THE PATHOLOGY OF FATAL EPIDEMIC HEPATITIS *

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CONTENTS

INTRODUCTION

During the spring and summer of 1942 an outbreak of jaundice of considerable magnitude occurred in the Army of the United States. General information concerning this outbreak has been given by the Surgeon General in a circular letter which was published in medical journals.[1] As stated in this circular, groups of investigators were assigned the study of various aspects of the disease; investigation of its pathology was conducted in the laboratories of the Army Medical Museum, where material from all available sources was assembled. This paper is based upon a study of 125 cases; the patients included

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the military personnel and, in addition, a number of civilians who died during the outbreak. The contents and arrangement of the paper are given above. The study does not include a consideration of the etiology, nor of the clinical manifestations of nonfatal cases; these aspects are dealt with by others,[2-4] in reports in which the relation of the administration of yellow fever vaccine, containing human serum, to the outbreak of hepatitis and jaundice are considered in detail.

Historical

Epidemics of Hepatitis. The disease which is variously known as epidemic hepatitis, infective or infectious hepatitis, or epidemic catarrhal jaundice is not new. Outbreaks with similar clinical and pathologic manifestations have occurred for at least the past 100 years.[5-8]

The disease has always been prevalent in armies, and particularly so in times of war. Hence English writers have referred to it as camp jaundice, or epidemic catarrhal jaundice of campaigns,[9] French writers as "jaunisse de champs," [10] German writers as a "Kriegs" icterus catarrhalis, or "Soldatenkrankheit" icterus.[11, 12]

One of the largest of recorded epidemics occurred in this country during the Civil War.[13] During the first year there were 10,922 cases with 40 deaths among the Federal troops (the mean strength of the U. S. Army being 279,371 men). During the second year 32,154 cases occurred with 119 deaths (mean strength of Army, 614,325 men). During the third year the epidemic declined; there were 9057 cases and 67 deaths (mean strength, 619,703). In the fourth year the number of cases had fallen to 294 with 5 deaths (mean strength of Army, 89,143). Woodward [14] in his book on "Outlines of the Chief Camp Diseases of the U. S. Armies," published in 1863, gives an excellent account of the clinical course of the disease.

"When this form of jaundice attacks a regiment or an Army, it usually appears in a number of cases simultaneously or in close succession like other epidemic disorders, lasts in each case from one to six weeks, or even longer, and then slowly disappears. The appearance of the icteroid hue is, as a rule, preceded by more or less derangement of the general health; sometimes, however, only by a few days of headache, constipation, and malaise, and occasionally the discoloration of conjunctiva and skin is the first noticeable symptom. The color of the skin may vary from a scarcely noticeable tinge to a deep tawny-orange color; this condition is accompanied by depressed spirits, intellectual torpor, loss of appetite, general debility, and uneasy sensations over the region of the liver and the stomach. Hepatic tenderness is a very variable symptom; enlargement of the liver, as indicated by an increased area of dullness on percussion, is more common. Sometimes there is nausea and vomiting. The stools are usually clay colored, and the bowels constipated, though at times there is diarrhoea. The urine is discolored from the presence of biliary matters. Very often the patient is so debilitated as to be quite unfit for duty, though not usually confined to his bed; at other times, however, he continues to perform service throughout the affection.

"After lasting a variable period, the symptoms slowly subside and the patient is gradually restored to health, the mental torpor and debility persisting often some time after the icteroid hue has disappeared. The first symptom of amendment is generally a change in the color of the stools, which gradually resume their normal appearance. Cases occasionally occur of a graver character than indicated above, the symptoms of biliary toxemia being aggravated to stupor or even coma, and such cases at times prove fatal."

This description of the epidemic of 1862 gives a good picture of the epidemic of 1942. Indeed, with minor variations, the clinical manifestations in the many epidemics have been remarkably similar.

During the Franco-Prussian War there were 2344 cases in the Prussian Army, 1311 cases in the Bavarian and 407 cases in the Saxon Army.[15, 16] During the South African War 5,648 cases were recorded.[10] In World War I, epidemics occurred in the armies of several nations. Among the British, so-called catarrhal jaundice first broke out in July, 1915, among troops stationed in Egypt; thereafter the epidemic spread rapidly to Gallipoli, where 2195 cases occurred from September to November, and then to Mesopotamia, where 1538 British and 2634 Indian troops were affected.[9, 17] The disease was as frequent among the French as among the British, but no cases occurred among the Turks. Among Rumanian troops there was a serious epidemic in the fall of 1917; one writer speaks of it as taking place in an almost explosive manner. Several thousand men were affected.[18] (See this paper for references to outbreaks among German troops.) No noteworthy epidemic occurred in the American Army during the war, but a relatively small outbreak developed in the Army of Occupation.[19]

Since the war, epidemic hepatitis has become widely prevalent among the populations of several countries. Blumer[20] recorded many outbreaks in the United States, of which more than 200 were observed during 1921 and 1922 in the State of New York alone. Cullinan[21] gave a list of reported outbreaks between 1926 and 1939 in England. Ruge[22] recorded an extraordinary rise in incidence of hepatitis between 1919 and 1929 in the German Navy. But it is in the Scandinavian countries that the disease became especially widespread and virulent. The extensive literature dealing with these Scandinavian epidemics is collected in the papers by Ehrström,[23] Wallgren,[24] Wickström[25] and Selander.[26]

In the present War, as in previous wars, the disease has at times been prevalent in the combatant forces: in the Army of the United States,[1] in British Forces[27, 28] and in the German Army.[12, 29,30] In discussing the occurrence of hepatitis in the German Army, Dietrich,[12] in 1942, stated that it had become one of the most important epidemic diseases.

Terminology. Until recent years, the disease under consideration was universally spoken of as catarrhal jaundice. This term reflected the views of Virchow[31] concerning its pathogenesis and nature. He believed that catarrhal jaundice is caused by inflammatory swelling of the orifice of the common bile duct, which, he thought, became obstructed by a plug of mucus and desquamated epithelium. Although he gave detailed directions for opening the duct so as to observe the occluding plug, the reader of his paper is left in doubt how often Virchow observed such an obstruction. In the course of time the correctness of Virchow's view was questioned by many clinicians, and the hypothesis was proposed that the site of the essential lesion is not in the extrahepatic bile ducts but in the liver.[32] So-called catarrhal jaundice gradually came to be regarded as an inflammatory process in the liver itself, *i.e.*, a form of hepatitis.

The term "epidemic hepatitis" was first applied by Lindstedt[33] in 1918 to the epidemic form of "catarrhal jaundice"; he proposed this term in contradistinction to "infectious hepatitis" or Weil's disease. Lindstedt's nomenclature has been followed particularly in the Scandinavian countries and on the European continent. In the United States and in Great Britain various terms are in use: infective jaundice, catarrhal jaundice, so-called catarrhal jaundice, infectious hepatitis, infective hepatitis, simple hepatitis, and epidemic hepatitis. None of these terms is wholly satisfactory. Probably not until the discovery of its etiologic agent will the disease receive a definitive name. In this paper, following the rules of priority in nomenclature, the disease will be referred to as epidemic hepatitis.

The Relation Between the Sporadic (Endemic) and the Epidemic Form of Hepatitis. It is the consensus at present that epidemic hepatitis is the epidemic form of the disease which in sporadic cases has hitherto been called catarrhal jaundice.[7, 24-26] The sporadic and epidemic forms are related in somewhat the same way as are sporadic and epidemic poliomyelitis or influenza.[5, 7] Many epidemics of hepatitis have been traced to sporadic cases, and the two forms cannot be distinguished on either clinical or epidemiologic grounds.[7]

Not every student of this disease, however, shares the view that the two forms are identical. Thus Selander[26] in his recent monograph stated that although the two forms have a very similar clinical picture, he yet considers sporadic catarrhal jaundice and epidemic hepatitis as two different diseases. He based his opinion on the more gradual development of the sporadic disease, which tends to affect adults, whereas the more rapidly developing epidemic form tends to affect children. Dietrich,[12] on the other hand, came to the conclusion that any differences in development or course merely represent reactions at two dif-

ferent age periods. All investigators agree that the question cannot be settled conclusively until the etiology of epidemic hepatitis is established.

Mortality. Like the sporadic form, epidemic hepatitis usually runs a mild course. The mortality is low; the rates in various epidemics, including the outbreak of 1942, have ranged from 0.13 to 0.44 per cent. During the Civil War there were 52,429 reported cases of jaundice and 231 deaths, with a mortality rate of 0.44 per cent.[13] During the previous World War, 1538 British and 2634 Indian troops stationed in Mesopotamia were affected, with a mortality of 0.4 per cent.[17] The incidence in the German Navy between 1919 and 1929 was approximately 2500, with a mortality of 0.13 per cent.[22] During a large epidemic in Finland, between 1933 and 1936, the mortality was 0.34 per cent.[24] Selander [26] estimated the mortality in recent Swedish epidemics as from 0.2 to 0.4 per cent.

In conformity with the policies of the War Department, specific statements concerning numbers of cases must for the present be omitted. It is possible, however, to state that in the 1942 outbreak the mortality was 0.24 per cent, *i.e.*, even lower than in most other recorded epidemics.

Pathology. Until the previous World War there was no precise information as to the lesions of catarrhal jaundice. During the war Eppinger [34] performed autopsies on three soldiers who died of trauma. The liver showed lesions which he regarded as a miniature form of acute yellow atrophy. For the first time it was shown by morphologic examination that catarrhal jaundice is in fact a disease of the liver. There was no obstruction of the extrahepatic biliary passages.

There have been but few other post-mortem examinations; a case was reported by Klemperer, Killian and Heyd,[35] one by Gaskell,[36] another by Schrumpf,[37] one by Barber and Osborn.[38] All confirmed Eppinger's findings that catarrhal jaundice is a disease which causes destructive changes in the liver.

To this meager information much has been added by the studies of Roholm and Iversen [39] and by those of Dible, McMichael and Sherlock.[40] These investigators examined material obtained for biopsy by aspiration of the liver during various stages of the disease. It became certain that catarrhal jaundice is a form of hepatitis.

Relation of Epidemic Hepatitis (Catarrhal Jaundice) to Idiopathic Yellow Atrophy. The studies previously mentioned deal with the lesion occurring in the usually benign, nonfatal case. During large epidemics, when perhaps the disease becomes more virulent, a much greater number of patients have been examined post-mortem. Invariably, the liver has shown the changes of idiopathic yellow atrophy. As early as 1912

Cockayne [5] reviewed the evidence for linking these two diseases which generally had been regarded as unrelated. He came to the conclusion that catarrhal jaundice and yellow atrophy are usually due to the same cause, a specific organism of unknown nature. Since the last war, many observers have commented on the increasing frequency of catarrhal jaundice, in both its sporadic and epidemic forms, and on the greater frequency with which acute yellow atrophy (not related to poisons or bacterial infection) has appeared at the autopsy table. Most of the cases of idiopathic yellow atrophy have occurred during or shortly following an epidemic of catarrhal jaundice. In the Scandinavian countries and in Great Britain both diseases seem to have been more prevalent than elsewhere; and in these countries many investigators have taken the view that yellow atrophy and benign catarrhal jaundice are but two extremes of one and the same disease.[5, 7]

This view is not shared by all investigators. During the serious outbreak of hepatitis in Sweden during 1927, Bergstrand [41] studied 95 fatal cases. Yellow atrophy of the liver was found in all. He regarded yellow atrophy merely as a complication of epidemic hepatitis. Bergstrand gave no adequate grounds for making this distinction, and his views were not generally accepted.

During the present war, several papers have dealt with the pathology of fatal epidemic hepatitis: Fox, Manso, Penna and Madureira Pará [42] reported 17 cases from Brazil, Cameron [27] reported 4 fatal cases from Palestine, and Siegmund [30] 3 from Germany. Yellow atrophy of the liver was the common finding in all.

The present study supports the view that idiopathic yellow atrophy represents the extreme lesion of epidemic hepatitis. It remains to be emphasized that this form of yellow atrophy differs anatomically from the yellow atrophies caused by arsenic, phosphorus and a large number of other chemical agents. It also differs from the yellow atrophy of eclampsia, and that of a number of bacterial infections, particularly those involving the peritoneum.

Material and Methods

The material available comprised clinical records, autopsy protocols and fixed tissues from 125 cases. In approximately two-thirds of the cases the complete clinical data were examined; in the remainder, more or less complete abstracts of the records. All cases had been studied in hospitals, and all had been diagnosed clinically as epidemic hepatitis (or as epidemic catarrhal jaundice). Most of the post-mortem examinations were performed by Army Medical Officers; their cooperation has greatly facilitated this study.

Paraffin sections were prepared from all tissues, and those of the liver were stained with hematoxylin and eosin, by the Masson-Mallory method for connective tissue and by Wilder's method for reticulum. In many instances various fat stains were used, and the Giemsa and the MacCallum stain for bacteria. Sections of organs other than liver were usually stained with hematoxylin and eosin, and frequently by the other methods. Frozen sections of the brain in selected cases were stained by Cajal's gold sublimate method and by Hortega's method for glia; Nissl stains, hematoxylin and eosin and myelin stains were used for paraffin sections.

Clinical Course of Fatal Epidemic Hepatitis

Epidemic hepatitis usually is a mild disease; its clinical course is well known and has been described in numerous papers. There is much less information concerning the course of hepatitis that terminates fatally. Therefore, in the present section an analysis is given of the clinical course of 125 fatal cases. In this analysis special emphasis is laid on the stages of the disease, on the times at which jaundice, ascites and nervous manifestations appeared, and on the more important laboratory findings. The data will be presented in the form of tables and graphs, so that only a brief summary need be given in the text. Abstracts of representative clinical records will be used to illustrate these data.

Age, Sex and Race of 125 Patients with Epidemic Hepatitis

The pertinent data are given in Table I. In the present series all except 4 patients were males; 94 per cent were whites, 6 per cent were colored. This distribution probably reflects the population in the Army, although no comparative figures are at present available. Seventy-

Table I

Age, Sex and Race of 125 Patients with Epidemic Hepatitis

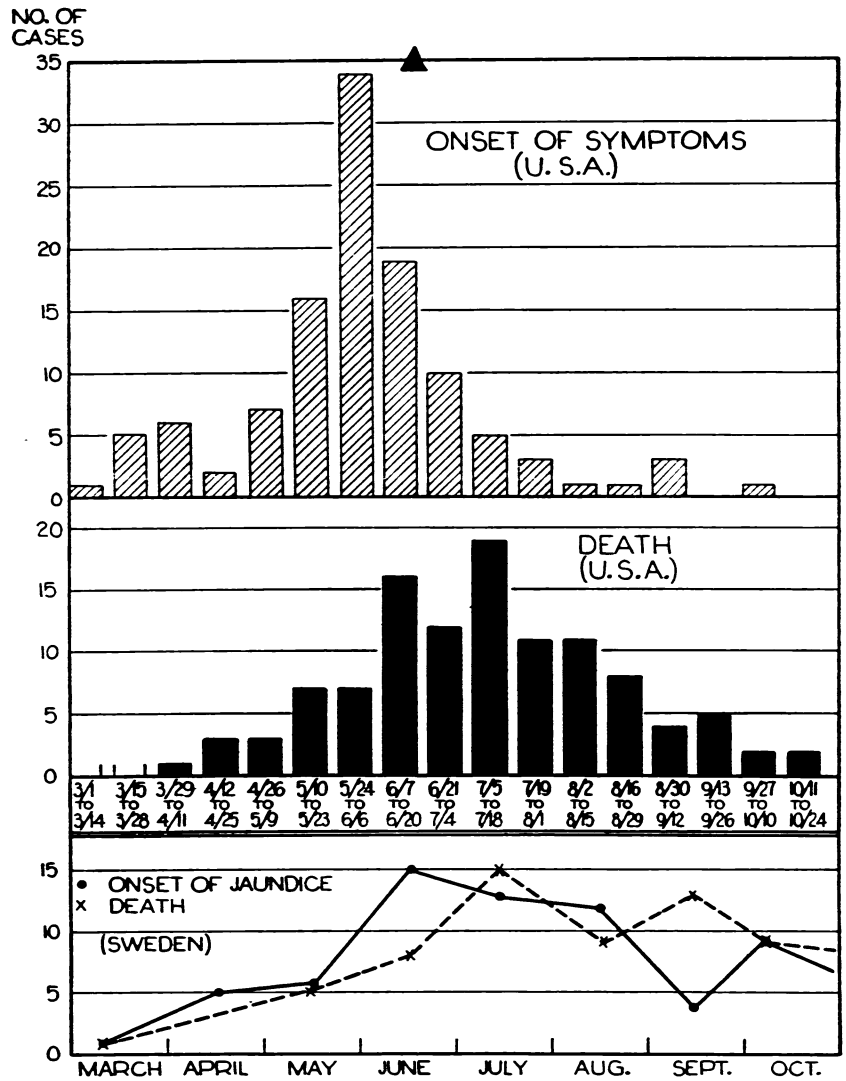
Age	Number of patients		
	White	Colored	Total
(*years*)			
20–24	*46 (37%)	4 (3%)	50 (40%)
25–29	*45 (36%)	2 (2%)	47 (38%)
30–34	9 (7%)	0	9 (7%)
35–39	11 (9%)	1 (1%)	12 (10%)
40–44	5 (4%)	0	5 (4%)
45–49	0	0	0
50–54	2 (2%)	0	2 (2%)
Total	118 (94%)	7 (6%)	125

All except 4 patients were males.
* Includes 2 females.

eight per cent were below 30 years of age. It is of interest to point out that fatal epidemic hepatitis was not entirely confined to the younger age groups; 22 per cent of the patients were above the age of 30.

Relation of Season to Onset of Symptoms and Death

The outbreak of hepatitis began in March, reached its peak toward the end of June and thereafter gradually declined, so that by the end



Text-Figure 1

of August few new cases were developing. It seems of interest to compare the onset of symptoms and the time of death of the fatal cases, first, with those of the entire outbreak and, secondly, with those in the

great Swedish epidemic of 1927. These relations are shown graphically in Text-Figure 1. Here the onset of symptoms and the time of death have been graphed in bi-weekly periods. It will be seen that the peak of onset of symptoms in fatal cases (shown in upper part of the figure) corresponds closely with the peak for all the cases of the epidemic (this peak is indicated by a solid triangle on the top line of the graph).

The modes in these two graphs are approximately 4 to 6 weeks apart.

TABLE II

Duration of Disease in 118 Cases of Epidemic Hepatitis

Duration	No. of cases	Per cent of cases
(*days*)		
Less than 10	0	0
10–19	14	11
20–29	20	16
30–39	31	26
40–49	20	17
50–59	8	7
60–69	8	7
70–79	9	8
80–89	0	0
90–99	5	5
Over 100	3	3

That this length of time represents the most frequent duration of the disease is confirmed by the data given in Table II.

A similar relation between onset and time of death is shown for the Swedish epidemic at the bottom of Text-Figure 1.

Course of Fatal Hepatitis

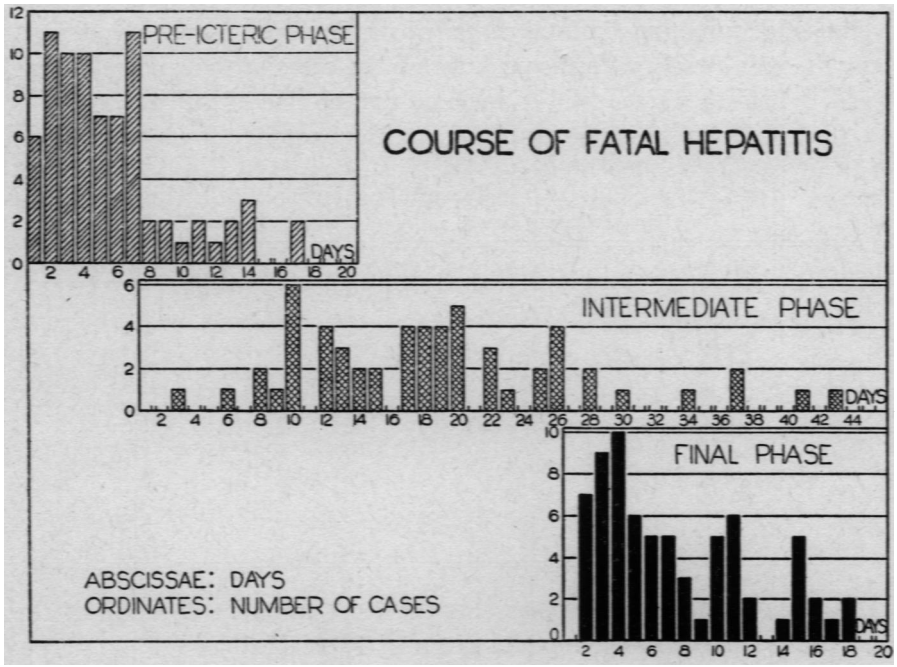
Three distinct phases in the clinical course of fatal hepatitis may be recognized: a pre-icteric, an intermediate and a final phase. The intermediate phase begins with the onset of jaundice and, in these fatal cases, usually ends abruptly with the appearance of new grave symptoms that presage the fatal termination. The time relation of the three phases is shown in a graph (Text-Fig. 2), where the ordinates give the number of cases, and the abscissae the duration. The pre-icteric phase in the great majority of cases lasted 7 days or less, and shows little scattering (see also Table III). In the intermediate phase, however, there is considerable scattering, though in the majority of cases the

TABLE III

Interval Between Onset of Symptoms and Appearance of Jaundice in 77 Cases of Epidemic Hepatitis

Interval	No. of cases
(*days*)	
1–4	37
5–9	29
10–14	9
15–19	2

duration was 26 days or less. The final phase, in the majority of cases, ran a course of 10 days or less.



Text-Figure 2

Initial Symptoms. The initial symptoms, *i.e.*, those of the pre-icteric stage, are presented in Table IV. The most common initial manifestations of the disease are anorexia, nausea, dark urine, abdominal

TABLE IV

Initial Symptoms in 120 Cases of Epidemic Hepatitis

Symptom	No. of cases	Per cent of cases
Anorexia	85	71
Nausea	62	52
Dark urine	39	33
Abdominal distress	37	31
Vomiting	29	24
Malaise	25	21
Weakness	24	20
Constipation	14	12
Headache	14	12
Fatigue	10	8
Backache	5	4
Coryza	3	3
Pruritus	3	3
Diarrhea	3	3
Chill	2	2
Urticaria	2	2
Epistaxis	1	1
Pain in joints	1	1
No pre-icteric symptoms	1	1

distress, vomiting, malaise and weakness. It should be emphasized that whereas approximately half the patients gave a history of nausea, only a quarter of the patients vomited.

Intermediate Phase. In the majority of cases the clinical picture in the intermediate phase gave no indication that the disease was not going to run the usual benign course. Many patients were ambulatory. In many instances the records contain statements such as "not acutely ill," "general condition good," "appears to be doing well," "uneventful course." In a considerable number the initial symptoms abated and the patients appeared to be steadily improving. Only in the exceptional case was the course grave from the beginning.

TABLE V

Duration of Final Phase in 73 Cases of Epidemic Hepatitis

Duration	No. of cases
(*days*)	
Up to 4	26
5–9	21
10–14	13
15–19	10
20 and over	3

Final Phase. A sudden dramatic change for the worse in 73 cases ushered in the final phase. The characteristic changes were nervous symptoms, ascites and persistent vomiting. The duration of this phase is shown in Table V. In over 60 per cent of the cases, death occurred within 10 days from the appearance of grave symptoms. Only 3 patients survived longer than 20 days (Table V).

Nervous Manifestations. In the great majority of cases the patients had signs of cerebral involvement. Particularly noteworthy were lethargy or coma, alternating with restlessness, excitement and delirium. Other manifestations were scanning speech, muscular weakness, and exaggeration of deep and superficial reflexes. Nervous manifestations usually ushered in the final phase; they marked the turning point. In a few cases, however, these manifestations appeared earlier or else were agonal (Table VI). The clinical course is illustrated by representative cases.

TABLE VI

Interval Between Onset of Nervous Manifestations and Death in 88 Cases of Epidemic Hepatitis

Interval	No. of cases	Per cent of cases
(*days*)		
Up to 4	53	60
5–9	19	22
10–14	8	9
15–19	6	7
20 and over	2	2

Illustrative Cases

Case 8

Clinical Course. The patient was a white male, 28 years old, who was well until the end of March, 1942. He then had anorexia, nausea and diarrhea; later, abdominal distress. On April 2, there was slight jaundice, but he was not ill and continued on duty until April 25, when he was admitted to hospital. Temperature, pulse and respiration were normal; liver enlarged, tender; urine, persistent traces of albumin and bile; stools, clay-colored. May 5: poor appetite; complained of being light-headed and dizzy; liver, enlarged and tender. May 8: slightly stuporous, somewhat confused. May 11: rapidly deepening stupor; sharp piercing cries; blood pressure, 150/85; disoriented and irrational; rapid change for the worse; alternating periods of coma and delirium. May 15: very toxic and delirious; did not respond to questions. May 16: comatose; rapid decline; vomited brownish material; died on this date.

Case 13

Clinical Course. The patient was a white male, 26 years old. On April 4, 1942, there was anorexia and later vomiting. April 9: jaundiced. Admitted on April 29, deeply jaundiced, tired, responsive; no fever; pulse, 76; abdomen flat; liver not palpable but slightly tender. May 5: temperature rose to 101° F.; blood pressure, 140/80; markedly dehydrated. May 6: somewhat stuporous; intermittent spasm of left sternocleidomastoid muscle; jerked head from side to side; tendon reflexes hyperactive but approximately equal on the two sides; sustained ankle clonus; Babinski reflex negative. May 17: abdomen distended; paracentesis, 600 cc. of fluid withdrawn. May 19: paracentesis, 1500 cc. of fluid withdrawn. May 21: paracentesis, 1500 cc. of fluid withdrawn. May 22: stupor progressed into coma. May 23: died.

Laboratory Findings.

Urinalyses

Date	Color	Specific gravity	Albumin	Acetone	Sugar	Bile
April 30	Dark	1.011	−		+	+
April 30	Coffee	1.015	+		−	+
May 1			−		−	+
May 2			+			++
May 5	Coffee	1.010	Faint trace	−	−	++
May 6						++

Blood Counts

Date	Red blood cells (*millions*)	White blood cells	Neutrophils (*per cent*)	Lymphocytes (*per cent*)	Monocytes (*per cent*)	Eosinophils (*per cent*)
April 30	4.85	9,300	59	27	2	1
May 1	5.48	7,200	60	23	12	2
May 4	5.62	7,450	48	42	9	
May 5	5.31	5,850	56	30	10	2

Examination of Feces

Date	
May 1	Gray, no bile present
May 6	Clay-colored

Chemical Examination of Blood

Date	Icterus index	Van den Bergh reaction	Serum protein Total (*gm. %*)	Albumin (*gm. %*)	Globulin (*gm. %*)	A/G ratio
May 2	164	+ (direct)				
May 3	132	+ (direct)				
May 5	120	+ (direct)				
May 25	120		5.4	1.5	3.9	0.45

Case 27

Clinical Course. The patient was a white male, 33 years of age. On May 13, he complained of headache, nausea and malaise. May 20: "dark" urine. May 23: light-colored stools; moderate degree of jaundice. Upon admission on May 23, did not appear acutely ill; liver moderately tender. May 26: no complaints. May 29: appetite decreased, jaundice more marked. Condition remained the same until June 3, when liver became moderately enlarged, tender. June 5: considerable epigastric distress. June 9: became delirious and irrational, slight convulsive movements; blood pressure, 116/64; temperature, pulse and respiration normal. June 11: after return to normal mental state, again extremely restless and semi-delirious; spasmodic movements at intervals, such as jerking of head and contracting of abdominal muscles, not convulsive; at times answered questions rationally, at other times was irrational; intensely jaundiced; no vomiting; later in day became very drowsy, fell asleep while examined. June 12: delirium persisted, noisy, very restless; cried out as if in pain; later comatose. June 13: condition essentially unchanged. June 14: much improved; responded to questions and was rational for short periods. June 15: again delirious; positive Babinski reflex; ankle clonus. June 16: vomited coffee-ground material; later, deep coma. June 17: bronchopneumonia evident; condition very poor. May 23 to June 11: temperature, 97.6° to 98.4° F.; pulse, 68 to 80; respiration, 18 to 20. June 11 to June 17: slightly febrile, temperature was 99.2° to 100.0° F. June 17: died.

Laboratory Findings.

Chemical Examination of Blood

Date	Icterus index	Nonprotein nitrogen (*mg. %*)	Sugar (*mg. %*)	Serum protein Total (*gm. %*)	Albumin (*gm. %*)	Globulin (*gm. %*)
May 26	42					
June 11	200	40	62			
June 12		44	70	6.2	3.0	3.2
June 15		45	112			
June 16	160					

Blood Counts

Date	Red blood cells (*millions*)	White blood cells	Polymorphonuclear leukocytes (*per cent*)	Lymphocytes (*per cent*)
June 12	4.8	10,000	81	16
June 16	4.5	10,000		

Urinalyses

Date	Albumin	Bile
June 12	+	+
June 15	+	+
June 16	+	+

Case 76

Clinical Course. The patient was a white female civilian, 27 years old. She had not received yellow fever vaccine. In April, her husband, an officer, had a mild attack of hepatitis which lasted about 1 month. The patient herself was well until August 1, 1942, when general malaise developed and her appetite began to fail. August 25: jaundice developed. Admitted on September 5, moderately jaundiced; blood pressure, 118/78; liver tender and moderately enlarged. During her early stay in the hospital was occasionally jaundiced but felt fairly well; appetite was good. September 9: jaundice had deepened; definite nausea. Uneventful, afebrile course with small improvement until October 11, when swelling of face developed due to infection of right lower molar tooth; slight irregular fever during this period; jaundice was decreasing. October 15: diplopia developed and continued. October

28: speech became like that of an intoxicated person; normal clear-cut pronunciation altered so that her words were difficult to understand. October 30: very emotional, alternating periods of euphoria and crying; disoriented with regard to time, but oriented with regard to place and person; speech thick and slurred; deep and superficial reflexes normal, no abnormal reflexes could be demonstrated; general decrease in motor power and muscle tone which was attributed to poor physical condition rather than to involvement of central nervous system; clinical impression of acute toxic encephalitis. October 31: violently delirious, screamed and tried to get out of bed; unable to take food by mouth. November 2: twitching movements of hands and feet. There had been a gradual rise in temperature to 106° F. from October 30 to November 4. November 4: died.

Laboratory Findings.

Blood Counts

Date	Red blood cells (*millions*)	White blood cells	Polymorphonuclear leukocytes (*per cent*)	Lymphocytes (*per cent*)
Sept. 5	3.4	4,300	65	30
Oct. 20	2.7	4,400	69	31
Oct. 22	2.7	4,700	70	27
Nov. 2	2.8	11,600	89	7

Chemical Examination of Blood

Date	Icterus index	Urea nitrogen (*mg. %*)	Nonprotein nitrogen (*mg. %*)	Serum protein Total (*gm. %*)	Albumin (*gm. %*)	Globulin (*gm. %*)
Sept. 7	100					
Sept. 9	109					
Sept. 14	123					
Sept. 25	154					
Oct. 5	147					
Oct. 12	156					
Oct. 29	76					
Nov. 3	116	34	64	7.2	3.9	3.3

Urinalyses

During early stay in hospital, no albumin; later, trace to moderate amount.

Case 121

Clinical Course. The patient was a white female civilian, 23 years of age, who had not received yellow fever vaccine. About December 1, 1942, there was dyspepsia, constipation, lassitude, progressive weakness; suddenly became jaundiced. December 18: admitted. December 19: temperature, 98° F.; pulse, 80; respiration, 18; blood pressure, 110/70; albuminuria; jaundice cleared considerably. By January 22, icterus index had fallen to 148. General condition improved; patient returned to her home. Upon readmittance on January 28, abdomen was distended; moderate irregular fever; complained of general aching. February 6: paracentesis, 1600 cc. of bile-stained fluid removed. February 8: fluid formed rapidly; patient became stuporous and irrational, later comatose; general condition poor. February 10: died.

Laboratory Findings.

Blood Counts

Date	Red blood cells (*millions*)	White blood cells
Dec. 19	4.8	8,400
Feb. 3	3.6	5,100
Feb. 6		8,100

Date	Chemical Examination of Blood		
	Icterus index	Urea nitrogen (*mg.* %)	Sugar (*mg.* %)
Dec. 19	188		
Jan. 22	148		
Feb. 6	140		
Feb. 7		22	104
Feb. 9	186		

Ascites. Ascites was common, occurring in about two-thirds of the cases. In many cases the day of appearance of ascites was known. The records stated that on one day the patient's abdomen was flat, and on the next it became distended. Thus, the onset of ascites was usually sudden. Ascites was a late manifestation; usually occurring only a few days before death (Table VII). There was one instance in which marked ascites developed relatively early, and after lasting several days disappeared.

TABLE VII

Interval Between Onset of Ascites and Death in 45 Cases of Epidemic Hepatitis

Interval	No. of cases	Per cent of cases
(*days*)		
1–4	22	49
5–9	10	22
10–14	3	7
15–19	4	9
20 and over	6	13

Case 100

Clinical Course. The patient was a white male, 27 years old. On June 12, appetite was poor; nausea but no vomiting; urine "dark"; itching at night. Some days later became severely nauseated but did not vomit; stools clay-colored; noticed that fatty foods particularly disagreed with him; slight pain in right upper quadrant. Admitted on June 22, with moderate jaundice; blood pressure, 130/60; abdomen flat; liver slightly tender, not enlarged. Condition remained about the same until June 28; patient was eating well; had no complaints; was ambulatory. July 4: jaundice deepened; still afebrile; went to mess hall and ate well. July 12: condition remained as stated. July 15: complained of not feeling well; jaundice of about same intensity; liver now painful and tender, not enlarged; no fever. July 20: had been vomiting; liver moderately enlarged; complained of pain in right upper quadrant; no abdominal fluid; no edema. July 21: nauseated; uncomfortable; pain in epigastrium; vomited occasionally; looked sick. July 22: abdominal fluid suspected; liver markedly tender; much pain in right upper quadrant; slight fever; seemed much worse; flanks slightly bulging. July 23: temperature, pulse and respiration were normal; abdomen more distended. July 24: slight rise in temperature; blood pressure, 120/65; abdominal fluid; suggestion of edema around ankles. July 25: paracentesis, 3500 cc. of bile-stained fluid removed; temperature, 101° F.; stools contained bile. July 26: condition considerably better; edema of ankles had cleared, but abdominal fluid had again accumulated. July 27: paracentesis, 3300 cc. of fluid withdrawn. July 28: continued to run low-grade fever; abdominal fluid recurrent; patient remained conscious and rational; liver slightly enlarged, but not tender. July 29: paracentesis, 2700 cc. of fluid withdrawn; liver still palpable, not

tender. July 30: patient in good spirits; felt better; temperature, pulse and respiration were normal; "ate three times today and for lunch had a lean steak." August 3: felt better, more alert, but had low-grade fever. August 5: paracentesis, 2300 cc. of fluid withdrawn. August 8: abdomen flat; no fluid; liver at costal margin; appetite still good. August 16: patient was not interested in food or in his surroundings; low-grade fever (temperature, 99.0° to 99.6° F.). August 21: no interest whatever; reflexes hypertonic. August 25: speech slurred and indistinct; response slow and frequently unintelligible; temperature, 100° F.; liver apparently had shrunken. August 28: bilateral ankle clonus, bilateral Babinski reflex; superficial reflexes hyperactive. August 31: stuporous. September 5: comatose; made smacking noises with lips; convulsive jerks of eyeballs; temperature, pulse and respiration were essentially normal. September 10: gradual rise in temperature to 104° F. on day of death. September 13: died.

