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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 ⅓ 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.

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.

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

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URINARY UROBILINOGEN	PROTHROMBIN
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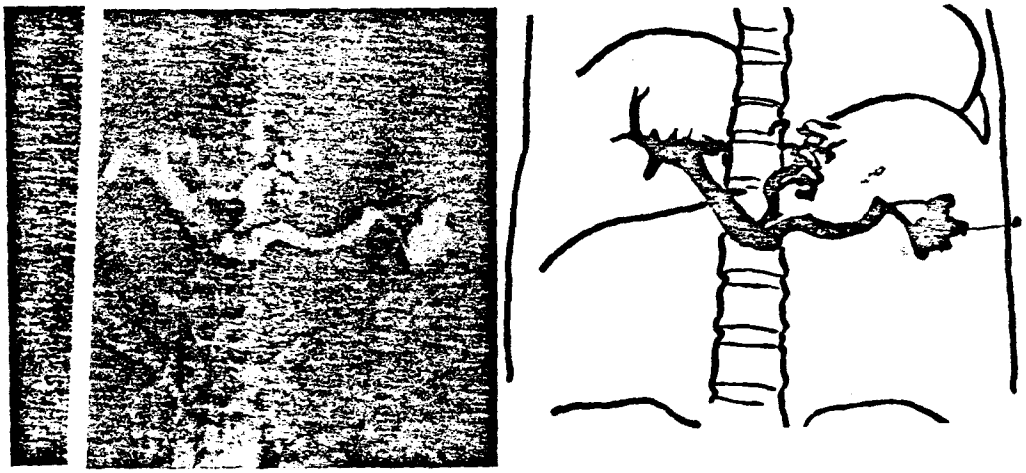
careful insp ı at laparotomy demonstrated a
patent, some dilated, portal system with definite
elevation of ortal pressure. Two generous liver-



A B

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

biopsy sı ns obtained two years apart demon-
strated o ıall and inconstant zones of periportal
congestic th no apparent progression or altera-
tion in vo-year interval. Serial liver-function
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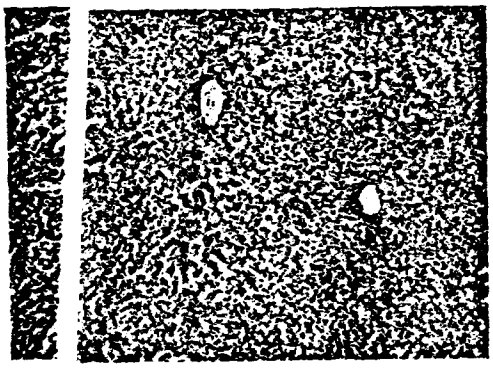
occasior interpreted as being due to post-trans-
fusion l sis. The changes in the spleen were
simply of mild chronic passive congestion.



FIGUR *ıotomicrograph of the Operative Liver-Biopsy*
Speciı Case 1, Showing Preservation of the Lobular
Patter a Normal Relation of the Portal Triad and
Centr (Masson Stain — Original Magnification X20).

Th inite portal-vein hypertension leading to
rupti sophageal varices occurred in the absence
of ar onstrable 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.

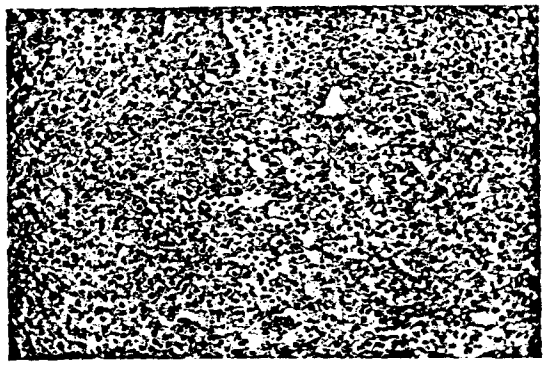


FIGURE 3. *Higher Magnification of the Specimen in Figure 2, Showing a Normal Parenchyma, with Dilatation of the Mid-Zonal Sinusoids and Moderate Intrasinusoidal Collections of Mononuclear Cells (Hematoxylin and Eosin Stain — Original Magnification X40).*

The family history was unremarkable.

