais sur l'animal en chauffant rapidement à l'aide d'un épiradiateur des plaquettes d'aluminium revêtues de polytétrafluoroéthylène, jusqu'à commencement de fusion du métal (P.F. = 658° C). Les résultats, consignés dans le tableau I, ont montré que la ménagère utilisant des ustensiles culinaires de ce type, ne courrait aucun risque en les oubliant sur le feu, les concentrations atteintes étant très inférieures à la teneur dangereuse.

CONCLUSIONS

Cette étude rapide a montré combien étaient complexes les problèmes toxicologiques qui pouvaient se poser dans l'industrie des matières plastiques. Pour les résoudre, il est nécessaire d'avoir recours aux branches les plus diverses de la toxicologie. C'est pourquoi le médecin d'usine devra toujours garder son attention en éveil, afin d'éviter que des manifestations toxiques nouvelles ne passent inaperçues.

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DISCUSSION

M. G. W. BOWLEY (*Technical Service and Development Department Imperial Chemical Industries Limited Plastics Division*), a donné les réponses suivantes aux questions posées au cours de la discussion :

1° *Avez-vous eu connaissance d'un accident survenu à une personne ayant fumé une cigarette souillée par du* Téflon ?

Je tiens à préciser que mes observations concernent le « Fluon » (P.T.F.E.) fabriqué par I.C.I. en Angleterre et non le « Téflon » qui est, comme vous le savez, fabriqué par Du Pont de Nemours aux U.S.A. Toutefois, ces deux produits sont chimiquement les mêmes et il n'y a pas de raison de croire que leurs toxicités diffèrent en quoi que ce soit. Je propose par conséquent que le produit soit désigné par son nom chimique polytétrafluoroéthylène (P.T.F.E.) et que soit évité l'emploi des désignations commerciales.

Il est à peu près certain, mais non démontré, qu'au moins quelques-uns des cas de fièvre des fumées de polymères signalés dans les articles décrivant les effets toxiques des produits de décomposition du polyfluoroéthylène peuvent être attribués au fait de fumer du tabac souillé de P.T.F.E.

2° *Que pensez-vous de la publicité faite autour de cette question ?*

Beaucoup de publicité indésirable a été faite autour de la mort prétendue survenue aux U.S.A. après avoir fumé une cigarette souillée de P.T.F.E.

Ce renseignement a paru dans un mémoire publié par le *National Advisory Council for Aeronaulics* (U.S.A.) en septembre 1956.

Des enquêtes très poussées du Ministère Britannique de la Ressource et de la I.C.I. ont abouti à la conclusion que de tels décès ne se sont pas produits.

Il est très troublant par conséquent de constater que cette rumeur non fondée persiste toujours et beaucoup de tort a été fait au développement du P.T.F.E. par suite de l'exagération de la toxicité que son emploi comporterait.

3° *Avez-vous constaté des troubles à la suite de l'utilisation du* Téflon ?

A ma connaissance, aucun usager au stade de la consommation n'a jamais éprouvé d'effets toxiques.

On ne peut pas en dire autant cependant des gens qui produisent le P.T.F.E. et un certain nombre de cas de fièvre des fumées de polymère ont été signalés, notamment au cours des débuts de la fabrication du produit.

Ces cas ont été provoqués habituellement par l'absence d'une ventilation adéquate pendant le procédé de frittage (chauffage à 380° C). L'expérience a montré que là où le P.T.F.E. est fabriqué dans des ateliers bien ventilés et qu'une ventilation locale aspirante est appliquée aux endroits où le produit est fritté (par exemple four ouvrant sur l'extérieur de l'immeuble); aucun effet pernicieux n'a été observé.

4° *Pensez-vous que l'emploi du* Téflon *dans l'industrie constitue une source importante de danger ?*

Le P.T.F.E. ne constitue pas un danger important dans l'industrie. Pour des raisons mécaniques ou autres, il n'est pas possible normalement de travailler les consti-

tuants du P.T.F.E. en continu à une température au-dessous de 300° C, bien que de courtes périodes au-dessus de 300° C peuvent être mise en œuvre. Il n'y a aucun rapport que quiconque ait souffert de maux dus au P.T.F.E. en dessous de 350° C.

