THE AMERICAN JOURNAL OF PATHOLOGY

VOLUME XXII SEPTEMBER, 1946 NUMBER 5

THE FULMINANT FORM OF EPIDEMIC HEPATITIS *

BALDUIN LUCKÉ, Colonel, M.C., and TRACY MALLORY, Lt. Col., M.C.

(From the Army Institute of Pathology, Washington 25, D.C.)

CONTENTS

* Received for publication, May 8, 1946.

INTRODUCTION

Epidemic hepatitis has attained pandemic proportions during this war. Large outbreaks have occurred in many parts of the world and in the armies of a number of nations.[1-23] The pathology of this disease as observed in the Army of the United States during the epidemic of 1942 has been dealt with in previous papers.[24, 25] More recently, an acute form of epidemic hepatitis of intense severity terminating fatally in less than 10 days has become prevalent; this we have termed the fulminant form. In a new series of 196 fatal cases occurring between August, 1943, and April, 1945, which we have studied at the Army Institute of Pathology, over half fall into this category. By contrast, in the previous series not a single equally fulminant case was encountered, and only one was reported in the great Swedish epidemic of 1927;[26] the usual duration of the fatal disease was then from 4 to 6 weeks; in other words, the course of fatal hepatitis was predominantly subacute. These divergences in duration reflect striking differences in the pertinent pathologic changes. Thus, in the more fulminant form, the parenchyma of the liver is destroyed completely and uniformly, and this destructive process is accompanied by an intense inflammatory reaction. In the more subacute form seen in 1942 and also in approximately one-fourth of the 1943–1945 series, destruction of the liver is incomplete, the involvement characteristically not uniform, regenerative hyperplasia of surviving parenchyma leads to the production of much new tissue, and inflammation is less pronounced.

Another significant difference is in the epidemiology. In 1942, hepatitis in many instances followed administration of yellow fever vaccine containing human serum. In the new series, such vaccine had not been used; but nearly one-half of the patients had sustained combat trauma. Since seriously wounded patients customarily received transfusion of whole blood, serum, or plasma, it may be assumed that a high proportion of the wounded in this series were thus treated. But it is not known in how many the causal agent of hepatitis was introduced by therapeutic procedures, especially as in several theaters of war large epidemics of hepatitis were prevalent. It is, therefore, an assumption to regard all the wounded cases as examples of "homologous serum hepatitis." This assumption is justified largely by the relatively long interval between date of wound (and presumably of first transfusion) and the clinical manifestation of the disease. The nonwounded cases, comprising approximately one-half of the series, represent both the epidemic and the endemic variants of "naturally" occurring hepatitis.

This study complements the previous report on the pathology of epi-

demic hepatitis [24] and gives a more comprehensive picture of the disease. It is based primarily on 94 fulminant cases in which the clinical duration did not exceed 9 days; however, 39 others with duration of from 10 to 19 days have been used to supply additional information on certain aspects of the disease. This latter group contains many examples indistinguishable from the fulminant form.

The scope and arrangement of this paper are outlined in the table of contents. The methods of study were similar to those employed in the earlier investigations at the Army Institute of Pathology.

Duration of Fatal Hepatitis

Of the 196 cases studied, the duration of the disease could be determined with fair accuracy in 178. In the remainder the records were inadequate, or the discrepancy between the clinical accounts and the

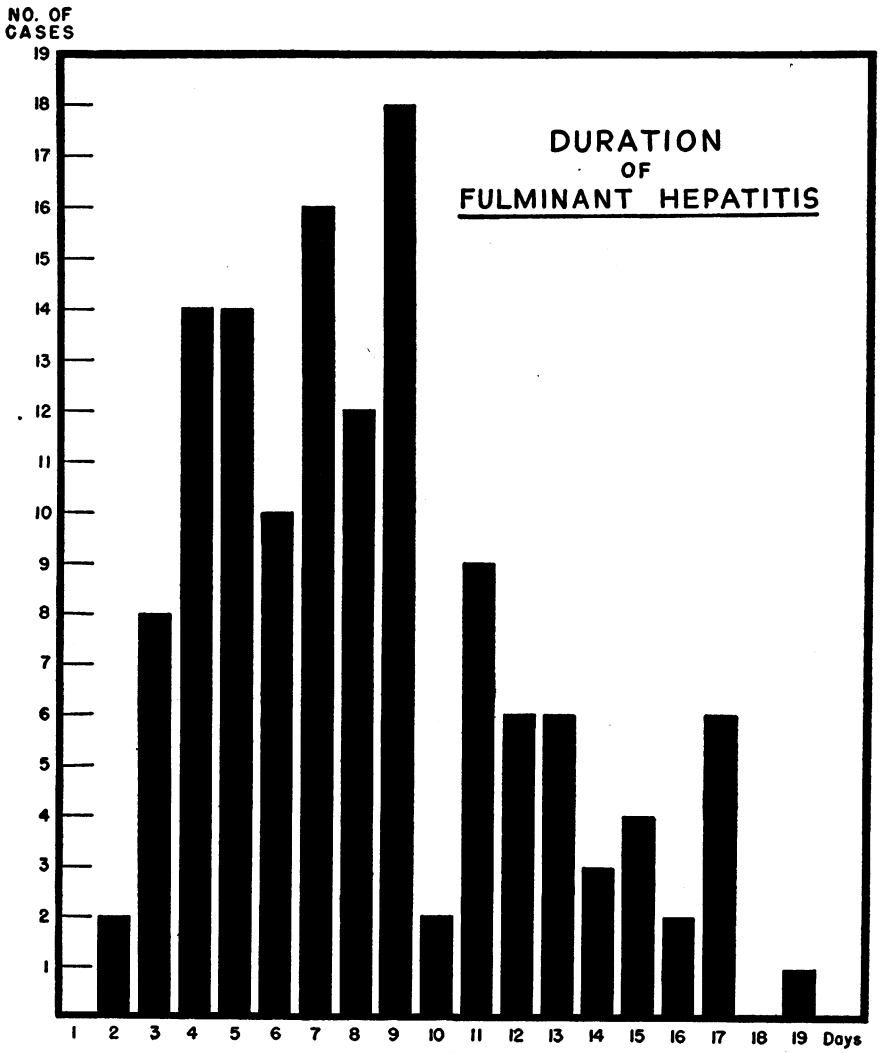
TABLE I

Duration of Fatal Hepatitis

	Old series: 118 cases (1942 to July, 1943)		New series: 178 cases (August, 1943, to April, 1945)	
Duration	No. of cases	Per cent of cases	No. of cases	Per cent of cases
(*Days*)				
Less than 10	0	0	94	53
10—19	14	11	39	21
20—29	20	16	10	6
30—39	31	26	13	7
40—49	20	17	4	2
50—59	8	7	2	1
60—69	8	7	1	0.5
70—79	9	8	3	2
80—89	0	0	1	0.5
90—100	5	5	3	2
Over 100	3	3	8	4

character of the lesions was so great that this group was excluded from analysis. The pertinent data for the series are given in Table I. It will be noted that in 53 per cent the course of the disease, from beginning of symptoms to death, was less than 10 days, and that in 74 per cent the disease terminated fatally within 20 days. A more detailed analysis of this group is shown graphically on a day-by-day basis in Text-Figure 1, where the vertical columns represent the number of cases and the abscissae the corresponding duration of disease. Inspection of the graph brings out, first, that the number of cases in which death occurred within so short a time as 4 days is considerable (21 per cent); second, that the number of fatalities on any one day between the fourth and the ninth is greater than the number for any subsequent day; and third, that there is a sharp drop in the number of deaths beyond the

ninth day which marks a turning point. This impression is strengthened by the character of the lesions: in almost all of the cases which ended fatally before the tenth day, destruction of liver cells was complete or nearly so, whereas in those with a longer survival period, de-



Text-Fig. 1. Duration of the disease in 133 cases of fulminant hepatitis.

struction usually was incomplete. It is for this reason that we have considered the cases terminating in less than 10 days as representing a fairly homogeneous type, namely, the fulminant form of hepatitis.

Comparison of the duration in the present series with that of the epidemics of 1942 in the United States Army, and of 1927 in the civilian population of Sweden brings out marked differences which have al-

ready been indicated. Suffice it to state that the median duration in the present series is 8 days, whereas in the other epidemics it exceeded 5 weeks.

The search for the elements responsible for the more fulminant course of hepatitis during the past 2 years is a cardinal task of this investigation.

Incidence of Previous Trauma and Transfusion

Factors that can clearly be correlated with duration of disease are previous trauma and subsequent transfusions of blood (Table II). In nearly all cases trauma—combat wounds or burns—was of serious

TABLE II

Incidence of Previous Trauma (Wound or Burn) in 178 Cases of Fatal Hepatitis (New Series)

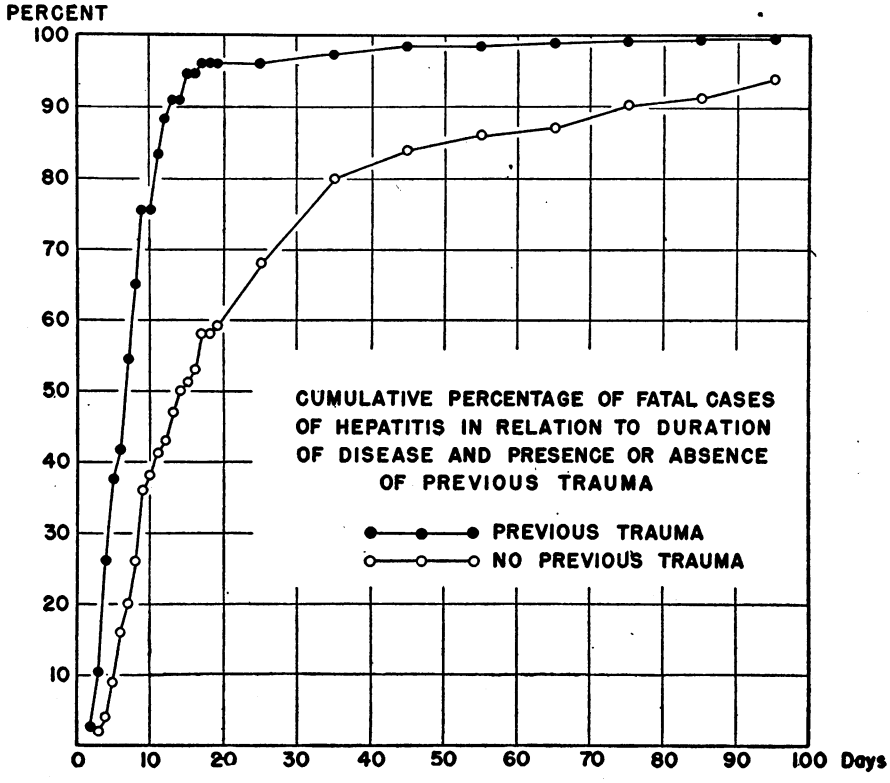
Duration of disease	Wounded	Burned	No previous trauma	Total number of cases
(*Days*)				
Less than 10	52 (55%)	6 (6%)	36 (38%)	94
10—19	16 (41%)	0	23 (59%)	39
20 and over	3 (7%)	0	42 (93%)	45
Total no. of cases	71 (40%)	6 (3%)	101 (57%)	178

degree and was sustained within 4 months of the onset of hepatitis. Most of the wounded received transfusions of blood or its derivatives within a few days of injury: hence these cases probably may be regarded as examples of homologous serum hepatitis. It is from this premise that we here analyze the relation of trauma to the duration of fatal hepatitis.

Consideration of Table II reveals the significant fact that the patients with hepatitis who had previously sustained trauma succumbed much sooner than those who had not been injured. Thus, while there was history of trauma in 61 per cent of the total group in which death occurred within 10 days, the incidence dropped to 41 per cent for the group with a duration of from 10 to 19 days, and to only 7 per cent when survival exceeded 20 days. Conversely, column 4 of the table shows a progressive increase in nontraumatic cases in proportion to duration. These variations are graphically represented in Text-Figure 2, where the cumulative percentage of fatal cases has been plotted in relation to duration of disease and presence or absence of previous trauma. Here it is shown that 76 per cent of those cases with a history of trauma ended fatally within 10 days of the onset of symptoms, and

96 per cent by the 20th day, whereas the corresponding percentages for the nontraumatic group are 38 and 59.

Computation of the median duration of hepatitis in the two groups gives 7 days for the wounded and 15 days, or twice as long, for the group without trauma. The contrast between the two groups is shown graphically on a day-by-day basis in Text-Figure 3 using the same



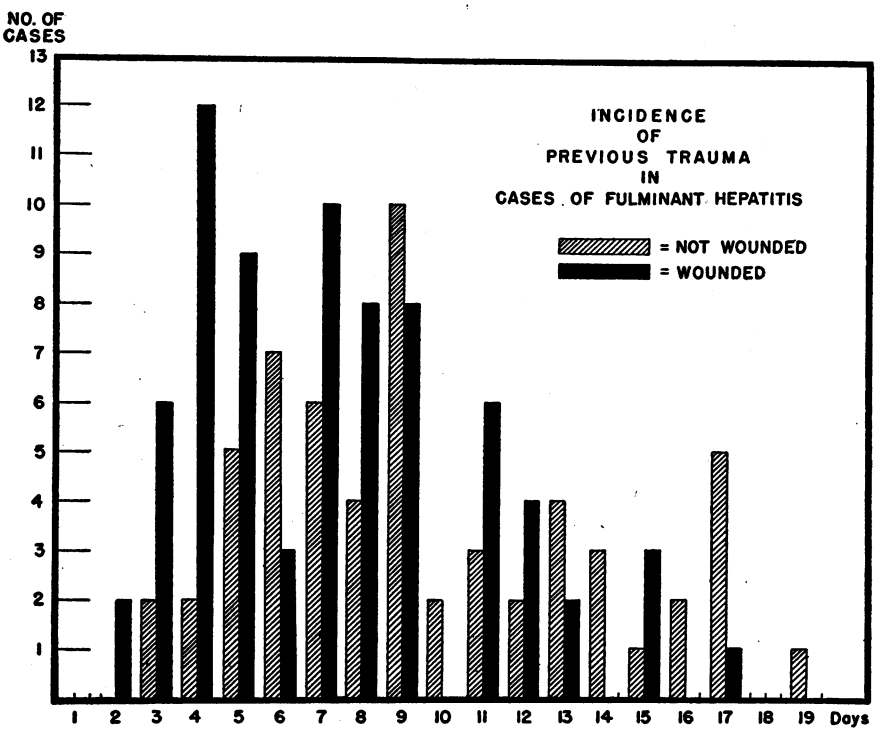
Text-Figure 2

data from which Text-Figure 2 was constructed. The graphs show that the course in the wounded group tends to be more fulminant than in the nonwounded; the mortality of patients with a history of trauma and transfusion was five times as great during the first 4 days after onset of symptoms. Evidence favors the conclusion that the type of fatal hepatitis which may follow trauma and transfusions of blood, *i.e.*, homologous serum hepatitis, tends to run a considerably more rapid course than does the naturally occurring disease.

Distribution of Cases According to Age and Race

The data from 130 cases of hepatitis in which the clinical course was less than 20 days are given in Table III. All were male soldiers (in-

cluding 7 Italian and German prisoners of war); 125 were white, 3 Negroes, one a Javanese, and one an American-born Japanese. The distribution is similar to that in the 1942 epidemic, and to that in a recent survey of 1,762 patients under treatment for hepatitis in Army General Hospitals.[27] It is almost exactly in direct ratio to the population in the Army. Factors of age, sex, or race, therefore, do not ac-



Text-Fig. 3. Comparative mortality on a day-by-day basis between nonwounded and wounded patients with fulminant hepatitis.

count for the preponderance of a more fulminant form of hepatitis in the present series.

TABLE III

Age in 130 Cases of Hepatitis in Which the Duration of the Disease Did Not Exceed 19 Days

Years	No. of cases	Per cent of cases
Less than 20	10	8
20—24	45	35
25—29	41	32
30—34	25	18
35—39	6	5
Over 40	3	2

Geographic Distribution and Epidemiologic Types of Fatal Hepatitis

In order to determine possible variations of the disease in relation to climate and other factors, the cases in the present series have been tabulated according to geographic location and duration of disease, and subdivided as wounded and nonwounded groups in each theater of war (Table IV). In this tabulation the European theater includes Great Britain and the continent except the Italian peninsula; the Mediterranean theater includes Italy, Africa, and the Middle East; the Pacific theaters include the islands of the Pacific, and India, China, and Burma. It will be noted that 90 per cent of the cases came from combat areas and only 10 per cent from the United States.

TABLE IV

Geographic Distribution of 178 Fatal Cases of Hepatitis (New Series)

Duration of disease	United States		European theater		Mediterranean theater		Pacific theaters	
	Wounded	Not wounded	Wounded	Not wounded	Wounded	Not wounded	Wounded	Not wounded
(*Days*)								
Less than 10	2	5	31	2	20	21	5	8
10—19	0	4	11	5	2	6	3	8
20 and over	0	7	1	6	2	8	0	21
Total	2	16	43	13	24	35	8	37

During the period covered by this study, extensive epidemics of hepatitis existed in the Mediterranean and Pacific areas, and were absent (except during the final months) in the European theater and in the United States. Cases in the first two areas may, therefore, be regarded as belonging predominantly to the epidemic type; in the latter areas, to the endemic or sporadic type.

In the wounded group each casualty has been credited to the theater in which the injury occurred, although the first symptoms of hepatitis often did not develop until after evacuation to the United States.

The cases in the series may, with certain assumptions, be classified on the basis of epidemiology. There were 29 examples of the endemic and 72 of the epidemic type of the "naturally" occurring disease, and 77 of homologous serum hepatitis, most of the latter coming from the European theater. Cases without trauma predominated slightly in those from the Mediterranean theater and strikingly so in those from the Pacific.

Mortality

In all recorded epidemics of hepatitis the mortality has been low, ranging from 0.2 to 0.4 per cent. Thus, during the United States Army epidemic of 1942 there were 51,337 cases reported,[11] with a mortality rate of 0.24 per cent. During the more recent Army epidemics, 68,000

cases (in round numbers) and 196 deaths have been recorded; that is to say, the death rate was 0.3 per cent. In view of the change in character of fatal hepatitis during recent years the agreement in mortality rates is surprising.

It should be emphasized, however, that the rate for the 1943–45 epidemics is based upon incomplete returns and must be regarded as an approximation. Actually, the mortality of "naturally" occurring hepatitis is probably lower, whereas that of homologous serum hepatitis may be higher. No precise information is as yet obtainable on either variant. Estimates are based largely upon cases which have been hospitalized; no account usually is taken of the mild and frequently nonicteric forms of the disease which escape recognition. For homologous serum hepatitis, attempts to determine case mortality have been particularly unsatisfactory, but the impression is that it may be several times as high as in the naturally occurring disease. The mortality of 0.3 per cent in the epidemics under discussion is an average, and has varied in different localities and at different times.

With regard to duration of the endemic type, it is interesting to note that there were 16 acute and 13 subacute fatal cases (defining the latter as running a course of more than 20 days); they were almost equally divided between the United States and Europe. In the epidemic group, subacute cases slightly outnumbered acute cases in the Pacific theater (21 to 16), whereas in the Mediterranean area the proportions were more than reversed (8 to 27).

No correlation was apparent between duration of illness and geographic location in the endemic type. For the epidemic type, however, the disease was predominantly acute in the Mediterranean and subacute in the Pacific areas. Measured by duration it appears to have been more virulent in the Mediterranean than in the Pacific areas.

In the homologous serum group, practically all cases ran an acute course without any apparent influence by geographic factors; only 3 were subacute. It would be a mistake, however, to assume at once that this is a general characteristic of this type of hepatitis.

Clinical Picture of Fulminant Hepatitis

A number of recent reports by American,[11-18] British,[4-10] and German [19-23] observers have dealt with the clinical picture of epidemic hepatitis in its usual benign form ending in recovery. Wherever the disease has occurred, the clinical pattern has been remarkably uniform; the symptoms and signs have varied in degree, not in kind.[28] There is an impression, however, that in recent years hepatitis has become more severe.

In this paper we are concerned with a fatal form in which nearly all

liver cells are destroyed within a few days. In an effort to correlate lesions and functional disturbances an analysis has been made of the clinical manifestations of the fulminant cases. The analysis is based primarily on the 94 cases of that group, but other cases are incorporated in certain sections since their clinical and anatomic manifestations were identical even though survival was longer (10 to 19 days). The general data have been augmented by abstracts of the clinical records of representative cases.

Similarity between "Spontaneous" and "Inoculation" Hepatitis

A question of great importance arose in connection with the analysis: Is "naturally" occurring fulminant hepatitis, as seen in either its endemic or epidemic variants, clinically distinguishable from the disease "artificially" induced by parenteral injection of blood or its derivatives? The answer can readily be given: Except for a tendency to a more rapid course in serum hepatitis, no differences were discernible. This finding is in accord with observations on nonfatal cases.[3,9,19,20,29-33] It is, therefore, permissible to combine the two groups for purposes of analysis.

Course of Fulminant Hepatitis

The three phases previously reported in the subacute form can usually be recognized in the fulminant disease: (1) an initial, prodromal or pre-icteric stage; (2) an intermediate stage which begins with the onset of jaundice, and (3) a final stage which generally is ushered in abruptly by grave nervous manifestations. The time relations were less sharply defined in the fulminant than in more protracted cases. The pre-icteric period varied greatly (Text-Fig. 4) but was generally 2 or 3 days. The duration of the terminal phase did not differ significantly from that of the previous series, ranging from 1 to 4 days. Since the total duration in the fulminant group was less than 10 days, it is evident that the intermediate stage was often very brief; indeed, in some instances the manifestations of the prodromal and final stages merged.

Initial Symptoms. Two usual combinations of initial symptoms may be recognized: (1) An "infectious" type in which the disease is ushered in suddenly by the symptoms common to many acute infections: fever, chilliness, or, more infrequently, shaking chills, malaise, generalized aching, pains in the joints, back, and eyes, with gastrointestinal symptoms usually following in a day or so but rarely dominating the picture. (2) A "gastrointestinal" type in which the initial symptoms are similar to those encountered in the subacute variety of the disease: anorexia, nausea, epigastric discomfort or pain, with variable elevation in tem-

perature. The onset usually is more gradual with the second than with the first group; but it may be acute with severe nausea and vomiting from the start.

Sometimes initial symptoms of both types appear simultaneously, with neither in the foreground. Rarely, the disease begins with mental disturbances. The distribution of these several types of onset is shown in Table V which is based upon the fulminant cases and 19 others of more than 9 days' duration but with similar manifestations. It will be seen that four-fifths of the cases belong to the two main groups, which, roughly, are represented equally.

The 3 cases in which cerebral symptoms ushered in the disease deserve special mention. An indication of the extent to which central

TABLE V

Predominant Types of Initial Symptoms in 113 Cases of Hepatitis in Which the Duration Did Not Exceed 19 Days

Symptoms	No. of cases	Per cent of cases
Gastrointestinal type	48	43
Acute infectious type	40	36
Mixed gastrointestinal and acute infectious type	22	19
Mental disturbances	3	3

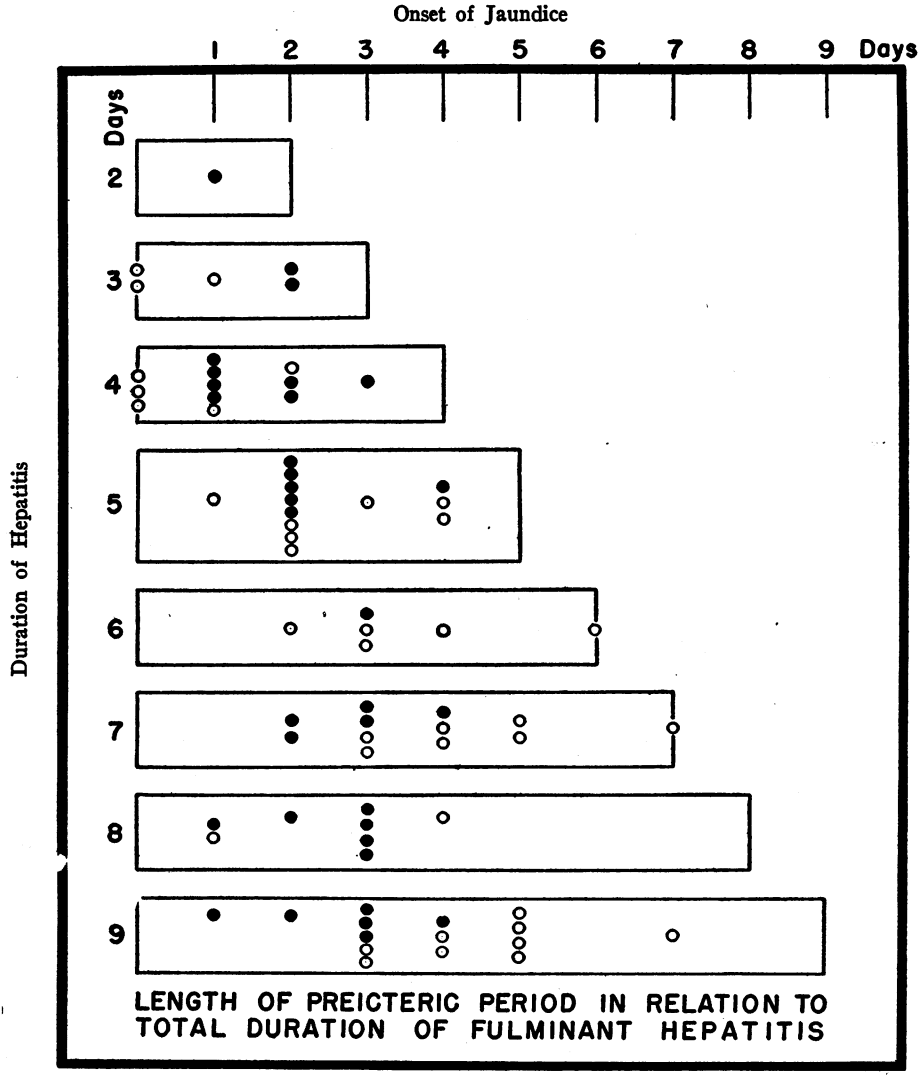
nervous manifestations may dominate the clinical picture is afforded by the fact that exploratory craniotomy was performed in 2 of these cases.

