BIOPSY OF THE LIVER IN INFECTIOUS MONONUCLEOSIS *

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Because of the relatively benign character of infectious mononucleosis there has been little post-mortem material from which to study the anatomical effects of this disease. There are 24 reported necropsies[1-13] on patients who died either during or shortly after an attack of infectious mononucleosis or glandular fever. Five of these necropsies[1-3] were performed prior to the introduction of the Paul-Bunnell test, so that the diagnoses may be regarded with some suspicion. Most of the necropsy reports agree that there are widespread effects of the disease and the liver usually has shown rather marked alterations. There has been some variation in the reported histologic details of the hepatic lesion. In only one of these fatal cases has death been attributed to hepatic dysfunction.[11]

Numerous articles have emphasized the frequency with which impairment of liver function can be demonstrated in non-fatal cases of infectious mononucleosis with or without jaundice. Most of these reports[14-26] have been based on the abnormal results obtained with various liver function tests. It is rather surprising, in view of such evidence, that there are few available reports of biopsy of the liver from non-fatal cases of this disease. Only seven articles[9,27-32] could be found recording 18 such biopsies from 16 patients with infectious mononucleosis.

The first reported biopsy of the liver in infectious mononucleosis was that described by Kilham and Steigman[27] in 1942. A biopsy specimen was obtained by liver punch from one of the 4 jaundiced patients in their series of 20 cases of infectious mononucleosis. This patient was deeply jaundiced. No mention was made of the time which had elapsed between the onset of symptoms and biopsy. A loss of liver cells, a well developed histiocytic reaction, and some early proliferation of the bile ducts were noted in the portal zones. Increased Kupffer cells and cells resembling monocytes were observed in other parts of the lobules and in the sinusoids. The glycogen content of the hepatic cells was said to be well preserved and the general appearance suggested to the authors that an earlier phase of necrosis had preceded the histiocytic reaction. No peripheral fibrosis was seen, but the re-

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ticular pattern in the affected portal zones was said to be disturbed. Retention of bile was not mentioned in the report.

The following year van Beek and Haex[28] reported upon 2 specimens obtained by liver puncture from a patient with infectious mononucleosis. The first specimen was taken 14 days after the onset of the illness, and the second 3½ weeks after the onset, when the patient was improved. In the earlier material the liver cells were interspersed with numerous monocytoid cells and some polymorphonuclear leukocytes. Numerous mitotic figures were described in the monocytoid cells. Mitotic figures were seen also in the liver cells. In the later specimen the liver tissue was said to have been practically normal, although the triangles of Kiernan were still rich in lymphocytes. Neither jaundice nor bile retention was mentioned in this report.

Liver biopsies of 4 jaundiced patients with infectious mononucleosis were reported by Bang and Wanscher[29] in 1945. By aspiration, material was obtained from the 4 patients on the 15th, 16th, 6th, and 17th days of illness, respectively. Small, thin, biliary thrombi were observed in the bile capillaries of the first and fourth patients. None were seen in the second and third patients. A periportal infiltration of lymphocytes and a proliferation of Kupffer cells were noted in all 4 cases. In none of these patients was the portal connective tissue considered to be increased. All of the livers showed mild degenerative changes in the hepatic cells. These authors concluded that the jaundice was due not to obstruction, but rather to primary damage to the liver, presumably caused by the specific agent of the disease.

By surgical excision, a specimen of the liver for biopsy was obtained 15 days after the onset of infectious mononucleosis in the course of an operation for a ruptured spleen in the patient reported by Davis, MacFee, Wright, and Allyn.[30] The sections of liver revealed moderate cloudy swelling of the liver cords. Most of the liver cells were swollen, containing fine granules in varying quantity, and a few mitotic figures were present. Several patchy accumulations of pigment were seen in the bile canaliculi. The sinusoids were slightly dilated and contained increased numbers of young lymphocytes, with occasional monocytes and polymorphonuclear cells. The Kupffer cells contained granular pigment in small quantities. No microscopic change was observed in the capsule. This patient apparently was not clinically jaundiced.

The specimen for liver biopsy mentioned in the comprehensive report on the pathology of infectious mononucleosis by Custer and Smith[9] is described only in conjunction with the livers from 7 necropsies. The changes were similar to those seen in the necropsied cases in which death occurred from 17 to 35 days after the onset of the disease.

Lymphocytic infiltration was most pronounced in the periportal connective tissue. "Quantitatively, this reaction varied from hardly more than the usual lymphocytic collar . . . . to a degree approaching that of lymphatic leukemia . . . ., with lymphoid cell aggregates extending into the adjacent lobular parenchyma." The capsule in most instances showed varying degrees of lymphocytic infiltration while its connective tissue appeared to be losing substance in proportion to the increase of lymphocytes. These authors saw no necrosis of the liver parenchyma except in one case in which thrombosis of the portal vein followed splenectomy. They saw no evidence of biliary obstruction. The incidence of jaundice in these 8 cases is not mentioned.

Results of biopsy of the livers of 5 young adults taken at the height of typical attacks of infectious mononucleosis without clinical evidence of hepatic disturbance were reported by Bertrand[31] in 1949. In one patient, whose recovery was delayed, specimens were obtained at 1 and 5 months after the onset of the disease. In each case there was a marked infiltration of the periportal connective tissue with mononuclear cells. There were increased mitotic figures in the liver cells. The blood vessels, bile ducts, and liver cells were essentially unaltered. There was marked hyperplasia of the Kupffer cells. Islets of necrosis were attributed to the displacement of trabeculae by masses of lymphocytes. Mitotic figures were found in the Kupffer cells and in the periportal mononuclear cells. Similar findings in specimens obtained for biopsy from 2 additional patients were recorded in a footnote.

The only report suggesting that cirrhosis of the liver might be a complication of infectious mononucleosis is that of Leibowitz and Brody.[32] They described a 24-year-old white male who was admitted to the hospital with jaundice of 7 weeks' duration. Fifty-nine days after the onset of jaundice, the heterophil antibody titer reached a peak of 1:800. Thirty-nine months after the onset of jaundice, material obtained by aspiration for biopsy of the liver revealed microscopic evidence of cirrhosis.