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

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

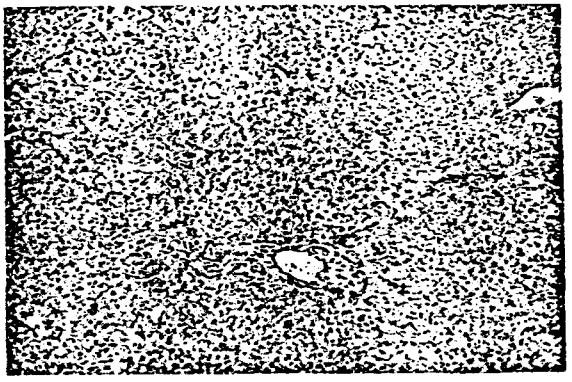


FIGURE 4. *Needle-Biopsy Specimen of the Liver in Case 2, Showing a Normal Lobular Pattern, with an Intact Central Vein and a Portal Triad with Slight Stellate Scarring (Hematoxylin and Eosin Stain — Original Magnification X20).*

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.

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.

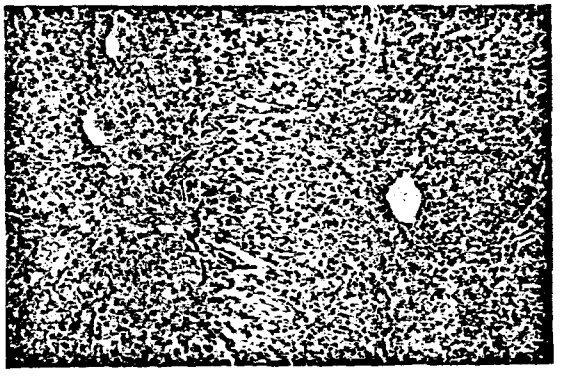


FIGURE 5. *Photomicrograph of the Operative Liver-Biopsy Specimen in Case 3, Demonstrating a Normal Lobular Pattern, Moderate Stellate Scarring of a Triad and Minimal Round-Cell Infiltration (Hematoxylin and Eosin Stain — Original Magnification X20).*

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.

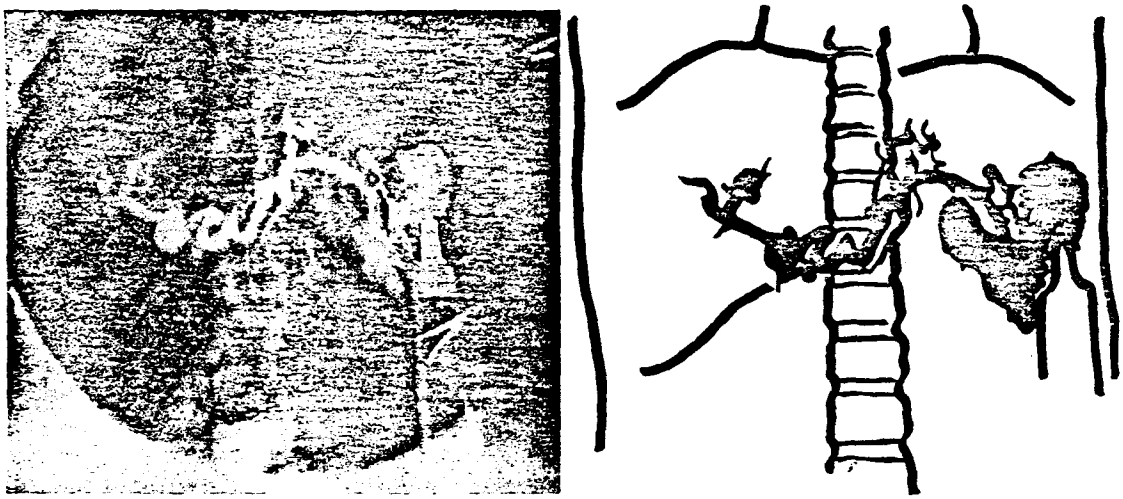


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FIGURE 6. *Operative Splenoportogram* (A) *and Tracing* (B) *in Case 4. The splenic and portal veins are tortuous but patent, and there is filling of several collateral vessels, including esophageal varices.*

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.

