HEPATIC LESIONS IN SICKLE CELL ANEMIA*

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Since 1923 when Sydenstricker *et al.*[1] made the first post-mortem study of sickle cell anemia, numerous reports concerning the pathologic findings of fatal sickle cell disease have appeared in the literature. The lesions of the liver rarely have been emphasized, although several investigators have commented on the incidence of palpable enlargement of the liver in fatal cases. It is conceivable that, because of the numerous vascular anastomoses in the liver, the lesions resulting from marked vascular and sinusoidal engorgement with sickled red blood cells have special significance.

Thirty-one cases of sickle cell anemia from the files of the Division of Pathology and Microbiology, University of Tennessee, which were necropsied during the years 1935 to 1955, have been studied. The ages of the patients range from 3 months to 45 years. Eighteen patients were under 20 years of age; the remaining 13 were 24 to 45 years of age.

Illustrative Case Histories

Case 1

A 27-year-old Negro male was admitted to the hospital with the chief complaints of severe joint pains mainly involving the knees and ankles and jaundice of approximately 4 weeks' duration. Epistaxis existed for 1 week prior to admission. Physical examination on admission revealed a jaundiced male with temperature of 104° F.; pulse, 108; respirations, 24; blood pressure, 120/80 mm. of Hg. An examination of the chest revealed minimal cardiac enlargement and the lungs were resonant throughout. The spleen was not palpable. The liver extended 5 cm. below the right costal margin and was slightly tender on palpation. No masses were felt in the abdomen.

The blood on admission gave a red cell count of 2.35 million per cmm., a hemoglobin of 7.5 gm. per 100 ml., and the peripheral blood smears revealed many sickled red cells, nucleated red cells, numerous target cells, diffuse basophilia with moderate anisocytosis and poikilocytosis. The white blood cell count was 33,500 per cmm. with a differential count of 12 per cent band forms, 75 per cent segmented forms, 6 per cent lymphocytes, and 7 per cent plasmacytes. The blood serum was icteric with a total serum bilirubin of 17.3 mg. per 100 ml. and a direct reaction of 8.6 mg. per 100 ml. Thrombocytes varied from 33 to 77 per 100 oil-immersion fields. The total serum protein was 6.2 gm. per 100 ml.; albumin, 2.8 gm.; globulin, 3.4 gm. The non-protein nitrogen of the blood was 28 mg. per

* Presented at the Fifty-third Annual Meeting of the American Association of Pathologists and Bacteriologists, Cincinnati, Ohio, April 26, 1956.

Received for publication, May 18, 1956.

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100 ml. A cephalin flocculation test was 3 plus at 24 hours. The blood cultures and the serologic test for syphilis were negative. The urinalysis revealed neither sugar nor protein, with a specific gravity of 1.017, bilirubin 4 plus, and a trace of urobilinogen. No hemosiderin granules were seen but a few white blood cells and numerous red blood cells were noted.

The patient was given 1,500 cc. of glucose intravenously, antibiotics, vitamins, and electrolytes. After 24 hours in the hospital he went into shock, failed to respond to 1,500 cc. of whole blood, and died.

Necropsy was performed 3 hours after death. The body was markedly icteric. Approximately 500 cc. of clear fluid were removed from the thoracic cavities. The heart weighed 370 gm. and a slight fibrinous exudate covered the pericardial surface. The lungs were heavy, deep red, and firm. The liver weighed 2,450 gm. and was a deep reddish brown with a nodular external surface. On cut section the nodules varied considerably in size, being separated by broad bands of fibrous tissue which were distributed irregularly throughout; the largest nodule was 1.5 cm. in diameter. The spleen was very small, weighing 4.2 gm., and was extremely fibrotic. There was an ulcer with sharp edges in the duodenum. The gallbladder, the extrahepatic biliary tract, and other organs were within normal limits.

Microscopically, the hepatic sinusoids were distended and practically occluded by the stagnation of the sickled erythrocytes. There were associated large areas of recent necrosis in the paracentral zones (Fig. 1). Focal necrosis was observed elsewhere without any constant lobular relationship. Many pigment-containing macrophages were seen in the necrotic areas in which the sinusoids were occluded by networks of interlacing sickle cells (Fig. 2). The reticulum appeared to be intact in the areas of recent necrosis. Fibrous proliferation was demonstrated in old areas of necrosis in the peripheral and paracentral zones. In the portal areas there was massive deposition of connective tissue that penetrated into the lobules and separated the hepatic cells (Fig. 3). A moderate degree of bile duct proliferation was seen in the scar tissue. The bile canaliculi were distended with bile, but no evidence of biliary obstruction was noted either in the intrahepatic or extrahepatic system. No calculi were found.

Sections of the lungs revealed severe congestion and slight fibrosis of the alveolar septa. Many of the capillaries contained agglutinative thrombi composed of sickle cells. There were many pigment-laden macrophages in the alveoli. The splenic pulp was replaced by fibrous connective tissue, much of which had become calcified. The splenic capsule was also markedly fibrosed. Agglutinative thrombi composed of sickled red blood cells were observed in vessels of the kidney, pan-

creas, and duodenum. The glomerular tufts were adherent to the outer layer of Bowman's capsule without any inflammatory reaction and the glomerular capillaries contained thrombi.

Case 2

A 34-year-old Negro male was admitted to the hospital with severe abdominal pain and moderate jaundice. He had complained of abdominal cramps which led to the clinical suspicion of a ruptured peptic ulcer with peritonitis. However, the acute distress and the signs of peritoneal irritation subsided soon after admission. Physical examination on admission revealed a well developed male with an enlarged liver and spleen. The heart appeared to be normal in size and shape. The lungs were clear. The liver was 6 fingerbreadths below the right costal margin and nodular. There was slight tenderness in the right lower quadrant. The spleen was firm and readily palpable. Roentgenologic examination of the chest and the abdomen revealed no evidence of neoplasm or gastric ulcer. Peripheral blood smears revealed marked sickling of the red blood cells with marked variation in size, shape, and staining quality. Numerous diffusely basophilic cells, target cells, and a few Howell-Jolly bodies were noted. The red blood cell count was 2.2 million per cmm. and the hemoglobin 7.5 gm. per 100 ml. The hematocrit reading was 19.5 mm., and the non-protein nitrogen of the blood was 42 mg. per 100 ml. The white blood cell count was 16,700 per cmm. with a differential of 3.5 per cent band forms, 63 per cent segmented forms, 0.5 per cent eosinophils, 5 per cent basophils, 23 per cent lymphocytes, 4.5 per cent monocytes, and 0.5 per cent atypical cells. Total serum protein was 7.4 gm. per 100 ml. and consisted of 3.3 gm. of albumin and 4.1 gm. of globulin. A cephalin flocculation test was 4 plus at 24 hours. Urinalysis revealed neither glucose nor albumin.

