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Sinusoidal portal hypertension

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Portal hypertension in infants and young adults is mainly of the presinusoidal type and is caused by portal vein obstruction or congenital hepatic fibrosis. Postsinusoidal obstructions are due to cirrhosis from hepatitis or various rare metabolic disorders. There remains a group of patients whose portal hypertension is referred to as "idiopathic" because no anatomic lesion can be demonstrated. The purpose of the present paper is to present a new type of intrahepatic obstruction, localized to the hepatic sinusoids and perisinusoidal areas.

CASE REPORTS

Case 1. E. O. F., a 7-year-old boy, product of a normal pregnancy and delivery, had a normal neonatal period. At 10 months of age, he developed an acute abdominal condition, and emergency laparotomy revealed a marked mesenteric adenitis whose nature was obscure. During the following two years, he experienced several episodes of melena and the spleen became enlarged. At the age of 3 he was admitted because of hematemesis, melena, and anemia. A barium swallow demonstrated esophageal varices (Fig. 1*A*), and he had splenomegaly with signs of hypersplenism. Splenoportograms (Fig. 1*B*) revealed patent splenic and portal veins and several portosystemic anastomoses. The intrahepatic portal vein radicals were slightly irregular and more closely approximated than usual, and the radiographs were considered indicative of a hepatic cirrhosis. Splenic pulp pressure was above 60 cm. H_2O.

For the next three years, there were a few mild episodes of melena, but at the age of 6½ years the patient was readmitted because of severe hemorrhage. At this time he had ascites, splenomegaly, hepatomegaly, thrombocytopenia (50,000), hypoprotalnemia (5.8 Gm. percent), and a PP (prothrombin-proconvertin) reading of 70 percent. Results of tests for erythrocyte sedimentation rate (ESR), serum glutamic oxalacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), thymol, and serum electrophoresis were within normal values.

Due to acute deterioration, with increasing ascites and abdominal pain, he was again operated upon as an emergency procedure. There were numerous intraperitoneal adhesions with dilated vessels. Surprisingly, the liver had a normal appearance and consistency. The spleen, which weighed 440 grams, was removed. Direct splenic vein pressure was 13 cm. H_2O and identical with the central venous pressure (CVP). The pressure was recorded independently by both surgeons, and we consider the result as reliable, but have no explanation for the discrepancy between the transoperative recording and the pressure obtained by splenic pulp puncture.

The postoperative course was uneventful, without hemorrhage or other complications. On the eighth day the platelet count was 210,000, and serum proteins also were normal. Celiac arteriography demonstrated a normal arterial supply of the liver and upper gastrointestinal tract. The patient was discharged three weeks after surgery.

At follow-up examination three months later, the general condition was considerably improved. There had been no gastrointestinal bleeding, ascites was barely demonstrable, and the patient had gained weight. Results of laboratory tests were grossly normal. Esophageal varices were still demonstrable by x-ray-examination, but appeared diminished as compared with preoperative radiographs.

Case 2. O. Ø., a 29-year-old man, had had a normal neonatal period, and there had been no liver disease or hereditary disorders in the family. At the age of 3, he had been operated upon for a perforated appendix with peritonitis. He had experienced episodes of melena at ages 19 and 27, but was not hospitalized. Heavy hematemesis and melena with syncope led to emergency admission at the age of 29. At this time, an enlarged spleen was detected, and there were slightly abnormal values of the tests for Bromsulphalein (BSP) and alkaline phosphatase. Results of tests for thymol, SGOT, SGPT, and serum electrophoresis were normal.

Esophageal varices were clearly demonstrable by x-ray-examination. The portal vein with intrahepatic radicals was normal. Splenic pulp pressure was 30 cm. H_2O. Arteriography (Fig. 1*C*) revealed a normal pattern of hepatic arteries. Venography of hepatic veins showed a rapid filling at the central vein level, and a marked shunting between the larger vein radicals (Fig. 1*D*). Recording with the catheter in wedge position gave a pressure of 8 cm. H_2O but, because of the extensive shunting, this may merely represent the CVP in the vena cava.

Splenectomy and splenorenal shunt were then performed. The congested spleen weighed 720 grams; otherwise no intra-abdominal disorder was detected. The liver, in particular, appeared normal upon inspection and palpation. Shunt flow at operation was 300 ml. per minute.

