THE STRUCTURE OF THE LIVER AFTER RECOVERY FROM EPIDEMIC HEPATITIS *

BALDUIN LUCKÉ, Lt. Col., M.C.

In the preceding paper,[1] the lesions produced by epidemic hepatitis were described as they occur in the liver and other organs in cases that terminated in death. The present paper is concerned with the far more numerous patients who recovered. What lesions, if any, remain in the liver, after the patient has been restored to health? Does the liver, when studied grossly and microscopically, show evidence of permanent damage, or, on the contrary, is repair complete, is lost tissue replaced, does healing occur without scarring? In a word, is clinical recovery accompanied by anatomic restitution so nearly complete as to justify the assertion that the liver has returned to its previous normal condition?

In order to answer these questions it was necessary to study patients who had recovered from a typical attack of epidemic hepatitis, and from whom later, as the result of accident or unrelated disease, the liver became available for examination. A series of such cases occurred during the outbreak of hepatitis in the Army in 1942. Of these, 14 cases have been studied. All these patients had typical hepatitis, the diagnosis being made by experienced clinicians during the course of an epidemic of the disease. Subsequent to the attack, 6 of the patients died from traumatic accident, and 6 from disease. In 2 other patients, a fragment of liver was removed during abdominal operations. These tissues were obtained from 1 to 14 months after clinical recovery from hepatitis.

To insure adequate sampling, blocks of liver were examined from a number of areas when possible. Sections from these were prepared by standard methods.[1] The pertinent clinical data and the results of the morphologic examination follow.

REPORTS OF CASES

Case 1

The patient was a white male, 27 years old.

Clinical Course. May 5, 1942: anorexia, weakness, constipation, headache, nausea, vomiting; later, jaundice. May 22: admitted; mildly jaundiced; liver not enlarged and not tender. May 24: appetite better; still complained of nausea; slight tender-

* From the Army Medical Museum, Institute of Pathology, Washington, D.C.

This investigation has been aided by a grant from the International Health Division of the Rockefeller Foundation, to the AMERICAN JOURNAL OF PATHOLOGY, for the illustrations of this paper.

Received for publication, February 28, 1944.

ness over epigastrium. Improved steadily; by May 31 felt as well as before onset of illness, but trace of jaundice persisted; discharged from hospital. Temperature, pulse and respiration were normal throughout course.

Laboratory Findings. May 23: urine negative for albumin and sugar. Blood count: red blood cells, 5.0 million; white blood cells, 6,300; polymorphonuclear leukocytes, 41%; lymphocytes, 46%; monocytes, 9%; eosinophils, 1%; basophils, 1%. Icterus index, 75.

On June 15, 1942, this man was struck by an airplane and killed instantly. Duration of hepatitis, 26 days; interval between discharge and death, 16 days.

Post-Mortem Examination

Liver. Weight, 1810 gm. Surface was pale red and smooth; capsule, thin. Cut surfaces were homogeneous in appearance and showed no deviation from the normal.

Microscopically, the lobular pattern of the liver was accentuated because of infiltration of the periportal stroma with moderate numbers of polymorphonuclear leukocytes and lymphocytes. The reaction extended for some distance along the peripheries of some, but not of all, lobules. With connective tissue stains no increase in collagen formation could be demonstrated. The lobular architecture was everywhere normal. The hepatic columns were well oriented; the efferent veins occupied normal positions. Many efferent veins had somewhat swollen walls, but no increase in fibrous components was demonstrable. The bile canaliculi were inconspicuous. In the innermost region of some lobules a few liver cells were still lacking. The loss of parenchyma was minimal, probably much less than 1 per cent. Many cells, particularly in the central parts of the lobules, were binucleated, which indicates regenerative activity. The Kupffer cells in the central parts of many lobules contained yellowish pigment, probably lipofuscin.

This liver appears to be well on the way to complete restoration.

Case 2

This patient was a white male, 33 years old.

Clinical Course. About May 18, 1942: malaise, loss of appetite, nausea, vague abdominal pains, "dark" urine. May 16: admitted; skin and sclerae jaundiced; liver was 2 fingersbreadth below costal margin and slightly tender; icterus index, 75; white blood cells, 8,200. Progressed well during first 10 days in hospital. Hepatitis became quiescent, as was indicated by clearing of jaundice and return of index to within normal range. Course was afebrile throughout. On 10th day of hospital stay, temperature rose to 101° F. June 8: chill. June 11: a rough presystolic murmur; the condition was now regarded as subacute bacterial endocarditis, probably precipitated by the attack of catarrhal jaundice. June 27: died (50 days after onset of symptoms of hepatitis).

Post-Mortem Examination

Liver. Slightly smaller than usual. Cut surface showed no gross changes.

Microscopically, the lobular pattern was uniform throughout the organ. The periportal stroma, however, was infiltrated to a moderate degree with lymphocytes, polymorphonuclear leukocytes, and occasional pigmented histiocytes; no increase in collagen had taken place. The small biliary ducts were somewhat conspicuous. The hepatic cords converged in normal manner toward centrally placed, thin-walled veins. In general, the cells were well preserved and of uniform size. Around the central lobular vein the cellular arrangement was somewhat less uniform, and the size of the cells varied; here, large cells with prominent hyperchromatic nuclei, or with two nuclei, were common. An occasional bile "thrombus" was encountered in this region (Fig. 3).

Case 3

The patient was a white male, 30 years old.

Clinical Course. During April, 1942, had an attack of epidemic hepatitis. No clinical details are available. Presumably made a good recovery and returned to duty. On June 2, 1942, died from an unrelated disease: dementia praecox with marked cachexia and hypostasis of the lungs. Interval between discharge from hospital and death, approximately 3 months.

Post-Mortem Examination

Liver. Normal in size and shape; surface was smooth; cut surfaces were grossly normal.

Microscopically, organ was normal. There was no scarring. All traces of previous injury had disappeared. This liver may be considered as an example of the complete repair which in all probability occurs in the vast majority of cases of hepatitis.

Case 4

This patient was a white male, age unknown.

Clinical Course. June 23, 1942: anorexia. July 3: jaundice. July 7: admitted. Steadily improved under treatment and was discharged on July 10. August 12: died of gunshot wound. Duration of hepatitis, approximately 17 days; interval between discharge and death, 32 days.

Post-Mortem Examination

Liver. Weight, 1440 gm. Surface was smooth. Cut surfaces revealed no gross changes.

Microscopically, the organ showed evidence of extensive regeneration. The lobular architecture was preserved; most lobules had a normal structural pattern, *i.e.*, cords of hepatic cells converged toward a common efferent vein. The argentophilic reticulum was intact, and its fibrils were normally delicate. Here and there, however, considerable variation in the size and shape of the lobules was encountered; many were uniformly enlarged, while others showed an eccentric in-

crease in size, so that the shape was distorted. In all lobules the great majority of the cells had stored an abundance of glycogen, and their nuclei were normal in appearance. Proliferative changes were most evident in the neighborhood of the central veins and at the lobular peripheries, where many cells were large and had smooth cytoplasm without glycogen granules and with prominent hyperplastic nuclei; binucleated and multinucleated forms were commonly encountered.