Material and Methods

During the 8-month period between June 15, 1951, and February 15, 1952, the diagnosis of infectious mononucleosis was made on 26 patients. Thirteen specimens obtained from 10 of these patients have provided the opportunity to compare the histologic changes in the liver with the clinical course of the patient, the heterophil antibody titers, the smears of the peripheral blood, and certain liver function tests. The specimens were all obtained from young adult males between the ages of 18 and 31 years. Liver tissue was obtained with

biopsy forceps during peritoneoscopy. With this method the liver could be seen and described and the site could be visualized before and after the tissue was removed. In each case the sample was taken from the right lobe of the liver.

The tissue removed was placed immediately in 10 per cent neutral formalin solution. Paraffin sections were stained with hematoxylin and eosin and with Gomori's silver stain for reticulum.[33] In some cases a portion was fixed in Zenker's fluid and stained with phloxine and methylene blue.

The heterophil antibody titer was determined according to the presumptive test of Davidsohn.[34] An agglutination in a final serum dilution of 1:224 or higher was considered significant. Absorption tests with guinea-pig kidneys and beef erythrocytes were not done.

Cephalin-cholesterol flocculation tests were done by the technic of Hanger.[35] Readings were recorded at the end of 24 and 48 hours. A reaction of 2 plus or more in 24 hours or of 3 plus or more in 48 hours was considered abnormal.

The thymol turbidity test was performed by Benotti's modification[36] of the Maclagan method with the reagents buffered at pH 7.8, measuring the turbidity in a colorimeter against standard barium chloride solutions. A value of more than 2 units was considered abnormal.

Total and direct bilirubin determinations were done by the method of Malloy and Evelyn.[37] Elevation of the total bilirubin above 1.0 mg. per 100 cc. was considered abnormal.

Total and free cholesterol determinations were done by the method of Schoenheimer and Sperry.[38] A value of less than 70 per cent for cholesterol esters was considered abnormal.

Alkaline phosphatase determinations were done by the method of Bodansky.[39] Values greater than 4 Bodansky units were considered abnormal.

Bromsulfalein retention was measured by the injection of 5 mg. of the dye per kg. of body weight. A retention of more than 5 per cent at the end of 45 minutes after injection was considered abnormal.

Results

Group I

Group I consisted of 2 patients from whom specimens were obtained for biopsy within 5 days of the onset of symptoms.

Case 1, a 24-year-old white male, typifies this group. The specimen was taken 2 days after the onset of severe pharyngitis with fever of 102.0° F. On the day of the biopsy his leukocyte count was 18,500 per cmm. with 74 per cent neutrophils and 26 per cent lymphocytes.

Three days later his heterophil antibody titer was 1:224. Thirteen days after the biopsy his peripheral blood contained 56 per cent lymphocytes, some of which were atypical. The spleen was palpable. There was no jaundice.

At the time of biopsy the liver was moderately enlarged, extending 4 cm. below the costal margin all along the hypogastrium. The gallbladder appeared normal. The liver edge was somewhat blunted, and its color was distinctly lighter than normal. Histologically, the capsule appeared intact except for a few scattered epithelioid cells. Only occasional lymphocytes were found in the periportal zones. The liver cords were well preserved. Occasional liver cells were somewhat shrunken, with pyknotic nuclei. There was some variation in the size and staining of the nuclei. Occasional liver cells were binucleate, with prominent nucleoli. Small, clear vacuoles were found in many of the liver cells. The Kupffer cells were not numerically increased, but some of them appeared swollen. Some of the liver cells had indistinct cell membranes and occasional neutrophils were found within the parenchyma as well as in the sinusoids. No mitotic figures were seen.

Case 2 was a 20-year-old white male from whom a specimen for biopsy was obtained 5 days after the onset of acute pharyngitis. Three days prior to the biopsy he had a leukocyte count of 18,700 per cmm. with 86 per cent neutrophils and 14 per cent lymphocytes. No atypical lymphocytes were demonstrated in the peripheral blood of this patient. On the day of biopsy his heterophil antibody titer was 1:112. Seven days later it was 1:224. There was no jaundice.

At the time of biopsy the liver was moderately enlarged, its edge was rounded, and its color was slightly lighter than normal. Histologically, the liver was similar to that of case 1. More of the liver cells were multinucleated. Some had three or four nuclei. The Kupffer cells were increased in both size and number. The periportal zones were somewhat accentuated by an infiltration of epithelioid cells, some lymphocytes, and occasional neutrophils. Scattered small foci of Kupffer cells appeared to be replacing liver cells in some areas.

Group II

Group II consisted of 4 patients from whom specimens for biopsy were obtained between 10 and 15 days after the onset of symptoms. Case 3 is representative of the group.

Case 3 was a 20-year-old white male from whom tissue was obtained 10 days after the onset of acute pharyngitis with lymphadenopathy and fever. He had no symptoms referable to his liver. Six days prior to the biopsy his leukocyte count was 12,250 per cmm. with 26

per cent neutrophils, 68 per cent lymphocytes, and 6 per cent monocytes. Many of the lymphocytes were designated "mononucleosis cells." There was no jaundice.

At the time of biopsy the liver appeared to be of normal size and its edge sharp. The color and texture appeared normal. The liver extended just to the level of the right costal margin. The capsule was smooth and glistening. The color was uniform and of a mahogany hue. Histologically, the liver showed a striking difference from those of group I. The capsule appeared thin. In some parts of the capsule there was a slight infiltration of lymphocytes and epithelioid cells. The portal zones were markedly accentuated by a dense infiltration of lymphocytes and epithelioid cells (Fig. 1) and a few scattered neutrophils and eosinophils. There was a moderate increase in bile ducts and a slight fibroblastic proliferation. The sinusoids appeared small but were conspicuous because of the numerous and swollen Kupffer cells which outlined them. Some of the Kupffer cells seemed to be free in the lumina of the sinusoids. Most of the parenchymal cells contained a faintly eosinophilic granular cytoplasm. Many of these cells had two or more nuclei. An occasional nucleus was elongated, with a slight constriction near the mid-point. Occasional mitotic figures were seen in the liver cells. Scattered cells and sometimes small groups of liver cells appeared shrunken, irregular in outline, and deeply eosinophilic, with small, dark-staining, homogeneous nuclei (Fig. 2). Some cells with the more intensely eosinophilic cytoplasm had small, irregular, pyknotic nuclei. A few cells were hyalinized, deeply eosinophilic, and without demonstrable nuclei (Fig. 3). Some of these cells appeared to be extruded from the liver cell columns. In some of the liver lobules many of the liver cells had large, clear nuclei suggesting excessive glycogen content (Fig. 4). An occasional small, irregular group of epithelioid cells appeared to occupy the space from which two or three liver cells had disappeared. Some of the liver cells near the central veins contained small granules of light brown pigment. No bile plugs were formed in the bile canaliculi. No mitotic figures were found in the Kupffer cells. An occasional mitotic figure was seen in the epithelium lining the bile ducts. Numerous lymphocytes were seen in the lumina of the sinusoids.