The prodromal symptoms observed in fulminant cases do not differ significantly in type or severity from those of the usual nonfatal cases. The predominant initial symptoms of the fulminant cases, as of those with recovery, have been independent of locality, and those of the two main types have coexisted during the same periods of epidemics although their relative frequency has varied. Thus, in an American Army Hospital in Italy, the "infectious" type occurred in 61 per cent, the "gastrointestinal" form in 39 per cent; [18] in a British garrison at Malta the proportions were reversed, only 37 per cent exhibiting the febrile type; [6] during an epidemic in the Middle East the two were represented equally.[34] The symptoms and signs of the febrile type have been described as closely resembling malaria,[19,36] influenza,[2,35] sand fly fever,[6,8] and "acute surgical abdomen." [4]

The observation that the subsequent clinical manifestations bear no relation to the character of initial symptoms is true for the fatal as well as for the nonfatal form of hepatitis.[34]

Onset of Jaundice. In Text-Figure 4 is shown the relation between

the onset of jaundice and the duration of disease in 72 fulminant cases. Those previously wounded (34 in number) are represented by solid circles; the nonwounded (38 in number), by open circles. The graph brings out several points of interest. First, it shows no significant dif-



Rectangles = duration of hepatitis; solid circles = onset of jaundice in wounded cases; open circles = onset of jaundice in nonwounded cases.

Text-Figure 4

ference in time of appearance of jaundice in wounded and nonwounded cases; in both the "spontaneous" and the "inoculation" variants there is considerable scattering. In several instances jaundice occurred at the onset of symptoms; in others it was delayed until the day of death; but on an average it appeared on the second or third day after the be-

ginning of symptoms. A positive correlation between onset of jaundice and duration of disease seems to be indicated by early jaundice in the more fulminant cases.

The time of appearance of jaundice and its subsequent intensity bore no relation to the type of initial symptoms. This same lack of correlation has been reported in nonfatal cases.[18,36]

Final Stage. The main features of the terminal phase were not appreciably different from those described in the earlier series. Usually a rather abrupt change for the worse was initiated by cerebral symptoms beginning with listlessness, drowsiness, increasing apathy; with restlessness, incoherence, disorientation; or with irritability and failure to cooperate. The symptoms of excitement often progressed to an acute maniacal state necessitating restraint. Frequently apathy and excitement alternated, but in the majority of cases deep coma eventually supervened. With the onset of cerebral symptoms hyperactivity of certain reflexes was the rule; a positive Babinski sign and persistent ankle clonus were common. Muscular twitching was frequent, while opisthotonos and generalized convulsions were occasional.

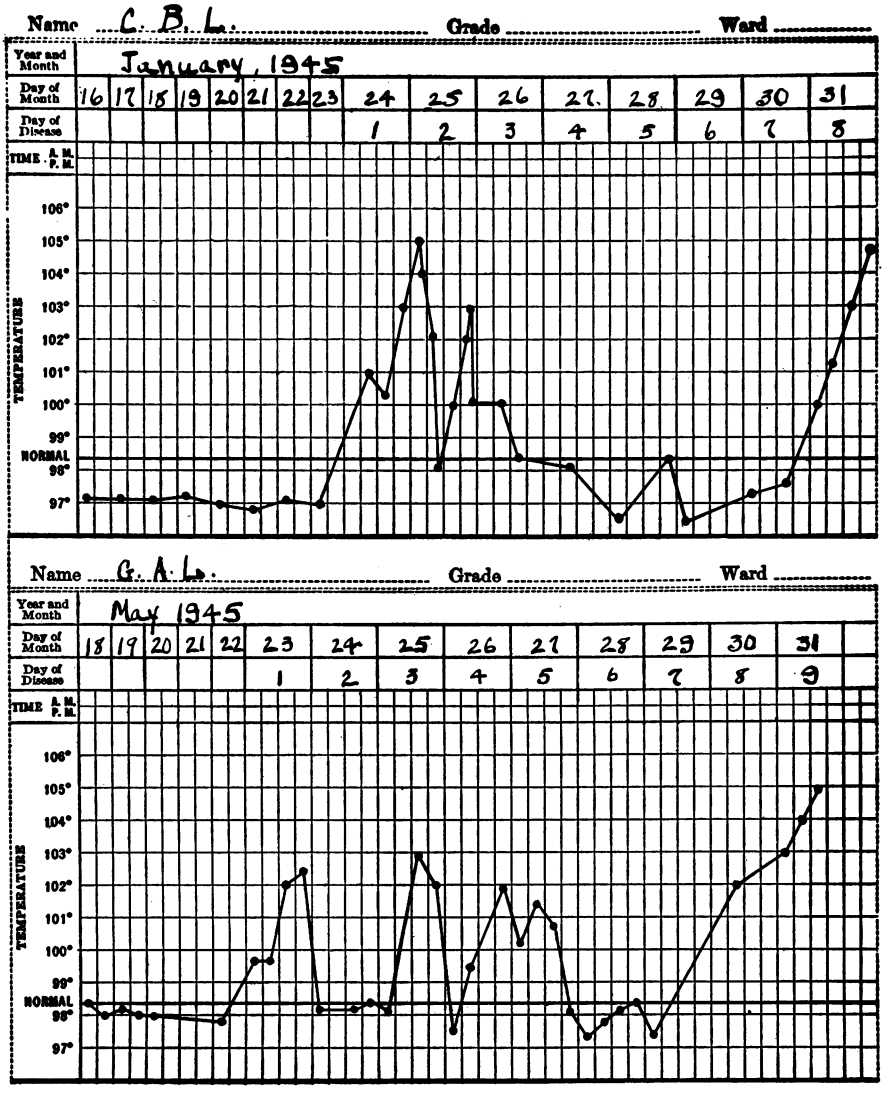
During the final phase jaundice often deepened rapidly. Vomiting frequently was severe and sometimes projectile. Bleeding from the gastrointestinal mucosa was evidenced by coffee-ground vomitus and melena, and was occasionally associated with purpuric phenomena or with frank gastrointestinal hemorrhage of considerable magnitude. Signs of pulmonary edema or patches of consolidation were found in the majority. Shock developed in a number of cases; in all there was a terminal rise of temperature.

Symptoms, Signs, and Laboratory Findings

The analysis of the data included the following features: temperature, pulse rate, palpation of liver and spleen, recurrence of disease, jaundice, icterus index, total and differential leukocyte count, plasma proteins, urine, nonprotein nitrogen and urea nitrogen of blood, and blood sugar. Abstracts of representative clinical records illustrate these data.

Temperature. Temperature records for the prodromal stage were available in 68 fulminant cases; in all but one fever ranged from 99° to 104° F. and averaged 102° F. The peak usually was attained on the second day. With the onset of jaundice the temperature, as a rule, fell to normal or slightly below normal (96° to 97° F.) and remained so for several days, but in about one-fourth of the cases irregular subsequent rises took place. During the final phase the temperature almost invariably rose sharply, usually to 103° to 105° F., occasionally

to as high as 107°. Representative temperature curves are given in Text-Figure 5. Except for the terminal fever, the temperature reactions in fulminant hepatitis are similar to those in nonfatal cases;

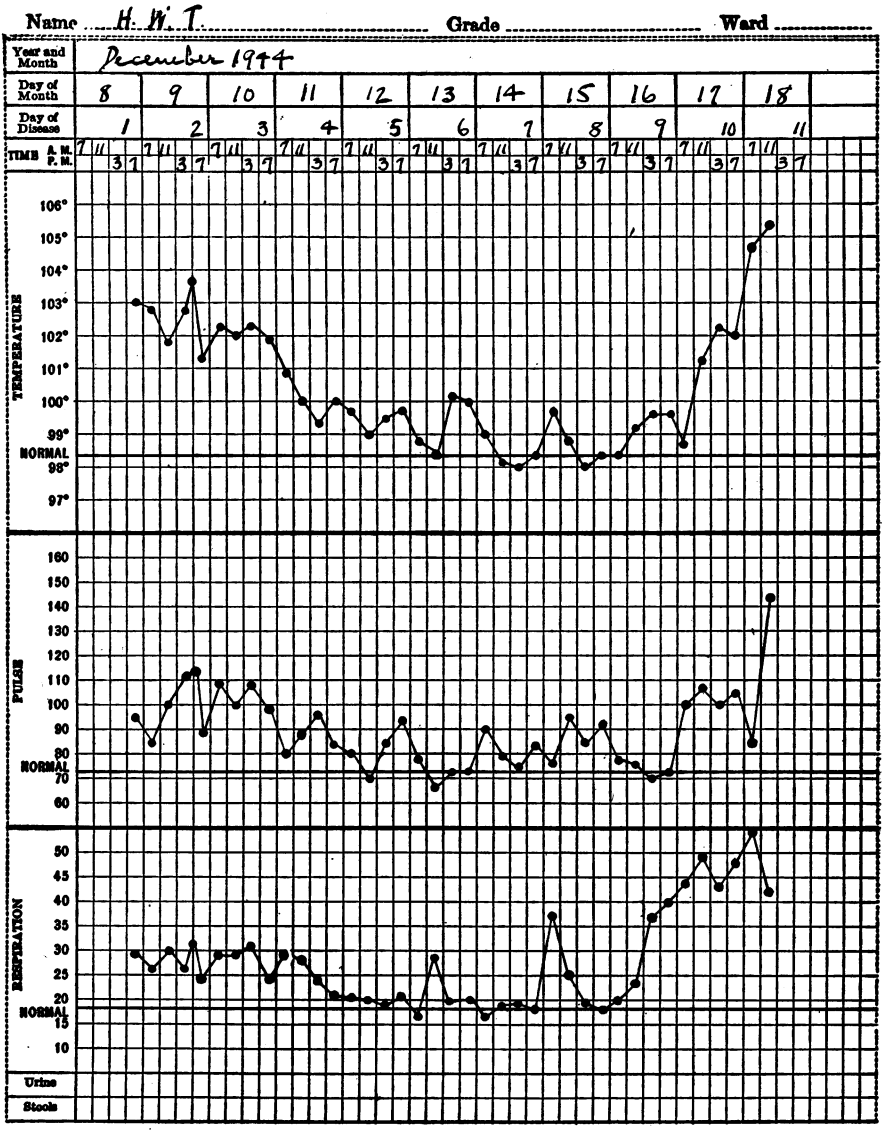


Text-Fig. 5. Representative temperature curves in cases of fulminant hepatitis.

most observers have reported a fever which was often high at the onset [2,4,6,8,9,16,18,19,34,36,37] and usually declined as jaundice appeared, although sometimes it was protracted.[8,10,34,37]

Pulse Rate. The pulse rate was nearly always elevated during febrile periods (Text-Fig. 6). Bradycardia was observed only in rare instances.

Palpation of Liver and Spleen. The liver was moderately enlarged and usually tender during the late prodromal and early icteric stages; as the disease progressed shrinkage was frequent but not invariable.



Text-Fig. 6. Clinical chart of a case of fulminant hepatitis with death on the eleventh day. Pulse rate rose during periods of fever.

Enlargement of the spleen was less constant; it was recorded throughout all stages in approximately 25 per cent of the cases. More precise statements concerning the sizes of these organs have little meaning because of the variability at different stages of the disease. In nonfatal

cases enlargement of the liver has been reported invariably when the disease was present in moderate or severe form, and frequently when it was mild; [37] other writers have recorded enlargement in the majority.[8,13,16,18,19,34]

For the spleen the figures usually given are 10 per cent or less; [13,14,16,18,34] although some observers have found readily palpable spleens more frequently, *i.e.*, in 13.6 per cent,[37] in 27 per cent,[8] or "usually." [22]

Recurrence. It is generally thought that a high degree of immunity is conferred by an attack of epidemic hepatitis, although accurate information is not available.[38] When second attacks do occur they are perhaps induced by nonspecific factors, by immunologically different strains, or by large doses of the infectious agent.[5]

TABLE VI
Icterus Index in 60 Cases of Fulminant Hepatitis

Icterus index	No. of cases	Per cent of cases
Below 50	9	15
50 — 99	31	53
100—149	15	24
150—over	5	8

In the present series 4 patients had a history of a previous attack within 3 years of the fatal disease; 1 within 3 months, the remainder within 2 to 3 years. It is interesting to note that the livers of these patients presented no scarring to indicate previous injury; this observation is in harmony with our earlier observations.[25]

Jaundice. In contrast to the predominant subacute form of the 1942 epidemic, icterus was light or moderate, and rarely deep even during the terminal stage. At least 2 of the fulminant cases remained completely free from jaundice, and in a third only the scleras were faintly tinged. The clinical abstracts of these anicteric cases are included among those chosen to give a representative picture of the disease as seen in individual cases.

Icterus Index. The values of the index usually conformed with the relatively light icterus. The data for 60 cases, based upon the highest values recorded, are given in Table VI. The index in approximately two-thirds of the series did not exceed 100. Values above 150 were found in only 8 per cent.

Total and Differential Leukocyte Count. During the prodromal period a tendency toward leukopenia was evident in 20 of 27 cases

(Table VII). The differential count disclosed a slight lymphocytosis, *i.e.*, 9 of 10 patients had a lymphocyte-monocyte count between 40 and 49 per cent. In the icteric phase total counts exceeded 11,000 in approximately one-half, the elevation probably resulting from pulmonary complications or hemorrhages. A slight neutrocytosis was also observed during this phase.

Plasma Proteins. Determinations made in 25 cases were slightly or definitely below the normal in almost every instance (Table VIII).

TABLE VII

Leukocyte Count in Cases of Fulminant Hepatitis

Leukocyte count	Pre-icteric period	Icteric period
Below—5000	7	0
5000 —6900	13	7
7000 —8900	4	7
9000 —10,900	0	8
11,000—12,900	2	10
13,000—14,900	0	4
15,000 and over	1	14
Total no. of cases	27	50

Because of therapeutic transfusions of blood or plasma, the value of these figures is questionable; without treatment much lower levels might have been obtained.

Urine. The urine was usually normal in the first day or two of illness, but as a rule by the third or fourth day changes were noted. The specific gravity was moderately elevated, bile was almost invariably present, albumin of slight degree appeared in two-thirds, and casts in approximately one-half. The casts were sometimes hyaline, sometimes granular, and frequently of both types. Leucine and tyrosine crystals were frequently searched for, but very rarely found.

TABLE VIII

Serum Proteins in 25 Cases of Fulminant Hepatitis

Below 5.0 gm./100 cc.	3
5.0 5.9 gm./100 cc.	5
6.0 6.9 gm./100 cc.	9
7.0 and over	8

Nonprotein Nitrogen; Blood Urea Nitrogen. Of 31 representative cases selected solely on the basis of completeness of records, the nonprotein nitrogen level of the blood fell within the normal range of 25 to 40 mg. per cent in 16 cases (Table IX). In 15 cases there was evidence of nitrogen retention. In 11 of these, the values ranged between 41 and 60 mg. per cent; in 4 cases they were above 70 mg. per cent.

Blood urea nitrogen was also determined in 10 instances. In 2 the values were 16 and 16.6 mg. per cent, respectively, and the ratio of

blood urea nitrogen to nonprotein nitrogen was approximately normal, *i.e.*, 1:2. In the remaining 8 the urea nitrogen levels were subnormal, ranging from 4 to 12.3 mg. per cent and the blood urea nitrogen/non-

TABLE IX

Nonprotein Nitrogen and Urea Nitrogen in Representative Cases of Epidemic Hepatitis in Which the Duration of Disease Ranged from 3 to 12 Days

Case no.	Onset	Death	Date of examination	Nonprotein nitrogen (*mg./100 cc. of blood*)	Blood urea nitrogen (*mg. per 100 cc. of blood*)
104032	12/3/43	12/12	1/10	40	
107351	3/16/44	3/20	3/19	55	
			3/20	72	
114638	3/10/44	3/15	3/14	27	
114947	6/3/44	6/12	6/12	60	
119114	9/1/44	9/8	9/7	35	
119183	7/22/44	7/31	7/26	40	
122399	9/5/44	9/9	9/8	50	
			9/9	48	
122680	11/29/44	12/5	12/4	42	
124566	10/10/44	10/15	10/14	43	
125602	7/14/44	7/23	7/22	48	
126048	9/9/44	9/12	9/11	56	
126049	9/7/44	9/12	9/12	50.5	12.3
126108	9/14/44	9/22	9/19	44.4	
			9/21	45.6	
126811	1/9/45	1/13	1/12	36.7	
128003	1/18/45	1/29	1/25	31	16
128072	1/7/45	1/18	1/15	32	4
128558	10/28/44	11/9	11/7	52	
128577	10/28/44	11/5	11/5	60	
128713	11/7/44	11/14	11/11	43	
			11/13	39	5.9
128714	11/11/44	11/16	11/14	36.5	
			11/15	35	
			11/16	35	5.6
129240	1/23/45	2/1	1/25	33	6.2
133205	1/19/45	1/30	1/28	72	
133183	7/30/44	8/4	8/3	103	
131875	12/8/44	12/19	12/19	20	6.2
133190	9/27/44	10/1	9/30	75	
133196	4/11/44	4/20	4/18	40	
133199	1/6/45	1/18	1/16	35	16.6
133201	12/5/44	12/11	12/10	27	5.4
133204	12/27/44	1/5	12/30	40	
131874	9/10/44	9/14	9/12	30	
131667	10/24/44	10/31	10/27	42.8	8.2

protein nitrogen ratios correspondingly varied from 1:3.1 to 1:8. The subnormal levels, both absolute and relative, clearly indicate decreased urea formation. As this substance is formed solely in the liver,[38,39] a decrease in blood concentration is important evidence of hepatic inefficiency.

In the group studied no relation was apparent between duration of disease and nitrogen retention.

Blood Sugar. In destructive disease of the liver the blood sugar would be expected to fall to a low level.[39] In most cases of this series such a fall was obscured by the therapeutic administration of glucose. There were, however, 16 cases in which low values were obtained (Table X). In these cases the determinations were made at a time when the patients exhibited central nervous manifestations, *i.e.*, when they were in the terminal stage. The values ranged from 35 to 73 mg. per cent; in 9 they were below, in the remainder above, 55 mg. per cent.

Illustrative Cases

Pertinent clinical data and laboratory findings are given for 21 representative cases, in which the clinical duration of the disease ranged from 1 to 11 days.

Table X

Low Blood Sugar in Cases of Fulminant Hepatitis in Which the Duration of the Disease Ranged from 3 to 11 Days

Case no.	Onset	Death	Date of examination	Blood sugar (*mg. per 100 cc. of blood*)	Remarks (date of examination)
104274	5/16/44	5/23	5/22	38	Drowsy
114638	3/10/44	3/15	3/15	72	Comatose, convulsions
119114	9/1/44	9/8	9/7	37	Alternating restlessness and stupor
122680	11/29/44	12/5	12/4	40	Comatose
122399	9/5/44	9/9	9/9	40	Shock
119183	7/22/44	7/31	7/25	51	Stuporous
124971	10/22/44	10/29	10/26	62	Disoriented, delirious
125482	11/19/44	11/30	11/28	59	Irrational
126048	9/9/44	9/12	9/11	40	Semicomatose, shock
126049	9/7/44	9/12	9/12	35	Comatose, opisthotonos, shock
127334	12/11/44	12/15	12/14	73	Restless
128003	1/18/45	1/29	1/26	63	Semicomatose, convulsions
133205	1/19/45	1/30	1/28	56	Comatose
133182	7/22/44	7/31	7/25	51	Comatose
141771	9/18/44	9/21	9/20	66	Comatose
133190	9/27/44	10/1	10/1	50	Comatose, convulsions

In cases 1 to 10 the predominant manifestations at the onset were those common to a variety of acute infections. Some patients of this group presented serious diagnostic problems; thus, in cases 1, 7, and 10, malaria was suspected. In the second group of cases, 11 to 16, the clinical course of hepatitis was of the more familiar type, being ushered in by gastrointestinal symptoms. A third group (cases 17 to 19) represented the mixed infectious and gastrointestinal form. Case 20 is an example of recurrent hepatitis. In case 21 the first manifestation of the disease was mental disturbance.

In the examples given, 2 patients (cases 2 and 5) remained free from jaundice throughout the course of the disease; in one other (case 7) only the scleras became faintly icteric. In 3 patients (cases 4, 6, and 7) the icterus index did not exceed 35. Six patients (cases 2, 4, 5, 6, 11, and 16) passed into a state of shock. In 5 cases (nos. 2, 4, 6, 8, 10, and 12) the blood sugar sank to low levels. In one case (no. 6) cerebral manifestations led to exploratory craniotomy.

Approximately one-half of these patients had sustained combat trauma and presumably received transfusions of plasma or blood; one patient, not wounded (case 15), had received multiple transfusions of plasma for the treatment of hypoproteinemia. It will be noted that the clinical features of hepatitis were the same in patients who had previously been wounded and received transfusions as in those not wounded, *i.e.*, who had the "naturally" occurring form of hepatitis.

Case 1

The patient (Army Institute of Pathology, 124057) was a white soldier, 22 years of age.

Clinical Course. On April 2, 1944, he complained of generalized aching, occipital headache, fever, nausea, and several bouts of vomiting. His temperature was 102.4° F.; later in the day it declined to 99.8° F.; pulse was 76; respirations, 18. There was rigidity of the voluntary muscles in the right upper quadrant and tenderness over the liver. Icterus became evident on April 4; the patient was restless, hyperactive, had severe pain in the upper abdomen, was persistently nauseated, and vomited repeatedly. His temperature was 96.4° F.; pulse, 90; respirations, 20. On April 5, he became deeply comatose. His pupils were moderately enlarged; there was left external strabismus. Abundant coffee-ground material oozed from mouth and nostrils. The liver was soft and its edge palpable one fingerbreadth below the costal margin. The pulse was of good quality. An algid type of malaria with secondary hepatitis was suspected, but no parasites were found on repeated examination of the blood. During the day the patient's temperature rose to 104.4° F., pulse to 152, respirations to 32; blood pressure dropped from 144/80 to 94/74 mm. Hg. Death occurred on April 5; duration of disease, 3 days.

Laboratory Findings. (April 2.) *Blood:* red blood cells, 4.9 million; white blood cells, 4,700, with 51 per cent polymorphonuclear leukocytes and 49 per cent lymphocytes and monocytes. *Urine:* specific gravity, 1030; 1 plus albumin. (April 4.) *Urine:* 1 plus bile. *Icterus index:* 54.

(For illustrations of lesions see Figs. 9, 10, 12, and 19.)

Case 2

The patient (Army Institute of Pathology, 126048) was a white soldier, 34 years of age.

Clinical Course. On July 29, 1944, he was wounded in action by shell fragments, suffering compound comminuted fractures of the left radius, and penetrating wounds of the left thigh and eye. Details of treatment other than debridement were not recorded. He improved steadily and was convalescing at a normal rate. On September 9 the patient felt chilly, had a fever of 103° F., and was nauseated. Examination of the throat, chest, abdomen, and nervous system revealed nothing of note. He felt "stronger" on September 10, but complained of headache and

appeared to be dull and apathetic; temperature was 100.8° F. He vomited a dark brown fluid on three occasions. Physical examination was still negative. On September 11 a sudden change took place; the abdomen became rigid; rectal temperature fell to 94° F.; pulse was rapid; respirations were intermittent and averaged from 40 to 60 per minute. Chest examination was negative. During the day the patient became semicomatose. The blood pressure dropped to 80/40 mm. Hg. The neck was not rigid; the eyes were open, the pupils widely dilated; the left eye was fixed to light, the right reacted slowly. The patient was treated for shock and the next day seemed slightly improved, with a temperature of 99° F., a pulse of 120, and respirations 40 and regular. During the day he became restless. Respirations became shallow and averaged 52 per minute. The temperature rose to 102° F. Jaundice did not develop during the course of the illness; the scleras remained clear. Death occurred on September 12; duration of disease, 3 days.

Laboratory Findings. (September 11.) *Blood:* red blood cells, 4.5 million; white blood cells, 11,750, with 72 per cent polymorphonuclear leukocytes and 28 per cent lymphocytes; nonprotein nitrogen, 56 mg. per cent; blood sugar, 40 mg. per cent. *Spinal fluid:* protein, 30 mg. per cent; sugar, 28.5 mg. per cent; white blood cells, 9,000; globulin, negative; color, light straw yellow.

(For illustrations of lesions see Figs. 3, 17, 18, and 23.)

Case 3

The patient (Army Institute of Pathology, 133177) was a white soldier, 31 years, of age.