Bile canaliculi were inconspicuous, and retention of bile within cells or within hepatic columns was not evident.

The periportal canals were normal. In most areas their stroma was normal in quantity and quality; here and there, however, it was somewhat more abundant, extended for a short distance along the lobular peripheries and was infiltrated with moderate numbers of histiocytes, lymphocytes and polymorphonuclear leukocytes. In such regions the small biliary ducts usually had undergone slight proliferative changes; that is to say, their number appeared to have doubled or tripled.

Occasionally, small clumps of histiocytes laden with lipofuscin were encountered within the periportal stroma or in the central zones of lobules. The pigment probably was derived from liver cells and served as an indicator of a disintegrative process long since passed.

In summary, the structural restitution of the liver was nearly complete. Traces of inflammatory reaction still lingered in the periportal stroma of some lobules. The hepatic cells were storing glycogen in a normal manner; there was no evidence of interference with the vascular supply or the biliary drainage.

Case 5

This patient was a white male, 23 years old.

Clinical Course. May 20, 1942: anorexia, headache, "dark" urine, constipation, later, jaundice. May 24: admitted; blood pressure, 124/80. Course in hospital was uneventful. July 3: discharged and returned to duty.

Laboratory Findings. May 24 and June 16: urine negative for albumin; positive for bile. July 3: urine negative for albumin and bile. May 24: red blood cells, 4.5 million; white blood cells, 7,700; polymorphonuclear leukocytes, 64%; lymphocytes, 36%. Icterus index: June 8, 30; June 16, 15.

July 20: Died as result of bullet wound. Duration of hepatitis, 43 days; interval between discharge and death, 17 days.

Post-Mortem Examination

Liver. Size and color were normal. Capsule was smooth. Cut surface showed normal architecture.

Microscopically, the liver showed well advanced repair. There was

complete preservation of the lobular pattern. The portal canals and their stroma were normal; no proliferation of smaller biliary ducts was evident. The hepatic columns radiated in normal manner toward the central efferent veins; the strands of supporting reticulum were unbroken. The appearance of the central parts of the lobules contrasted with that of the peripheral zones: many of the central cells were larger and had richly chromatic nuclei; binucleated cells were commonly encountered. These central cells obviously were newly formed by multiplication. In contrast, the peripheral cells were smaller, their nuclei less prominent, and their cytoplasm was laden with glycogen. In some lobules the central cells were still loosely arranged and the tissue contained a few scattered lymphocytes as indicators of past damage. Many of the efferent veins still had a swollen edematous wall, but endophlebitis, such as is commonly observed in cases terminating fatally, was not present.

The conspicuous feature in the central lobular regions was the number of large pigmented macrophages, probably mobilized Kupffer cells; they had ingested a dark brown granular pigment which gave no reaction with iron stains but did react with fat stains.

Repair of the liver may be considered practically complete (Fig. 4).

Case 6

The patient was a white male, age unknown.

Clinical Course. Early in July, 1942, complained of nausea and vomiting and later became jaundiced. July 12: admitted. Course uneventful. July 25: discharged and returned to duty.

September 9: killed in automobile accident. Course of hepatitis, approximately 25 days; interval between discharge and death, 45 days.

Post-Mortem Examination

Liver. Weight, 1795 gm. Surface was smooth. Cut surface showed no significant alteration.

Microscopically, the organ showed little evidence of previous damage aside from the large size and irregular shape of many lobules. The portal canals were normal and their supporting stroma was of average quantity and normally cellular except in a few areas where slight proliferation had led to the extension of thin stromal strands part way about adjacent lobules. Practically all lobules had a normal structural pattern. The cells everywhere were well preserved; in the central lobular zones there were occasional clumps of histiocytes containing lipofuscin; here, binucleated liver cells were common. Many efferent veins had slightly thickened walls. Restoration of this liver is practically complete (Fig. 7).

Case 7

This patient was a white male, 25 years old.

Clinical Course. During August, 1942, had an attack of acute catarrhal jaundice. No clinical details are available. October 18: was operated upon for acute appendicitis. October 22: suddenly went into shock and died as result of obstruction of right pulmonary artery by embolus, probably arising from thrombus in left hypogastric vein. Duration of hepatitis unknown; interval between discharge and death, approximately 2 months.

Post-Mortem Examination

Liver. Weight was approximately 1300 gm., and consistency was normal. Surface was smooth. Capsule was thin. Cut surfaces had normal color and showed normal architectural pattern. No evidence of pathologic change was found.

Microscopically, the architecture was normal. The portal canals and their stroma were completely normal. The hepatic lobules were of average size, and their cords converged in normal manner toward the centrally placed efferent veins. The individual liver cells were normal in size, shape and details of structure. The canaliculi were inconspicuous. No bile "thrombi" were evident. The efferent veins had normal walls. The sinusoids were well filled, and their lining was intact. Reticulum stains showed that the framework had a normal pattern. No traces of previous injury were observed in this liver; restoration following the attack of epidemic hepatitis was complete (Figs. 5 and 6).

Case 8

The patient was a white male, 31 years old.

Clinical Course. About June 13, 1942: loss of appetite, nausea, vomiting, headache, weakness, malaise, "dark" urine. June 19: admitted; sclerae and skin icteric; no tenderness over abdomen; liver and spleen not palpable. Stay in hospital uneventful. June 26: free of symptoms; felt well; jaundice disappearing. June 28: discharged in good condition though still slightly jaundiced.

Went on drinking bout and died on July 5 from acute alcoholism. The alcohol which was drunk was probably impure and unfit for consumption. Duration of hepatitis, approximately 15 days; interval between discharge and death, 7 days.

Post-Mortem Examination

Liver. Except for slight congestion, grossly normal.

Microscopically, the liver was involved in a uniform manner. The lobules presented a similar appearance; in each the columns of liver cells were normally arranged and converged toward a central vein. But the cells immediately surrounding the vein had been destroyed, so that the innermost part of each lobule appeared empty. At the central terminals of the columns the cells were large and had prominent hyperchromatic nuclei; many were binucleated; some had become detached. The cells here were obviously multiplying and restoring lost tissue.

Regenerative activity, however, was not confined to the lobular centers. At the periphery of each lobule many minute biliary ducts were seen at the terminals of the hepatic columns, and larger biliary ducts with numerous branches were present in the periportal stroma. The liver cells also were multiplying, as was indicated by the presence of many richly chromatic nuclei and binucleated cells. This liver exemplifies the fact that the peripheral zone next to the portal area usually takes an active part in the restoration of injured tissue.

Apart from the loss of cells and the multiplication of neighboring survivors, there were no noteworthy changes in the hepatic cords. The component cells had a somewhat lumpy cytoplasm, probably as a result of glycogen storage; no fat could be detected by appropriate stains. The nuclei were normal. The bile canaliculi were inconspicuous and contained no inspissated material.