Case 4 was a 23-year-old white male from whom material for biopsy was obtained 11 days after the onset of acute pharyngitis. Three days before biopsy his leukocyte count was 10,500 per cmm. with 22 per cent neutrophils, 65 per cent lymphocytes, 2 per cent monocytes, and 11 per cent staff cells. Atypical lymphocytes were seen in the smear. On the day of biopsy the heterophil antibody titer was 1:224 and the

cephalin-cholesterol flocculation test was negative at 24 and 48 hours. Serial laboratory examinations were not obtained on this patient. There was no jaundice.

At the time of biopsy the liver appeared grossly normal. Histologically, it (Fig. 5) was quite similar to that seen in case 3. The periportal lymphocytic infiltration and Kupffer cell activity were not quite as marked but the acidophilic degeneration of individual hepatic cells was more pronounced.

Case 5 was an 18-year-old white male upon whom biopsy was performed 13 days after the onset of acute pharyngitis associated with fever, lymphadenopathy, and splenomegaly. One week prior to the biopsy his leukocyte count was 11,100 per cmm. with 38 per cent neutrophils, 2 per cent eosinophils, 55 per cent lymphocytes, and 5 per cent monocytes. Atypical lymphocytes were seen in the smear. At the time of the biopsy the heterophil antibody titer was 1:224. The cephalin-cholesterol flocculation test was 1 plus at 24 hours and 2 plus at 48 hours. Six days later the cephalin-cholesterol flocculation test was negative at 24 and 48 hours. The spleen was palpably enlarged. There was no jaundice.

At the time of biopsy the liver was slightly enlarged. The color was uniformly light pink. There was some blunting of the mesial edge of the right lobe. Histologically, the liver was similar to that of case 3. The periportal infiltration was not quite as marked and the Kupffer cell activity was not nearly as marked. There was a moderate acidophilic degeneration of individual hepatic cells, but no evidence of mitotic activity in the liver cells.

Case 6 was a 21-year-old white male from whom tissue for biopsy was obtained 14 days after the onset of chills, weakness, and anorexia. When first seen he had a single extensive chain of enlarged cervical lymph nodes. Six days prior to the biopsy his leukocyte count was 11,000 per cmm. with 48 per cent neutrophils, 1 per cent staff cells, 48 per cent lymphocytes, and 3 per cent monocytes. Atypical lymphocytes were seen in the smear. Four days prior to biopsy the heterophil antibody titer was 1:7168. On the day after biopsy the cephalin-cholesterol flocculation test was 1 plus in 24 hours and 3 plus in 48 hours. The same sample of blood showed an elevated thymol turbidity of 4.2 units. Repeat tests performed 8 and 15 days respectively after the biopsy showed no abnormalities. There was no jaundice.

At the time of biopsy the liver was slightly enlarged and its edge blunted. The color was a brilliant deep red. Histologically, the liver was similar to that of case 3. The periportal infiltration and Kupffer cell activity were not quite as marked but the acidophilic degeneration

of individual liver cells and the mitotic activity of the liver cells were fairly marked. In scattered areas there was excessive glycogen deposition in the nuclei of the liver cells. There was moderate increase in the bile ducts.

Group III

Group III included only case 8, a 21-year-old white male whose course was more protracted than that of the previous cases. His biopsy specimen was obtained 28 days after the onset of severe pharyngitis and marked lymphadenopathy. Three days after the onset his leukocyte count was 7,500 per cmm. with 22 per cent neutrophils, 28 per cent staff cells, 33 per cent lymphocytes, 9 per cent monocytes, 6 per cent eosinophils, and 2 per cent basophils. No atypical lymphocytes were seen at this time. Fourteen days after onset his leukocyte count was 18,200 per cmm., with 1 per cent neutrophils, 13 per cent staff cells, 79 per cent lymphocytes, and 7 per cent monocytes. Most of the lymphocytes were atypical.

At the time of biopsy his liver was only slightly enlarged but the liver edge was definitely blunted. The color was a brilliant deep red. Histologically, the liver was similar to that of case 3. The periportal infiltration and Kupffer cell activity were not quite as pronounced. The acidophilic degeneration of individual liver cells was quite marked.

Group IV

Group IV includes 3 patients from whom more than one specimen of liver was obtained. Case 7 was a 20-year-old white male with a history of pharyngitis, fever, cervical lymphadenopathy, enlarged spleen, and tender liver. Three days after the onset his leukocyte count was 14,700 per cmm. with 15 per cent neutrophils and 85 per cent lymphocytes, most of which were atypical. The first liver biopsy was performed 19 days after the onset of his illness. At that time the liver was somewhat enlarged. Its edge was considerably blunted and its color a brilliant red. Histologically, the liver was quite similar to case 3 but the infiltration extended into the liver lobules (Fig. 6). The mitotic activity of the liver cells was extremely marked (Fig. 7). More liver cells were in mitosis than in any other specimen of the entire series. There was a moderate multiplication of the bile ducts (Fig. 8). Occasional mitotic figures could be seen in epithelial cells lining the bile ducts. There was moderate acidophilic degeneration of individual liver cells. The second liver specimen from case 7 was obtained 59 days after the onset of illness. The liver appeared slightly larger than normal and its edge was slightly blunted. The color was slightly lighter than normal. The site of the previous removal was

noted and the second specimen was obtained adjacent to the site of the first. There was a striking difference histologically between the two. Periportal infiltration and Kupffer cell activity were much less marked in the second (Fig. 9). Only an occasional mitotic figure could now be found in the liver cells. There were only a few liver cells showing degenerative changes. A significantly elevated heterophil antibody titer persisted for at least 42 days.

