# LIVER DAMAGE IN ULCERATIVE COLITIS*

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Little is known about the occurrence of liver damage in so-called non-specific ulcerative colitis, and the scant information available reveals widely divergent opinions. Our experience has shown that it is of both academic and practical importance to know the nature and frequency of liver disease associated with ulcerative colitis. Should a causative relationship exist, should liver damage occur with significant frequency, the management of ulcerative colitis and particularly resort to intestinal surgery should be guided by this knowledge. We have therefore undertaken a review of the literature and shall present a statistical analysis of our own material and that of the Armed Forces Institute of Pathology. This study reveals that various types of liver damage occur in ulcerative colitis with a frequency higher than expected from previous reports.

## REVIEW OF THE LITERATURE

Most reviews concerning the pathogenesis and etiology of hepatic cirrhosis and hepatitis have failed to refer to ulcerative colitis as a possible causative condition (Rössle,[1] Karsner,[2] and Moon[3]). Likewise, discussions of various complications of ulcerative colitis commonly have ignored liver damage (Jankelson, McClure, and Sweetsir[4]), although the occurrence of cirrhosis and of frequent fatty changes was mentioned by Monaghan.[5] In a recent monograph, Bargen[6] referred to a variety of hepatic lesions in thrombo-ulcerative colitis but did not give detailed account of his observations except for the relative frequency of fatty changes. His series was concerned only with ulcerative colitis of streptococcal origin, not including the "non-specific" type. We failed to make this distinction.

Ricketts and Palmer,[7] in a clinical study of complications of ulcerative colitis, reported the occurrence of hepatitis in 0.48 per cent, but their publication does not indicate that specific examinations of liver function were undertaken systematically in their series.

An editorial in the British Medical Journal in 1949[8] stated bluntly, "The attempt to relate the cirrhosis or other hepatic lesion to the co-existing colitis is most unconvincing."

Cirrhosis of the liver with ulcerative colitis was first described by Bargen[9] in 1929, when he reported a case proved by necropsy in a

male, 15 years old. Subsequently, he[10] presented an additional case "apparently secondary to thrombosis of hepatic veins" in a female, 33 years of age, with a history of ulcerative colitis of 3 years' duration. In 1947 Tumen, Monaghan, and Jobb[11] published 5 instances of hepatic cirrhosis with ulcerative colitis, although one was a chronic alcoholic patient. An additional case was described by Ross and Swarts[12] as hepatic cirrhosis and necrosis with evidence of regeneration. Their second case cannot be fully evaluated since no histologic examination was made and the description indicates biliary obstruction, possibly unrelated to ulcerative colitis.

In 1949 Mallory[13] presented 2 cases of hepatic cirrhosis in association with ulcerative colitis which he interpreted as being of the postnecrotic type. Warren and Sommers,[14] in the same year, found cirrhosis in 3 of 60 necropsy cases of ulcerative colitis. Two of these were classified as toxic, the third as cirrhosis from fatty changes.

We have not found more than 11 case reports of hepatic cirrhosis associated with chronic ulcerative colitis in the literature.

Apparently, fatty livers are found very frequently in patients with ulcerative colitis. Mallory[13] spoke of 80 per cent with massive fatty infiltration in the liver among cases of ulcerative colitis. Warren and Sommers[14] found it in approximately 55 per cent, and Ross and Swarts[12] in 41 per cent. Even though the degree of fatty change may be evaluated differently by individual observers, it seems to be certain that severe fatty changes occur with significant frequency.

Other changes in the liver, however, have been mentioned only occasionally. A single case of multiple abscesses was presented by Lansbury and Bargen.[15] Two instances of so-called toxic hepatitis, described as perilobular chronic inflammatory infiltration with fibrosis and disorganization of lobular architecture, were reported by Warren and Sommers.[14] The cases of toxic hepatitis mentioned by Ross and Swarts[12] probably were the same as those reported by Warren and Sommers. The latter also observed small foci of necrosis with inflammation and infiltration in 6 cases. An isolated report of chronic hepatitis with recurrent necrosis (Harrell and McBryde[16]) closes the list of references specifically concerned with this subject.

That the accumulated tabulation of cases is incomplete can be demonstrated by an article on amyloidosis (Thompson and Rice[17]) in which the necropsy report on a male, 27 years old, mentioned parenthetically, "there was also periportal hepatic cirrhosis and ulcerative colitis." The degenerative and inflammatory lesions of the liver which Stewart and Jones[18] observed in rats suffering from chronic ulcerative cecitis may possibly be added to the findings in humans.

Purely clinical observations are of fundamental importance, since they demonstrate that ulcerative colitis may be associated with transient hepatic changes. Comfort, Bargen, and Morlock,[19] in 1938, reported 4 cases of hepatic insufficiency in which the symptoms and signs of liver disease were accentuated concomitantly with bouts of diarrhea. In one of these cases the liver disease apparently preceded the intestinal symptoms. McCannel[20] reported a similar observation, a case in which bromsulfalein retention was associated with exacerbations of chronic ulcerative colitis. Two cases of hepatic insufficiency in chronic ulcerative colitis have been reported by Johnson,[21] in only one of which improvement of both hepatic involvement and colitis was achieved. The second patient showed no improvement of either condition.

The only systematic study of liver function in ulcerative colitis which we have been able to find is that of Ross and Swarts,[12] who examined 20 patients with ulcerative colitis with the aid of various liver function tests. They came to the conclusion that there was no greater incidence of hepatic insufficiency than occurs in other maladies when uncorrected factors of severe anemia, weight loss, and/or negative nitrogen balance appear. They noticed a definite trend toward hepatic insufficiency, manifested mainly by low serum protein levels with reversal of the albumin-globulin ratio, when extensive ulcerative colitis was associated with weight loss and anemia. Hypo-albuminemia was found also in 5 cases of hepatic cirrhosis in ulcerative colitis.[11]

## MATERIAL

Our own analysis is based upon a small series of 12 cases from the Charlotte Memorial Hospital and a large series which was kindly put at our disposal by the Armed Forces Institute of Pathology. From the total number of available cases of ulcerative colitis we eliminated all instances in which specific etiology was known. This included a variety of parasitic and bacterial diseases, heavy metal poisoning, uremia, and other miscellaneous conditions. There remained 81 instances of ulcerative colitis of unknown etiology from the material of the Armed Forces Institute of Pathology, which we have included in our total of 93 cases.

## FINDINGS

Our study has revealed various hepatic lesions with ulcerative colitis, differing greatly in nature and extent. We shall divide the presentation of our findings into groups of degenerative and inflammatory lesions, describing the salient points of each type to which our interpretations are added. Each group will be illustrated by one or more

case reports. In the choice of these, cases in which significant clinical observations were available were given preference.

## DISSOCIATION AND NECROSIS

Dissociation and necrosis were found in 8 cases, or 8.6 per cent. Only 2 cases of advanced dissociation of liver cell cords were encountered in which there was neither necrosis nor inflammatory reaction (cases A-163 and A-917). In portions of the sections it could be recognized that the process of disintegration had begun in the center of hepatic lobules, a narrow peripheral margin still being intact (Figs. 1 and 2). There was no evidence of passive congestion. In a great number of cases central dissociation was observed, but not included in the tabulation because of the doubtful significance of this finding. The diffuse dissociation in the 2 cases mentioned was so conspicuous that we had to take cognizance of this lesion although there was no evidence of regeneration.

Six cases of focal necrosis were observed. In 2 of them there was found inflammatory reaction about foci of necrosis in the form of infiltration with polymorphonuclear leukocytes (A-242 and A.F.I.P. Acc. 139406).* The inflammation varied in intensity and some of the foci in the same liver showed no inflammatory reaction.

In 2 cases (A.F.I.P. Acc. 153167 and 96518) numerous bile pigmented macrophages could be found within the areas of necrosis and many of the detached and partially disintegrated liver cells were loaded with bile pigment (Fig. 4). Two of the cases revealed large areas of necrosis (Fig. 5) without any reaction (A-57 and A.F.I.P. Acc. 167759) except for a zone of hyperemia in one of them (A.F.I.P. Acc. 167759). The changes were so conspicuous that they deserve notice. In one instance the foci were so large as to become confluent in many areas. In all of these cases the necrotic foci frequently were found in an eccentric position, often in juxtaposition to the central vein.

The question has been raised as to whether the dissociation of liver cells and central necrosis should not be regarded as agonal processes. Evidence presented by Popper[22] is indeed convincing. However, it is difficult to conceive that the severe lesions to which we have reference could be a post-mortem product. If they result from agonal destruction, we must assume that damage to liver cells prior to death predisposes to the change observed at necropsy. Without evaluating the significance of this process at this time, we register the occurrence of

* The cases from the Armed Forces Institute of Pathology are cited according to the accession number (Acc.).

severe dissociation and necrosis in 8 cases, of which 5 showed reaction of mesenchymal tissue, while 3 were without reaction.

## Illustrative Cases

M. W. (A-242) was a white male, 67 years old, who was admitted to the Charlotte Memorial Hospital on April 11, 1943, complaining of vertigo, dyspnea, and tarry stools. On admission the red blood cell count was 1,750,000; the white blood cell count was normal. The prothrombin time was 56 per cent of normal. In spite of blood transfusions and other supportive measures, the patient failed to respond and died 4 days after admission, on April 15, 1943. The clinical diagnosis was acute ulcerative colitis.