The supporting reticulum was completely preserved, and where liver cells had been lost unbroken lines of reticulum swept toward the central vein. The latter, in most lobules, had a normal wall; occasional veins with somewhat thickened walls were encountered, but endophlebitis was nowhere seen. The sinusoids were patent and filled with blood.

An indicator of previous destruction of liver cells was furnished by the conspicuous number of swollen and pigmented Kupffer cells. Many had become detached and isolated or, in small clusters, lay in the stroma, particularly in the "empty" center of the lobules and in the periportal stroma. The pigment stained the cells diffusely; it occurred as small brown granules, gave no reaction for free iron, did not have the appearance of bile and stained deeply with Sudan and with silver. The latter, probably by encrustation, caused the granules to appear much coarser than they seemed unstained. This pigment was probably derived from the breakdown of liver cells; it belongs in the large and heterogeneous group of lipochromes.

The peripheries of the lobules were clearly marked, and here the portal stroma still contained a moderate excess of lymphocytes and plasma cells, occasional leukocytes and many pigmented histiocytes. The proliferative changes in the bile ducts, mentioned previously, helped in making the lobular peripheries prominent. The portal canals were normal. There was no evidence of connective tissue overgrowth. It is to be expected that the reactive changes will eventually subside.

Summarizing, this liver shows evidence of destruction of cells in the innermost portions of the lobules (Fig. 2). Through regenerative multiplication of the adjacent surviving cells all but approximately 5 per cent of the parenchyma has been restored. The small amount still lacking to complete restoration is negligible, in view of the enormous

reserve of hepatic tissue. What part alcohol and associated faulty diet played in the hepatic picture of this case is problematic. From the history it is evident that death was due directly or indirectly to excessive use of alcohol; moreover, the alcohol used was probably impure and unfit for consumption. There is a distinct possibility that because of excessive consumption of alcohol complete restoration of hepatic tissue has been delayed.

Case 9

The patient was a white male, 23 years old.

Clinical Course. May 22: anorexia, nausea, fatigue, constipation; later, "dark" urine. May 28: icteric sclerae. June 4: admitted; moderately jaundiced; slight tenderness in right upper quadrant; liver not palpable. The course was afebrile. Appetite remained poor for several days, then gradually returned to normal.

Laboratory Findings. Icterus index: June 8, 90; June 15, 50; June 17, 30. June 4: urine was positive for bile. June 5: red blood cells, 4.9 million; white blood cells, 4,700; polymorphonuclear leukocytes, 72%; lymphocytes, 28%.

October 29: killed in an automobile accident. Duration of hepatitis, 25 days; interval between discharge and death, 102 days.

Post-Mortem Examination

Liver. Grossly normal except for a traumatic tear through the capsule.

Microscopically, the architecture of the liver was preserved. The portal canals were normal. The cellular contents of the supporting stroma were within the normal range. The hepatic lobules had average size and shape; their cords converged toward centrally placed efferent veins. The latter usually had thin walls, though here and there a vein with a thick edematous wall was encountered. The individual liver cells were normal in staining qualities; occasional binucleated forms were present, particularly in the more central portions of the lobules. The reticulum framework was normal in arrangement and amount. This liver appeared to have been completely restored.

Case 10

This patient was a white male, 35 years old.

Clinical Course. About July 15 he was seen as an out-patient because of icteric sclerae, with the usual symptoms of catarrhal jaundice. Because of mild character of the attack, he was not placed in hospital. July 22: dyspnea and signs of bronchopneumonia developed. July 23: died.

This patient had an attack of mild epidemic hepatitis and a virulent form of hemorrhagic bronchopneumonia developed while he was recovering from the hepatitis. The total duration of the hepatitis is difficult to estimate from the history, but it was probably 2 weeks. No further information is available.

Post-Mortem Examination

Liver. Average size, had a smooth surface and thin capsule. Cut surface showed no significant deviation from the normal.

Microscopically, the architecture was preserved. The portal stroma was normally cellular; the bile ducts showed no proliferative changes. Small groups of liver cells had been lost in patches which were usually adjacent to the central lobular veins. In these regions the sinusoids were moderately engorged, and scattered histiocytes and lymphocytes were present. The efferent veins had somewhat swollen walls, some of which were sparsely invaded by lymphocytes. Active regeneration of liver cells in the destroyed areas was indicated by the presence of numerous binucleated and multinucleated cells. In many lobules the intracolumnar canaliculi were conspicuously dilated and contained clumps of inspissated bile.

This liver is an example of early restoration which is not as yet complete (Fig. 1).

Case 11

This patient was a white male, 35 years old.

Clinical Course. In June, 1942, became fatigued and was intermittently nauseated. During July, lost his appetite; tenderness developed in the upper abdomen; the urine became dark; and jaundice appeared, which gradually deepened. About August 1 the stools became clay-colored. Diagnosis of acute catarrhal jaundice was made on August 3. August 8: patient was transferred to a General Hospital; was nauseated and deeply jaundiced; complained of itching but had no other objective or subjective symptoms; blood pressure, 104/70. After 1 week in bed he improved considerably. September 2: felt much better; stools darker; liver slightly enlarged and tender. September 6: temperature, 100° F.; complained of discomfort in upper abdomen. September 14: no complaints; jaundice much improved; edge of liver no longer below costal margin. October 2: in good condition. From then on progress was uneventful. November 11: patient discharged and returned to duty.

On December 13, signs of perforated peptic ulcer developed. At operation the perforated area was found on the anterior wall. The liver had a normal appearance. The edge was slightly thickened. A specimen approximately 2 by 1.5 cm. was removed for examination. Duration of hepatitis, approximately 6 months; interval between discharge and taking of specimen for biopsy, 32 days.

Laboratory Findings.

Date	Icterus index	Date	Icterus index	Date	Icterus index
August 10	121	Sept. 6	43	Oct. 7	15
August 17	200	Sept. 12	31	Oct. 23	12
August 24	135	Sept. 21	26	Nov. 6	16
August 30	100	Sept. 30	23	Nov. 11	12

Blood Count. August 14: red blood cells, 4.2 million; white blood cells, 8,500; polymorphonuclear leukocytes, 59%; lymphocytes, 37%. October 30: red blood cells, 4.3 million; white blood cells, 8,800; polymorphonuclear leukocytes, 69%; lymphocytes, 31%.

Microscopic Examination of Specimen Removed from Liver

Microscopically, the specimen consisted of a triangular piece of tissue measuring 17 mm. at the base and 8 mm. in height. The capsule was of average thickness. Its vessels were engorged and a few capil-

laries had ruptured; the resulting small hemorrhages were probably due to the operative procedures. The architectural pattern of the liver was normal. The size and shape of the lobules were unaltered; the lobules were composed of normal hepatic cords which converged toward central efferent veins. The individual cells were of average size and their nuclei had a normal appearance; the cytoplasm was dotted with many small irregular vacuoles which indicated normal glycogen storage. Occasional cells contained a few sharply contoured droplets of fat. The reticular framework of the lobules was intact and was normally delicate. The efferent hepatic veins and the portal canals were likewise normal. The portal stroma was infiltrated by moderate numbers of lymphocytes and leukocytes. In some of the portal vessels, and here and there in the sinusoids, were small clusters of well preserved leukocytes which probably indicated a recent infection or destructive process in the abdomen. Hepatic damage had been successfully repaired, and restoration may be considered complete (Fig. 8).