Clinical Course. On June 16, 1944, he complained of severe backache, headache, and intermittent chills. Temperature was 101.6° F.; pulse, 88; respirations, 20. On June 17 he experienced severe nausea with occasional vomiting. The liver was enlarged to 2 fingersbreadth below the costal margin, and was moderately tender. His scleras were icteric. On June 18 the temperature had dropped below normal; vomiting was persistent. That night the patient was extremely restless; he hiccoughed and vomited repeatedly. On June 19 he became stuporous, tossed about, and failed to respond to questions. Pupils were contracted; the remainder of the physical examination was negative; blood pressure was 110/80 mm. Hg. The patient sank into coma; pulmonary edema developed. Death occurred on June 20; duration of disease, 4 days.

Laboratory Findings. (June 17.) *Icterus index,* 65. *Urine:* 2 plus albumin; 2 plus bile. (June 19.) *Urine:* 1 plus albumin; 2 plus bile.

Case 4

The patient (Army Institute of Pathology, 122399) was a white soldier, 30 years of age.

Clinical Course. On June 26, 1944, he was wounded in action by a mortar shell, suffering multiple perforating wounds of bones and chest, and compound fractures of the right humerus and left tibia. Treatment consisted of debridement, plasma, sulfathiazine, and penicillin. On July 4 the left leg was amputated; healing of wounds progressed satisfactorily.

On September 5 he had a chill and a fever of 103.4° F.; he complained of headache and diarrhea. Jaundice developed on either September 5 or 6. The patient seemed improved during the day of September 7, but he sweated profusely that night, and on September 8 suddenly went into shock from which he failed to rally despite transfusions of plasma and other treatment. The skin was cold, the pulse thready, and the blood pressure not measurable. The temperature fell to 97.4° F.; later in the day, however, it rose to 102° and the blood pressure to 100/70 mm. Hg; respirations became shallow and rapid. Death occurred on September 9; duration of disease, 4 days.

Chemical Examination of the Blood

Date	Icterus index	Nonprotein nitrogen (*mg. per cent*)	Sugar (*mg. per cent*)
Sept. 8	20	50	133
Sept. 9	33	48	40

Blood Counts

Date	Red blood cells (*millions*)	White blood cells	Polymorphonuclear leukocytes (*per cent*)	Lymphocytes and monocytes (*per cent*)
Sept. 6	4.2	5,000	52	48
Sept. 7		6,500		
Sept. 8	4.7	13,000	54	45

Urine

Sept. 6 Albumin, negative
Sept. 8 Albumin, trace
Sept. 9 Albumin, + +

Agglutinations

Sept. 7 Heterophil, negative; typhoid "O," negative
Typhoid "H," negative; *Leptospira icterohaemorrhagiae:* negative

Case 5

The patient (Army Institute of Pathology, 126423) was a white soldier, 25 years of age.

Clinical Course. He was wounded in action by a rifle bullet on July 25, 1944. Laparotomy the following day revealed a laceration of the posterior wall of the bladder, multiple lacerations of the ileum, a laceration of the sigmoid, and the peritoneal cavity full of blood and urine. Transfusions, plasma, penicillin, and sulfadiazine were given and by August 5 he was strong enough to be transferred to a general hospital. On arrival he was found to have a functioning colostomy, a suprapubic cystotomy, a urinary fistula through the right buttock, and a pleural effusion. The effusion cleared spontaneously, and despite an episode of thrombophlebitis in the left leg it was possible to deal surgically with his fistulas. Improvement was gradual but steady, and he was evacuated to the United States on October 13. On October 14 his temperature suddenly rose to 104° F. Physical examination and roentgenologic examination of the chest and abdomen were negative. The white blood cell count was 10,150. At 9:30 a.m. on October 15 he vomited; by 1:00 p.m. he was restless, with signs of impending shock. He began to vomit coffee-ground material and passed tarry stools. His white count rose to 19,000, with 72 per cent polymorphonuclear leukocytes and 28 per cent lymphocytes. At 4:15 a.m. on October 16 he began to cough up blood-tinged sputum. Blood pressure was 120/84 mm. Hg; pulse, 116; respirations, 14. At 6:25 a.m. he had a convulsive seizure and went into profound shock. Jaundice did not develop during the course of the illness. Death occurred on October 17; duration of disease, 4 days.

(The cut surface of the liver is shown in Fig. 4.)

Case 6

The patient (Army Institute of Pathology, 126049) was a white soldier, 19 years of age.

Clinical Course. On July 18, 1944, he was wounded in action, receiving multiple

bullet wounds of the right upper arm which produced a severe compound comminuted fracture of the humerus. Secondary closure of the wounds was done and he convalesced rapidly. On September 7 generalized aching developed and his temperature rose to 102.8° F. On September 8 he complained of nausea; on September 9 his temperature was 101° F. General physical examination was negative, and when the cast was removed in order to inspect the wounds, they were found to be healing satisfactorily. On September 11, although the temperature was normal, nausea and vomiting persisted. The patient fell out of bed during the night and afterward seemed disoriented, although physical examination was still negative. The following day, September 12, jaundice was evident. Irrationality was rapidly followed by deep coma, interrupted by repeated convulsive seizures, some of which were associated with opisthotonos. The pupils were equal; no papilledema was present. There were bilateral positive Babinski signs, and bilateral sustained ankle clonus; abdominal and cremasteric reflexes were absent, as were Chvostek's and Trousseau's signs. It was thought that a subdural hematoma might have resulted from the fall out of bed; however, cranial exploration showed no evidence of intracranial bleeding and the ventriculogram was normal. Blood pressure fell during the operation from 190/100 to 70/55 mm. Hg. Death occurred on September 12; duration of disease, 5 days.

Laboratory Findings. (September 11.) *Blood:* white blood cells, 8,250. (September 12.) Chemical examination: nonprotein nitrogen, 50.5 mg. per cent; urea nitrogen, 12.3 mg. per cent; sugar, 35 mg. per cent; icterus index, 35. *Spinal fluid:* total protein, 20 mg. per cent; cells, 22 (16 polymorphonuclear leukocytes and 6 lymphocytes and monocytes). *Urine:* color, dark amber; specific gravity, 1.027; albumin, 3 plus; sugar, negative; acetone, 1 plus; diacetic acid, negative.

Case 7

The patient (Army Institute of Pathology, 133183) was a white soldier, 26 years of age.

Clinical Course. On July 30, 1944, he complained of chills, fever, headache, and general aching which came on suddenly and persisted for several days, accompanied by anorexia, nausea and vomiting. He was admitted to the hospital on August 2 when he appeared acutely ill. Temperature was 102.6° F.; pulse, 100; respirations, 20. The only positive finding on physical examination was a palpable and tender spleen. A tentative diagnosis of tertian malarial fever was made; however, repeated blood smears were negative for malarial parasites. There was no improvement during the night and on the morning of August 3 the temperature had risen to 104.4° F.; pulse, 96; respirations, 20. The patient complained of headache, and pain in the chest. The icterus index was 28; the blood nonprotein nitrogen, 103 mg. per cent. The physical findings were unchanged. During the day the temperature subsided to 98° F. and by the next morning, August 4, to 96.4°. He became disoriented and had hallucinations. The liver and spleen were palpable. The lungs appeared clear; there was no roentgenologic evidence of pneumonic consolidation or fluid. The heart was normal. The deep reflexes were hyperactive; the superficial reflexes diminished. During the day the patient gradually became cyanotic. Definite jaundice never developed and only a faint icteric tint was noted in the scleras post-mortem. Death occurred the evening of August 4; duration of disease, 6 days.

Case 8

The patient (Army Institute of Pathology, 124971) was a white soldier, 24 years of age.

Clinical Course. He was wounded in action by an exploding shell on August 13, 1944, sustaining damage to both orbital regions. For several weeks he continued to have a draining orbital sinus; his eyesight was lost; his general physical

condition was good. On October 22 he awakened with a severe throbbing headache and during the day his temperature was between 99° and 100° F. On October 23, it rose to 103.5° F.; he vomited and complained of considerable muscular aching. His skin took on an icteric tint; no other physical findings of significance were noted. Between October 23 and 26 jaundice deepened, and his condition became progressively worse. The temperature remained between 99° and 100° F. He was disoriented. On October 29 he had several generalized convulsions and became deeply comatose. Death occurred on October 29; duration of disease, 7 days.

Chemical Examination of the Blood

Date	Icterus index	Sugar (*mg. per cent*)	Urea nitrogen (*mg. per cent*)	Serum protein (*gm. per cent*)	Albumin (*gm. per cent*)	Globulin (*gm. per cent*)
Oct. 25	33					
Oct. 26	64	62	9.3	5.2	3.3	1.9

Blood Counts

Date	Red blood cells (*millions*)	White blood cells
Oct. 22	4.0	5,900
Oct. 23		6,500

Case 9

The patient (Army Institute of Pathology, 125602) was a white soldier, 30 years of age.

Clinical Course. On July 14, 1944, malaise and general aching began and the patient was admitted to the hospital. His temperature was 104° F.; he was not jaundiced; the only significant physical finding was enlargement of the liver. On July 18 a moderate degree of jaundice of the skin and scleras was noted. On July 21 the patient became drowsy and difficult to arouse, later sinking into coma. There was a terminal fever of 106° F. Death occurred on July 21; duration of disease, 7 days.

Chemical Examination of the Blood

Date	Icterus index	Nonprotein nitrogen (*mg. per cent*)	Blood sugar (*mg. per cent*)
July 19	54		
July 22	108	48	100

Blood Counts

Date	Red blood cells (*millions*)	White blood cells	Polymorphonuclear leukocytes (*per cent*)	Lymphocytes and monocytes (*per cent*)
July 19	5.12	5050		
July 21		10400	57	43

Urine

Date	Albumin	Bile
July 19	++	
July 21	++	+

(For photomicrograph of kidney see Fig. 30.)

Case 10

The patient (Army Institute of Pathology, 133205) was a white male, 25 years of age.

Clinical Course. On January 19 his illness was ushered in with ocular headache, general aching, chills, fever, loss of appetite, and mild nausea. He was admitted to the dispensary on January 20. Symptoms became progressively worse during the next 3 days, and on January 23 jaundice became evident. The patient was sent to the hospital with a diagnosis of malaria or hepatitis. On admission, temperature was 100.8° F.; pulse, 82; respirations, 16. He complained of headaches, mild abdominal pain, complete loss of appetite, occasional nausea and vomiting. Physical examination revealed moderate jaundice; the liver was slightly enlarged and tender; the spleen also was enlarged and tender; the chest was clear. Neurologic examination was negative. On January 25 the patient appeared slightly improved; he was afebrile, but liver and spleen were very tender, and icterus was deepening. He vomited during the night. On January 27 he was very drowsy but could be aroused easily, was well oriented, looked critically ill, and had vomited two or three times. By January 28 the patient was deeply jaundiced; he was in coma but responded to painful stimuli. The liver was palpable two fingersbreadth below the costal margin. On January 29 the coma deepened; there was some rigidity of the extremities; pulmonary edema developed. Death occurred on January 30; duration of disease, 11 days.

Chemical Examination of the Blood

Date	Nonprotein nitrogen (*mg. per cent*)	Blood sugar (*mg. per cent*)	Icterus index
Jan. 27			133
Jan. 28	72	56	124

Blood Counts

Date	Red blood cells (*millions*)	White blood cells	Polymorphonuclear leukocytes (*per cent*)	Lymphocytes and monocytes (*per cent*)
Jan. 24	4.9	9,000	74	26
Jan. 27	4.7	8,000	71	29
Jan. 29	4.5	10,000	76	24

Blood Examinations for Malarial Parasites

Jan. 24, 25, 26, 27, 28, and 29 Negative

Case 11

The patient (Army Institute of Pathology, 126811) was a white soldier, 31 years of age.

Clinical Course. On October 3 he received a perforating gunshot wound of the abdomen necessitating laparotomy and colostomy. He made a good recovery, gained 10 pounds, and felt well for the next 3 months. On December 28 the colostomy was closed under local anesthesia; the postoperative course was uneventful. On January 9 he complained of pain in the epigastrium, became nauseated and vomited. On January 11 he was still slightly nauseated; the abdomen was soft and flat; the lungs were clear. On January 12 temperature mounted to 104° F.; the patient vomited and was nauseated; by evening he was somewhat disoriented. The conjunctiva was definitely icteric; the urine was dark; the stools light brown; the abdomen was soft and tender over both the hepatic and splenic regions, but the liver was not palpable. On January 13 the patient suddenly collapsed; the

pulse became very rapid and almost imperceptible; respiration was strained as in marked air hunger; blood pressure fell to 84/66 mm. Hg; temperature was 103.2° F. by rectum. The patient was alternately comatose and awake and restless. Blood pressure measurements were made repeatedly and, although they could not be accurately obtained, approximated 88/60 mm. Hg. The pulse became very thready and weak, the breathing shallow. Death occurred on January 13; duration of disease, 4 days.

Laboratory Findings. Chemical examination of the blood: Nonprotein nitrogen (January 12), 37 mg. per cent; icterus index (January 13), 60. *Urine* (January 12): albumin, 2 plus; bile, 0.

(For photomicrographs of kidney see Figs. 31 and 32.)

Case 12

The patient (Army Institute of Pathology, 128714) was a white soldier, 28 years of age.

Clinical Course. On January 9, 1944, he suffered severe burns on the legs, when gasoline spilled on his uniform and was ignited. The resulting burns were debrided, sulfadiazine ointment was applied, and he received plasma intravenously. On October 25 multiple grafts were applied to the wound and by November 5 they had taken. On November 11 the patient complained of abdominal fullness and distress. On November 13 he vomited, and also noticed that his skin had become yellow and his urine dark. On November 14 he vomited a great deal but had no other complaints. On November 15 his condition appeared good; blood pressure was 120/80 mm. Hg. He took small amounts of fluid eagerly and retained them. In the afternoon, however, he became increasingly restless and later delirious. Respirations were labored and pulse weak. Edema of the lungs was noted. Death occurred on November 16; duration of disease, 5 days.

Chemical Examination of the Blood

Date	Nonprotein nitrogen (*mg. per cent*)	Urea nitrogen (*mg. per cent*)	Icterus index	Blood sugar (*mg. per cent*)
Nov. 14	36		77	
Nov. 15	35			111
Nov. 16 (a.m.)	35	5.6		97
Nov. 16 (p.m.)	44	5.5	175	44

Blood Counts

Date	Red blood cells (*millions*)	White blood cells	Polymorphonuclear leukocytes (*per cent*)	Lymphocytes and monocytes (*per cent*)
Nov. 14	5.3	8,350	72	28
Nov. 16	5.2	16,450	90	10

Case 13

The patient (Army Institute of Pathology, 114947) was a Javanese soldier of the Dutch Army, 31 years of age.

Clinical Course. On or about June 3 he noticed vague abdominal pain and began to vomit. His stools became light in color. When he was admitted to the hospital on June 9 the temperature was normal, liver and spleen were neither palpable nor tender, and the abdomen was soft. The scleras were then normal,

but on June 10 became slightly icteric. The stools were clay-colored. The patient vomited coffee-ground material. On June 11 he became irrational, over-active, and then listless. On June 12 scleras were definitely icteric; the patient sank into coma. For the first time since the onset of symptoms there was fever, which rose to 104° F. Death occurred on June 12; duration of disease, 9 days.

Chemical Examination of the Blood

Date	Icterus index	Nonprotein nitrogen (*mg. per cent*)
June 11	85	
June 12	160	60

(For photomicrograph of liver see Fig. 11.)

Case 14

The patient (Army Institute of Pathology, 104032) was a white soldier, 22 years of age.

Clinical Course. On December 3, 1943, he complained of nausea and vomiting. He was admitted to the hospital on December 4, appearing neither acutely ill nor in discomfort; nausea and vomiting were not severe; there was slight tenderness in the upper abdomen. Temperature was 99° F.; pulse, 88; respirations, 22; blood pressure, 100/80 mm. Hg. On December 7 an icteric tint to the scleras was noticeable. During the next 2 days jaundice deepened rapidly and became intense by December 10. The liver edge was palpable. The patient became irrational, later comatose. Death occurred on January 12; duration of disease, 9 days.

Chemical Examination of the Blood

Date	Icterus index	Nonprotein nitrogen (*mg. per cent*)
Dec. 8	25	
Dec. 10		40
Dec. 11	75	

Blood Counts

Date	Red blood cells (*millions*)	White blood cells	Polymorphonuclear leukocytes (*per cent*)	Lymphocytes and monocytes (*per cent*)
Dec. 4	4.3	6,350	76	24
Dec. 5	4.3	6,000	60	40
Dec. 8	4.1	6,850	77	23
Dec. 10	4.8	5,100	79	21

Urine

Date	Bile
Dec. 4	0
Dec. 8	+
Dec. 10	+

Case 15

The patient (Army Institute of Pathology, 111844) was a white soldier, 22 years of age.

Clinical Course. He was admitted to the hospital in January, 1944, with edema of the hands and feet. Hypoproteinemia was found, without alteration of the albumin-globulin ratio. The origin of the protein deficiency was obscure; all tests for liver function were normal. He was placed on a suitable diet and given five plasma transfusions. Within 4 weeks his blood proteins had reached normal levels and he was discharged. On April 5 he complained of abdominal pain and nausea, and jaundice appeared. When the patient was admitted to the hospital on April 12 the liver was enlarged and tender and the urine dark brown. His condition deteriorated rapidly. On April 14 he was delirious, his abdomen was distended, and jaundice was deepening; coma ensued. The clinical course in the hospital was entirely afebrile. Death occurred on April 15; duration of disease, 10 days.

Chemical Examination of the Blood

Date	Icterus index	Urea nitrogen (*mg. per cent*)	Serum protein (*gm. per cent*)	Albumin (*gm. per cent*)	Globulin (*gm. per cent*)
April 12	60				
April 14	105	12	6.9	3.0	3.9
April 15	105	14	7.0	3.2	3.8

Blood Counts

Date	Red blood cells (*millions*)	White blood cells	Polymorphonuclear leukocytes (*per cent*)	Lymphocytes and monocytes (*per cent*)
April 12		7,500	63	37
April 14		9,150	70	30

(See Fig. 26 for photomicrograph of proliferating bile ducts.)

Case 16

The patient (Army Institute of Pathology, 128072) was a white soldier, 26 years of age.

Clinical Course. On October 23, 1944, he was wounded in action by an enemy mine, sustaining traumatic amputation of the lower part of the left leg. Early treatment included administration of sulfadiazine, penicillin, and transfusions of whole blood and blood plasma. Convalescence was uneventful; the soldier was returned to the United States and under further treatment the stump healed satisfactorily. On January 7, 1945, he complained of vague abdominal discomfort, loss of appetite, aversion to greasy foods, general malaise, nausea and vomiting. During the next few days, loss of appetite and abdominal discomfort continued, but nausea and vomiting subsided. On January 13 he had a mild attack of urticaria and became slightly jaundiced. The liver was not definitely palpable, but was slightly tender and increased in size to percussion. Diagnosis of acute hepatitis was made and treatment instituted. The patient's condition remained essentially unchanged until the morning of January 17, when he suddenly became confused, then disoriented, and finally stuporous and comatose. Oozing of bloody fluid from the mouth became profuse. Icterus deepened in intensity; the liver, which 3 days before had been somewhat enlarged, now was found to be definitely smaller to percussion. The blood pressure fell from 155/90 to 84/40 mm. Hg. There was a terminal rise of temperature to 105° F. Death occurred on January 18; duration of disease, 11 days.

Laboratory Findings. (January 15.) *Blood:* icterus index, 76; white blood cells, 10,400; (January 17) blood nonprotein nitrogen, 32 mg. per cent; blood urea nitrogen, 4 mg. per cent.

Case 17

The patient (Army Institute of Pathology, 129051) was a white soldier, 27 years of age.

Clinical Course. On August 7, 1944, he was wounded in action by a rifle bullet, sustaining a compound fracture of the left os calcis. A suppurating sinus persisted, and he was evacuated to the United States. Between November 15 and December 22 he was treated with penicillin. At Christmas he was well enough to receive a convalescent furlough. On his return, penicillin therapy was again instituted. Although evidence of healing of the bone defect could be seen in the roentgenogram, a sinus still persisted which required surgical treatment. Before the contemplated operation the patient was granted another furlough. On February 14, upon arriving at the home of his sister, he stated that he was not feeling well and complained of pain in the right hip, nausea and vomiting. It was noted that his scleras were yellowish and his skin slightly jaundiced. He declined to return to the hospital as he did not believe himself seriously ill. On February 15 he stayed overnight with a friend and on the morning of February 16 he was restless and at times irrational. He was taken by ambulance to an Army hospital, arriving on the morning of February 18. On admission he was semiconscious. His pupils were unequal, the left being larger than the right; both reacted to light. His neck was definitely rigid. Spinal puncture was done; the fluid was clear and apparently not under increased pressure. Physical examination disclosed slight icterus and hyperactive reflexes. The abdomen was soft and the lower extremities were spastic. Râles were heard over the chest. The diagnosis of meningitis was entertained although examination of the spinal fluid was not confirmatory. Pulmonary edema developed. Death occurred on February 18; duration of disease, 4 days.

(For photomicrograph of liver see Fig. 16.)

Case 18

The patient (Army Institute of Pathology, 128329) was a white soldier, 23 years of age.

Clinical Course. On May 26 anorexia, nausea, and fever developed, and he was admitted to the hospital on May 27. He appeared acutely ill; temperature was 100°, later 103° F. The spleen and liver were not palpable or tender. Chest examination was negative. On May 28 his general condition was improved; temperature dropped to 99.2° F., and subsequently remained normal. The patient was eating well. On May 31 jaundice was noted for the first time; he also complained of nausea. On June 1 he appeared ill, with lassitude, nausea and vomiting; jaundice deepened rapidly. On June 2 he became semistuporous and restless; there was slight tenderness in the upper abdomen. On June 3 profound coma set in, but there were no abnormal neurologic findings. Pulmonary edema developed. Death occurred on June 4; duration of disease, 9 days.

Chemical Examination of the Blood

Date	Icterus index	Urea nitrogen (*mg. per cent*)	Serum protein (*mg. per cent*)	Albumin (*gm. per cent*)	Globulin (*gm. per cent*)
May 31	65	5.7	5.8	3.5	2.3

Urine

Date	Albumin	Bile
May 28	++	o
May 31		+
June 2		+
June 4	++	

Case 19

The patient (Army Institute of Pathology, 129240) was a white soldier, 27 years of age.

Clinical Course. On October 23, 1944, he was wounded in action, suffering traumatic amputation of the left foot. He was treated by debridement, transfusions of plasma and whole blood, and penicillin. Convalescence was uneventful until January 23, 1945, when anorexia and nausea appeared and he noticed that his urine was becoming darker and his feces lighter than normal. Sensations of chilliness and general malaise were followed by a rise in temperature to 102° F. On January 24 he had a second chill; his temperature now rose to 104° F. He was jaundiced. The liver edge extended 2 fingersbreadth below the costal margin and was not tender. The spleen was easily palpable. On January 26 temperature fell to normal and remained between 97° and 99° F. for the next few days; nausea diminished; his appetite, however, remained very poor. On January 28 the patient suddenly became much worse; he vomited repeatedly; jaundice increased in intensity; the liver appeared to diminish in size; he became mentally confused and delirious; bled from the mouth and nose; and lapsed into coma. Death occurred on February 1; duration of disease, 9 days.

Chemical Examination of the Blood

Date	Icterus index	Nonprotein nitrogen (*mg. per cent*)	Serum protein (*gm. per cent*)
Jan. 25	33	36	6.2
Jan. 28	120		

Blood Counts

Date	Red blood cells (*millions*)	White blood cells	Polymorphonuclear leukocytes (*per cent*)	Lymphocytes and monocytes (*per cent*)
Jan. 25	4.5	5560	60	40

Repeated examinations of blood for malarial parasites were negative.

Case 20

The patient (Army Institute of Pathology, 133194) was a white soldier, 21 years of age.

Clinical Course. He had been hospitalized for "hepatitis without jaundice," once for 2 months, beginning April, 1944, and a second time for 4 months, beginning June 20, 1944. His symptoms consisted chiefly of distress in the upper abdomen radiating to the back, anorexia, and intolerance for greasy foods. He was also thought to be psychoneurotic with seclusiveness and dependency; a diagnosis of "anxiety state" had been made. On the third entry to the hospital, on November 6, physical examination was negative; liver and spleen were not palpable. Laboratory studies the week after admission were negative; icterus index, 8; cephalin flocculation, 0/0; blood phosphatase, 4.4 units. Hemoglobin, 85 per cent; red blood cells, 4,500,000; white cells, 5,250, with 62 per cent polymorphonuclear leukocytes and 38 per cent lymphocytes. He complained of constant upper abdominal pain throughout the several weeks he was observed as a psychoneurotic patient. On November 22 he complained of headache, anorexia, and nausea. On November 23 he felt feverish; temperature rose to 100° F.; abdominal pain became more severe. Physical examination showed tenderness but no rigidity in the right upper quadrant. That evening he had a chill lasting 30 minutes. The morning urine,

November 24, was dark; the scleras were questionably icteric. Tenderness in the right upper quadrant persisted, but the liver could not be felt. By November 28 the scleras were definitely icteric and the icterus index was 27. He became acutely ill with severe vomiting. The right upper quadrant was exquisitely tender. On November 30 restlessness alternated with lethargy, vomiting continued, and the patient went into coma. Death occurred on December 1; duration of disease, uncertain (terminal illness, 8 days).

Case 21

The patient (Army Institute of Pathology, 123465) was a white soldier, 25 years of age.