At necropsy there was an acute ulcerative colitis of the sigmoid colon. The liver weighed 1650 gm. and was normal grossly. Histologically, there were diffusely distributed foci of necrosis involving the centers of nearly all lobules (Fig. 3). The parenchymatous elements were markedly disintegrated, many of the cells being small, relatively dark-staining, and partially fragmented. The nuclei were pyknotic and fragmented. Other cells within the centers of lobules, and often in direct contiguity with those described, were rather large and possessed a foamy cytoplasm, which did not contain fat, nor did it give a positive glycogen reaction with periodic acid stain. Some of these cells had undergone the same disintegration as had the cells in the centers of the lobules. There was an associated moderate inflammatory infiltration composed of polymorphonuclear leukocytes within the zones of necrosis, but this was not encountered in all necrotic areas. The reticulum was found to be collapsed within the necrotic areas. The latter were most often eccentrically located, although they occasionally completely encircled the central veins. There were diffusely distributed foci of marked inflammatory infiltration composed of lymphocytes, plasma cells, polymorphonuclear leukocytes, and infrequently eosinophils in the periportal spaces. However, all triads were not involved.

Impression. Central and eccentric necrosis with little inflammatory reaction.

F. H. (A.F.I.P. Acc. 96518), a white male, 27 years of age, was admitted to an army general hospital on February 23, 1943, with a history of annual recurrent attacks of mild diarrhea for 7 years. A persistent severe bloody diarrhea of 1 month's duration led to his admission. Physical examination revealed evidence of marked dehydration, moderate abdominal distention, and a palpable liver 1 fingerbreadth below the right costal margin. There was slight tenderness in the right lower quadrant of the abdomen. On admission the red blood cell count was 2.54 millions per cmm.; hemoglobin was 50 per cent; the white blood cell count was 4,250 per cmm. Repeated blood cultures were negative. Repeated stool examinations were negative for ova, parasites, and pathogenic organisms. Routine agglutinations were normal. Despite therapeutic measures, the diarrhea increased in

severity, ranging from ten to thirty movements daily. Because of his poor condition, surgical treatment was not attempted and he died on April 24, 1943. The clinical diagnosis was chronic ulcerative colitis, mild, intermittent, with acute fulminating exacerbation.

At necropsy a severe chronic ulcerative colitis was demonstrated. Histologically, the liver architecture was preserved but somewhat obscured by large foci of central necrosis which occasionally were confluent. The necrotic foci were sharply delineated and there was no inflammatory reaction within or around them. They comprised one-third to two-thirds of the hepatic lobule. Within the areas of necrosis were found pigmented macrophages and increased amounts of pigment in some of the necrotic liver cells proper. The interlobular inflammatory infiltration was insignificant.

*Impression.* Extensive central necrosis without inflammatory reaction.

### FATTY CHANGES

Fatty changes were studied from 14 cases, or 15 per cent: A-20, A-796, A.F.I.P. Acc. 217561, 239546, 75963, 151307, 204696, 230037, 33244, 38883, 57932, 59597, 89867, 106603. Two additional cases were excluded because the fatty changes in the liver could be related to conditions other than ulcerative colitis: one patient was known to be alcoholic (Acc. 158198); the other, a child (Acc. 84159), showed findings in the pancreas compatible with early cystic fibrosis.

The relative infrequency with which we have encountered significant degrees of fatty changes has been surprising to us. The great variation in previous reports, ranging from 40 to 80 per cent, seems to indicate that subjective interpretation of the degree of fatty infiltration plays an important part in the evaluation of the findings. Our own evaluation of 15 per cent is probably explained by the fact that only severe involvement was tabulated. We have gained the impression that in most of the lesser degrees, the fatty infiltration was either confined to, or was by far more prominent in, the periphery of the lobules.

It may be noteworthy that the liver cells in these cases frequently demonstrated evidence of accelerated regeneration. In some of them the nuclear changes were conspicuous, but definite correlation with the course or duration of the colitis could not be established.

### Illustrative Case

A. W. (A.F.I.P. Acc. 204696) was a white male, 20 years of age, who was transferred to the Walter Reed General Hospital on August 4, 1947, from another army hospital because of a progressively severe bloody diarrhea of approximately 3 months' duration. Repeated bacteriologic and serologic examinations disclosed no specific etiologic agent. Various antibiotics, as well as emetine, had been ineffective. At admission he was acutely ill, dehydrated, and underweight. There was general-

ized abdominal tenderness as well as hyperactive peristalsis. Admission blood counts were normal. Subsequently, the total serum proteins were 5.2 gm. with 2.5 gm. of albumin per 100 cc. The prothrombin time was 19 seconds with a control of 13 seconds. A barium enema revealed extensive changes throughout the entire colon, as well as the terminal ileum, suggestive of ulcerative colitis. Since conservative therapeutic measures were to no avail, an ileostomy was performed on September 17, despite which the diarrhea became more severe. The icterus index on September 29 was 18. The patient had massive rectal hemorrhages, and died on October 5, 1947. The clinical diagnosis was subacute continuous fulminating ulcerative colitis.

At necropsy there was a non-specific ulcerative colitis. Except for severe, diffuse, fatty metamorphosis, the liver was not remarkable.

### METALLAXIS OF LIVER PARENCHYMA

Some degree of metallaxis of liver parenchyma was found in 3 cases, or 3.2 per cent. In only one case (A-1089) was definite cirrhosis observed. It was associated with moderate fatty changes, moderate interlobular fibrosis, and bile duct proliferation. Periportal round cell infiltration was insignificant. There can be no doubt that in this instance the replacement of normal liver tissue by pseudolobules constituted the fundamental pathologic process, which was out of proportion to the relatively insignificant changes in the periportal areas.

In 2 additional cases similar lesions were noted but to a much lesser degree (A-15 and A-423). Some lobules still showed normal architecture, but in many the configuration and the radiating arrangement of liver cell cords was obscured (Figs. 7 and 8). The central veins were either displaced or could not be found. In neither of these instances were there significant changes in the periportal tissue, but in both were found areas of fibrosis in centrolobular position immediately next to the walls of central veins.

It can be stated that the liver changes in these 3 cases were not due to inflammatory lesions, but in all probability were related to metabolic disturbances. The irregular distribution of metallaxis and central lobular fibrosis cannot be held against such a supposition. The formation of pseudolobules, particularly in early phases, must not be expected to be necessarily uniform in distribution. A tendency to at least potentially impaired liver function associated with hypoproteinemia may be assumed in a relatively large number of cases of severe ulcerative colitis (Ross and Swarts[12]) in which the organ is at the threshold of protein deficiency. Since protein deficiency, among other factors, is known to result in necrosis of the parenchyma, functional variation in intralobular blood supply may account for topographic variations in the severity of its effect.

Centrolobular fibrosis is not commonly associated with pseudolobulation or hepatic cirrhosis in man other than in cases of chronic passive congestion. Experimentally, however, this form of hepatic cirrhosis has been produced in dogs under various conditions related to dietary and other factors (Gillman and Chaikoff[23]) and therefore it appears permissible to associate the central fibrosis in our 2 cases with the metallaxis of the hepatic parenchyma. We have therefore interpreted these 3 cases as liver damage based on metabolic disturbances, 2 of them showing changes only in a more focal distribution in an early stage, one of them in the form of fully developed cirrhosis.

### Illustrative Cases

J. B. (A–423). a white male, 60 years old, was admitted to the Charlotte Memorial Hospital on September 23, 1944, with a history of recurring attacks of bloody diarrhea for a period of 15 to 20 years. On admission the liver was enlarged 2 fingersbreadth below the right costal margin. The red blood cell count was 2,610,000 per cmm. with 7.4 gm. of hemoglobin. The white blood cell count was normal. A roentgenologic examination of the lower bowel revealed changes typical of chronic non-specific ulcerative colitis. During his third hospital week he began to have repeated hemorrhages from the lower bowel, and subsequently expired on October 23, 1944. The clinical diagnosis was chronic ulcerative colitis, intermittent, with a severe fulminating exacerbation.

At necropsy the entire colon showed typical changes of severe chronic diffuse ulcerative colitis. The liver weighed 1700 gm. The surface was finely granular. The cut surface showed accentuation of lobulation. The extrahepatic bile ducts were somewhat distended, but were patent throughout.

Histologically, the lobular architecture was obscured (Figs. 9 and 10). The central vein could be found only occasionally. There was a rather marked, predominantly periportal, fatty change of parenchymatous cells, apparently accounting for the accentuated lobulation noticed grossly. In some lobules there was marked fibrosis around the central veins. The periportal spaces showed only insignificant round cell infiltration and no fibrosis. The bile ducts were not involved.

*Impression.* Pseudolobulation with occasional areas of central fibrosis. The findings were not compatible with biliary cirrhosis, which was taken into consideration because of dilatation of extrahepatic bile ducts.