Case 12

The patient was a white male, 25 years old.

Clinical Course. June 16, 1942: admitted to hospital with history of feeling tired and having poor appetite for past 2 weeks. Sclerae became jaundiced on June 15. On admission he was ambulatory and not acutely ill. Liver was not tender or palpable. Clinical course was uneventful and afebrile. Remained in hospital until December 15 and was then given sick leave. In January, 1943, upper abdominal pain developed which was not affected by food, activity, or pressure; he was not nauseated and did not vomit. February 13, 1943: x-ray examination revealed numerous stones in the gallbladder. Impression of the surgeons was that the stones originated during attack of acute hepatitis in summer of 1942. March 23: cholecystectomy showed the gallbladder had slightly thickened walls and contained seven dark brown stones. At this operation a small portion of the liver was removed for examination.

Duration of hepatitis, approximately 3 months; interval between discharge and taking of specimen for biopsy, approximately 4 months.

Laboratory Findings.

Date	Icterus index	Date	Icterus index	Date	Icterus index
July 7	230	August 1	32	Jan. 1	17
July 10	125	August 11	26	Jan. 8	18
July 19	41	Sept. 6	25	Jan. 11	18
July 24	49	Sept. 13	12		

Microscopic Examination of Specimen Removed from Liver

Two fragments of tissue, each measuring approximately 18 by 5 mm. were examined. Both were from the region of the gallbladder. The tissue changes in the two sections were somewhat dissimilar. In one, the architectural pattern was normal, although several lobules were exceptionally large. The portal canals and their supporting stroma

showed no alteration. The efferent veins had thin walls; occasional ones were eccentrically located. The liver cells generally were large and of uniform size; all were well preserved; their nuclei were intact and their cytoplasm contained a normal store of glycogen. In the other section thin strands of stroma partly encircled some of the lobules. Otherwise the appearances of the two sections were similar. The slight focal perilobular fibrosis was similar to that which commonly occurs in regions of the liver adjacent to a chronically inflamed gallbladder; it probably represented an extension of a local chronic inflammatory reaction. Restoration of the hepatic parenchyma was complete.

Case 13

The patient was a white male, 32 years old.

Clinical Course. About June 27, 1942, generalized aching, malaise, anorexia and nausea; later, jaundice and "dark" urine. July 3: admitted; temperature, pulse and respiration were normal; liver not definitely palpable and not tender. While in hospital jaundice deepened markedly. Patient remained afebrile except for occasional rises in temperature up to 99.2° F. September 1: discharged and given 30 days sick leave.

Laboratory Findings. On admission, icterus index was 25; it gradually increased during the next 3 weeks to a maximum of 230, after which it dropped; it was 10 at the time of discharge. During the early stages of jaundice, the urine contained bile. Blood chlorides on July 28 were 412 mg.%.

April 10, 1943: died from bullet wound. Duration of hepatitis, approximately 3 months; interval between discharge and death, 8 months.

Post-Mortem Examination

Liver. Weight, 1580 gm. External surface was smooth, capsule was thin, and cut surfaces were grossly normal.

Microscopically, the lobular pattern was completely normal. The size of the lobules in general varied but little from the average; in occasional areas a few lobules appeared enlarged, and a few others were reduced in size. The portal triads also were normal; most of them lay in a scanty stroma which here and there contained a slightly increased number of lymphocytes. The hepatic cords converged in regular manner toward thin-walled, centrally placed veins. The liver cells were fairly uniform in size; their nuclei were well preserved; their cytoplasm had an abundant store of glycogen. Only one indicator of previous damage remained: in some lobules the cells immediately adjacent to the central veins were large and had prominent, deeply chromatic nuclei; binucleated cells were commonly encountered.

Case 14

This patient was a white male, 22 years old.

Clinical Course. July 7, 1942: loss of appetite, general malaise, nausea, vomiting, "dark" urine; later, jaundice. Uneventful course in hospital. July 24: discharged.

Patient was readmitted about 1 year later with evidence of chronic glomerulonephritis and died on September 24, 1943. Diagnosis was confirmed by post-mortem examination. Duration of hepatitis, approximately 17 days; interval between discharge and death, 14 months.

Post-Mortem Examination

Liver. Grossly normal.

Microscopically, the lobules were normal in size, shape and arrangement. The periportal stroma was scanty and contained no excessive number of cells. The bile ducts and vessels were normal. The hepatic cords had the usual radiating pattern, and their component cells were normal. The efferent veins had thin walls. Repair of this liver was complete.

Comments on the Gross and Microscopic Appearance of the Liver

Without exception, the liver in each of the 14 cases studied had macroscopically a normal appearance. The size and shape were within normal limits, the surface was smooth, the capsule thin, the consistency unaltered. The structural pattern of the cut surface was uniform.

Microscopically, the appearance varied somewhat, depending on the length of time between the attack of hepatitis and death or biopsy. In all cases, however, the lobular architecture was preserved, and the reticulum frame was intact.

In summarizing the microscopic appearances it is convenient to describe first the hepatic parenchyma, and afterwards the periportal stroma, ducts, and vessels.

The Hepatic Parenchyma

In 2 cases, restitution of lost parenchyma was not yet complete. One of these patients (case 10) had died of intercurrent infection during convalescence from hepatitis, the other (case 8) from acute alcoholism only 1 week after leaving the hospital. In these livers the process of repair could still be observed.

Thus in case 10, in the central portions of most lobules, the columns of liver cells appeared broken, and small patches of parenchyma were lacking (Fig. 1). Many bile canaliculi were dilated with clumps of bile. Numerous binucleated or multinucleated liver cells indicated active regeneration.

With the exception of these two examples of incompleted repair, restitution of hepatic parenchyma was very nearly complete in 3 cases, and entirely complete in the other 9. The patients (cases 1, 2 and 5) of the first group died within approximately 3 weeks after clinical re-

covery from jaundice. The lobular structure in all had been restored completely, and only an occasional liver cell was still lacking. Some traces of previous damage, however, were discernible. Thus, in case 2 numerous large cells with one or two hyperchromatic nuclei were clustered in the immediate neighborhood of the central lobular vein, and a few canaliculi in this region still contained bile "thrombi" (Fig. 3). The appearance of the reticulum in the central zone of a lobule, *i.e.*, in the previously damaged region, is shown in another, similar case (Fig. 4). The arrangement, delicacy and complexity of the reticulum network are entirely normal.