5° *Avez-vous effectivement constaté un état de panique parmi les personnes utilisant et connaissant bien* le Téflon ?

Les personnes qui manipulent le P.T.F.E. ne doivent pas avoir de raisons de s'alarmer. Tous les fabricants du polymère recommandent une bonne ventilation quand le produit est fritté, et que l'on prenne soin d'éviter la contamination du tabac. Je suis à même de discerner cependant que bien que beaucoup de fabricants aient installé un système de ventilation convenable, pas tous n'imposent une règle « Interdiction de fumer » dans leurs ateliers.

Pour résumer tout cela il y a une toxicité due au hasard dans la fabrication du P.T.F.E. mais elle peut être évitée en prenant des précautions simples et sûres. Les dangers certainement courus ne justifient pas les rumeurs malveillantes qui continuent à circuler.

Je voudrais profiter de cette occasion pour vous dire combien j'ai été heureux de vous rencontrer à la récente conférence et que j'envisage nos futures rencontres dans le même état d'esprit.

La technologie des matières plastiques.

Par M. V. JANS.

Les matières de base de la fabrication des matières plastiques ne présentent qu'exceptionnellement les propriétés requises, à l'état pur. Une préparation de la matière plastique consistant très souvent à opérer un mélange d'une résine synthétique avec des adjuvants qui se présenteront à l'état solide ou liquide, est nécessaire.

L'homogénéisation s'opère dans des appareils de divers types, soit à cuve (mélangeurs-masticateurs, pétrisseurs-malaxeurs, mélangeurs-malaxeurs, dont la plupart sont analogues à ceux utilisés dans l'industrie du caoutchouc), soit à cylindres (mélangeurs à cylindres, employés notamment pour la plupart des thermoplastiques) et ce n'est qu'après cette opération comportant parfois l'incorporation de nombreux ingrédients que sera obtenue la « matière plastique » telle qu'elle sera travaillée.

Dans le cas de résines relativement faciles à amener à l'état liquide, la matière première, par exemple, un phénoplaste ou un aminoplaste, est introduite, avec les ingrédients appropriés, dans des autoclaves verticaux à agitateurs ; le mélange liquide est évacué, il se solidifie, puis il est concassé.

Les poudres à mouler thermodurcissables sont, en général amenées sous forme d'un sable grossier, celles à base de matières thermoplastiques sont obtenues à partir de feuilles que l'on a déchiquetées et amenées à l'état de rognures, flocons ou petits cubes. Bien souvent également, les matières plastiques sont préformées, c'est-à-dire réduites à l'état de formes simples (pastilles, tablettes, etc.) de poids connu.

Les principaux produits d'addition utilisés à cette phase des opérations sont :

Les STABILISANTS, agents destinés à empêcher, ou, tout au moins retarder, le vieillissement de la matière plastique en permettant à cette dernière de conserver ses propriétés essentielles en résistant aux effets de la lumière, de l'humidité, des variations de température.

Bon nombre de ces stabilisants renferment des produits toxiques et leur emploi pose des problèmes techniques qui n'ont pas toujours reçu une solution entièrement satisfaisante.

Les PLASTIFIANTS tendent à modifier dans le sens de la plasticité le produit auquel on les incorpore, en même temps qu'à apporter certaines améliorations comme celle

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WEEKLY REPORT

For Week Ending February 9, 1974

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE

DATE OF RELEASE: FEBRUARY 15, 1974 – ATLANTA, GEORGIA 30333

EPIDEMIOLOGIC NOTES AND REPORTS

ANGIOSARCOMA OF THE LIVER AMONG POLYVINYL CHLORIDE WORKERS – Kentucky

Between September 1967 and December 1973, 4 cases of angiosarcoma of the liver were diagnosed among men employed in the polyvinyl chloride polymerization section of a B.F. Goodrich plant near Louisville, Kentucky. This section of the plant began operations in 1938. It employs about 270 persons and produces polyvinyl chloride as well as a variety of copolymers by polymerization of vinyl chloride monomer. All 4 men had worked continuously in the section for at least 14 years prior to onset of illness (Table 1); all 4 had worked directly in various phases of the polymerization process.