J. R. (A–1089) was a white male, 19 years old, who was admitted to the Charlotte Memorial Hospital because of a recurrence of bloody diarrhea for 4 days prior to admission. There was a history of periodic attacks of bloody diarrhea of variable intensity, generally severe, occurring every 2 to 3 months over the previous 6 years. A barium enema showed changes characteristic of chronic ulcerative colitis. On admission the abdomen was distended, tympanitic, and tender throughout. The red blood cell count was 3,890,000 per cmm. with 11 gm. of hemoglobin.

The total leukocyte count and differential count were normal. The total serum proteins were 6.2 gm. per 100 cc. Following blood transfusions, he was subjected to a partial colectomy on November 2, 1948. On the following day he was deeply jaundiced, with an icterus index of 88. After repeated severe rectal hemorrhages, he expired on November 8, 1948, on his sixth postoperative day. The surgically removed specimen showed changes typical of severe chronic ulcerative colitis as did that portion of colon remaining at necropsy. The clinical diagnosis was chronic ulcerative colitis, with acute exacerbation.*

The liver was enlarged, weighing 2,245 gm. The capsular surface was diffusely finely granular and tan-yellow. On dissection it was likewise finely and diffusely granular, possessing nodules of variable size, the largest of which measured 0.2 cm. in diameter. These nodules were separated by fine, grayish white, interlacing bands of rather firm fibrous tissue. The inferior margins of the liver were somewhat rounded.

Histologically, pseudolobulation was a conspicuous feature (Fig. 6). In addition, there were areas of irregularly distributed, rather marked dissociation of liver cell cords. Moreover, many of these cords were markedly distorted, mainly in the vicinity of the areas in which parenchymatous cells showed mild fatty changes with subsequent disintegration and actual necrosis without inflammatory reaction. The disintegration occurred mainly in mid-zonal areas with associated collapse of the reticulum. Occasionally encountered were bile casts, predominantly near the areas of degenerative changes.

*Impression.* Cirrhosis with small foci of necrosis.

### BILE CASTS

Bile casts were found in only 2 cases, or 2.2 per cent: A.F.I.P. Acc. 190983 and 108270. In spite of the paucity of morphologic changes in the liver parenchyma, the occurrence of numerous bile casts appears to be significant. In one case casts were found in a few bile ducts. In neither instance could their presence be explained by obstruction of the bile system. The morphologic observations do not offer tangible evidence for their pathogenesis, but their presence indicates indisputable evidence of functional liver damage at the time of death or in the recent past.

### Illustrative Case

S. Z. (A.F.I.P. Acc. 190983) was a white male, 23 years old, who was admitted to the Walter Reed General Hospital on October 21, 1946, with a history of recurrent short bouts of diarrhea in 1942 and again in 1945. In June, 1946, diarrhea became progressively more severe and subsequently bloody, despite treatment. On September 25, 1946, an ileostomy was performed with no permanent alleviation of

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* In reviewing the literature on this subject, it occurred to us that this case might have been identical with one reported by Johnson.[21] This was verified by personal communication.

symptoms. Following subsequent massive hemorrhages, he was transferred to the Walter Reed Hospital where his red blood cell count was 2,900,000 per cmm. with hemoglobin 9.7 gm. The white blood cell count was normal. The serum bilirubin was 3.6 mg. per cent. Bacteriologic studies were negative. Despite antibiotics and blood transfusions he maintained a spiking daily fever, continued to bleed rectally, and subsequently expired on November 4, 1946. The clinical diagnosis was sub-acute fulminating ulcerative colitis.

At necropsy a severe chronic ulcerative colitis was found. Histologic sections through the liver showed well preserved architecture. There was a mild peripheral lobular fatty change and some evidence of re-generation. The conspicuous feature was the presence of numerous, irregularly distributed bile casts in bile capillaries and occasionally in small bile ducts (Fig. 11). Histologic sections and the gross protocol gave no explanation for bile stasis.

*Impression.* Intrahepatic bile stasis.

### SMALL FOCI OF INFLAMMATION

Small foci of inflammation were found in 5 cases, or 5.4 per cent: A.F.I.P. Acc. 217561, 239546, 236758, 271764, 75963. These may occur anywhere within the lobule or in the periportal tissue. Those occurring in the parenchyma proper were associated with necrosis of liver cells, but the inflammatory infiltrations seemed to be the pre-dominating feature. They resembled closely the lesion illustrated by Warren and Sommers,[14] but designated by them as focal necrosis. They also appeared similar to parenchymatous changes in cases of severe interlobular hepatitis in which the inflammatory process ex-tended into the lobule. We have therefore interpreted these foci as probably transitory, diminutive lesions, analogous in other respects than size to the massive changes designated as interlobular hepatitis. Even though these foci are small, scattered, and infrequently observed, they may serve as evidence of transitory embolic involvement of the liver in ulcerative colitis. Phlebitis of small intrahepatic portal branches illustrates this assumption.

### Illustrative Case

M. C. (A.F.I.P. Acc. 236758) was a white male, 52 years of age, who became ill suddenly on June 7, 1948, with severe abdominal pain. An exploratory laparot-omy is said to have shown gangrenous areas in the descending colon. A loop colostomy was performed. On August 12, 1948, he developed diarrhea with four to six movements daily, most of which contained pus. On August 27, he was admitted to the Lawson Veterans Administration Hospital, at which time he was extremely emaciated and dehydrated. The abdomen was moderately distended with fluid, and the enterostomy opening drained loose, mucoid material. The hemoglobin was 14 gm. The leukocyte count was normal. The total serum proteins were 5.3 gm. per cent. The cephalin flocculation was 3 plus at 48 hours; thymol turbidity,

4.2 units; serum bilirubin, 2.3 mg. per cent. He expired on September 10, 1948. The clinical diagnosis was subacute fulminating ulcerative colitis.

At necropsy there was an ulcerative colitis. Histologic sections through the liver showed a small and discrete focus of polymorphonuclear leukocytic infiltration within the wall of a central vein, extending somewhat into the adjacent connective tissue, and in an irregular manner into the adjacent liver tissue proper (Figs. 12 and 13). There was a moderate passive congestion and there were regenerative changes in liver cells, particularly next to foci of central dissociation.

*Impression.* Focus of inflammatory infiltration of central vein, and adjacent liver tissue (may be forerunner of central fibrosis?).

### INTERLOBULAR HEPATITIS

Nine cases, or 9.7 per cent, showed interlobular hepatitis: A.F.I.P. Acc. 277125, 78852, 141078, 149528, 211619, 212899, 269837, 106603, and A-860. A tenth case was omitted (Acc. 111785) because of the possibility that the interlobular hepatitis may have been cholangitic, secondary to marked chronic cholecystitis. The lesion consisted of marked inflammatory infiltration of the interlobular connective tissue with a variety of round cells, including lymphocytes, polymorphonuclear leukocytes, plasma cells, and macrophages (Figs. 16, 17, 18, 22, 23, and 24). It appears that the lobular architecture is at first well preserved. In many instances the inflammatory infiltration encroaches upon adjacent parenchyma with necrosis of liver cells. In later phases, bile duct proliferation is recognizable and finally pseudolobulation may set in. The latter is irregularly distributed, meaning that in some areas the lobules are well preserved and in others, particularly where the interlobular inflammation is most marked, they become irregular in shape and size. Their central veins are displaced or are not recognizable.

The irregularity with which the inflammatory process is spread throughout the section is a remarkable feature. In one case so little infiltration was seen in one section that it would not have been classified as interlobular hepatitis except that large massive patches were encountered in an additional block of tissue. We feel, therefore, that more cases of interlobular hepatitis possibly would have been registered if more tissue had been available. It is likewise difficult to determine how much interlobular infiltration should be looked upon as physiologic and when to classify the lesion as pathologic. We realize that this, to some extent, is left to the experience of the observer, but for this study we have included only cases which left no doubt concerning the severity of the process.

In later phases the infiltration may subside somewhat, but fibrosis and bile duct proliferation remain (A-860).

We interpret this process tentatively as a reaction to "toxins" or bacteria which invade the liver by the portal system. In favor of such an assumption is the occasional portal phlebitis, the lack of parenchymatous involvement in the earlier phases or lesser degrees, and the fact that the biliary tree is not involved.

### Illustrative Cases

J. B. (A.F.I.P. Acc. 149528), a Hungarian white male, 45 years old, was an inmate of the Dachau Concentration Camp. He was admitted to the 127th Evacuation Hospital on May 6, 1945, for incision of a large fluctuant abscess overlying the right scapula. Prior to admission the patient had been treated for enterocolitis which had developed apparently following typhus fever. On May 10, he developed severe diarrhea with seventeen liquid, blood-tinged stools daily. He expired on May 18, 1945. This case could not be classified because of inconclusive history.

At necropsy there was severe ulcerative colitis. Histologically, the lobular architecture of the liver was partially preserved. Occasional pseudolobules were found. Fatty changes were absent and degenerative changes of liver cells were found only in the immediate vicinity of inflammatory changes. The outstanding feature was a heavy inflammatory infiltration (Figs. 19, 20, and 21) composed mainly of lymphocytes with occasional polymorphonuclear leukocytes and eosinophils in the interlobular connective tissue, extending, in an ill defined fashion, deep into the hepatic lobules. These latter areas showed a much richer infiltration of polymorphonuclear leukocytes. In many of the lobules, the walls of the branches of the portal vein were diffusely and heavily infiltrated by similar inflammatory cells, and in some areas, portions of the vein were completely replaced by such an infiltration. Also there were occasional portal triangles with fibrosis as well as marked bile duct proliferation. The changes were widespread, but irregularly distributed. Bile ducts were not involved, and there was found no evidence of bile stasis.