We now come to the group of 9 cases in which the lost tissue was entirely restored. In these cases a longer time, from 1 to 14 months, had elapsed since discharge from the hospital. In most of them the structure of the lobules was normal, while in 2 cases slight variations in size and shape of some of the restored lobules suggested previous injury and subsequent repair. The hepatic cells had a healthy appearance. Fat and glycogen storage appeared to be within the usual limits, and the cytoplasm contained no abnormal constituent. In summary, restitution of lobular parenchyma was very nearly complete 3 weeks after recovery from hepatitis, and entirely complete 1 month after clinical recovery.

The Periportal Stroma

A slight to moderate increase in cellularity was observed in nearly one-half the cases. The cells were mainly lymphocytes and larger mononuclear cells, but polymorphonuclear leukocytes were also present, although in relatively small numbers. This increase in cellularity was generally confined to the livers of those patients who had recovered less than a month previously.

In 3 cases of the series (1, 6, and 12) thin strands of cellular connective tissue were found to extend for some distance along the periphery of the lobules. Encircling of lobules or significant scarring was observed in none. Moreover, the slight fibrosis was focal and never diffuse.

Biliary Ducts

In 3 cases the small bile ducts showed a slight to moderate degree of proliferation. Conspicuous branching, such as is a prominent feature in fatal cases, occurred in none.

Vasculature

The branches of the portal vein and of the hepatic artery were normal. The sinusoids had an average blood content. The central lobular vein in 4 cases had somewhat swollen walls; in one instance

(case 10) the subendothelial intima was sparsely infiltrated with lymphocytes (this patient died during early convalescence). Definite endophlebitis, a notable feature in fatal cases, was not observed. None of the cases showed perivenous condensation of reticulum or of collagenous connective tissue.

Histiocytes with Lipofuscin Granules

In 5 cases pigmented histiocytes, isolated or in small clusters, were found, particularly in the central zones. These cells may be regarded as indicators of past destruction of liver cells.[1]

Summary of Microscopic Findings

The results of microscopic examinations may now be summarized as follows. In all 14 cases of the series, the lobular architecture was preserved, and the reticular framework was intact. Two patients who had died during, rather than after, convalescence showed incompleted repair, in the sense that small patches of hepatic parenchyma were still lacking in the central zone of the lobules.

In the remaining 12, restitution of the parenchyma was very nearly complete in 3, and entirely so in 9 cases. In the periportal stroma traces of inflammatory reaction lingered in 6 cases; in 3 of them slight focal increase of the stroma had taken place. Scarring was present in none. Slight proliferation of the small bile ducts was observed in 3 cases. Phagocytic cells containing lipofuscin were found in 5 cases. In 4 cases the walls of the central lobular veins were somewhat thickened. Briefly, the changes observed represent slight traces of preceding hepatic injury; they do not indicate persistent or progressive damage. The hepatic parenchyma has been restored in normal manner.

Discussion

The liver is known to have great powers of regeneration.[2-4] Whether after destruction of liver substance regeneration is complete, with restoration to the previous normal condition, or whether extensive scarring and permanent damage occurs, depends on two circumstances.[5-8] The first is whether the damage is confined to the cells of the hepatic parenchyma. If so, regeneration may be complete, as these cells have great ability to multiply and restore themselves. If, however, damage involves the reticulum of the lobule or if the hepatic veins or the portal vessels and their stroma are destroyed, then restoration of the hepatic lobule occurs in an abnormal fashion, with more or less extensive fibrosis, and permanent damage.

The second factor is whether damage to the liver occurs only once

or whether insults are repeated. Recovery from a single injury affecting only the parenchymal cells may be complete whereas repeated destruction of cells, especially at short intervals, may result in fibrosis and permanent damage.

Such is the pattern of reaction of the liver to injury, as ascertained both through experimental work and from study of human material.

Thus Whipple and Sperry[9] found that after chloroform had been administered to dogs in amounts sufficient to cause necrosis of two-fifths or three-fifths of every hepatic lobule, the livers of surviving animals regenerated perfectly in 3 weeks. Similar complete recovery of the liver occurred after single doses of carbon tetrachloride (Cameron and Karunaratne[8]), though not after repeated doses unless time for regeneration was allowed between doses.

In monkeys infected with yellow fever (Klotz and Belt[6]), two-thirds died and showed extensive liver necrosis, but of those that recovered all showed complete and scarless hepatic regeneration.

That the liver of epidemic hepatitis conforms to this reaction pattern has been shown by the present study. In hepatitis the destruction of liver cells occurs acutely, not as a continued process with progressive damage and fibrosis. Further, destruction is confined to the hepatic cells; reticulum, intralobular vasculature, portal canals and stroma are left intact. Therefore, complete regeneration is possible. The results of this investigation show that complete regeneration is in fact the rule; that in nonfatal cases of hepatitis there is no progressive or residual damage to the liver; that just as clinical recovery is complete, so the liver parenchyma is restored to its previous anatomic condition.

There have recently appeared two important papers[7,10] on the pathology of the liver in epidemic hepatitis. In a number of patients, specimens for biopsy were taken both during the acute attack and after recovery. At the first biopsy there were many necrotic liver cells in the center of the lobules, but at the second biopsy the liver was found restored to normal, as is shown by photographs. The authors concluded that most cases of hepatitis end in complete recovery of the liver. In a few other cases, scars were found. The histories of these patients suggest that the scarring antedated hepatitis or else that the patients suffered from liver diseases other than hepatitis. Furthermore, a sharp distinction must be made between harmless focal scars and cirrhosis, a progressive disease affecting the liver diffusely. This distinction has lately been re-emphasized in an excellent paper by Karsner.[11]

Lastly, there is a wealth of clinical evidence which favors the view that acute hepatitis, either in its epidemic or its sporadic form, tends to heal without leaving a permanently damaged liver such as is found

in cirrhosis. There has been no increase in cirrhosis following the numerous outbreaks of hepatitis. In fact, Rössle [12] stated that during the first World War and in the years immediately following, 1914 to 1922, the incidence of cirrhosis noticeably decreased, whereas during the same period occurred a rise in the incidence of so-called catarrhal jaundice.

It must not be forgotten that both epidemic hepatitis and cirrhosis of the liver are common diseases; hence patients suffering from cirrhosis may sometimes give a history of a previous attack of "catarrhal jaundice." Such a history does not, however, prove a causal relationship.

Summary

Only a small fraction of the cases of epidemic hepatitis terminate in death. The great majority of patients make a clinical recovery that is complete and apparently permanent. Whether in these recovered cases the liver is fully restored to a normal condition, or whether, on the contrary, there is residual damage or even progressive pathologic changes is the subject of this investigation.

The structure of the liver was studied in 14 cases after recovery from epidemic hepatitis. From 1 week to 14 months after the attack, these livers became available for examination as the result of fatal accident or unrelated disease.