Laboratory Findings.

	Urinalyses			
Date	Specific gravity	Albumin	Sugar	Bile
June 23	1020	o	None	+
July 21	1015	o	None	+
July 25	1013	o	None	
July 27	1015			
Aug. 19	1014	+	None	
Aug. 31	1004	++++	Trace	
Sept. 8	1028	Trace	++	
Sept. 11	1014	++++	+	
Sept. 13	1020	+++	+	

Chemical Examination of Blood

Date	Icterus index	Nonprotein nitrogen (mg. %)	Serum protein Total (gm. %)	Albumin (gm. %)	Globulin (gm. %)
June 23	90				
July 21			5.28	2.79	2.49
July 23	116	43.5			
July 26	135	35			
July 30	92				
Aug. 7	50	35			
Aug. 17	57	36	8.24	6.68	1.56
Aug. 24	37				
Sept. 4	28				

Symptoms and Laboratory Findings

Analysis of symptoms and the results of laboratory examinations have been restricted to the following: temperature, pulse rate, blood pressure, examination of liver by palpation, recurrence of attack, hemorrhages, red blood count, leukocyte count, differential white count, plasma proteins and icterus index. In this analysis, the intermediate phase has arbitrarily been divided into two periods, namely, the first 3 days after the onset of jaundice, and the later period.

Temperature. An analysis of temperature is given in Table VIII. It will be seen that 92 per cent of the patients were afebrile during the first 3 days after the onset of jaundice. However, subsequent to this period 41 per cent developed fever. This usually was of brief duration. Since in many cases plasma, glucose, or whole blood was administered

intravenously, the febrile episodes cannot, with certainty, be attributed to hepatitis. Perhaps the most significant fact of the analysis is that approximately 60 per cent of the patients were afebrile throughout the intermediate period, but during the final period fever developed in the great majority, 89 per cent. Usually there was a sharp rise in temperature during the last 2 or 3 days of life when the patient was moribund (Text-Fig. 3).

Pulse Rate. In contrast to the bradycardia which is so common in other hepatic diseases, slowing of the pulse in this series was observed but seldom.

TABLE VIII

Temperature in Cases of Epidemic Hepatitis

	Number of cases		
	Intermediate period		Final period
	First 3 days after jaundice	Subsequent to first 3 days after jaundice	
Afebrile	24 (92%)	20 (59%)	6 (11%)
Febrile	2 (8%)	14 (41%)	49 (89%)
Total no. of cases	26	34	55

Blood Pressure. During the intermediate period the blood pressure was usually normal. With the onset of nervous manifestations, the pressure tended to rise. Representative examples follow: 144 systolic, 94 diastolic; 170/90; 100/80; 155/70; 150/92.

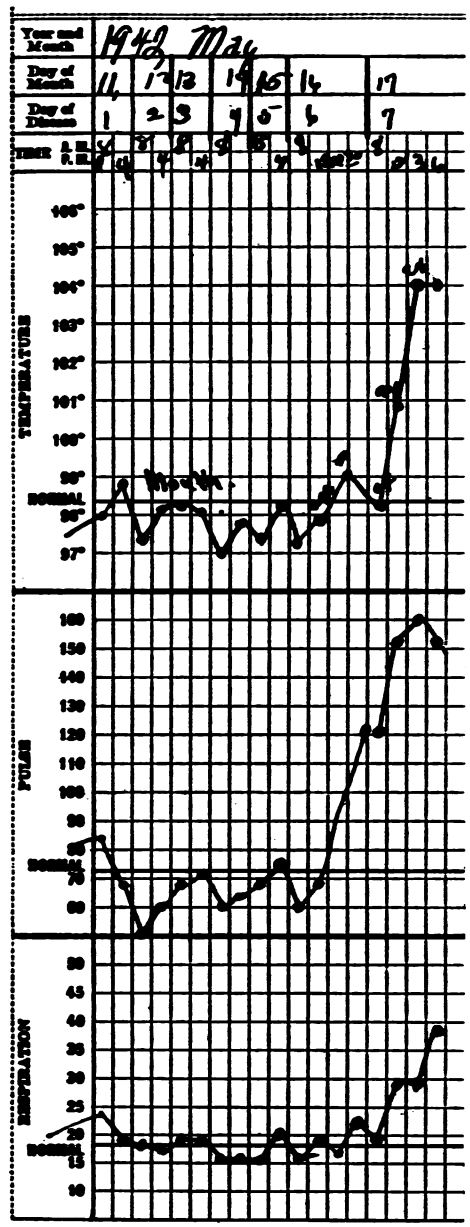
Palpation of Liver. During the first 3 days after the onset of jaundice, enlargement of the liver was found in approximately one-half the patients (15 of 28). Later, in the intermediate stage, enlargement was still more common (29 of 34 cases). Enlargement was usually associated with tenderness. During the final phase the majority showed shrinkage of the liver.

Recurrence. In only one instance did symptoms recur after an apparent recovery.

Case 117

Clinical Course. The patient was a white male, 22 years of age. In April, 1942, he noticed increased malaise and frequent nosebleeds. He later became jaundiced and was admitted to hospital, where he remained for 7 weeks. Course was uneventful except for daily rise in temperature, which usually reached a peak of 103° F. in the evening. Icterus index was as high as 113. His course, except for the fever, was similar to that of about 20 other patients with jaundice who were at that time hospitalized. June 8: transferred to another hospital; moderately ill, undernourished and jaundiced; liver enlarged and tender. Icterus index varied from 20 on admission to 120 on July 27, and then gradually fell to 11. Afebrile. Temperature, pulse and respiration had been normal since June 23. Steady improvement in general condition. September 14 to October 13: sick leave. October 27:

returned to duty. November 27: again became jaundiced. December 5: readmitted, apparently not acutely ill. December 11: ambulatory; did not feel ill, no fever. December 14: nausea and vomiting; jaundice had deepened; dull aching pain in right upper quadrant; stools had varied from clay-colored to light gray. December



Text-Figure 3

18: icterus index, 110; white blood cells, 4,500. December 20: icterus index, 150. December 21: vomited bile-stained material; stools brown. December 23: jaundice somewhat decreased; slight soreness in right upper quadrant. December 28: definitely worse; disoriented; later semicomatose and stuporous. December 29: died.

Hemorrhages. Hemorrhages were common, especially in the late period. Their incidence and distribution were as follows: petechiae of the skin in 20 instances, vomiting of blood in 20, epistaxis in 11 and other hemorrhagic phenomena (bleeding from bowel, hematuria and bleeding from respiratory tract) in 16 instances.

Blood Counts and Hemoglobin Determination. Representative examples of blood counts and hemoglobin determinations from 7 cases are given in Table IX. The differential white counts include only neutrophils and lymphocytes.

Erythrocyte Count. Erythrocyte counts in the different phases of hepatitis are summarized in Table X. During the first 3 days after

TABLE IX

Blood Counts in Representative Cases

Case no. and duration	Date	Red count	Hemoglobin	White count	Neutrophils	Lymphocytes
		(*million*)	(*per cent*)		(*per cent*)	(*per cent*)
No. 25. A.M.M.* no. 83171						
Onset, 5/29/42	6/6/42	4.26	75	7,500	64	32
Death, 6/27/42	6/26/42	3.88	70	4,550	57	34
No. 30. A.M.M. no. 83312	5/28/42	4.41	85	6,800	52	48
Onset, 5/24/42	6/19/42	4.00	80	5,200		
Death, 6/18/42						
No. 52. A.M.M. no. 83747	5/14/42	4.50	80	4,250		
Onset, 4/30/42	7/8/42	3.10	80	13,500		
Death, 9/15/42	7/15/42	3.80	80	9,100		
	8/2/42	2.75	55	10,800		
No. 59. A.M.M. no. 83833	7/7/42	4.65	78	8,000	50	41
Onset, 6/ 4/42	7/8/42	4.55	75	7,000	65	30
Death, 7/13/42	7/13/42	3.73		5,000	79	21
No. 84. A.M.M. no. 84422	6/16/42	4.6	80	3,600	51	49
Onset, 5/24/42	6/21/42	5.3	95	9,200	56	44
Death, 8/27/42	6/23/42			2,800	40	60
	7/2/42			5,600	50	50
	7/6/42	4.9	80	4,100	64	36
	7/29/42	4.3	85	4,400	63	37
	8/12/42	3.2	75	5,300	78	21
	8/14/42					
	8/18/42	2.9		4,900	68	30
	8/24/42	4.0	80	9,400	84	15
No. 86. A.M.M. no. 84506	6/21/42	4.50		6,700		
Onset, 5/25/42	7/7/42	3.25	80	4,200	67	33
Death, 7/26/42	7/16/42	3.00	75	5,800		
	7/19/42	2.20	65	5,600	63	37
	7/25/42	3.47	65	9,700		
No. 100. A.M.M. no. 85431	6/22/42	4.1	85	6,400	70	29
Onset, 6/12/42	7/20/42			6,200	63	33
Death, 9/13/42	7/23/42	3.8	87	5,500	62	38
	8/2/42	3.9		7,700	61	38
	8/11/42	3.2		9,000	65	32
	8/12/42			7,100	75	35
	8/16/42	4.3		9,500		
	8/24/42	3.1	73	7,700	74	21
	9/10/42			21,000	80	20
	9/10/42		76	22,000	83	17
	9/11/42	3.7		31,000	83	18

* A.M.M. = Army Medical Museum.

jaundice developed, the counts were approximately normal. Later the erythrocyte count fell. During the final phase definite anemia of secondary type was evident in approximately 40 per cent of the cases.

Leukocyte Count. The results of leukocyte counts are given in Table XI. Slight leukopenia was evident in nearly half of the cases early in

TABLE X

Erythrocyte Count in Cases of Epidemic Hepatitis

Erythrocyte count	Number of cases		
	Intermediate period		Final period
	During first 3 days after jaundice	Subsequent to first 3 days after jaundice	
(*millions*)			
Over 5	5 (22%)	9 (27%)	9 (24%)
4—4.9	18 (78%)	16 (48%)	14 (38%)
3—3.9	0	5 (15%)	10 (27%)	
2—2.9	0	3 (9%)	4 (12%)
Total number of cases	23	33	37

the intermediate phase. Leukocytosis during the intermediate period occurred in relatively few. The counts during the final period were strikingly different. Then few patients showed leukopenia, the majority having mild leukocytosis. This leukocytosis was probably related to terminal events, such as lobular pneumonia and phlegmonous inflammation of the gastrointestinal tract.

Differential White Blood Cell Counts. The results of differential

TABLE XI

Leukocyte Count in Cases of Epidemic Hepatitis

Leukocyte count	Number of cases		
	Intermediate period		Final period
	During first 3 days after jaundice	Subsequent to first 3 days after jaundice	
(*thousands*)			
Below 3.0	0	1 (2%)	1 (2%)
3.0—3.9	0	0	1 (2%)
4.0—4.9	5 (17%)	4 (10%)	4 (7%)
5.0—5.9	9 (30%)	9 (22%)	1 (2%)
6.0—6.9	2 (7%)	7 (17%)	5 (9%)
7.0—7.9	3 (10%)	9 (22%)	4 (7%)
8.0—8.9	6 (20%)	6 (15%)	6 (11%)
9.0—9.9	3 (10%)	1 (2%)	6 (11%)
10.0—10.9	1 (3%)	2 (5%)	7 (13%)
11.0—11.9	0	0	0
12.0—12.9	0	0	7 (13%)
13.0—13.9	1 (3%)	0	2 (4%)
14.0—14.9	0	1 (2%)	7 (13%)
15.0 and over	0	1 (2%)	5 (9%)
Total number of cases	30	41	56

counts are shown in Table XII. In this table the dotted horizontal lines mark the boundary between the normal and the abnormal. There was a relative lymphocytosis in two-thirds of the cases during the early days of the intermediate period. By contrast, during the final period a relative lymphocytosis was uncommon.

Plasma Proteins. In severe damage to the liver the plasma proteins would be expected to fall. In this series such a fall frequently did not

TABLE XII

Differential White Blood Cell Counts in Cases of Epidemic Hepatitis

	Number of cases		
	Intermediate period		Final period
	During first 3 days after jaundice	Subsequent to first 3 days after jaundice	
Polymorphonuclear leukocytes (*per cent*)			
40—49	0	2 (10%)	0
50—59	5 (28%)	6 (30%)	3 (12%)
60—69	10 (56%)	10 (50%)	2 (8%)
70—79	3 (17%)	2 (10%)	10 (38%)
80—89	0	0	8 (31%)
90 and over	0	0	3 (12%)
Total number of cases	18	20	26
Lymphocytes (*per cent*)			
50—59	0	2 (10%)	0
40—49	5 (28%)	7 (35%)	1 (4%)
30—39	7 (39%)	2 (10%)	4 (15%)
20—29	5 (28%)	8 (40%)	9 (35%)
Below 20	1 (6%)	1 (5%)	12 (46%)
Total number of cases	18	20	26

occur, probably because of therapeutic administration of plasma or whole blood. Representative examples are given in Table XIII.

Icterus Index. The icterus index in a number of representative cases, together with clinical abstracts, is given in Table XIV. The index is above normal. It fluctuates irregularly, but in the majority of cases it tends to rise. Exceptions to this are summarized in Table XV.

The icterus index during the three phases of hepatitis is shown in Table XVI. During the first 3 days the index was below 100 in the great majority of the cases. Subsequently it tended to rise, particularly so in the final period.

PATHOLOGIC ANATOMY

As has been stated, in every instance the fatal cases of epidemic hepatitis presented lesions in the liver that correspond to so-called idiopathic yellow or red atrophy. This condition has been described

in detail by numerous writers, and the literature on the subject has been exhaustively summarized by Roman [43] and by Herxheimer and Thölldte.[44] The paper by Wilson and Goodpasture [45] serves as an excellent introduction to the subject. It would be repetitious, therefore, to go into morphologic minutiae.

The changes observed will be presented in the following order: liver,

TABLE XIII

Plasma Proteins in Representative Cases
(gm. per 100 cc.)

Case no. and duration	Date	Total protein	Albumin	Globulin	Remarks
No. 52. A.M.M.* no. 83747	5/16/42	6.5	3.7	2.8	No ascites
Onset, 4/30/42	5/29/42	6.9	5.2	1.6	
Death, 9/15/42	6/ 6/42	7.7	3.0	3.9	
	6/15/42	6.7	4.4	3.3	
	6/29/42	5.5	3.1	2.9	
	7/15/42	5.0			
	7/20/42	5.4			
	7/29/42	6.7			
	8/ 5/42	7.2	4.9	2.3	
	8/10/42	7.6	5.0	2.6	
	8/17/42	7.3	5.7	1.5	
	8/24/42	9.2	6.5	2.4	
	8/31/42	7.2	4.7	2.5	
	9/ 7/42	7.2			
No. 84. A.M.M. no. 84422	7/ 8/42	5.26	3.31	1.95	Ascites since
Onset, 5/24/42	7/13/42	4.40	2.75	1.65	7/2/42;
Death, 8/28/42	7/16/42	4.9			repeated
	7/20/42	4.69	2.87	0.15	paracente-
	7/23/42	3.61	2.10	1.27	ses
	7/29/42	3.99	2.59	1.14	
	7/30/42	5.14	2.54	2.40	
	8/ 3/42	5.08	3.03	2.05	
	8/13/42	5.90	3.65	2.25	
No. 89. A.M.M. no. 84856	6/25/42	5.68			Ascites dur-
Onset, 6/1/42	7/ 4/42	6.6	4.3	2.3	ing last
Death, 8/18/42	7/20/42	6.65	3.7	2.6	few days
	8/10/42	4.1			of life
	8/15/42	3.4			

* A.M.M.=Army Medical Museum.

gallbladder, regional lymph nodes, ascites, spleen, gastrointestinal tract, hemorrhagic phenomena, bone marrow, kidney, testis, and brain.* No significant changes were found in the other organs.

Since no verbal description can give an adequate picture of the gross and microscopic changes of any disease, this paper is liberally documented by photographic illustrations.

* Major Philip Custer examined many sections of the bone marrow and spleen, and Captain Webb Haymaker those of the brain. This study has been greatly aided by their advice.

Liver

In all cases the liver is the site of the principal lesions and presents a characteristic picture. Without exception the changes are typical of idiopathic yellow atrophy.

Gross Appearance of the Liver

Grossly the organ is usually reduced, at times to less than one-half its normal size. Most often it weighs between 800 and 1200 gm. Reduction in weight, however, is not invariably found; in approximately one-fifth of the cases the weight of the liver falls within normal limits or is actually above the normal. Generally speaking, the smallest livers

TABLE XIV
Icterus Index in Representative Cases

Case no. and duration	Date	Icterus index	Clinical abstract
59 Onset, 6/4/42 Death, 7/13/42	6/13 6/17 6/24 6/29 7/1 7/7 7/10 7/11 7/13	36 78 143 127 136 177 210 190 204	White, male, 26 years old. 6/4: weakness, nausea, headache, anorexia, generalized aching, "dark" urine. 6/12: admitted; temperature, pulse and respiration normal; blood pressure, 114/80. 6/15: liver slightly enlarged. No change until 6/26, then abdominal pain; liver more enlarged and tender. 6/29: stuporous; occasional nausea and vomiting; apathetic. 7/3: jaundice increased. 7/8: blood pressure, 146/80; liver at costal edge. 7/10: blood pressure, 140/90; seemed less toxic; ate breakfast; responded to questions. 7/12: abdomen distended. 7/13: temperature, pulse and respiration began to rise; ascites noted; blood pressure, 140/78; temperature, 102° F. in morning, rose to 104° F. by afternoon; pulse, 130 to 150; respirations, 30 to 40.
57 Onset, 5/26/42 Death, 7/9/42	6/8 6/15 6/18 6/22 6/26 6/29	28 30 32 30 40 50	White, male, 20 years old. About 5/26: weakness, anorexia, nausea, headache, "dark" urine; later jaundice; said to have lost about 10 pounds; no itching. 6/8: admitted; ambulatory; not acutely ill; blood pressure, 104/68. Course in hospital stormy; persistent nausea and vomiting; deepening jaundice. 6/10: marked increase in size of liver to 4 fingersbreadth below costal margin; thereafter gradual decrease, by 6/30 to costal rim, during last week of life to 3 fingersbreadth above costal rim. 7/3: stuporous; comatose; spasmodic twitching of facial muscles; blood pressure, 84/50.
84 Onset, 5/24/42 Death, 8/28/42	6/20 6/29 7/6 7/8 7/10 7/18 7/20 7/24 7/27 7/30 8/7 8/10	160 160 150 150 150 100 90 60 60 45 45 35	White, male, 24 years old. About 5/24: anorexia, headache, backache, "dark" urine, clay-colored stools. 6/1: sclerae icteric. 6/4: admitted. Until 6/16, felt fairly well; then malaise, nausea, vomiting; liver tender, enlarged; "prognosis appears to be good." 7/2: ascites; repeated paracenteses. 7/23: jaundice declining; general condition improved. 8/10: appetite good. 8/13: greatly improved; condition satisfactory. 8/15: condition changed; became restless; dull; drowsy. 8/16: symptoms more marked; speech scanning; disoriented; progressive decline. During last several days ran irregular fever, temperature of 103° to 104° F.

TABLE XIV (*Continued*)
Icterus Index in Representative Cases

Case no. and duration	Date	Icterus index	Clinical abstract
23	5/5	28	White, male, 26 years old. 4/29: nausea, vomiting, headache, constipation. 5/3: sclerae yellow. 5/5: admitted; temperature, pulse and respiration normal; liver not enlarged, slightly tender; blood pressure, 96/60; stools clay-colored. Remained in approximately same condition until 5/22, when jaundice became marked and vomiting began; liver markedly tender. 5/26: very restless; vomiting. 5/27: vomiting dark material containing blood; comatose.
Onset, 4/29/42	5/9	80	
Death, 5/27/42	5/11	180	
	5/13	170	
	5/21	224	
	5/23	146	
	5/25	106	
52	5/16	170	White, male, 27 years old. 4/30: nausea and anorexia. 5/2: "dark" urine. 5/4: jaundice; itching. 5/11: admitted; afebrile; liver just palpable. 6/17: said to have lost 21 pounds in 4 weeks; at times dull aching pains over region of gallbladder, thought to be due to obstruction of ducts. 6/22: exploratory operation; liver slightly enlarged, no gross abnormality; specimen taken for biopsy; gallbladder was small, wrinkled, almost empty, no stones; common duct was small, no stones. 7/15: edema of feet and ankles; marked itching. 8/3: itching continued; strength good. 8/10: patient continued to be up and about; felt well except for itching. 8/18: condition the same. 8/25: slightly weaker; irritable; appetite was less. 9/1: was gradually becoming weaker, walking only with crutches. 9/6: very weak, confined to bed; irrational at times. 9/14: comatose; weak; appeared to be dying from sheer exhaustion.
Onset, 4/30/42	6/5	285	
Death, 9/15/42	6/15	200	
	6/18	300	
	6/29	290	
	7/6	261	
	7/15	200	
	7/20	167	
	7/27	176	
	7/29	235	
	8/3	182	
	8/10	210	
	8/17	236	
	8/24	201	
	8/31	300	
	9/7	322	

occur in patients who have died within 5 weeks. At later periods, weight loss tends to be replaced by compensatory hyperplasia of the remaining parenchyma.

The surface is usually smooth or finely wrinkled in the early case; at this stage its color is variable and not distinctive. Later, ivory colored or yellowish green coarse nodules, or larger, tumor-like masses project from the surface of the organ in some regions, whereas elsewhere the surface is sunken, dull red or grayish. The consistency, also, is variable. Usually flaccid in the early stages, the collapsed parts soon be-

TABLE XV
Trend of Icterus Index in 51 Cases of Epidemic Hepatitis

Trend		No. of cases	Per cent of cases
Remains below 50		6	12
Rises steadily		33	65
Rises, falls:			
(A) Rises, then falls slightly	9	11	22
(B) Rises, then falls to nearly normal	2		
Rises, then falls and afterwards rises again		1	2

come tough and meat-like. The nodular parts differ but little from the consistency of normal liver.

On the *cut surface* the irregular distribution of the lesions is even more conspicuous. There are large, red, meat-like areas which ooze blood, and in which the landmarks are indistinct or obliterated. In sharp contrast to these red areas are irregularly distributed patches of pale yellow or bile-tinted tissue which are distinctly lobulated. These yellow patches range in size from small nodules to large confluent masses which may occupy the major part of the organ. The component

TABLE XVI

Icterus Index in Cases of Epidemic Hepatitis

Icterus index	Number of cases		
	Intermediate period		Final period
	During first 3 days after jaundice	Subsequent to first 3 days after jaundice	
Below 50	8 (35%)	2 (3%)	4 (8%)
50–99	12 (52%)	12 (20%)	7 (13%)
100–149	2 (9%)	18 (30%)	6 (11%)
150–199	1 (4%)	16 (27%)	9 (17%)
200–249	0	7 (12%)	10 (19%)
250–299	0	2 (3%)	9 (17%)
300–349	0	1 (2%)	5 (10%)
350–399	0	1 (2%)	2 (4%)
400 and over	0	1 (2%)	1 (3%)
Total	23	60	53

lobules are abnormally large and vary greatly in size and shape. This tissue is ischemic. Usually it has a "healthy" appearance; it is not fatty nor turbid.

The relation of size of the liver to duration of the disease is given in a graph (Text-Fig. 4), and the data from which the graph was constructed are presented in Table XVII. Disregarding for the present the association with ascites, it will be seen that marked reduction in size generally occurs when the duration of the disease is short, whereas large livers are more often found when the course has been protracted.

Irrespective of the duration of the disease, the weights of the liver show considerable scattering; they range from 600 to 2400 gm. In approximately one-fifth of the cases, the weight of the liver is normal or above normal (taking 1400 to 1600 gm. as the average normal weight). In four-fifths of the cases the liver is smaller than normal. This reduction is extreme in 10 livers, which weigh from 600 to 800 gm. Hence, the liver in yellow atrophy usually is shrunken, but occasionally is enlarged.

The variability in size is equalled by the variability in shape, color, consistency and appearance of the cut surface. This variability is

TABLE XVII

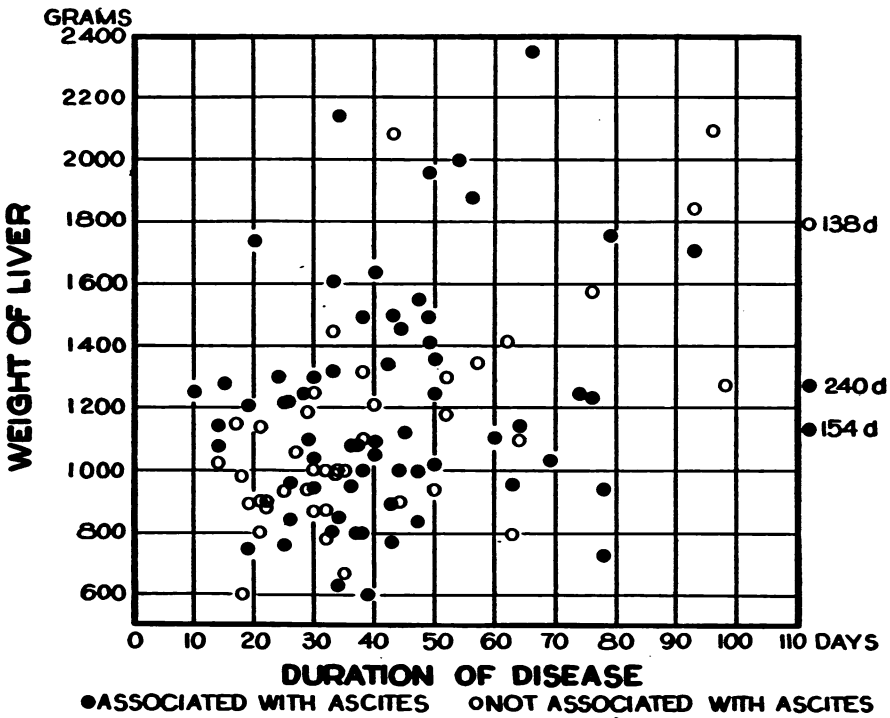
Relation of Duration of Disease to Size of Liver and Occurrence of Ascites in 108 Cases of Epidemic Hepatitis

Duration of disease	Weight of liver (gm.)												Total		Grand total
	600–799		800–999		1000–1199		1200–1399		1400–1599		1600 and over				
	Ascites	No ascites	Ascites	No ascites	Ascites	No ascites	Ascites	No ascites	Ascites	No ascites	Ascites	No ascites	Ascites	No ascites	
(*days*) 10–19	1	1		2	2	2	3	0					6	5	11
20–29	1		2	6	1	3	3	1			1		8	10	18
30–39	2	2	6	2	4	6	2	2	1	1	2		17	13	30
40–49	1		2	1	5		1	1	5		2	1	16	3	19
50–59				1	1	1	1	2			3		5	4	9
60 and over	2		1	1	4	1	2	1		2	4	3	13	8	21
Total	7	3	11	13	17	13	12	7	6	3	12	4	65	43	108
Grand total	10		24		30		19		9		16		108		

characteristic of epidemic hepatitis; the liver is not damaged uniformly, but the extent of damage in different areas varies widely. Large masses of parenchyma are destroyed completely, whereas elsewhere damage is moderate.

The gross changes found may now be briefly described in representative cases.

The External Appearance of the Liver. The liver shown in Figure 1 represents the external appearance seen in the majority of cases. The



Text-Figure 4

duration of hepatitis was 36 days. The liver weighed 1320 gm. The left lobe is seen to be disproportionately shrunken. The surface is uneven and varies in color. Over approximately half of the right lobe, the tissue protrudes in the form of irregularly elevated, yellow nodules. Elsewhere, the surface is sunken, gray-red, and the capsule is smooth or finely wrinkled. In the left lobe the surface is deeply furrowed. When fresh the consistency of this lobe was meat-like; by contrast, the yellowish elevations of the right lobe felt approximately like normal liver.

A much greater shrinkage and deformity of the liver is shown in Figure 10, although in this case the duration of hepatitis was prac-

tically the same as in the case from which the preceding one was obtained, namely, 37 days. The organ weighed 800 gm. Large, yellowish green bosses project from the surface. Between these, the surface is grayish red, smooth, or finely wrinkled. Thus, in two cases of practically the same duration, the livers appear very different.

An even greater deviation is shown in Figure 9. The duration of hepatitis was 69 days. The liver weighed 1040 gm. Many large, greenish masses project like tumors above sunken, reddish patches, the surface of which has the appearance of coarsely grained leather. In gross appearance this liver is reminiscent of hepar lobatum.

The *cut surface* of the liver in one of the early cases of the series is shown in Figure 2. The duration of hepatitis was 19 days, and the weight of the liver was 890 gm. In the right lobe are large confluent nodular areas of ivory color. They are notably ischemic. Lobulation is distinct; most of the individual lobules are conspicuously large. In contrast to the ischemic yellow areas the cut surface of the rest of the liver is uniformly reddish brown. Because of the color, there is a superficial resemblance to liver parenchyma, but there is no lobular pattern.

Little further change in the appearance of the cut surface is shown at a later stage of hepatitis, 43 days in duration (Fig. 3). The organ weighed 850 gm. Two contrasting regions are seen, one a yellow-green nodular mass, the other, a reddish brown, meat-like tissue.

In the four examples given, the livers were shrunken. Enlarged livers are shown in Figures 11 and 12. Fig. 11 illustrates the cut surface of a liver which weighed 1710 gm. The duration of hepatitis was 93 days. Most of the tissue consists of strikingly large, pale lobules. They bulge above sunken, smooth tissue which, when fresh, was gray-red and firm.

Another enlarged liver (2100 gm.) is shown in Figure 12. The duration of the hepatitis was 96 days, *i.e.*, practically the same as in the preceding case. The entire right lobe is uniformly composed of irregular lobules having pale peripheries and dark centers. The left lobe is small and gray.

Microscopic Appearance

Parenchymal Destruction. In sections from the red areas, the liver cells have disappeared completely, but the lobules are still outlined by small proliferating bile ducts. The fact that, despite complete destruction of the parenchyma, the outlines of the lobules may still be recognized is highly characteristic of epidemic hepatitis. A low-power view of this appearance is shown in Figure 17. It is seen that, because of the disappearance of liver cells, the portal triads lie nearer together and that lobular outlines are indicated by small bile ducts. Greater

detail is shown in Figure 18, where numerous small bile ducts appear to form a fence around the lobules.

The *sinusoids* in areas of "red atrophy" are preserved and are often greatly engorged (Fig. 4). Sometimes, however, the sinusoids are collapsed, and grossly such areas appear gray.

The reticular *framework* of the lobules is not destroyed. Its meshes are narrowed, or even collapsed, and its fibers thickened. The preservation of the reticulum is shown in a case of average duration, 30 days, and in one of prolonged duration, 96 days (Figs. 19 and 20). Through this framework are scattered numerous lymphocytes, plasma cells, granulocytes and macrophages; their relative proportions vary from case to case, and with the duration of the disease. Thus, as the result of a destructive process, entire lobules throughout large areas of the liver are reduced to their skeletal frames. Here, an inflammatory reaction is evident; that is, a hepatitis.

Absence of Scarring in Areas of Destruction. Although the reticulum fibers may become densely compressed, there is little or no formation of collagen. Scarring such as occurs in cirrhosis and accompanies the healing of abscesses or gummas is characteristically absent in epidemic hepatitis.

Rapid Disappearance of Liver Cells. The sequence of events that have led to the emptying of the lobules cannot be traced with certainty. None of the livers in this series were in the early stages of destruction; indeed, so far as I have been able to learn from the literature, no one has ever seen the earliest stages in this disease, which rarely terminates in its most acute stages. All that is known with certainty is that cell destruction occurs rapidly and that cell débris is removed speedily. In the present series, by the tenth day (the earliest case of the series) practically all traces of dead cells have been swept away, presumably by enzymic action, and nothing remains in the lobules but vascular framework and inflammatory cells. We find here no evidence of slow cell death—fatty changes, coagulation of cytoplasm—such as are characteristically seen in yellow atrophies due to chemical poisons, bacterial toxins, yellow fever, or eclampsia. Rapidity and completeness of cell destruction is a distinguishing feature of epidemic hepatitis.

Distribution of Lesions in the Lobule. The destructive change usually, if not always, begins in the central part of the lobules, for in the earliest cases of the series only the central zones of the lobules are involved (Fig. 13). Even in more protracted cases many lobules are encountered in which the damage is limited to the central regions, leaving intact a peripheral rim of liver tissue (Fig. 14). The lesions do not involve all lobules to the same degree; they range from destruction of

approximately one-third of the central portions in the better preserved areas to complete destruction of all liver cells in large areas of the organ. Every conceivable intermediate step may be encountered. But whenever even a fragment of hepatic parenchyma remains, it is found in the peripheral zone. For example, in another early case, only scattered groups of liver cells are left at the lobular peripheries (Fig. 15).

Inflammatory Reaction. In epidemic hepatitis destruction of liver cells is invariably accompanied by an inflammatory reaction. By inspection of Figures 13 to 15, which show zones of destruction, it may be seen that the parts of the lobules from which the parenchyma has disappeared have a granular aspect. This granularity is due not to remaining débris but to the presence of inflammatory cells. In early stages polymorphonuclear leukocytes, lymphocytes, plasma cells and macrophages occur in approximately equal proportions (Fig. 16); later, the polymorphonuclear leukocytes become less numerous. The inflammatory cells linger in the depleted stroma for long periods, only gradually becoming less numerous. For example, in a case with a course of 240 days, the inflammatory changes did not differ appreciably from those in the average case of a few weeks' duration.

Lipofuscin. Conspicuous among the inflammatory cells are macrophages which have engulfed small granules of yellow-brown pigment (Fig. 6 a). This pigment is not dissolved in the process of preparing paraffin sections; in such sections it is stained by Sudan III and similar fat stains (Fig. 6 b). It is somewhat acid-fast, and can be demonstrated by the Ziehl-Neelsen method.

Silver stains, such as Wilder's reticulum stain, render the granules black. The pigment is lipofuscin, or so-called "waste-pigment."[46, 47] Lipofuscin is probably a normal pigment of liver cells which is liberated and rapidly phagocytized when these cells disintegrate. It thus serves as an indicator of breakdown of hepatic parenchyma. Like the other types of cells previously discussed, the pigmented macrophages may persist for long periods.