Clinical Course. On July 30, 1944, he was admitted to a clearing company in a state of mental agitation. The diagnosis was "battle fatigue." While on the ward he became disturbed, fearing Japs were going to attack him. He had no other complaints and physical examination was negative except for evidence of recent loss of weight. There was no jaundice. Under mild sedation he became somewhat quieter. In the evening of the same day his respiration ceased suddenly and no pulse was perceptible. Death was thought to have occurred instantly, due either to cardiac stoppage as a result of vagus stimulation secondary to fright, or to pulmonary embolism. Death occurred on July 30; duration of disease, uncertain (clinically, 1 day).

(For photomicrographs of liver see Figs. 8, 15, 24, and 27.)

Pathologic Anatomy

In fulminant hepatitis, lesions other than those in the liver are not striking. The changes in the gallbladder, extrahepatic bile ducts, regional lymph nodes, bone marrow, and the hemorrhagic phenomena are of the same general type as described previously. We may limit ourselves, therefore, to accounts of the liver, ascites, spleen, intestines, kidney, and brain.* Consideration of the prostate will be reserved for a future communication. No noteworthy pathologic changes were found in the other organs.

Similarity of Lesions of "Spontaneous" and "Inoculation" Hepatitis. The lesions of the several epidemiologic forms of hepatitis included in this study are in every respect indistinguishable. Hence an account of the pathologic anatomy may be given for the entire series.

LIVER

Two processes characterize the pathologic picture of the liver in fulminant hepatitis: extreme and often complete destruction of liver cells, and marked inflammatory response. From naked-eye examination of the organ, however, it is not possible to surmise the extensive destruction of the parenchyma or the degree of inflammation. The vague term "acute yellow atrophy," although connoting rapid break-

* We are grateful to Lt. Col. Philip Custer for examining many sections of spleen, and to Dr. Nathan Malamud and Major Webb Haymaker for advice regarding the changes in the brain.

down of hepatic parenchyma, is not descriptive of the appearance, and cannot properly be applied.

Gross Appearance

In the great majority of cases the liver is reduced in size, but the shrinkage is usually moderate. The weights are given in Table XI: in one-half they range between 1000 and 1400 gm., and in approximately one-third of the series they are below 1000 gm. Excessive reduction to below 800 gm. occurs in only 6 per cent, and, at the other extreme, weights exceed 1600 gm. in 11 per cent. The median for the entire group is 1150 gm. The data upon which Table XI is based are graphically analyzed in Text-Figure 7 (p. 904), first, with respect

TABLE XI

Weight of Liver in 101 Cases of Fulminant Hepatitis

	No. of cases	Associated with ascites
Below 800 grams	6	1
800 —999	25	5
1000—1199	28	9
1200—1399	22	6
1400—1599	9	1
1600—1799	8	6
Over 1800	3	2
Total	101	30

to duration of disease; second, with reference to the two main epidemiologic forms (represented in the figure as "wounded" and "not wounded"), and, third, in relation to the presence or absence of ascites. Great scattering of weight and absence of correlation with duration are evident. For example, the livers from the 12 cases having a duration of 4 days weigh from 600 to 1800 gm., with a median of 1200 gm. Livers from cases having durations of only 2 or 3 days present as great shrinkage or as little change in size as those with a longer course. Livers from fatal cases of "naturally" occurring hepatitis do not differ significantly in weight from those of "inoculation" hepatitis. The relation to ascites will be discussed later.

The surface is always either smooth or finely wrinkled (Fig. 1); it is never deformed by the nodular or tumor-like elevations characteristic of the subacute stage. The shape is little altered, except that the anterior edge commonly is sharp. The capsule is usually transparent. Small subcapsular hemorrhages are common. The color is not distinctive and varies through shades of red, purple, and brown; mottling is common and such combinations as gray-red and purple, or tan and red, are often observed. The organ is usually soft and flabby, sometimes to

such an extent that it flattens when laid on the table; but the flabbiness may be masked by such great engorgement that the organ is tense.

The cut surface nearly always shows diffuse involvement, most frequently in the form of an exaggerated "nutmeg" pattern (Figs. 3 to 7). The lobular peripheries are outlined by pale grayish or yellow-gray bands of variable width, which contrast with the dark red or purple of the slightly sunken inner part of the lobules. In other cases, on the contrary, the landmarks are so indistinct that the cut surface resembles that of an acutely congested spleen (Fig. 2). The blood content also varies considerably; in some instances the inner zones of every lobule ooze blood copiously, in others the entire organ is relatively ischemic; sometimes areas of engorgement and relative bloodlessness alternate. The cut surfaces nowhere have a greasy sheen; the bands which outline the lobules have the fresh appearance of healthy tissue; the lobular interiors, when not too greatly congested, are dull grayish red, but not fatty.

In roughly 10 per cent of the cases the changes are most marked in the left lobe, which is more shrunken and has a more wrinkled surface.

Microscopic Appearance

In this section we shall deal principally with the lesions typical of the fulminant form of hepatitis in which the clinical duration of disease is less than 10 days. Later a brief account will be given of the changes found in two other groups of cases, namely, those which survive from 10 to 19 days, and those of unknown clinical duration. These two groups are important because they not only show transition stages to the subacute form previously studied, but they also illustrate the disparity which may exist between the clinical course and the anatomic changes.

As already stated, two processes dominate the microscopic picture of fulminant hepatitis: extensive destruction of liver cells and marked inflammatory reactions. Regenerative hyperplasia of surviving parenchyma, which is so prominent a feature of the subacute form, is lacking or minimal, and is confined to biliary rather than to hepatic epithelium.

Destruction of Liver Cells. The destructive process, in the majority of cases, involves all parts of the liver uniformly. As a rule, destruction of liver cells is extensive and, in many instances, complete (Figs. 8, 9, and 15); but often a narrow rim, a few cells in width, persists at the lobular periphery (Fig. 16). Very rarely the destruction instead of being predominantly central is peripheral, sparing small isolated patches of parenchyma in the interior.

In a few of the most rapidly fatal cases a scattering of shadow forms

of liver cells sometimes remain but it is distinctive that the dead cells are removed rapidly. In the entire series no example of the earliest stage in the necrotic process was encountered; cell destruction was always advanced. As a rule, even in cases with a clinical history of only 3 or 4 days no traces of dead cells were found. These facts suggest that the agent bringing about necrosis effects speedy lysis and enzymic digestion rather than cell coagulation as seen in the necrosis of anoxemia and after many hepatic poisons. Less commonly the few remaining cells show degenerative changes, such as small irregular droplets of fat or other vacuoles in the cytoplasm. These changes are regarded as secondary to the profound disturbances of blood supply that accompany necrosis of the parenchyma.

Persistence of Reticulum and of Sinusoids. The destructive process specifically affects liver cells; the other components of the lobule escape. The reticulum, in all cases, is intact (Fig. 17). The inter-reticular spaces, formerly occupied by liver cells, in some instances become packed with monocytes and erythrocytes and little shrinkage occurs (Fig. 21); in other instances the meshes are empty and collapsed. The sinusoids usually are widely engorged (Figs. 9 and 22); small hemorrhages occasionally occur. In brief, the liver in fulminant hepatitis is rapidly reduced to a spongy framework, infiltrated by inflammatory cells and often distended with blood.

Inflammatory Reaction. In the present series, inflammatory cellular infiltration is considerably more marked than in the subacute form. The cell reaction is most conspicuous at the lobular periphery, *i.e.*, in the portal stroma and the interlobular boundary (the "septum vasculare").[10,19,20] Within the lobular remnants inflammation is less prominent and of somewhat different type.

Often whole lobules are outlined by bands of densely packed cells (Figs. 8 and 9). The composition of the infiltrate varies from case to case; a fairly representative picture is shown in Figure 11. It will be noted that the cells are well preserved and that there is no indication of breakdown. They are chiefly mononuclear forms—reticulo-endothelial derivatives, plasma cells, and lymphocytes—but neutrophils and eosinophils in relatively small numbers are almost invariably present (Fig 13).

Within the lobular remnants, mobilized and proliferated macrophages predominate; frequently they become so large and numerous as to give a spurious appearance of a "parenchyma" consisting of disunited but preserved liver cells (Fig. 14). The macrophages commonly contain a brownish, sudanophilic, and faintly acid-fast pigment, lipofuscin, which probably is derived from the disintegrated hepatic cells.

Lymphocytes, plasma cells, and granulocytes, while not numerous, are present also.

Inclusion bodies, cytoplasmic or intranuclear, such as occur in many different virus infections, are not encountered in any kind of cell.

Efferent Veins. In the subacute form of hepatitis of the 1942 series, endophlebitis of the efferent veins was a conspicuous, though not a pathognomonic, feature. In the fulminant form it is less commonly encountered. Frequently, however, the walls of the central lobular and smaller collecting veins are much thickened and of homogenous, hyaline texture (Fig. 18).

Regeneration of Liver Cells. In no case of the fulminant group is there any noteworthy degree of regenerative hyperplasia. At most, the persistent cells are large, irregular in outline, and multinucleated; significant increase in number is not apparent. Regeneration obviously cannot take place when destruction of the parenchyma is complete.

Proliferative Changes in Bile Ducts. It is of importance to note that in most cases, even the most acute, the small twigs of the bile ducts, both septal (perilobular) and interlobular, exhibit some evidence of proliferation. These little ducts normally are inconspicuous. The degree of proliferation attained is illustrated by representative photomicrographs. In Figure 23 is shown a septal duct composed of large, closely packed cells with prominent nuclei; the duration of disease in this case was only 3 days. In Figure 24 may be seen a more conspicuously proliferating duct lying in the portal stroma; the duration in this case was, clinically, less than 1 day. In 2 cases with duration of 9 or 10 days, the ducts have irregular shapes, due to budding and branching, and the nuclei of the component cells are deeply chromatic (Figs. 25 and 26).

These examples illustrate the rapid proliferation of which biliary epithelium is capable.

Lesion in Patients Surviving from 10 to 19 Days. In approximately one-third of the patients surviving 10 to 19 days the lesions were identical with those of the more fulminant cases. Thus, in some instances, the microscopic picture of the liver from patients who survived for 10 or more days was indistinguishable from that when death occurred within 3 or 4 days after onset. More often, however, the lesions were similar to those encountered at corresponding periods of survival in the 1942 series. In agreement with the findings in that series the involvement of the liver in the less fulminant group is not uniform. This difference is shown in Figures 28 and 29, which represent fields from two hepatic areas of a patient who survived for 12 days. Figure 28 shows a region in which destruction of hepatic parenchyma is in-

complete, while Figure 29 is from an area in which destruction is practically complete and the lobular remnants are outlined by proliferating bile ducts.

Correlation between Gross and Microscopic Changes. The degree of engorgement and of inflammatory infiltration are clearly correlated with size and appearance of the liver. As to the former, the content of blood accounts for the great variations of weight, despite the fact that in all cases only traces of parenchyma remain. The predominant "nutmeg" pattern of the cut surface is brought about by a combination of the marked inflammatory infiltration at the lobular periphery and the engorgement in the interior of the lobular remnants. In cases where the cut surface resembles that of a congested spleen, engorgement outbalances inflammation.

As has been stated, the gross appearance of the liver gives no indication of the extreme destruction of the parenchyma.

Disparity between Lesions and Clinical Duration

The clinical duration is not always correlative with the pathologic findings; sometimes the process is obviously older than the history suggests, less often the reverse is true. For example, in many instances no relation can be established between duration of disease and degree of inflammatory reaction; its severity in some of the shortest cases makes the conclusion inescapable that the reaction must have antedated the first symptoms. Similarly, there is often no correspondence to the extent of parenchymatous destruction or to the degree of proliferation of the small bile ducts. For example, the lesions shown in Figures 8, 15, 24, and 27 are from a patient with a clinical course of less than 1 day; but all traces of dead liver cells have been removed and the bile ducts exhibit active proliferation. In numerous other very early cases like pictures are obtained. Again, in some of the most fulminant cases, jaundice appeared on the first day; no doubt disintegration of the liver was advanced before symptoms began.

An even greater discrepancy between clinical history and pathologic changes was noted in a group of 18 cases which purposely were omitted from the analysis of duration given in Tables I, II, IV, and XII. In this group, 5 cases with a short course showed evidence of well marked regeneration with nodularity of the livers. In contrast, 8 cases prolonged for more than 20 days presented the acute changes characteristic of the fulminant form. It is possible that some of the latter were recurrent infections which ran an acute course.

It may be concluded that in the more rapidly fatal cases the lesions are older than the clinical manifestations; in other words, when symp-

toms appear the liver is already definitely involved; in some instances the clinical course may be "silent," or the symptoms minimal even when death occurs within a few days. These conclusions are borne out by the studies of specimens taken for biopsy at different stages of the disease in nonfatal cases; here also the lesions frequently appear older than the clinical duration.[19,40]

Ascites

The incidence of ascites has been tabulated for 140 cases (Table XII). There is a definite correlation between ascites and clinical duration of disease: the incidence rose from 24 per cent when death occurred within 10 days, to 43 per cent when it was delayed from 10 to 19 days, and to 70 per cent when the course was more protracted. The amount of fluid in the fulminant cases was usually less than 1 liter, whereas in the others, larger volumes (2 or 3 liters) were the rule.

TABLE XII

Occurrence of Ascites in 140 Cases of Hepatitis (New Series)

Duration of disease	Total no. of cases	Ascites	Per cent of cases
To 9 days	68	16	24
10—19 days	33	14	43
Over 19 days	39	27	70

The relation between ascites, weight of liver, and duration of disease is shown for wounded and nonwounded cases in a distribution graph (Text-Fig. 7). It will be noted that ascites occurred even in the most fulminant cases. The relation to weight of liver is interesting: ascites was more common when the liver was but little shrunken or was actually enlarged, than when its bulk was considerably decreased. Thus, in the 25 cases with livers weighing above 1300 gm. ascites was observed 11 times, whereas it occurred only 4 times in the 25 cases having the smallest livers (below 920 gm.).

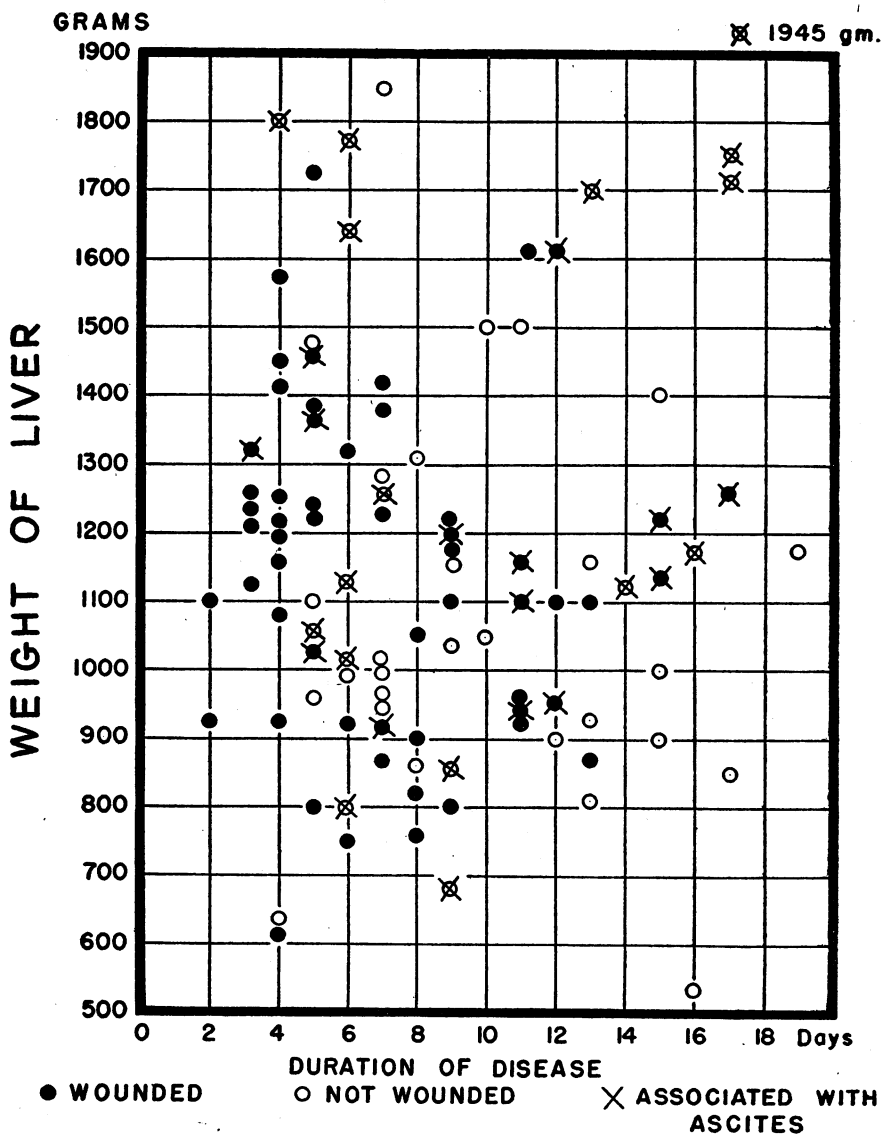
The differences in the incidence of ascites in the wounded and nonwounded groups are probably due to the more rapid course of the disease in the former.

SPLEEN

In approximately two-thirds of the cases the spleen was enlarged and its weight exceeded 200 gm.; in about one-fourth it weighed more than 300 gm. (Table XIII).

Detailed information pertaining to the relation of weight to duration for the wounded and nonwounded groups is given in Text-Figure 8.

It is clear that in these fulminant cases there is no definite relation of weights either to duration of illness or to the epidemiologic forms of hepatitis. For example, in the 6 cases in which death occurred 3 days



Text-Fig. 7. Distribution of hepatic weights in respect to duration of disease for wounded and nonwounded patients.

after onset of symptoms, 3 of the spleens weighed approximately 450 gm., the 3 others less than one-half as much. The somewhat greater number of large spleens among the wounded probably is relative to the preponderance of this group.

Grossly, the spleens in the fulminant cases usually had a tense capsule, but when bisected were found to be soft. The cut surface was dark red and congested. The follicles were large and in many instances contained a central opaque fleck.

Microscopically, the majority presented a well marked hyperplasia of reticulo-endothelial and lymphoid components. The follicles usually were prominent and their germinal centers were enlarged and often degenerated or necrotic (Fig. 27). Similar small focal areas of necrosis were frequently observed in the pulp. Occasionally the organ was conspicuously infiltrated with eosinophils and plasma cells. Nearly all spleens were greatly congested, often to such an extent that small

TABLE XIII

Weight of Spleen in 94 Cases of Fulminant Hepatitis

(gm.)	Number of cases
To 99	2
100—199	28
200—299	43
300—399	7
400—499	9
Over 500	5

hemorrhages had occurred. Rigidity of the sinuses with depletion of pulp, such as was the rule in the subacute cases, was not observed.

The common enlargement of the spleen in fulminant hepatitis is due to hyperplasia of its component cells and to acute congestion.

INTESTINES

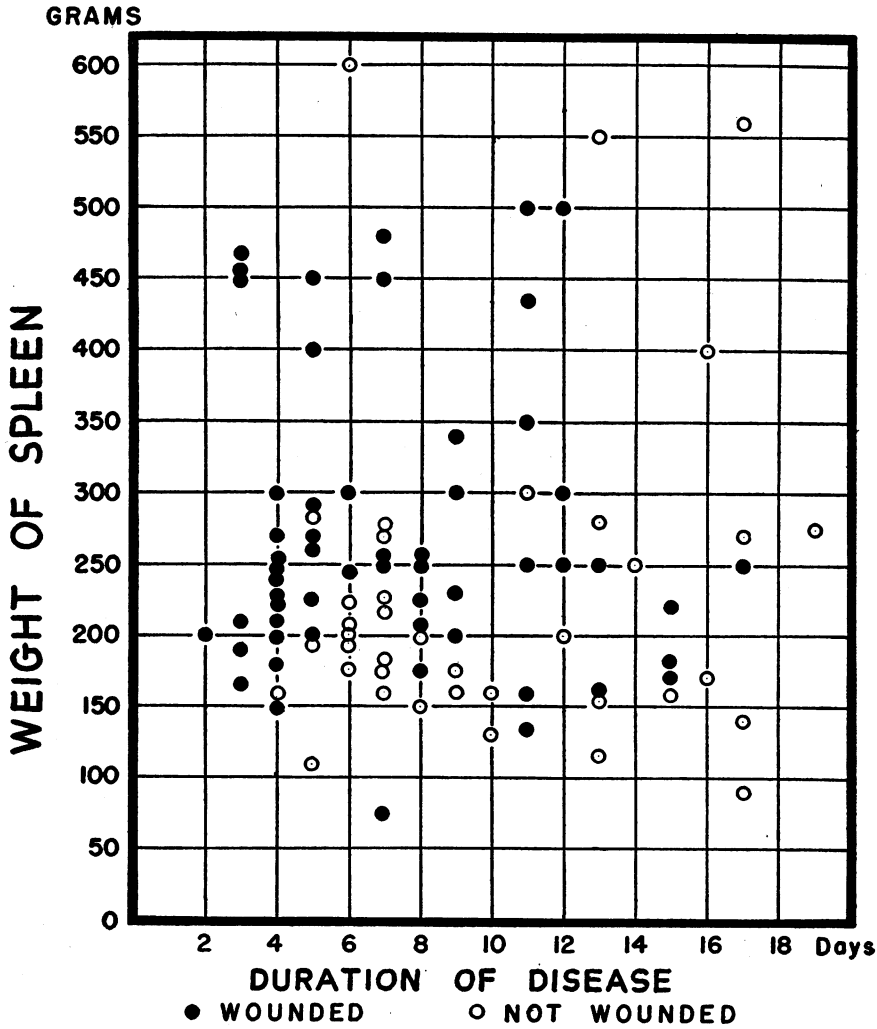
Phlegmonous inflammation of the colon, which occurred in 15 per cent of the subacute cases,[24] was not present in any fulminant ones. Occasionally there was a moderate degree of edema, always associated with ascites. Mucosal hemorrhages were equally as extensive as in the earlier series.

KIDNEYS

The kidneys were slightly swollen in most cases, 20 per cent being of normal size, 40 per cent weighing from 350 to 400 gm., and the remaining 40 per cent slightly above 400 gm.; no enlargement over 500 gm. was recorded. The variation in color was wide; some kidneys were dark from congestion; others were pale. In very few was any bile discoloration evident, and then it was confined to tinting of the pelvic epithelium; none was deeply bile-stained.

Microscopically, as observed in routine paraffin sections, there were few conspicuous changes. The glomeruli were uniformly normal except

for the presence in some instances of albuminous precipitates in the capsular spaces. The epithelium of the proximal convoluted tubules was generally slightly swollen and frequently showed basal vacuolization; the nuclei were well preserved and normally chromatic. Very



Text-Fig. 8. Distribution of splenic weights in respect to duration of disease for wounded and nonwounded patients.

little bile staining could be recognized in the epithelial cells, and bile-stained casts were seldom found. No severe degenerative changes and no necrosis were present at any level of the tubules. There was no interstitial reaction.

Fat deposits were usually conspicuous when frozen sections were stained with sudan stains. They were most marked in the proximal convoluted tubules (Figs. 28 and 29), beginning in the neck and con-

tinuing through the entire length; were less constant and less severe in the ascending limbs of Henle (Fig. 30), and still less so in the distal convoluted tubules. The deposits were always most apparent in the basal portion of the cells; the individual droplets were generally minute, but some attained the diameter of the nucleus. No fat was seen in the glomeruli, in the descending limbs of Henle, in the collecting tubules, or in the interstitial tissues. With polarized light the fat did not prove doubly refractile.

The degree of deposition of fat was estimated on a 1 to 3 plus scale in 39 cases chosen at random. No relation was found between its intensity and the degree of nitrogen retention, but when the amount of fat vacuolization was compared with duration of disease a distinct relationship became apparent. In 23 cases showing heavy deposits the average duration of hepatitis was 6 days. No fat, or only traces of it, was observed in 16 cases in which the average survival period was 11 days. Either the process is more severe when hepatitis is most fulminant, or it is a transitory phenomenon which tends to disappear with the passage of time. The lack of other evidences of epithelial degeneration suggests that it is a storage phenomenon, possibly dependent on the sudden liberation of large amounts of fat from the destroyed liver cells.

The absence or mildness of the degeneration observed in this series contrasts sharply with the severe grades of bile nephrosis noted in the subacute cases previously reported.[24]

BRAIN

The brain grossly presented no significant changes. Particularly noteworthy was the absence of hemorrhage. Microscopically, a nonspecific encephalopathy of mild degree was nearly always observed. In the most fulminant cases the bodies of many ganglion cells were swollen, the nuclei distorted and their chromatin granules dispersed and scattered. When the disease lasted more than 10 days some ganglion cells usually were shrunken and had dense pyknotic nuclei. Satellitosis and neuronophagy were moderate in some locations, but nowhere were they conspicuous. No perivascular round cell infiltrations, such as in the subacute form, were observed either in the meninges or the nervous system proper.

The glia presented interesting alterations. "Naked nuclei" were frequently numerous; they were poorly chromatic, somewhat swollen, and often slightly distorted. Nuclei of this kind have been described in many forms of hepatic disease; they are, however, not specific. The glial reaction was most evident in the basal ganglia.

