INFECTIOUS CIRRHOSIS*

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Infectious cirrhosis may be regarded as one of the less common diseases of the liver. It is rare to find it in a pure uncomplicated form. More often it occurs in combination with the obstructive type of cirrhosis. The two types, namely the infectious and the obstructive, occurring either alone or together are often considered as a common entity and grouped together with certain other diseases of the liver under the rather confusing and much misused term of biliary cirrhosis.

It is not the intention of this paper to describe a new and original entity. Infectious cirrhosis is not a new disease: its signs and symptoms as well as its pathological anatomy have long been recognized. One finds, however, in practice, and also in text-books of medicine and pathology considerable uncertainty and misinterpretation in the use of this term. Such confusion may be explained in several ways. First, the disease is not common, consequently the clinician seldom has a fair opportunity to study it; second, the clinical manifestations are rather variable, indeed may be so vague or so slight that an infectious process within the liver is often unsuspected. Similarly, the pathologist who may recognize the disease when seen in its well advanced stages, may overlook it in its earliest form or fail to interpret the varied lesions that one sees in the acute, healing, chronic and healed stages, as nothing more or less than different phases of a single disease. In addition to these facts, one finds the view still prevailing that the terms infectious cirrhosis and obstructive cirrhosis are simply two names for a similar entity; that uncomplicated and prolonged obstruction to the outflow of bile will produce neither recognizable nor constant histological changes; that prolonged biliary obstruction is always complicated with infection within the bile ducts, and that any gross or histological findings that are to be seen within the liver are only the natural result of an inflammatory reaction incited by some form of bacterium.

The purpose of this paper is (1) to define infectious cirrhosis, and to describe it from both the pathological and clinical aspects; (2) to

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point out that infectious cirrhosis and obstructive cirrhosis should not be considered as a single entity but that they differ in respect to etiology, pathological anatomy and in their clinical manifestations, and (3) to show how these two conditions may occur in combination — in which case the pathological and clinical manifestations would depend upon which of the two processes was playing the leading rôle.

LITERATURE

In a paper in 1876 by Charcot and Gombault [1] the term biliary cirrhosis was used to describe lesions of the liver associated with stones in the Ampulla of Vater, cancer of the head of the pancreas and infectious cholangitis. As no attempt at that time was made to differentiate these conditions, the term "biliary cirrhosis" (we adopt Weber's definition [2]) as meaning "any cirrhosis of the liver originating from diseases of the bile ducts or obstruction to the outflow of bile," is quite acceptable.

Heineke [3] in 1897 differentiated two distinct types of biliary cirrhosis; first, one arising from an inflammatory reaction within and around the small bile capillaries and extending outward into the periphery of the lobule, the process being infectious and of an ascending nature. The second type was based on prolonged biliary obstruction.

Mallory [4] in 1911 described infectious cirrhosis as being a type of cirrhosis of the liver resulting from an infection within and around the smaller bile ducts, which corresponds to the infectious type of biliary cirrhosis reported by Heineke.

Rolleston [5] expressed little doubt that the factor which determines fibrosis about the intrahepatic ducts in gall stone obstruction is infection, and regarded the microscopic findings in cases of mechanical biliary obstruction as being of neither clinical nor pathological significance.

MATERIAL FOR STUDY

In a study of the livers from several thousand autopsies performed at the Boston City Hospital, together with a large quantity of material sent in from other hospitals, a total of sixty-five cases was collected showing lesions within the liver which could be grouped as types of "biliary cirrhosis," using again Weber's defi-

nition. Five of this group could be classified as uncomplicated infectious cirrhosis; thirteen were cases of combined infectious and obstructive cirrhoses; thirty-nine were cases of uncomplicated obstructive cirrhosis; while the remaining eight were cases of obstructive cirrhosis that had terminated fatally with an acute suppurative cholangitis with abscesses in the liver. Since this last group showed no cirrhotic changes of infectious origin, they were not included in this series.