Lipofuscin must be distinguished from another pigment that may also occur in the liver and which in recent years has attracted considerable attention, namely, ceroid. The main points of difference are that ceroid forms coarse globules that often lie extracellularly, it is strongly acid-fast and even less soluble in fat solvents than lipofuscin, and in paraffin it stains deeply with fat stains.[48]

Endophlebitis of Efferent Blood Vessels. The efferent vessels show marked alterations. All but the largest hepatic veins are the site of endophlebitis. The process is seen particularly in the central lobular veins and in the sublobular veins (Figs. 21 and 22). In these vessels

the intima is densely infiltrated with cells of the same types as those scattered throughout the skeletal remnants of the lobules. Where inflammatory cells are abundant in the stroma, they are usually abundant in the intima of veins that drain the area. In early stages the endothelium of the intima is unbroken; in later stages it may become ruptured, spilling the invading cells into the vascular lumen. Rupture of the intima is commonly followed by thrombosis.

Not only the intima but other layers of the vessels are altered. Often their walls are greatly thickened, and have a hyaline appearance (Fig. 21). They usually stain rather lightly with eosin, but densely by the Masson-Mallory aniline-blue method for connective tissue. By silver impregnation methods, the walls of the veins are found to have a loose, fibrillar structure, which differs but little from the normal (Fig. 23). It is evident that the collagenous substance, which gives the hyaline appearance to the wall, lies between the component fibers, which themselves remain unchanged. Perhaps this collagenous substance becomes more prominent through imbibition of fluid.

Endophlebitis usually is more conspicuous in relatively early cases, although lesser degrees are found even in protracted cases. In the latter group, however, fibrous obliteration of the veins rather than acute inflammatory reaction is the more common.

This form of endophlebitis is not specific for the damaged liver of epidemic hepatitis. It may occur in other destructive processes involving liver parenchyma.

Hyperplasia of Liver Cells

The preceding sections have dealt with the microscopic appearance of the liver in areas which grossly are collapsed and red; here, the parenchyma has been destroyed. In contrast, in areas which appear nodular and yellow, the tissue is in a state of regenerative hyperplasia. An abundance of new parenchyma has formed by hypertrophy and multiplication of cells that have escaped destructon. The architectural pattern of the new parenchyma, however, only rarely approaches the normal; in most regions it is exceedingly atypical. The process of restoration begins early. By the tenth day numerous buds of binucleated or multinucleated liver cells extend from the remaining portions of the hepatic columns into the depleted stroma (Figs. 24 to 26). In less than 20 days a large mass of new liver tissue has formed. This tissue usually is composed of atypically built "lobules." They vary in size and shape. Most of them have fused with neighboring "lobules"; less often patches of parenchyma are isolated by bands of collapsed stroma.

The microscopic appearance of such a region in one of the earlier cases (19 days in duration) is illustrated in Figure 31. The section comes from the pale yellow part of the liver shown in a colored photograph (Fig. 2). Inspection of the photomicrograph discloses at once the absence of the lobular pattern characteristic of normal liver. Instead, the parenchyma consists of ill-defined patches, in none of which the component cords of cells converge toward a common central lobular vein. These patches represent hyperplastic remnants of former lobules.

An illustration of the atypical structural arrangement of the newly formed tissue in a case of prolonged duration (93 days) is given in Figure 32. There are seen great confluent patches of parenchyma but no typical lobules.

These two illustrations represent the microscopic picture observed in nearly every case. Only occasionally, and then in small areas only, is normal lobulation found restored (Fig. 33).

The hyperplastic parenchyma is composed chiefly of compact cords of liver cells, but often such cords have formed only at the periphery of the individual "lobules." The central part is frequently occupied by newly formed cells which are not organized into cords (Fig. 34).

Areas of regeneration are usually ischemic (Fig. 5). Well defined spaces, with endothelial lining, lie between the cell cords; but the blood content of the spaces is usually slight, and only in rare instances approaches the normal. The marked degree of ischemia of hyperplastic tissue stands in contrast to the great engorgement of the tissue in areas of "red atrophy" (Fig. 4).

The hyperplastic tissue differs from the normal not only in general arrangement but in structure of its component parts. The cords of liver cells are usually distinctly broader than the normal. In longitudinal sections the cords often have a conspicuous central cleft. In transverse sections the cords are seen to have a tubular structure; such tubules have from six to eight cells spaced around a lumen (Fig. 37). The clefts or lumina are dilated bile canaliculi. Many are obstructed with coarse branching masses of bile (Figs. 37 and 38). Throughout large areas, almost every canaliculus contains obstructing masses.

The individual liver cells generally are large. In some the cytoplasm is smooth; in others it contains coarse granules of bile. Fatty changes in the cells are rare. The nuclei are usually prominent, and the nucleoli are swollen and stain deeply (Fig. 36). Inclusion bodies, such as occur in many virus diseases, are not found.*

* I am grateful to Dr. Thomas Rivers of the Rockefeller Institute, to Dr. E. V. Cowdry of the Washington University School of Medicine, and to Dr. Alfred M. Lucas of Iowa State College for examining a number of my sections and for their helpful advice.

The foregoing paragraphs have dealt with the appearance of tissue in which the hepatic cells have formed cords. Here and there, however, the regenerating cells do not become arranged in columns but lie isolated or in small groups within an otherwise empty stroma. Such cells tend to form multinucleated syncytia (Figs. 27 and 28), or disorderly groups which invade the stroma in a manner faintly suggestive of neoplasia (Fig. 29). Still others form giant tubules reminiscent of those seen at early developmental stages or in the livers of frogs or turtles (Fig. 5).

In most areas the cells of the hyperplastic parenchyma, whether arranged as cords or in isolated groups, have a healthy appearance. There is no evidence of progressive destruction of tissue. But in a few areas the regenerated cells may undergo secondary degeneration, as shown in Figure 35. Here there is a large group of newly formed cells with prominent nuclei which obviously are disintegrating. The tissue is invaded by numerous polymorphonuclear leukocytes.

Among the factors that lead to such secondary destruction are probably ischemia and the accumulation of metabolic products, which are not removed because of stasis of blood and of bile.

Proliferative Changes in the Bile Ducts

Besides regenerative phenomena in the liver cells there are proliferative changes in the bile ducts. Before discussing them it is well to recall that a sharp distinction should be made between interlobular and perilobular (septal) bile ducts.[49] The former are relatively large, and, together with branches of the portal vein and hepatic artery, lie within a thick mantle of connective tissue. The lining epithelium of these ducts is prominent. At the outskirts of the stroma which enfolds the portal triads, and extending around the lobular peripheries, lie the much smaller septal biliary ducts. Unlike the large interlobular ducts, the smallest septal ducts have a very scanty connective tissue stroma. They are tributaries of the interlobular ducts, and they accompany the fine twigs of the portal veins and hepatic arteries which encircle the lobular peripheries. In the smallest of these minute ducts the epithelium is inconspicuous and so flat that it resembles the lining of the vessels. Even in the larger branches the cells are relatively small and hence the nuclei appear crowded. The cytoplasm stains rather lightly in contrast to the deeply eosin-staining cytoplasm of liver cells; the nuclei are round or oval, and much denser than those of hepatic cells. Into these ducts empty the bile canaliculi of the hepatic cords; the junction usually is expanded into an ampulla.

The large interlobular ducts show no changes in epidemic hepatitis. Their cells remain normal and their lumina patent (Fig. 39). On the contrary, the small septal ducts do proliferate markedly. This is shown in Figure 40. (The duration of the disease in this case was 14 days.) At the periphery of the portal stroma are numerous small bile ducts; all of them show budding. The ducts and their buds soon elongate, forming extensively branching tubular structures (Fig. 41). Often their lumina contain inflammatory cells, similar to those within the stroma of the lobular remnants. Ducts of this kind outline the periphery of former lobules (Figs. 17, 18 and 30).

The fate of these proliferated ducts has long been a subject of discussion. It is certain that in many instances they remain entirely unchanged for long periods. Thus, Figure 42 shows the appearance of an area of "red atrophy" from a case of 240 days' duration. The ducts here do not seem much different from those shown in Figure 40, a case of 14 days' duration. In this and similar regions from other cases which have had a protracted course, there is no indication that the ducts tend to differentiate into other types of cells.

Conditions, however, are not always as simple. There are found in early, as well as in late, cases, at the periphery of former lobules, tubular structures which cannot with certainty be recognized as bile ducts. For example, in Figure 43 there are seen several tubules, some parts of which are lined by cells resembling bile duct epithelium, whereas other parts are lined by elements resembling liver cells. More complicated still is the interpretation of pictures such as that shown in Figure 8. Here the lumen of a branching bile duct is continuous with that of a tubule composed of liver cells. Surrounded by the epithelium of the bile duct lie several large and typical liver cells. This appearance suggests a possible transformation of biliary epithelium into hepatic epithelium. Equally complicated is the interpretation of the condition shown in Figure 44. Here are seen two large clumps of inspissated bile. One clump lies within a dilated tubule, the lining cells of which resemble biliary epithelium. The other clump lies within a dilated lumen of a hepatic cord which on one side is composed of biliary epithelium. Similarly, in Figure 45 are shown a number of tubules at the periphery of lobular remnants; the lumina of these tubules contain thick clumps of bile; the cells which compose these tubules cannot with certainty be identified either as biliary epithelium or hepatic epithelium. Still another puzzling condition is shown in Figure 49. In this case the tubules at the periphery of the lobules are composed of cells which closely resemble liver cells; and, similarly, in Figure 47 there is a whole cluster of tubules which appear to be made up of hepatic epithelium. Lastly,

there is shown in Figure 7 a not uncommon finding. Here a branching bile duct is in contact with two large hyperplastic hepatic columns; the lumen of the duct clearly is continuous with the lumina of these columns.

Pictures such as have been shown raise again the long debated question: is biliary epithelium transformed into liver cells? This question has been debated for many years. Pearce [50] wrote in 1906: "Some difference of opinion exists in regard to the solid and tubular cell-strands usually described as newly-formed or pseudo bile ducts. All recent investigators have abandoned the idea that these structures are atrophied rows of liver cells, but consider them as sprouts from the small interlobular bile ducts growing into the necrotic lobule. By a gradual transformation of the cells of such sprouts true functioning liver cells are formed."

Pearce [50] expressed well the debated problem. In recent years Herxheimer and Thölldte,[44] and others again have taken the opposite view, namely, that the structures so characteristically seen at lobular peripheries are not bile ducts but altered liver cells. This opinion is based largely upon the fact that within these structures bile canaliculi or masses of bile may be demonstrated. It might be suggested, however, that, when much of the liver parenchyma has been destroyed, the cells of proliferating bile ducts may acquire a compensatory capacity to metabolize bile.

The question cannot possibly be settled by examination of post-mortem material. In my opinion, biliary epithelium may differentiate into hepatic epithelium. Such differentiation, however, occurs only in a few insignificant patches and contributes very little to the restoration of tissue which at best is atypical.

Gallbladder and Extrahepatic Bile Ducts

The condition of the gallbladder was recorded in 87 cases; in 36 it was described as normal, in 30 as small, and in 21 as distended. In about half the cases the wall was edematous and occasionally showed small hemorrhages (Fig. 55). In these cases ascites was almost invariably present.

The extrahepatic ducts were carefully examined in nearly all cases, with particular attention to their patency. In only two instances was obstruction found. In these two, small plugs of inspissated material occurred in the common duct near the duodenal opening. It is probable that in both instances the obstruction was a sequel to the hepatic lesion, not its cause.

Material for microscopic examination from the extrahepatic ducts

and the papilla of Vater was available in only 11 cases. In 6 there was inflammatory edema, always associated with edema of the duodenum. The duodenal inflammation was not a localized condition but widespread, involving at times almost the entire gastrointestinal tract.

Lymph Nodes

In nearly all cases, particularly in those in which the duration of hepatitis was less than 1 month, the hepatic, and in many instances the mesenteric, lymph nodes were considerably swollen, their capsules tense, and their cut surfaces bulging and succulent (Fig. 1). Occasionally individual nodes measured as much as 35 mm. in diameter. Microscopically, the sinusoids were dilated and frequently packed with polymorphonuclear cells and macrophages. The reticulo-endothelial lining was prominent. The lymphoid tissue was markedly edematous. In occasional nodes, small foci of necrosis and hemorrhages were encountered. Briefly, the changes in the regional lymph nodes were edema, acute hyperplasia, or acute lymphadenitis, *i.e.*, the usual reactions found near areas of tissue destruction. Involvement of lymph nodes was never generalized.

Ascites

Ascites occurred in 60 per cent of the cases. The amount of fluid usually was large, two or more liters being the average. The fluid was nearly always tinged with bile, less often with blood. Turbidity due to the presence of inflammatory cells was common when phlegmonous inflammation of the gut coexisted (this condition will be discussed later).

The relation between ascites, duration of disease and size of liver is shown in a distribution graph (Text-Fig. 4) and in Table XVII. The weight of the liver has been plotted against duration of disease; cases with ascites are represented by solid circles, those without ascites by open circles. The graph brings out several points. First it shows that ascites may occur at all stages of the disease; no matter whether the course is short or protracted. The occurrence of ascites is not definitely correlated with duration of disease (see Table XVII).

Regarding the relation of size of liver to occurrence of ascites, there is again no apparent correlation. Thus, the incidence of ascites when the liver was greatly shrunken (below 800 gm.) is about the same as when it was enlarged (above 1600 gm.).

In approximately one-fourth of the cases with ascites there was pleural effusion; and in approximately one-half the cases, slight edema of the ankles. The clinical records indicate that ascites precedes ankle

edema, which was probably due to mechanical interference with venous return.

In Bergstrand's[41] series of 95 fatal cases, ascites was observed in 20 per cent. Fox and his co-workers[42] found ascites in most of their 17 cases.

In summary, it is shown that ascites is common and that it is unrelated to the total duration of the hepatitis or to the size of the liver. The mechanism responsible for the accumulation of abdominal fluid will be discussed later.

Spleen

The spleen was enlarged in about three-fourths of the cases. The weights are given in Table XVIII. In one-third of the series the weight exceeds 300 gm.; in somewhat less than half the weight falls between

TABLE XVIII

Relation of Weight of Spleen to Occurrence of Ascites in 89 Cases of Epidemic Hepatitis

Weight of spleen (gm.)	Number of cases		
	Ascites	No ascites	Total
Below 100	0	1 (1%)	1 (1%)
100—199	10 (11%)	11 (12%)	21 (24%)
200—299	23 (26%)	15 (17%)	38 (43%)
300—399	15 (17%)	6 (7%)	21 (24%)
400—499	2 (3%)	1 (1%)	3 (3%)
500 and over	4 (5%)	1 (1%)	5 (6%)
Total	54 (61%)	35 (39%)	89

200 and 300 gm., in only one-fourth of the cases is the weight approximately normal.

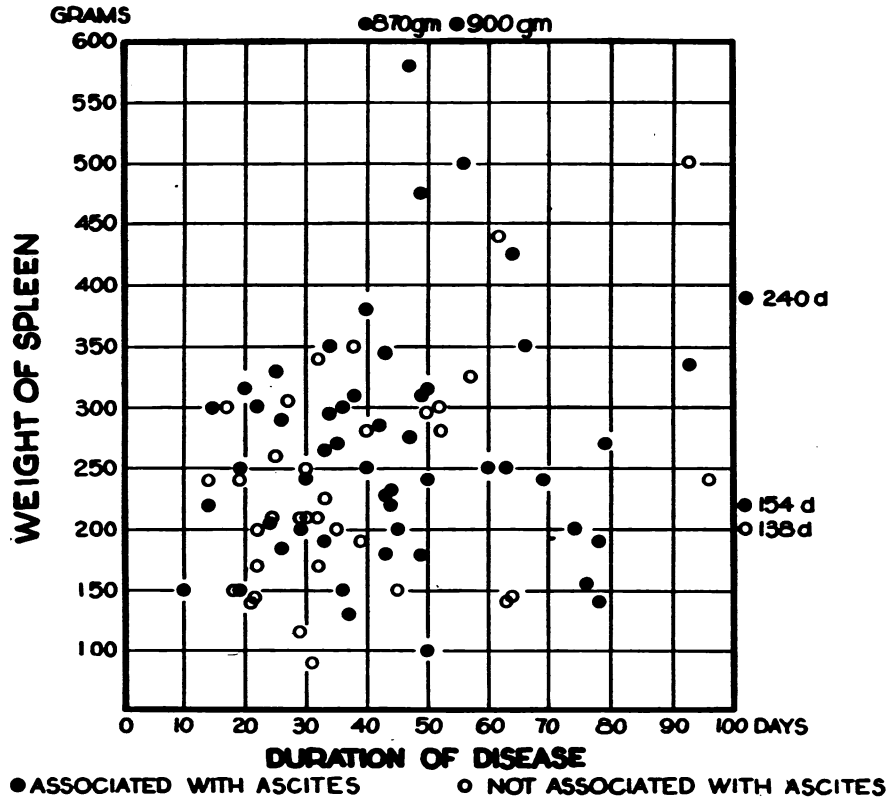
The relation of weight of spleen to duration of hepatitis is shown in Text-Figure 5. There is much scattering but, generally speaking, large spleens, above 300 gm., are more numerous when the disease has been prolonged (see also Table XVIII).

In consistency, the spleen in early cases was flaccid, in later cases, firm. On the cut surface the lymphoid follicles were usually distinct at early stages, and small or indistinct later. At all stages, the blood content of the spleen was increased.

The microscopic appearance also varied with the duration. In relatively early cases, the lymphoid tissue was prominent (Fig. 56); the sinusoidal veins and the pulp cords were only moderately congested. At later stages, the sinusoids were conspicuously distended and had thickened rigid walls (Fig. 57). The lymphoid tissue was often markedly depleted (Fig. 58). The picture then was that usually associated with portal hypertension.

Correlating the gross and microscopic findings, it becomes evident that the enlargement of the spleen in early stages is not the result of engorgement but is predominantly due to a cellular proliferation. At later stages sinusoids become dilated; then swelling is due to engorgement.

The early lymphoid hyperplasia is probably a reaction to products of tissue breakdown in the liver. It cannot be denied, however, that the agent which damages the liver may itself excite a reactive process in the spleen. The depletion of lymphoid tissue, during later stages of hepatitis, may result from portal hypertension, that is, from overload-



Text-Figure 5

ing of the spleen with venous blood under increased pressure.

This interpretation is supported by recent experimental studies of British investigators. Thus Orr [51] studied the spleens of rats, the livers of which had been damaged by "butter-yellow" (a substance which induces a cancerous cirrhosis of the liver). Enlargement of the spleen developed early, long before the liver became cirrhotic. Orr favors

the view that such early enlargement of the spleen is due to cellular hyperplasia. Menon [52] induced hepatic destruction and late cirrhotic changes by carbon tetrachloride. He found a marked proliferative reaction in the spleen during the early stages of liver damage. Similarly, experiments of Cameron and de Saram [53] suggest that splenic changes associated with cirrhosis of the liver (a condition of progressive damage) are the result of two separate processes, namely, pulp hyperplasia and congestion.

Gastrointestinal Tract

Lesions of several kinds and of great interest were encountered in the gastrointestinal tract. The most striking of these was an extensive phlegmonous inflammation with massive edema involving the ileocecal region, less commonly other portions. In addition, noninflammatory edema of both the small and large intestines was frequent, and the lower end of the esophagus was often ulcerated.

Phlegmonous Inflammation

In approximately 15 per cent of the cases in which the gastrointestinal tract was examined (17 of 113), large parts of the gut were phlegmonous. The lesion was usually most marked in the ileocecal region, but sometimes extended more widely, involving the ascending and transverse colon. The wall of the cecum sometimes exceeded 20 mm. in thickness. It was extremely boggy, and its mucosa was thrown into thick folds. The wall of the gut appeared as if artificially injected with a watery fluid (Figs. 48 and 49). Microscopically (Figs. 50 and 51), the entire wall was edematous and everywhere invaded by leukocytes and macrophages. Usually the mucosa was unbroken. Occasionally, superficial hemorrhages were found, but actual erosions were rare. The submucosal layer was especially distended, and even in paraffin sections (in the preparation of which edematous tissue shrinks) exceeded 1 cm. in thickness. The fibers of the mucosa were forced apart, and in some foci appeared to be degenerating. Also the subserosal layer was often considerably distended and invaded by inflammatory cells.

Most of the infiltrating cells had well stained nuclei and intact cytoplasm; they were obviously recent invaders (Fig. 52). The proportion of the cells varied; in some regions polymorphonuclear leukocytes, and in others macrophages, predominated, while lymphocytes and plasma cells were scanty. With stains for bacteria an abundance of small Gram-negative bacteria and larger Gram-positive rods were seen. Coccoid forms were not found. Many of the leukocytes and macro-

phages had ingested these organisms, and some macrophages, particularly, were packed with bacteria.

In nearly all cases, other parts of the small and large intestines were conspicuously edematous, and in some areas the distended tissue showed early inflammatory reaction. In only two cases was a phlegmon found in the stomach.

Without exception, the phlegmonous inflammation was associated with ascites. Careful examination of the clinical records gave no hint of the intestinal lesion. The duration of the phlegmon was always short, as shown by the condition of the exudate; it was evidently a terminal inflammation.

What is the relation between hepatitis and the inflammation of the intestine? The phlegmon gives every appearance of being a terminal event. Therefore it is obvious that the hepatitis is not the result of the intestinal condition. Rather, the phlegmon is a complication which results from invasion by bacteria of an edematous bowel.

In his monograph on yellow atrophy of the liver, Bergstrand [41] merely mentions phlegmonous inflammation of the intestine in several of his autopsy protocols. Recently, Pollack and Gerber [54] have reported a number of cases, in all of which the lesion was associated with primary disease of the liver. I have been able to find no other references in the literature.

Because intestinal phlegmon is a little known condition, brief abstracts of the anatomic findings in the 17 cases are given below.

Illustrative Cases

Case 8

This patient was a white male, 28 years old. Duration of hepatitis, 43 days. (See page 482 for clinical course.)

Pathologic Findings. ***Esophagus:*** (G)* superficial ulceration at cardio-esophageal junction; (M)* ulceration; inflammatory reaction extending to muscularis. ***Stomach:*** (G and M) normal. ***Intestine:*** (G) marked edema beginning just above ileocecal valve and extending to sigmoid; moderate edema of remainder of small and large intestine. ***Duodenum and papilla of Vater:*** (M) mucosa normal, intense congestion; submucosa invaded by numerous polymorphonuclear leukocytes and histiocytes. ***Cecum:*** (M) mucosa intact; wall markedly edematous, dense leukocytic and histiocytic infiltration throughout entire wall; fibrinocellular exudate on serosa.

Case 10

The patient was a white male, 22 years of age. Duration of hepatitis, 30 days.

Pathologic Findings. ***Stomach:*** (G) mucosa congested; pylorus markedly edematous; (M) marked edema of submucosa. ***Duodenum and papilla of Vater:*** (G)

*The letter (G) signifies results of gross examination, and (M), of microscopic examination.

extremely marked edema; (M) marked edema; slight leukocytic infiltration; subserous hemorrhages. *Jejunum and ileum:* (G) hemorrhagic; (M) submucosa and subserosa markedly edematous; slightly infiltrated with leukocytes. *Large intestine:* (G) ascending and transverse colon hemorrhagic; (M) mucosa intact; entire wall markedly edematous and heavily infiltrated with polymorphonuclear leukocytes and histiocytes; phlegmon most pronounced in submucosa; serosa showed no reaction.

Case 11

This patient was a white male, 41 years old. Duration of hepatitis, 64 days.

Pathologic Findings. Esophagus: (G) congestion at lower end. *Stomach:* (G and M) multiple petechiae of mucosa. *Small intestine:* (G) moderately edematous; terminal portion of ileum markedly edematous; (M) marked polymorphonuclear, neutrophilic and eosinophilic, infiltration in all layers but particularly of submucosa. *Large intestine:* (G) cecum and first portion of ascending colon: marked edema; subserosal hemorrhages; (M) massive leukocytic and histiocytic infiltration, particularly in submucosa and subserosa.

Case 13

The patient was a white male, 26 years of age. Duration of hepatitis, 49 days. (See page 482 for clinical course.)

Pathologic Findings. Esophagus: (G) congestion of lower third; (M) slight erosion; submucosal scattering of lymphocytes. *Stomach:* (G and M) normal. *Duodenum and papilla of Vater:* (M) moderate submucosal edema; moderate degree of leukocytic and mononuclear cell infiltration in submucosa. *Ileum and jejunum:* (G) normal. *Cecum:* (G) large hemorrhagic areas in submucosa; edema; (M) phlegmonous infiltration.

Case 22

The patient was a white male, 28 years old. Duration of hepatitis, 17 days.

Pathologic Findings. Esophagus and stomach: (G) normal. *Small intestine:* (M) moderate degree of submucosal edema; sparse scattering of histiocytes and lymphocytes. *Large intestine:* (G) cecum was markedly edematous; ascending colon, appendix and terminal ileum not noticeably involved; (M) surface of cecum intact; mucosal glands well preserved; submucosa greatly distended; its thickness exceeded 1 cm.; fibers of muscle layer forced apart; subserosal tissue loosely textured. Throughout submucosa and subserosa, diffuse infiltration with histiocytes and leukocytes. Lower colon had edematous walls, but no cellular exudate had occurred.

Case 29

This patient was a white male, 35 years of age. Duration of hepatitis, 45 days.

Pathologic Findings. Esophagus: (G) superficial erosion; congestion; (M) submucosal edema; foci of lymphocytes and plasma cells. *Stomach:* (G and M) normal. *Duodenum and papilla of Vater:* (G) moderately edematous; slight submucosal edema; sparse scattering of leukocytes. *Ileum and jejunum:* (G) no significant changes. *Large intestine:* (G) almost all portions, but particularly cecum, showed massive edema but no ulceration; (M) mucosa intact; all layers edematous; diffusely infiltrated with leukocytes and histiocytes.

Case 43

The patient was a white male, 24 years old. Duration of hepatitis, 20 days.

Pathologic Findings. Stomach: (G) normal. *Duodenum and papilla of Vater:* (G) no significant changes. *Ileum and jejunum:* (G) no significant changes. *Large*

intestine: (G) mucosa intact; marked congestion and edema; (M) extreme edema and diffuse cellular infiltration throughout all layers; thickness of wall ranged from 8 to 10 mm. Mucosa unbroken; glands normal; supporting stroma infiltrated with scanty numbers of plasma cells, histiocytes and granulocytes. Submucosa the main site of inflammatory edema; its fibers were widely separated and thickly invaded with leukocytes and histiocytes. Venules had collars of exudative cells. In muscular and subserous layers, phlegmonous changes were of somewhat less degree than in submucosa. Muscle fibers in many patches showed degenerative changes.

Case 54

The patient was a white male, 24 years of age. Duration of hepatitis, 36 days.

Pathologic Findings. Stomach and small intestine: (G) hyperemia; (M) moderate degree of edema of small intestine. *Large intestine:* (M) moderate degree of edema and phlegmonous inflammation, most marked in submucosa and subserosa.

Case 55

This patient was a white male, 23 years old. Duration of hepatitis, 29 days.

Pathologic Findings. Esophagus: (M) two superficial ulcers at cardiac end; subjacent tissue edematous and massively infiltrated with lymphocytes and leukocytes; base of ulcer covered with fibrin. *Stomach:* (G) multiple petechiae. *Small intestine:* (G) multiple petechiae. *Large intestine:* (G) marked edema, particularly of cecum and ascending colon; multiple petechiae; (M) mucosa preserved; extensive phlegmonous infiltration, particularly of cecum.

Case 59

The patient was a white male, 26 years old. Duration of hepatitis, 38 days. (See page 493 for clinical course.)

Pathologic Findings. Esophagus: (G) no significant changes. *Stomach:* (M) edema of submucosa; scattered inflammatory cells. *Duodenum:* (G) slight edema. *Ileum:* (G) lower portion markedly edematous but not congested. *Large intestine:* (G) cecum, ascending and transverse colon; intense edema; no congestion; (M) diffuse phlegmonous infiltration of cecum and ascending colon; remainder of colon edematous.

Case 61

The patient was a white male, 25 years of age. Duration of hepatitis, 40 days.

Pathologic Findings. Esophagus: (G) several small longitudinal erosions in lower third. *Stomach:* (G) multiple superficial ulcers. *Duodenum and papilla of Vater:* (G) edematous; congested. *Ileum and jejunum:* (G) edematous. *Large intestine:* (G) marked edema, especially in sigmoid; here wall averaged 1 cm. in thickness, section had a yellowish gray appearance; mucosa preserved; (M) entire wall densely and diffusely infiltrated with granulocytes, including many eosinophils, and macrophages; exudate most conspicuous in submucosa but all layers crowded with cells; in appendix, same changes but less marked.

Case 94

This patient was a white male, 35 years of age. Duration of hepatitis, 50 days.

Pathologic Findings. Esophagus and stomach: (G and M) no significant changes. *Duodenum and papilla of Vater:* (G) wall very edematous; mucosa hyperemic. *Jejunum:* (G) slightly edematous; mucosa congested. *Large intestine:* (G) walls very soggy; mucosa not ulcerated; (M) mucosa intact; submucosa extremely edematous with numerous leukocytes and histiocytes; remainder of wall moderately edematous and diffusely infiltrated with inflammatory cells. *Ileum:* (G)

moderately edematous; (M) edematous; wall diffusely infiltrated with leukocytes and histiocytes.

Case 97

The patient was a white male, 50 years old. Duration of hepatitis, 74 days.

Pathologic Findings. Esophagus: (G) no significant changes. ***Stomach:*** (G) moderately edematous; (M) edema; scattered histiocytes in submucosa and muscularis. ***Small intestine:*** (G) walls thickened and moist; (M) moderate edema of submucosa and serosa; scattered histiocytes in subserous layer. ***Large intestine:*** (G) wall thickened and markedly edematous; mucosa thrown up in folds, giving a coarse nodular appearance; (M) marked edema of entire wall with diffuse infiltration of granulocytes, histiocytes, lymphocytes and plasma cells; process was most marked in submucosa and muscularis.

Case 100

This patient was a white male, 27 years of age. Duration of hepatitis, 93 days. (See page 485 for clinical course.)

Pathologic Findings. Esophagus, stomach and small intestine: (G) no significant changes. ***Large intestine:*** (G) appendix was normal; wall of ascending colon markedly edematous; no ulceration; (M) conspicuous edema of submucosa and infiltration with histiocytes, granulocytes and plasma cells.

Case 103

This patient was a white male, 22 years old. Duration of hepatitis, 49 days.

Pathologic Findings. Esophagus: (G) no gross ulceration; surface discolored by reddish black material; (M) superficial ulceration with conspicuous polymorphonuclear and histiocytic reaction; underlying tissue slightly edematous and sparsely infiltrated with inflammatory cells. ***Stomach:*** (G) multiple petechiae; (M) no significant changes. ***Duodenum and papilla of Vater:*** (G) congestion of mucosa. ***Jejunum and ileum:*** (G) intense congestion of mucosa; (M) congestion. ***Large intestine:*** (G) normal; (M) edema of submucosa; diffuse infiltration with leukocytes and histiocytes.

Case 107

The patient was a white male, 26 years of age. Duration of hepatitis, 50 days.

Pathologic Findings. Stomach: (G) no significant changes. ***Duodenum:*** (M) diffuse sprinkling of lymphocytes, histiocytes and occasional eosinophile cells throughout all layers. ***Ileum and jejunum:*** (G) no noteworthy changes. ***Large intestine:*** (G) normal; (M) edema of submucosa, diffuse infiltration with granulocytes and histiocytes.

Case 112

This patient was a white male, 38 years old. Duration of hepatitis, 40 days.

Pathologic Findings. Esophagus, stomach and small intestine: (G) no significant changes. ***Large intestine:*** (G) subserosal hemorrhages in descending colon and sigmoid; (M) marked edema; diffuse inflammatory reaction throughout wall; mucosa intact.

Noninflammatory Edema of the Intestine

In addition to the 17 cases with phlegmon, there was noninflammatory edema of small and large intestines in 26 other cases. The edema varied in degree, and involved especially the submucosa (Fig. 53). In all of the cases there was associated ascites.

Ulceration of the Esophagus

The lower one-third of the esophagus in many cases showed changes such as are frequently regarded as due to post-mortem autolysis. The mucosal surface had partly sloughed away, and there were small longitudinal erosions, often covered by chocolate brown débris. Because these lesions are so commonly looked upon as post-mortem changes, material for histologic examinations was available in only 20 cases. In 9 of them, there was superficial ulceration, accompanied by an inflammatory reaction that usually extended to the muscularis, and more rarely throughout the entire wall. The appearance in a representative case is shown in Figure 54. Here, small superficial erosions were present at the cardio-esophageal junction. The denuded tissue was the site of an acute inflammatory reaction that extended laterally beyond the eroded portions and down to the muscularis.

Erosion of this type is too well known to merit further description. It probably occurred more often in the present series than the figures indicate. Most writers on the subject agree that the action of the gastric juice plays an important part in the pathogenesis of esophageal ulceration.[55-57] It is when vomiting is protracted that erosions occur. Even nausea, without vomiting, by relaxation of the cardiac sphincter and regurgitation of gastric juice may induce the lesion. Nausea and vomiting alone, however, are not sufficient; poor circulation in the esophagus, and a state of debilitation of the patient appear to be prerequisites. These factors—nausea, protracted vomiting, debilitation and, probably, impaired circulation in the esophagus (due to interference with the circulation through the liver)—are found in nearly all fatal cases of epidemic hepatitis.

Hemorrhagic Phenomena

As in other forms of hepatic disease, hemorrhages were found in epidemic hepatitis. The location of the hemorrhages in 109 cases is shown in Table XIX. Microscopic hemorrhages are not included in this tabulation. Most common were hemorrhages in the intestinal tract,

TABLE XIX

Location of Hemorrhages in 109 Cases of Epidemic Hepatitis

Location	No. of cases	Per cent of cases
Intestines or mesentery	80	73
Lungs	74	68
Heart	43	39
Kidney	14	13
Skin	8	7
Brain	5	5

which occurred in approximately three-fourths of the series. In degree, they varied from petechiae beneath the serosa and in the mucosa to larger hemorrhages, which were usually at the attachment of the gut to the mesentery or mesocolon (Fig. 63).

Almost as frequent were hemorrhages in the lungs, in which dark red, almost black, hemorrhagic patches with ill-defined outlines were scattered through all lobes. The bronchial walls were dusky red. Sometimes the supporting tissue around the larger vessels was hemorrhagic. Microscopically, in large areas the air sacs and bronchial walls were flooded with blood. It is probable that the pulmonary hemorrhages predispose to bacterial invasion, for in a great majority of cases foci of terminal pneumonia were found at autopsy.

Next in frequency were hemorrhages in the heart, where they were located in the epicardium and, commonly, beneath the septal endocardium of the left ventricle, near the undefended space (Fig. 62).

In the kidney, the hemorrhages were usually pelvic in location. In other organs hemorrhages were found more rarely.

Bone Marrow

Bone marrow specimens were available for histologic examination in 22 cases, the tissue having been selected usually from rib, sternum, or vertebra. This relatively small series fortunately represents early cases, cases of average duration and others with a protracted course. When one takes into consideration the variables dependent on the age of the patient and the site of the particular specimen, certain generalities can be established.