Case 9 was a 31-year-old white male with a history of pharyngitis, fever, and cervical lymphadenopathy. Three days after onset the leukocyte count was 14,150 per cmm. with 18 per cent neutrophils, 77 per cent lymphocytes, and 5 per cent monocytes. Many of the lymphocytes were atypical. Eight days after the onset the heterophil antibody titer was 1:3584 and 20 days later was 1:7168. In the meantime the cephalin-cholesterol flocculation test was 4 plus in 24 hours and the thymol turbidity was 9.4 units. The total cholesterol was 225 mg. per 100 cc. with 74 per cent esters. The patient was jaundiced and the total bilirubin was 2.5 mg. per 100 cc. The first liver biopsy was done 57 days after the onset of illness when the cephalin-cholesterol flocculation test and thymol turbidity were still elevated, although the bilirubin had reached normal levels. At this time the liver was slightly larger than normal. It had lost some of its brownish tint and was smooth without evidence of scarring or fatty infiltration. Histologically, there was only slight evidence of active inflammation. There was very little periportal infiltration and very little Kupffer cell activity (Fig. 10). Only occasional liver cells showed acidophilic degeneration. A few liver cells had multiple nuclei. No mitotic figures were seen. There was no evidence of periportal scarring. The second specimen for biopsy was obtained 121 days after the onset of illness. The patient was still presenting symptoms of his disease. He showed no retention of bromsulfalein at the end of 45 minutes. The liver appeared nearly the same as before, both grossly and histologically (Fig. 11). The Kupffer cells seemed slightly more active and there were more liver cells with multiple nuclei and prominent nucleoli. There now appeared to be very slight periportal fibroblastic proliferation and some increase in bile ducts. There was slight retention of bile in some of the canaliculi.

Case 10 was a 31-year-old white male with a protracted history starting with a 2-day period during which his friends noticed that he was jaundiced. He then felt perfectly well for approximately 2 months when he developed nausea and vomiting and noticed that his sclerae were yellow and his urine dark. Five days later the total bilirubin was 5.4 mg. and the direct reacting bilirubin 3.0 mg. per 100 cc. The urinary urobilinogen at this time was positive in a dilution of 1:640.

The alkaline phosphatase was 6.2 Bodansky units but the cephalin-cholesterol flocculation was negative at 24 and 48 hours, and the bromsulfalein retention was only 2.5 per cent in 45 minutes. Two weeks before the second biopsy the total serum cholesterol was 149 mg. per 100 cc. with 75 per cent esters. The first liver biopsy was done 120 days after the first episode of jaundice. For 6 days prior to biopsy he had received 40 mg. of ACTH every 6 hours. At that time the cephalin-cholesterol flocculation and thymol turbidity values were still elevated. The bilirubin was 1.5 mg. per 100 cc. The liver appeared normal by peritoneoscopy. Histologically, the periportal infiltration and Kupffer cell activity were minimal. A few scattered liver cells showed degenerative changes. There were a moderate number of binucleate liver cells. No mitotic figures were seen. Retained bile could be seen in some of the bile canaliculi (Fig. 12). There was no evidence of periportal scarring. The second biopsy was done 225 days after the first episode of jaundice. The total bilirubin was then 1.2 mg. per 100 cc. At that time the liver appeared normal at peritoneoscopy. Histologically, the liver now showed moderate Kupffer cell activity. Clear vacuoles were demonstrable in occasional liver cells. Most of the liver cells had a fairly uniform appearance, but there was a moderate variation in the size and staining ability of the nuclei (Fig. 13). A moderate number of binucleate liver cells were seen. There was an occasional mitotic figure. There were scattered small focal areas of necrosis of liver cells. Small collections of retained bile could be seen in some of the small bile canaliculi. There was very slight periportal scarring. The reticular pattern of the liver lobules was, for the most part, well maintained (Fig. 14).

Discussion

The study of biopsy specimens from the livers of 10 patients with infectious mononucleosis offers additional evidence of liver damage in this disease. In each patient upon whom biopsy was done, the liver showed morphologic evidence of liver damage. This varied considerably both in the type and intensity of the reaction, as shown in Table I. In those patients from whom specimens were obtained within 5 days of the onset of symptoms (group I), the pathologic changes in the liver were minimal. In case 1 the tissue appears to have been taken almost at the peak of the heterophil antibody titer, but 2 weeks prior to the development of a positive cephalin-cholesterol flocculation test. A repeat biopsy 2 weeks later might have shown more marked pathologic changes. Case 2 is an example of a mild case of infectious mononucleosis with minimal changes in the liver.

In those specimens obtained 10 to 30 days after the onset of symptoms (cases 3 to 8) there was evidence of marked periportal infiltration, marked Kupffer cell activity, and considerable acidophilic degeneration of individual liver cells. It is to be noted that the maximum mitotic activity of liver cells was seen in the specimen obtained 19 days after the onset of symptoms. In this group we find there was

TABLE I

Summary of 13 Biopsies of the Liver in 10 Patients

Case no.	Elapsed days	Heterophil antibody	Cephalin-cholesterol flocculation		Thymol turbidity	Total bilirubin	Periportal infiltration	Kupffer cell activity	Hepatic cell destruction	Mitosis of hepatic cells
			240°	480°						
1	2	224	2	3	1.9	0.8	1	1	1	0
2	5	224	0	1	2.2	1.0	2	2	1	0
3	10	224	1	2	1.7	0.6	4	4	2	1
4	11	224	0	0			3	3	3	1
5	13	224	0	0			3	2	2	0
6	14	7168	1	3	4.2		3	3	2	2
7A	19	1792	3	4	3.1	0.7	4	3	2	3
8	28	1792	3	4	4.6	1.4	3	3	2	1
9A	57	7168	4	4	9.4	2.5	2	2	2	0
7B	59	1792	3	4	3.1	0.7	2	2	2	1
10A	120	1792	2	3	3.1	5.4	1	1	1	0
9B	121	7168	4	4	9.4	2.5	2	2	1	0
10B	225	1792	2	3	3.1	5.4	1	3	2	1

For each case are shown the days elapsed since onset of symptoms, the highest recorded heterophil antibody titer, the highest cephalin-cholesterol flocculation reading, the highest thymol turbidity, the most elevated total serum bilirubin, the intensity of the periportal mononuclear infiltration (graded 1 to 4), the intensity of Kupffer cell activity (graded 1 to 4), the amount of hepatic cell destruction (graded 1 to 4), and the degree of mitotic activity in the liver cells (graded 1 to 4).

an apparent lack of correlation between the structural changes in the liver and liver function tests. In case 3 the histologic changes on the tenth day were striking but the cephalin-cholesterol flocculation tests, the thymol turbidity tests, and bilirubin determinations were all within normal limits on the 7th, 15th, 19th, and 28th days after the onset of symptoms. In cases 4 and 5, in which there was histologic evidence of moderate liver damage, the liver function tests showed no abnormalities although they were done within 3 days of the date of biopsy. In case 6 the cephalin-cholesterol flocculation and thymol turbidity tests were slightly elevated the day after biopsy, but the former became negative within a week after biopsy. In case 8 we had the best correlation between the high heterophil titer, elevated cephalin-cholesterol flocculation and elevated thymol turbidity, and the histologic

appearance of an active hepatitis. It is of interest that the thymol turbidity remained elevated for 1 month after the cephalin-cholesterol flocculation test became negative. When thymol turbidity reached its peak, the total serum bilirubin was 1.4 mg. per 100 cc. The patient was never jaundiced clinically.