The postoperative course was unremarkable, and the patient was discharged 13 days after the operation. At follow-up examination four months later, he was in good health and had not experienced any episodes of hemorrhage. Results of all laboratory tests were normal, including x-rays of the esophagus.

Macroscopic examinations of Cases 1 and 2. At operation, the liver did not exhibit any gross lesions in either case. The surfaces of both lobes were smooth and glistening, and the parenchyma showed a normal color. Upon thorough palpation, the consistency was normally soft, without nodules, bands, or firmer areas. This observation was surprising because both case histories and the preoperative x-ray studies were suggestive of hepatic cirrhosis.

A large, wedge-shaped biopsy specimen, with a depth of 4 cm., was taken from the anterior aspect of the left lobe in both patients. In Case 2, pieces 2 by 2 mm. from several areas were immediately immersed in glutaraldehyde and processed for electron microscopy.

Light microscopy of Cases 1 and 2. The specimens were processed according to standard methods and sections were stained with hematoxylin and eosin, van Gieson–elastin, Masson's trichrome stain, periodic acid-Schiff (PAS), Best's carmine, reticulin (Wilder), iron-hematoxylin, methyl green-pyronine, and Congo red. The microscopical pictures in the two cases appeared identical, and will be described together.

The specimens presented a normal liver architecture, with well-preserved lobules separated by normal portal triads. The capsule of Glisson appeared normal, and there was no increase in connective tissue along the portal triads. The portal veins, small arteries, and bile ducts were also normal (Fig. 2*A*), without evidence of fibrosis, bile duct proliferation, or inflammatory reactions. The only abnormal feature of the periportal areas was a moderate dilatation of some lymph vessels.

The parenchymal liver cells were normal in all areas (Figs. 2*A* and 2*D*), with well-preserved cytoplasm and normal contents of glycogen. There were no signs of degeneration, fatty changes, necrosis, cellular infiltration, giant-cell transformation, or pseudolobule formation.

The central veins were patent and normally configurated; some had a slightly larger diameter than usual. Upon close examination, a certain increase of connective tissue elements could be seen around the central veins (Fig. 2*B*). By means of special staining, this impression was verified, and in several areas the strands of connective tissue could be followed in between the hepatic cells, that is, along the hepatic sinusoids (Figs. 2*C* and 2*D*). This observation prompted us to investigate the morphology of the sinusoidal/parasinusoidal areas by means of electron microscopy.

Electron microscopy of Case 2. Specimens were kept in the 2.5 percent glutaraldehyde solution for 2 hours at 4° C., postfixed in osmium tetroxide for 4 hours, dehydrated in graded ethanols, and embedded in Epon 812. Thin (0.5 mμ) sections for light microscopy were stained with alkaline toluidine blue, and ultrathin (0.1 mμ) sections were stained with uranyl acetate and lead citrate and examined in a Siemens Elmiskop 1.

When examined by electron microscopy, the hepatocytes showed a normal appearance with well-preserved cytoplasmic elements (Fig. 3*A*), and the cell borders were normally configurated. The light microscopic impression of normal portal triads and periportal areas was also verified. The bile canaliculi and their surrounding structures presented the usual morphological picture (Fig. 3*A*), and there was no increase of connective tissue in these regions.

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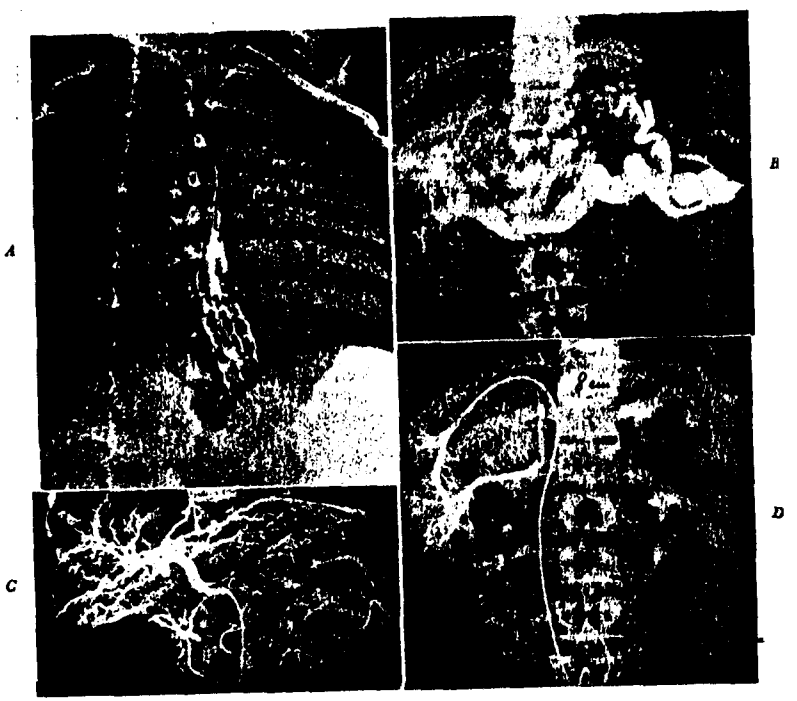