Case 1 presented in August 1967 with an epigastric mass and thrombocytopenia. An exploratory laparotomy was performed in September 1967; liver biopsy revealed angiosarcoma. Case 2 presented in January 1970 with gastrointestinal (GI) bleeding. Recurrent bleeding in May 1970 led to an exploratory laparotomy at which time a diagnosis of angiosarcoma was made on liver biopsy. Case 3 presented in January 1964 with GI bleeding which recurred in May 1965 with

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TABLE I. CASES OF SPECIFIED NOTIFIABLE DISEASES: UNITED STATES
(Cumulative totals include revised and delayed reports through previous weeks)

DISEASE	6th WEEK ENDING		MEDIAN 1969-1973	CUMULATIVE, FIRST 6 WEEKS		MEDIAN 1969-1973
	February 9, 1974	February 10, 1973		1974	1973	
Aseptic meningitis	34	29	35	213	238	218
Brucellosis	1	3	1	9	11	11
Chickenpox	3,609	5,305	– – –	18,811	27,061	– – –
Diphtheria	1	2	2	7	12	17
Encephalitis:						
Primary: Arthropod-borne and unspecified	19	21	18	86	95	120
Post-Infectious	12	4	5	27	20	26
Hepatitis, Viral:						
Type B	135	120	128	934	805	805
Type A	871	1,027	1,067	4,914	5,775	6,407
Type unspecified	153			812		
Malaria	6	6	39	18	17	243
Measles (rubeola)	521	704	704	2,414	3,461	3,663
Meningococcal infections, total	34	34	50	156	174	331
Civilian	34	34	49	156	166	307
Military	–	–	2	–	8	15
Mumps	1,762	2,145	2,502	9,148	10,400	12,594
Pertussis	72	– – –	– – –	182	– – –	– – –
Rubella (German measles)	258	441	823	1,098	2,269	2,964
Tetanus	2	1	1	6	6	6
Tuberculosis, new active	529	562	– – –	3,040	3,027	– – –
Tularemia	2	2	2	10	10	10
Typhoid fever	6	4	4	35	22	26
Typhus, tick-borne (Rky. Mt. spotted fever)	–	1	–	12	6	3
Venereal Diseases:						
Gonorrhea	16,810	14,259	– – –	97,831	85,951	– – –
Syphilis, primary and secondary	462	516	– – –	2,661	2,917	– – –
Rabies in animals	43	69	67	267	327	347

TABLE II. NOTIFIABLE DISEASES OF LOW FREQUENCY

	Cum.		Cum.
Anthrax:	1	Poliomyelitis, total:	–
Botulism: Wash. 2	2	Paralytic:	–
Congenital rubella syndrome: Ida. 1, Tex. 1	7	Psittacosis: Tex. 1	2
Leprosy: Hawaii 1	4	Rabies in man:	–
Leptospirosis: Hawaii 1, Ida. 1	6	Trichinosis: N.Y.C. 1, Okla. 1	13
Plague:	–	Typhus, murine: Calif. 1, Va. 1	2

ANGIOSARCOMA – Continued

signs of portal hypertension. A portacaval shunt was performed, and liver biopsy yielded a diagnosis of cirrhosis. Repeat biopsies in October 1970 and September 1972 confirmed this diagnosis. Autopsy in March 1973 revealed angiosarcoma. Case 4 presented in July 1973 with hepatosplenomegaly, weight loss, and jaundice. Two liver biopsies were interpreted as showing severe cirrhosis. Autopsy in December 1973 revealed angiosarcoma.