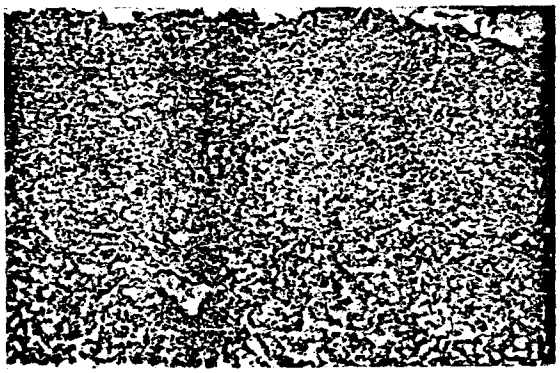

FIGURE 7. *Needle-Biopsy Specimen of the Liver in Case 4 Obtained Four Years after Splenorenal Shunt, Demonstrating a Normal Lobular Architecture, with an Intact Central Vein and Moderate Dilatation of the Mid-Zonal Sinusoids (Masson Stain — Original Magnification X20).*

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[3]: 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 splenic veins and borderline hypertension.[26] Hunt[16] has recorded portal pressures of up to 390 mm. of saline solution in patients with the splenomegaly of myelosclerosis and primary splenic anemia. Although simple splenectomy is rarely considered the operation of choice in cases with splenomegaly and portal hypertension, dramatic lowering of portal pressure and cessation of variceal bleeding may follow this procedure,[16] suggesting that the venous return from the spleen affects the portal pressure directly.

Finally, in considering possible causes of increased portal blood flow that may result in portal hypertension, disturbances of the intrahepatic arteriovenous circulation must be evaluated. That distorted vascular channels within the livers of patients with cirrhosis may produce increased portal blood flow was demonstrated by Herrick.[27] Dock,[28] on the basis of perfusion studies of normal and cirrhotic livers, concluded that increased blood flow through the hepatic artery accounts in large part for the portal hypertension frequently observed in patients with alcoholic cirrhosis. Ligation of the hepatic artery of cirrhotic patients has been performed to decrease intrahepatic blood flow and thus to lower portal pressure.[29] It is possible that similar abnormal arteriovenous anastomoses, perhaps accompanied by increased blood flow through the portal vein or hepatic artery, were present in the livers of the 4 patients under discussion. If such vascular lesions were small and erratically distributed, they could have escaped detection by both splenoportographic studies and microscopical examination of liver-biopsy specimens.

We were unable in this study to demonstrate the factors responsible for portal hypertension in our 4 patients. Gross and microscopical structural lesions capable of producing increased resistance to flow within the portal vein and its intrahepatic radicles appear to have been excluded. However, the possibility of increased vascular resistance due to functional changes, such as increased venous tone of the portal trunk and its intrahepatic branches, has not been ruled out. Such vasomotor reactions seem to maintain portal venous pressure at normal levels after acute experimental alterations in portal blood flow,[30] but their role in clinical disease of the portal system has yet to be elucidated.

Increased portal blood flow seems the most likely cause of the venous hypertension observed in the cases under discussion. Although gross arteriovenous anastomoses involving the splenic and portal veins were not found, functional or structural alterations of the vessels of the gastrointestinal tract, spleen and the liver may have permitted increased flow of blood into the portal vein, with a resultant rise in pressure. Despite the compensatory dilatation of the main portal vessels and the opening of numerous venous collaterals, portal pressures remained 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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