In case 7, with biopsies on the 19th and 59th days after the onset of symptoms, there was an initial correlation between the hepatic histologic picture and the liver function tests. When the first biopsy was taken the heterophil antibody titer was 1:1792 and the cephalin-cholesterol flocculation test was abnormal. A few days later the thymol turbidity test became abnormal. However, there were histologically demonstrable liver lesions at the time of the second biopsy when the liver function tests were within normal limits.

In case 9 the histologic changes, although relatively slight, persisted for some time after the cephalin-cholesterol flocculation was negative. In spite of the protracted course of this patient, he had no bromsulfalein retention 3 months after the onset of his illness.

In case 10 the first biopsy, 120 days after the onset of symptoms, showed only minimal histologic change in spite of elevated cephalin-cholesterol flocculation and thymol turbidity tests. The total serum bilirubin at this time was 1.5 mg. per 100 cc. In spite of the prolonged course, the liver showed only slight residual structural damage. The patient continued to show mitotic activity in the liver cells at the time of the second biopsy.

The study of these liver specimens taken at intervals from 2 to 225 days after the onset of infectious mononucleosis suggests an explanation for the discrepancy in previously reported histologic findings in this disease. As might be expected, the histologic features appear to depend upon the time interval which has elapsed since the onset of the disease, upon the severity of the infection and, to some extent, upon the presence or absence of jaundice. Only minimal changes in the liver were found in the first 5 days of the disease. They consisted of slight lymphocytic infiltration in the periportal zones, degenerative changes in the liver cells, evidence of regeneration of liver cells, and activity of the Kupffer cells. After 10 days these processes all appeared to be more active. The peak of degenerative and regenerative activity was reached between the 10th and 30th days. During this period periportal infiltration and Kupffer cell activity were most pronounced. At the end of 60 days the periportal infiltration and Kupffer cell activity had subsided considerably but were still present in the protracted cases. Some evidence of isolated degeneration and regeneration of liver cells was still to be seen as long as 225 days after onset. The

histologic changes in the liver are similar to those described in non-fatal cases of epidemic hepatitis.[40] Endophlebitis or inclusion bodies were not seen.

SUMMARY

Liver specimens were obtained by forceps, at peritoneoscopy, in 10 patients with infectious mononucleosis. Biopsies were done from 2 to 225 days after the onset of symptoms. The gross and histologic findings are similar to those described in the livers of patients with non-fatal epidemic hepatitis. Serial liver function studies were performed on most of these patients. An attempt has been made to correlate the histologic findings with the clinical course and the laboratory data. The degree of anatomical change does not parallel the degree of abnormality of the liver function tests.

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[*Illustrations follow*]

DESCRIPTION OF PLATES

PLATE 155

FIG. 1. Liver, case 3 (K. L. M.), 10 days after onset. Periportal mononuclear infiltration with fair preservation of lobular architecture. Hematoxylin and eosin stain. × 115.

FIG. 2. Liver, case 4 (C. L. W.), 11 days after onset. Early stages of acidophilic degeneration of individual hepatic cells. Some cells show hydropic degeneration. Hematoxylin and eosin stain. × 950.

FIG. 3. Liver, case 4 (C. L. W.), 11 days after onset. Late stage (hyalinization) of acidophilic degeneration of individual hepatic cells. Mononuclear cells in sinusoids. Hematoxylin and eosin stain. × 950.

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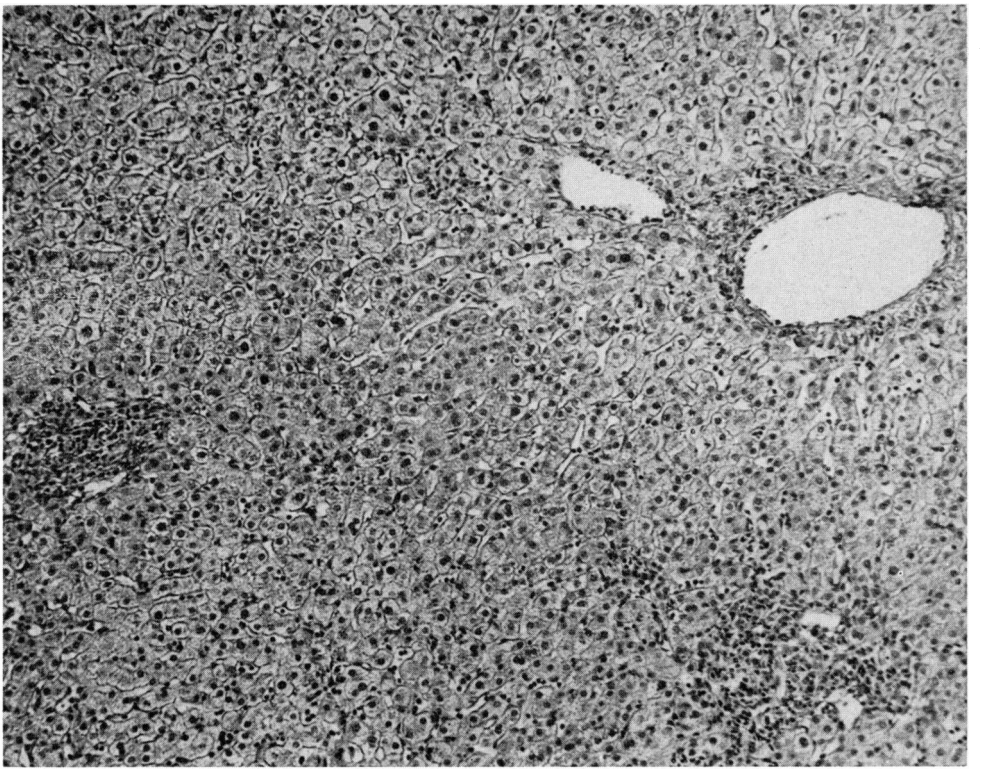