In each case, pathologic material revealed the presence of extensive cirrhosis of a non-alcoholic type in addition to angiosarcoma. In 2 cases, the diagnosis of angiosarcoma was made only at autopsy, cirrhosis having been diagnosed 7 years before in Case 3 and 5 months before in Case 4. None of the patients gave histories of prolonged alcohol use or exposure to hepatotoxins outside their work place. In particular, none had ever had exposure to thorium dioxide or to arsenic, 2 materials known specifically to induce hepatic angiosarcoma in man *(1,2)*.

(Reported by John Creech, M.D., Plant Physician, B.F. Goodrich Chemical Company, Louisville, Kentucky; Maurice N. Johnson, M.D., Director of Environmental Health, B.F. Goodrich Chemical Company, Akron, Ohio; Bradford Block, M.D., Medical Consultant, Kentucky Occupational Safety and Health Administration, Kentucky State Department of Labor; National Institute for Occupational Safety and Health, and the Cancer and Birth Defects Division, Bureau of Epidemiology, CDC.)

Editorial Note

Angiosarcoma of the liver is an exceedingly rare tumor. It is estimated that only about 25 such cases occur each year in the United States. Four cases, therefore, among a small number of workers at a single plant is a most unusual event, and one which raises the possibility of some work-related carcinogen, conceivably vinyl chloride itself. Although no data are yet available concerning the occurrence of angiosarcoma among workers at other vinyl chloride plants in the United States, it seems distinctly possible that the problem may be industry-wide. Epidemiologic studies have started to determine the extent of the problem in the United State with respect both to angiosarcoma of the liver and to its po sible relationship to post-toxic cirrhosis.

Table 1
Cases of Angiosarcoma of the Liver among Polyvinyl Chloride Workers
B. F. Goodrich Plant
Louisville, Kentucky

Case	Age at illness onset	Date of			Years worked with PVC before illness
		Illness onset	Diagnosis	Death	
1	43	Aug. 1967	Sept. 1967	Jan. 7, 1968	17
2	36	Jan. 1970	May 1970	Sept. 27, 1971	14
3	41	Jan. 1964	Mar. 1973	Mar. 3, 1973	14
4	58	July 1973	Dec. 1973	Dec. 19, 1973	27

Published data concerning the potential hepato-toxicity and oncogenicity of vinyl chloride are limited. Studies in Germany have suggested a link between hepatic damage and occupational exposure to vinyl chloride *(3)*, while Italian workers have suggested that vinyl chloride may cause a wide variety of tumors in animals *(4)*. The chemical concentrations used in these latter experiments, however, far exceed levels likely to be encountered in industrial environments. Efforts to confirm such observations and to measure effects at lower dose levels are now in progress.

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WILD MUSHROOM POISONING – Pennsylvania

On October 9, 1973, 37 nuns ate their evening meal at a convent in Berks County, Pennsylvania. Between ¾ and 4¼ hours later (median—approximately 2 hours), 17 nuns developed an illness characterized by profuse sweating (76%), watery diarrhea (76%), chills (58%), and abdominal pain (42%) (Table 2). Six of the nuns were hospitalized; none died.

Food-specific attack rates for foods ingested in the 24 hours before illness strongly implicated mushrooms as the intoxicating food (Table 3). Stool specimens from 4 of the ill nuns and bacteriologic cultures of the remaining mushrooms yielded no enteric pathogens. Remnants of the mushrooms were identified as *Clitocybe sp.* and *Lepiota sp.* Some species of the former genus are known to contain muscarine, which produces parasympathomimetic effects.

The mushrooms had been picked on the grounds of the convent on the afternoon of the outbreak. For several years, the nuns had eaten these mushrooms at meals, and no apparent illness had occurred. On October 9, however, the nun who

Table 2
Symptoms in 17 Ill Nuns
Berks County Convent – October 9, 1973

Symptom	Percent with Symptom
Diarrhea	76
Sweating	76
Chills	58
Abdominal pain	42
Nausea	35
Vomiting	23
Excessive salivation	23
Feverish feeling	18
Dry mouth	12
Blurred vision	12
Headache	6
Weakness	6
Faint feeling	6

(Continued on page 55)

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