The clinical impression was sickle cell anemia with an acute exacerbation. The patient was given large amounts of glucose intravenously, vitamins, morphine, and 500 cc. of whole blood. He died 2 days after admission.

Necropsy was performed 6 hours after death. The body was moderately icteric. Approximately 100 cc. of serosanguineous fluid was removed from the peritoneal cavity. No peritonitis or ruptured gastric ulcer was found. The heart weighed 325 gm. and there were no significant alterations in structure.

The liver weighed 2,910 gm. and was a reddish brown throughout. There were broad bands of fibrous tissue dividing the parenchyma into nodules of varying size (Fig. 4). The gallbladder and the intrahepatic and extrahepatic bile ducts were normal. The spleen weighed 350 gm. The capsule was thickened and the pulp was firm and dark red. The lymph nodes were enlarged and slightly firm. The remaining organs were within normal limits.

On microscopic study the hepatic parenchyma was irregularly divided by wide anastomosing bands of dense fibrous connective tissue. Heavy round cell infiltration was noted in the collagenous tissue. In the lobules the sinusoids were markedly distended and packed with large numbers of sickle cells. The associated central and paracentral

areas were necrotic. Marked fibrosis was noted in the paracentral necrotic areas. Large amounts of hemosiderin pigment were noted mainly within the liver cells, but a scant amount of iron-positive pigment was present in the Kupffer cells (Fig. 5). The scar tissue was free of pigmentation. Bile duct proliferation was limited. The broad fibrous bands contained many dilated veins occluded by sickle cells.

In the spleen were well circumscribed hemorrhagic infarcts containing numerous sickled red cells. The white pulp was extremely atrophic. A small amount of iron-positive pigment was identified. Subcapsular fibrosis was marked. The glomerular capillaries of the kidneys were markedly congested and their walls thickened. The basement membranes also were moderately thickened.

Case 3

A 15-year-old Negro boy was brought to the hospital after massive hematemesis with circulatory collapse. He had been admitted 7 years previously with the diagnoses of meningitis and sickle cell anemia. The hemoglobin level at that time was about 8.0 gm. per 100 ml. and the sickle cell preparation was immediately positive. The bleeding time, clotting time, and platelet count, however, were normal. The liver was enlarged and firm with a questionably nodular surface. The spleen was readily palpable and firm. Following his recovery from meningitis, the white blood cell count was 7,250 per cmm. with a differential count of 12 per cent band forms, 55 per cent segmented forms, 1 per cent eosinophils, 1 per cent basophils, and 29 per cent lymphocytes and 2 nucleated red blood cells.

On the final admission the patient was in severe shock without detectable blood pressure, respirations, or heart sounds. There was a history of massive hematemesis on two previous occasions. The liver was palpable 3 cm. below the right costal margin and was nodular. The spleen was enlarged, firm, and nodular. The hematocrit reading was less than 10 mm., and the hemoglobin was less than 2.5 gm. per 100 ml. The white blood cell count was 40,000 per cmm. and segmented neutrophils predominated. After the administration of intravenous fluids, epinephrine, caffeine, oxygen, plasma, and 500 cc. of whole blood, the blood pressure rose to a maximum of 96/50 mm. of Hg. The heart rate was 72, and respirations were slow and irregular. Response to treatment was transitory and death occurred 6 hours after admission.

Necropsy was performed 1 hour after death. The sclerae were icteric. The liver weighed 1,700 gm. and was extremely nodular and firm (Fig. 6). The parenchyma was separated into nodules, which varied in size, by broad ribbons of gray fibrous tissue. The largest nodule was 4 cm. in diameter and was dark red. The gallbladder and the extrahepatic and intrahepatic bile ducts were normal. Material was taken from the liver for the culture of Brucella and other organisms. The spleen weighed 900 gm., and consisted of a firm, dark pulp in which were numerous discrete nodules. Both lungs were heavy and hemorrhagic. Varices were present in the lower portion of the esophagus. The heart and the remaining organs were within normal limits.

Microscopically, the hepatic lobules were irregularly penetrated by strands of connective tissue accompanied by a heavy round cell infiltration and slight bile duct proliferation. The sinusoids were extremely dilated and occasionally packed with sickle cells. In some areas patchy, recent necrosis involved the peripheral zones. The central veins could not be definitely identified. Arteries and veins were occluded by agglutinative sickled red blood cells. In the adjacent areas there was a marked separation of parenchymatous cells and round cell infiltration (Fig. 7). The sickle cells in some of the distended veins were arranged perpendicularly to the vessel wall (Fig. 8). A few hepatic arterioles were occluded also by agglutinative thrombi. Small amounts of iron-positive pigment were noted only in the hepatic cells. The reticulum was collapsed in the necrotic areas (Fig. 9).

Large, well circumscribed, hemorrhagic areas in the spleen were separated by atrophic white pulp. A moderate amount of iron-positive pigment was present but there was no fibrosis. The glomerular capillaries were packed with sickled red blood cells. The tubular epithelial cells contained small amounts of iron pigment. Agglutinative thrombi were observed in the vessels of the lungs, kidneys, and pancreas.

Case 4

A 35-year-old Negro male farmer was admitted to the hospital complaining of pain in both feet, in the para-umbilical area, left thigh, and back of the head for approximately 2 weeks. Three weeks before admission the onset of a "cold and fever" was accompanied by persistent productive cough. During this period, weakness and dizziness had kept him from work. Two years previously he had suffered a torsion injury of the left knee.

On admission his temperature was 100° F.; pulse, 85; respirations, 28; blood pressure, 125/65 mm. of Hg. There were discrete, non-painful, enlarged posterior cervical and supraclavicular lymph nodes. The veins of the neck were moderately distended, and the conjunctivae and mucous membranes were markedly icteric. There was a systolic murmur at the cardiac apex. The liver was palpable 4 cm. below the right costal margin and questionably nodular. The spleen was not palpable. There was atrophy of the lower part of the left thigh.