*Impression.* Severe interlobular hepatitis.

H. M. (A.F.I.P. Acc. 277125) was a white male, 69 years of age, who was first admitted to the Veterans Administration Hospital, Bay Pines, Florida, in February, 1947, with bloody diarrhea. Following that admission he did fairly well for 2 years when, after severe diarrhea of from twelve to fourteen movements daily for a period of 1 month, he was readmitted on July 29, 1949. On admission there was evidence of dehydration. The liver border was palpable, firm, hard, and at the right costal margin. The red blood cell count was 5,280,000, with hemoglobin 77 per cent. The white blood cell count was 12,900. Repeated stool examinations were negative. Cephalin flocculation was 4 plus at 48 hours and the thymol turbidity was 10 units. The serum bilirubin was 0.89 mg per cent. Wassermann and

Kahn reactions on the blood were positive. Barium enema revealed a severe ulcerative colitis involving the entire colon. Despite treatment, he became severely anemic, and expired on August 15, 1949. The clinical diagnosis was chronic intermittent ulcerative colitis, with an acute protracted fulminating exacerbation.

At necropsy severe ulcerative colitis, involving the entire colon, was encountered. Histologically, the lobular architecture of the liver was preserved, although some central dissociation with increased pigmentation of liver cells was seen. There were found numerous extensive foci of necrosis of liver cells with very heavy inflammatory infiltration, mainly polymorphonuclear leukocytes and lymphocytes (Figs. 14 and 15). The foci were large and situated in either the mid-zone or the periphery of lobules. They were often ill defined, with a great number of polymorphonuclear leukocytes, infiltrating irregularly the adjacent portions of hepatic lobules. Infiltration by polymorphonuclear leukocytes was found in such areas in which the liver cell necrosis was not clearly demonstrable. With this process were large collections of pigmented macrophages in some, but not all of the foci of necrosis. The periportal spaces were moderately infiltrated, predominantly with lymphocytes, but there was no fibrosis. There was no bile duct involvement and no evidence of bile stasis. The distribution of inflammatory foci was irregular but diffuse.

*Impression.* Acute interlobular hepatitis with necrosis. The impression was gained that inflammatory infiltration was so preponderant that it could not be regarded merely as reaction to liver cell necrosis. The latter might, in fact, be secondary to the inflammation.

## DISCUSSION

### RELATION OF COLITIS TO LIVER DAMAGE

Of the 93 cases analyzed, pathologic conditions were observed in the livers of 37 (40 per cent). If one assumes that interlobular hepatitis, pseudolobulation, cirrhosis, multiple bile casts, and severe fatty changes are of actual or potential clinical significance, it is noteworthy that 26 such cases (28 per cent) were found in our series. In our opinion these observations indicate that the relationship between ulcerative colitis and liver damage is more than coincidental.

It becomes necessary to distinguish between two pathogenetically separate groups of liver changes, namely, those of degenerative and those of inflammatory nature. Not all of the cases can be segregated strictly in this manner since some of them showed lesions of both types. It is possible, however, to summarize the cases in a table presenting the preponderant type of involvement.

Since quantitative estimation of degree of severity enters into the

evaluation of findings and may thus affect the statistical results, we reviewed 1000 necropsies, applying the same criteria used in the cases of colitis. From the control series were excluded all cases with liver changes attributable to known specific causes, such as inflammatory lesions of the bile system, septicemia, exogenous toxins, vascular lesions, trauma, and also all premature and newborn infants. The following table indicates the relative frequency of liver damage in the control series compared to that of ulcerative colitis.

|  | Ulcerative colitis 93 cases | | Control series of 1000 cases |
| --- | --- | --- | --- |
|  | Number | Per Cent | Per Cent |
| Degenerative lesions |  |  |  |
| Cirrhosis | 1 | 1.08 | 2.3 |
| Pseudolobulation | 2 | 2.15 | 0.8 |
| Multiple bile casts | 2 | 2.15 | 0.4 |
| Necrosis and dissociation | 8 | 8.60 | 6.6 |
| Fatty changes | 14 | 15.05 | 1.4 |
|  | 27 | 29.03 | 11.5 |
| Inflammatory lesions |  |  |  |
| Interlobular hepatitis | 9 | 9.68 | 1.1 |
| Foci of inflammation | 5 | 5.38 | 1.0 |
|  | 14 | 15.06 | 2.1 |

It is apparent that fatty changes and inflammatory lesions occur with much greater frequency than would be expected if their relationship to ulcerative colitis were purely coincidental. The degree of fatty infiltration designated as "severe" was observed more than ten times as frequently in the colitis group than in the control series. The type and severity of inflammation, designated as interlobular hepatitis, occurred nine times as frequently, and small inflammatory foci were seen more than five times as often as in unselected cases. It is likewise apparent that diffuse changes of the hepatic parenchyma, manifested by metallaxis with formation of atypical lobules (pseudolobulation) and by the presence of numerous bile casts, are significant since these "degenerative" lesions are found two and one-half and five times, respectively, as often as in the control series. Cirrhosis seems to be less common in cases with ulcerative colitis, but these figures are misleading because the age distribution was not taken into consideration. In the light of the other observations, particularly the frequency of fatty changes, even a single instance at the age of 19 among 93 cases is of significance. Zonal necrosis and severe degrees of dissociation were not observed more often in cases of ulcerative colitis than in the control series.

In evaluating the frequency with which ulcerative colitis is asso-

ciated with liver damage, it is necessary to consider that liver involvement may be transitory and, therefore, not be found at the time of death. Bargen's[9] original observation and those of others are important in this respect. These authors observed accentuation of clinical signs and symptoms of liver disease during bouts of diarrhea. The frequency, therefore, with which reversible changes, such as necrosis and fatty change, are observed at necropsy may depend upon the presence of fleeting attacks of liver involvement at the time of death. Only when colitis is continuous, fulminating, and unabated, may permanent liver damage be expected. All of our cases of interlobular hepatitis and the one instance of cirrhosis fell into this category. The reverse, however, does not hold true. Not all cases of continuous fulminating colitis showed liver damage. One may quite reasonably ask why liver damage is not found clinically or anatomically with greater frequency than 40 per cent. We have already implied a partial answer by pointing out that the most common remittent form of chronic ulcerative colitis gives the liver sufficient time for repair during the period of remission.

The study of our cases and those from the literature has given us ample reason to postulate that both degenerative and inflammatory lesions of the liver are direct results of ulcerative colitis.

### DEGENERATIVE CHANGES

Fatty changes, necrosis, and cirrhosis are known to result from nutritional deficiencies. There is experimental evidence that diets deficient in protein can produce acute hepatic necrosis. Fatty changes in the liver and diffuse fibrosis likewise have been produced in a similar manner (Himsworth and Glynn[24] and others[23,25]). Ulcerative colitis is associated with inadequate intake of food, faulty utilization, and poor absorption, probably connected with the rapid transit of intestinal content. According to Jankelson and McClure,[26] hypoproteinemia with a normal albumin-globulin ratio develops in 55 per cent of the cases of ulcerative colitis.

The tabulation of our cases reveals an additional observation which seems to corroborate Himsworth and Glynn's[24] contention that fatty infiltration serves as protection against necrosis. As mentioned previously, in many of the cases more than one type of change was observed. Among 16 cases of severe fatty changes we encountered 3 with small foci of inflammation, one with interlobular hepatitis, and one with cirrhosis. Foci of necrosis, however, or dissociation were not observed in severe fatty livers. It appears to us that most of the degenerative changes under discussion are reversible and that permanent damage in the form of cirrhosis is a rare complication of ulcerative colitis.

## INFLAMMATORY CHANGES

### Foci of Inflammation

There are two reasons for including the seemingly insignificant scattered foci of inflammation in our tabulation. In the first place, as pointed out previously, those foci demonstrate that a transitory invasion of the liver by either toxins or bacteria through the portal system can occur. Inflammatory lesions in the liver have been produced experimentally by injection of streptococci into the radicles of the portal system (MacMahon and Mallory[27]). In the second place, it is possible that they merely indicate a more diffuse damage to the liver tissue, which otherwise finds no significant morphologic manifestation. Of the 5 cases with foci of inflammation, 2 revealed clinical evidence of additional liver involvement. In one case an associated fatty change may have accounted for it, but in the second case (A.F.I.P. Acc. 236758) jaundice and laboratory evidence of functional hepatic deficiency could not be accounted for by histologic findings in the liver parenchyma. The foci of inflammation alone could not explain the diffuse liver damage.