Despite the prominence of nervous manifestations in the terminal

stage of hepatitis, the histologic changes usually are not impressive. This has been attributed to the tempo of the disease, for cerebral manifestations as a rule precede death by but few days.[41]

Clinicopathologic Correlations and Discussion

Fulminant hepatitis differs in numerous features from the subacute form which, until 2 or 3 years ago, had prevailed in all recorded epidemics. Is it a different disease? Are particular etiologic or epidemiologic factors responsible for its fulminant character? What is the mechanism of jaundice and of ascites in this form? What effect does rapid destruction of the liver have on the kidney? These are the questions we have selected for brief discussion. None can adequately be answered; rather, discussion can only indicate the need for further investigation.

Clinical and Epidemiologic Forms of Epidemic Hepatitis

Clinically, the fulminant form of hepatitis is characterized by the short and stormy course, the frequency of fever during the prodromal stage, and the brevity of the icteric stage. Biochemically, the fall in blood sugar and the low value of blood urea nitrogen reflect rapid and massive necrosis of the hepatic parenchyma. Pathologically, the outstanding lesions are extensive and comprise uniform destruction of liver cells, minimal evidence of regeneration, and marked inflammatory infiltration especially of the portal areas and the perilobular boundaries.

Consideration must be given the possibility that we are dealing with a disease different from epidemic hepatitis. Against this hypothesis two arguments can be raised. First, the similarities are greater than the differences, and these differences, in turn, are quantitative rather than qualitative. No new features, either clinical or pathological, have appeared in the current form, although some have been exaggerated or minimized. Second, all grades of transition between the fulminant and subacute forms have been observed. The conclusion is warranted, therefore, that fulminant hepatitis is a form of epidemic hepatitis, although final proof must wait upon advances in the determination of etiologic factors and upon controlled experimentation.

The specific causal agent of epidemic hepatitis has the attributes of a filtrable virus.[28,37,42-45] The virus has not as yet been cultivated, nor has any animal susceptible to it been found.[5,43] At present the only means of demonstrating the virus is by human transmission; in recent years this has been accomplished with volunteers.[33,42,44,46] The infectious agent has been shown to exist in the blood, the feces, the urine,

and nasal washings. Under natural conditions the disease probably is transmitted either through the alimentary tract by ingestion of contaminated food or water, or through the nasopharynx as droplet infection.[5,28,44] Under artificial conditions it may be transmitted by parenteral injection of blood, plasma, or serum from an individual harboring the virus.

Two main epidemiologic variants of the disease may be recognized: naturally occurring hepatitis (in endemic or epidemic form), and inoculation hepatitis. The latter may develop after transfusions of blood or its derivatives (homologous serum hepatitis),[5,27,29,30,32,42,54] after inoculation of vaccine containing small amounts of infectious serum (post-vaccinial hepatitis),[5,11,47,48] after injections of therapeutic agents through needles or syringes contaminated with blood from an infected person (hepatitis after insulin injection, post-arsphenamine hepatitis).[49-51] Transmission experiments indicate that the specific causal agents of these variants are similar or closely related.[33,37,42,45,46]

From the epidemiologic point of view the present series, regardless of duration, comprises 57 per cent of spontaneous (*i.e.*, naturally-occurring) cases (of which 16 per cent are regarded as endemic and 41 per cent as epidemic), and 43 per cent are believed to represent homologous serum hepatitis. Cases of the controversial post-arsphenamine hepatitis have been excluded, and there are no examples of post-vaccinial hepatitis. This study has shown that in the fulminant form the manifestations of the disease and the lesions of spontaneous and transfusion hepatitis are in every respect indistinguishable. Similarily, the less fulminant examples of this series present pathologic changes indistinguishable from those observed in cases of comparable duration in the 1942 epidemic (in which the majority could be regarded as post-vaccinial hepatitis), and from those reported in the Swedish epidemic of 1927 (which represented the naturally-occurring disease). These findings are in agreement with clinical observations[5,29,31,32,50,51] and with biopsy studies of nonfatal cases.[19,20,52]

It is concluded that the epidemiologic variants of the disease do not differ in their clinical manifestations.

Factors Responsible for the Fulminant Form of Fatal Hepatitis

Epidemic hepatitis is the only disease of this war which has become pandemic. With widespread prevalence there are indications that the disease has become more severe; thus many observers have reported that in a high proportion of cases, instead of the common insidious onset, the symptoms are those of an acute febrile infectious disease. Yet the mortality rate, so far as can be judged from figures at present

available, has not significantly altered. However, the course of fatal hepatitis has been more fulminant during the past 2 or 3 years. To what this may be attributed—whether to host factors, which have promoted an increase in individual susceptibility, or to changes in the infectious agent—is difficult to assess. It is not known whether a fulminant course is associated with an especially virulent strain or an especially large dose of virus. As to host factors which may increase susceptibility to the infection, either in fatal or nonfatal cases, a number have been suggested: age, physical strain, diet, other diseases,[5] combat fatigue,[8,12] accidental variation in resistance,[2] and a poor nutritional state.[3] In the present series we may at least rule out the factors of age, climate, or other variables depending on geographic location. All the other factors may well have played a part. They are interrelated; the most tangible ones are the effects of trauma and consequent transfusions, and the effects of nutritional disturbances. Even if we cannot, at this time, arrive at the correct evaluation of these factors, a discussion of them may point the way to future inquiry.

Trauma and Transfusion

Ninety per cent of the cases in this series occurred among combat troops in overseas theaters of war. Of the fulminant group nearly two-thirds (61 per cent) had sustained severe battle injuries or extensive burns; in sharp contrast, only 2 per cent of the group which survived for more than 20 days had been injured. Practically all casualties may be assumed to have received transfusions of blood or its derivatives. It is thus possible that the specific agent of hepatitis was transmitted directly and perhaps in large amounts. But tens of thousands of other men have sustained equally severe wounds, and have received transfusions wthout developing hepatitis. There is no accurate information as to how often hepatitis did develop. We do know that during the period of this study, covering nearly 2 years, the disease was fatal in less than 100 individuals who had been wounded and transfused.

Trauma, directly, cannot be implicated as the cause of fulminant hepatitis, but it may be important because it lowers individual host resistance in some manner.

The evidence that an infectious agent was transmitted by means of transfusion is circumstantial. It rests upon the well documented fact that the interval between parenteral introduction of virus and outbreak of symptoms, for all types of inoculation hepatitis, usually falls within a period of from 2 to 4 months.[27,29,37,42,47,48] The incubation period for the naturally-occurring disease is much shorter, and on the average

runs from 20 to 40 days.[37,42,45] The intervals between trauma and onset of symptoms in the present series is shown for 64 cases of fulminant hepatitis in Table XIV. It is a safe assumption that, for the majority of the casualties, plasma and transfusion therapy was concentrated within a few days of injury. Six cases of burns have not been included in this tabulation since these patients received plasma and whole blood for many weeks. From inspection of Table XIV it is evident that in the majority (69 per cent) the interval between transfusion therapy and onset of the disease fell within the limits of 50 and 89 days, the median duration being 70 days. It is very prob-

TABLE XIV

Interval between Receiving Wound and Initial Symptoms in 64 Cases of Fulminant Hepatitis

Interval	Number of cases	Per cent of cases
(*Days*)		
30—39	4	6
40—49	4	6
50—59	11	17
60—69	11	17
70—79	10	16
80—89	12	19
90—99	6	9
100—109	4	6
Over—110	2	3

able, therefore, that in these cases we are dealing with examples of hepatitis in which the virus was transmitted parenterally and not by "natural" means.

One distinct difference between naturally-occurring hepatitis and serum hepatitis in this series is the duration of disease; the course of the serum type tends to be more rapid (see Tables II and IV and Text-Figs. 1 to 3). Whether this is a general characteristic of this type of hepatitis cannot yet be stated with certainty; it may depend on the particular strains of virus injected, and on nonspecific individual host factors incident to combat trauma. In this connection the classical experiments of Opie [53] may be recalled. He demonstrated that the activity of a hepatic poison may be so enhanced by bacterial infection that a quantity of the poison which alone produces little change may, in combination with infective agents, cause destruction of almost the entire hepatic parenchyma. Opie believed it probable that those instances of acute yellow atrophy which accompany streptococcic infections are dependent upon some disturbance of metabolism or other form of intoxication which renders the liver unusually susceptible. Pertinent, too, are experiments of Bennett, Drinker, and Warren [55] on the effects of certain chlorinated hydrocarbons which may produce

extensive necrosis of the liver. These compounds are extensively used in industry, but the incidence of "acute yellow atrophy" in workers exposed to the compounds is very low. This fact suggests that certain individuals may be more susceptible, or that in fatal cases liver damage may have been augumented by some other agent. The latter hypothesis was tested by experiments on rats with confirmatory results; the effect of the compounds under discussion was found to be much enhanced by small sublethal doses of other hepatic poisons.

Nutritional Disturbances

It is well known that liver injury may be produced by purely nutritional factors.[56,57] Several observers have implicated improper or inadequate diet and poor nutritional states as increasing susceptibility to the infectious agent of hepatitis.[3,5] What actual part such factors have played in the present series cannot be determined. Even on an adequate Army diet, some soldiers lose appetite and weight; it may be assumed that the strain and the exigencies of warfare have brought about very considerable disturbances of the nutritional state, and thus, perhaps, of resistance to the infectious agent. The recent experiments of Glynn and Himsworth [58,59] have great interest in relation to this problem. These investigators demonstrated that massive necrosis may be produced in rats without the intervention of any exogenous toxic agent, chemical or infective, solely as the result of a deficient diet. The essential factor in which it is deficient appears to be an amino acid. The destruction of hepatic parenchyma in these rats has many resemblances to that of fatal epidemic hepatitis in man. It develops abruptly after a latent period of several weeks, during which the liver is morphologically normal. The latent period probably represents the time required to deplete the reserve of certain essential constituents in the body's store of labile proteins. The lesions appear in two forms: a generalized massive necrosis when the diet is grossly deficient in necessary protein constituents, or a necrosis confined to certain parts of the liver, especially the left lobe, when the diet is less deficient but still not adequate.

Mechanism of Jaundice

In the previous study of hepatitis [24] the general mechanism of jaundice has been discussed. Here it remains to inquire whether the same mechanism is operating in the rapidly destructive fulminant form of the disease.

In the subacute form of hepatitis the cause of jaundice appears to be principally a mechanical obstruction by bile "thrombi" of the

intralobular canaliculi in the surviving or regenerating liver tissue. Similarly, in liver taken for biopsy from nonfatal cases the canaliculi are occluded by plugs of altered and inspissated bile.[40] In fulminant hepatitis destruction of liver cells is often complete; at best only small rims of peripheral cells are spared. Necrosis of the hepatic columns leads, of course, to destruction of the delicate bile clefts, the canaliculi; obstructive factors cannot, therefore, be considered. Jaundice can only be accounted for by the rapid destruction of liver cells; the absence of liver cells makes it impossible to remove bilirubin from the circulating blood (or from the Kupffer cells).

But what of fulminant hepatitis without jaundice? This explanation gives no clue to the situation there. Careful study of the several examples in this series disclosed no differences in lesions. In examples included among representative cases (nos. 2, 5, and 7), the duration of the disease was 3, 4, and 6 days respectively, a sufficient time for jaundice to have appeared. No explanation can be offered for the absence of jaundice despite complete destruction of liver. Even though anicteric fatal hepatitis is the exception, it indicates the need for reinvestigation of the complex mechanism of jaundice.

Ascites

The mechanism of ascites is equally complex. It is surprising to find that approximately one-fourth of the fulminant cases are associated with ascites. Its incidence is definitely correlated with duration of disease, rising to 70 per cent in subacute hepatitis. This suggests that the factors which lead to the accumulation of fluid become more pronounced as the disease is protracted. There is also a correlation between ascites and weight of liver, in that ascites is most frequently associated with livers that are but little shrunken. As has been shown, the weight of the liver in the fulminant group is largely a function of its blood content. Destruction of the columns of liver cells tends to bring about dilation and congestion of the sinusoids, that is to say, stasis. But stasis does not invariably occur, nor is it always uniformly distributed throughout the liver. It is possible that such variations in blood content of the liver are due to alterations in the action of the diaphragm. This muscle renders an important aid to venous flow; it has been likened to a hand which rhythmically squeezes a sponge filled with blood.[60] Since clinical evidence shows that ascites develops usually during the terminal phase of the disease, more or less simultaneously with disturbances of the central nervous system, there exists the possibility that diaphragmatic innervation and action may be impaired. Whatever the rôle of the diaphragm may be, it seems plausible

that interference with venous escape from the liver is one of the chief causes of the ascites of fulminant hepatitis.

One other point deserves mention. In the experimental massive necrosis resulting from dietary deficiency, ascites commonly develops.[58] Mann and Bollman also have pointed out that ascites may be produced by dietary means.[56,57] Whether and to what extent such factors operate in fulminant hepatitis is problematical. Disturbances of plasma proteins resulting from destruction of liver, and their bearing on ascites cannot, in our series, be properly evaluated.

Fulminant Hepatitis and the Hepatorenal Syndrome

Does the massive and rapid disintegration of liver cells which is characteristic of fulminant hepatitis lead to the symptom complex known as the "hepatorenal syndrome"?

Heyd [61] is generally given credit for having focused attention, in 1924, on certain types of "liver death" most commonly seen following surgical operations upon the biliary tract or severe trauma to the liver. His original description was amplified in subsequent reports [62] and his concept has been added to and modified by numerous other authors, notably Cave,[63] Helwig and associates,[64–66] Boyce and McFetridge,[67] and Wilensky.[68,69] Most recent authors have emphasized a renal as well as a hepatic element, and the term "hepatorenal syndrome" has become widely used, but has never been clearly defined. The present consensus, as summarized by Thorn,[70] distinguishes two symptom complexes: one characterized by sudden onset of hyperthermia, delirium and coma; the second by renal failure and uremic death, often preceded by an episode of circulatory collapse or other shock-like state. Evidence for a renal component in the first syndrome is minimal and consists of vaguely described, nonspecific changes of kidney structure, falling within the limits of "cloudy swelling," or of bile nephrosis in cases in which jaundice precedes the acute episode. In the second syndrome, degenerative changes of greater severity have usually, though not invariably, been recorded, but no constant picture emerges from the reports. At the time when they were published, neither clinicians nor pathologists were aware of the profound renal damage which may follow shock regardless of whether the liver is diseased or traumatized.

A sharp distinction must be made between the hepatorenal syndrome and bile, or cholemic, nephrosis. The former is ill defined, the latter well recognized.[71–73] Briefly stated, cholemic nephrosis is associated with prolonged jaundice; it occurred in most cases of subacute

hepatitis.[24] The essential lesions are tubular degeneration of varying severity, the presence of bile casts, and alterations in glomerular permeability. It is usually assumed, and experimental evidence supports the hypothesis,[74] that bile salts are injurious to renal epithelium and are the primary cause of degenerative damage. Since bile salts are formed in the liver, massive destruction of this organ would tend to lessen rather than to increase their excretion by the kidney. Clinical studies of renal function in jaundiced patients [75,76] likewise demonstrated renal damage and proved, furthermore, that it was ordinarily reversible since the albuminuria, cylindruria, and slight grades of azotemia cleared with disappearance of icterus. Nearly all authorities agree that simple bile nephrosis does not explain the severe renal insufficiency of the "hepatorenal syndrome." [65,74]

Two hypotheses have been repeatedly suggested to account for this syndrome: (a) that a toxic substance is elaborated by the sudden destruction of liver parenchyma, and (b) that a malfunctioning liver fails to detoxify an unknown nephrotoxic agent from some other source. If either of these hypotheses were correct, fulminant hepatitis with its massive and rapid destruction of liver parenchyma should provide many examples of the hepatorenal syndrome.

If one accepts a broad definition of this syndrome [68,69] and includes hyperthermic deaths and all forms and degrees of simultaneous or successive impairment of liver and kidney function, our data provide positive evidence for its existence in fulminant hepatitis since the majority of cases showed both clinical and histologic evidence of some renal injury. A definition so inclusive is, however, all but meaningless. If the more usual and narrower definition of the hepatorenal syndrome is accepted, namely, that of renal damage consequent to liver disease and so severe that it leads to uremic death, our data are essentially negative.

Pathologically, in the fulminant cases of hepatitis no significant renal changes other than storage of fat were observed and the decreasing degree of this phenomenon with longer periods of survival indicates that it was reversible and transitory in character. From the clinical point of view the only important evidence suggestive of renal insufficiency was azotemia, but in only 4 cases were nonprotein nitrogen levels above 60 mg. per cent recorded, with a maximal figure of 103 in one case. Azotemia of even higher levels would constitute inadequate proof of renal impairment in view of the rapid and extensive liberation of protein which must result from the massive necrosis of liver cells. There was no correlation between degree of fat storage

and nitrogen retention. It is concluded that fulminant hepatitis is not associated with the "hepatorenal syndrome" as this syndrome is usually defined.

SUMMARY

A fulminant form of epidemic hepatitis which runs a fatal course in less than 10 days has appeared during the past 3 years. In a new series of 196 cases of fatal hepatitis which occurred in the U. S. Army between August, 1943, and April, 1945, approximately one-half (53 per cent) were of this type. By contrast, not a single such case was observed during the Army epidemic of 1942 and only one during the Swedish epidemic of 1927; then the median duration of fatal hepatitis exceeded 5 weeks. The clinical features and pathologic changes of the fulminant form differ significantly from those of the subacute variety which predominated in previous epidemics.

On the basis of epidemiology the present series includes 29 examples of the endemic and 72 of the epidemic variant of "spontaneous" hepatitis, and 77 cases presumed to be "homologous serum hepatitis" following trauma and transfusions of blood or blood derivatives. Analysis makes it evident that the epidemiologic type does not determine the clinical form of hepatitis, whether fulminant or more protracted.

This study is based principally on 94 cases in which the clinical course of the disease did not exceed 9 days. Thirty-nine others with a duration of from 10 to 19 days have been used to supply additional information, for many of them had lesions indistinguishable from those of the more fulminant form. The remainder of the series, *i.e.*, the subacute cases, which clinically and pathologically resemble those of the 1942 epidemic, are considered only in connection with certain analyses, such as the significance of geographic factors.

No precise information is available as to whether the mortality rates are the same or different in the several epidemiologic variants. The average mortality during the period covered by this study was 0.3 per cent. Serum hepatitis tended to run a considerably more rapid course than the naturally occurring disease, but otherwise there were no discernible differences, either clinical or pathologic, between these variants.

Clinically, fulminant hepatitis was characterized by a sharp and stormy course. It usually was ushered in by one of two syndromes: (1) an "infectious" type in which high fever, chilliness, malaise, and general aching dominated the picture, and (2) a "gastrointestinal" type with anorexia, nausea and epigastric discomfort in the foreground. These two types were represented in approximately equal proportions, and during various epidemics often occurred side by side. The subse-

quent clinical manifestations bore no relation to the prodromal symptoms. Because of the brevity of the course, the initial symptoms sometimes merged with those of the terminal stage.

Temperature records were available for 68 of the fulminant cases. In all but one the onset was febrile. The temperature ranged from 95° to 104° and averaged 102° F., fever declining as a rule with the onset of jaundice. During the final stage of the disease there was almost invariably a sharp rise in temperature coincident with profound cerebral disturbances.

In contrast to the deep jaundice commonly observed in the subacute form, the degree of jaundice in fulminant hepatitis was often mild. Several anicteric cases are included in this series.

Among noteworthy laboratory findings were moderate degrees of nitrogen retention and lowering of blood sugar.

Pathologically, lesions other than those in the liver were relatively slight; the changes found in "spontaneous" and in "inoculation" hepatitis were in every respect similar. The lesion of the liver was characterized by extreme and often complete destruction of hepatic cells, and by a marked inflammatory reaction. Typically, the involvement was uniform. The gross appearance of the liver was not pathognomonic and gave no indication either of the extent of parenchymatous destruction or of the degree of inflammatory infiltration. The organ usually was flaccid and moderately shrunken, and the capsule was smooth or finely wrinkled. The cut surface most often presented an exaggerated "nutmeg" pattern, though sometimes it resembled that of an acutely congested spleen.

Microscopically, the destructive process was limited specifically to liver cells. Even in the more rapidly fatal cases the earliest stages of cell disintegration could not be observed; the dead cells had undergone lysis and the resultant débris had already been removed. The inflammatory infiltration was most conspicuous at the lobular peripheries and less so within the lobular remnants. The predominating cells were mononuclear forms—reticulo-endothelial derivatives, plasma cells, and lymphocytes. Regenerative hyperplasia of surviving parenchyma was minimal and confined to biliary rather than to hepatic epithelium. There was often a marked disparity between the apparent age of the lesions and the duration of symptoms. The pathologic changes in the liver were, in many instances, obviously older than the clinical history suggested; less frequently the reverse was true.

The spleen usually showed acute congestion and hyperplasia of its component cells. Focal areas of necrosis were common in the follicles and in the pulp.

The kidneys in the majority of cases were the site of marked fat storage, especially within the cells of the proximal convoluted tubules. The storage was not associated with significant degenerative changes; it probably was the result of sudden liberation of large amounts of fat from the destroyed liver cells. There was no correlation between degree of fat storage and nitrogen retention. The rapid destruction of the hepatic parenchyma did not lead to the development of the "hepatorenal syndrome" as it is usually defined.

Despite the marked nervous disturbances in the terminal stage of hepatitis, histologic changes in the brain were usually slight and consisted of a mild nonspecific encephalopathy.

The mechanism of jaundice in fulminant hepatitis is complex. The extensive and often complete destruction of liver cells must be considered a chief cause. No adequate explanation can be offered for the occasional occurrence of entirely anicteric cases of fulminant hepatitis.

Ascites was present in approximately one-fourth of the cases of fulminant hepatitis. The principal factor in its production is believed to be acute venous stasis in the liver.

The factors responsible for the appearance, during recent epidemics, of hepatitis in a fulminant form are difficult to assess. It is suggested that more or less interrelated host factors, such as fatigue, trauma and nutritional disturbances, rather than the strain or the amount of the infectious agent, play a dominant part.

We wish to express our grateful appreciation to the Staff of the Army Medical Library for the translation of a Russian article and for bibliographic assistance.

REFERENCES

1. Stowman, K. Epidemic outlook in Europe. *Epidemiol. Inform. Bull.*, 1945, 1, 101–111.
2. Lyon, E. Infective hepatitis with special reference to Palestine. *M. Press*, 1945, 213, 164–169.
3. Kligler, I. J., Btesh, D. S., and Koch, W. Observations on two epidemics of infective hepatitis in Palestine among recent immigrants. *J. Infect. Dis.*, 1944, 74, 234–246.
4. Somerville, A., and Clark, J. S. Epidemic jaundice. *Canad. M. A. J.*, 1944, 51, 120–123.
5. McFarlan, A. M. The epidemiology of infective hepatitis in some units of the British Army in Sicily and Great Britain, 1943–4. *Quart. J. Med.*, 1945, 14, 125–146.
6. Hartfall, S. J. Infective hepatitis. *Brit. M. J.*, 1944, 2, 21.
7. Spooner, E. T. C. The 1942 epidemic of infective hepatitis in the Middle East. *Proc. Roy. Soc. Med.*, 1944, 37, 171–172.
8. Cameron, J. D. S. Infective hepatitis. *Quart. J. Med.*, 1943, 12, 139–155.
9. Witts, L. J. Some problems of infective hepatitis. *Brit. M. J.*, 1944, 1, 739–743.
10. Walton, C. H. A. Infective hepatitis. *Canad. M. A. J.*, 1945, 53, 573–578.

11. Walker, D. W. Some epidemiological aspects of infectious hepatitis in the U. S. Army. *Am. J. Trop. Med.*, 1945, **25**, 75–82.
12. Sapero, J. J., and Butler, F. A. Highlights on epidemic diseases occurring in military forces in the early phases of the war in the South Pacific. *J. A. M. A.*, 1945, **127**, 502–506.
13. Hayman, J. M., Jr., and Read, W. C. Some clinical observations on an outbreak of jaundice following yellow fever vaccination. *Am. J. M. Sc.*, 1945, **209**, 281–296.
14. Gezon, H. M. Investigation of a jaundice epidemic in Tunisia; preliminary report. *U. S. Nav. M. Bull.*, 1944, **43**, 579–589.
15. Bercovitz, Z. T., and Knoch, H. R. Infective hepatitis. II. Clinical study of patients with hepatitis not related to yellow fever vaccination or infectious jaundice (Weil's disease). *Gastroenterology*, 1944, **3**, 79–89.
16. Barker, M. H., Capps, R. B., and Allen, F. W. Acute infectious hepatitis in the Mediterranean theater, including acute hepatitis without jaundice. *J. A. M. A.*, 1945, **128**, 997–1003.
17. Barker, M. H., Capps, R. B., and Allen, F. W. Chronic hepatitis in the Mediterranean theater; a new clinical syndrome. *J. A. M. A.*, 1945, **129**, 653–659.
18. Finks, R. M., and Blumberg, R. W. Epidemic hepatitis with and without jaundice. *Arch. Int. Med.*, 1945, **76**, 102–113.
19. Axenfeld, H., and Brass, K. Klinische und bioptische Untersuchungen über den sogenannten Icterus catarrhalis. *Frankfurt. Ztschr. f. Path.*, 1942, **57**, 147–236.
20. Axenfeld, H., and Brass, K. Weitere Beiträge zur Morphologie und Pathogenese der Hepatitis epidemica insbesondere zur Frage der Hepatitis epidemica sine iktero. *Frankfurt. Ztschr. f. Path.*, 1943–44, **58**, 220–238.
21. Holler, G. Zur Klinik der Hepatitis epidemica. In: Zimmer, A. (ed.). Wehrmedizin. F. Deuticke, Wien, 1944, **3**, pp. 379–392.
22. Buding, A. (and others). Ueber Hepatitis epidemica. *Med. Klin.*, 1943, **39**, 785–789; 831–837.
23. Beckmann, K. Hepatitis epidemica. F. Enke, Stuttgart, 1944.
24. Lucké, B. The pathology of fatal epidemic hepatitis. *Am. J. Path.*, 1944, **20**, 471–593.
25. Lucké, B. The structure of the liver after recovery from epidemic hepatitis. *Am. J. Path.*, 1944, **20**, 595–619.
26. Bergstrand, H. Über die akute und chronische gelbe Leberatrophie. G. Thieme, Leipzig, 1930.
27. Sartwell, P. E. Personal communication.
28. Findlay, G. M., and Willcox, R. R. Infective hepatitis. Transmission by faeces and urine. *Lancet*, 1945, **2**, 594–597.
29. Grossman, E. B., Stewart, S. G., and Stokes, J., Jr. Post-transfusion hepatitis in battle casualties and a study of its prophylaxis by means of human immune serum globulin. *J. A. M. A.*, 1945, **129**, 991–994.
30. Neefe, J. R., Stokes, J., Jr., Reinhold, J. G., and Lukens, F. D. W. Hepatitis due to the injection of homologous blood products in human volunteers. *J. Clin. Investigation*, 1944, **23**, 836–855.
31. Morgan, H. V., and Williamson, D. A. J. Jaundice following administration of human blood products. *Brit. M. J.*, 1943, **1**, 750–753.
32. Rappaport, E. M. Hepatitis following blood or plasma transfusions. Observations in 34 cases. *J. A. M. A.*, 1945, **128**, 932–939.
33. Paul, J. R., Havens, W. P., Jr., Sabin, A. B., and Philip, C. B. Transmission experiments in serum jaundice and infectious hepatitis. *J. A. M. A.*, 1945, **128**, 911–915.