In most instances there was a mild to moderate degree of hyperplasia (Fig. 64) due more to increased activity of the erythrocytic than of the granulocytic series. Megakaryocytes were normal in structure and distribution and varied in number with the degree of general hyperplasia. There was no disturbance of maturation in the several developmental series, and most cells were found in the midstage (*i.e.*, erythroblasts, myelocytes) or beyond. Degenerative changes were not evident. Pigment, presumably hemosiderin, was often noted within histiocytes.

Certain cases displayed maximal hyperplasia, fat being completely replaced by hematopoietic tissue, which in some instances was predominantly erythroid (Fig. 66), in others myeloid (Fig. 65). The changes bore no constant relation to length of disease. They suggest, however, that a certain degree of hyperplasia of bone marrow occurs at all stages of fatal epidemic hepatitis, probably as the combined result of hemorrhages and of hepatic destruction.

Kidneys

In the majority of cases the kidneys were swollen, flaccid, and bile-stained. The combined weights, tabulated in 88 cases, are as follows: Below 300 gm., 1 case; 300 to 399, 25 cases; 400 to 499, 36 cases; 500 to 599, 17 cases; over 600 gm., 9 cases. The kidneys were therefore considerably swollen, *i.e.*, they weighed over 400 gm. in 70 per cent of the cases. Microscopically, the lesions in most of the kidneys were typical of cholemic nephrosis. The glomeruli were well filled and normally cellular. Precipitated protein in the capsular space, frequently present, indicated alterations in permeability of the filtering capillaries. Pigmented casts lay in the lumina of various parts of the tubular system, particularly in the distal convoluted and the collecting tubules (Fig. 59). Degenerative changes of varying degree were evident, ranging from simple "cloudy swelling" to actual necrosis similar to that of mercurial poisoning (Fig. 60). In severely damaged kidneys, regeneration seemed to go hand in hand with destruction, and it was common to see tubules relined by flat epithelium (Fig. 61).

Cholemic nephrosis has received much less attention than the condition merits.[58-60]

Testis

Cirrhosis of the liver is not infrequently associated with atrophy of the testis. It is therefore a matter of much interest to examine this organ in cases of fatal epidemic hepatitis. Material was available in 38 cases. In 7 cases the organs were found to be completely atrophic and fibrotic: in 5 some degree of disturbance of spermatogenesis was evident, and in 26 cases the testes were normal. In the 7 cases of complete atrophy and fibrosis, the duration of hepatitis was from 26 to 64 days. The testicular process in all appeared to be of much longer duration.

In the 5 cases in which there was a varying degree of interference with spermatogenesis, there was some edema of stroma but without fibrosis. Hepatitis had been present from 52 to 76 days in 4, and 138 days in one. In these cases it is not certain whether the testicular changes can be related to the hepatic damage.

It may here be pertinent to recall the relation of the liver to the testis. The liver is important in the metabolic disposal of sex hormones. When, because of hepatic insufficiency, this disposal does not take place, estrogens accumulate; these substances, in excessive concentration, very probably damage the sperm-forming cells of the testis and thus may lead to severe atrophy.[61]

In a recent study of 34 cases of hepatic failure other than cirrhosis (carcinoma, amyloidosis, hemochromatosis) Morrione [62] found that in

order to result in atrophy of the testis, damage in the liver must be severe, extensive and long-standing. Whether in any case of the present series the testicular damage can be related to the hepatic damage is doubtful. Study of much additional material is required to aid in the solution of this complicated problem.

Brain

Grossly, the brain showed little alteration, except edema. In 62 cases, blocks from representative areas were available for microscopic examination. The changes found were of two kinds. One was acute degeneration of ganglion cells, the other inflammatory reaction around vessels and in the meninges.

The changes in the ganglion cells were of types such as occur commonly in many different diseases (Figs. 67 to 69). Satellitosis around damaged cells was rare. The ganglion cell changes were irregular in distribution; no part of the brain was especially affected. Occasionally, isolated cells were completely destroyed; their remnants usually were invaded by glial elements (Figs. 70 and 71). In a few instances there were found tiny glial nodules (Fig. 72). Otherwise, glial reactions of any kind were sparse.

The vessels had normal walls; hemorrhages were rare. Edema of varied degree was usually present. There were nowhere any areas of demyelination. All these changes are nonspecific.

A different and more important lesion was found in the basal meninges and around the vessels of the brain stem (including the hypothalamus), in the periventricular system and the nucleus basalis. In these regions occasional small vessels were cuffed by lymphocytes (Fig. 73). Such perivascular infiltration was never pronounced. Figure 74 is representative of the average degree. The meninges showed a similar and often more diffuse lymphocytic infiltration (Figs. 75 and 76). The vessel walls were never necrotic. The lesions did not occur in the cortex or the subjacent white matter.

The perivascular and meningeal infiltrations were present in approximately 15 per cent of the brains examined. The lesions are sufficient in degree to be considered a mild meningo-encephalitis.

Pathologic Physiology of Fatal Epidemic Hepatitis

It is beyond the scope of this paper to discuss all of the varying functional faults encountered in fatal cases of epidemic hepatitis. Rather, I shall briefly discuss the mechanism underlying the jaundice, the ascites, the hemorrhagic phenomena and the cerebral manifestations.

Jaundice

Jaundice indicates a disturbance of the balance between the rates of bile pigment production and its excretion by liver cells into the biliary system. Regarding the pathogenesis of jaundice there are two main schools. By one, following the teaching of McNee,[63] three types of jaundice are recognized: hemolytic jaundice, toxic jaundice and obstructive jaundice. In hemolytic jaundice the rate of bile pigment formation, due to excessive destruction of red corpuscles, is so great that it exceeds the rate with which the liver cells can modify and then eliminate the pigment. Hence, an excess of bilirubin accumulates in the circulation and tints certain tissues. In the second type of jaundice, the toxic variety, the liver cells are severely damaged or actually killed and hence cannot take up the bilirubin of normal hemoglobin breakdown from the circulating blood. In the third type, obstructive jaundice, the rate of pigment formation by the reticulo-endothelial cells is normal and the liver cells are able to secrete the pigment into the intracolumnar canaliculi. Due to obstruction somewhere in the excretory duct system, the delicate canaliculi become distended beyond their capacity and rupture, spilling bile into the space of Disse or directly into the circulating blood.

A somewhat different view concerning the mechanism of jaundice is expressed by Rich.[64] He recognizes only two main types: retention jaundice and regurgitation jaundice. The former is practically synonymous with hemolytic jaundice of other writers. It occurs in various anemias and in any condition associated with increased destruction of red blood cells. The other form, regurgitation jaundice, is due to a reflux of bile from the intralobular canaliculi into the blood stream. It results from rupture of the delicate canaliculi, brought about either by necrosis of liver cells or by obstruction of the outflow of bile anywhere within the biliary system. The regurgitation jaundice of Rich, therefore, includes both the toxic and obstructive variety. He believes catarrhal jaundice to be a form of regurgitation jaundice of unknown pathogenesis.

McNee, Rich, and other students of jaundice agree that the causes of jaundice cannot always be placed in these separate compartments; there is often a combination of several factors.

Catarrhal jaundice for many years was thought to be due to obstruction at the lower end of the biliary duct system. In contrast, the jaundice of idiopathic yellow atrophy of the liver—a condition formerly regarded as an unrelated disease—was usually attributed to damage or destruction of liver cells. It has been shown, however, that catarrhal jaundice and yellow atrophy of the liver are not different diseases but

different forms of the same disease, namely, epidemic hepatitis. If this be true, then it may be expected that in both forms the pathogenesis of jaundice is the same. Actually, in both forms, the cause of jaundice appears to lie principally in obstruction of the intralobular canaliculi by bile thrombi. In biopsies reported by Scandinavian and British investigators, and in rare post-mortem examinations of patients who have died from accidental causes, the liver in catarrhal jaundice has always shown, within bile canaliculi, plugs of altered and inspissated bile. In fatal cases of epidemic hepatitis, *i.e.*, in "idiopathic" yellow atrophy, these plugs occur in great numbers within the intralobular canaliculi. In contrast the extralobular ducts, small and large, are patent. No doubt, injury to the liver may be an additional factor in early stages of epidemic hepatitis in both its benign and malignant forms. But it is more than probable that mechanical obstruction of the intralobular canaliculi is the most important cause of the persistent jaundice of epidemic hepatitis.

Ascites

Ascites is a common event in fatal epidemic hepatitis. It occurs in approximately two-thirds of the cases. Most often ascites appears rather suddenly, during the final phase of the disease. It should be emphasized, however, that it may occur also, though less often, in patients who recover.

The mechanism of ascites is complex. At least two factors are usually involved: (1) alteration of the plasma proteins which leads to lowering of the colloid osmotic pressure, and (2) increase in portal blood pressure due to interference with venous flow through the liver. The resulting states will, in turn, bring about anoxic increase in capillary permeability.

It is well known that extensive damage to the liver tends to lower the quantity of the plasma proteins and alter their relative proportion.[65] In many cases of this series, the plasma proteins were depleted. Ascites, however, often appeared before the protein level dropped. This was especially true when the course of hepatitis was rapid. In a considerable number of cases the plasma proteins showed little alteration. Moreover, the accumulation of fluid was commonly limited to the abdominal cavity; general edema was rare. There is, however, no constant relation between the level of plasma proteins and the colloid osmotic pressure of the blood. This subject was discussed in a recent paper by Butt, Snell and Keys.[66] These investigators brought together experimental and clinical evidence which indicates that in hepatic disease the proteins may be altered both in quantity and in quality.

They were unable to demonstrate a constant "edema level" by measuring the colloid osmotic pressure. They cited the results of unpublished experiments of Bollman, who found no direct relation between the appearance of ascites and any exact serum protein concentration or level of the colloid osmotic pressure. But Bollman did find the rapidity of appearance of ascites more directly related to the extent of the hepatic injury. All these facts suggest that fall in the plasma proteins or in osmotic pressure is usually not the main cause of ascites in fatal epidemic hepatitis.

We may now consider another factor that may be responsible for ascites, namely, obstruction to the flow of blood in the liver. In epidemic hepatitis many efferent veins are severely injured. There is marked endophlebitis, sometimes thrombosis and complete obliteration. Moreover, there are changes in the distribution of blood within the liver. Where new parenchyma has been formed the tissue is markedly ischemic. Where tissue has been destroyed there is great engorgement, perhaps stagnation. There is, therefore, the possibility that even in early stages of hepatitis portal flow may be impaired.

That portal obstruction actually exists is shown by comparison of spleens from patients with ascites and from those without ascites. The spleen in the ascitic group is enlarged twice as often as in the group without ascites. This enlargement may be regarded as evidence of portal obstruction. Although this does not furnish positive proof, it suggests that obstruction to portal flow is at least one factor in the pathogenesis of ascites.

Besides mechanical obstruction, other factors may be concerned. The liver normally stores a large proportion of ingested water.[67] Destruction of much of the parenchyma in fatal hepatitis may interfere with the function of water storage and thus contribute to the establishment of ascites.

Hemorrhagic Phenomena

The hemorrhagic phenomena of epidemic hepatitis are doubtless due to disturbance in prothrombin formation in the damaged liver. The relation of hemorrhage to liver damage has been reviewed in recent papers.[68, 69]

Cerebral Manifestation

Mental and nervous manifestations are almost invariably present during the final phase of fatal hepatitis. These are somewhat paralleled by the symptoms observed in experimental animals subjected to complete removal of the liver. In such animals the symptoms produced, and the death of the animals, must be attributed chiefly to hypoglycemia which takes places after the liver, the chief storehouse of

glycogen, is removed. However, animals in which some hepatic tissue remains do not show the typical symptoms that are present when the liver is removed completely. Death in such animals cannot always be attributed to hypoglycemia.[65]

Severe hepatic injury must inevitably lead to serious disturbances in the chemical composition of the body fluids, on the stability of which depends the normal state of all tissue. It seems reasonable to assume that it is the general imbalance of tissue fluids rather than the disturbance of a single component, such as sugar, which is responsible for the cerebral manifestations and for death.

The anatomic background of the cerebral symptoms is ill-defined. In this series, two main kinds of changes were found on microscopic examination. One was acute nonspecific degeneration of ganglion cells, such as accompanies many different diseases. These changes occurred in all cases. The other was a mild form of meningo-encephalitis located particularly in the brain stem, including the hypothalamus, the periventricular system and the nucleus basalis; the cortex and the subjacent white matter remained untouched. These changes occurred in approximately 15 per cent of the brains.

The lesions are different from those found in virus diseases, such as measles, mumps, or vaccinia. In these, foci of demyelination and often necrosis of small arteries are characteristic; such alterations are not found in cases of hepatitis.

The cerebral symptoms of hepatitis have some points in common with Wernicke's syndrome, in which the clinical manifestations are lethargy or drowsiness terminating in coma, and sometimes periods of excitement. Frequently, these nervous manifestations are associated with vomiting.[71] In the pathogenesis of Wernicke's syndrome, vitamin deficiency, particularly deficiency in Vitamin B_1, is thought to play an important part. Deficiencies of several vitamins probably occur when the liver is as extensively damaged as it is in fatal hepatitis. However, anatomically the lesions of Wernicke's encephalopathy differ from those found in cases of epidemic hepatitis. In Wernicke's encephalopathy the lesions consist mainly of vascular proliferations, a varying degree of glial proliferation, and absence of perivascular lymphocytic cuffing.[70, 71] In hepatitis, on the other hand, vascular and glial proliferations are inconspicuous or absent, but perivascular lymphatic infiltration is present. Because of these differences there is no ground for believing that the cerebral lesions of hepatitis are the result of vitamin B_1 deficiency.

We may now consider whether the changes in the brain may result from toxic substances passing through the damaged liver. The portal

blood always contains an abundance of toxic products of digestion which in the normal liver are detoxified. Through the greatly damaged liver of fatal hepatitis they may pass unaltered. Certain experiments of Baló and Korpássy [72] have a bearing on this point. When dogs with Eck's fistula were fed meat, 6 of 8 animals presented symptoms of encephalitis. In the brains of 3 dogs, histologic changes were found which corresponded to nonsuppurative encephalitis; they were located particularly in the striate body. These lesions were of similar kind, but of greater degree, than those found in hepatitis. Baló and Korpássy concluded that the encephalitis in their experimental animals was due to intoxication caused by exclusion of the liver.

It seems probable that in fatal hepatitis the detoxifying function of the liver is so altered as to permit the circulation of substances normally bound or destroyed in this organ. The working hypothesis is proposed that the cerebral changes of hepatitis result chiefly from loss of the detoxifying function of the liver.

Summary

This study is based upon 125 fatal cases of hepatitis which occurred in the U. S. Army during the epidemic of 1942.

In an historical summary it has been shown that hepatitis is not a new disease; many epidemics have occurred. In all epidemics the clinical picture has been remarkably similar. The mortality has always been low, from 0.2 to 0.4 per cent.

Prior to World War I there was little information concerning the lesions of epidemic hepatitis. It has gradually come to be recognized that the lesions in the livers of fatal cases correspond to those long known as idiopathic acute yellow atrophy. Nevertheless, the view that yellow atrophy and epidemic hepatitis are but two extremes of the same disease has not been accepted by all. The present studies leave little doubt that idiopathic yellow atrophy represents the end stage of fatal epidemic hepatitis.

The clinical course in the fatal cases has been analyzed. There were three distinct phases: pre-icteric or initial, intermediate, and final. In the great majority, the initial phase lasted 7 days or less, the intermediate phase no more than 26 days, the final phase no more than 10. The initial symptoms were the same as those in cases of the nonfatal disease. The intermediate phase began with the onset of jaundice; during its early stages there was no indication that the disease was not going to run its usual benign course. However, in the majority there was a sudden dramatic change which initiated the final phase of the disease; it usually was marked by the development of cerebral manifestations, persistent vomiting and ascites. The cerebral symptoms

were, principally, lethargy and coma alternating with excitement and delirium.

The patient was usually afebrile, except during the terminal stage. The pulse was rarely slow. The blood pressure was normal, except during periods of excitement in the final phase.

During the stages preceding the final phase the liver was usually enlarged and tender. Later it shrank rapidly.

As the disease progressed, moderate anemia appeared. In all but the final stage, there was usually slight leukopenia with relative lymphocytosis.

The chief lesions were found in the liver. They were those typical of yellow atrophy. Characteristically, involvement of the liver was not uniform. In large areas all the parenchyma was destroyed, leaving only skeletal remnants of the lobules, whereas elsewhere destruction was incomplete. The remains of lobules were outlined by small proliferating bile ducts. The destruction affected only the liver cells, the framework and sinusoids remaining unaltered. Scarring did not occur. It is characteristic of the destructive process that the dead cells were removed rapidly. In the areas of destruction there was an inflammatory reaction that persisted for a long time. Macrophages filled with lipofuscin were particularly prominent. The efferent veins were the site of marked endophlebitis.

Hyperplasia of surviving cells led to the formation of much new tissue which grossly appeared coarsely nodular or tumor-like. Microscopically, this tissue almost never had a normal lobular structure. The new parenchyma was formed almost exclusively from pre-existing liver cells. However, there is some morphologic evidence that liver cells are sometimes derived from bile ducts. While it is impossible to decide on morphologic grounds whether bile ducts can actually form liver cells, it is probable that they do so.

The newly formed parenchyma was markedly ischemic and overladen with bile, due to obstruction in the intralobular canaliculi. The extralobular bile ducts were normal. There was no evidence of progressive destruction of tissue. But in some areas the newly formed parenchyma degenerated because of ischemia, bile stasis, and, perhaps, accumulation of metabolic waste products.

The gallbladder showed no significant change.

The regional lymph nodes of the liver were edematous and often hyperplastic.

The spleen in the majority of instances was enlarged. In early stages, enlargement was due to cellular proliferation, and in later stages to congestion.

The bone marrow usually was moderately hyperplastic.

In the gastrointestinal tract edema was commonly found, and in about 15 per cent of the cases there was a phlegmonous inflammation, particularly in the cecal region. The phlegmon was probably a late event, as the inflammatory cells were well preserved.

The kidney usually showed the picture of cholemic nephrosis.

In the brain two kinds of changes were present: an acute nonspecific degeneration of ganglion cells, and a mild meningo-encephalitis which occurred in about 15 per cent of the cases.

Hemorrhages were found particularly in the lung, intestine, epicardium, endocardium and kidney. Hemorrhagic phenomena may be attributed to disturbances in vitamin-K metabolism and to changes in the level of prothrombin, both due to destruction of liver.

Ascites occurred in two-thirds of the cases; its frequency was unrelated to the total duration of hepatitis. It usually developed late in the disease. Ascites is thought to be due principally to interference with blood flow through the liver, although other factors may be concerned, such as change in plasma proteins and interference with the water-storage capacity of the liver.

The mechanism of jaundice is believed to be obstruction of the intralobular canaliculi.

The cerebral lesions are believed to be due to loss of the detoxifying function of the liver, although here, too, the exact mechanism is not known.

REFERENCES

1. Office of the Surgeon General, Circular Letter No. 95. The outbreak of jaundice in the army. *J. A. M. A.*, 1942, **120**, 51–53; also: *Mil. Surgeon*, 1942, **91**, 386–393.
2. Bayne-Jones, S., and Walker, D. The occurrence of jaundice in the United States Army, 1931–42. (To be published.)
3. Turner, R. H., Snavely, J. R., Grossman, E. B., Buchanan, R. N., and Foster, S. O. Some clinical studies of acute hepatitis occurring in soldiers after inoculation with yellow fever vaccine, with especial consideration of severe attacks. *Ann. Int. Med.*, 1944, **20**, 193–218.
4. Sawyer, W. A., Meyer, K. F., Eaton, M. D., Bauer, J. H., Putnam, P., and Schwentker, F. F. Jaundice in army personnel in the western region of the United States. *Am. J. Hyg.*, 1944. (In press.)
5. Cockayne, E. A. Catarrhal jaundice, sporadic and epidemic, and its relation to acute yellow atrophy of the liver. *Quart. J. Med.*, 1912–13, **6**, 1–29.
6. Fröhlich, C. Ueber Icterusepidemien. *Deutsches Arch. f. klin. Med.*, 1879, **24**, 394–406.
7. v. Bormann, F. Hepatitis epidemica. *Ergebn. d. inn. Med. u. Kinderh.*, 1940, **58**, 201–284.
8. Hennig, A. Ueber epidemischen Ikterus. *Samml. klin. Vortr., n. F., Leipz.*, 1890, no. 8 (Innere Med., no. 4, 77–108).
9. Macpherson, W. G. (ed.). Great Britain. History of the Great War Based on Official Documents. Medical Services. Diseases of War. H. M. Stationery Office, London, 1922.

10. Willcox, W. H. The epidemic jaundice of campaigns. *Brit. M. J.*, 1916, 1, 297–300; Jaundice: with special reference to types occurring during the war. *Brit. M. J.*, 1919, 1, 671–675.
11. Buchbinder, W. Beitrag zur Klinik der Icterus catarrhalis. *Arch. f. Verdauungskr.*, 1920, **26**, 231–249.
12. Dietrich, S. Der sogenannte katarrhalische Ikterus und die Hepatitis epidemica. *Deutsche med. Wchnschr.*, 1942, **68**, 5–10.
13. Woodward, J. J. The Medical and Surgical History of the War of the Rebellion (1861–65). Government Printing Office, Washington, 1875, 1, pt. 1.
14. Woodward, J. J. Outlines of the Chief Camp Diseases of the U. S. Armies. J. B. Lippincott Co., Philadelphia, 1863.
15. Seggel, C. Die Krankenbewegung bei dem Königl. Bayerischen I. Armee-Corps während des deutsch-französischen Krieges 1870–1871. *Deutsche mil.-ärztl. Ztschr.*, 1872, 1, 24–38; 79–94.
16. Hübener, E. Über die Weilsche Krankheit. Katarrhalischer Ikterus. *Ergebn. d. inn. Med. u. Kinderh.*, 1917, **15**, 50–54.
17. Hurst, A., Barber, H. W., Knott, F. A., and Ross, T. A. Medical Diseases of War. Arnold & Co., London, 1941.
18. Brugsch, T., and Schürer, J. Ueber gutartige epidemische Gelbsucht. *Berl. klin. Wchnschr.*, 1919, **56**, 601–603.
19. Michie, H. C. "Acute catarrhal jaundice." *Mil. Surgeon*, 1923, **52**, 390–421.
20. Blumer, G. Infectious jaundice in the United States. *J. A. M. A.*, 1923, **81**, 353–358.
21. Cullinan, E. R. The epidemiology of jaundice. *Proc. Roy. Soc. Med.*, 1939, **32**, 933–950.
22. Ruge, H. Einige Beobachtungen über das Auftreten von Gelbsucht unter besonderer Berücksichtigung von 1642 Fällen in der Marine. *Ztschr. f. klin. Med.*, 1926, **103**, 272–285; Zehn Jahre Gelbsucht in der Marine (1919–1929). *Ergebn. d. inn. Med. u. Kinderh.*, 1931, **41**, 1–112.
23. Ehrström, R. Icterus catarrhalis, akute gelbe Leberatrophie und chronische Hepatitis als Äusserungen derselben Krankheit, Hepatitis epidemica. *Acta med. Scandinav.*, 1926–27, **65**, 573–581.
24. Wallgren, A. Erfahrungen über epidemischen Icterus (sog. Icterus catarrhalis). *Acta paediat.*, 1930, **9**, suppl. 2, 1–90.
25. Wickström, J. Der Grad der Übertragbarkeit der Hepatitis epidemica. *Acta paediat.*, 1940–41, **28**, 385–389.
26. Selander, P. Epidemischer und sporadischer Ikterus. *Acta paediat.*, 1939, **23**, suppl. 4, 1–250.
27. Cameron, J. D. S. Infective hepatitis. *Quart. J. Med.*, 1943, **12**, 139–155.
28. MacCallum, F. O. Infective hepatitis. *Brit. M. Bull.*, 1943, 1, 112–113.
29. Gutzeit, K. Icterus infectiosus. *München. med. Wchnschr.*, 1942, **89**, 161–164; 185–190.
30. Siegmund, H. Zur pathologischen Anatomie der Hepatitis epidemica. *München. med. Wchnschr.*, 1942, **89**, 463–469.
31. Virchow, R. Ueber das Vorkommen und den Nachweis des hepatogenen, insbesondere des katarrhalischen Icterus. *Virchows Arch. f. path. Anat.*, 1865, **32**, 117–125.
32. Lichtman, S. S. Diseases of the Liver, Gall Bladder and Bile Ducts. Lea & Febiger, Philadelphia, 1942.
33. Lindstedt, F. Beitrag zur Kenntnis des Icterus catarrhalis mit besonderer Rücksicht auf die Inkubationszeit dessen epidemischen Formen. *Nord. med. Ark.*, 1919, **51**, Avd. 2, 583–610.
34. Eppinger, H. Die Leberkrankheiten. J. Springer, Vienna, 1937.

35. Klemperer, P., Killian, J. A., and Heyd, C. G. The pathology of "icterus catarrhalis." *Arch. Path.*, 1926, **2**, 631–652.
36. Gaskell, J. F. The changes in the liver in a fatal case of epidemic "catarrhal" jaundice. *J. Path. & Bact.*, 1933, **36**, 257–262.
37. Schrumpf, A. Un cas d'ictère "catarrhal" avec biopsie. *Ann. d'anat. path.*, 1932, **9**, 17–22.
38. Barber, H., and Osborn, G. R. The morbid anatomy of a sporadic case of infective hepatic jaundice. *J. Path. & Bact.*, 1939, **49**, 581–585.
39. 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.
40. Dible, J. H., McMichael, J., and Sherlock, S. P. V. Pathology of acute hepatitis. *Lancet*, 1943, **2**, 402–408.
41. Bergstrand, H. Über die akute und chronische gelbe Leberatrophie. G. Thieme, Leipzig, 1930.
42. Fox, J. P., Manso, C., Penna, H. A., and Madureira Pará. Observations on the occurrence of icterus in Brazil following vaccination against yellow fever. *Am. J. Hyg.*, 1942, **36**, 68–116.
43. Roman, B. Acute yellow atrophy of the liver. *Arch. Path.*, 1927, **4**, 399–436.
44. 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.
45. Wilson, J. D., and Goodpasture, E. W. Yellow atrophy of the liver. *Arch. Int. Med.*, 1927, **40**, 377–385.
46. Connor, C. L. Studies on lipochromes. IV. The nature of the pigments in certain organs. *Am. J. Path.*, 1928, **4**, 293–308.
47. König, P. Untersuchungen am Abnutzungspigment des Herzens und der Leber. *Beitr. z. path. anat. u. z. allg. Path.*, 1926, **75**, 181–215.
48. Endicott, K. M. Similarity of the acid-fast pigment ceroid and oxidized unsaturated fat. *Arch. Path.*, 1944, **37**, 49–53.
49. Pfuhl, W. Die Leber. In: von Möllendorff, W. Handbuch der mikroskopischen Anatomie des Menschen. J. Springer, Berlin, 1932, **5**, pt. 2, 235–425.
50. Pearce, R. M. Regenerative changes in the liver: a study of experimental lesions in the dog. *J. M. Research*, 1906, **15**, 99–112.
51. Orr, J. W. The histology of the rat's liver during the course of carcinogenesis by butter-yellow (p-dimethylaminoazobenzene). *J. Path. & Bact.*, 1940, **50**, 393–408.
52. Menon, T. B. Venous splenomegaly: a study in experimental portal congestion. *J. Path. & Bact.*, 1938, **46**, 357–365.
53. Cameron, G. R., and de Saram, G. S. W. A method for permanently dissociating the spleen from the portal circulation (the "marsupialised" spleen) and its use in the study of experimental liver cirrhosis. *J. Path. & Bact.*, 1939, **48**, 41–47.
54. Pollack, A. D., and Gerber, I. E. Abdominal visceral lesions associated with primary disease of the liver. *Arch. Path.*, 1943, **36**, 608–611.
55. Bartels, E. C. Acute ulcerative esophagitis. *Arch. Path.*, 1935, **20**, 369–378.
56. Selye, H. The experimental production of peptic haemorrhagic oesophagitis. *Canad. M. A. J.*, 1938, **39**, 447–448.
57. Pearce, J., and Dagradi, A. Acute ulceration of the esophagus with associated intranuclear inclusion bodies. *Arch. Path.*, 1943, **35**, 889–897.
58. Wilbur, D. L. The renal glomerulus in various forms of nephrosis. *Arch. Path.*, 1934, **18**, 157–185.

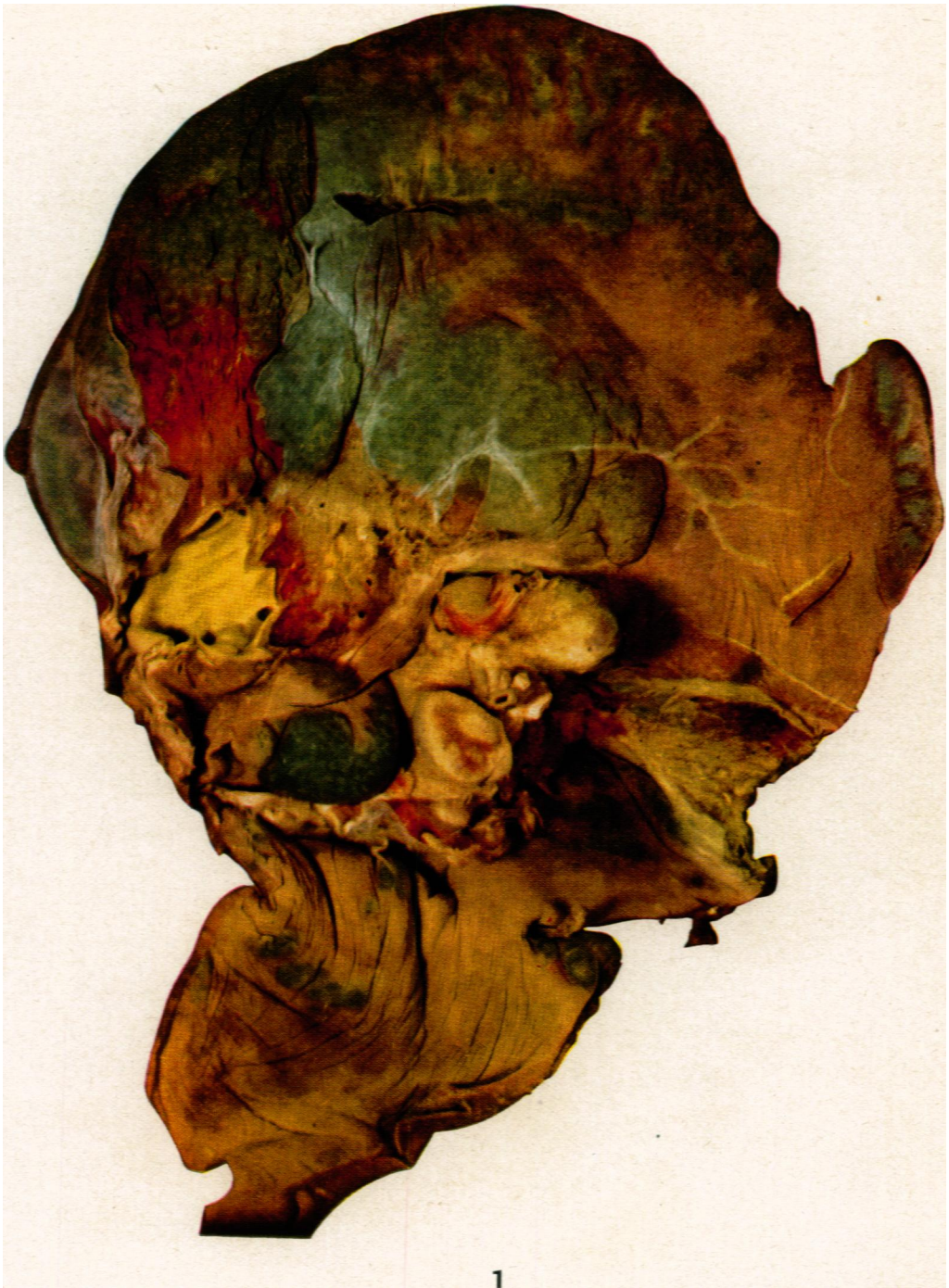
59. Ayer, D. Renal lesions associated with deep jaundice. *Arch. Path.*, 1940, 30, 26–41; also: Ayer, D., and Gauld, A. G. Uremia following blood transfusion. *Arch. Path.*, 1942, 33, 513–532.
60. Thompson, L. L., Jr., Frazier, W. D., and Ravdin, I. S. The renal lesion in obstructive jaundice. *Am. J. M. Sc.*, 1940, 199, 305–312; also: Elsom, K. A. Renal function in obstructive jaundice. *Arch. Int. Med.*, 1937, 60, 1028–1033.
61. Biskind, M. S. Personal communication. Also: Biskind, M. S., and Biskind, G. R. Effect of vitamin B complex deficiency on inactivation of estrone in the liver. *Endocrinology*, 1942, 31, 109–114; Inactivation of testosterone propionate in the liver during vitamin B complex deficiency. *Ibid.*, 1943, 32, 97–102.
62. Morrione, T. G. Effect of estrogens on the testis in hepatic insufficiency. *Arch. Path.*, 1944, 37, 39–48.
63. McNee, J. W. Jaundice: a review of recent work. *Quart. J. Med.*, 1922–23, 16, 390–420.
64. Rich, A. R. The pathogenesis of the forms of jaundice. *Bull. Johns Hopkins Hosp.*, 1930, 47, 338–377.
65. Bollman, J. L., and Mann, F. C. The physiology of the impaired liver. *Ergebn. d. Physiol.*, 1936, 38, 445–492.
66. Butt, H. R., Snell, A. M., and Keys, A. Plasma protein in hepatic disease. *Arch. Int. Med.*, 1939, 63, 143–155.
67. Crandall, L. A., Jr., and Roberts, G. M. Increased water exchange following Eck fistula in dogs. *Am. J. Physiol.*, 1936, 117, 318–322.
68. Butt, H. R., and Snell, A. M. Vitamin K. W. B. Saunders Co., Philadelphia, 1941.
69. Almquist, H. J. Vitamin K. *Physiol. Rev.*, 1941, 21, 194–216.
70. Zimmerman, H. M. Pathology of Vitamin B Group Deficiencies. In: The Role of Nutritional Deficiency in Nervous and Mental Disease. Research Publications, Association for Research in Nervous and Mental Disease, Williams & Wilkins Co., Baltimore, 1943, 22, 51–79.
71. Campbell, A. C. P., and Biggart, J. H. Wernicke's encephalopathy (polioencephalitis haemorrhagica superior): its alcoholic and non-alcoholic incidence. *J. Path. & Bact.*, 1939, 48, 245–262.
72. Baló, J., and Korpássy, B. The encephalitis of dogs with Eck fistula fed on meat. *Arch. Path.*, 1932, 13, 80–87.

[*Illustrations follow*]

DESCRIPTION OF PLATES

PLATE 88

FIG. 1. Case 24. Duration of hepatitis, 36 days. Under surface of a liver which weighed 1320 gm. The liver is shrunken, particularly the left lobe. The surface of the right lobe shows a number of flat or elevated nodular areas, between which the tissue is finely wrinkled. The surface of the left lobe is deeply furrowed. At the hilum is a cluster of enlarged, edematous lymph nodes. (For microscopic appearance of liver see Fig. 30; hemorrhages in heart and gut of this case are shown in Figs. 62 and 63.)