Fig. 1*A*. Case 1. Esophageal varices demonstrated on barium swallow.
Fig. 1*B*. Case 1. Splenoportogram. Portal vein and intrahepatic portal radicals patent; coronary vein heavily distended with anastomoses to splenoportal system.
Fig. 1*C*. Case 2. Arteriogram of celiac axis. Normal hepatic arterial supply.
Fig. 1*D*. Case 2. Venography of hepatic vein with catheter in wedge position. Smaller hepatic vein branches visualized but marked shunting between larger hepatic vein radicals.

Fig. 2*A*. Case 1. Light micrograph of portal triad with normal portal vein branches *(PV)*, arterioles *(A)*, and bile capillaries *(BC)*. (Hematoxylin and eosin; ×100.)

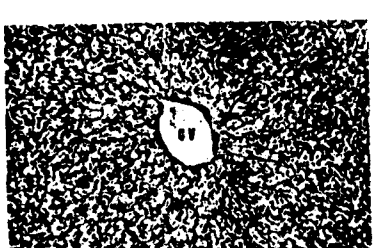

Fig. 2*B*. Case 1. Normal architecture of liver lobule around central vein *(CV)*. Deposits of connective tissue around margin. (Reticulin [Wilder]; ×100.)

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Key: *BC*, Bile canaliculus; *H* or *HC*, hepatocyte; *IS*, intercellular space; *LY*, lysosomal body; *COL*, collagen; *KC*, Kupffer cell; *N*, Kupffer cell nucleus; *RBC*, red blood cell.