34. Gordon, I. Infective hepatitis, with special reference to the oral hippuric acid test. *Brit. M. J.*, 1943, **2**, 807–811.
35. Wayburn, E. Epidemic infectious hepatitis. *Gastroenterology*, 1945, **4**, 147–153.
36. Sherman, W. B. The occurrence of fever at the outset of catarrhal jaundice. *M. Bull. North African Theat. Op.*, 1944, **1**, 30–31.
37. Findlay, G. M., Martin, N. H., and Mitchell, J. B. Hepatitis after yellow fever inoculation; relation to infective hepatitis. *Lancet*, 1944, **2**, 301–307; 340–344; 365–370.
38. Trowell, O. A. Liver function in health and disease. *Edinburgh M. J.*, 1944, **51**, 84–100.
39. Snyder, C. D. Recent advances in knowledge of the liver. *Physiol. Rev.*, 1942, **22**, 54–73.
40. Horan, T. H., Jolliffe, L. S., and Mallory, T. B. Peritoneoscopic biopsies in non-fatal epidemic hepatitis. (In press.)
41. Stokes, J. F., Owen, J. R., and Holmes, E. G. Neurological complications of infective hepatitis. *Brit. M. J.*, 1945, **2**, 642–644.
42. Neefe, J. R., Stokes, J., Jr., and Gellis, S. S. Homologous serum hepatitis and infectious (epidemic) hepatitis. Experimental study of immunity and cross immunity in volunteers; a preliminary report. *Am. J. M. Sc.*, 1945, **210**, 561–575.
43. Havens, W. P., Jr., and Ward, R. Failure to transmit infectious hepatitis to chimpanzees. *Proc. Soc. Exper. Biol. & Med.*, 1945, **60**, 102–104.
44. Havens, W. P., Jr., Paul, J. R., van Rooyen, C. E., Ward, R., Drill, V. A., and Allison, N. H. Human transmission of infective hepatitis by the oral route. *Lancet*, 1945, **1**, 202–203.
45. Havens, W. P., Jr. Epidemiological studies on infectious hepatitis. *Am. J. Pub. Health*, 1946, **36**, 37–44.
46. Oliphant, J. W. Jaundice following administration of human serum? *Harvey Lectures*, 1944, **39**, 254–272.
47. Sergiev, P. G., Tareev, E. M. (and others). [Virus jaundice; epidemic hepatitis in relation to immunization with human serum.] *Ter. Arkh.*, 1940, **18**, 595–611.
48. 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 and its relation to vaccination against yellow fever. *Am. J. Hyg.*, 1944, **39**, 337–430; 1944, **40**, 35–107.
49. Editorial. Syringe transmitted hepatitis. *J. A. M. A.*, 1945, **129**, 278–279.
50. Beattie, J., and Marshall, J. The aetiology of post-arsphenamine jaundice. *Brit. M. J.*, 1944, **1**, 547–550.
51. Salaman, M. H., King, A. J., Williams, D. I., and Nicol, C. S. Prevention of jaundice resulting from antisyphilitic treatment. *Lancet*, 1944, **2**, 7–8.
52. Dible, J. H., McMichael, J., and Sherlock, S. P. V. Pathology of acute hepatitis. *Lancet*, 1943, **2**, 402–408.
53. Opie, E. L. On the relation of combined intoxication and bacterial infection to necrosis of the liver, acute yellow atrophy and cirrhosis. *J. Exper. Med.*, 1910, **12**, 367–387.
54. Memorandum prepared by medical officers of the Ministry of Health. Homologous-serum jaundice. *Lancet*, 1943, **1**, 83–88.
55. Bennett, G. A., Drinker, C. K., and Warren, M. F. Morphological changes in the livers of rats resulting from exposure to certain chlorinated hydrocarbons. *J. Indust. Hyg. & Toxicol.*, 1938, **20**, 97–123.
56. Bollman, J. L., and Mann, F. C. The physiology of the impaired liver. *Ergebn. d. Physiol.*, 1936, **38**, 445–492.

57. Mann, F. C. Diet in relation to hepatic physiology and pathology: A review of pertinent data. *Collected Papers of the Mayo Clinic*, 1943, **35**, 34–45.
58. Himsworth, H. P., and Glynn, L. E. Massive hepatic necrosis and diffuse hepatic cirrhosis (acute yellow atrophy and portal cirrhosis); their production by means of diet. *Clin. Sc.*, 1944, **5**, 93–123.
59. Glynn, L. E., and Himsworth, H. P. Massive acute necrosis of the liver: its significance and experimental production. *J. Path. & Bact.*, 1944, **56**, 297–305.
60. Wenckebach, K. F. Ueber pathologische Beziehungen zwischen Atmung und Kreislauf beim Menschen. In: Sammlung klinischer Vorträge. J. A. Barth, Leipzig, 1907, no. 465 (Inn. Med., no. 140, pp. 131–187). See also: Lucké, B. The Diaphragm. In: Piersol, G. M. (ed.). The Cyclopedia of Medicine, Surgery and Specialties. F. A. Davis Co., Philadelphia, 1941, **5**, 1–42.
61. Heyd, C. G. The liver and its relation to chronic abdominal infection. *Ann. Surg.*, 1924, **74**, 55–78.
62. Heyd, C. G. The concept of liver deaths. *J. A. M. A.*, 1943, **121**, 736–737.
63. Cave, H. W. Dangers incident to cholecystectomy. *Ann. Surg.*, 1926, **84**, 371–378.
64. Helwig, F. C., and Orr, T. G. Traumatic necrosis of the liver with extensive retention of creatinine and high grade nephrosis. *Arch. Surg.*, 1932, **24**, 136–144.
65. Helwig, F. C., and Schutz, C. B. A liver kidney syndrome. Clinical, pathological and experimental studies. *Surg., Gynec. & Obst.*, 1932, **55**, 570–580.
66. Helwig, F. C., and Schutz, C. B. A further contribution to the liver and kidney syndrome. *J. Lab. & Clin. Med.*, 1935, **21**, 264–277.
67. Boyce, F. F., and McFetridge, E. M. So-called "liver death"; a clinical and experimental study. *Arch. Surg.*, 1935, **31**, 105–136.
68. Wilensky, A. O., and Colp, R. Relation of nitrogen bodies of blood to surgical problems in liver and in biliary tract disease. III. Status of nitrogen bodies of blood in severe cases of biliary tract disease and its use in differentiating a terminal hepatic and a terminal renal group of cases. *Arch. Surg.*, 1927, **15**, 635–659.
69. Wilensky, A. O. Occurrence, distribution and pathogenesis of so-called liver death and/or the hepatorenal syndrome. *Arch. Surg.*, 1939, **38**, 625–691.
70. Thorn, D. S. Liver deaths and the hepatorenal syndrome. *McGill M. J.*, 1945, **14**, 235–245.
71. Fahr, T. Cholämische Nephrose. In: Henke, F., and Lubarsch, O. Handbuch der speziellen pathologischen Anatomie und Histologie. J. Springer, Berlin, 1925, **6**, Pt. 1, 281–284.
72. Wilbur, D. L. The renal glomerulus in various forms of nephrosis. *Arch. Path.*, 1934, **18**, 157–185.
73. Ayer, D. Renal lesions associated with deep jaundice. *Arch. Path.*, 1940, **30**, 26–41.
74. Stewart, H. L., and Cantarow, A. Renal lesions following injection of sodium dehydrocholate in animals with and without biliary stasis. *Arch. Path.*, 1935, **20**, 866–881.
75. Elsom, K. A. Renal function in obstructive jaundice. *Arch. Int. Med.*, 1937, **60**, 1028–1033.
76. 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.

[*Illustrations follow*]

DESCRIPTIONS OF PLATES

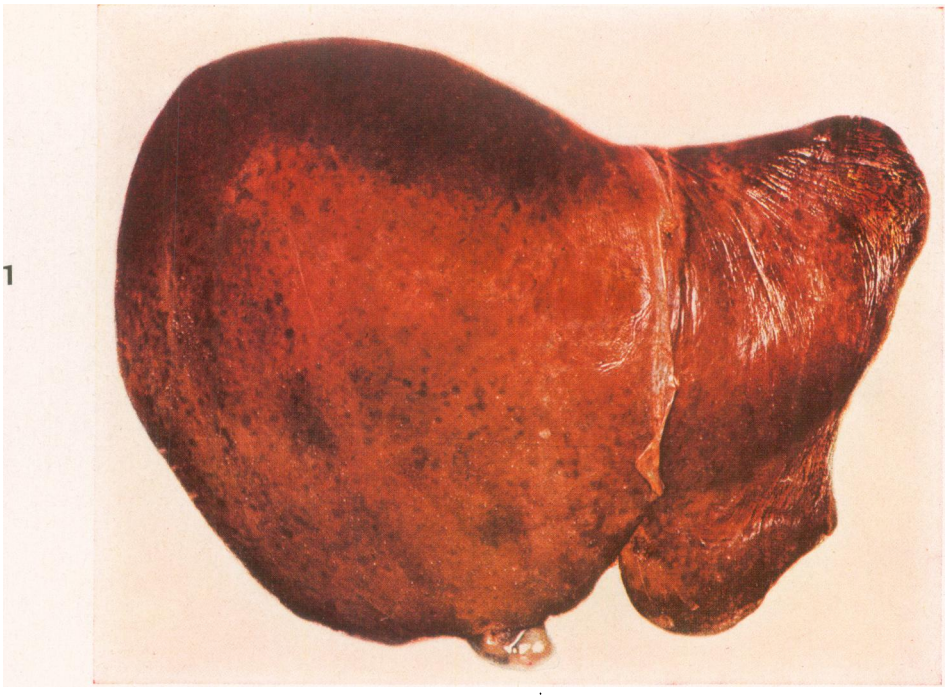
PLATE 164

FIG. 1. Clinical duration of hepatitis, 4 days. Upper surface of the liver, which weighed 1200 gm. The surface of the right lobe is smooth; there are a number of subcapsular hemorrhages. The surface of the left lobe is finely wrinkled. (Army Institute of Pathology accession no. 148911.)

FIG. 2. Cut surface of liver shown in Figure 1. The appearance is similar to that of an acutely congested and hyperplastic spleen.

FIGS. 3 to 7. Representative areas of cut surfaces of livers from five cases of fulminant hepatitis; all have an exaggerated "nutmeg" mottling. Naked-eye examinations of these livers gave no indication of the extent of the parenchymatous destruction or of the prominence of inflammatory infiltration.

Fig.	Duration of disease	Weight of liver	Case no.
3	3 days	1205 gm.	126048
4	4 days	1200 gm.	126423
5	5 days	1025 gm.	128680
6	8 days	Normal size	103350
7	8 days	Shrunken	128577


1

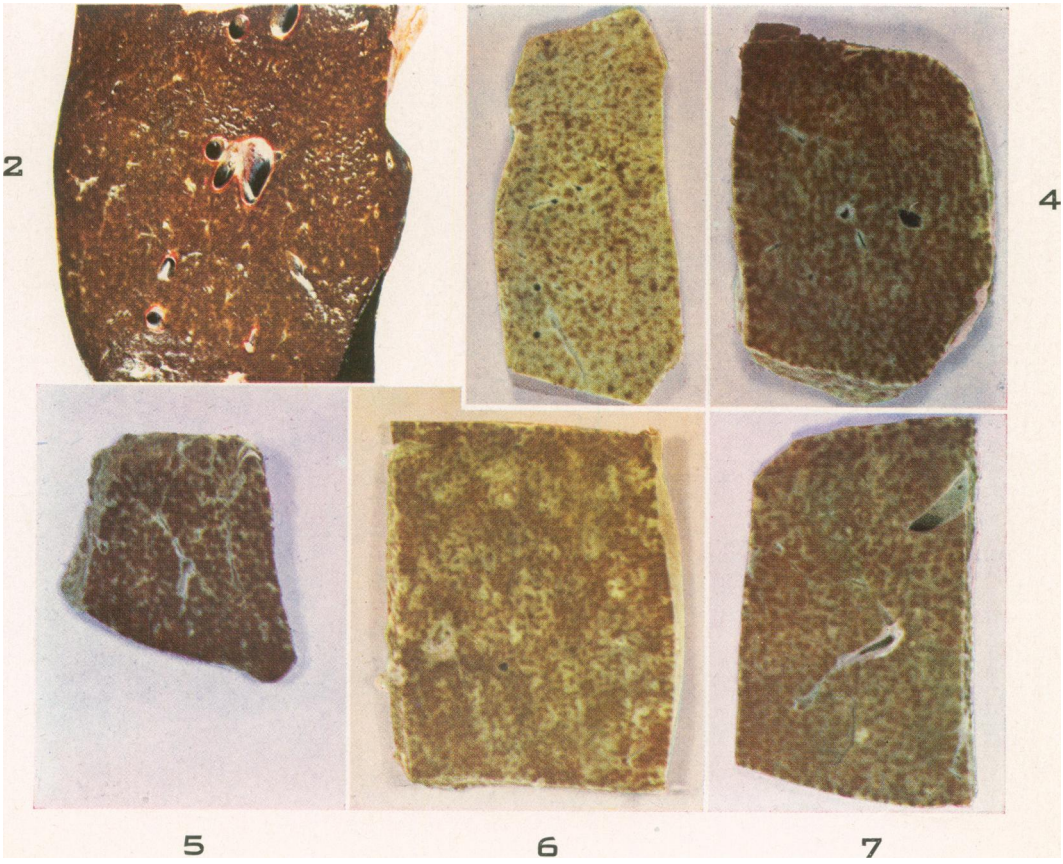
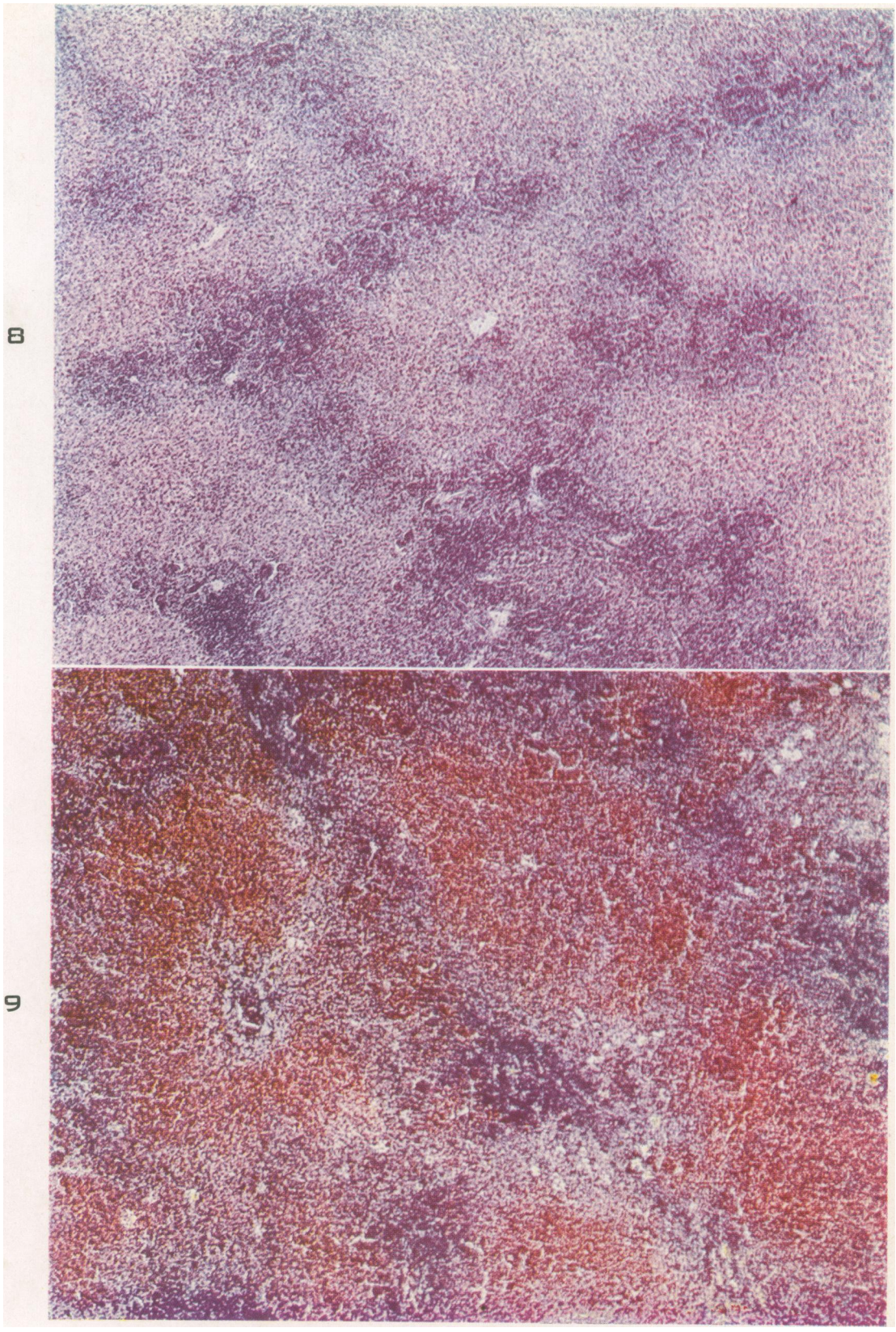

2
4
5
6
7

PLATE 165

FIG. 8. Duration of disease, clinically less than 1 day. (See case report 21.) Microscopic appearance of the liver at low magnification. The hepatic parenchyma has been destroyed. The portal regions and the perilobular boundaries are densely infiltrated with inflammatory cells. (See Fig. 15 for appearance of a lobule at higher magnification, Fig. 24 for details of the inflammatory reaction, and Fig. 27 for changes in spleen.) × 25. (A.I.P. acc. 123465.)

FIG. 9. Duration of disease, 3 days. (See case report 1.) Photomicrograph of liver at low magnification. The hepatic cells have been destroyed. The lobular remnants are engorged with blood. The peripheries are outlined by bands of inflammatory cells. (Fig. 10 shows a portal region at higher magnification, Fig. 12 details of the cells, and Fig. 19 illustrates the observation that in areas of parenchymatous destruction the reticulum framework is preserved.) × 25. (A.I.P. acc. 124057.)



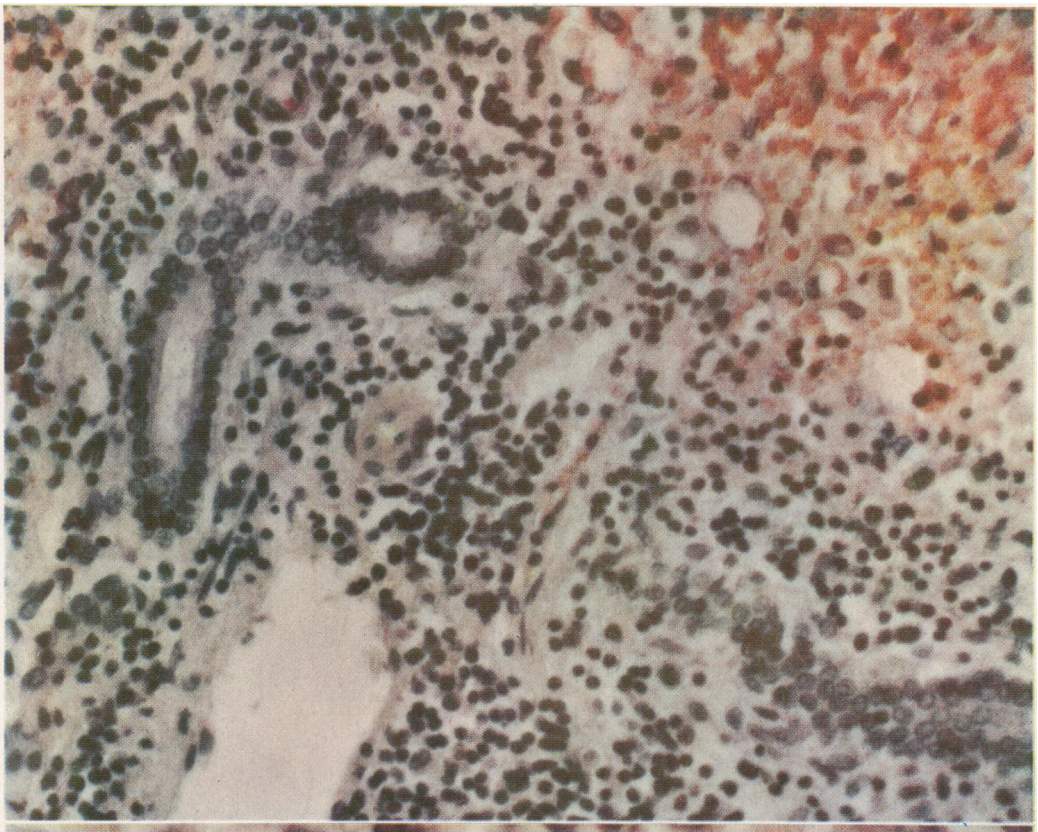
Lucké and Mallory The Fulminant Form of Epidemic Hepatitis

PLATE 166

FIG. 10. Duration of disease, 3 days. (See case 1.) Cell infiltration of the portal stroma at higher magnification than in the preceding photomicrograph. In the upper right-hand corner of the figure is shown the complete destruction of hepatic cells and great engorgement of the lobular remnants. Several bile ducts are sending out solid buds of proliferative epithelium. (See also Figs. 9, 12, and 19). × 400. (A.I.P. acc. 124057.)

FIG. 11. Duration of disease, 9 days. (See case 13.) A representative picture of the cellular composition of the infiltrate at the lobular peripheries. Most of the cells are large mononuclears, but some plasma cells and lymphocytes are also present. × 900. (A.I.P. acc. 114947.)