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Lucké Pathology of Fatal Epidemic Hepatitis

PLATE 89

FIG. 2. Case 81. Duration of disease, 19 days. Cut surface of a liver which weighed 890 gm. Over one-half of the organ has a fleshy, red appearance; here all liver cells have been destroyed. The yellow nodular patches are relatively ischemic, and are composed of large "lobules" of regenerating tissue. (The microscopic appearance of the red part is shown in Fig. 4.)

FIG. 3. Case 8. Duration of disease, 43 days. Vertical cut section of a liver which weighed 850 gm. The large, red, fleshy area consists entirely of vascular stroma and bile ducts; all liver cells have been destroyed. The remainder of the organ is composed of yellowish green nodular areas of regenerating parenchyma. (The microscopic appearance of the latter is shown in Figs. 27 and 28. For microscopic appearance of the esophagus from this case see Fig. 54.)

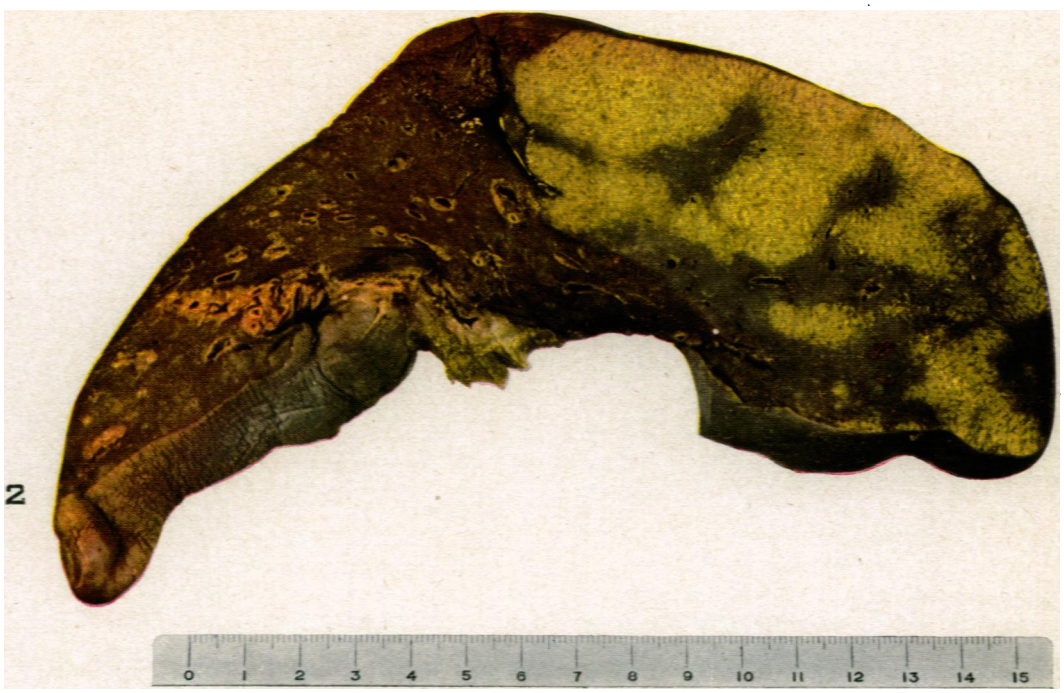
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PLATE 90

FIG. 4. Case 81. Duration of disease, 19 days. Microscopic appearance of the red, fleshy area of the liver shown in Fig. 2. The parenchyma has been destroyed. The lobular outlines are indicated by numerous, small, biliary ducts. The sinusoids are greatly engorged. Masson's trichrome stain. × 250.

FIG. 5. Case 84. Duration of disease, 93 days. Microscopic appearance of the pale nodular areas of regenerative hyperplasia shown in Fig. 11. Cords of liver cells form a pseudolobule which is noticeably ischemic. Elsewhere small bile ducts and large tubules composed of hepatic cells are scattered throughout the collapsed stroma; these large tubules are reminiscent of the liver in the early stage of embryonic development. × 250.

FIG. 6a. Case 115. Duration of disease, 18 days. Numerous macrophages with yellow-brown granules are scattered throughout the lobular stroma from which the liver cells have been removed. × 500.

FIG. 6b. A section from an area similar to the one shown in Figure 6a, but stained with Sudan III. The pigment granules take the fat stain well. × 500.

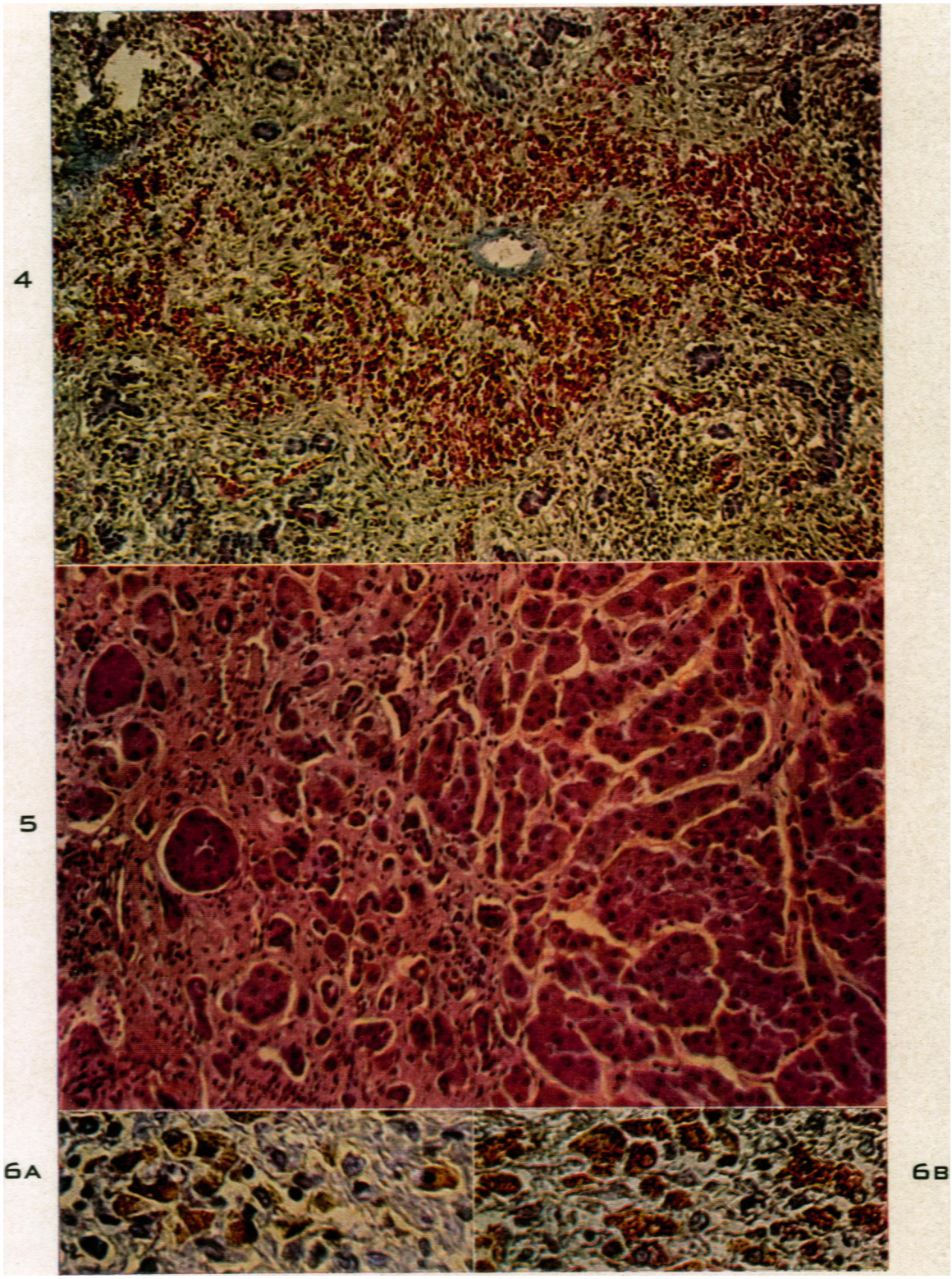
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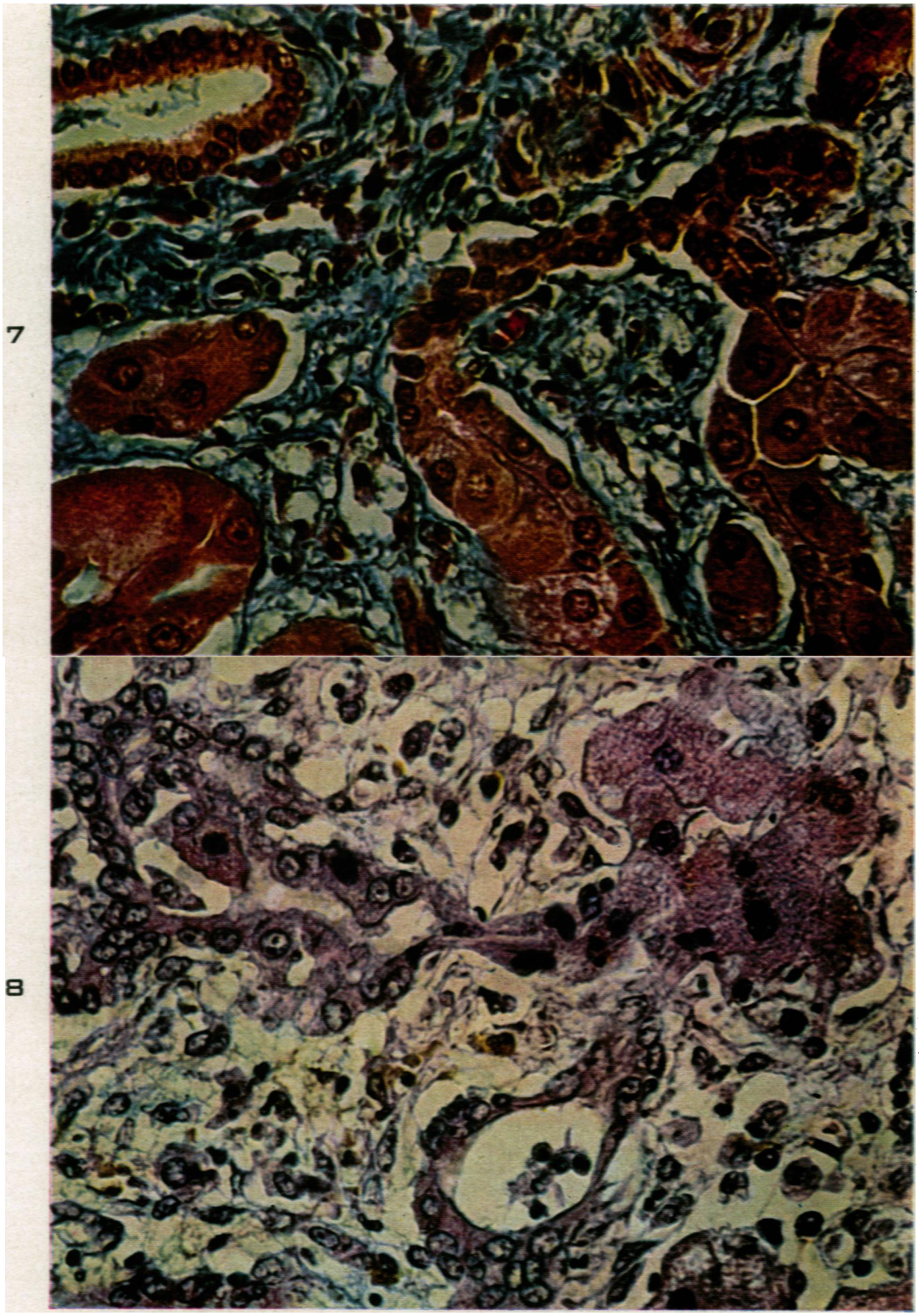
PLATE 91

FIG. 7. Case 104. Duration of disease, 98 days. A branching bile duct, the lumen of which is in continuity with the canaliculi of two atypical and probably regenerated hepatic columns. This appearance suggests a possible transformation of biliary epithelium into liver cells. × 650.

FIG. 8. Case 28. Duration of disease, 21 days. The lumen of a branching bile duct is continuous with that of a tubule composed of liver cells. Surrounded by the epithelium of the bile duct lie several large typical liver cells; as in Figure 7, this suggests a transformation of biliary cells into hepatic cells. The section comes from an area of "red atrophy." × 650



Lucké

Pathology of Fatal Epidemic Hepatitis

PLATE 92

FIG. 9. Case 92. Duration of hepatitis, 69 days. Weight of liver, 1040 gm. Massive tumor-like areas of hyperplastic regenerated tissue project above sunken patches. The surface of sunken regions has the appearance of coarse-grained leather.

FIG. 10. Case 124. Duration of disease, 37 days. Weight of liver, 800 gm. Under surface of organ shows numerous coarse nodules; the remainder has a smooth or finely wrinkled appearance. (See Figs. 73 and 75 for changes in the brain of this case.)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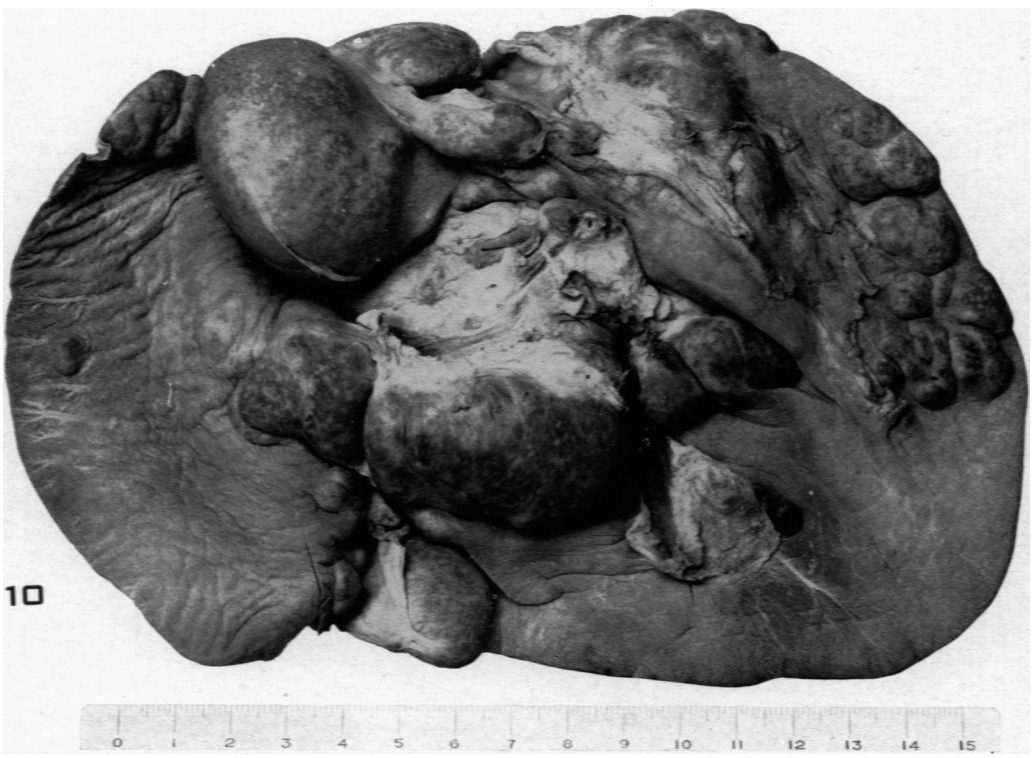
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PLATE 93

FIG. 11. Case 84. Duration of disease, 93 days. Weight of liver, 1710 gm. The cut surface shows extensive pale areas of regenerated "lobules"; between them lie depressed patches of tissue having a smooth texture and a fleshy appearance. (The microscopic structure of a regenerated "lobule" is shown in Figs. 5, 32, 37 and 46. For structure of the kidney of this case see Figs. 60 and 61; for brain changes see Figs. 71 and 72.)

FIG. 12. Case 76. Duration of disease, 96 days. Weight of liver, 2100 gm. This is an example of massive regenerative hyperplasia limited almost exclusively to the right lobe; the left lobe consists chiefly of collapsed stroma. (See Fig. 20 for appearance of reticulum in left lobe, and Figs. 67, 68, 69 and 76 for changes in the brain.)


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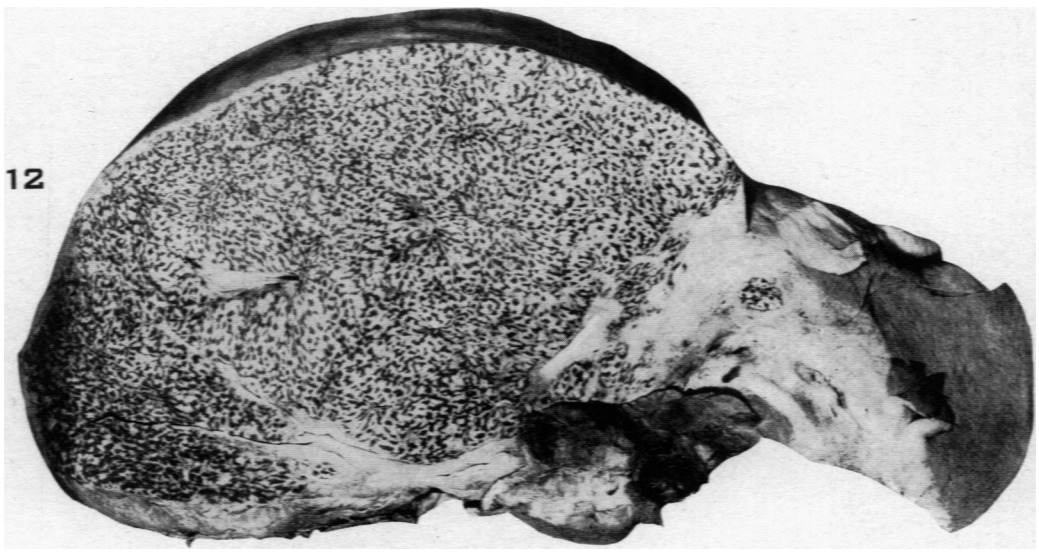
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PLATE 94

FIG. 13. Case 4. Duration of disease, 10 days. The central parts of the lobules have been destroyed; the peripheral rim of hepatic cells has remained more or less intact. (See Fig. 16 for details of cellular reaction within the stroma of the central portion of the lobules, Fig. 21 for changes in an efferent vein, Figs. 24, 25 and 26 for early regenerative activity, and Fig. 39 for appearance of portal canals and interlobular bile ducts.) × 35.

FIG. 14. Case 18. Duration of hepatitis, 30 days. The central zones of the lobules are largely destroyed, leaving a peripheral rim of parenchyma. × 120.

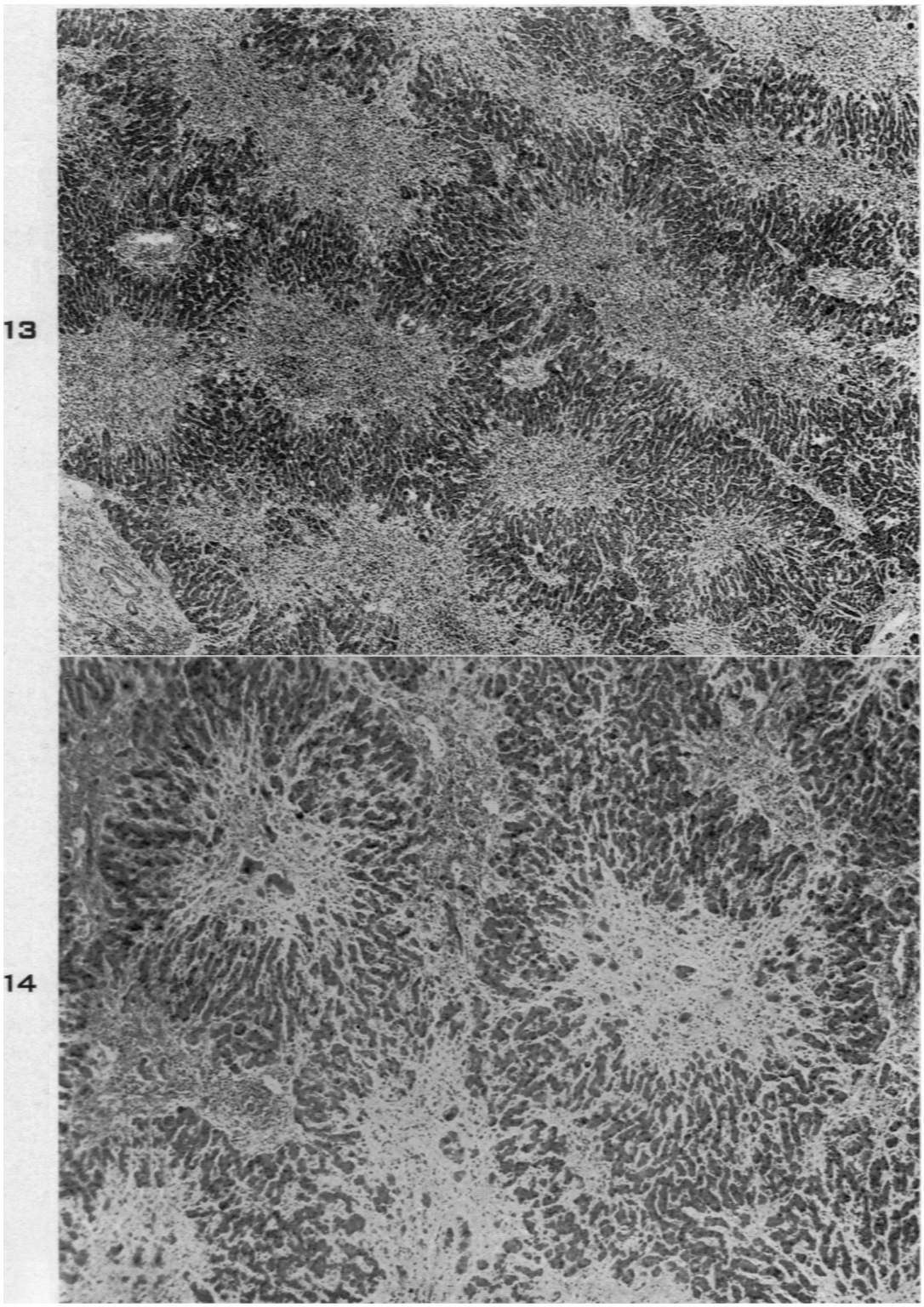

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PLATE 95

FIG. 15. Case 15. Duration of hepatitis, 14 days. The figure shows extensive destruction of parenchyma leaving only isolated broken columns of cells at the periphery of some lobules. The stroma is infiltrated with macrophages and exudative cells. (See Fig. 40 for appearance of interlobular and septal bile ducts.) × 135.

FIG. 16. Case 4. Duration of disease, 10 days. The photomicrograph shows the central part of a lobule, the stroma of which is infiltrated with polymorphonuclear leukocytes, lymphocytes, plasma cells and pigmented macrophages. This pigment is lipofuscin. A clump of multinucleated liver cells is evidence of early regenerative activity. (See Fig. 24.) × 810.

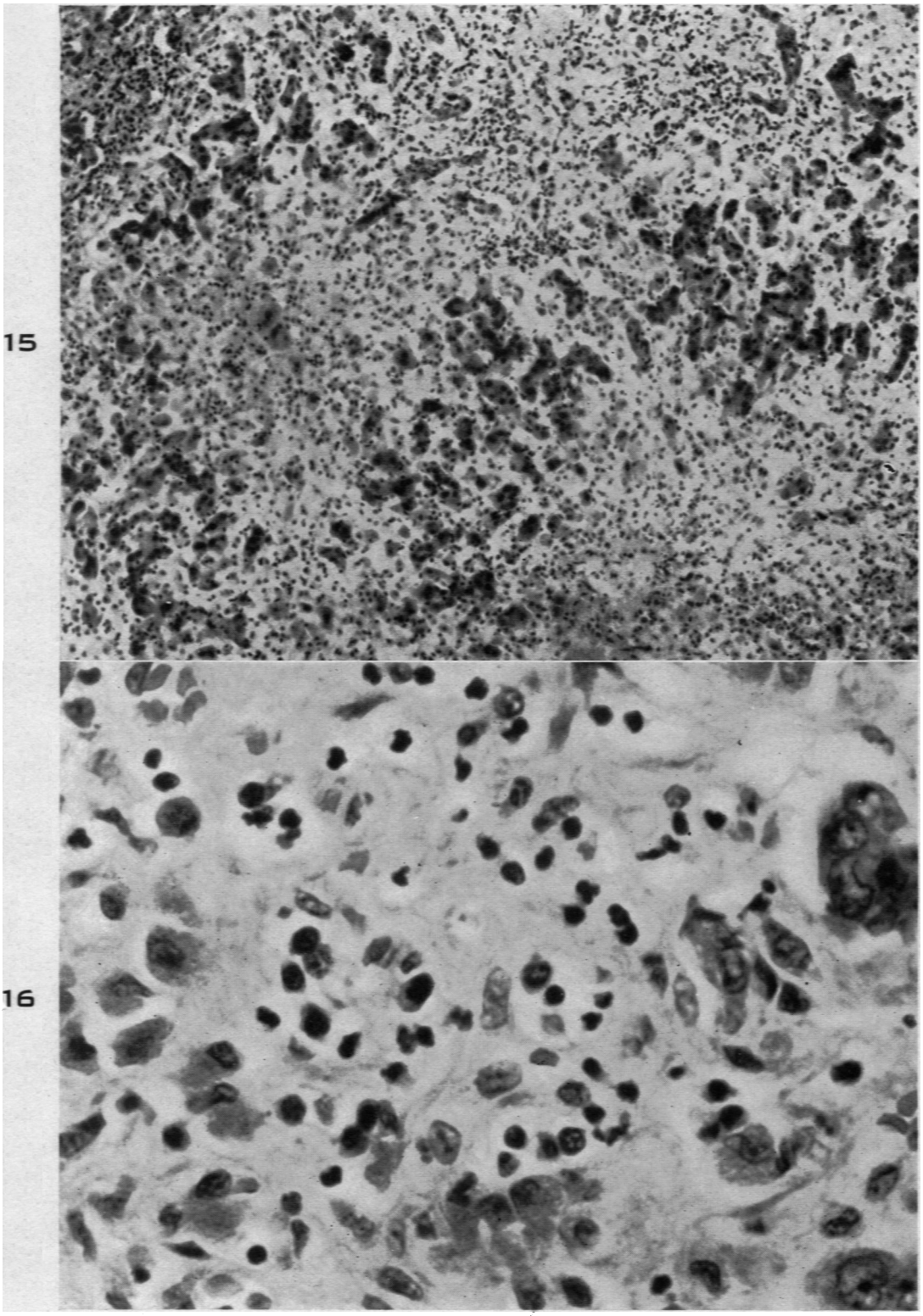

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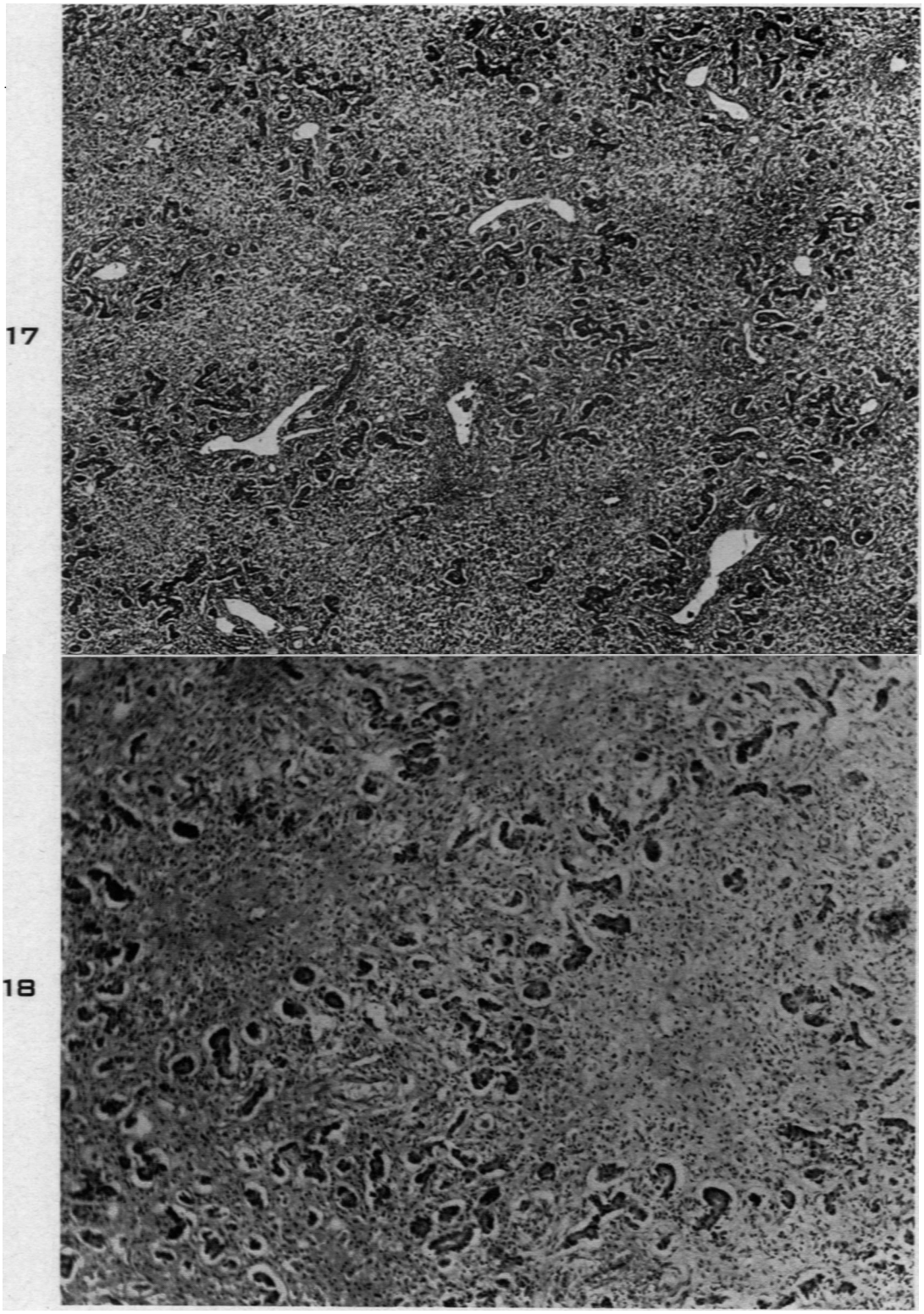
PLATE 96

FIG. 17. Case 79. Duration of hepatitis, 57 days. The section is from an area of "red atrophy." The periphery of the lobular remnants is more or less outlined by stockades of branching bile ducts. (The condition of efferent veins from this case is shown in Figs. 22 and 23.) × 35.

FIG. 18. Case 93. Duration of disease, 76 days. From an area of "red atrophy." The outlines of lobular remnants are indicated by numerous small proliferating biliary ducts. (Elsewhere the liver from this case showed atypical regeneration of parenchyma; Fig. 34.) × 85.



Lucké Pathology of Fatal Epidemic Hepatitis

PLATE 97

FIG. 19. Case 80. Duration of hepatitis, 30 days. The interlobar stroma from an area of "red atrophy" has remained intact. Because of loss of liver cells the meshes of the reticulum framework are narrowed and partly collapsed. Wilder's reticulum stain. (Branching bile ducts from this case are shown in Fig. 41; a photomicrograph of the spleen, in Fig. 57.) × 330.

FIG. 20. Case 76. Duration of disease, 96 days. The lobular reticulum is intact and, in general, has a normal pattern, although its meshes are somewhat distorted. The section is taken from the atrophic left lobe of the liver shown in Figure 12. (For changes in the brain of this case see Figs. 67, 68, 69 and 76.) × 170.

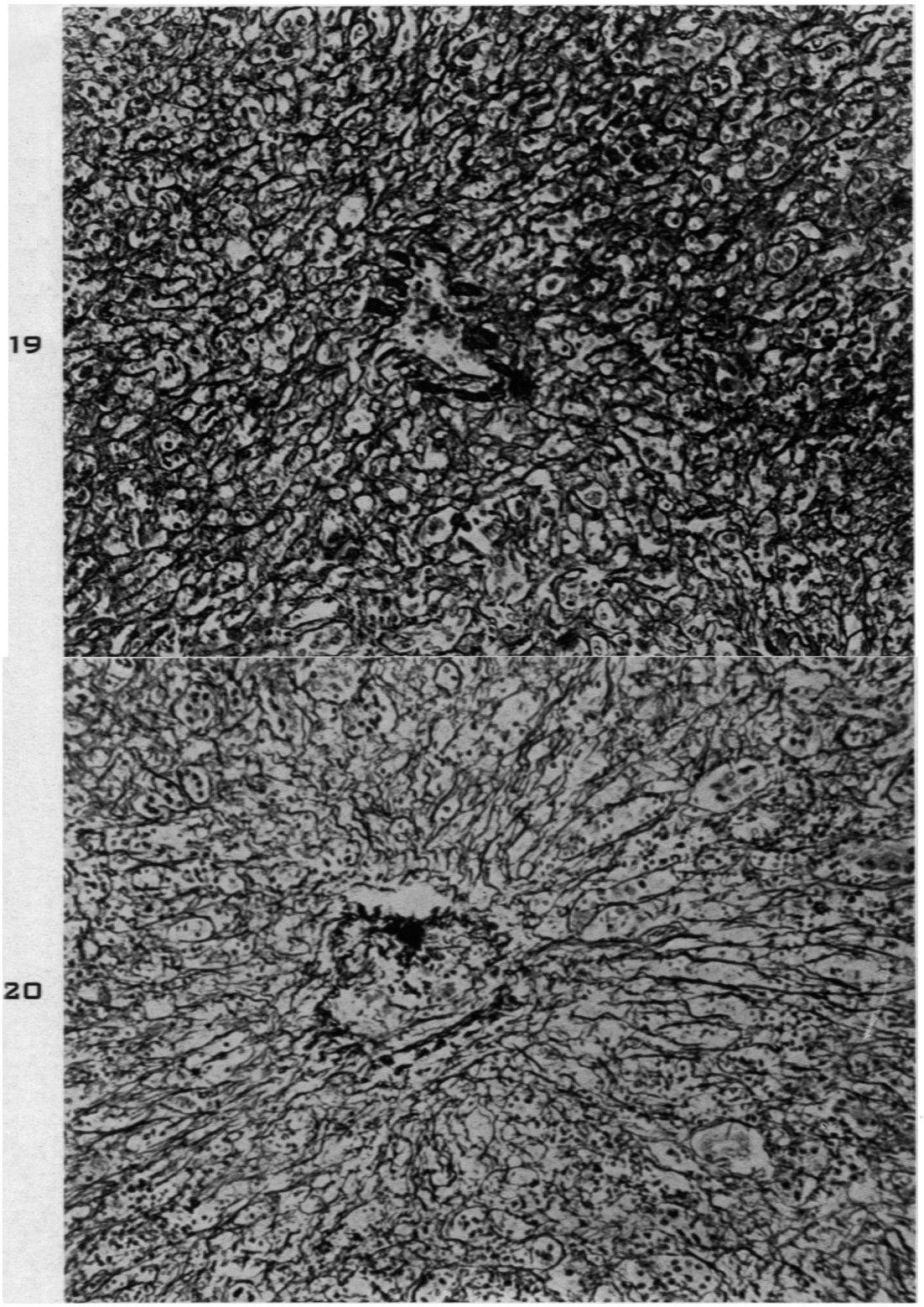

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PLATE 98

FIG. 21. Case 4. Duration of disease, 10 days. A central lobular vein has a greatly thickened wall which appears hyalinized. The subendothelial layer of the vein is infiltrated with cells of the same types as shown in Figure 16; the endothelial lining is intact. (See Figs. 13, 16, 24, 25, 26 and 39 for other photomicrographs of liver from same case.) × 500.