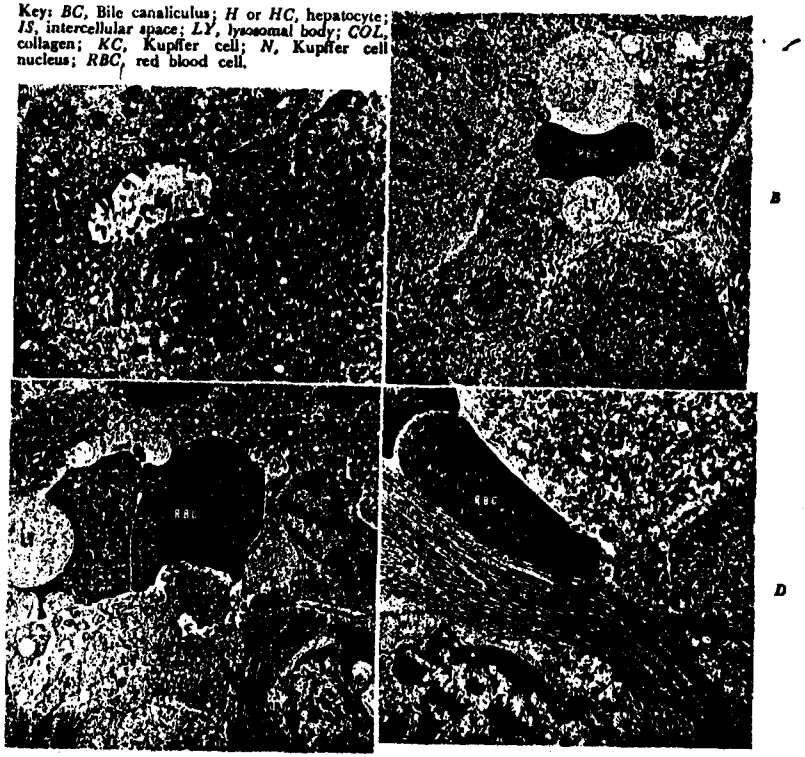

Fig. 3A. Case 2. Electron micrograph of 3 normal hepatocytes facing BC. H separated by IS which are normally configurated. No indication of cellulardamage or intercellular fibrosis. (×15,000.)
Fig. 3*B*. Electron micrograph of hepatic sinusoid. Enlarged *KC* with large *LY* are lining narrow sinusoid, which contains *RBC*. Bundles of *COL* in space of Disse. *HC* present normal morphology. (×12,000.)
Fig. 3*C*. Large sinusoid with perisinusoidal area. *LY* in enlarged *KC* seem to make impressions of *RBC* in sinusoidal lumen. Heavy amounts of *COL* fibers in perisinusoidal areas. (×12,000.)
Fig. 3*D*. Bundles of *COL* appear to obliterate space of Disse between *HC* and sinusoidal lumen. Sickle-shaped *RBC* inside sinusoid. Large *LY* within cytoplasm of *KC*. (×24,000.)

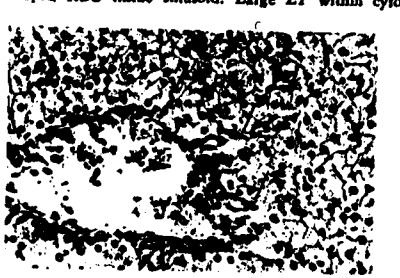

Fig. 2*C*. Connective tissue elements at periphery of central vein extend along the sinusoids and between parenchymal cells. Strands of collagen indicated by arrows. (Masson's trichrome; ×400.)

Fig. 2*D*. Case 2. Large Kupffer cells *(K)* along narrow sinusoids. Heavy collagen deposits along sinusoids clearly outlined *(arrows)*. Parenchymal cells normal. (Masson; ×900.)

The sinusoidal areas, on the other hand, displayed definite pathological features. The Kupffer cells appeared markedly enlarged and irregular, with cytoplasmic protrusions into the sinusoids (Figs. 3*B* and 3*C*). Hence, the sinusoidal lumina were considerably diminished, and the erythrocytes inside the sinusoids were polygonal, flattened, or even sickle-shaped (Figs. 3*B* and 3*D*). The cytoplasm of the Kupffer cells contained numerous large inclusions of lysosomal character, surrounded by a triple-layered membrane. Their interior was occupied by an amorphous matrix of low electron density (Figs. 3*B* and 3*C*). The mitochondria and endoplasmic reticulum appeared normal, whereas the vermiform structures typical of resting Kupffer cells were absent. Platelets were seen adherent to the sinusoidal lining in some areas, but there was no evidence of thrombosis in the sinusoids.

The space of Dissé, which normally separates the sinusoidal endothelium from the surface of the hepatocytes, was obliterated in the majority of sections. The space was occupied by heavy deposits of collagen fibers arranged in bundles (Figs. 3*C* and 3*D*). Accordingly, the distance between the sinusoids and adjacent hepatocytes was considerably increased. This perisinusoidal fibrosis corresponded well to the strands of connective tissue as observed by light microscopy (Figs. 2*C* and 2*D*).

The perisinusoidal connective tissue contained some cells identified as fibroblasts and a few macrophages. In general, the cellular elements of this compartment were scarce, and there were no signs of active inflammation.

DISCUSSION

In the following section the reported observations will be related to the already known causes of portal hypertension. It appears convenient to distinguish between pre- and postsinusoidal flow obstructions.[8]

Presinusoidal obstructions.

Intrahepatic. Upon x-ray examination, the intrahepatic portal vein radicals appeared slightly irregular but open. This finding might have been consistent with the syndrome of portal fibrosis[1] or hepatoportal sclerosis.[8] By means of microscopy, however, the intrahepatic portal vein branches were shown to be normal. The presence of open and normal portal radicals also excluded the diagnosis of portal fibrous dysplasia.[11] Congenital hepatic fibrosis[3, 6] is characterized by the fibrous bands that interweave throughout the liver substance. The histological aspects also are quite distinctive, the main features being dense fibrosis of the portal areas and proliferation of bile ducts. Such changes were absent in the present specimens.