### Interlobular Hepatitis

Of particular interest to us were the cases designated as interlobular hepatitis. A comparison of the 9 cases in our series seems to indicate clearly that the process begins in the portal triangles, extending in the more severe instances around most of the circumference of the lobules. The process involves the parenchyma in a diffuse fashion only in its later phases, when pseudolobules are formed. The lesion described is in no way specific, but its occurrence in conjunction with ulcerative colitis seems to have escaped attention. Two cases of Warren and Sommers' series,[14] recorded as toxic cirrhosis, resemble, by description, later phases of our interlobular hepatitis. The high percentage of our series stands in contrast to previous reports. An explanation may be found in the irregular patchy distribution. Extensive lesions in one block of tissue may be absent in another.

We have chosen the purely descriptive term of interlobular hepatitis because we possess merely circumstantial evidence that the "toxic" or bacterial agent reaches the lesion by the portal system. The cases showed no evidence of generalized septicemia and no biliary obstruction except for some dilatation of the common bile duct in one instance. Microscopically, no specific relation of the inflammatory infiltration to bile ducts could be noticed. The latter were often situated within the areas of periportal inflammation, but showed no significant changes of

their walls, and did not contain polymorphonuclear leukocytes. Involvement of the wall of the portal vein branches, however, was observed. Since foci of portal phlebitis have been described in cases interpreted as primary biliary infection (MacMahon[28-30] and others), we can state only that our findings, though highly suggestive of portal origin, cannot be taken as complete proof.

It is of interest to note that interstitial pancreatitis recently has been reported in 53 per cent of cases of ulcerative colitis by Ball, Baggenstoss, and Bargen.[31] Whether pancreatitis and hepatitis are pathogenetically related cannot be stated definitely. We noticed several cases with pancreatic changes resembling cystic fibrosis. In fact, one such instance in a child with massive fatty infiltration of the liver was excluded from our series of ulcerative colitis on the assumption that the liver changes were related not to the colitis but to the pancreatic lesion.

The possibility that an interlobular inflammation may be the result of hyperergia cannot be ruled out. Even parenchymatous changes, such as focal necrosis, have been interpreted as allergic reactions and have been produced experimentally (Hartley and Lushbaugh[32]). Also, antibiotics used in cases of ulcerative colitis have been held responsible for liver damage. Our observations do not contribute substantially to the evaluation of a possible allergic factor one way or another.

Although some of the cases of ulcerative colitis showed peritonitis, it is highly improbable that the peritonitis can be held responsible for the inflammatory changes in the liver parenchyma. There exists no directly demonstrable or statistical relationship. In addition, in the 11 cases of interlobular hepatitis of the control series, only one revealed peritonitis.

With all the evidence in view, we have, at least tentatively, concluded that interlobular hepatitis of this type is vascular in origin.

No conclusive statement can be made concerning the clinical significance of this hepatic lesion. We were impressed with the contrast between the conspicuous and often extensive anatomical findings and the lack of clinical signs and symptoms. Only one of 9 cases showed jaundice and a 4-plus cephalin flocculation test. This may be explained by the fact that in the majority of instances, diffuse parenchymatous changes were not present. Clinical signs of functional impairment, however, were not noticed even in cases in which pseudolobulation could be demonstrated. A clinicopathologic correlation therefore must be deferred until specific and more complete clinical data are available in future cases.

## Clinical Observations

The clinical information, as may be expected from our approach to the problem through necropsy records, was incomplete in most instances. Liver function tests were omitted in some cases in which clinical findings suggested the possibility of liver damage. One case illustrates the inadequacy of clinical examination most clearly. The necropsy (A.F.I.P. Acc. 108270) showed multiple bile casts, but the clinical records do not refer to previous or present liver involvement. The latter may have been transitory, but this experience demonstrates that liver involvement in ulcerative colitis cannot be ruled out clinically unless repeated examinations specifically directed toward determination of liver function are made. The conduct of such tests should be guided by the knowledge that evidence of liver damage may be found only during the periods of diarrhea.

Even though available records were deplorably incomplete, certain important conclusions can be drawn. In all cases analyzed, a palpably enlarged liver was mentioned 3 times: in one instance, associated with pseudolobulation (A-423); in one, with necrosis (A.F.I.P. Acc. 96518); and in one, with fatty liver and foci of inflammation (A.F.I.P. Acc. 239546). Jaundice was noted in 6 instances (A-1089, and A.F.I.P. Acc. 204696, 230037, 190983, 277125, 236758), and in 2 others (A.F.I.P. Acc. 151307 and 269837) in which it could have been the result of transfusion reaction. Insufficient data on the charts do not permit definite conclusions in this respect. There was an additional case (A.F.I.P. Acc. 217561) showing low total protein content in the blood and a 2-plus cephalin flocculation test which was not considered sufficient evidence of liver damage. Jaundice was noted in 3 cases of fatty changes, in one case of cirrhosis, in one case of hepatitis, and in one case of intrahepatic bile stasis.

It can be stated, therefore, that clinical evidence of liver involvement was present in 9 cases, that is, approximately 10 per cent (jaundice in 6.5 per cent, enlargement of liver in 3.5 per cent). We believe that these data are of significance, particularly since we have pointed out the evidence supporting our contention that specific examination along this line is likely to reveal a greater frequency of cases of impaired liver function in ulcerative colitis.

### SUMMARY

The examination of livers in 93 cases of non-specific ulcerative colitis showed various pathologic changes in 40 per cent of the cases.

The frequency of some hepatic lesions in cases of ulcerative colitis exceeds by five to ten times that in a large control series.

In our series degenerative changes occurred approximately twice as often as inflammatory lesions and with much greater frequency than previously reported. It is assumed that most of these changes are transitory.

It is likely that most degenerative changes are related to recurrent attacks of diarrhea and are metabolic in origin.

Diffuse metallaxis of liver parenchyma is not common and actual cirrhosis is rare.

Severe, irregularly distributed, interlobular hepatitis was observed in almost 10 per cent of the cases. It is assumed that this lesion is portal in origin.

Definite correlations between the morphologic changes and clinical signs and symptoms could not be established because of incomplete clinical observations. Even under these circumstances, however, 10 per cent of the cases of ulcerative colitis revealed clinical evidence of liver involvement.

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## DESCRIPTION OF PLATES

### PLATE 34

FIG. 1. A–163. Advanced dissociation of liver cell cords, less marked in the periphery of the lobule. × 70.

FIG. 2. A–917. Severe diffuse dissociation of liver cell cords. × 70.

FIG. 3. A–242. Focal necrosis with associated moderate polymorphonuclear leukocytic infiltration. × 100.