Etiology of Infectious Cirrhosis

As the name implies, this type is due to an infection within the terminal bile ducts which invades the adjoining lobules. Cultures of the liver were taken in only two of the five cases and although the colon bacillus was isolated in pure culture from each of these, such evidence is quite insufficient to ascribe to it any definite etiological rôle. However, in one of these two cases microscopic examination showed rather small slender bacilli in the lesions, whereas in the other no organisms could be demonstrated although the lesions had not passed the acute inflammatory stage. Of the three remaining cases, two showed only old healed lesions; therefore, it is not surprising that organisms could not be found. In the last of the five cases, slender bacilli could be demonstrated within the chronic inflammatory lesions. Unfortunately, this case had not been cultured.

A temporary obstruction to the outflow of bile may possibly have been an important contributing factor in the etiology of these five cases, because in each there was a history of a transient, though slight degree of jaundice. However, at autopsy no obstruction was found and a histological examination of the liver showed no lesion suggesting biliary obstruction.

The manner in which organisms reach the terminal bile ducts is probably by an ascending course from the duodenum through the large and small bile ducts. However, the possibility of infection reaching the liver by way of the circulation and lymphatics cannot be entirely disregarded. This phase of the problem has recently been fully reviewed by Brulé [6] who discusses in detail all the possible paths by which infection may reach the liver.

HISTOLOGICAL FEATURES OF INFECTIOUS CIRRHOSIS

The picture at first is merely that of acute inflammation within the portal areas, resulting from the presence of pathogenic organisms within the terminal bile ducts; from here the inflammatory reaction spreads among the surrounding liver cells (Fig. 1) so that the lesion is confined not alone to the portal areas but also to the peripheral zones of the lobules.

The portal areas which appear to suffer the brunt of the infection are the rather small or medium sized ones; however, even the smallest and largest may at times become involved. Furthermore, the inflammatory reaction may not be equally advanced in all portal areas within the liver so that some may show acute inflammation, others a rather chronic reaction, whereas in others the process may be almost or entirely healed. In order to interpret the histological findings in a liver in which the process has entirely healed, it is necessary to have traced and to know thoroughly the development of the lesion from its early beginning to its end.

The small bile duct is the center of an acute inflammatory reaction; the lumen is distended with polymorphonuclear or endothelial leucocytes (Fig. 4), depending on the number and virulence of the infecting organism. The epithelial cells are stretched and show regressive changes, and the surrounding stroma is infiltrated with an acute inflammatory exudate. As the organisms invade the tissue around the ducts (Figs. 2 and 3) and the process extends, the liver cells in the outer portions of the lobules show retrograde changes; even at this early stage one may find proliferation of fibroblasts. Later, there is a zone of degenerating and necrotic liver cells infiltrated with polymorphonuclear and endothelial leucocytes surrounding the portal area. The endothelial cells lining the sinusoids, and the supporting connective tissue are also damaged so that the normal architecture of the periphery of the lobules is entirely lost.

Very early, the bile duct epithelium begins to proliferate, mitoses are numerous, and any small periportal ducts that have not been destroyed, elongate and give rise to many new ducts which extend out into the surrounding zone of necrosis to link up with the free ends of bile capillaries.

Occasionally one finds the walls of vessels also involved in the in-

flammatory reaction and fibrin thrombi adherent to the damaged endothelium partially obstructing the lumina. The lymphatics in the capsule and large portal areas are filled with endothelial and polymorphonuclear leucocytes, coagulated albumin and fibrin.

In the healing stage, when the process is less active and the bacteria have died out, the exudate consists chiefly of endothelial leucocytes, many of which are phagocytic and contain necrotic cellular débris. Long before this period, as already mentioned, fibroblasts have begun to proliferate, largely as the result of direct injury to the connective tissue by the bacteria and their toxins, but also in part to form stroma for the greatly increased number of small bile ducts.