The hemoglobin was 7.5 gm. per 100 ml. The red blood cell count was 1.2 million per cmm., and the white blood cell count was 41,650 per cmm. with a differential count of 72 per cent segmented forms, 25 per cent lymphocytes, and 3 per cent monocytes. The total serum protein was 7.7 gm. per 100 ml.; albumin, 3.5 gm.; globulin, 4.2 gm. The total serum bilirubin was 64.5 mg. per 100 ml. and the 1 minute value was 18.9 mg. per 100 ml. Fifty-one platelets were counted in 100 oil-immersion fields. The four-tube clotting time was 62 minutes and no clot retraction was observed in 4 hours. The upper part of the clot consisted of deeply icteric material resembling chicken fat. The non-protein nitrogen of the blood was 44 mg. per 100 ml. Urinalysis revealed 2 plus protein; sugar, negative; specific gravity, 1.014; pH, 7.5. The urine was clear and dark, resembling the color of Coca Cola. The foam test for bilirubin was positive, and urobilinogen was positive at 1:40 dilution. The preparation for sickle cells was immediately positive. Roent-

genologic examination of the abdomen revealed generalized osteoporosis and accentuation of the trabecular pattern of the lumbar vertebrae, iliac wings, and femur. The patient was critically ill during the entire period in the hospital and had repeated nasal hemorrhages. One thousand cc. of whole blood, vitamin K, calcium gluconate, and glucose solutions were administered. Bleeding from the nose, throat, and gastro-intestinal tract continued and the patient expired on the eighth hospital day.

Necropsy was performed 4 hours after death. There was obvious icterus and the peritoneal cavity contained about 400 cc. of a yellow translucent fluid. No fluid was found in the pleural cavity. The heart was slightly enlarged owing to some hypertrophy of the left ventricle. Numerous petechiae were scattered throughout the epicardium. In the tips of the papillary muscles dark purple areas of discoloration and calcification were noted. The lungs weighed 640 gm. each and were moderately edematous. The spleen weighed 30 gm. and was markedly fibrosed; the architectural markings were lost. Both kidneys were swollen and deeply stained with bile.

The liver weighed 2,250 gm. The entire organ was a deep mahogany color, firm and moderately nodular. The cut surface showed a definite increase in fibrous tissue which separated the parenchyma into nodules of varying size. The gallbladder was dilated but contained no stones. The extrahepatic and intrahepatic bile ducts were normal. Throughout the gastro-intestinal tract a considerable amount of blood was present. The veins of the lower portion of the esophagus were markedly dilated but no point of rupture was found.

On microscopic examination the hepatic lobules were partially replaced by very broad masses of fibrous scar tissue in which there were numerous round cells and many proliferated bile ducts. These fibrocollagenous bands separated the parenchyma into nodules of varying size. The sinusoids were extremely distended and filled with agglutinative sickle cells. In a few peripheral areas the necrotic hepatic cords were replaced by fibrillar tissue (Fig. 10). The majority of the hepatic cells were heavily pigmented. A few of the hepatic veins were obliterated by agglutinative thrombi.

Sections of the spleen revealed no recognizable splenic architecture, only dense hyalinized fibrous tissue containing numerous calcific particles. The capillaries of the alveolar walls of the lungs were extremely dilated and filled with sickle cells. The glomerular capillaries contained agglutinative thrombi and a few glomeruli were partially fibrosed. There was pigmentation of the renal tubular epithelium. The structure of the lymph nodes was partially destroyed by severe hemorrhage.

Case 5

An 11-year-old Negro girl was admitted to the hospital with the chief complaint of pain in the epigastric area for 24 hours. The pain had commenced in the left lower quadrant, radiated to the epigastrium, and persisted. There was no nausea or vomiting. The patient noted edema the day before admission. There was no family history of sickle cell anemia. Physical examination on admission revealed temperature of 101° F.; pulse, 88; respirations, 22 per minute. There was bleeding from the upper gums. The sclerae were icteric. The heart was not remarkable and the lungs were resonant. The spleen was not palpable. The liver was enlarged and slightly tender. The skin of the lower extremities was ulcerated. Roentgenologic examination of the chest revealed calcified hilar lymph nodes but the lung fields were clear.

The red blood cell count was 1.75 million per cmm. with a hemoglobin of 6 gm. per 100 ml. The red blood cells showed marked anisocytosis and poikilocytosis. Numerous sickled cells were seen in a peripheral blood smear. White blood cell count was 17,500 per cmm. and a differential count included 1 per cent eosinophils and 16 per cent blast forms. The urine was dark amber and without sediment; albumin, sugar, and acetone were negative. The specific gravity was 1.013. Serologic test for syphilis was negative. The clinical impression was an acute exacerbation of sickle cell anemia. The patient continued to complain of severe abdominal pain, and the heart rate remained rapid. She died 6 days after admission.

Necropsy was performed 2 hours after death. There was obvious icterus of the sclerae. The heart weighed 240 gm., and both ventricles were dilated; no valvular lesions were noted. The lungs weighed 200 gm. each and were grossly consolidated. The spleen weighed 35 gm. and was markedly fibrosed. The liver weighed 1,740 gm., and was dark red. The surface was irregular and a few nodules projected from the capsule. On cut section the organ was very firm and islands of parenchyma were surrounded by fibrillar tissue. The intrahepatic and extrahepatic bile ducts, the gallbladder, and other viscera appeared normal.

Numerous microscopic sections of the liver revealed distended sinusoids occluded by hemolyzed sickle cells (Fig. 11). The central and paracentral areas showed necrosis and a thickened reticulum. The fibrous connective tissue, which separated the hepatic cells in the paracentral necrotic areas, contained a moderate number of round cells and a few eosinophils. There was a moderate degree of pigmentation of the hepatic cells. The Kupffer cells were not remarkable.

The spleen showed marked siderofibrosis with slight calcification. The lungs revealed interstitial pneumonia but no thrombi. There was slight pigmentation of the renal tubular epithelium. There were no significant lesions in the remaining viscera, including the gastrointestinal tract.

Case 6

A 14-year-old Negro boy was admitted to the hospital on May 22, 1945, and died 8 days later. From early infancy until his death, he had been subject to attacks of febrile illness with rheumatic pains. The sclerae were icteric and the urine dark, and during the periods of sickness, jaundice became more marked. Eight years prior to the final admission the patient was admitted with the complaints of priapism and inability to void.