Extrahepatic. Occlusion, stenosis, or congenital malformations of the portal vein[10] could be excluded with certainty in the present cases. Both showed a patent portal vein by splenoportography, and there was no suggestion of cavernous transformation.[12] Furthermore, patent splenic and portal veins were demonstrated at operation.

Postsinusoidal obstructions.

Intrahepatic. Apart from the inflammatory condition in both cases (see below), there was no suggestion of previous hepatitis in the case histories. None of the patients had experienced jaundice, and results of the liver function tests were grossly normal. The degenerative and reparative changes in posthepatitic cirrhosis were absent from the histological picture. Biliary atresia with cirrhosis also could be ruled out with certainty from the clinical picture and from the finding of normal biliary radicals. There was no indication of familial hepatic or renal disease.[2]

The various inborn errors of metabolism (hepatolenticular degeneration, galactosemia, tyrosinosis, and the like) were excluded, because the parenchymal damage and fibrosis seen in these conditions were lacking. The same view pertains to hereditary telangiectases, fibrocystic disease, and cystic disease of the liver.[9]

There was no suggestion of lipodystrophies (Hurler, Gaucher, Niemann-Pick) affecting the liver, and the spleen showed only changes associated with venous congestion. Neither was there any indication of abnormal hepatocellular glycogen storage (von Gierke, Pompe, and others). The intrahepatic vessels also were examined for collagen disease and amyloid deposits, with negative results.

Extrahepatic. Both patients had a normal cardiopulmonary state, and a chronic venous congestion of the liver could be ruled out with certainty. The possibility of a hepatic vein thrombosis (Budd-Chiari syndrome)[10] was excluded by microscopy and by venographic demonstration of patent hepatic veins (Fig. 1*D*). The shunting between some of the hepatic vein radicals, however, might suggest a venous occlusion at a more peripheral level, i.e., "veno-occlusive disease."[9] This condition is characterized by a centrilobular fibrosis and a complete or partial occlusion of the central veins. In the present cases, however, these had a normal or even increased diameter. Furthermore, the fibrosis was detected only after special staining and by means of repeated examination.

Sinusoidal obstructions. In the present study, the electron microscopic examinations verified and extended the observations made by light microscopy, and revealed a triad of anatomic lesions.

1. The Kupffer cells were hypertrophic and contained large cytoplasmic inclusions with the morphological pattern of lysosomes.[4] Compared to normal Kupffer cells, these lysosomes or phagosomes were much larger and less electron dense than usual. Their appearance was not consistent with that of lipodystrophies, and the nature of their content could not be established from the morphological appearance. The general impression, however, was that of abnormally enlarged Kupffer cells, possibly with signs of hyperactivity.

2. The sinusoidal lumina were considerably diminished in diameter, owing to the enlargement of the Kupffer cells. In several sections, the sinusoids seemed barely to allow the passage of one erythrocyte.

3. There was a heavy perisinusoidal fibrosis, with increased amount of collagen in the space of Dissé, which frequently appeared to be occluded.

It is our opinion that these observations may well explain the portal hypertension in the present cases, combined with the angiographic patterns and the normal liver function tests. It is likely, also, that the dilatation of periportal lymphatics may be caused by obliteration of the space of Dissé with impairment of lymph circulation.

Similar observations have not been encountered in the available literature. Boyer and associates[1] reported on two cases that did not seem to fit into their syndrome of portal fibrosis, since the latter was very moderate. Electron microscopy demonstrated a definite increase of collagen in the space of Dissé, and those two cases may be similar to the syndrome presented in this report. A thorough comparison cannot be made, since the paper by Boyer and associates is devoid of electron micrographs.

The pathogenesis of the present syndrome is at present a matter of speculation. Parenchymal disease, biliary and portal affections, cirrhosis, hepatic congestion and veno-occlusive disease have all been excluded as causative mechanisms. Hepatic damage secondary to shock from esophageal hemorrhage[7] or secondary to hypersplenism[5] must be considered very unlikely in the present cases.

Attention is, however, focused on the history of an acute abdominal condition (mesenterial adenitis?) in Case 1 and an inflammatory peritonitis in Case 2. It is tempting to suggest the possibility of immunological reactions with affection of the reticuloendothelial system,[4] leading to Kupffer cell proliferation and perisinusoidal fibrosis.