Grossly all livers appeared entirely normal. Microscopically the appearance varied somewhat with the elapsed time since recovery, but in every instance the integrity of all liver lobules was preserved. In 2 patients who died of intercurrent disease during convalescence, repair of the liver lobules was still under way, and cells lost from the central part of the lobules had not been entirely replaced. In 3 cases examined within a month after clinical recovery, the liver lobules were entirely reconstituted, but slight evidence of previous damage still remained. In 9 other cases examined from 1 to 14 months after recovery, the liver parenchyma was restored completely. In less than half of the cases, traces of previous damage were found in the portal triads, but in none was found significant scarring.

It is concluded that complete restoration of hepatic parenchyma occurs in nonfatal cases of hepatitis. This conclusion is in agreement with what is known about the ability of the liver to regenerate. Regeneration is usually complete providing that destruction is acute and injury not continued, and providing that destructive changes involve only the hepatic cells, not the framework or vessels. This is the case in epidemic hepatitis. In the present investigation there was found no evidence of permanent damage to hepatic parenchyma, and restoration of the liver was practically complete.

REFERENCES

1. Lucké, B. The pathology of fatal epidemic hepatitis. *Am. J. Path.*, 1944, 20, 471–593.
2. Fishback, F. C. A morphologic study of regeneration of the liver after partial removal. *Arch. Path.*, 1929, 7, 955–977.
3. Bollman, J. L., and Mann, F. C. The physiology of the impaired liver. *Ergebn. d. Physiol.*, 1936, 38, 445–492.
4. Herxheimer, G., and Thölldte, M. Regeneration und Hypertrophie (Hyperplasie) der Leber. In: Henke, F., and Lubarsch, O. Handbuch der speziellen pathologischen Anatomie und Histologie. J. Springer, Berlin, 1930, 5, pt. 1, 988–1037.
5. Adami, J. G. Principles of Pathology. Lea & Febiger, Philadelphia, 1910, ed. 2.
6. Klotz, O., and Belt, T. H. Regeneration of liver and kidney following yellow fever. *Am. J. Path.*, 1930, 6, 689–697.
7. Dible, J. H., McMichael, J., and Sherlock, S. P. V. Pathology of acute hepatitis. *Lancet*, 1943, 2, 402–408.
8. Cameron, G. R., and Karunaratne, W. A. E. Carbon tetrachloride cirrhosis in relation to liver regeneration. *J. Path. & Bact.*, 1936, 42, 1–21.
9. Whipple, G. H., and Sperry, J. A. Chloroform poisoning. Liver necrosis and repair. *Bull. Johns Hopkins Hosp.*, 1909, 20, 278–289.
10. Roholm, K., and Iversen, P. Changes in the liver in acute epidemic hepatitis (catarrhal jaundice) based on 38 aspiration biopsies. *Acta path. et microbiol. Scandinav.*, 1939, 16, 427–442.
11. Karsner, H. Morphology and pathogenesis of hepatic cirrhosis. *Am. J. Clin. Path.*, 1943, 13, 569–606.
12. Rössle, R. Entzündungen der Leber. In: Henke, F., and Lubarsch, O. Handbuch der speziellen pathologischen Anatomie und Histologie. J. Springer, Berlin, 1930, 5, pt. 1, 243–505.

[*Illustrations follow*]

DESCRIPTION OF PLATES

PLATE 121

FIG. 1. Case 10. Area from central part of a lobule in which restoration of parenchyma is incomplete; small groups of liver cells are lacking. The sinusoids are distended. The stroma is edematous, and through it are sparsely scattered lymphocytes and histiocytes. In two hepatic columns, shown in cross section, the canaliculi are dilated with bile. × 500.

FIG. 2. Case 8. In the central part of this lobule the destroyed parenchyma has not as yet been completely restored. The hepatic cords converge in normal manner toward the lobular center. At the terminals of the cords the cells are large, and have prominent hyperchromatic nuclei; these regenerating cells are invading the empty stroma. The latter contains a moderate number of lymphocytes and histiocytes. The periportal stroma shows similar cells, and a few small proliferating bile ducts. There is no evidence of new formation of collagenous connective tissue. × 100.