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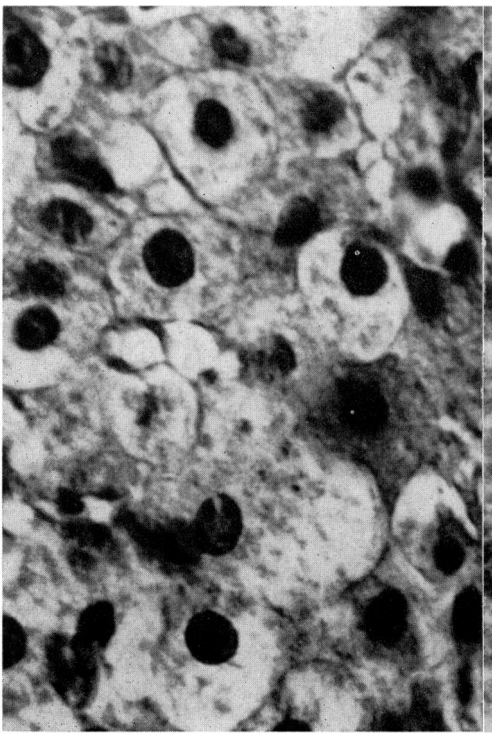

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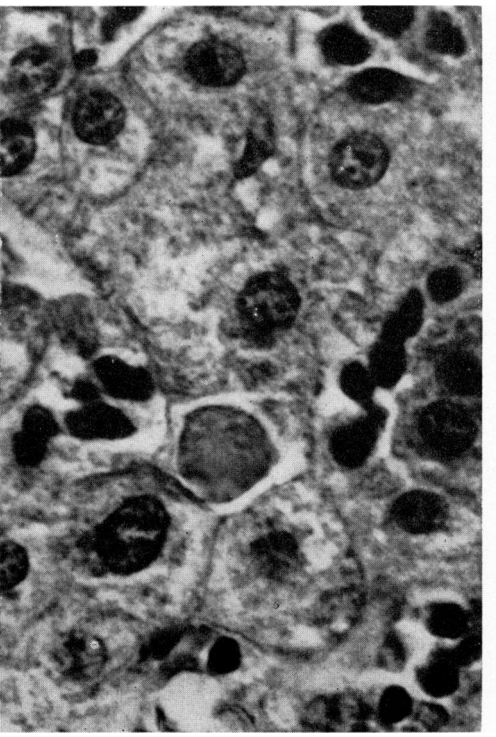

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Liver in Infectious Mononucleosis

PLATE 156

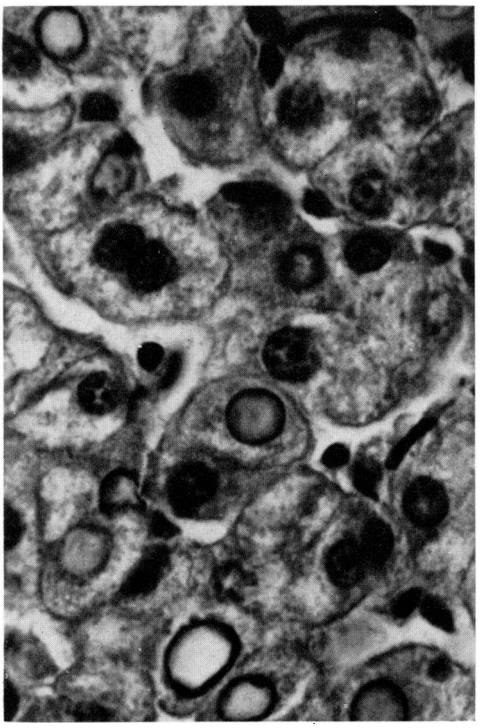
FIG. 4. Liver, case 3 (K. L. M.), 10 days after onset. Numerous hepatic cell nuclei with excessive glycogen content. Binucleate liver cells. Kupffer cells increased in size and number. Hematoxylin and eosin stain. × 940.

FIG. 5. Liver, case 4 (C. L. W.), 11 days after onset. Periportal mononuclear infiltration. Moderate variation in size, shape, and staining reaction of hepatic cells and nuclei. Hematoxylin and eosin stain. × 115.

FIG. 6. Liver, case 7 (L. G. H.), 19 days after onset. Mononuclear infiltration not only in periportal areas but also in scattered foci throughout the liver lobule. Hematoxylin and eosin stain. × 115.

FIG. 7. Liver, case 7 (L. G. H.), 19 days after onset. Binucleate hepatic cells and three mitotic figures in hepatic cells. Hematoxylin and eosin stain. × 950.

4



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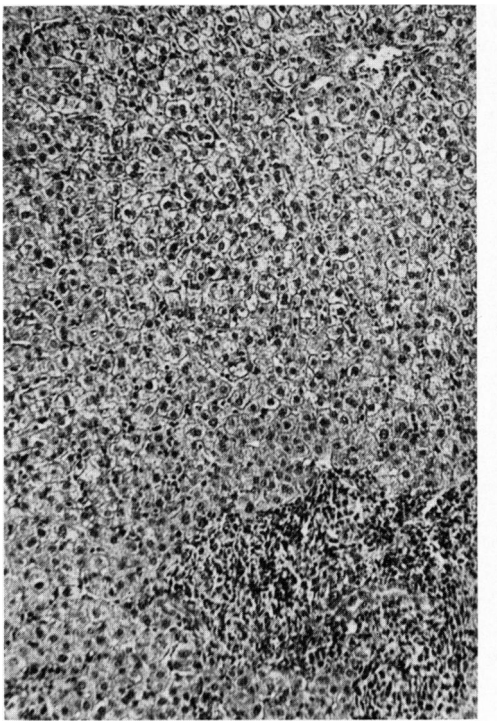