In the smaller portal areas the lesion spreads very uniformly as an expanding circle from the bile duct toward the surrounding hepatic veins, but in the larger portal areas, where there may be several ducts and where the ducts are so eccentric, the infection may not reach each of the adjacent lobules but may extend out in a semicircular fan-shaped manner destroying the periphery of only one or more lobules along one side. On the whole, however, the true lobular arrangement is more or less perfectly preserved and the portal areas, as a result of the extensive exudate, of the necrosis of the liver cells and of the encroachment and proliferative activity on the part of the terminal bile ducts and connective tissue, show up as broad bands running rather regularly among the lobules of liver cells.

In contrast to the lesion in the acute or healing stages, the healed lesion is much less conspicuous. The necrotic cells have been removed; a few scattered lymphocytes, singly or in foci, are all that remain of the inflammatory exudate; the stroma is shrunken and the small bile ducts are compressed. The portal areas now stand out simply as bands of dense fibrous tissue containing many small bile ducts. The portal vessels are frequently sclerosed, and here and there, lying near the portal areas, are small isolated clumps of liver cells.

Anatomical Features of Infectious Cirrhosis

In the early stage of infectious cirrhosis, the liver is normal in size and contour, the capsule is smooth, the fresh surface may be bile-stained and the portal areas may be slightly accentuated, but there

is so little grossly to suggest the histological changes that the lesion at this stage may be readily overlooked.

As the process becomes more chronic and more extensive the liver enlarges from a third to double its normal size. The capsule is smooth and tense. The consistence is increased and the liver cuts with more resistance. The fresh surface may be a little bile-stained or deeply congested, but the broad portal areas even at this stage are not very clearly defined.

The healed stage is characterized by a contraction of the newly formed stroma so that once again the liver may return to about normal size. The surface is rather uniformly and finely nodular with the nodules sometimes measuring nearly one centimeter in diameter. The consistence is firm and the liver cuts with greatly increased resistance. The cut surface presents a striking picture (Fig. 5). There is a marked increase in the amount of connective tissue about the portal areas so that they appear as grayish white, fibrous bands which may be traced from the transverse sinus to the capsule.

Clinical Aspects of Infectious Cirrhosis

Since these are so dependent on the nature of the lesion within the liver, they will of course vary considerably. The onset may be gradual and unaccompanied by any diagnostic sign or symptom; however, as is so commonly the case, jaundice, perhaps very slight and only transient, is one of the first things to be noticed. Lassitude, drowsiness and gastro-intestinal disturbances, accompanied later by loss of strength and weight are clinical findings common to each case. The temperature may vary slightly from day to day but seldom rises above 100 F. Similarly, the blood count may show no appreciable change, except a slight leucocytosis which sometimes reaches twelve or fifteen thousand cells per cubic millimeter.

In the early stage, as already pointed out, the liver is normal in size; in the chronic and healing stages it is enlarged, while later, if recovery ensues, it may shrink again to normal size and is then uniformly nodular. The spleen may be somewhat enlarged from the onset. As the process in the liver regresses, with a gradual contraction of the newly formed connective tissue, the portal circulation becomes appreciably obstructed so that in the healed stages the spleen may

be considerably enlarged, due to chronic passive congestion. Ascites and esophageal varices were found in one case. In the healed stage there is neither jaundice nor histological evidence of bile stasis.

Summary of the Pathological Findings in Infectious Cirrhosis

The outstanding features of infectious cirrhosis can be stated briefly; a sequence of changes may be followed beginning with an infection within the terminal bile ducts, which soon spreads and destroys the surrounding liver cells. This not infrequently causes damage to the walls of the vessels as well. Bile ducts and connective tissue rapidly regenerate and, with the disappearance of the inflammatory exudate and the necrotic cellular débris, the late characteristics of this type of cirrhosis soon become well established.