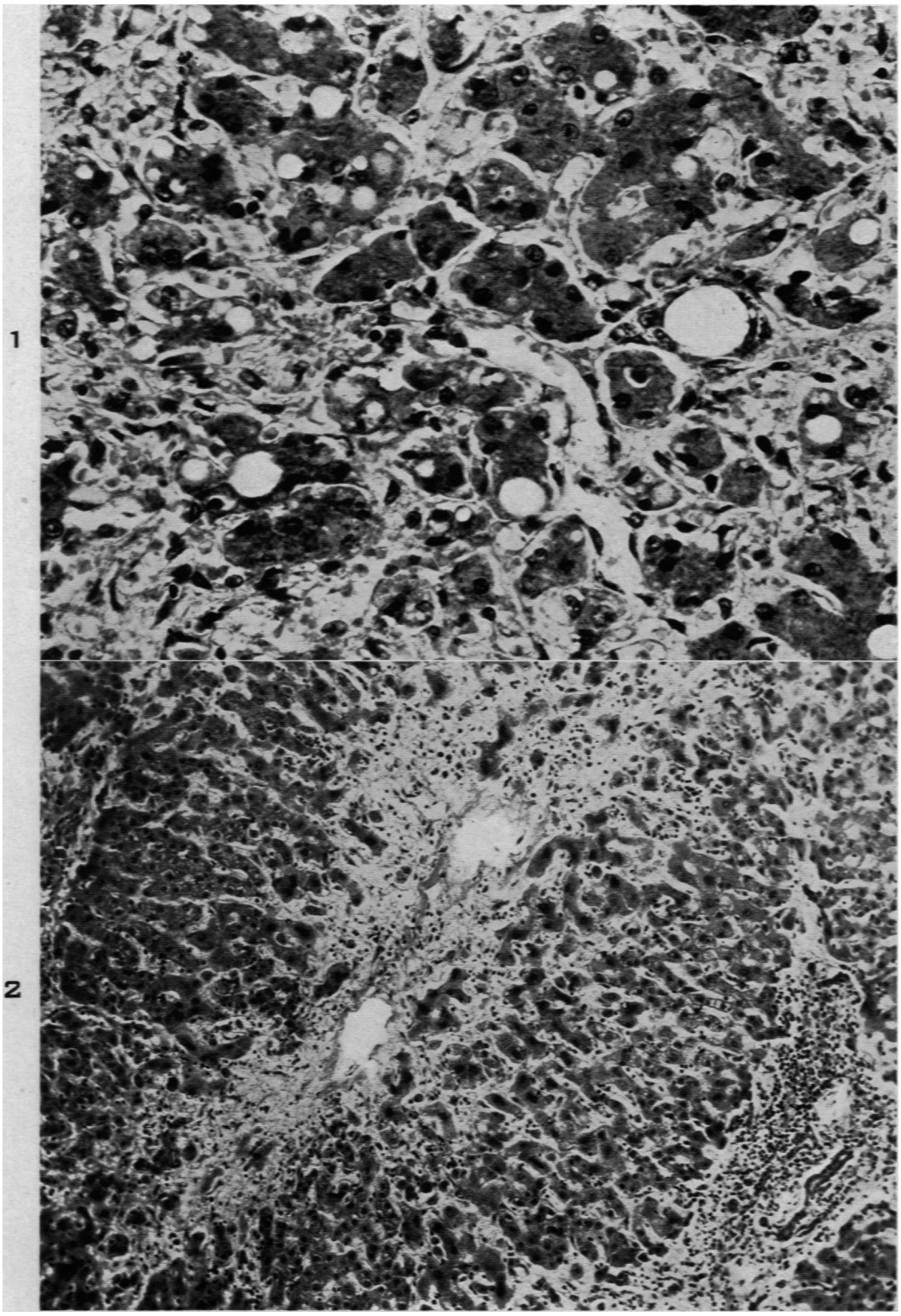
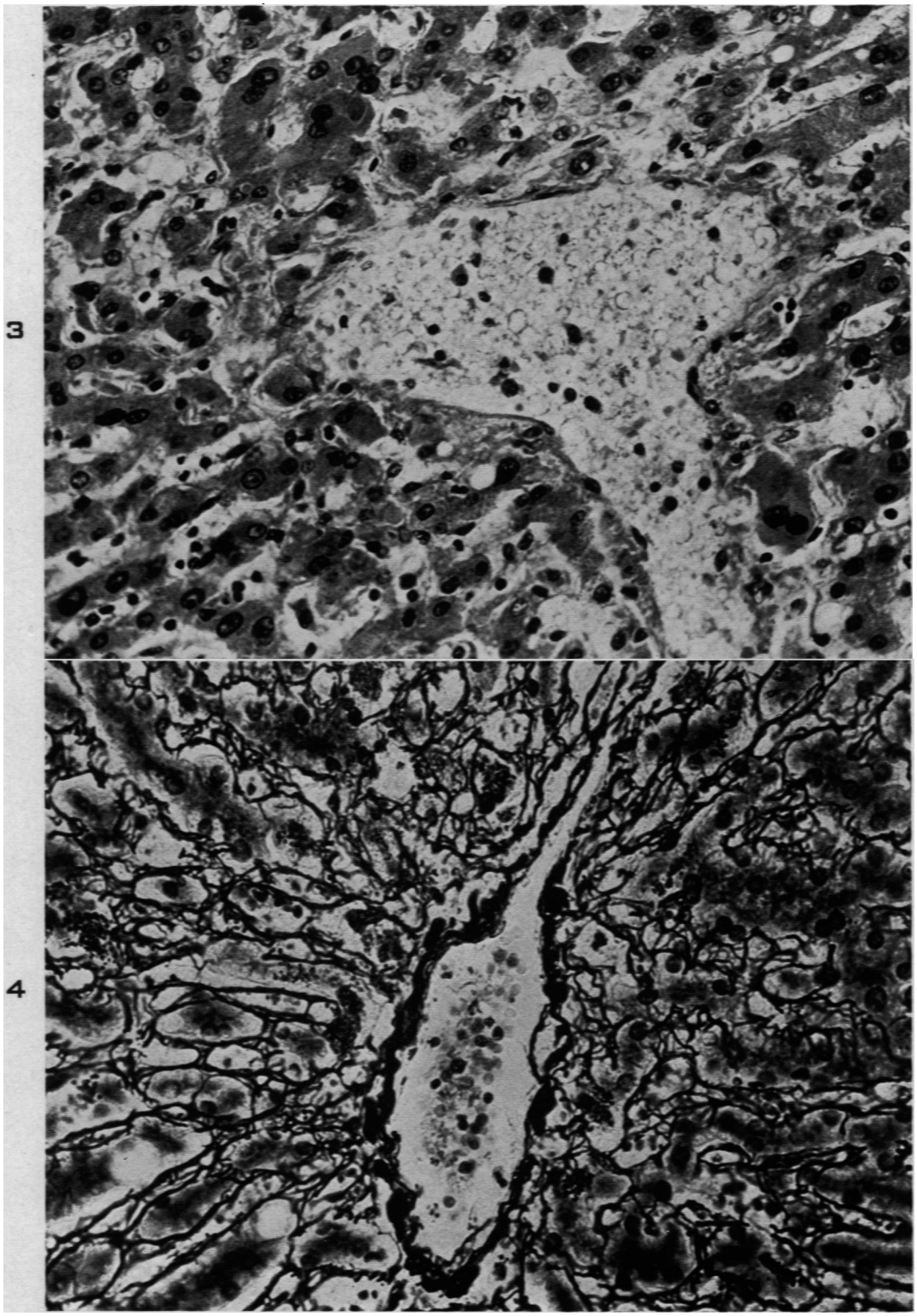


PLATE 122

FIG. 3. Case 2. Central part of a lobule showing an efferent vein and the adjacent hepatic parenchyma. The wall of the vein is normal. The parenchyma has been restored; a number of liver cells are conspicuously large and have one or two prominent hyperchromatic nuclei. In one of the hepatic cords a bile "thrombus" may be seen above and to the left of a large vein. × 500.

FIG. 4. Case 5. Central part of a lobule. The reticulum has a normal pattern. Here and there, a few liver cells are still lacking. The stroma contains numerous macrophages with ingested lipofuscin, the granules of which are blackened by the silver stain. Elsewhere, the reticular meshes enfold normal regenerated liver cells. Wilder's reticulum stain. × 500.