Physical examination on the last admission revealed a temperature of 99° F.; pulse, 84; respirations, 24; slight generalized lymphadenopathy; hypertrophied tonsils; a slightly enlarged heart with a soft systolic murmur; a distended abdomen; and a firm erect penis which was painful when touched. The spleen was not palpable. The muscles were poorly developed. The liver extended 3 fingerbreadths below the right costal margin. A red blood cell count was 2.15 million per cmm.; hemoglobin was 6.5 gm. per 100 ml.; the white blood cell count was 22,400 per cmm. and showed an essentially normal differential count. The routine urinalysis was negative. The urologist's examination revealed a hard swelling just back of the glans penis and general engorgement of the vessels. A large needle inserted in the corpora cavernosa failed to drain them. Circumcision was performed, following which the child was slow to regain consciousness. Engorgement of the penis was less, but pain continued. Five days after the procedure the child became dyspneic and complained of pain in his right chest. Cough and signs of consolidation of the right upper lobe were present. Sulfapyridine was given without improvement. The clinical impression was sickle cell anemia and pneumonia of the right lung with cardiac enlargement. The patient died 7 days after the operation.

Necropsy was performed 9 hours after death. The body was that of a poorly developed male child with obvious icterus. The heart weighed 220 gm., and was diffusely enlarged. The right auricle and ventricle were dilated, but the valves were not unusual. The cardiac muscle appeared normal. The right lung weighed 420 gm. and was markedly consolidated; the left lung weighed 320 gm. and was extremely congested. The spleen weighed 8 gm. and was very firm and dark purple. The kidneys were extremely congested. The liver was mahogany red, weighing 1,700 gm.; the surface was relatively smooth. The cut sections revealed an increase in fibrous tissue with a nodular configuration. The bile ducts were not prominent. The gallbladder contained a few brownish stones.

On microscopic examination of the liver, agglutinative thrombi composed of sickle cells were found in the veins of the portal areas. The sinusoids were distended and were partially occluded by hemolyzed sickled red blood cells. In a few areas the hepatic cells appeared to be floating in pools of sickled cells. There were many areas of focal necrosis without any definite relation to the lobular pattern. The periportal fibrous tissue was irregularly distributed, separating groups of hepatic cells. There was moderate round cell infiltration. Golden yellow granules of pigment which gave a positive reaction for iron were present in the hepatic cells. Bile duct proliferation was rarely ob-

served in the scar tissue. In the hepatic lobules, the central veins were occluded by thrombi consisting of numerous sickled red blood cells and polymorphonuclear leukocytes.

The spleen was markedly fibrosed and contained a large amount of iron-positive pigment. In the sections of the kidneys, sickled red blood cells almost completely filled the space between the layers of Bowman's capsule. The cells of the convoluted tubules were filled with yellow-brown to black granules. Bronchopneumonia involved the entire upper lobe of the right lung. Many of the pulmonic veins of the left lung were occluded by agglutinative thrombi and there was extensive intra-alveolar hemorrhage. Sections of the corpora cavernosa revealed thrombosis of the vessels and extreme engorgement. A small ulcer was demonstrated in sections of the skin of one leg. The lymph nodes were extremely congested.

Review of Pathologic Findings

Size and Color of Liver. Grossly, the livers were consistently enlarged and a deep purple or mahogany red. Similar changes were described by Corrigan and Schiller,[2] who stated that the enlarged livers varied from deep brown to deep purple. Lowe and Adams[3] commented that the hepatomegaly probably was due to stagnation of sickled red blood cells in the hepatic sinusoids, and Lash[4] reported that the portal capillaries were engorged with sickle cells in the enlarged liver of his case.

Stagnation of the Sickled Erythrocytes in the Hepatic Sinusoids. The most prominent and constant microscopic feature of all of the cases was severe distention of the sinusoids by sickled red blood cells. In a few of our cases isolated hepatic cells appeared to be floating on pools of sickle cells and had no connection with the hepatic cords. Similar changes were mentioned by Green *et al.*,[5] who described congestion of the sinusoids by sickle cells and widespread phagocytosis of large numbers of red blood cells by the Kupffer cells. Ryerson and Terplan[6] presented 2 cases of fatal sickle cell disease in which the hepatic lobules were obscured by marked sinusoidal dilatation and the hepatic cells were moderately degenerated. In our series the sinusoids frequently were occluded by masses of sickled red blood cells forming a fibrin-like network as illustrated by Figure 2.

Phagocytosis of erythrocytes by the Kupffer cells in the engorged sinusoids was not observed frequently in our cases, although Jaffé[7] noted that the Kupffer cells were generally swollen, contained prominent granules, and showed phagocytosis of sickled red blood cells.

The Kupffer cells observed in the present series were slightly swollen but otherwise not remarkable.

Hepatic Necrosis and Atrophy. Necrosis and atrophy were most severe in the paracentral areas as illustrated by Figure 1, and degenerative changes were less severe in the central zones. In practically all cases there was marked sinusoidal stagnation of the sickle cells and varying degrees of atrophy and focal necrosis of hepatic cells. In 6 cases a more widespread recent necrosis was present which showed no constant relationship to either central or peripheral regions. Fibrous proliferation was confirmed by special stains in some of the necrotic areas while the other areas showed a relatively intact reticular network. Similar findings were observed by Heilbrun[8] and Hamman,[9] who described marked atrophy of the hepatic cells with pigmentation, extreme dilatation of sinusoids, and round cell infiltration about the portal areas.

Degree of Pigmentation. The degree of hemosiderosis was variable and not related to the duration of the disease in our cases. In most livers, hemosiderin as well as other pigments was found primarily in the hepatic cells and only rarely in the Kupffer cells and scar tissue. A severe degree of hemosiderosis was observed in a 5-year-old child whose hepatic cells contained a tremendous amount of iron-positive pigment. On the other hand, a 32-year-old patient who had received a large amount of whole blood had a minimal degree of pigmentation of hepatic cells but many pigment-laden macrophages were present in the necrotic regions. Sydenstricker *et al.*[1] reported marked pigmentation of the hepatic cells with a considerable degree of atrophy in a 5-year-old male child.