Comparison Between Infectious and Obstructive Cirrhoses

First as regards etiology; one results from an infection within the terminal bile ducts, the other from prolonged biliary obstruction. The infectious type of cirrhosis lacks a uniform general distribution, whereas in the obstructive type of cirrhosis [7] the histological changes characterized by an elongation and apparent increase in bile ducts are found in every portal area within the liver. Furthermore, whereas the outstanding features in the early stage of infectious cirrhosis are infection, inflammation and necrosis, in the obstructive type it is the extreme degree of bile stasis which first attracts attention.

Grossly, the liver in uncomplicated cases of obstructive cirrhosis is normal in size, and the surface is smooth except when the obstruction has been of very long standing, and then it assumes a very finely granular Morocco leather appearance.

Lastly, while the classical signs of a severe degree of obstruction to the portal circulation, namely esophageal varices, a large spleen and ascites, are found in long-standing and healed cases of infectious cirrhosis, they are lacking in cases of the obstructive type.

INFECTIOUS CIRRHOSIS COMBINED WITH OBSTRUCTIVE CIRRHOSIS

This combined form of cirrhosis, though much less common than the simple obstructive type, is encountered more frequently than the infectious type alone, and is simply the result of an infection within the terminal bile ducts of a liver that has already begun to show the characteristic changes resulting from prolonged biliary obstruction. Hence, the lesion is merely the picture of one type of cirrhosis superimposed on another, and because the inflammatory process resulting from the infection spreads quickly it soon becomes the outstanding feature both grossly and microscopically (Figs. 6, 7 and 8).

This combined form of cirrhosis may occur at any age; two examples were in infants several months old, one in an adolescent, and the remainder in adults. In our small series males and females were about equally affected. As in the simple uncomplicated type of infectious cirrhosis, the infection probably reached the liver by way of the biliary system; however, since two of our cases were in infants that at the time of the autopsy were considered to show complete atresia of the common bile duct, the possibility of the infection coming from the vascular or the lymphatic system should also be considered. The infecting organism in three of the cases that were cultured was the colon bacillus; unfortunately, no bacteriological studies were carried out in the others, but in eight, bacilli were demonstrable histologically within the lesions.

At this point it is quite unnecessary to repeat the description of the histological lesions of both the obstructive and infectious types of cirrhosis and consequently only the most characteristic findings will be mentioned. The lesions of infectious cirrhosis may be in the acute or chronic stage, but since this combined type of cirrhosis almost invariably ends fatally, a liver showing the combined healed infectious and obstructive lesions is extremely rare and was encountered in only one of our cases, and in this the obstructing agent had disappeared.

One of the remarkable features of this combined type of cirrhosis is the large number of infarcts seen in the periphery of the lobules which resemble in every way those that are occasionally found in the uncomplicated type of obstructive cirrhosis. Sooner or later many of these become infected and are then distended with an inflamma-

tory exudate which compresses the surrounding liver cells. The origin of these areas of necrosis,[8] which occur rarely in simple obstructive cirrhosis and more commonly in the combined form of obstructive and infectious cirrhosis, can be explained on several grounds. First, there is a mechanical interference with the blood supply in these areas as a result of wide distention of the bile ducts compressing the vessels in the portal area; (2) in the process of inflammation there is a slowing of the circulation, and (3) as a result of the injurious agent the vascular endothelium is injured and thrombi are frequently formed. With this explanation these areas of necrosis may be interpreted simply as infarcts which have undergone unusually rapid liquefaction as a result of imbibition with bile.

Another finding in this combined form of cirrhosis is the relatively inconspicuous rôle bile stasis plays in the picture, so that instead of seeing the bile capillaries distended with bile they are collapsed and almost empty. This may probably be explained either by the escape of bile from the free ends of the bile capillaries into the periportal zone of inflammation and necrosis, or on the basis that the liver cells, in the presence of infection, cease to carry out their secretory function, and consequently bile is not being formed.