FIG. 22. Case 79. Duration of hepatitis, 57 days. A sublobular vein shows marked endophlebitis. (See Fig. 17 for appearance of the surrounding tissues.) × 175.

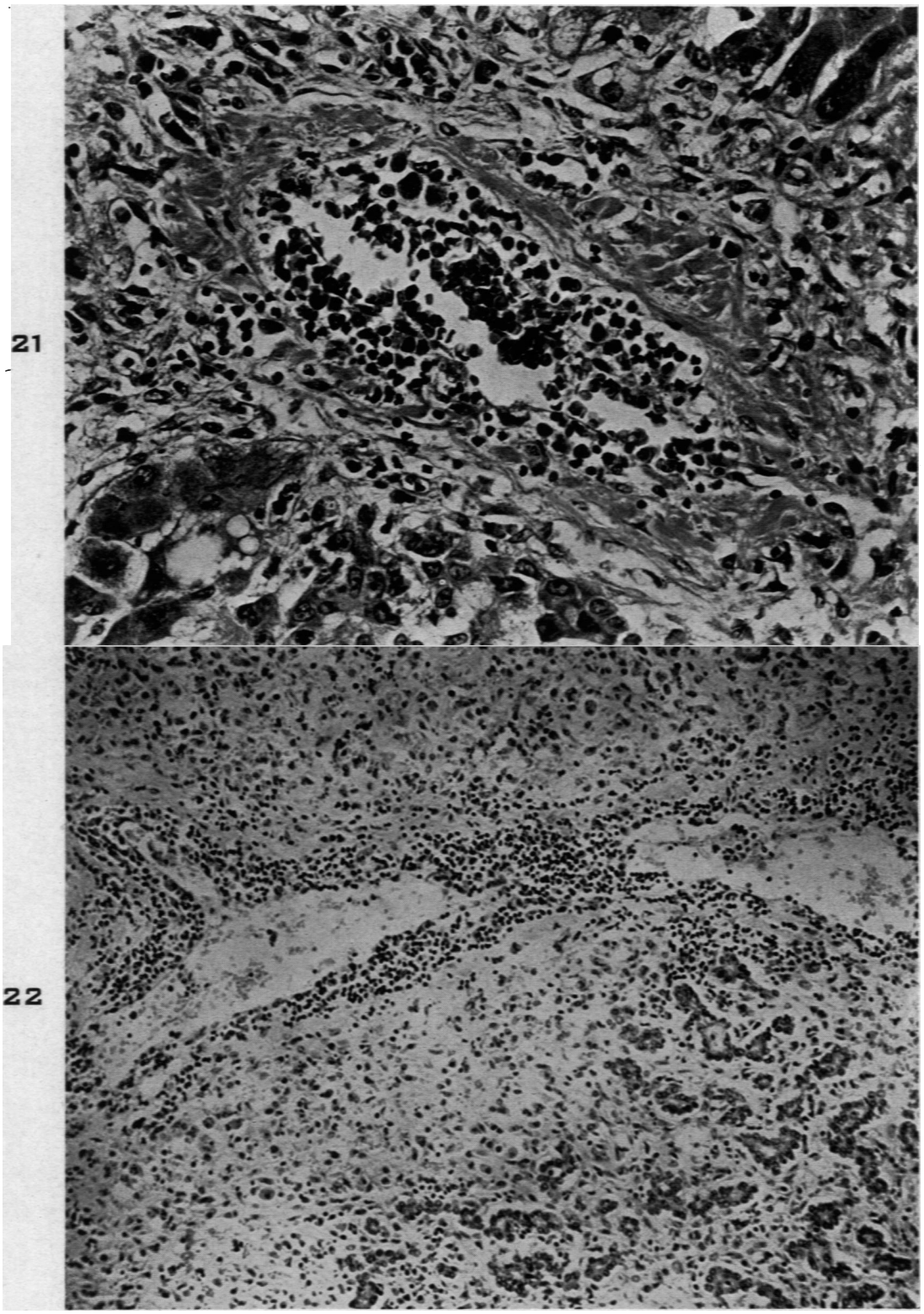

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PLATE 99

FIG. 23. Case 79. Duration of disease, 57 days. A sublobular vein stained by Wilder's reticulum stain shows that the endothelium of the intima is intact. The subendothelial layer is infiltrated with numerous cells, some of which are pigmented macrophages. The walls of the vein have a loose structure. × 500.

FIG. 24. Case 4. Duration of disease, 10 days. Early multiplication of liver cells is shown adjacent to a region from which the parenchyma has disappeared. The regenerating cells have closely aggregated, deeply staining large nuclei. The stroma of the central part of the lobule is infiltrated with wandering cells, details of which are shown in Figure 16. The central lobular vein exhibits marked endophlebitis. (See Fig. 21 for details.) × 110.

FIG. 25. Case 4. Duration of disease, 10 days. The partly broken columns of liver cells show early regeneration, as indicated by numerous closely placed hyperchromatic nuclei; many cells are binucleated. × 330.

FIG. 26. Another field from the section shown in Figure 25. × 330.

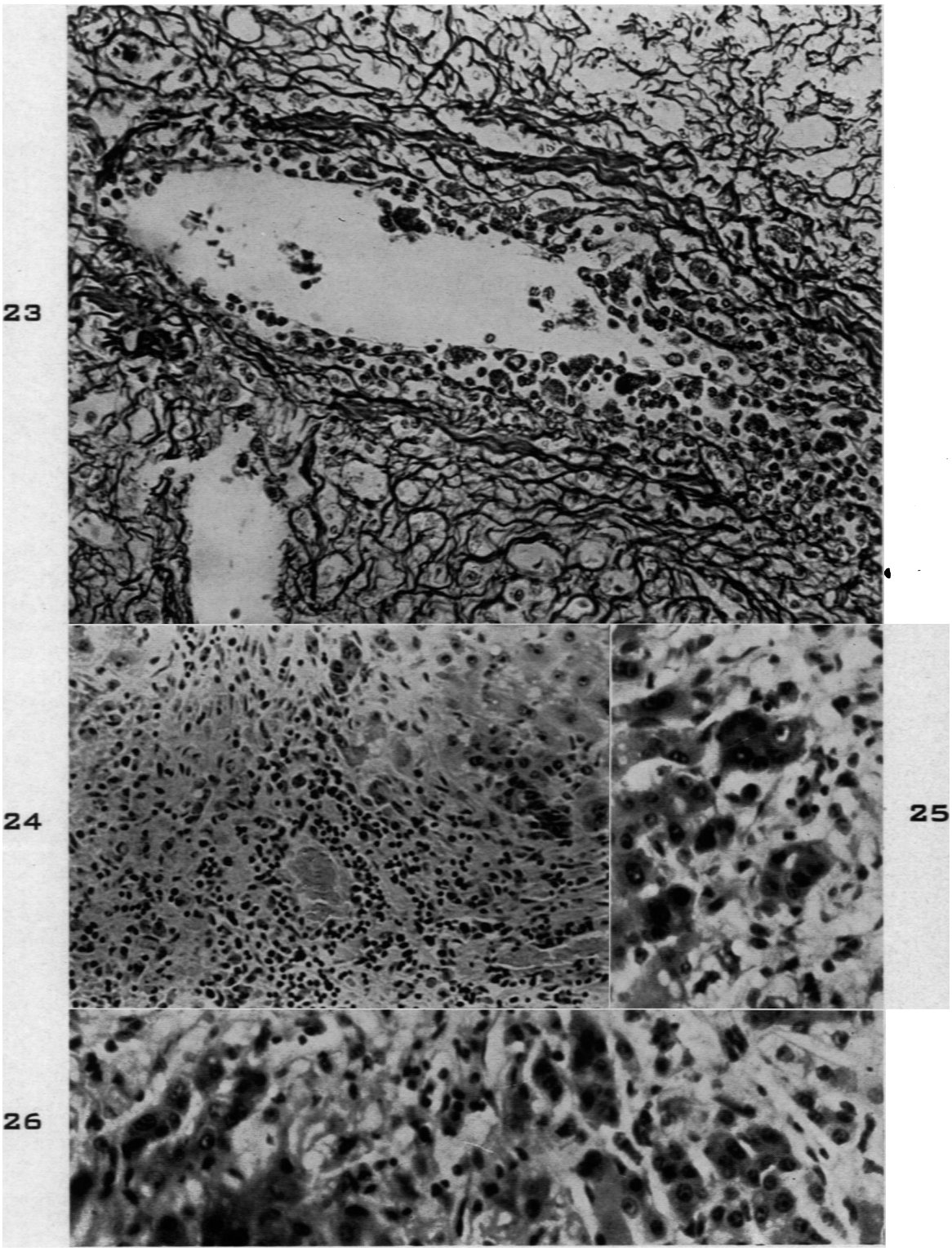
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PLATE 100

FIG. 27. Case 8. Duration of disease, 43 days. A large multinucleated liver cell from an area of regeneration. The section is taken from the nodular areas of regeneration shown grossly in Figure 3. × 300.

FIG. 28. Case 8. Duration of disease, 43 days. A multinucleated liver "giant" cell at higher magnification than in Figure 27. The cytoplasm of the cell contains granules of bile pigment. × 700.

FIG. 29. Case 53. Duration of disease, 34 days. A group of liver cells, which are arranged in such a disorderly manner as to simulate neoplasia. A number of cells are multinucleated. The cytoplasm of most cells has a granular appearance because of the presence of bile. × 200.

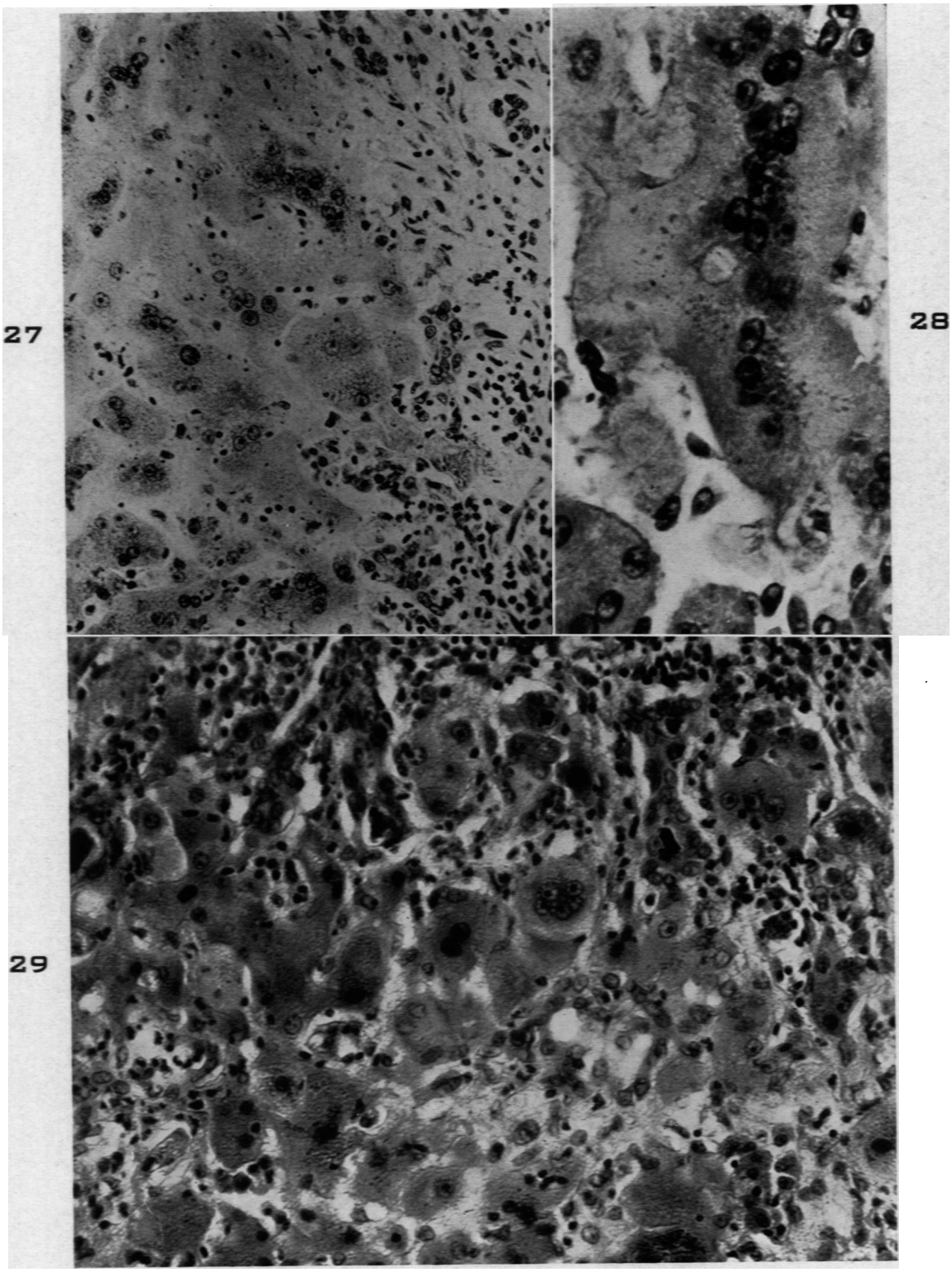
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PLATE 101

FIG. 30. Case 24. Duration of disease, 26 days. The photomicrograph shows the edge of a region of regenerative hyperplasia. The section was taken from the liver illustrated in Figure 1. The hyperplastic parenchyma has no orderly arrangement. Where complete destruction has occurred, the lobular outlines are still indicated by proliferating bile ducts. The empty stroma stains darkly because of excessive blood in the sinusoids. × 35.

FIG. 31. Case 81. Duration of disease, 19 days. The section has been taken from one of the yellow patches of regenerating "lobules" shown in Figure 2. The newly formed "lobules" are large, have an atypical structure and are noticeably ischemic. (Fig. 4 shows the microscopic appearance of the liver from this case in the regions of "red atrophy"; here the sinusoids are prominently distended.) × 50.

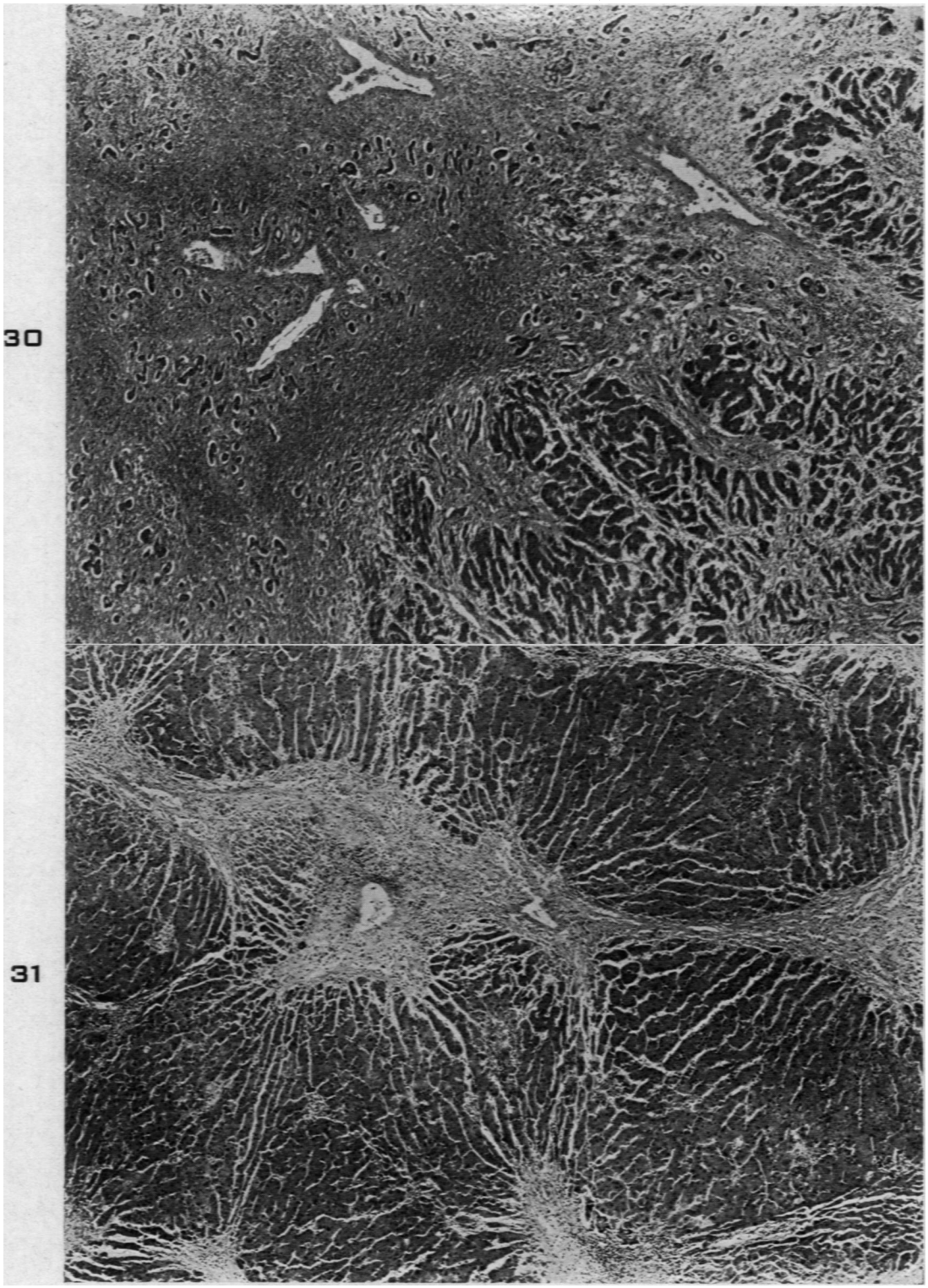
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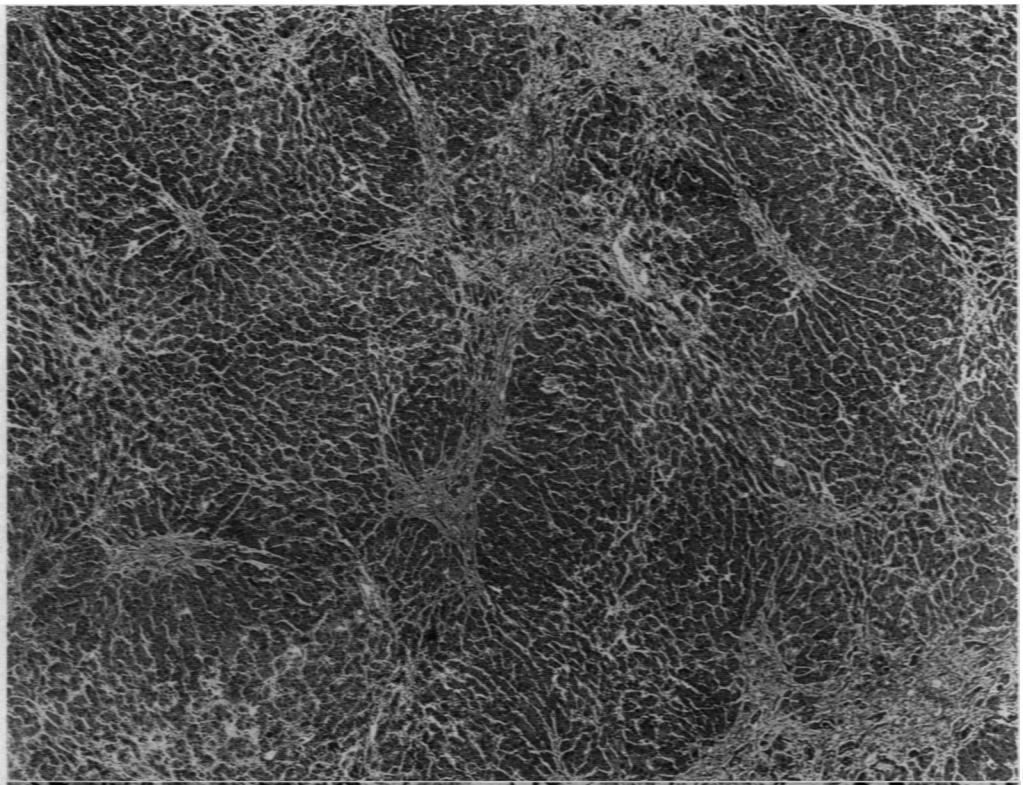
PLATE 102

FIG. 32. Case 84. Duration of disease, 93 days. Section from nodular areas shown grossly in Figure 11. Large, confluent patches of parenchyma are seen; there is no arrangement into definite lobules. (See Figs. 37 and 46 for higher magnification; the changes in the kidney from this case are shown in Figs. 60 and 61; the brain changes in Figs. 71 and 72.) × 35.

FIG. 33. Case 86. Duration of disease, 62 days. The reticulum framework and the columns of liver cells converge in normal manner toward the central lobular vein. (See Fig. 70 for changes in the brain.) × 200.

32



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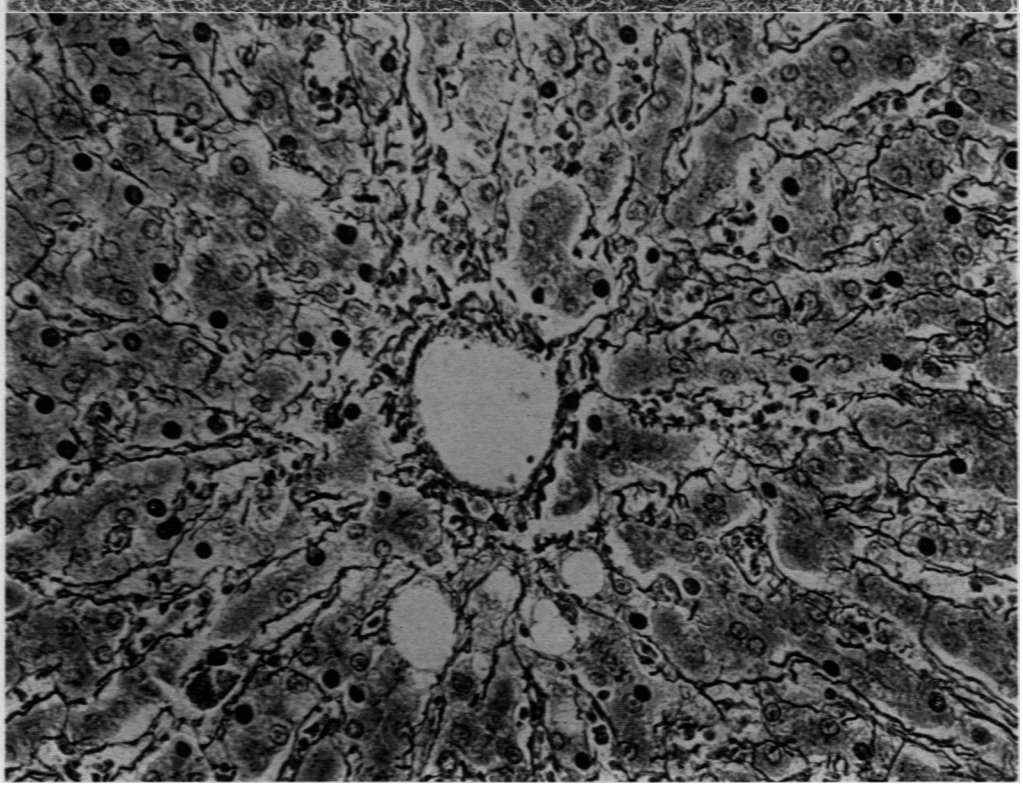

PLATE 103

FIG. 34. Case 93. Duration of disease, 76 days. A large hyperplastic "lobule," the central region of which is made up of atrophic and more or less disunited liver cells, whereas the cells at the periphery form columns. (Fig. 18, from the same case, shows a region of complete destruction of hepatic parenchyma, with preservation of the bile ducts.) × 60.

FIG. 35. Case 58. Duration of disease, 40 days. Secondary degeneration in an area of regenerative hyperplasia. Because of marked ischemia and perhaps other factors, the newly formed cells are undergoing degenerative changes. (The large size and hyperchromatic nuclei of the hyperplastic liver cells are noteworthy features.) A marked lymphocytic and polymorphonuclear reaction is seen in the stroma. × 200.

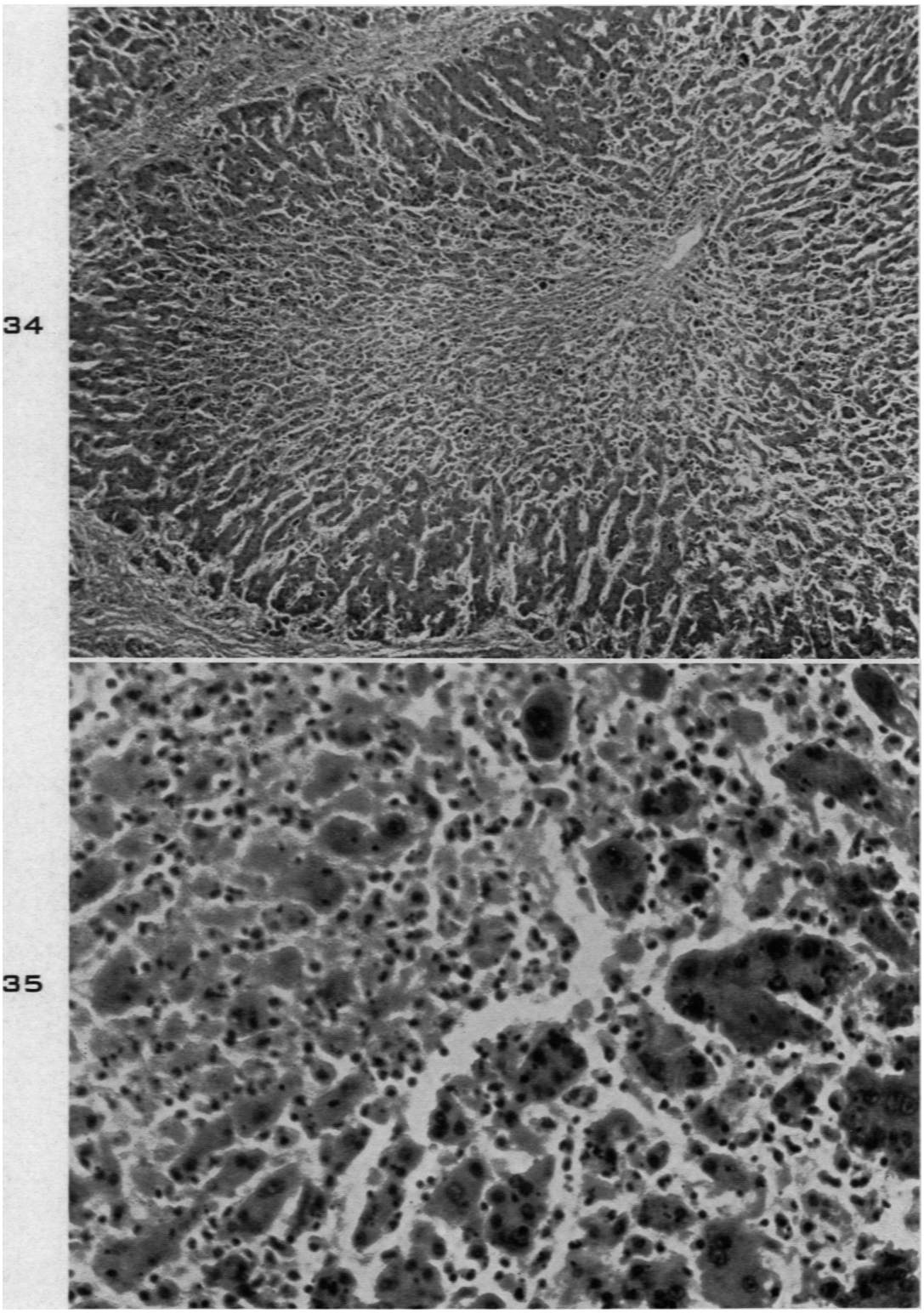

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PLATE 104

FIG. 36. Case 66. Duration of disease, 24 days. A multinucleated "giant" liver cell, the nuclei of which have prominent nucleoli. The latter must not be mistaken for intranuclear inclusion bodies. × 1000.

FIG. 37. Case 84. Duration of disease, 93 days. The bile canaliculus of an hepatic column is distended with a plug of inspissated bile. The liver cells are well preserved. (The gross appearance of this liver is shown in Fig. 11; for general structural changes see Figs. 5, 32 and 46; for lesions in the kidney, Figs. 60 and 61, and for brain changes, Figs. 71 and 72.) × 1000.

FIG. 38. Case 117. Duration of disease, 240 days. Section is stained with Wilder's reticulum stain. Near the center of the figure is seen a thick branching bile "thrombus"; several other bile "thrombi" lie within the nearby canaliculi; the individual liver cells contain coarse granules of bile. × 850.

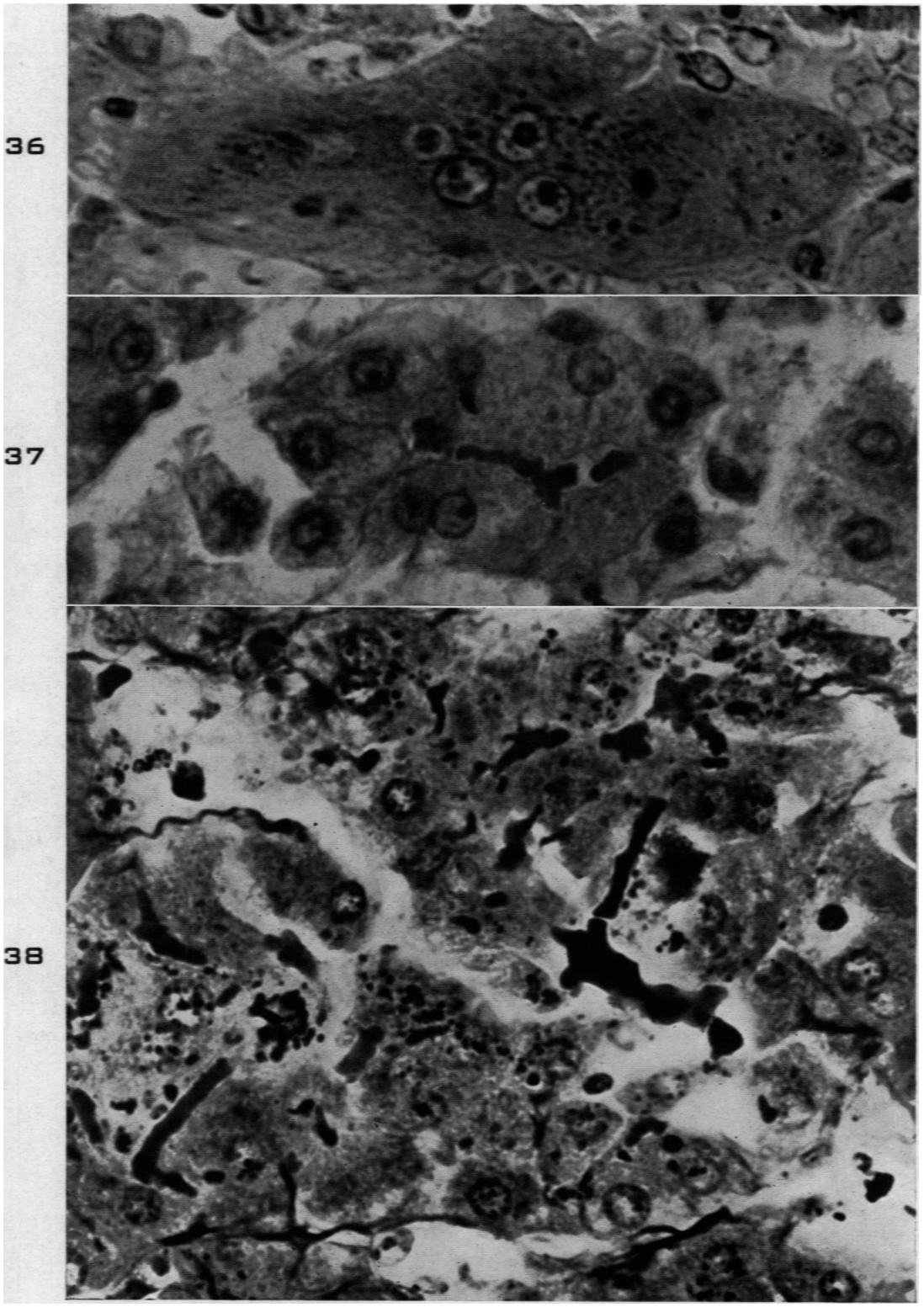
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PLATE 105

FIG. 39. Case 4. Duration of disease, 10 days. A portal triad with several large interlobular bile ducts having normal structure. The branches of the portal vein and hepatic artery likewise are normal. × 100.

FIG. 40. Case 15. Duration of disease, 14 days. Early budding of biliary ducts. The portal stroma is richly cellular. (Fig. 15 shows the extent of parenchymatous destruction in nearby parts of the liver of the same case.) × 125.

FIG. 41. Case 80. Duration of disease, 30 days. Proliferating bile duct at the periphery of a lobule. The lining cells have closely placed oval nuclei and scanty cytoplasm. × 350.