Cholecystitis and Cholelithiasis. Chronic cholecystitis and cholelithiasis were observed in 2 cases. The extrahepatic and intrahepatic biliary tracts were normal and showed no developmental anomalies. In four instances bile plugs were observed in the dilated bile canaliculi, but there was no evidence of obstruction in the biliary system.

Occlusion of the Sinusoids by Intrasinusoidal Hemolysis. In 7 of our cases the hepatic sinusoids were partially occluded by hyaline thrombi, as illustrated by Figure 11. Green *et al.*[5] described similar findings in 2 of their cases, hyaline fibrin-like thrombi of unknown cause. Our investigation suggests that they probably were caused by the hemolysis of sickle cells.

Thrombi. Agglutinative thrombi in the hepatic arterioles and venous capillaries, as illustrated by Figures 7 and 8, were observed in six instances, or 20 per cent of the cases. A central vein was occluded

by an agglutinative thrombus in one case. The hepatic capillaries in the portal areas were most frequently occluded by thrombi. In case 3, many veins were occluded by agglutinative thrombi and this resulted in marked separation of hepatic cells with round cell infiltration, as illustrated by Figure 7. The thrombosed veins were distended and contained many sickled red blood cells arranged perpendicularly to the vascular walls.

In their report of a case, Ching and Diggs[10] described agglutinative thrombi in hepatic capillaries around which heavy round cell infiltration was apparent. Crastnopol and Stewart[11] reported on liver biopsies in patients with sickle cell anemia, and stated that the hepatic capillaries were occluded by agglutinative thrombi and that the lesions were sufficient to establish a diagnosis of chronic hepatitis. Kimmelstiel[12] described many areas of hepatic necrosis surrounded by narrow hemorrhagic zones in a fatal case of the disease in an 11-year-old girl. No vascular thrombi were noted by him.

Patterns of Fibrous Proliferation. Seven of 31 cases (2 children, 5½ and 9 years of age, and 5 adults) showed a considerable amount of fibrosis in the peripheral zones, which probably represented healed massive necrosis as illustrated by Figure 10. The patterns of fibrous proliferation were irregular, and bands of tissue penetrated all regions of the lobules. Those livers which showed necrosis in the central and paracentral zones also revealed increased amounts of connective tissue in the necrotic areas. Similar changes were described previously by Steinberg,[13] who presented 7 cases of sickle cell anemia in which the livers showed increased connective tissue in the central and paracentral lobular zones, as well as an increase in the periportal connective tissue. Steinberg's observation is confirmed by our study. Marked fibrosis associated with hemosiderosis was reported by Tomlinson.[14] Fibrosis of diffuse type was mentioned previously by Hargrove and Mathews,[15] who presented a case of hemochromatosis in which the cells were extremely pigmented and diffuse fibrosis was present. Round cell infiltration was seen throughout the tissue.

Cirrhotic Changes. Nine of the 31 patients had advanced cirrhosis. Three of them were under the age of 15 years and gave no history of blood transfusions prior to admission to the hospital. One of the cirrhotic livers showed massive deposits of iron-positive pigment in the liver cells and small amounts of pigment in the Kupffer cells, but the scar tissue was free from pigmentation as illustrated by Figure 5.

The gross appearance of the liver illustrated by Figures 4 and 6 suggested a macronodular or a postnecrotic cirrhosis. Many broad

bands of loose fibrillar material penetrated the atrophic lobules. Foci of recent necrosis were observed in these cases. Dale[16] and Graham[17] presented examples of chronic hepatitis in sickle cell anemia which showed extensive cellular degeneration and fine, patchy, irregularly distributed fibrous scars with lymphocytic infiltration. Ryerson and Terplan[6] observed similar changes and suggested the term subacute toxic dystrophy. Legant and Ball[18] reported a case of hepatic cirrhosis in fatal sickle cell disease and also cited 4 other cases which showed extensive degeneration and massive necrosis of the hepatic cells. None of these patients gave a history of infectious hepatitis or other specific infectious disease. Green *et al.*,[5] in their extensive analysis of 21 cases of fatal sickle cell anemia, reported 4 examples of cirrhosis.

Discussion

The lesions of the liver in sickle cell disease appear to be related to various mechanisms: (1) long-standing severe anemia, (2) a prolonged hemolytic process with increased excretion of bilirubin and deposition of pigment, (3) repeated blood transfusions which might lead to exogenous hemochromatosis, (4) stagnation of sickled red blood cells in the sinusoids with sinusoidal obstruction, (5) vascular occlusion by agglutinative thrombi.

It is conceivable that prolonged severe anemia may contribute to the hepatic damage. However, a pronounced degree of hepatic damage is rarely observed in patients with chronic anemia, such as congenital spherocytic or hemolytic anemia. Patients with anemia may show cardiac hypertrophy or dilatation, and chronic congestive cardiac failure could account for the hepatic lesions. In our series, marked cardiac dilatation was observed frequently. No evidence of congestive cardiac failure was noted for the patients although a few showed electrocardiographic alterations. Usually, the liver became enlarged and firm prior to the development of cardiac enlargement.

According to Higgins,[19] the heart is enlarged in 72 per cent of patients with sickle cell anemia, but correction of the anemia frequently results in a return of the heart to normal size and a disappearance of the murmurs. Klinefelter[20] pointed out that the cardiac hypertrophy and dilatation compensate for the prolonged anoxemia in patients with sickle cell anemia, and that congestive cardiac failure, which does not respond to digitalis, is seen only in the terminal stages of the disease.

The prolonged hemolytic process with pigment deposition and increased excretion of bilirubin could provoke a biliary tract disorder

with the formation of calculi or the stagnation of bile in the liver. Chronic cholecystitis and cholelithiasis were observed in only 2 cases, and the biliary tract in the remaining cases was not remarkable. It seems clear from our study that the hepatic damage in sickle cell anemia cannot be attributed solely to the anemia or to the hemolytic process.

Repeated blood transfusions in patients with chronic anemia may lead to liver damage by serum hepatitis or by the production of exogenous hemochromatosis. There was no clinical history indicating that any of the patients developed serum hepatitis from blood transfusion. The liver was enlarged prior to any transfusion in most of our cases. One child 9 years of age had received six blood transfusions, the last having been administered 5 days before death. At necropsy, the liver showed broad bands of loose fibrillar material penetrating atrophic lobules, with foci of recent necrosis and a small amount of iron-positive pigment in the hepatic cells. The Kupffer cells and the scar tissue were not pigmented. No correlation between hepatic lesions and transfusion reaction could be established. The cirrhosis in 9 instances was thought not to be due to transfusions.