Comment

Uncomplicated infectious cirrhosis is one of the rarer diseases of the liver. It is caused probably in most instances by the colon bacillus, and is characterized by a variable degree of connective tissue and bile duct proliferation about the portal areas.

Obstructive cirrhosis resulting from prolonged biliary obstruction is a much more common condition although less conspicuous and hence frequently overlooked.

Most cases of infectious cirrhosis are found in combination with obstructive cirrhosis, but even this combined type is relatively rare and is almost invariably fatal.

Summary

1. The gross and histological lesions of infectious cirrhosis, when occurring alone or in combination with obstructive cirrhosis, are described.

2. Infectious cirrhosis is contrasted with obstructive cirrhosis from the pathological and clinical aspects.

3. The literature bearing on infectious cirrhosis is briefly reviewed.

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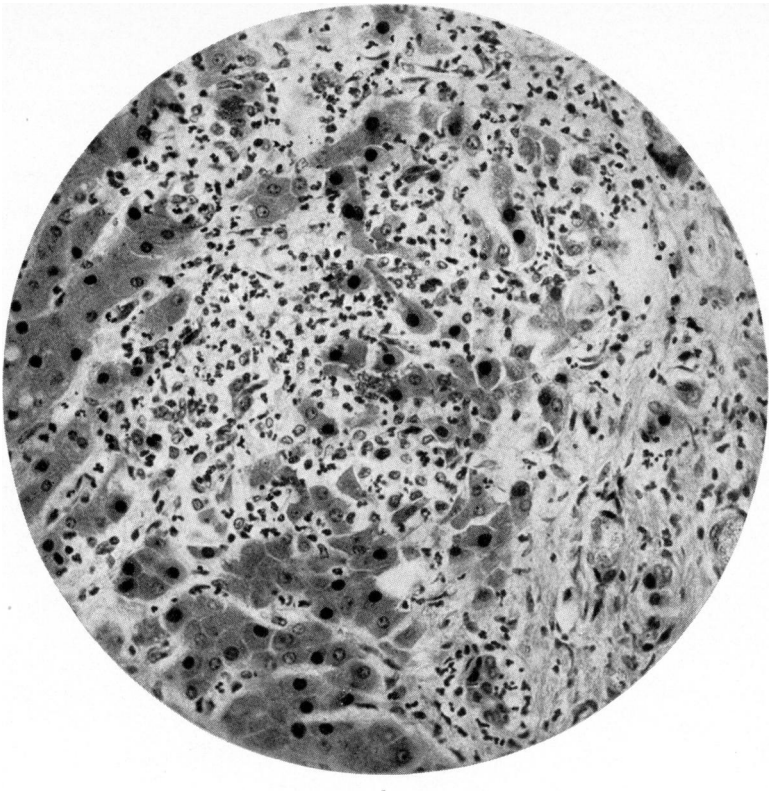
DESCRIPTION OF PLATES

PLATE 14

FIG. 1. Periphery of a lobule, showing invasion by colon bacilli, destruction of liver cells and an inflammatory exudate of polymorphonuclear and endothelial leucocytes. The periportal connective tissue is increased in amount. From a man aged 85 years. × 250.

FIG. 2. Invasion of liver parenchyma by colon bacilli: acute inflammatory exudate consisting of polymorphonuclear leucocytes. From the same case as Fig. 1. × 1000.