FIG. 4. Armed Forces Institute of Pathology Accession 153167. Eccentric centrolobular necrosis with many bile pigmented macrophages and few polymorphonuclear leukocytes. The centrolobular vein is on the left. × 95.
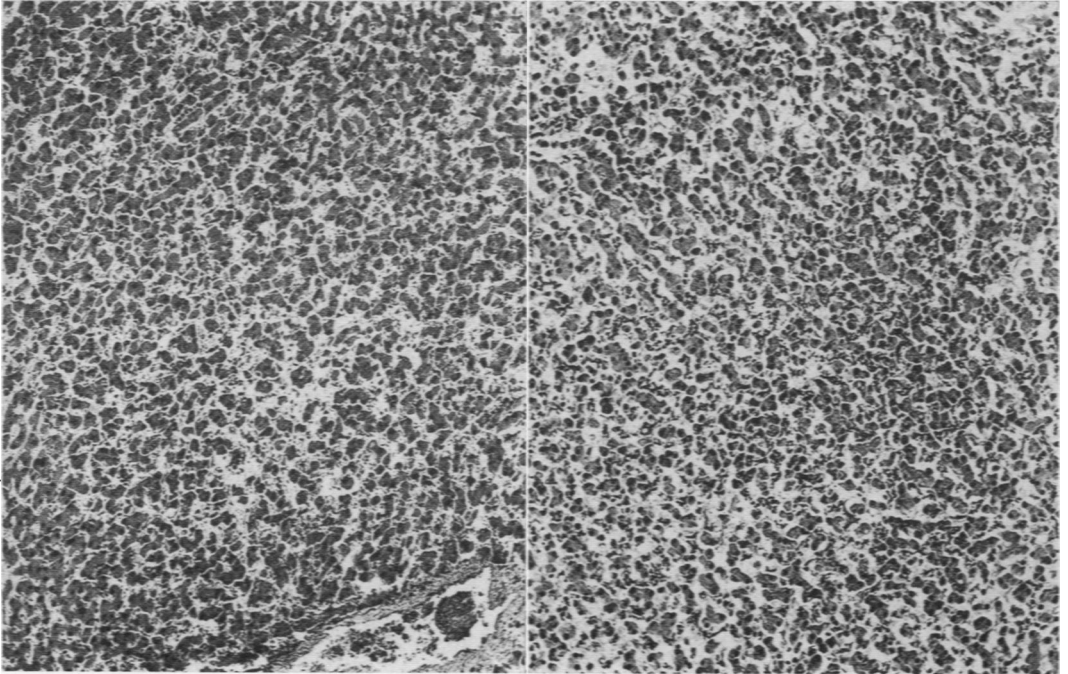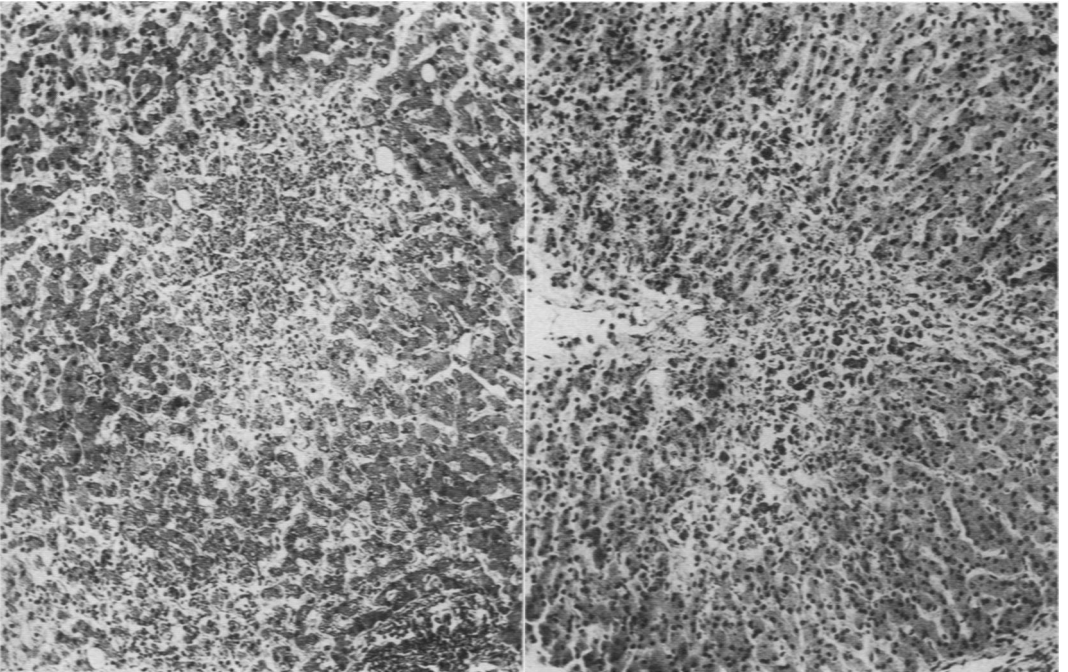
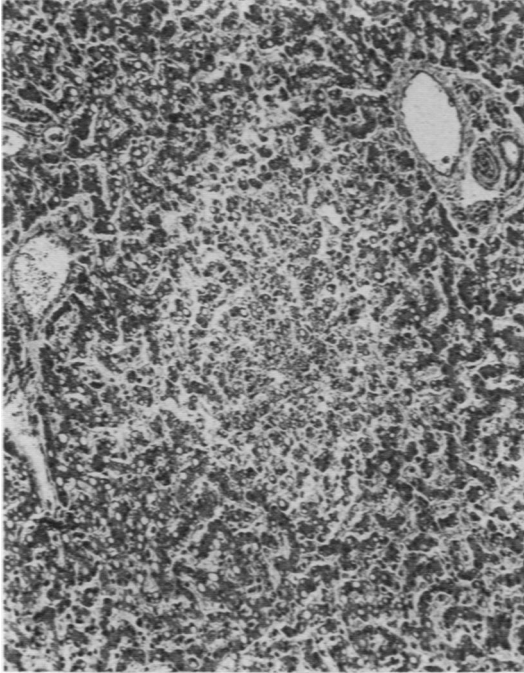Kimmelstiel, Large, and Verner                     Liver Damage in Ulcerative Colitis

PLATE 35

FIG. 5. A–57. A large area of central necrosis has no inflammatory reaction about it. × 95.
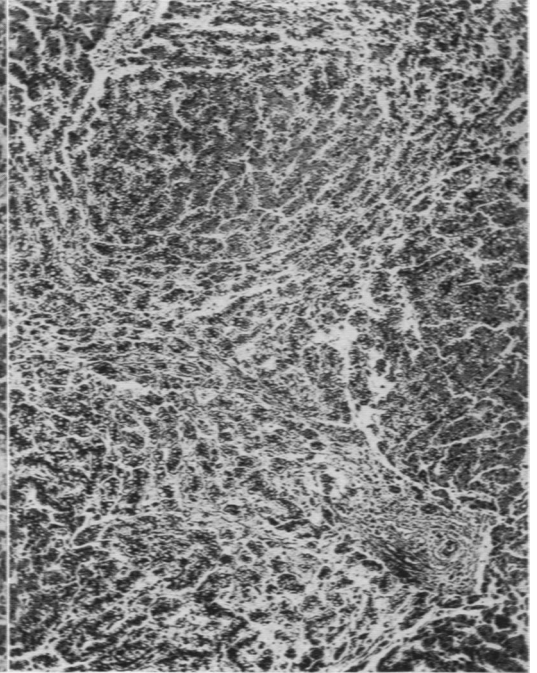
FIG. 6. A–1089. Cirrhosis. × 75.

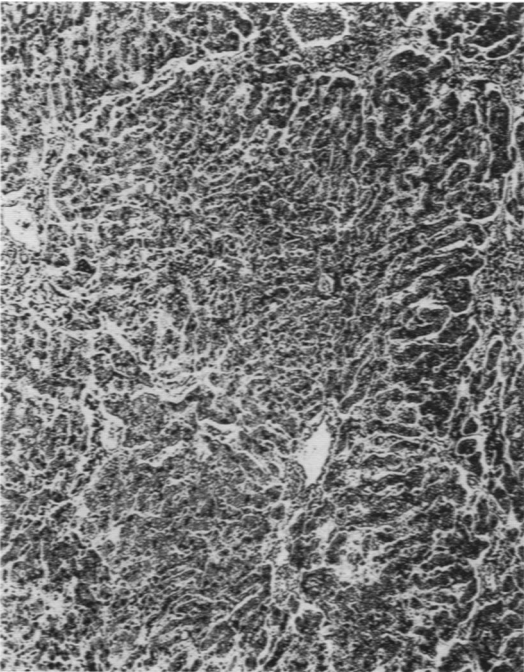FIG. 7. A–15. Pseudolobulation. × 80.

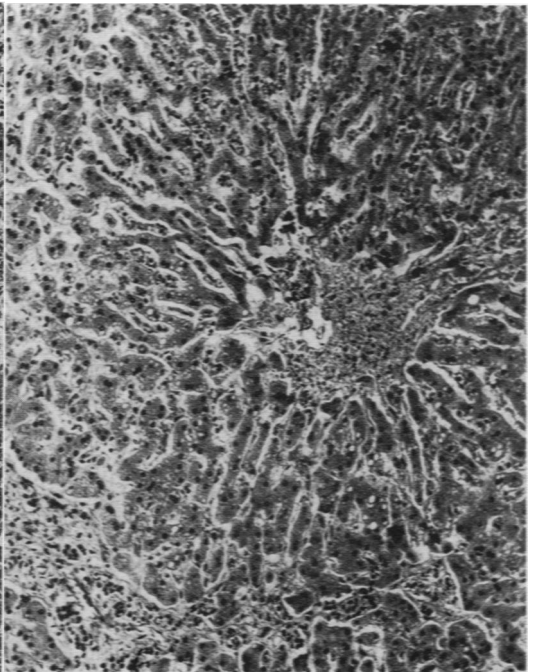FIG. 8. A–15. A focus of eccentric centrolobular fibrosis is adjacent to the central vein. × 115.

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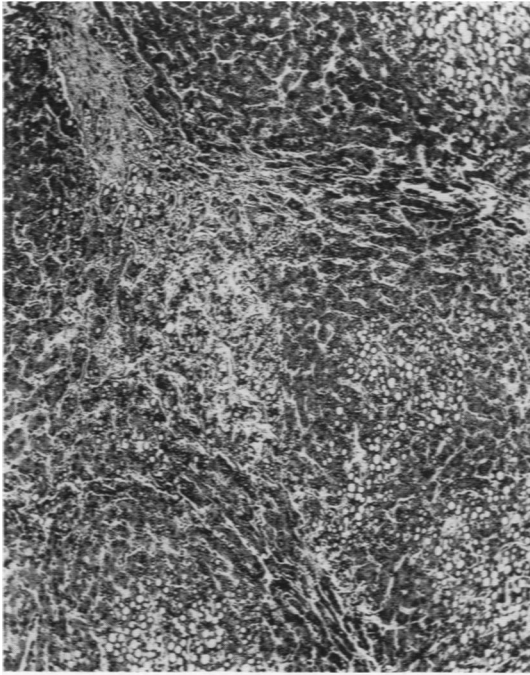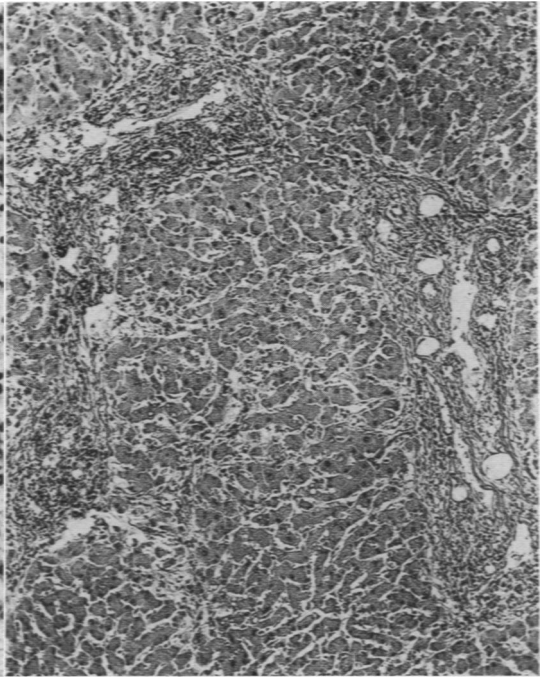Kimmelstiel, Large, and Verner                    Liver Damage in Ulcerative Colitis

FIG. 9. A–423. Conspicuous pseudolobulation with bile duct proliferation. × 60.