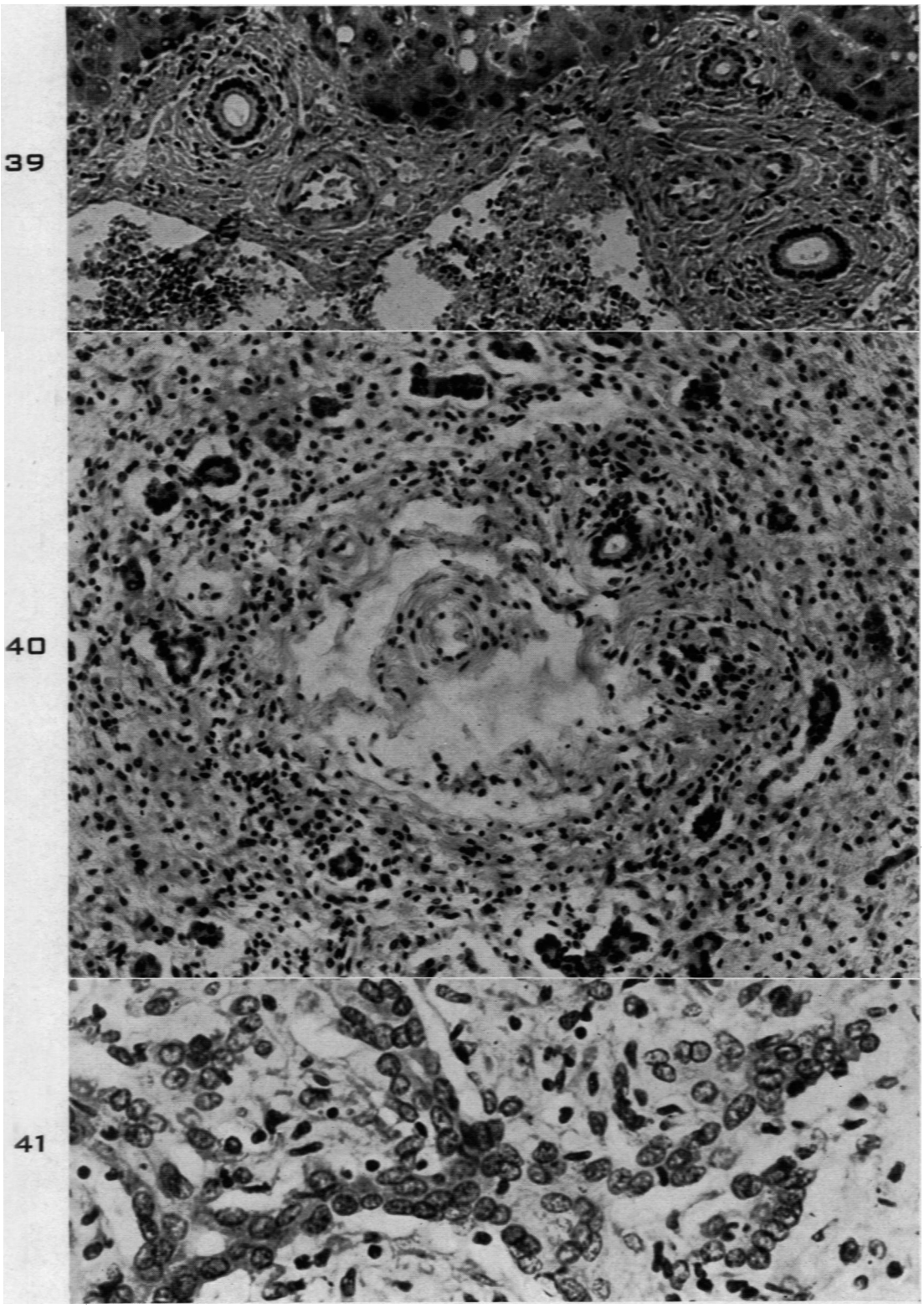
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PLATE 106

FIG. 42. Case 117. Duration of disease, 240 days. In regions in which the hepatic cells had been destroyed completely, proliferated small bile ducts remain in a richly vascular stroma. × 150.

FIG. 43. Case 46. Duration of disease, 15 days. Tubular structures at the periphery of a lobule; some parts of the tubules are lined by cells resembling bile duct epithelium, whereas other parts are lined by elements resembling liver cells. × 400.

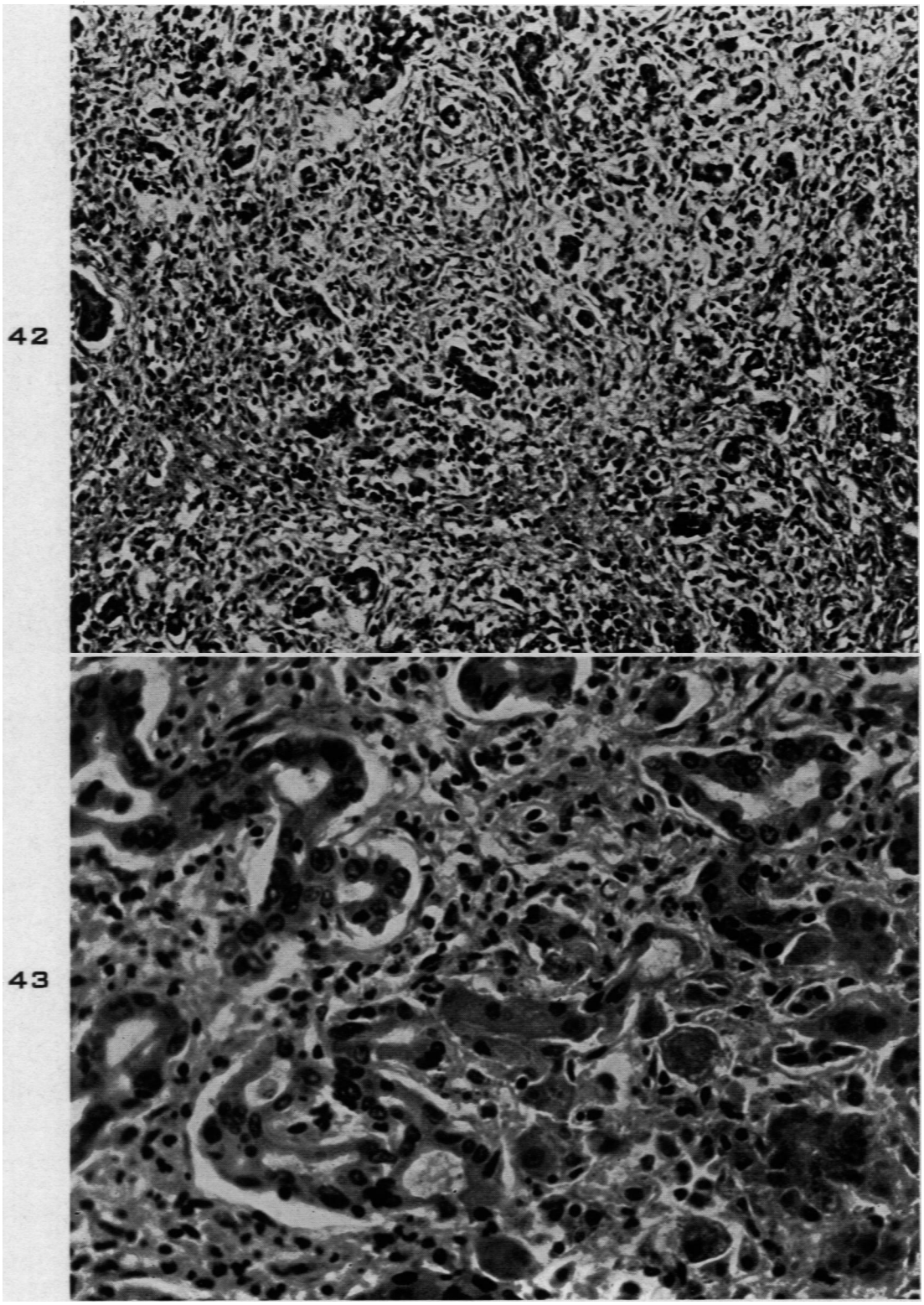
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PLATE 107

FIG. 44. Case 92. Duration of disease, 69 days. Two large clumps of bile, one lying in a widely dilated intracolumnar canaliculus, the other in a tubule apparently lined by biliary epithelium. (See Fig. 9 for gross appearance of liver, and Fig. 59 for changes in kidney.) × 550.

FIG. 45. Case 113. Duration of disease, 154 days. The lumina of tubular structures at the periphery of lobular remnants contain clumps of bile. It is impossible to be sure whether these tubules are composed of biliary epithelium or of liver cells. × 350.

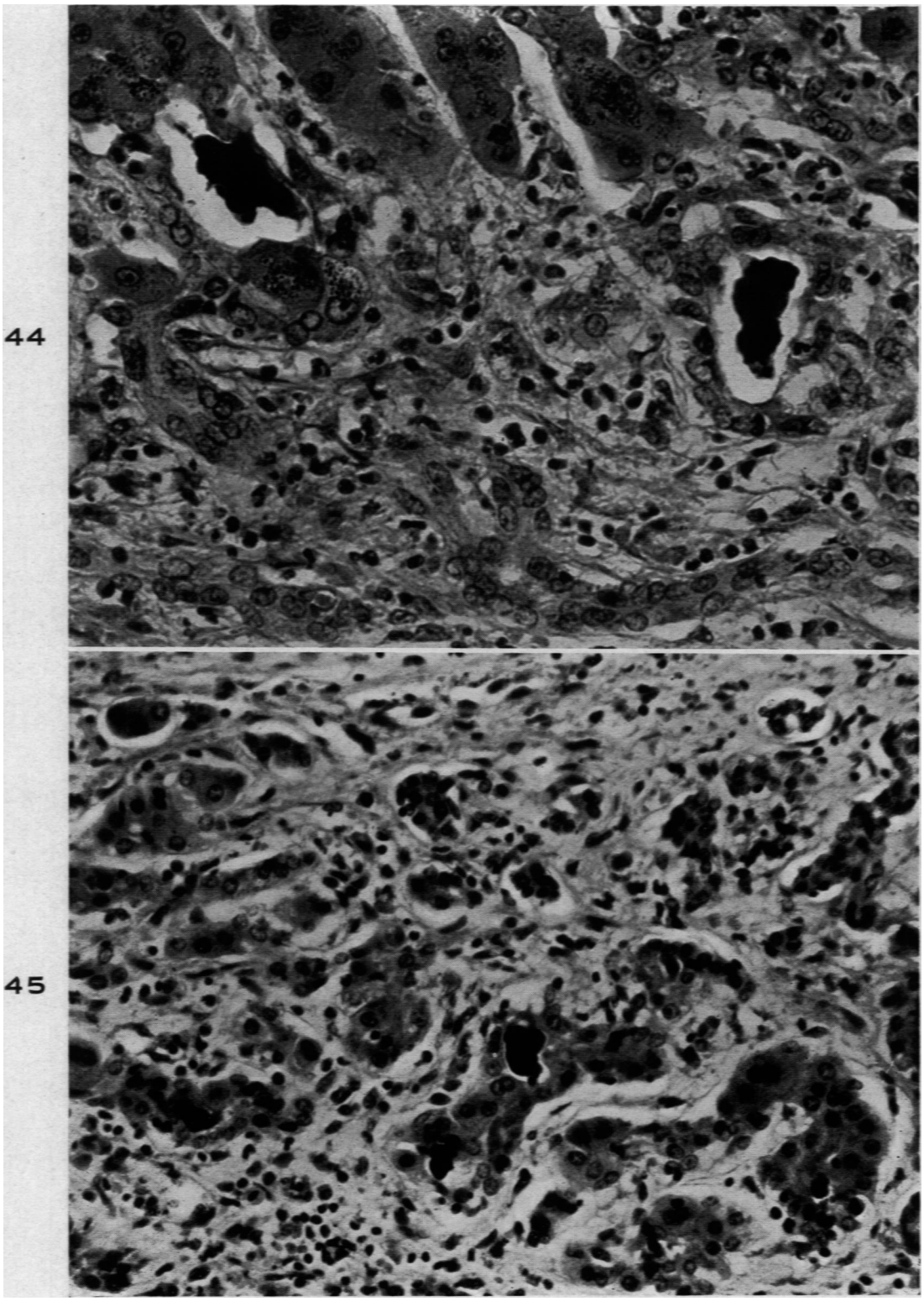
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PLATE 108

FIG. 46. Case 84. Duration of disease, 93 days. The cells of the regenerated tubules closely resemble liver cells. Whether these cells are derived from biliary epithelium or from pre-existing liver cells is debatable. (See also Figs. 5, 11, 32, 37, 60, 61, 71 and 72 for photographs of other lesions in this case.) × 550.

FIG. 47. Case 104. Duration of disease, 98 days. A cluster of tubules lined by liver cells lies at the periphery of a lobule. The location and appearance of the tubules suggest that they have been derived from bile ducts. (See also Fig. 7 from the same case which shows a branching bile duct connected with regenerated columns of liver cells.) × 300.

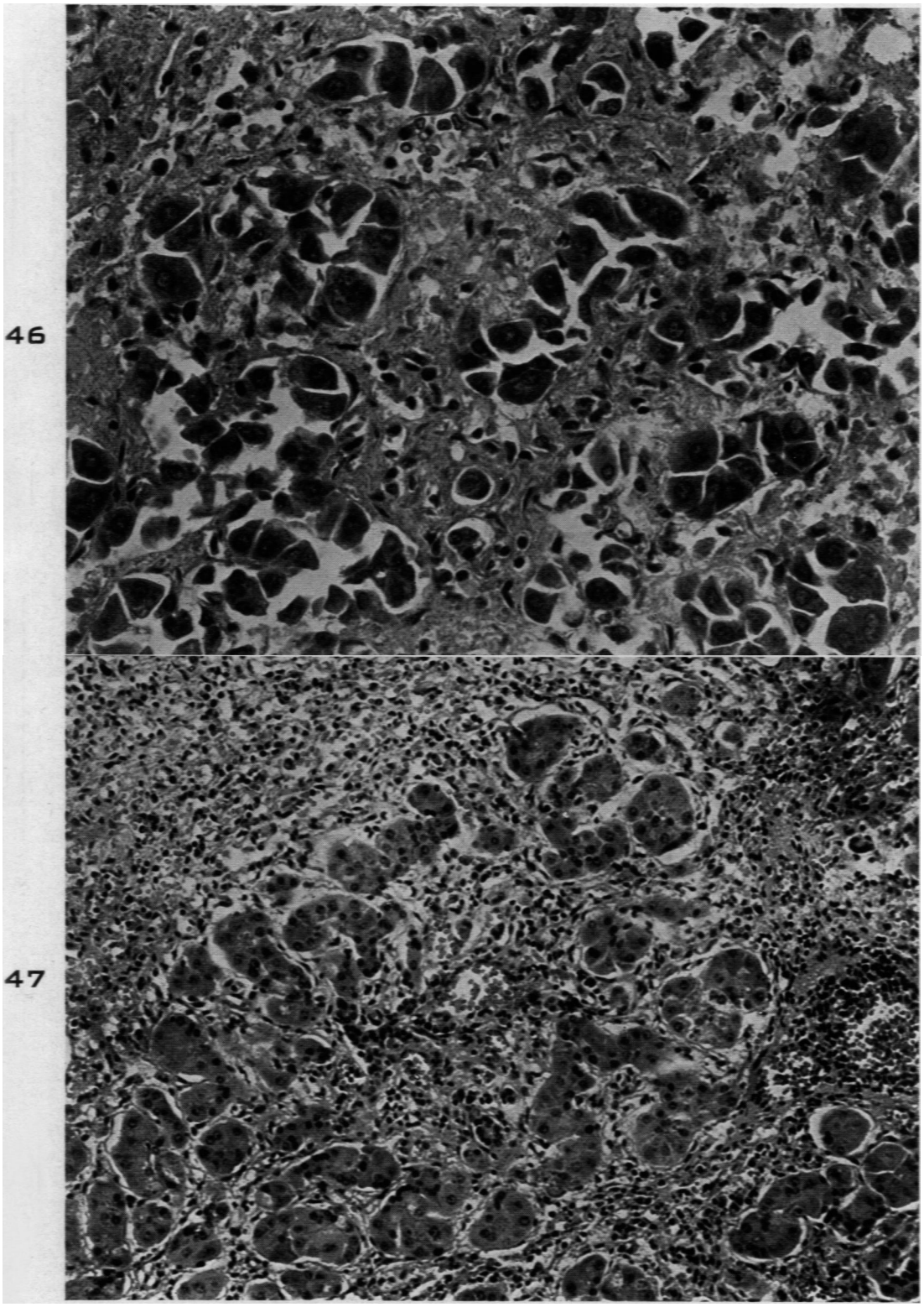

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PLATE 109

FIG. 48. Case 22. Duration of hepatitis, 17 days. Cecum. The tissue is extremely edematous; the mucosa is thrown into thick folds. (See Fig. 51 for microscopic appearance.)

FIG. 49. Case 11. Duration of hepatitis, 64 days. Transverse sections of lower ileum showing edematous thickening of wall and of mesenteric attachment.

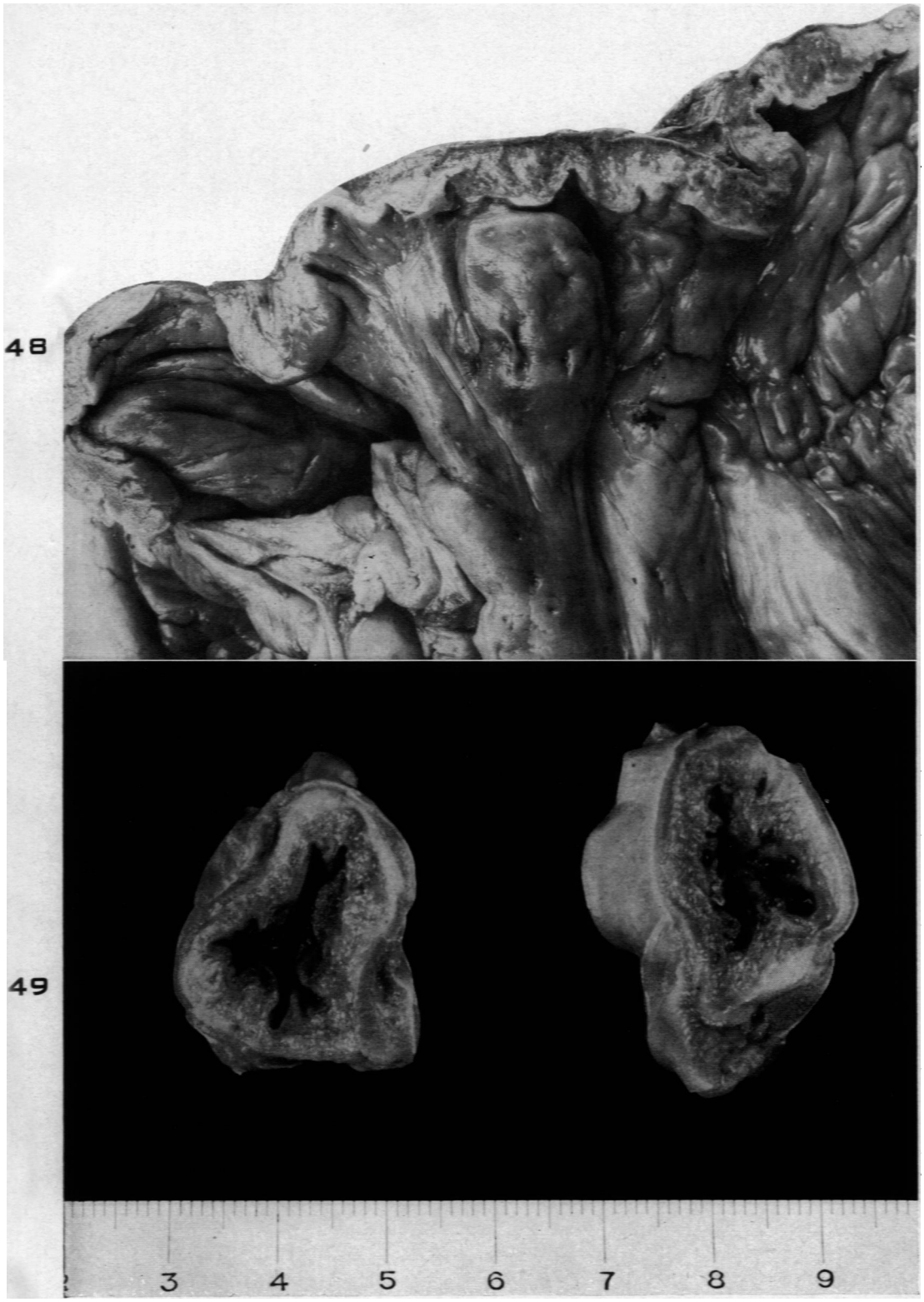
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PLATE 110

FIG. 50. Case 43. Duration of hepatitis, 20 days. Low-power view of colon to show marked inflammatory edema of submucosa. The mucosa is intact. (See Fig. 52 for details of cellular reaction.) × 10.

FIG. 51. Case 22. Duration of disease, 17 days. Low-power view of cecum shown in Figure 48. There is marked phlegmonous inflammation which is especially pronounced in the submucosa. The mucosa is preserved. × 10.

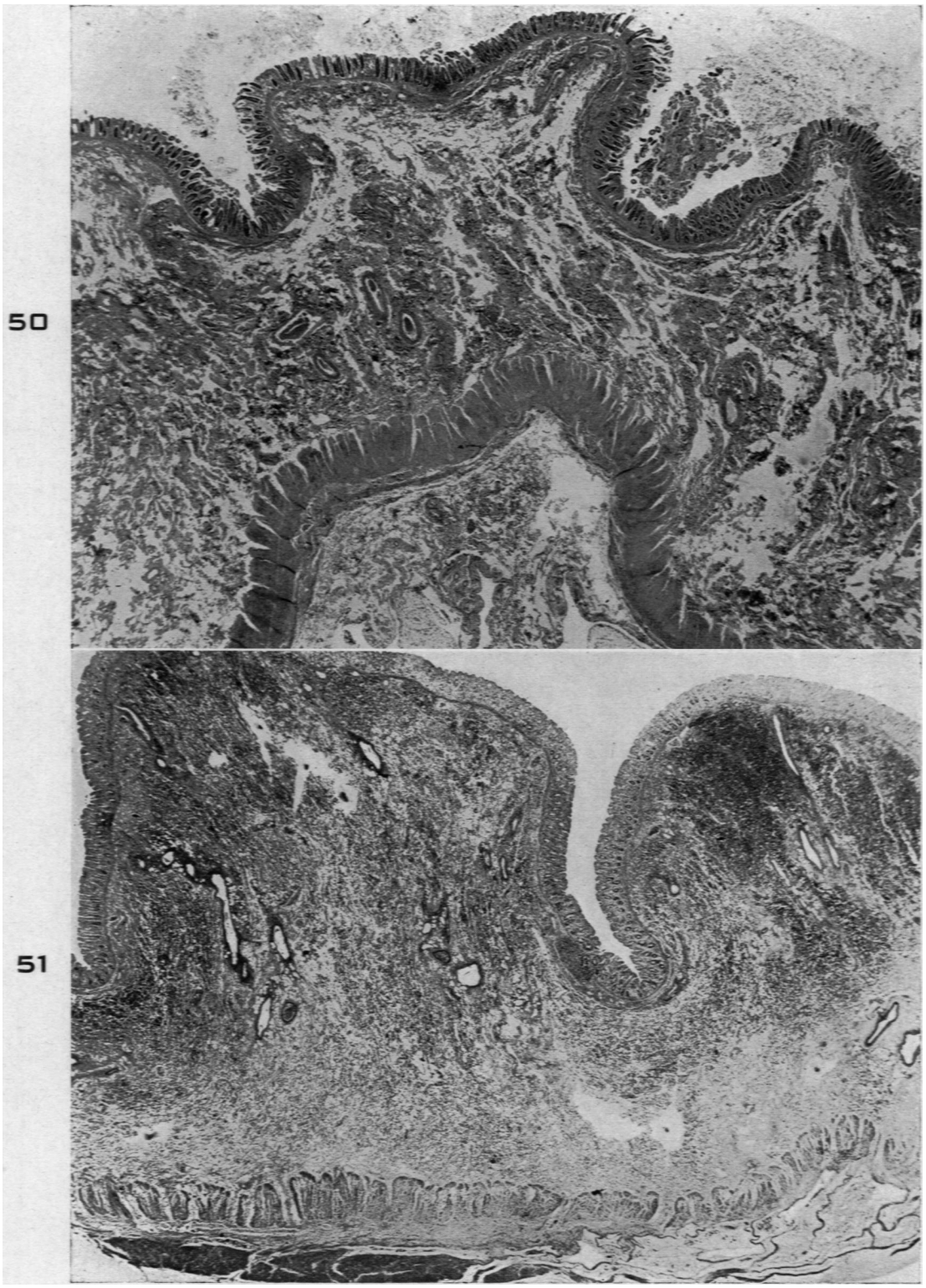
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PLATE 111

FIG. 52. Case 43. Duration of hepatitis, 20 days. Details of inflammatory edema of wall of cecum shown in Figure 50. The tissue is widely distended and everywhere invaded by polymorphonuclear leukocytes and macrophages. × 550.

FIG. 53. Case 94. Duration of hepatitis, 50 days. A low-power view of ileum showing marked distention of submucosa by edema. No inflammatory reaction is present. The mucosa is preserved. × 12.

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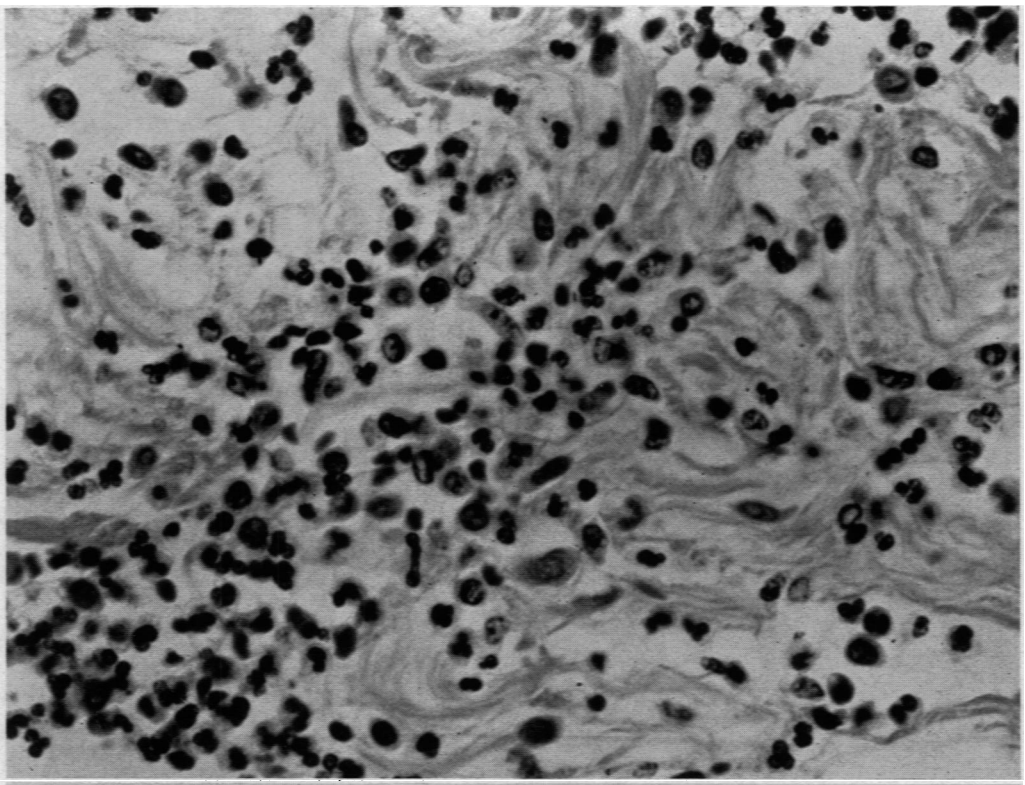

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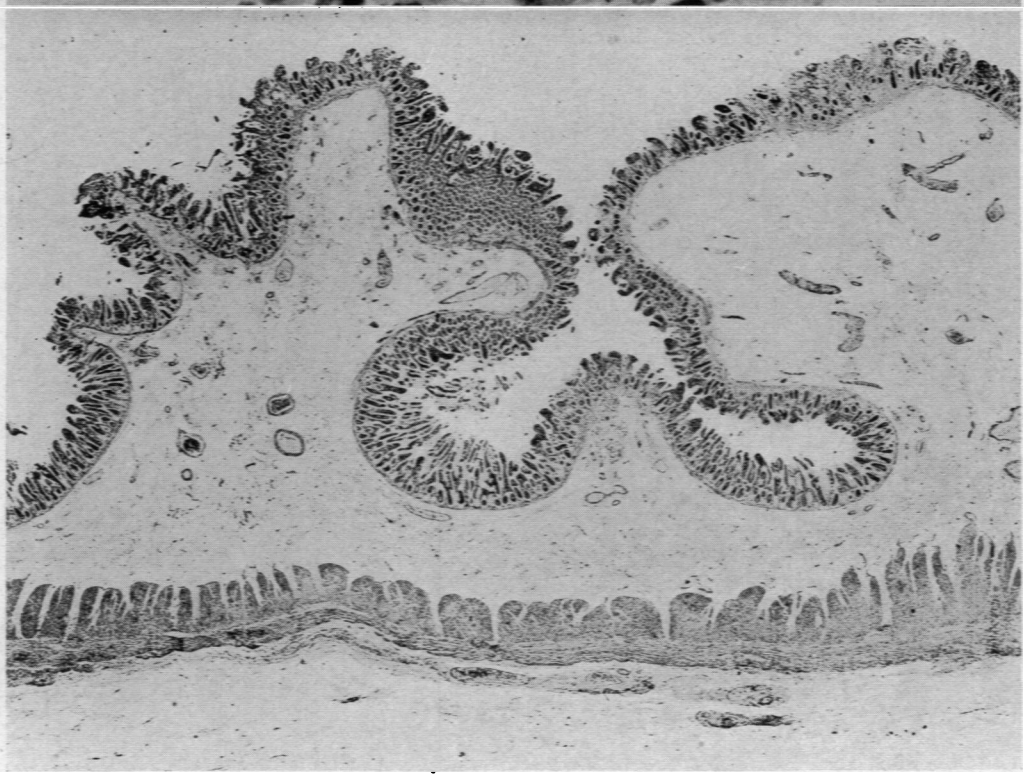

PLATE 112

FIG. 54. Case 8. Duration of hepatitis, 43 days. Ulceration of lower portion of esophagus with inflammatory reaction extending into deeper layers. (A gross photograph of the liver from this case is shown in Fig. 3, and the microscopic appearance of the liver in Figs. 27 and 28.) × 75.

FIG. 55. Case 39. Duration of hepatitis, 34 days. Gallbladder showing marked edema and hemorrhages in mucosa. × 25.

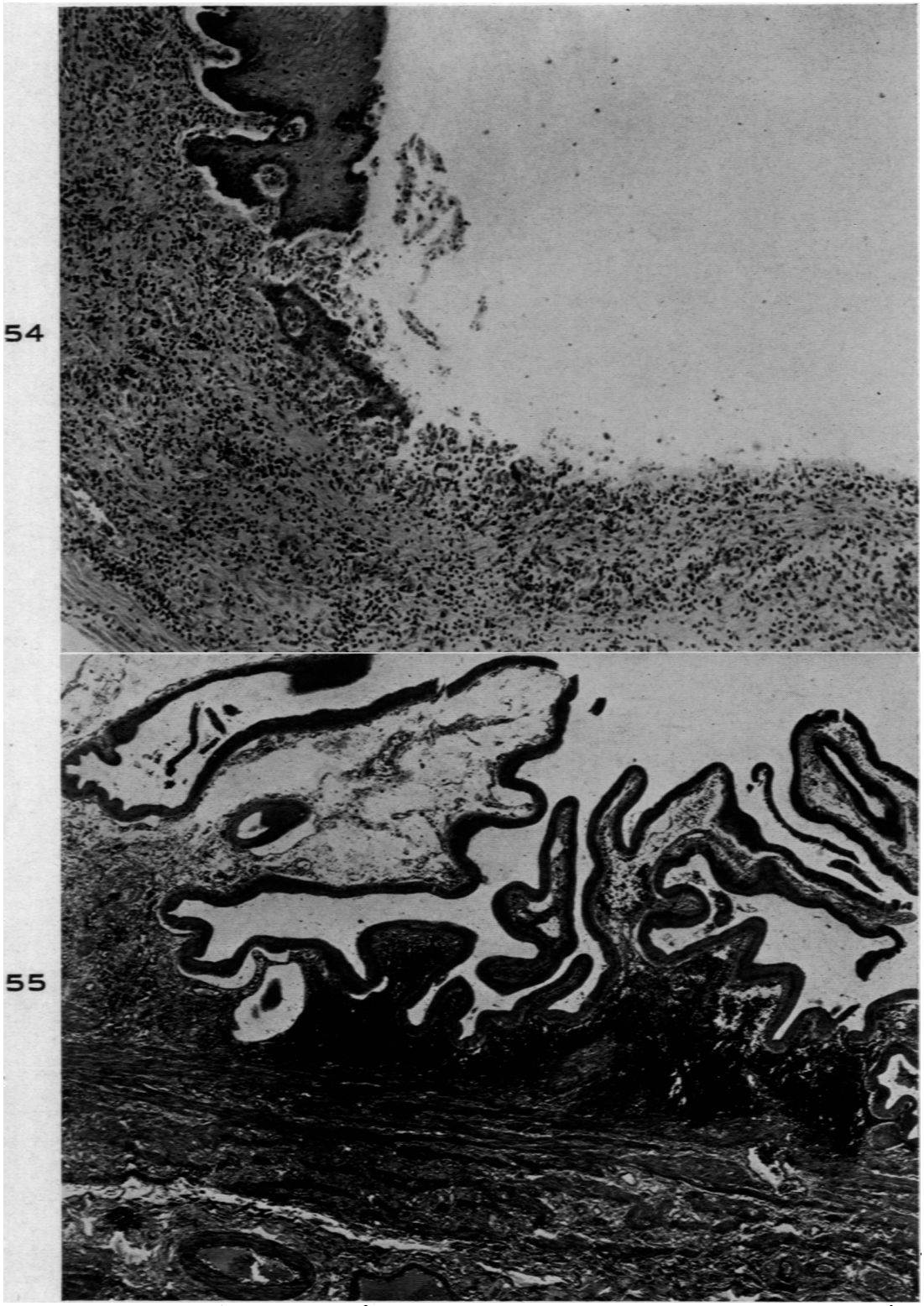

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PLATE 113

FIG. 56. Case 43. Duration of hepatitis, 20 days. Spleen. Hyperplasia of a follicle and of lymphoid tissue in pulp. × 50.

FIG. 57. Case 80. Duration of hepatitis, 30 days. Spleen. Marked engorgement of sinusoids, the walls of which have a rigid appearance. (See Figs. 19 and 41 for changes in the liver.) × 80.

FIG. 58. Case 108. Duration of hepatitis, 39 days. Spleen, showing depletion of lymphoid tissue; the follicle is atrophic. The sinusoids have rigid walls. × 50.