The serologic tests for syphilis, when done, were negative. No clinical or pathologic evidence of syphilitic infection existed. Severe dietary deficiency was not of significance in our series.

The sinusoidal stagnation of sickled red blood cells and the agglutinative thrombi in the liver seemed to be responsible for necrosis by blocking the blood flow and reducing the blood supply. Hyaline thrombi caused by intrasinusoidal hemolysis also impaired the circulation and resulted in necrosis. Kimmelstiel[12] described massive necrosis of the liver in a young girl who had had no transfusions and in whose liver there was no evidence of vascular occlusion. He assumed that the lesions were the result of acute vascular spasm. Theoretically, vascular spasm might produce a massive infarct but no such lesions were found in our series.

Summary and Comment

Thirty-one necropsies performed on patients who had died of proved sickle cell anemia were reviewed. Morphologic evidence of hepatic cell damage was noted in all cases, and in 9 cases cirrhosis was found. Histologic study of these livers suggested that the lesions in sickle cell anemia were caused by an impairment of blood flow resulting in an anoxic necrosis of the hepatic cells. Sinusoidal blockage by stagnation of the sickled red blood cells, or by hyaline thrombi caused

by intrasinusoidal hemolysis, and the vascular agglutinative thrombi of the hepatic capillaries appeared to be responsible for the anoxic necrosis.

In the cirrhotic livers the changes appeared to be of a macronodular or a postnecrotic type. This type of cirrhosis seems to be a unique manifestation of fatal sickle cell disease.

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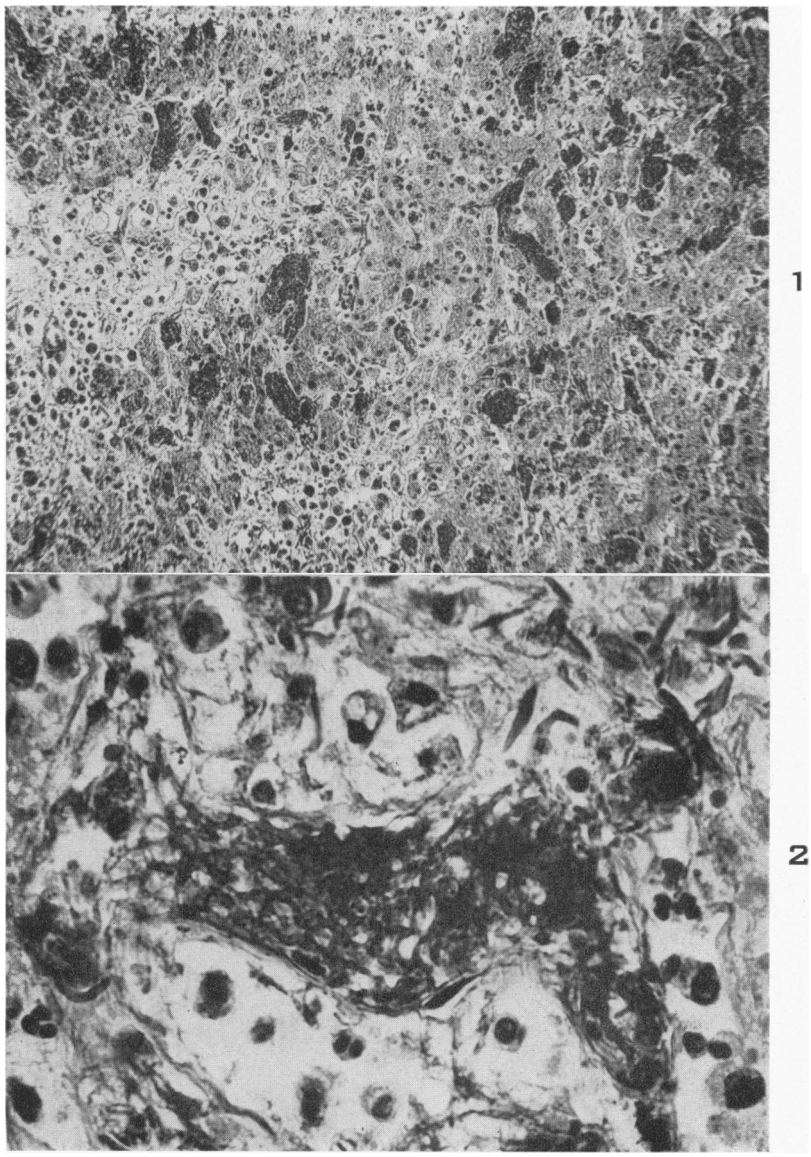


LEGENDS FOR FIGURES

FIG. 1. Case 1. Large area of necrosis. Masson's trichrome stain. × 160.

FIG. 2. Case 1. High-power view of necrotic area shown in Figure 1. Anoxic necrosis is caused by sinusoidal obstruction which is due to the formation of a network of sickled red cells. Masson's trichrome stain. × 430.