SUMMARY

Two patients with portal hypertension were operated upon at 7 and 21 years of age, respectively. The portal vein was patent in both cases, and the liver appeared normal upon gross examination.

Light and electron microscopic studies of wedge-shaped biopsy specimens of the liver revealed marked hypertrophy of Kupffer cells and narrowing of the sinusoidal lumina. There was a heavy perisinusoidal fibrosis with obliteration of the space of Dissé. The hepatic parenchymal cells and the portal triads were normal. Pre- and postsinusoidal obstruction could be excluded in both patients. The observations suggest that the portal hypertension in the present cases is caused by a flow obstruction at the sinusoidal level. These findings seem to add a new aspect to the pathogenesis of "idiopathic" portal hypertension.

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ADDENDUM

After this manuscript had been completed, two more patients were examined for a similar type of intrahepatic portal hypertension with bleeding esophageal varices. A 9-year-old boy and a 6-year-old girl have both been subjected to shunt procedures for this reason. Both presented slightly compressed intrahepatic vein branches but otherwise normal liver by angiography and macroscopic examination. Light microscopy showed perisinusoidal fibrosis continuous with connective tissue around central veins. The Kupffer cells appeared enlarged and sometimes arranged in larger nests. The girl has now reached the age of seventeen and will be subjected to another shunt operation for recurrent bleeding. Liver specimens from this patient are being processed for electron microscopy.

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Pseudomyxoma peritonei: Case report including in vitro mucolysis

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Pseudomyxoma peritonei has been associated with a spectrum of pathologic states varying from benign mucocele of the appendix to adenocarcinoma.[1] The determination of proper management is difficult for many reasons. This condition is seen infrequently, and therefore most surgeons lack extensive previous experience. The degree of malignancy, when present, is variable, thus affecting the prognosis. The presence of large quantities of gelatinous material within the peritoneal cavity gives rise to local mechanical complications, especially intestinal obstruction, and also impedes the usefulness of local chemotherapeutic agents.

Various agents, such as hyaluronidase and trypsin, have been used in an effort to liquefy the gelatinous material. Denize and Lauf-man[2] have demonstrated in vitro dissolution of the mucinous material with the use of trypsin, even though in vivo therapy failed to modify the course of their patient's disease.

A case of pseudomyxoma peritonei secondary to mucinous adenocarcinoma of the appendix is here presented with the results of in vitro attempts to liquefy the gelatinous material found in the patient's peritoneal cavity.

CASE REPORT

A 33-year-old man had an emergency appendectomy at another hospital 18 months prior to his admission to the Hospital of the University of Pennsylvania. The diagnosis at that time was perforated adenocarcinoma of the appendix, and much gelatinous material was noted to be present in the peritoneal cavity. He was again hospitalized elsewhere two months prior to his admission to this hospital because of a one-year history of increasing obstipation, tenesmus, and blood-streaked stools. An exploratory laparotomy revealed much gelatinous material covering multiple tumor implants, the largest of which involved the rectum; a left transverse loop colostomy was performed. The patient was referred to this hospital for possible further therapy.

Positive physical findings upon admission to our hospital were restricted to the abdomen. A functioning left transverse colostomy was noted. The patient's umbilicus was involved with tumor from which gelatinous material could be expressed. No organomegaly was found and there were normal bowel sounds. Rectal examination revealed a tumor-laden Blumer's shelf compressing the rectum posteriorly in such a way that digital examination was restricted. The patient also had back pain involving the area of the lumbar spine and sacroiliac joints bilaterally; but no tenderness was found.

Admission laboratory studies revealed a hemoglobin of 11.5 Gm. percent. White blood cell count, fasting blood sugar, blood urea nitrogen, serum electrolytes, serum bilirubin, serum alkaline phosphatase, and bromsulphalein retention were all within normal limits. X-rays of his chest, lumbar spine, and an intravenous pyelogram were free of disease and revealed no evidence of metastasis. Barium enema revealed an extrinsic pressure defect displacing the rectum posteriorly and a filling defect at the splenic flexure of the colon. A liver scan revealed a possible intrahepatic metastatic lesion involving the left lobe.

Examination with a pediatric proctoscope revealed a hard white tumor starting at 4 cm. that almost completely encircled the rectum. Biopsy revealed mucin-producing adenocarcinoma. An

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