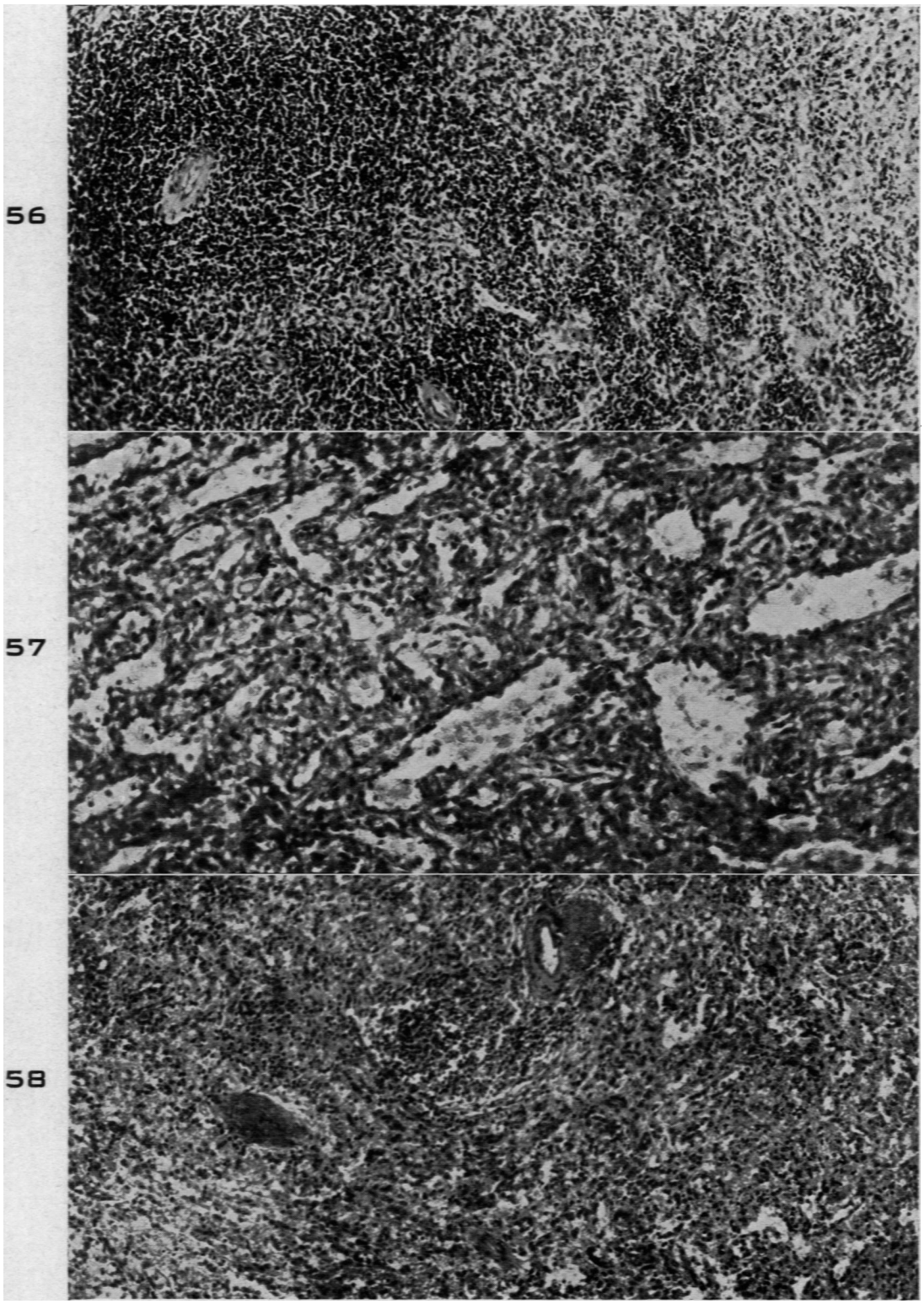
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PLATE 114

FIG. 59. Case 92. Duration of hepatitis, 67 days. Kidney, showing an intact glomerulus, and many tubules with bile casts. (A gross photograph of the liver of this case is shown in Fig. 9, and a photomicrograph in Fig. 44.) × 125.

FIG. 60. Case 84. Duration of hepatitis, 93 days. Several tubules are blocked with necrotic cells, beneath which is seen flat epithelium indicative of early regeneration. × 550.

FIG. 61. From the same case as Figure 60. In this tubule the necrotic cells have been removed. The lining epithelium is flat and has the appearance characteristic of early regeneration. × 375.

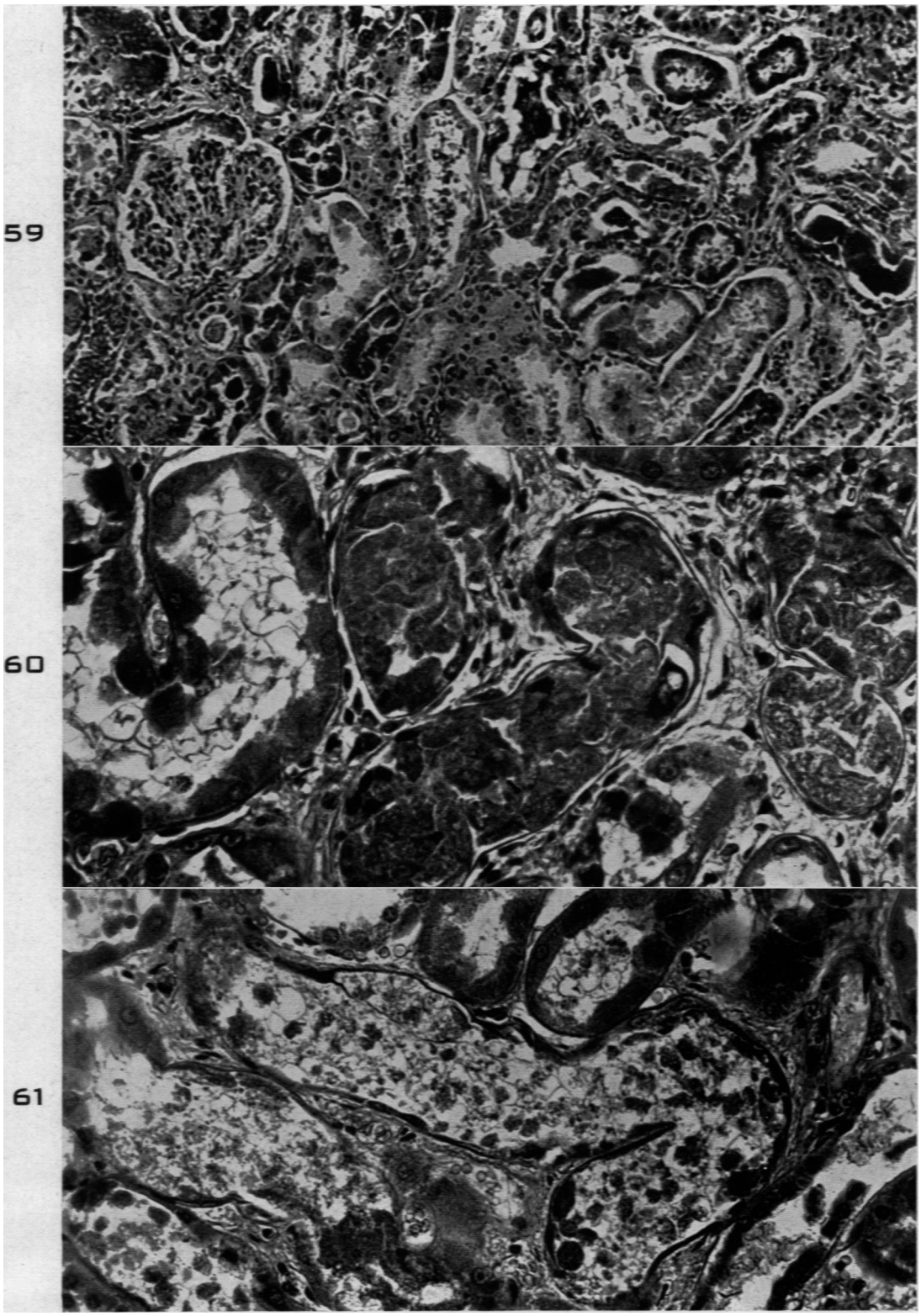
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Plate 115

Fig. 62. Case 24. Duration of hepatitis, 36 days. Heart showing petechiae of epicardium and ecchymosis beneath the endocardium of the interventricular septum, near the bases of the aortic cusps.

Fig. 63. Colon with mesocolon and epiploic appendages, from case 24. An extensive hemorrhage is seen in the mesocolon.

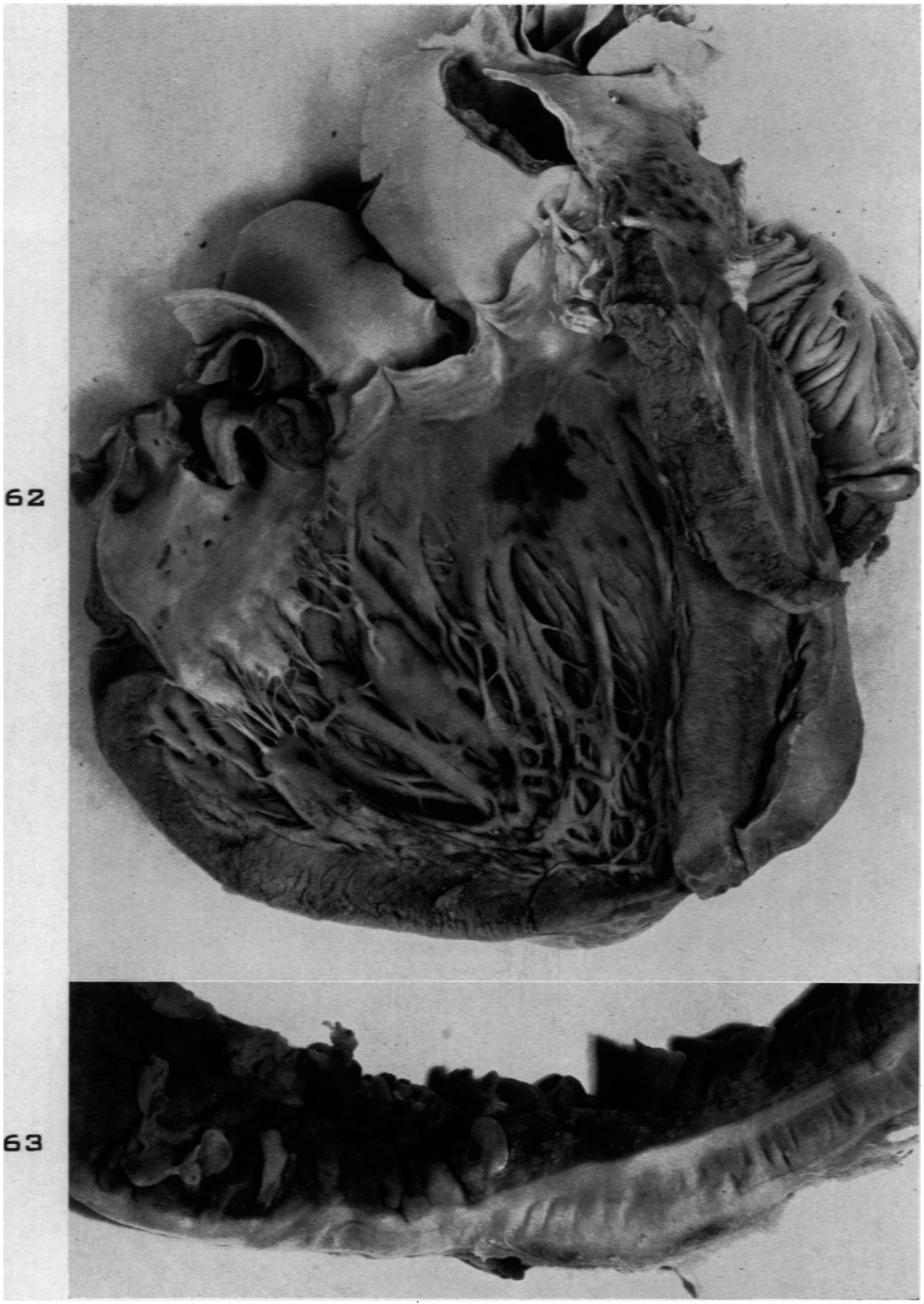

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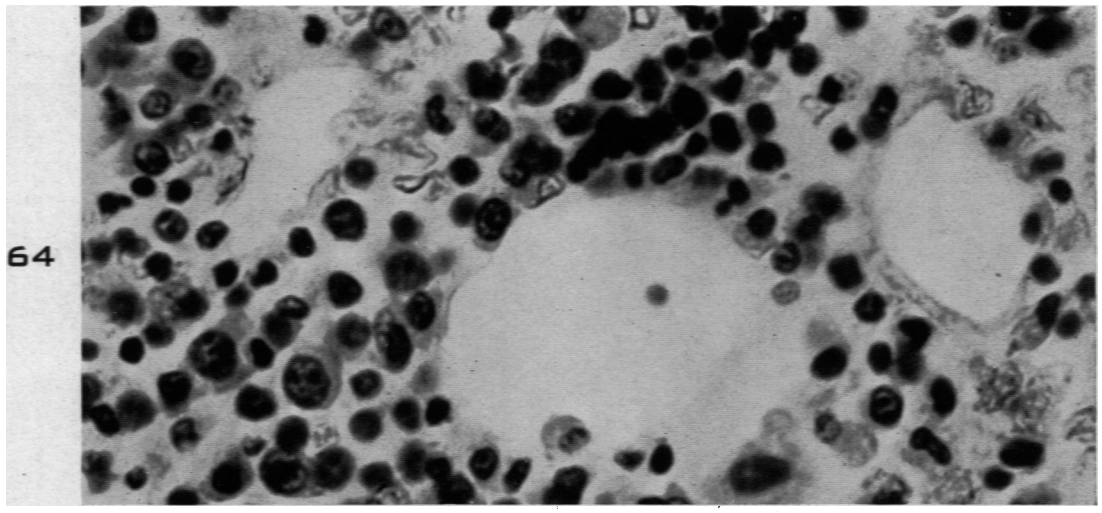
PLATE 116

FIG. 64. Case 94. Duration of hepatitis, 50 days. Bone marrow, showing a moderate degree of hyperplasia, particularly of the red cell series. × 450.

FIG. 65. Case 71. Duration of hepatitis, 49 days. Bone marrow, showing diffuse hyperplasia, particularly of the myeloid elements. × 450.

FIG. 66. Case 67. Duration of disease, 19 days. Bone marrow, showing marked hyperplasia, particularly of the red cell series. × 450.



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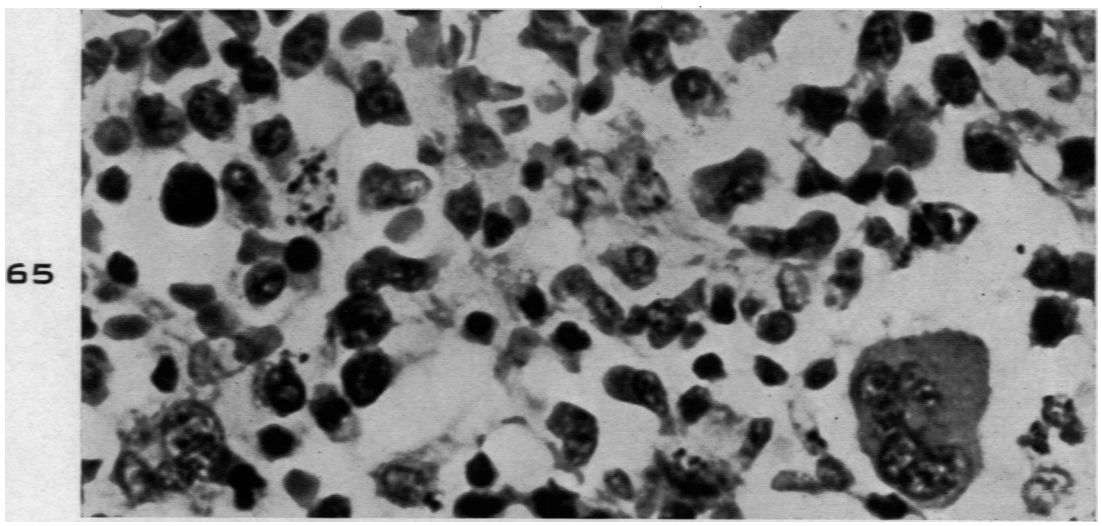

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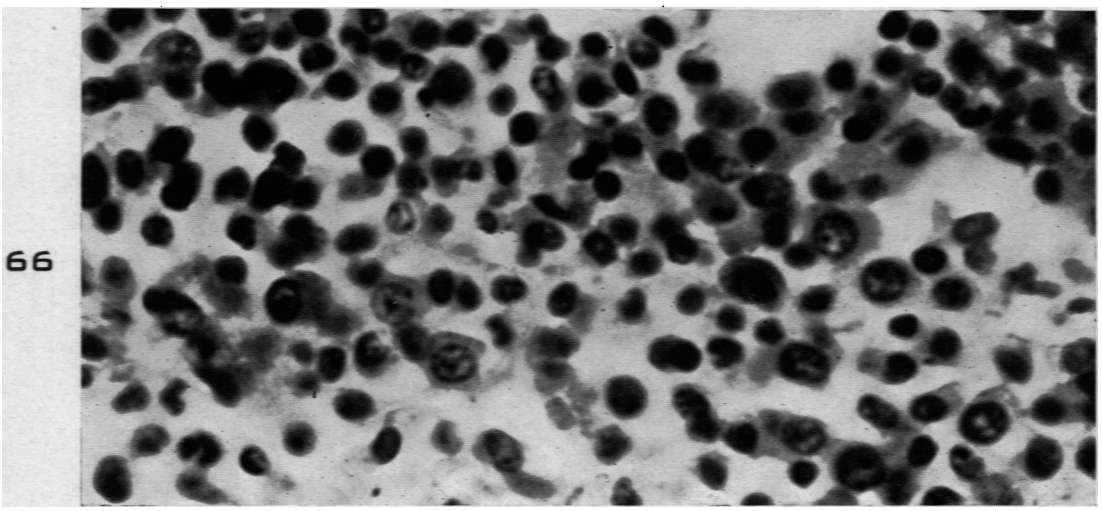

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PLATE 117

FIG. 67. Case 76. Duration of hepatitis, 96 days. Base of brain; section through nucleus basalis. The ganglion cells show various stages of disintegration. There is no glial reaction. (For other changes in the brain of this case see Figs. 68, 69 and 76; the gross appearance of the liver is shown in Fig. 12, and a photomicrograph in Fig. 20.) × 200.

FIG. 68. Case 76. Brain; third layer of cortex. The photomicrograph shows three large ganglion cells. The upper cell has a broad apical dendrite and a well preserved nucleus and nucleolus. In the middle cell the apical dendrite is broadened; the nucleus has almost disappeared; the chromatin has been largely dissolved. The lower cell has been converted into a "ghost." (See Fig. 67.) × 800.

FIG. 69. Case 76. Brain; section through midcortex. The ganglion cells have shrunken, densely staining bodies. The apical dendrites are prominent and tortuous. The change corresponds to "chronic" cell degeneration. (See Fig. 67.) × 680.

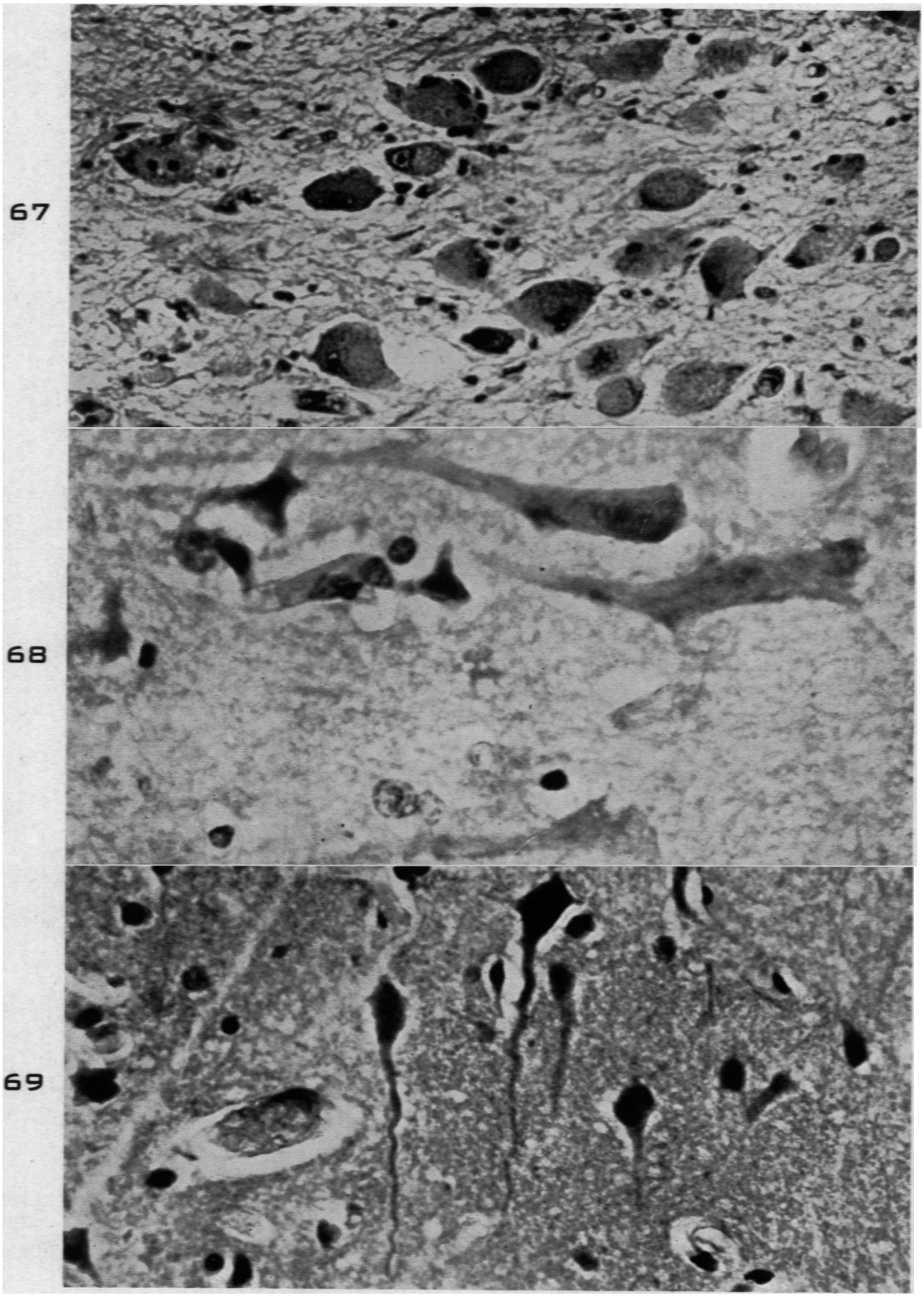
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PLATE 118

FIG. 70. Case 86. Duration of hepatitis, 86 days. Brain; section through medulla oblongata. Invasion of a disintegrated ganglion cell by glial elements (neuronophagia). × 1000.

FIG. 71. Case 84. Duration of hepatitis, 93 days. Brain; section through nucleus basalis. A disintegrated ganglion cell invaded by glial elements (neuronophagia). A nearby ganglion cell is intact. (Gross appearance of liver from this case is shown in Fig. 11, and photomicrographs in Figs. 5, 32, 37 and 46.) × 435.

FIG. 72. Case 84. Brain; section through nucleus basalis. A small glial nodule has replaced a destroyed ganglion cell. The ganglion cells shown in the photomicrograph are in varying stages of degeneration. × 435.

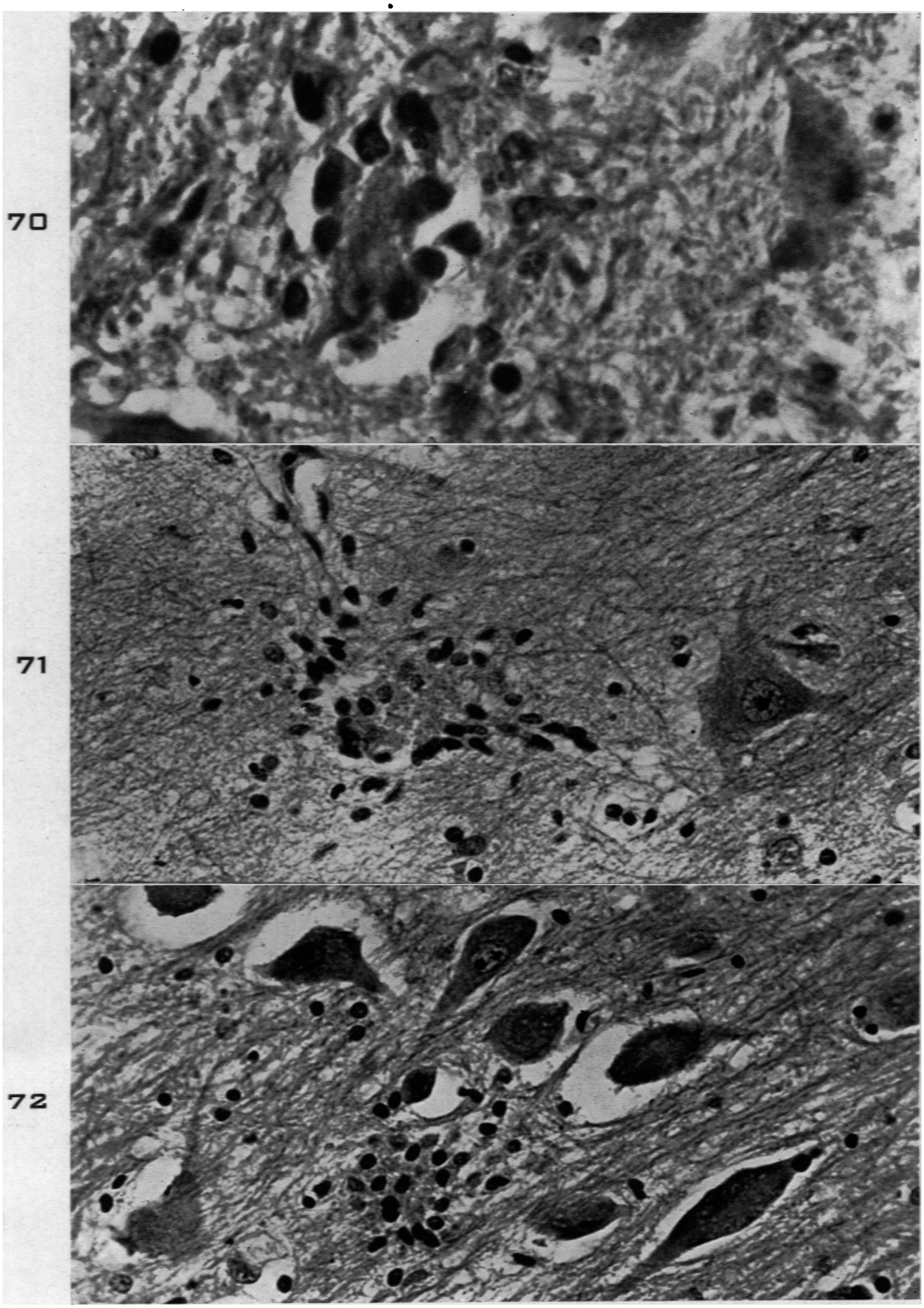
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PLATE 119

FIG. 73. Case 124. Duration of hepatitis, 37 days. Brain; periventricular system adjacent to thalamus with perivascular lymphocytic infiltration. The vessel involved is located beneath the ependyma of the third ventricle. (For reaction in meninges see Fig. 75; gross appearance of liver is shown in Fig. 10.) × 300.

FIG. 74. Case 78. Duration of hepatitis, 64 days. Tegmentum of pons. Slight perivascular lymphocytic infiltration. This represents the average degree of perivascular infiltration observed in the present series. × 175.

FIG. 75. Case 124. Brain. Mild degree of lymphocytic infiltration in leptomeninges; subpial edema. (See Fig. 73.) × 200.

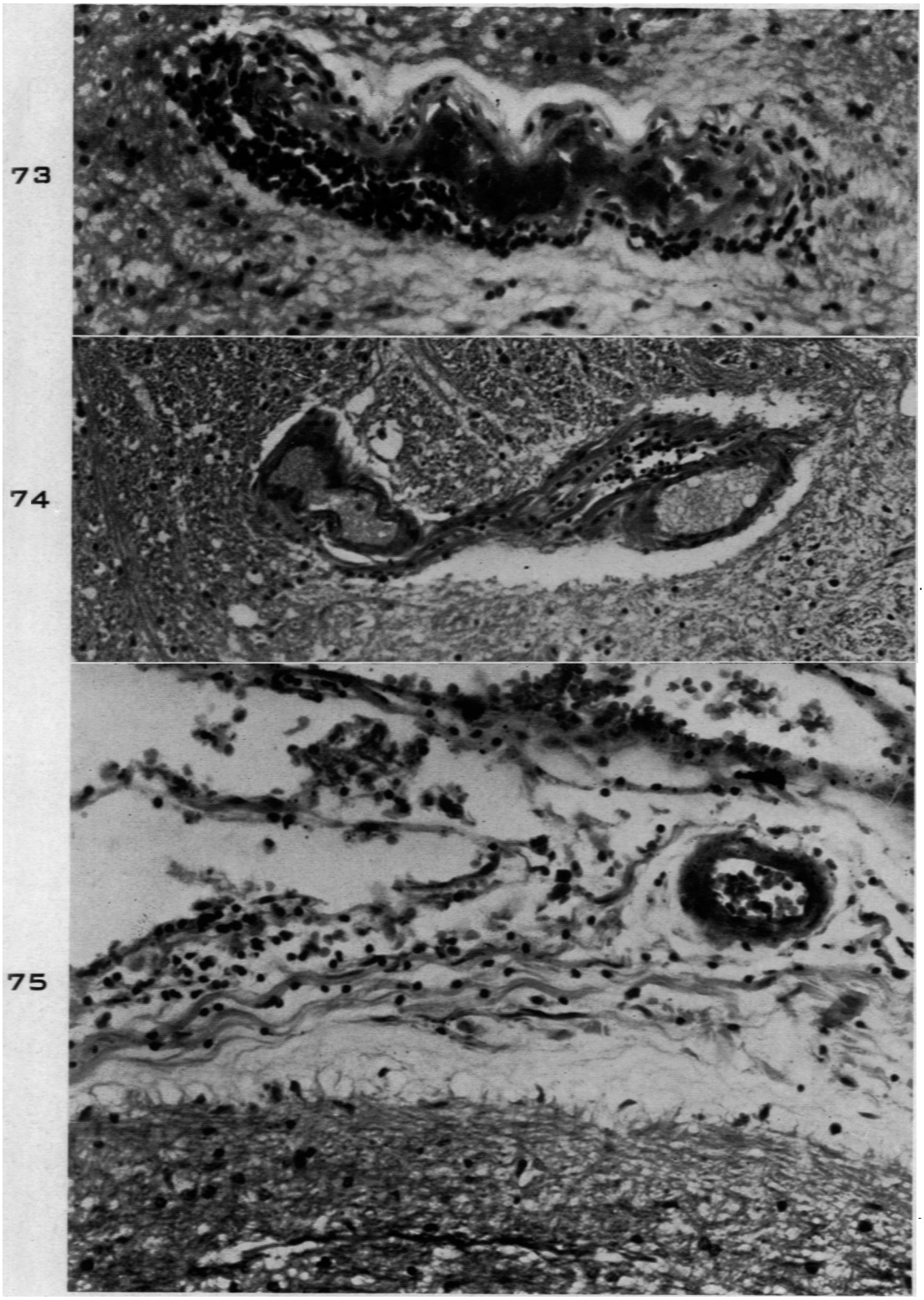
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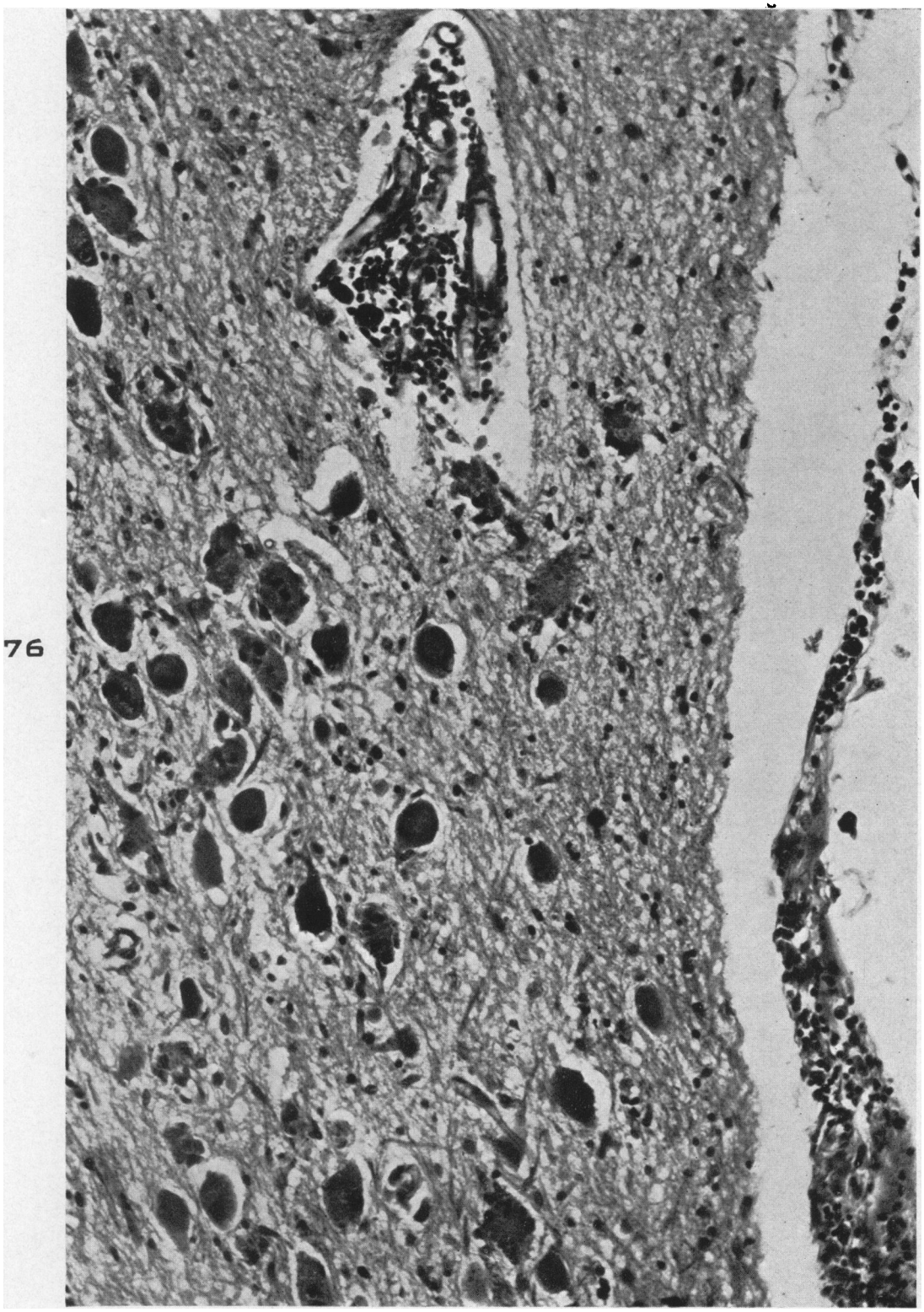
PLATE 120

FIG. 76. Case 76. Duration of hepatitis, 96 days. Brain; section through nucleus basalis lateral to anterior hypothalamic region. The meninges are infiltrated to a moderate degree with lymphocytes and histiocytes. In the subjacent cortex a similar infiltrate is noted around a small vessel. In nearly all ganglion cells the cytoplasm is swollen; in many the nucleus is shrunken and distorted. Around a few of the more disintegrated cells, satellitosis is evident. (See Figs. 67 to 69 for details of changes in ganglion cells.) × 240.



Lucké Pathology of Fatal Epidemic Hepatitis