10



11

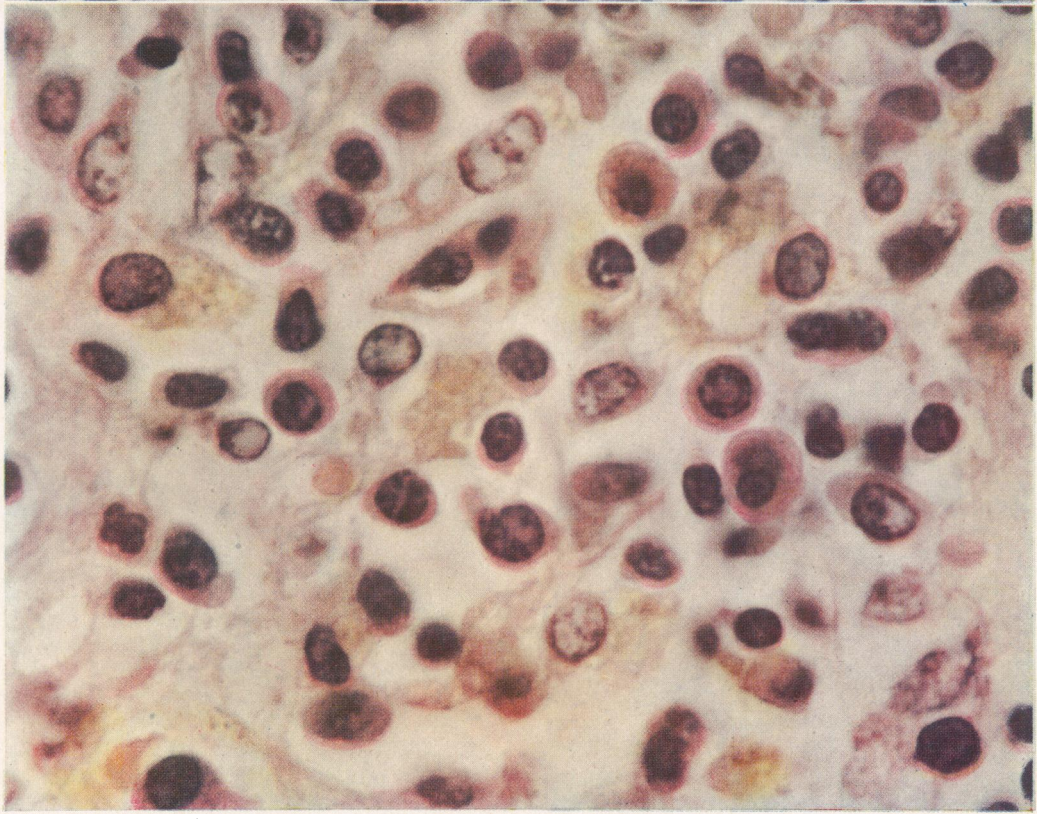
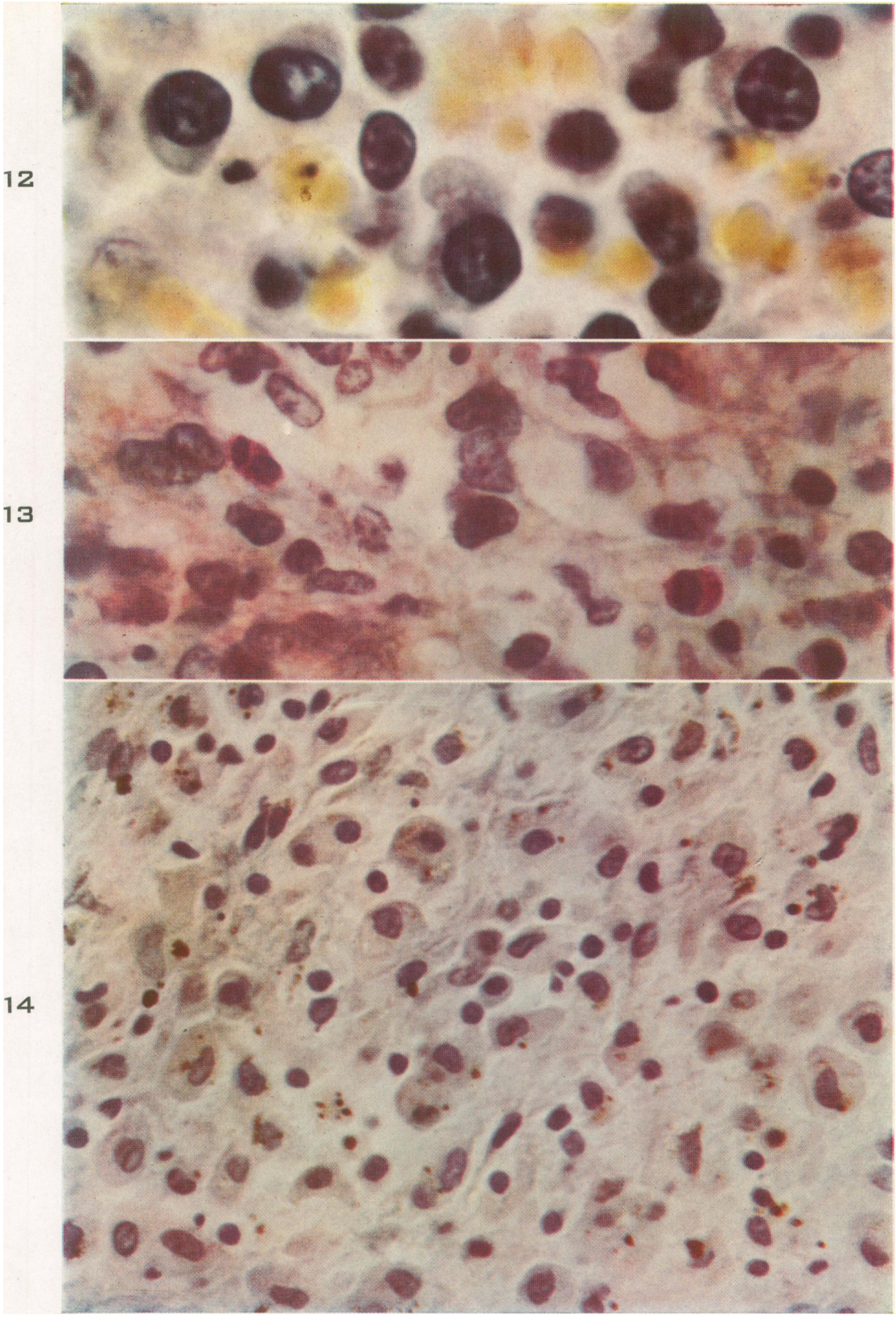


PLATE 167

FIG. 12. Duration of disease, 3 days. (See case 1.) The figure shows a group of plasma cells. In many cases these cells are numerically conspicuous, although they rarely predominate. (See also Figs. 9, 10, and 19.) × 2280. (A.I.P. acc. 124057.)

FIG. 13. Duration of disease, 7 days. Several eosinophils may be seen among the cells at a lobular periphery. × 1300. (A.I.P. acc. 133951.)

FIG. 14. Duration of disease, 9 days. Cell reaction within the lobular remnants. The predominant cells are mobilized and proliferated macrophages; many have ingested a brownish pigment, lipofuscin. × 1300. (A.I.P. acc. 131876.)



12

13

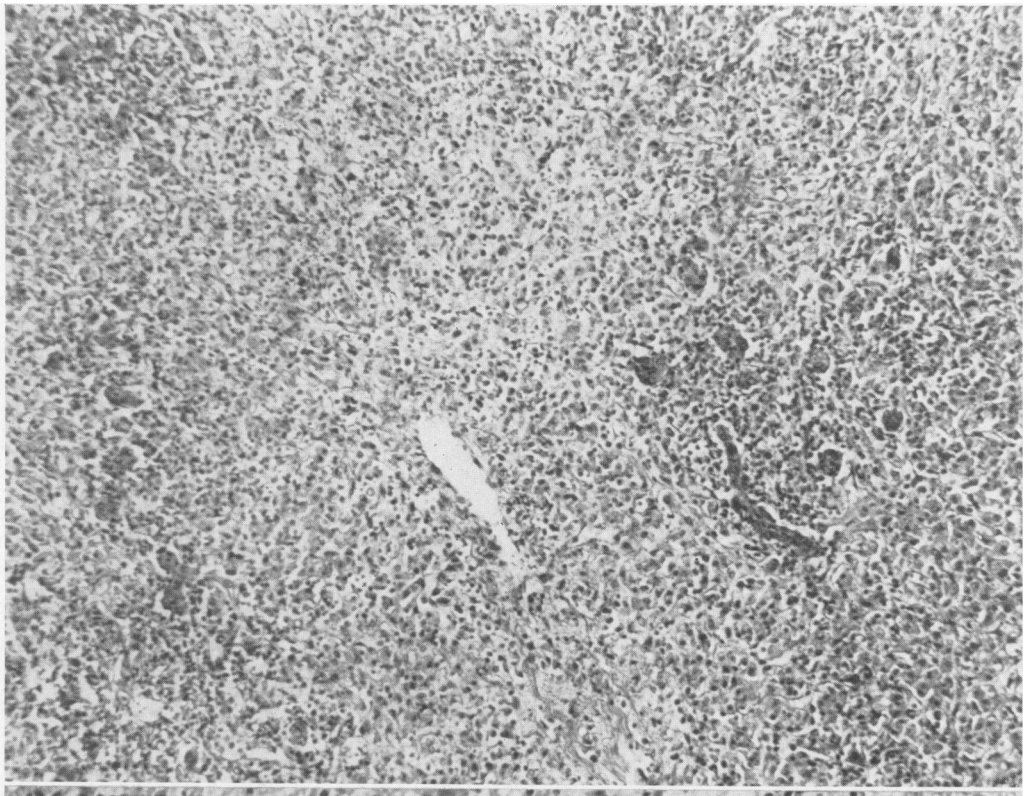
14

PLATE 168

FIG. 15. Duration of disease, clinically less than 1 day. (See case report 21.) A hepatic lobule at higher magnification than shown in Figure 8. In the photomicrograph the central lobular vein may easily be recognized; the lobular boundaries are indicated by small proliferating bile ducts, the significance of which is discussed in the text. The hepatic parenchyma has been destroyed; the lobular remnants are invaded by inflammatory cells, the nuclei of which appear as black dots. (See also Figs. 8, 24, and 27.) × 145. (A.I.P. acc. 123465; neg. 86343.)

FIG. 16. Duration of disease, 4 days. (See case report 17.) The figure shows a portal region with vein and bile duct cut longitudinally. The stroma is infiltrated with mononuclear cells which extend into the interior of the adjacent lobules. Isolated liver cells remain at the extreme periphery of the lobule; the great bulk of the parenchyma is destroyed. × 175. (A.I.P. acc. 129051; neg. 86333.)

15



16

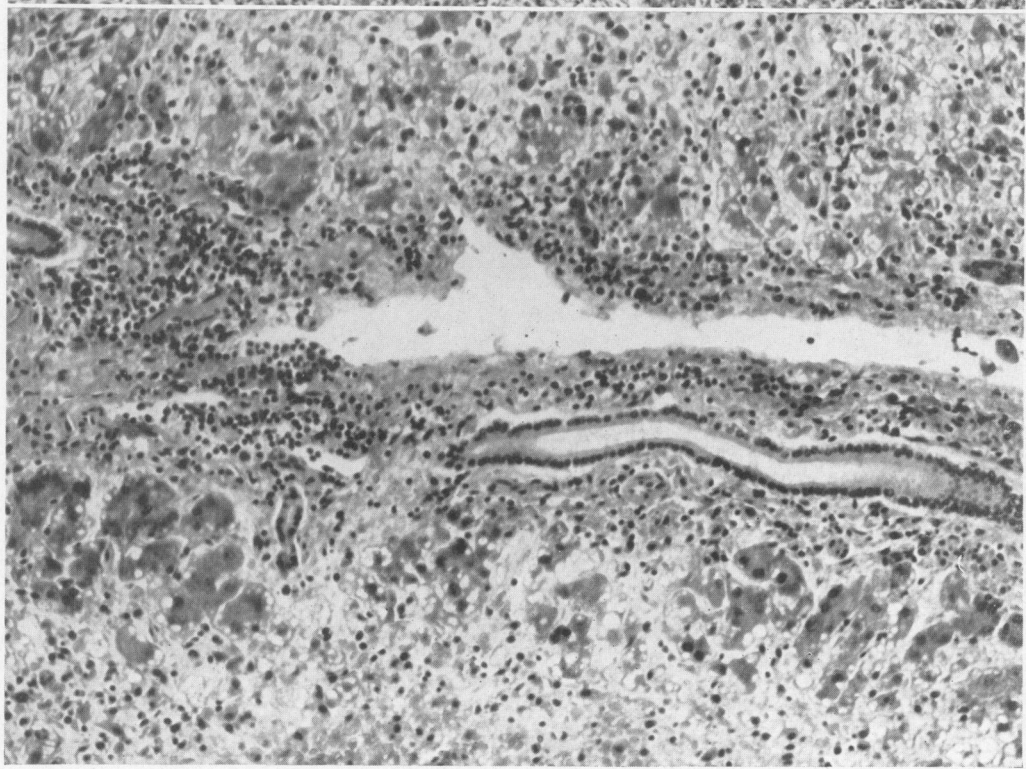
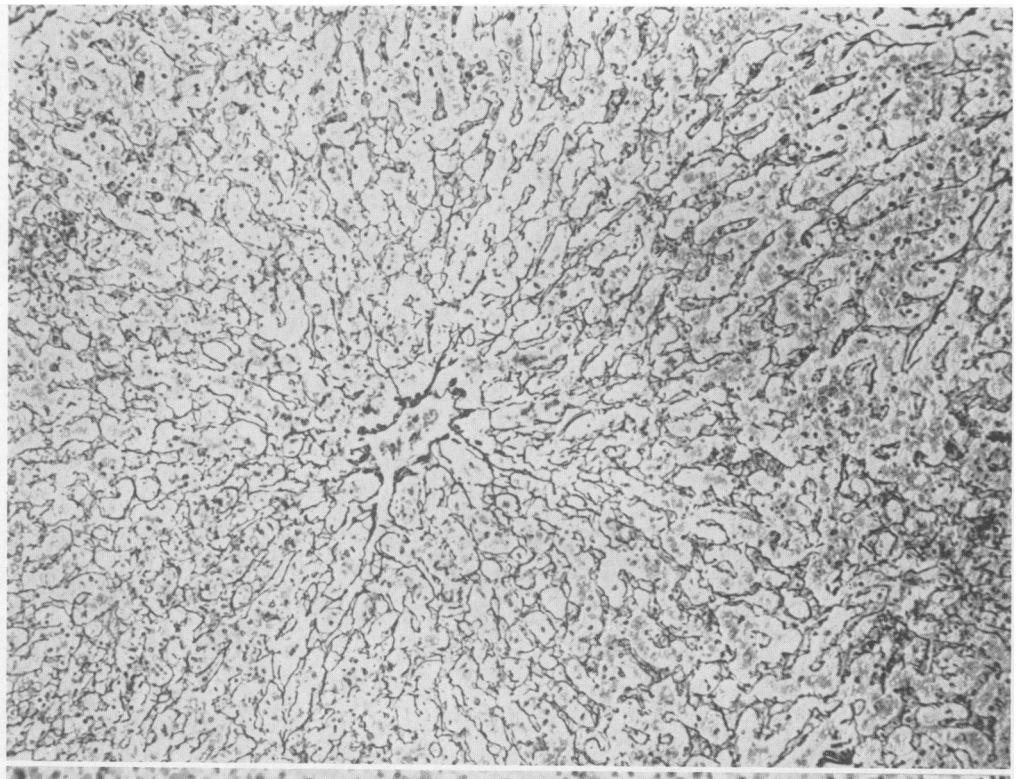


PLATE 169

FIG. 17. Duration of disease, 3 days. (See case report 2.) The figure shows the intact reticulum frame of a lobule, the parenchyma of which has been completely destroyed. (See Fig. 3 for gross appearance of cut surface of liver; Fig. 18 for change in central lobular vein, and Fig. 23 for proliferation of septal bile ducts.) Wilder's reticulum stain. × 145. (A.I.P. acc. 126048; neg. 86345.)

FIG. 18. Duration of disease, 3 days. (See case report 2.) A central lobular vein has a conspicuously thickened wall which appears hyalinized, and is invaded by a few inflammatory cells. The surrounding tissue is congested and infiltrated with mononuclear cells. The hepatic parenchyma has been destroyed. (See Fig. 17 which shows that the reticulum framework is preserved.) × 205. (A.I.P. acc. 126048; neg. 86344.)

17



18

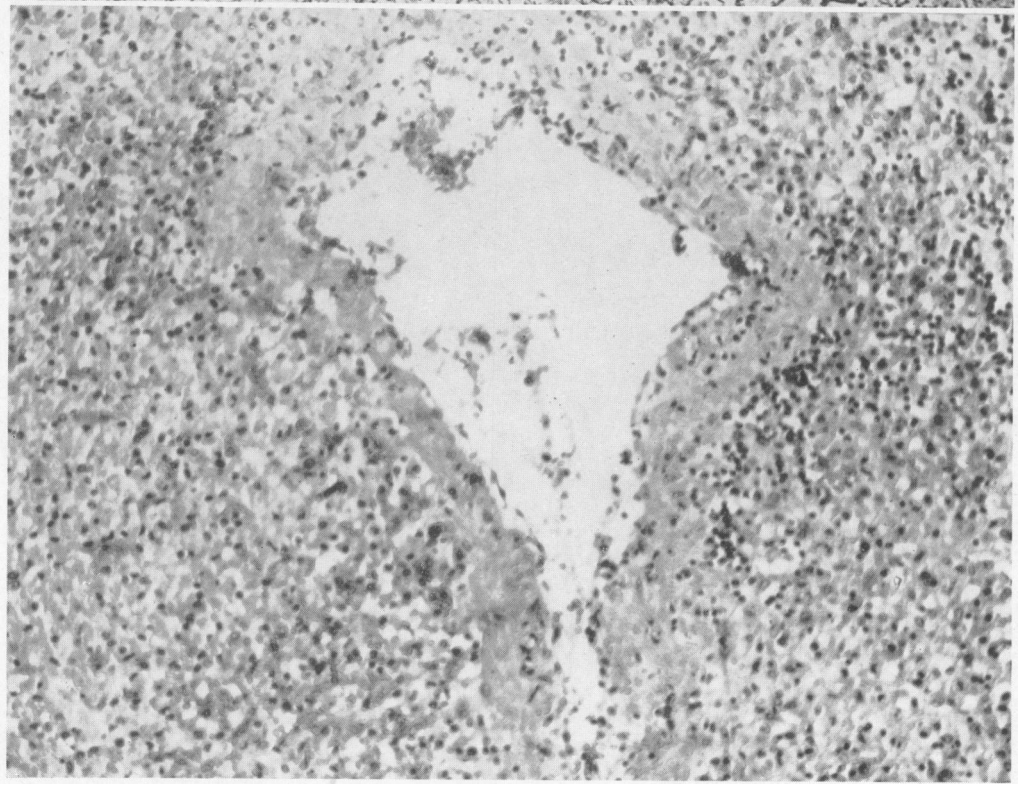
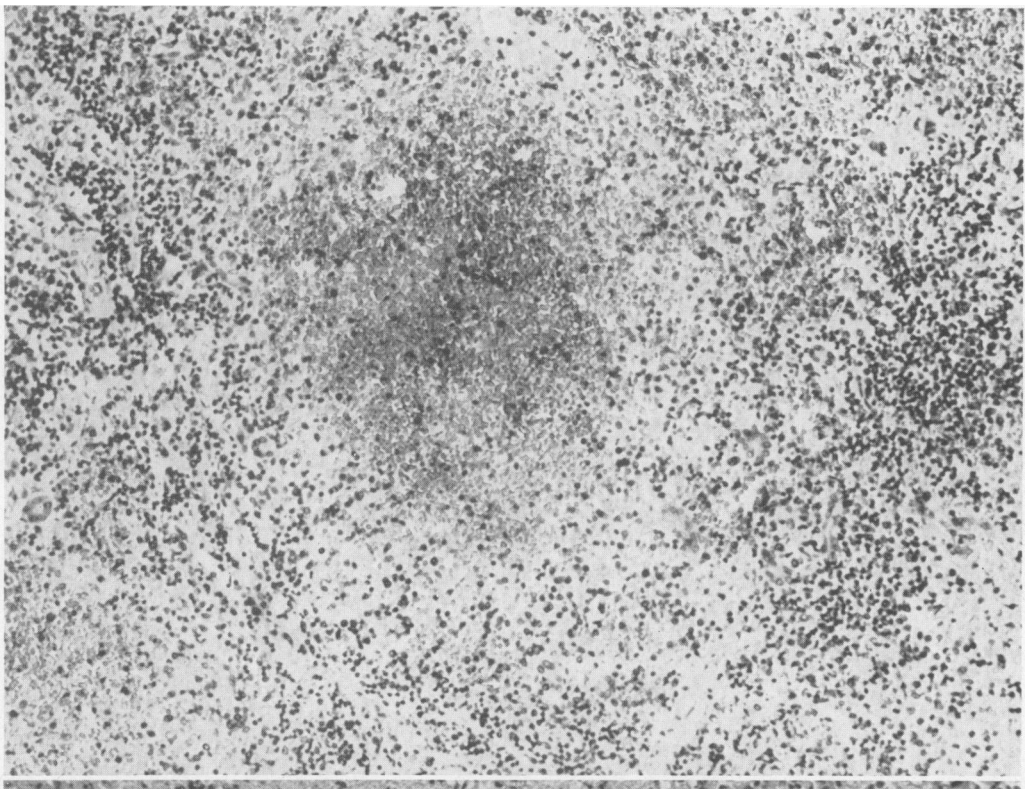


PLATE 170

FIG. 19. Duration of disease, 3 days. (See case report 1.) A hepatic lobule, the periphery of which is densely infiltrated with inflammatory cells which extend into the interior of the lobule. The hepatic parenchyma has been entirely destroyed and traces of liver cells have disappeared. The reticulum framework, however, was preserved. The lobular remnants are greatly engorged with blood. (See Fig. 9 for a photomicrograph in color showing a larger field at lower magnification, and Figs. 10 and 12 for cellular details.) × 160. (A.I.P. acc. 124057; neg. 86346.)

FIG. 20. Duration of disease, 8 days. A portal triad at the junction of three adjacent lobules. There is a conspicuous inflammatory reaction which extends along the twigs of the bile ducts and vessels into the perilobular boundaries. The liver cells have disappeared. (See Fig. 7 for gross appearance of cut surface of liver.) × 145. (A.I.P. acc. 128577; neg. 86336.)

19



20

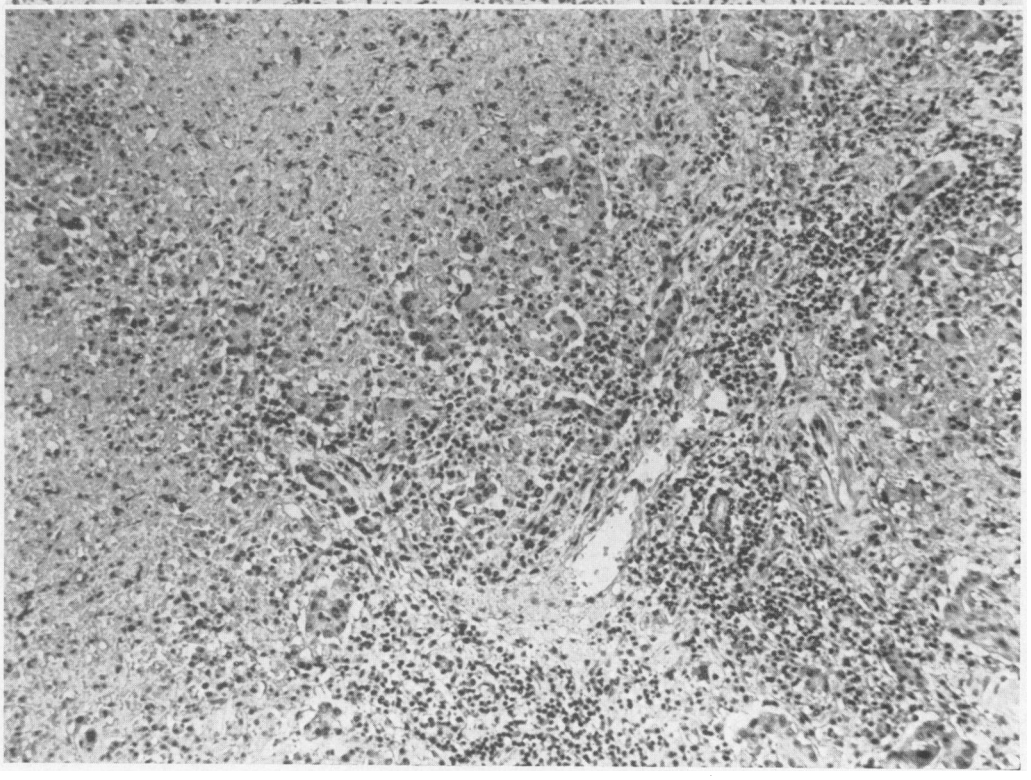
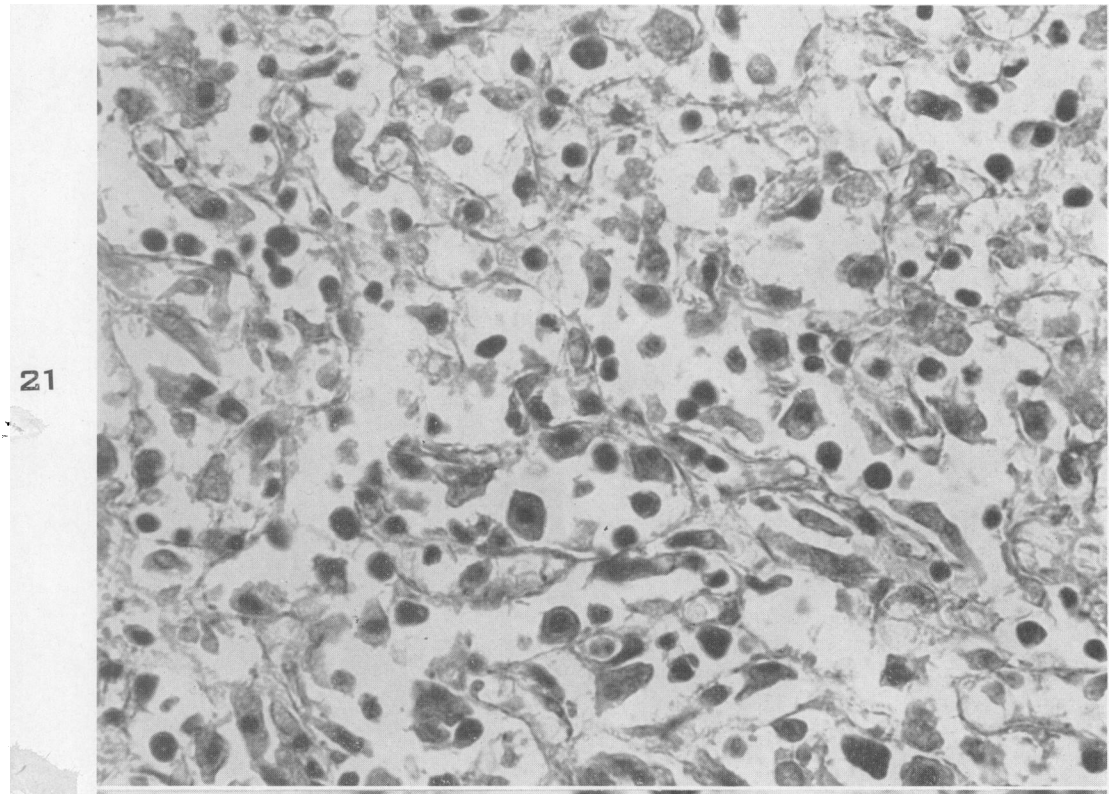