FIG. 10. A–423. Marked eccentric centrolobular fibrosis with fatty changes in liver cells. × 80.

FIG. 11. A.F.I.P. Acc. 190983. Several intracanalicular bile casts are present in a high-power field. × 305.

FIG. 12. A.F.I.P. Acc. 236758. A focus of polymorphonuclear leukocytic infiltration involves the wall of a centrolobular vein as well as the adjacent liver tissue. × 185.

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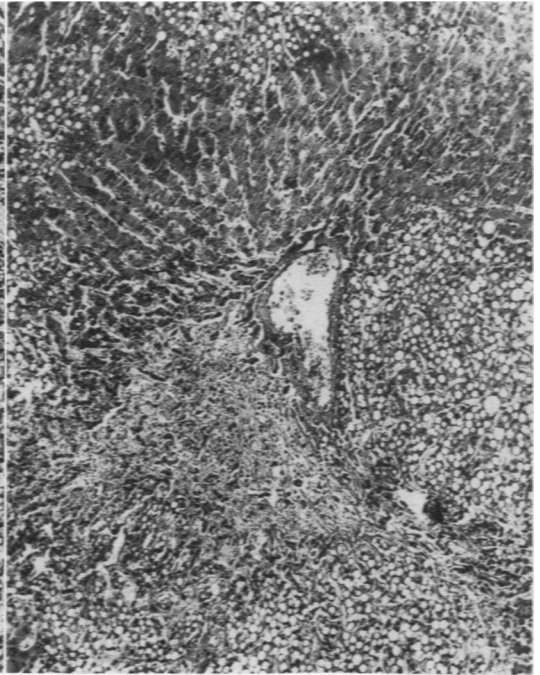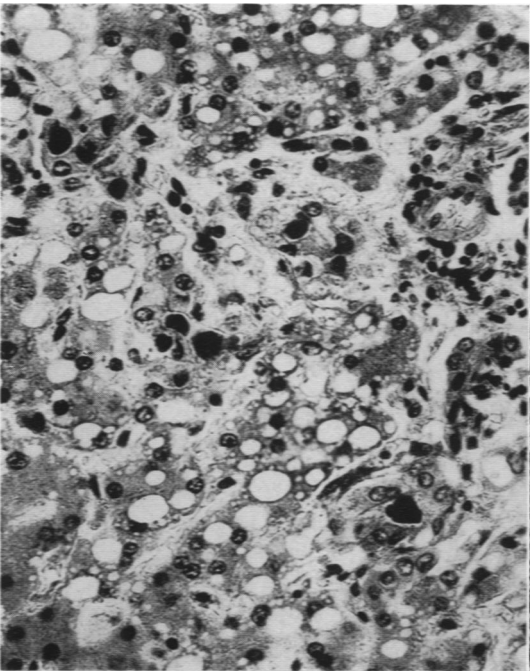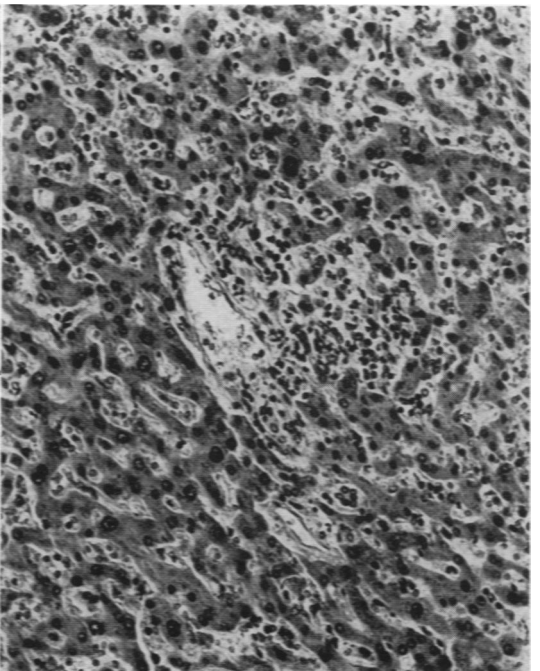
Kimmelstiel, Large, and Verner        Liver Damage in Ulcerative Colitis

PLATE 37

FIG. 13. A.F.I.P. Acc. 236758. Leukocytic infiltration in and around the wall of the vein shown in Figure 12. × 390.

FIG. 14. A.F.I.P. Acc. 277125. Interlobular hepatitis with severe inflammatory infiltration in the periphery of hepatic lobules. × 40.

FIG. 15. A.F.I.P. Acc. 277125. High-power view of the upper right-hand corner of Figure 14, showing pleomorphic nature of leukocytic infiltration and predominance of polymorphonuclear leukocytes. × 195.

FIG. 16. A.F.I.P. Acc. 78852. Interlobular hepatitis with marked inflammatory infiltration on the left and an increase in the interlobular connective tissue on the right. Of note is the formation of pseudolobules in the center. × 75.
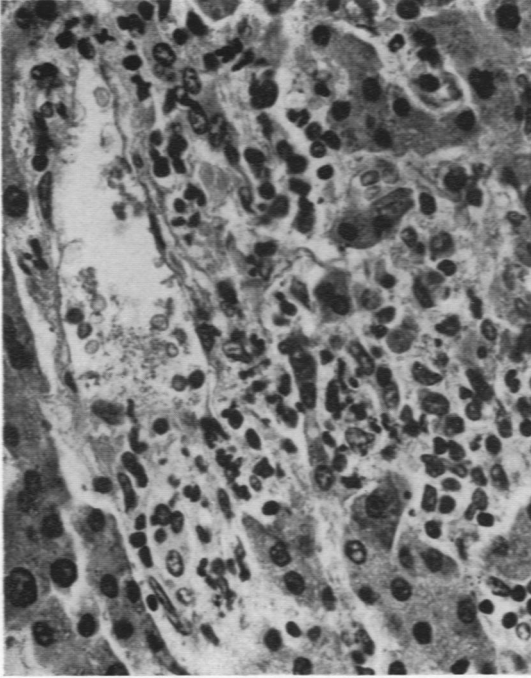
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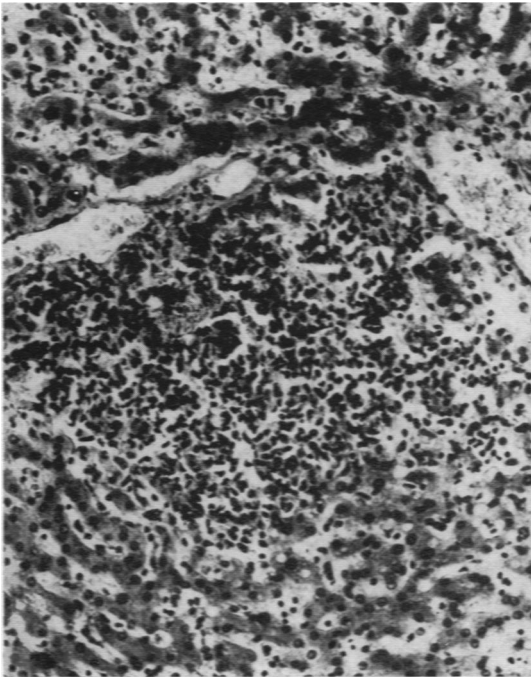


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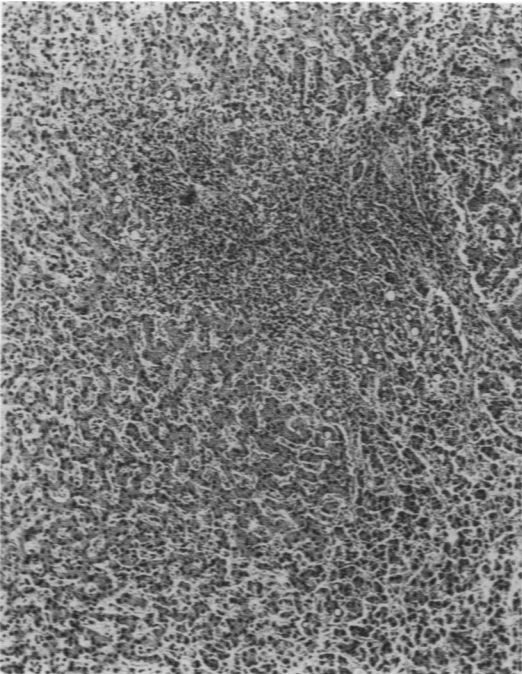Kimmelstiel. Large. and Verner                                Liver Damage in Ulcerative Colitis

FIG. 17. A.F.I.P. Acc. 78852. Same case as seen in Figure 16. showing a solitary focus of lymphocytic infiltration about a centrolobular vein. × 195.