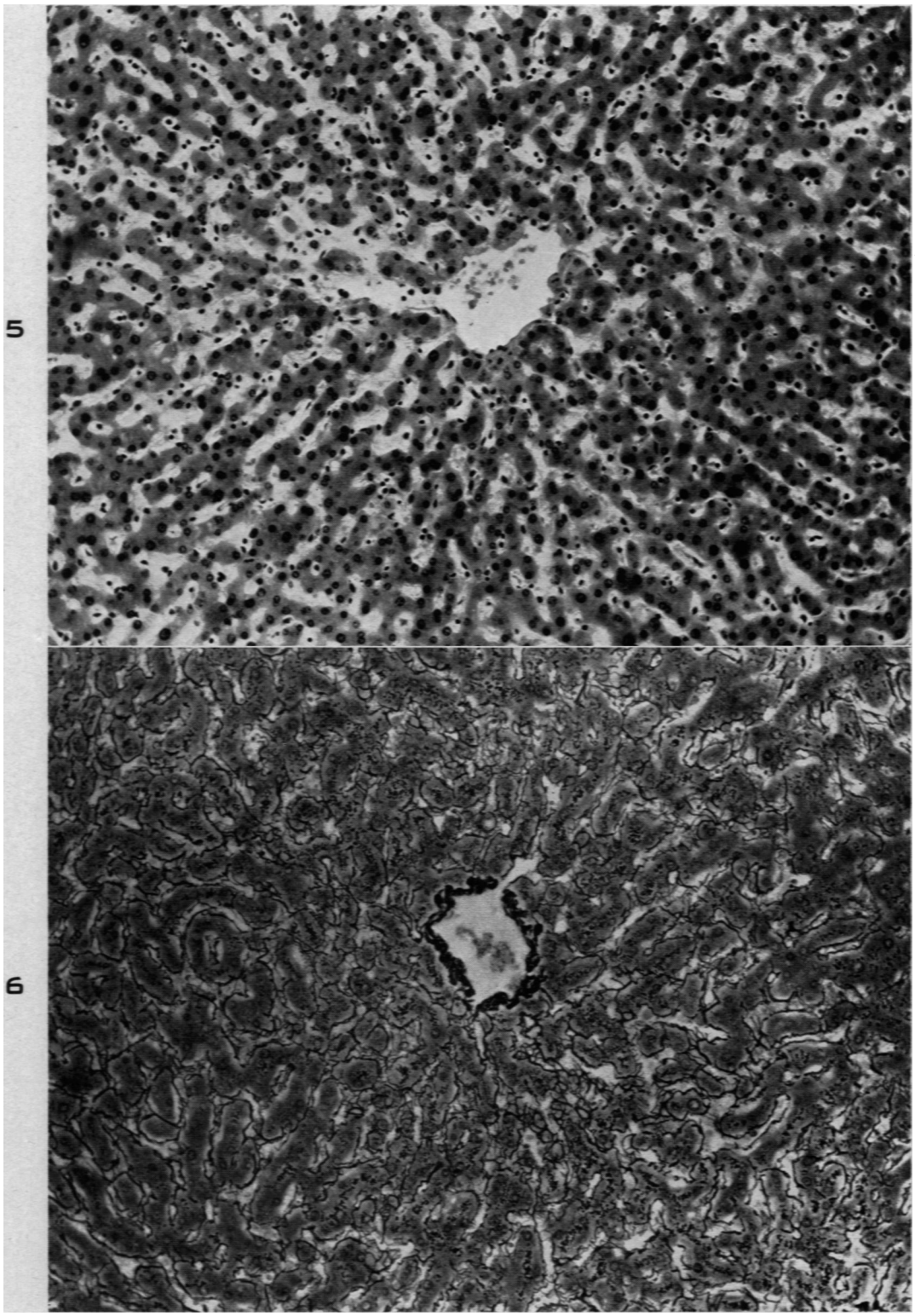
3

4

PLATE 123

FIG. 5. Case 7. A hepatic lobule with columns of normal appearing hepatic cells converging toward a thin-walled central vein. No traces of previous injury can be observed. Restoration following the attack of epidemic hepatitis is complete. × 150.

FIG. 6. Case 7. Another lobule from the liver shown in preceding figure. The section has been stained by Wilder's method. The reticulum framework has a normal pattern of arrangement; its meshes enfold normal liver cells. × 150.



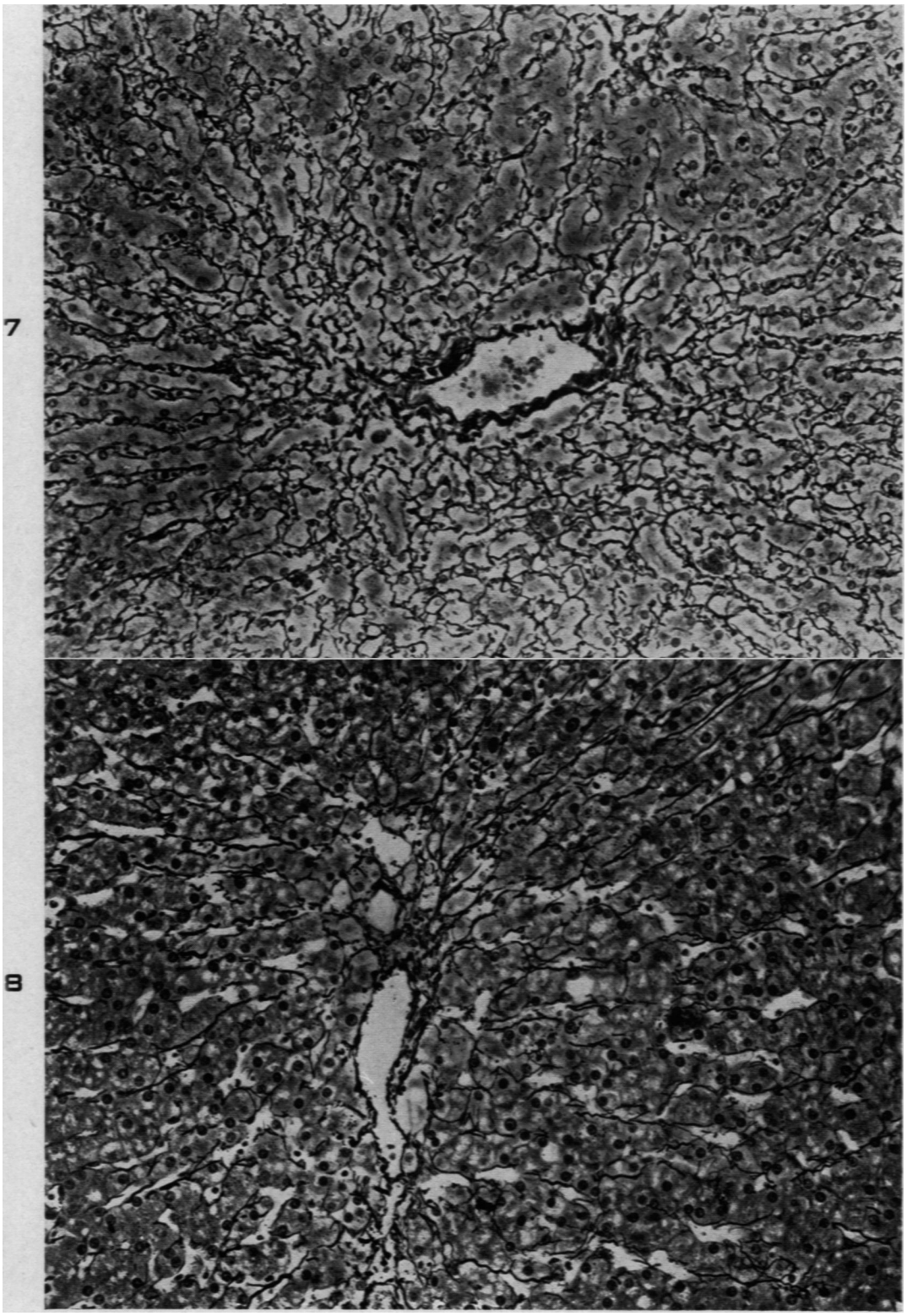
5

6

PLATE 124

FIG. 7. Case 6. Central part of a lobule showing efferent vein, converging columns of liver cells and reticulum frame. The pattern of arrangement is normal. Restoration of this liver is practically complete. Wilder's reticulum stain. × 275.

FIG. 8. Case 11. Hepatic lobule, showing normal pattern of arrangement of cell cords and reticulum. Restoration of structure is complete. Wilder's reticulum stain. × 250.


7
8