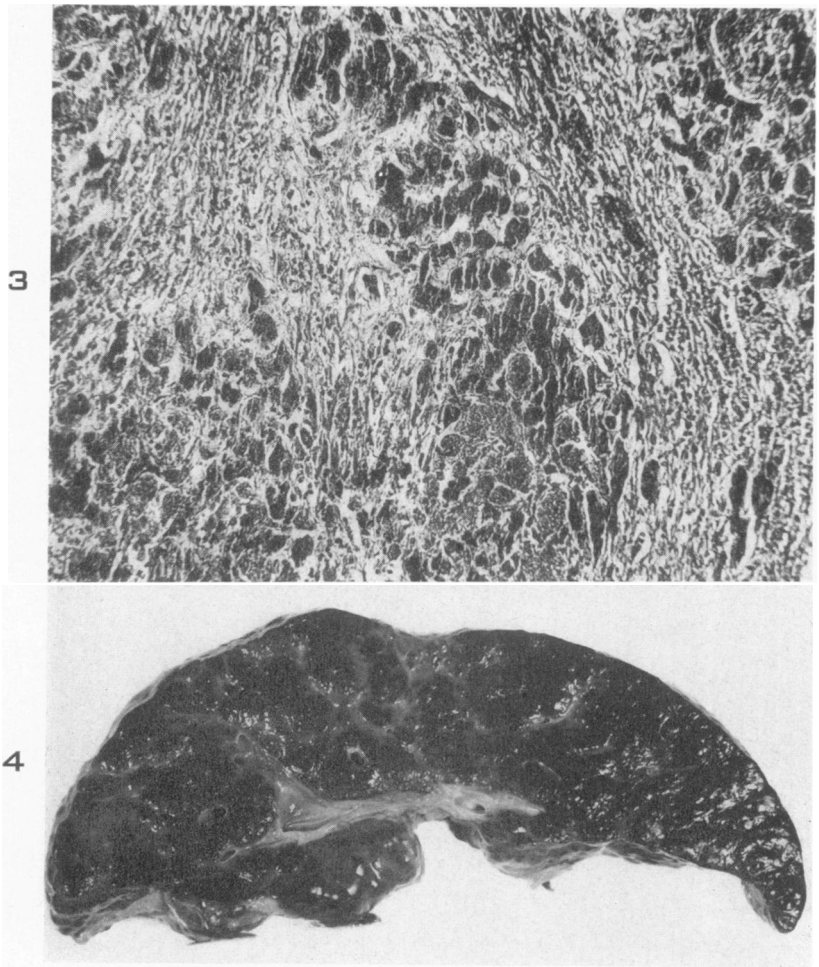


FIG. 3. Case 1. Bands of connective tissue penetrate the hepatic lobules. Masson's trichrome stain. × 330.

FIG. 4. Case 2. Gross picture of the liver. Grayish fibrillar material divides the hepatic parenchyma into nodules of various size.

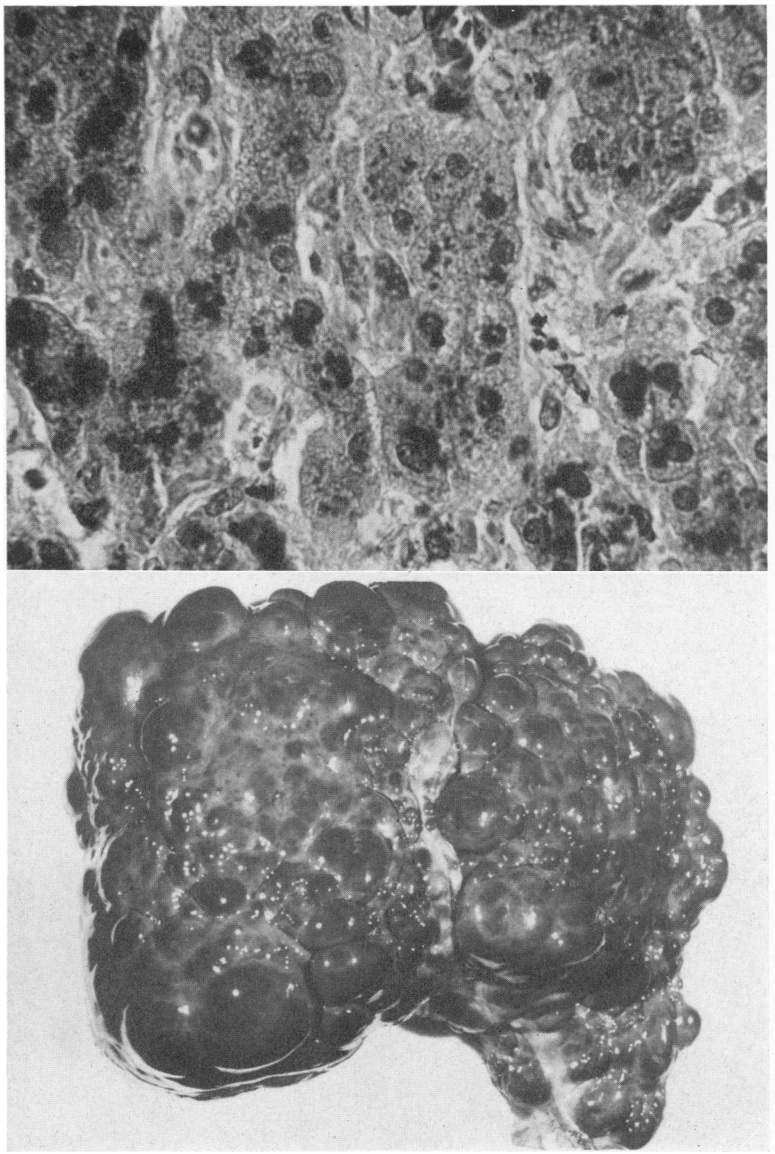
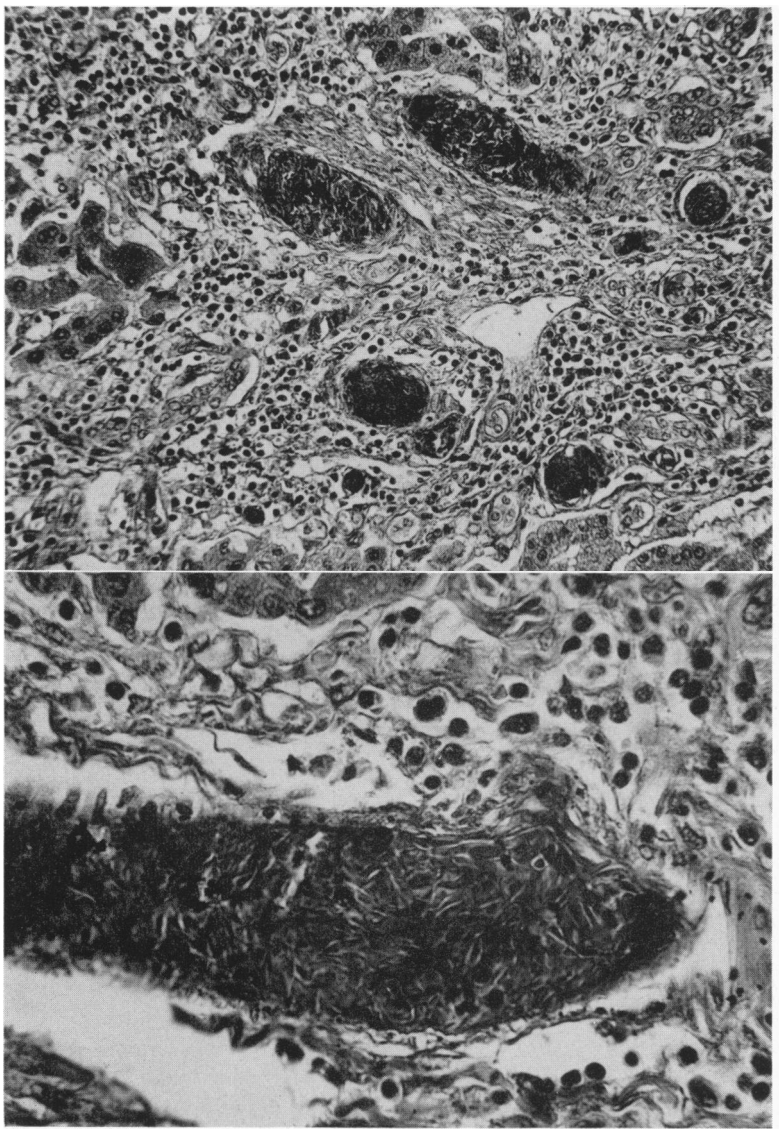