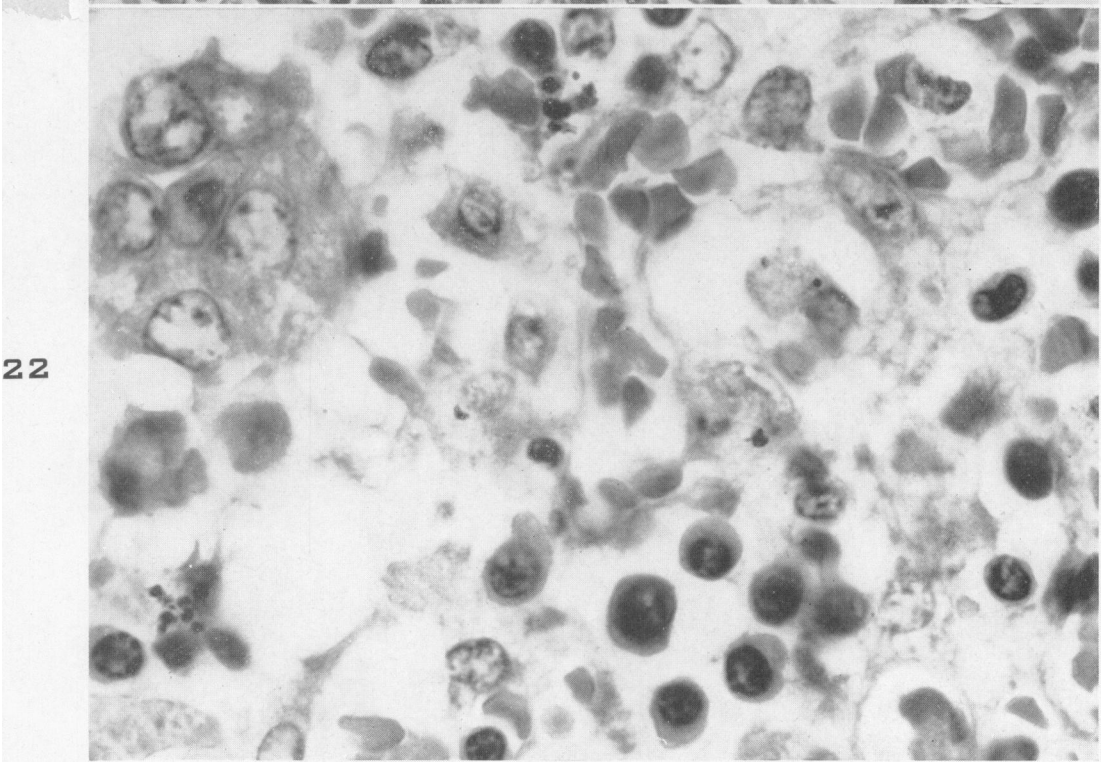
PLATE 171

FIG. 21. Duration of disease, 7 days. Inflammatory reaction within a lobule. The parenchymatous cells have been destroyed and their débris has been removed. The section has been stained by Masson's trichrome method to bring out the boundaries of the sinusoids, and thus to show the distribution of the inflammatory cells. It will be noted, first, that the sinusoids are widely dilated (due to the loss of the hepatic columns); second, that the inflammatory cells (mostly mononuclear) lie both within and between the sinusoids; and third, that because of these changes, the hepatic tissue resembles splenic pulp. The dark appearance of some histiocytes is due to ingestion of a pigment, lipofuscin. × 600. (A.I.P. acc. 126143; neg. 86326.)

FIG. 22. Duration of disease, 7 days. The figure shows a field near the periphery of a lobule. The parenchyma has been destroyed; the vascular stroma is invaded by plasma cells. The large coherent cells in the upper left of the photograph probably are proliferating biliary epithelium. In the upper center may be seen a congested sinusoid with intact walls. × 1360. (A.I.P. acc. 133195; neg. 86342.)



21



22

PLATE 172

FIG. 23. Duration of disease, 3 days. (See case report 2.) Proliferation of septal (perilobular) bile ducts at the boundary of two adjacent lobules. These little ducts are normally inconspicuous and resemble vascular twigs. Here, their cells are prominent, crowded together, and have large hyperchromatic nuclei. In the upper half of the photograph are shown several sinusoids with intact walls. The intervening hepatic cells have disappeared, and the lobular remnants are greatly engorged. (See also Figs. 3, 17, and 18.) × 650. (A.I.P. acc. 126048; neg. 86332.)

FIG. 24. Duration of disease, clinically less than 1 day. (See case report 21.) Portal region. A proliferating bile duct, composed of large cells with prominent nuclei, lies diagonally across the photograph. On one side of the duct the stroma is densely infiltrated with mononuclear cells, among which may be seen a few polymorphonuclear leukocytes. The large pale cells on the opposite side of the duct are swollen histiocytes. (See also Figs. 8, 15, and 27.) × 915. (A.I.P. acc. 123465; neg. 86347.)

FIG. 25. Duration of disease, 9 days. Inflammatory cells in the portal stroma: plasma cells, lymphocytes, and histiocytes predominate. The mass in the upper left-hand corner consists of proliferating bile duct epithelium. × 1360. (A.I.P. acc. 126110; neg. 86331.)

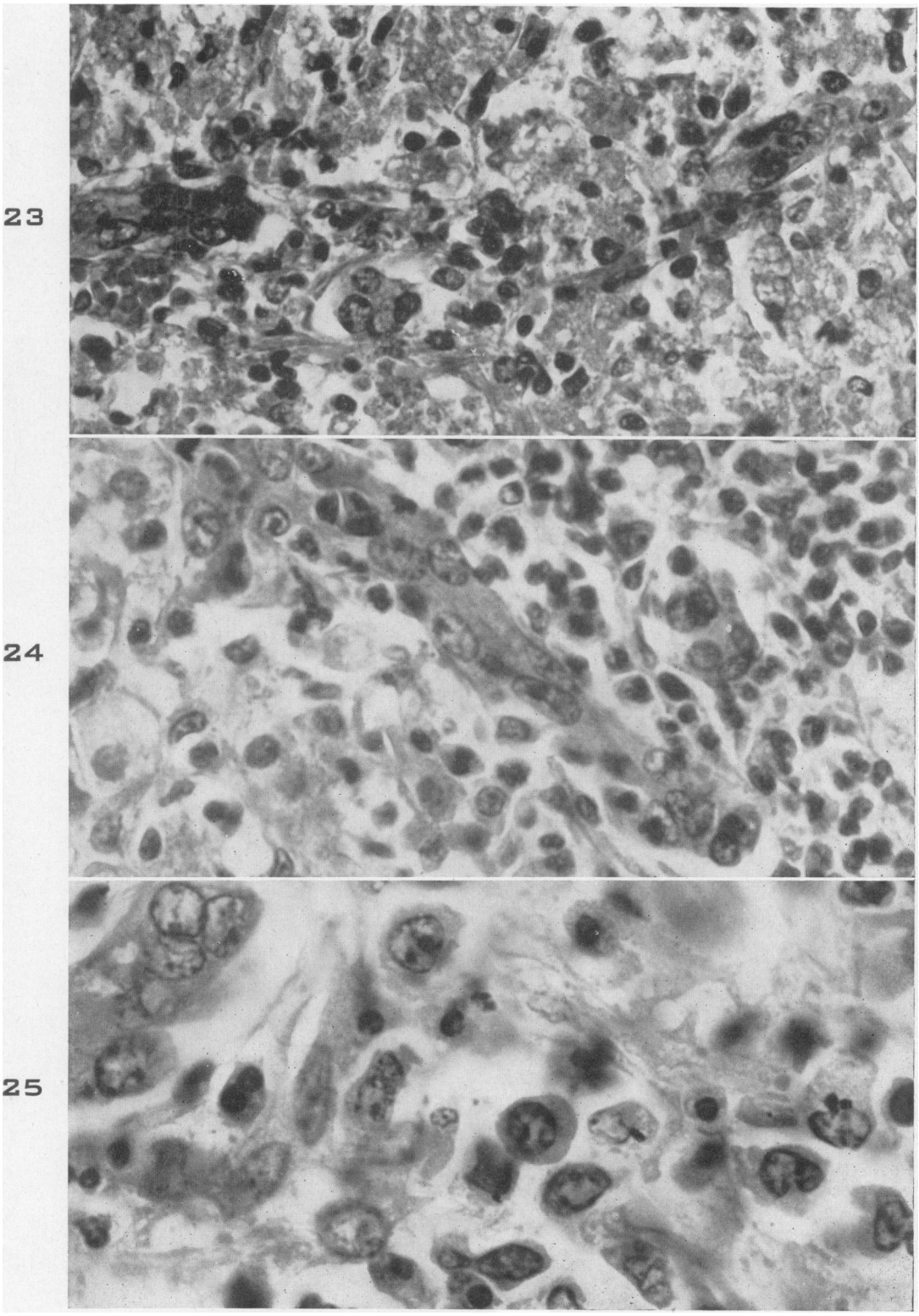

23
24
25

PLATE 173

FIG. 26. Duration of disease, 10 days. (See case 15.) Portal region of liver. Early proliferation of biliary ducts. The proliferating ducts have an irregular shape, due to budding and branching. The component cells are relatively large and have deeply chromatic nuclei. The stroma is densely infiltrated with inflammatory cells. × 230. (A.I.P. acc. 111844; neg. 86340.)

FIG. 27. Duration of disease, clinically less than 1 day. Spleen. The figure shows an enlarged follicle with a prominent and partly necrotic germinal center. (See also Figs. 8, 15, and 24.) × 300. (A.I.P. acc. 123465.)

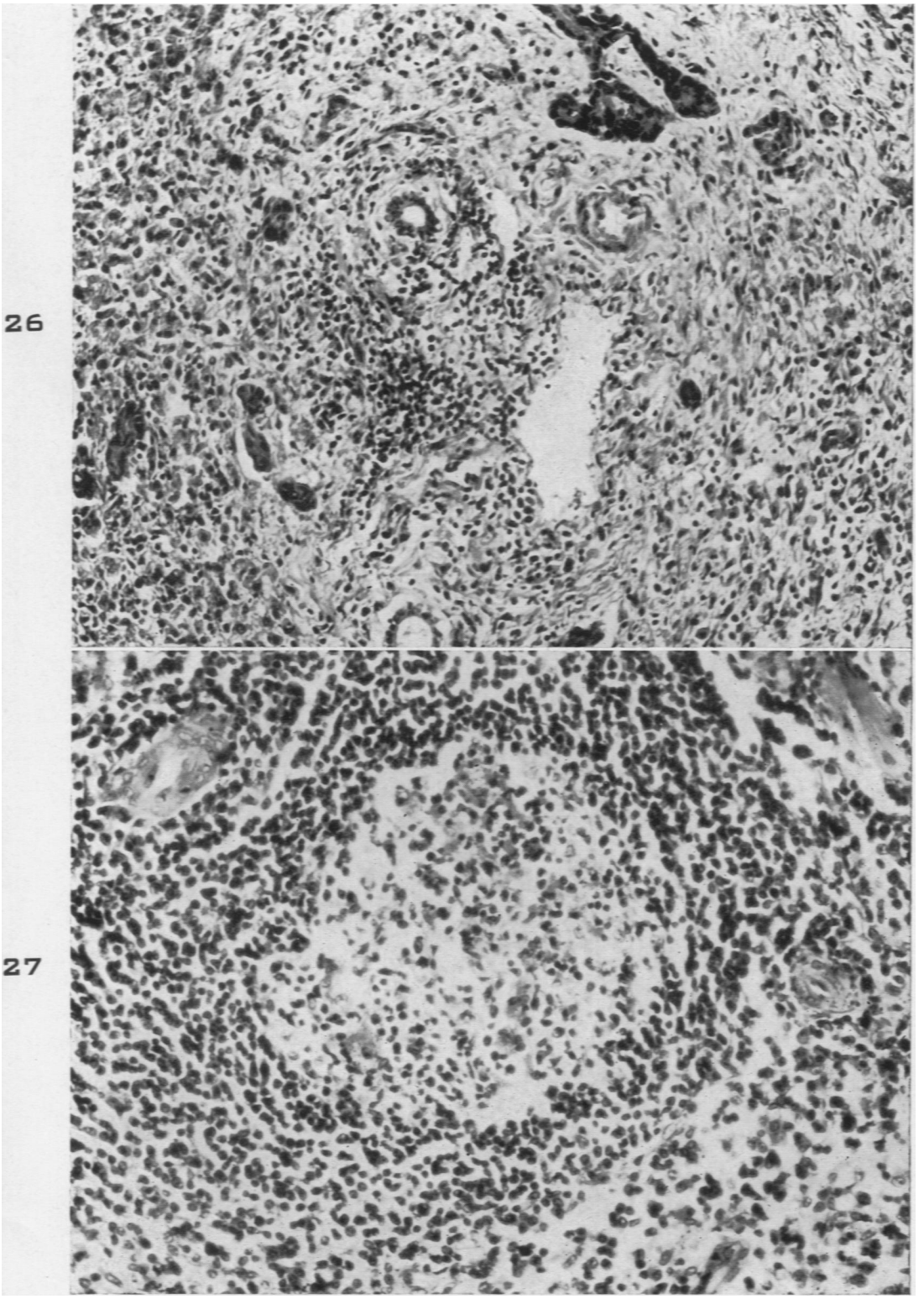
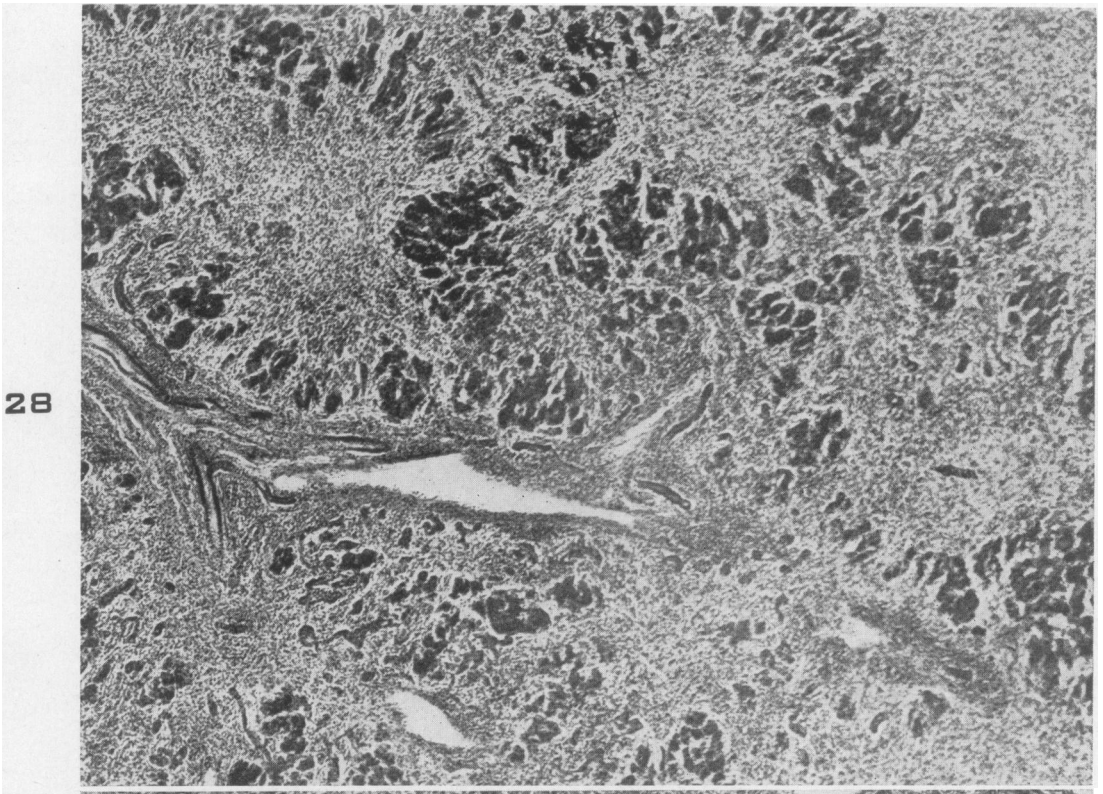

26
27

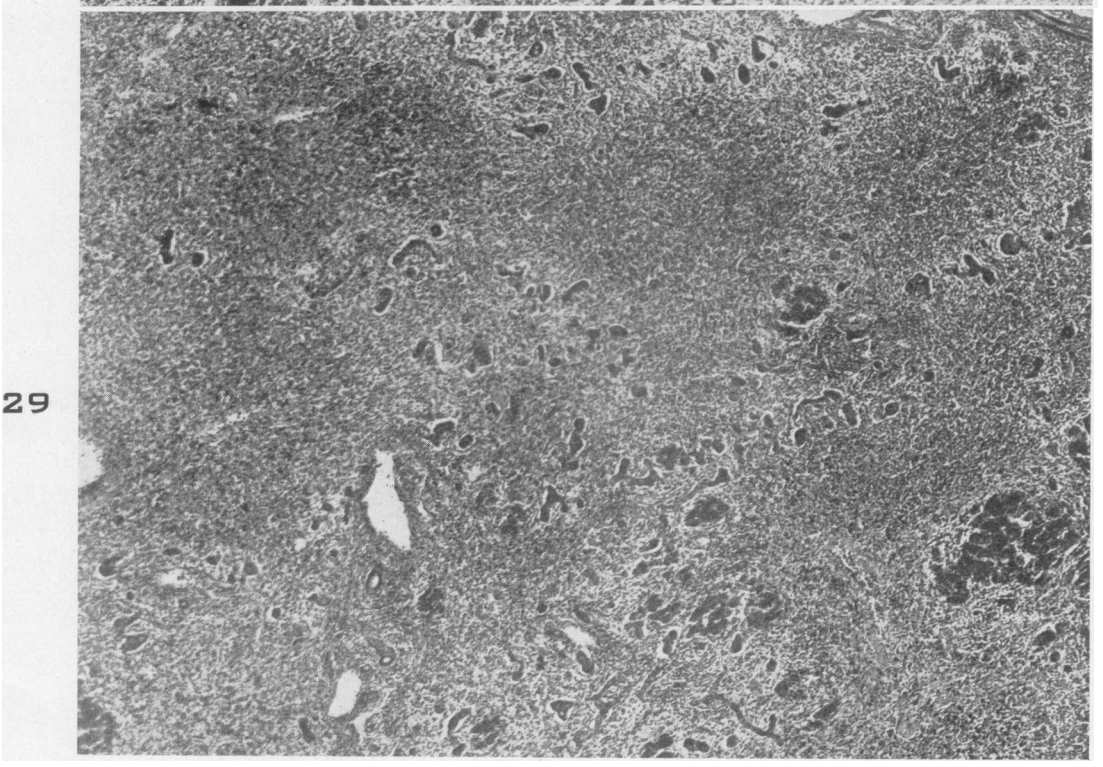
PLATE 174

FIG. 28. Duration of disease, 12 days. Appearance of liver at low magnification. The photograph shows a region in which destruction of hepatic parenchyma is incomplete. A thin, irregular rim of liver cells is preserved in the peripheral zone of the lobules. The portal regions and lobular remnants are densely infiltrated with inflammatory cells. (The section photographed was cut thick in order to bring out these features.) × 50. (A.I.P. acc. 123473; neg. 86017.)

FIG. 29. Another field from the liver shown in the preceding figure at the same magnification. In this area only occasional clumps of liver cells have been preserved. Where destruction is complete, the lobular remnants are outlined by proliferating bile ducts. The granular appearance of the interior of the lobules is the result of intense congestion and invasion by inflammatory cells. This and the preceding photograph give evidence that even in rapidly fatal cases of epidemic hepatitis involvement of the hepatic parenchyma is sometimes not uniform throughout the organ: while in large regions destruction may be complete, elsewhere patches of parenchyma are preserved. In the subacute form of epidemic hepatitis involvement of the liver characteristically is not uniform. × 50. (A.I.P. acc. 123473.)



28



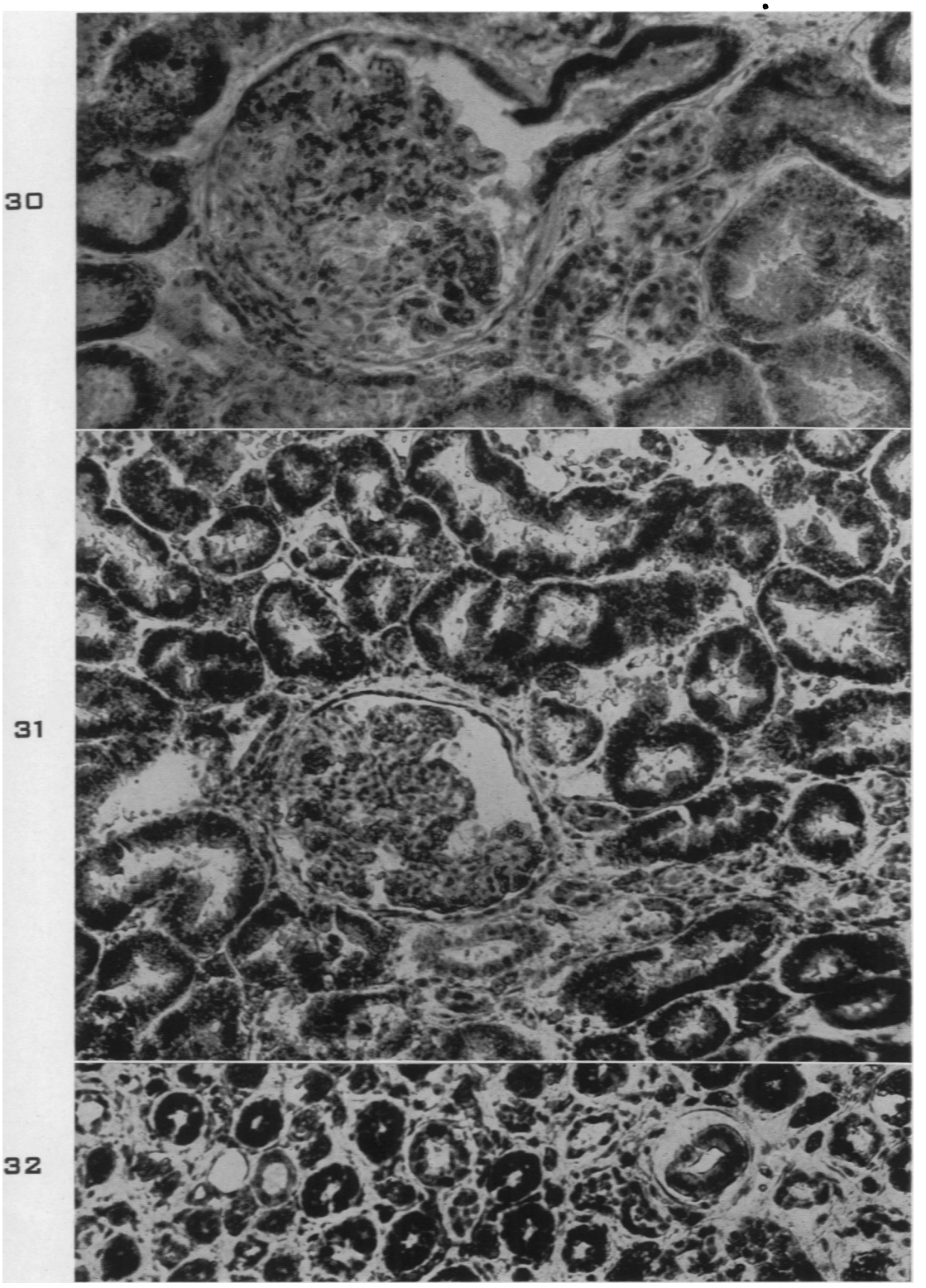
29

PLATE 175

FIG. 30. Duration of disease, 7 days. (See case report 9.) Kidney; thick frozen section, stained with sudan. The epithelium of the neck of the proximal tubule and the convoluted segments are packed with fat. In contrast, the distal tubules, adjacent to the glomeruli, contain very little stainable fat. × 230. (A.I.P. acc. 125602; neg. 87069.)

FIG. 31. Duration of disease, 4 days. (See case report 11.) Kidney; thick frozen section, stained with sudan. The cells of the proximal convoluted tubules are packed with fat which appears black in the photomicrograph. No fat is demonstrable in the glomerulus and very little in the adjacent loops of distal convoluted tubules. (See also Fig. 32.) × 175. (A.I.P. acc. 126811; neg. 87068.)

FIG. 32. Boundary zone of kidney from the same case as shown in Figure 31. Thick frozen section, sudan stain. The cells of the thick limbs of Henle are laden with fat, whereas those of the thin limbs and of the collecting tubules contain very little or no demonstrable fat. × 230. (A.I.P. acc. 126811.)


30
31
32