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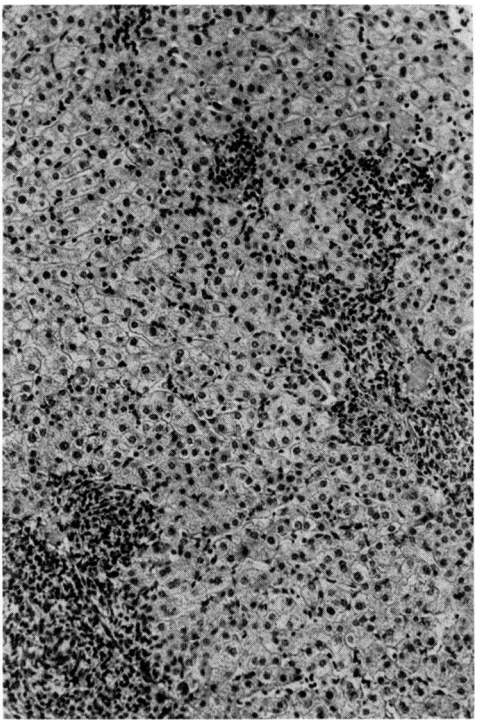

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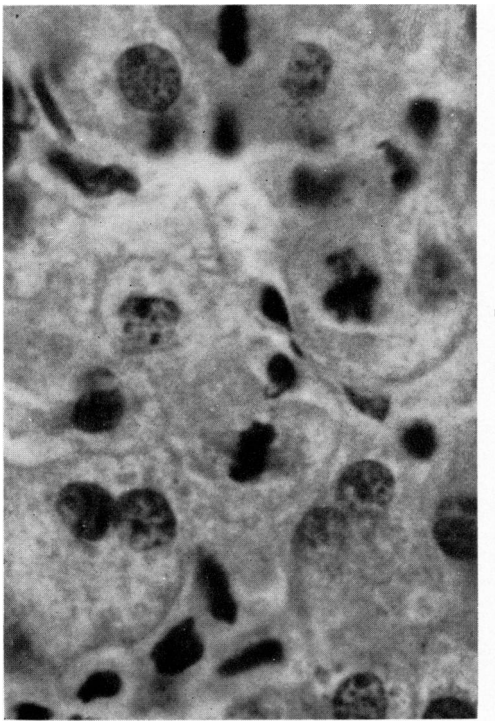

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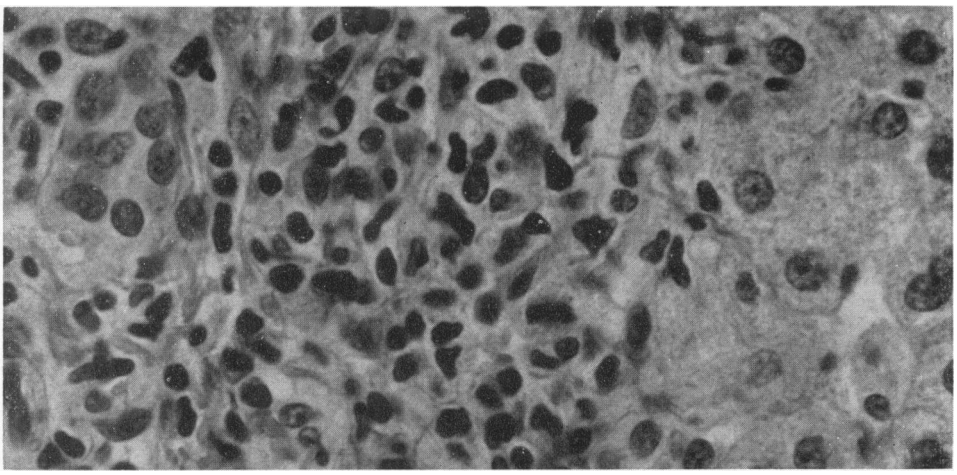
PLATE 157

FIG. 8. Liver, case 7 (L. G. H.), 19 days after onset. Marked periportal mononuclear infiltration. Reduplication of bile ducts. Hematoxylin and eosin stain. × 900.

FIG. 9. Liver, case 7 (L. G. H.), 59 days after onset. Marked reduction in periportal mononuclear infiltration. Reduction in Kupffer cell activity. Hematoxylin and eosin stain. × 115.

FIG. 10. Liver, case 9 (E. R. D.), 57 days after onset. Slight periportal mononuclear infiltration. A few binucleate liver cells. Hematoxylin and eosin stain. × 115.

8



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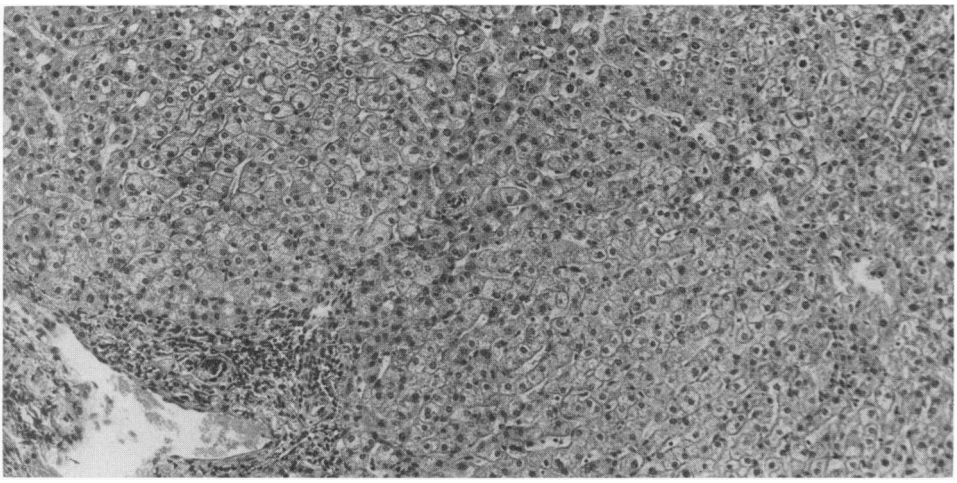