FIG. 5. Case 2. Hemosiderin pigment within the liver cells. Prussian blue stain × 430.

FIG. 6. Case 3. Cirrhosis of macronodular type.

FIG. 7. Case 3. A group of vessels is occluded by agglutinative sickle cells. Marked fibrosis and round cell infiltration about the vessels may be noted. Masson's trichrome stain. × 160.

FIG. 8. Case 3. High-power view of thrombosed vein. Masson's trichrome stain. × 460.



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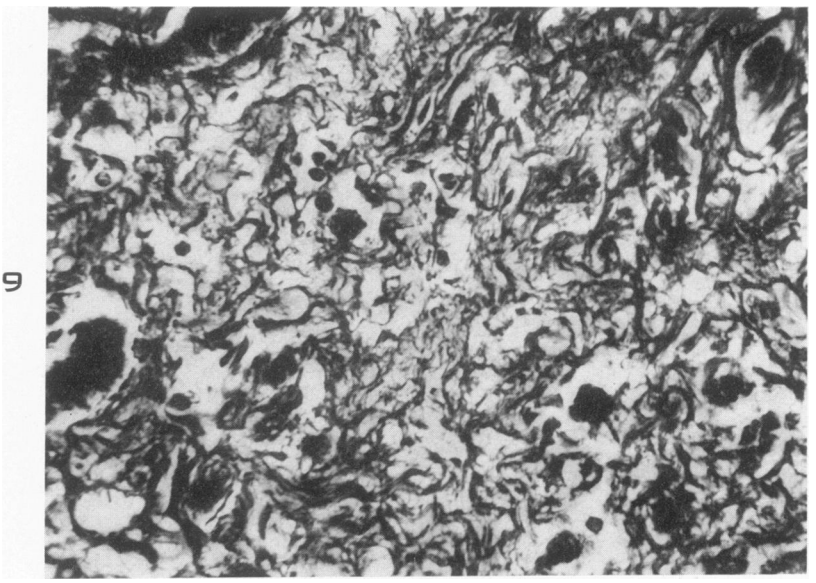
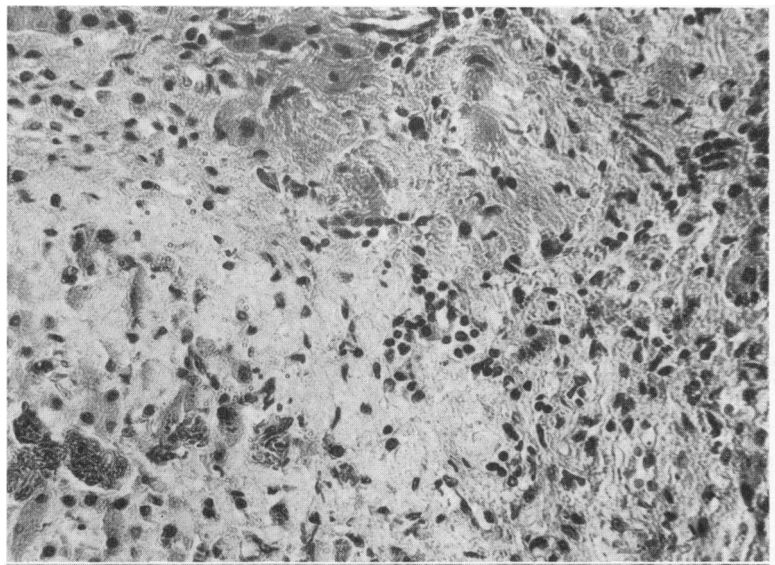


FIG. 9. Case 3. Thickened and partially destroyed reticular structures in the necrotic area. Reticulin stain. × 430.

FIG. 10. Case 4. Fibrous scar tissue in the peripheral zone. Hematoxylin and eosin stain. × 360.

FIG. 11. Case 5. The hepatic sinusoids contain a homogeneous material caused by hemolysis of sickled red blood cells. Hematoxylin and eosin stain. × 430.



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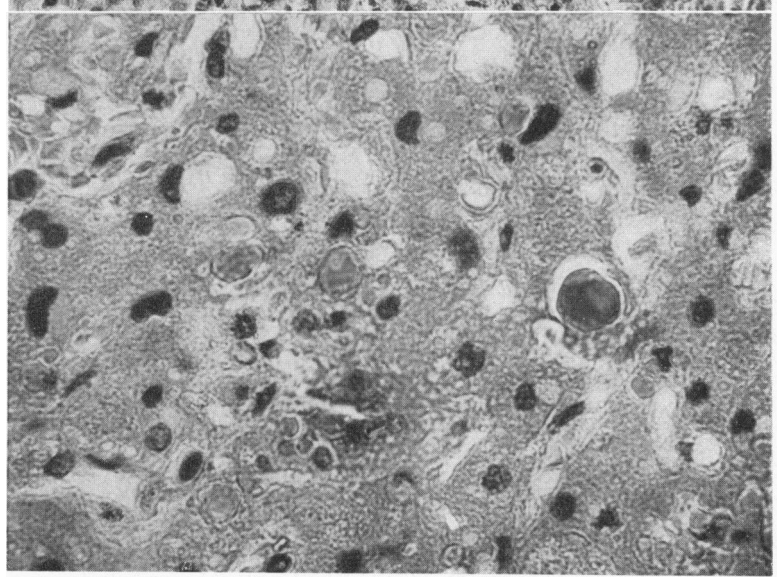

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