FIG. 18. A.F.I.P. Acc. 141078. Interlobular hepatitis. with marked widening of periportal spaces by a heavy pleomorphic inflammatory infiltration. There is some proliferation of bile ducts. × 70.

FIG. 19. A.F.I.P. Acc. 149528. Interlobular hepatitis. The portal triad is heavily infiltrated with a variety of small round cells. The infiltration extends into the periphery of adjacent lobules. × 75.

FIG. 20. A.F.I.P. Acc. 149528. Same case as seen in Figure 19. showing another area with more severe involvement of periphery of lobules including destruction of parenchymatous elements. × 80.
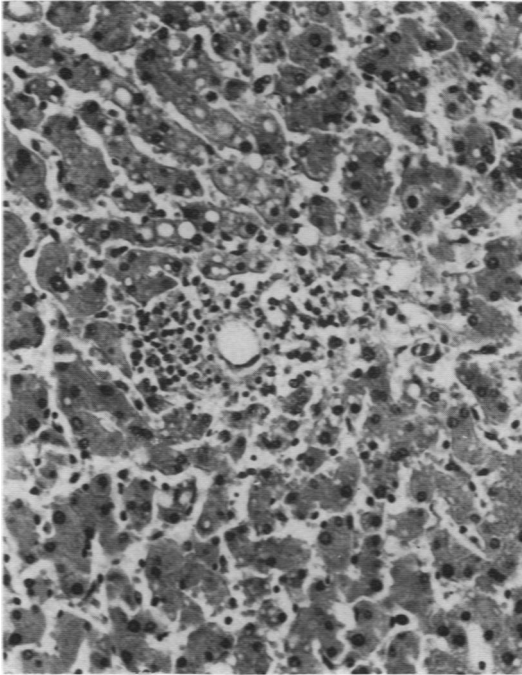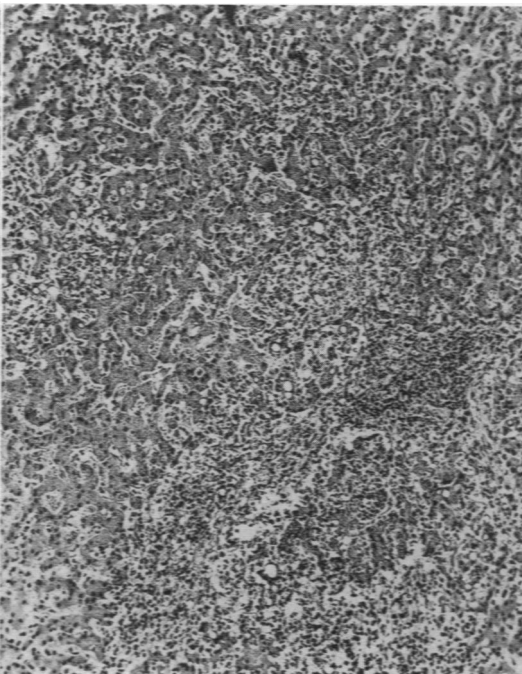
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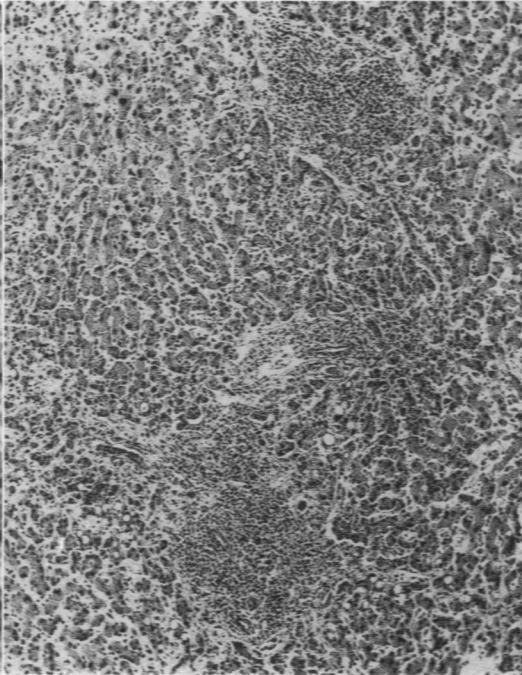


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Kimmelstiel, Large, and Verner
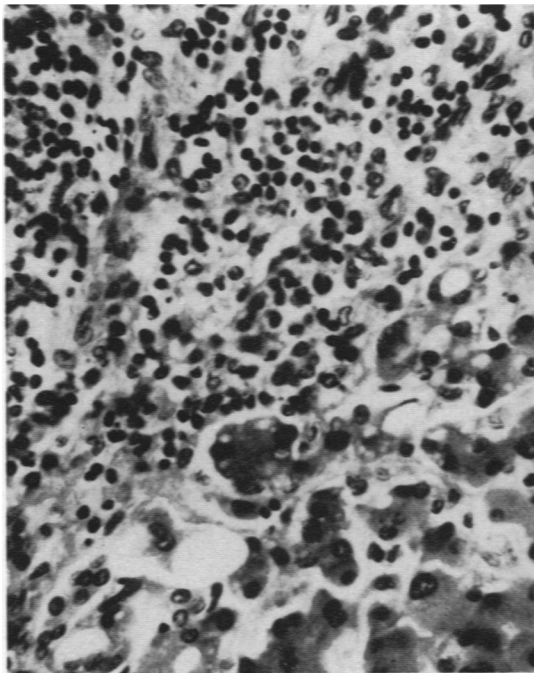
Liver Damage in Ulcerative Colitis

PLATE 39

FIG. 21. A.F.I.P. Acc. 149528. Same case as seen in Figures 19 and 20, with a focus of portal phlebitis with severe infiltration of wall of portal vein by lymphocytes and polymorphonuclear leukocytes. × 310.

FIG. 22. A.F.I.P. Acc. 269837. Focal interlobular hepatitis with severe infiltration of portal space with polymorphonuclear leukocytes and a few lymphocytes. × 110.

FIG. 23. A–860. Interlobular hepatitis, showing heavy round cell infiltration in periportal connective tissue, encroaching upon periphery of lobules. There is some fatty change in the liver cells. × 40.

FIG. 24. A–860. Same case as seen in Figure 23, with severe pleomorphic round cell infiltration in periportal space and in periphery of hepatic lobules. × 380.
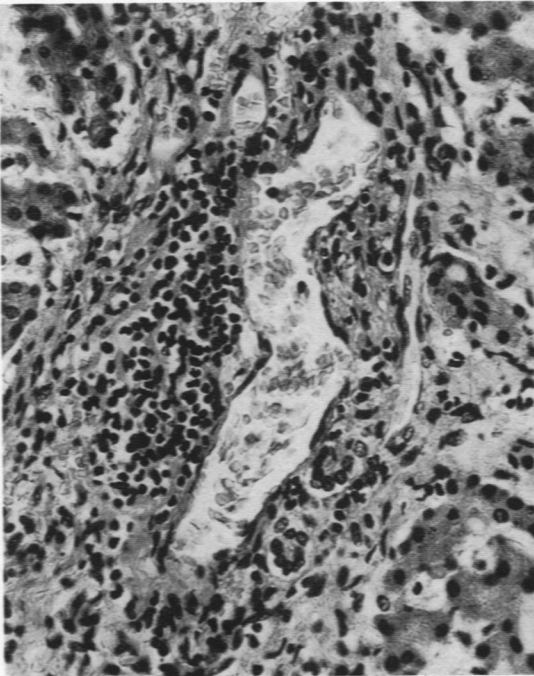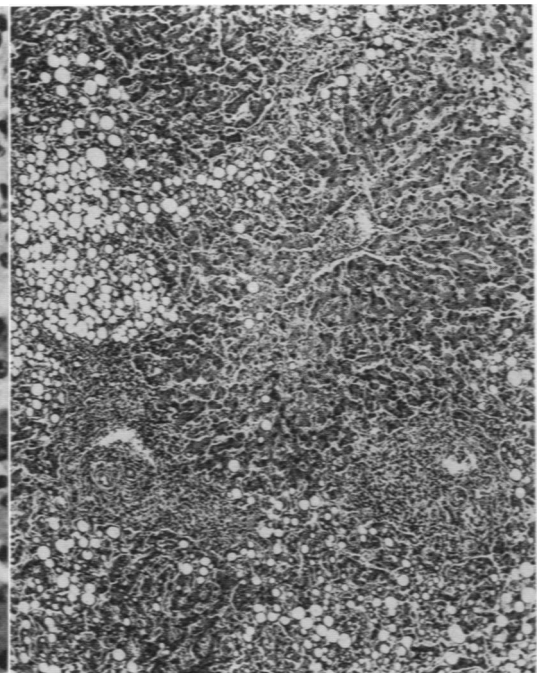
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Kimmelstiel, Large, and Verner　　　　　　　　　　Liver Damage in Ulcerative Colitis