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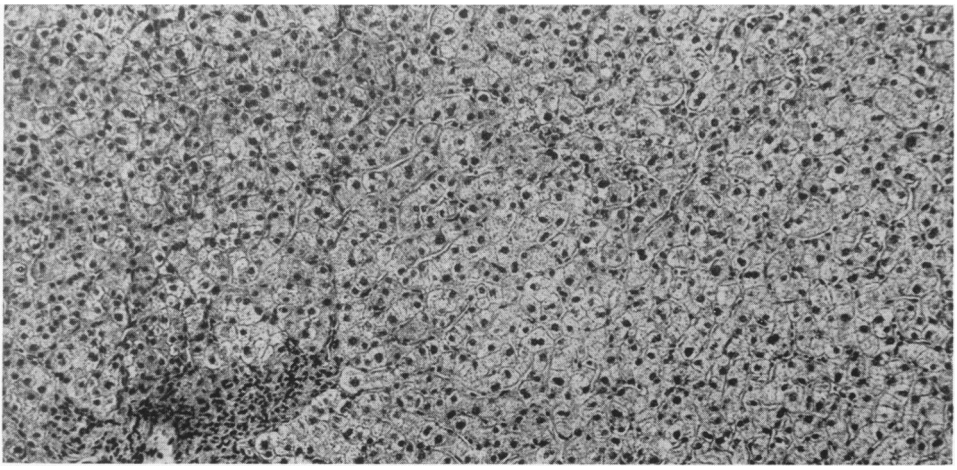

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PLATE 158

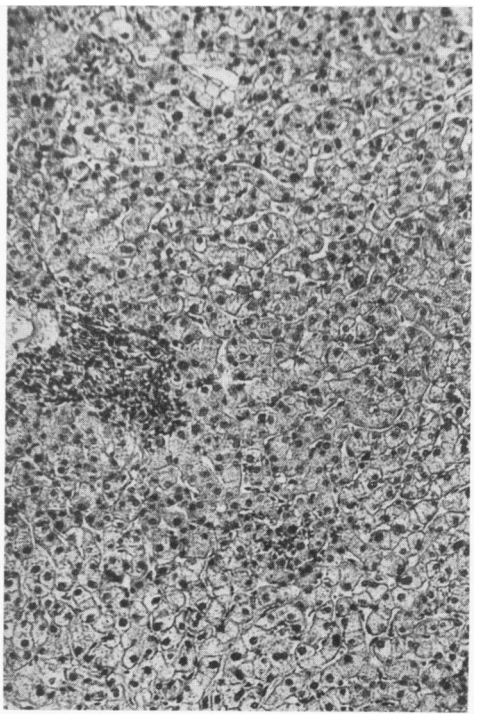
FIG. 11. Liver, case 9 (E. R. D.), 121 days after onset. Slight periportal mononuclear infiltration; for comparison with Figure 10. Hematoxylin and eosin stain. × 115.

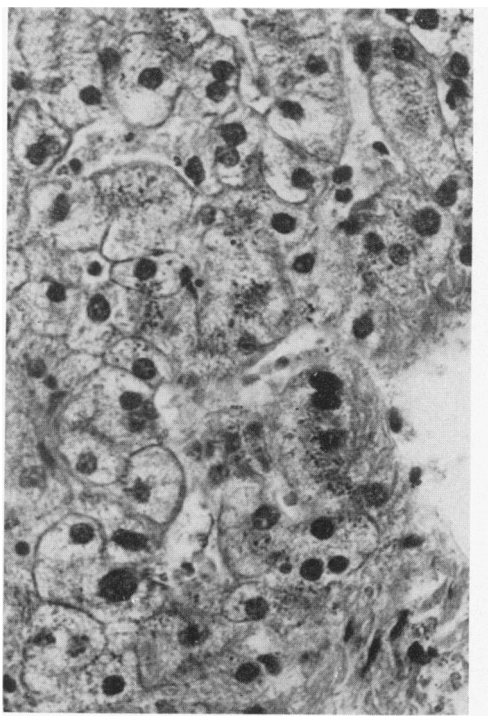
FIG. 12. Liver, case 10 (W. G. E.), 120 days after onset. Bile retention in liver cells and small bile canaliculi about central vein. Binucleate liver cells. Hematoxylin and eosin stain. × 420.

FIG. 13. Liver, case 10 (W. G. E.), 225 days after onset. Practically no periportal mononuclear infiltration. Moderate number of binucleate liver cells. Moderate variation in size and staining of liver cell nuclei. Hematoxylin and eosin stain. × 115.

FIG. 14. Liver, case 10 (W. G. E.), 225 days after onset. Lobular pattern well preserved. Gomori's silver stain for reticulum. × 250.

11





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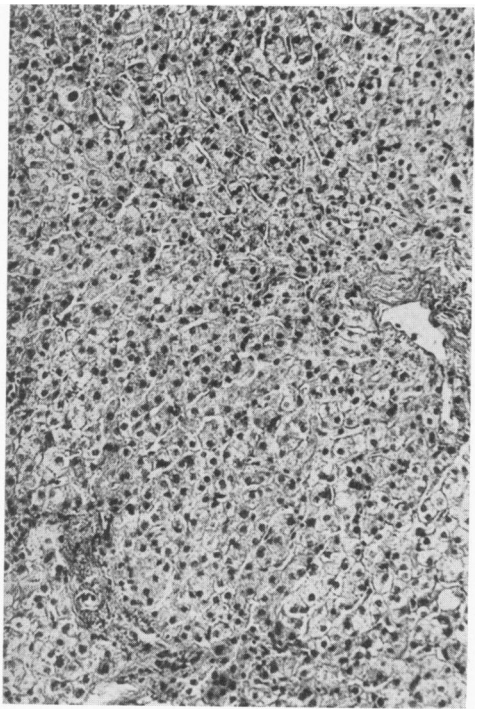

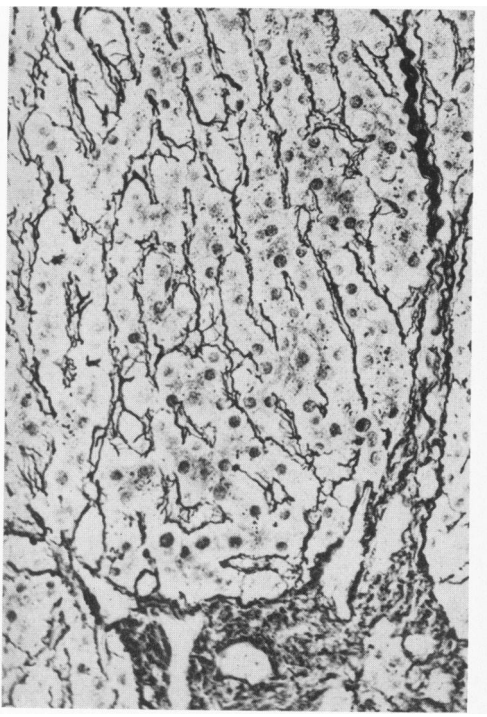

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