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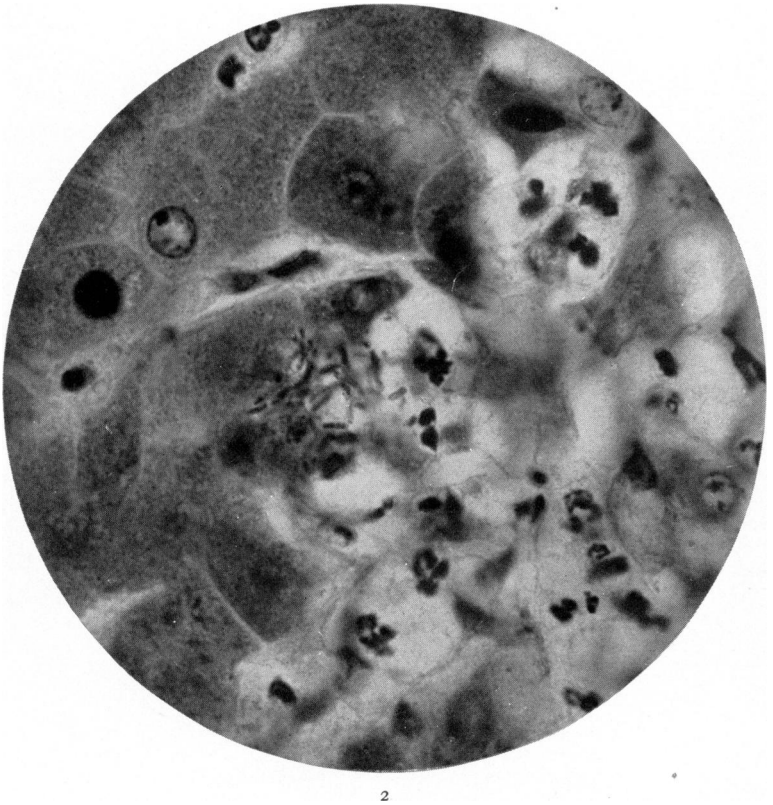

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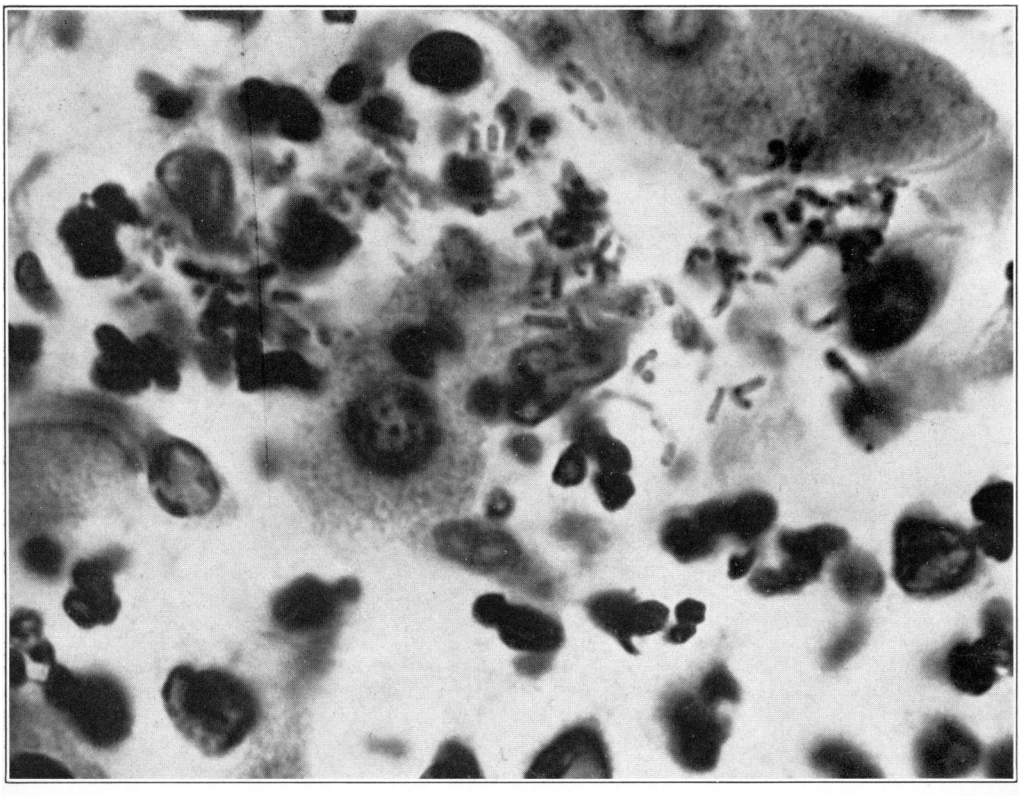
Plate 15

Fig. 3. Invasion of liver parenchyma by colon bacilli: acute inflammatory exudate consisting of polymorphonuclear and endothelial leucocytes. From the same case as Figs. 1 and 2. × 2000.

Fig. 4. Bile duct dilated: contains an irregular cylindrical mass of inspissated bile and an exudate of endothelial leucocytes. The surrounding stroma is infiltrated by endothelial and polymorphonuclear leucocytes and a few lymphocytes. From a girl 13 years of age whose liver was twice normal size. × 1000.



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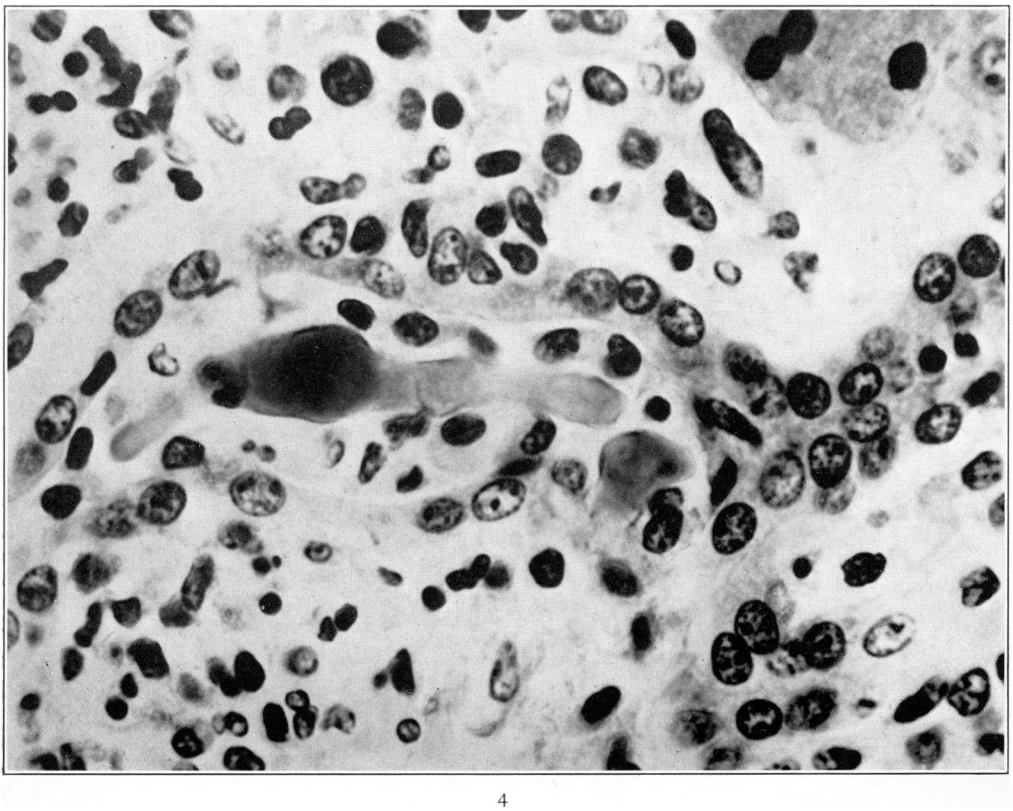

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PLATE 16

FIG. 5. Healed infectious cirrhosis. The lesion is more or less irregularly distributed. From a woman 25 years of age. Weight of liver 1090 gm. Ascites but no jaundice.

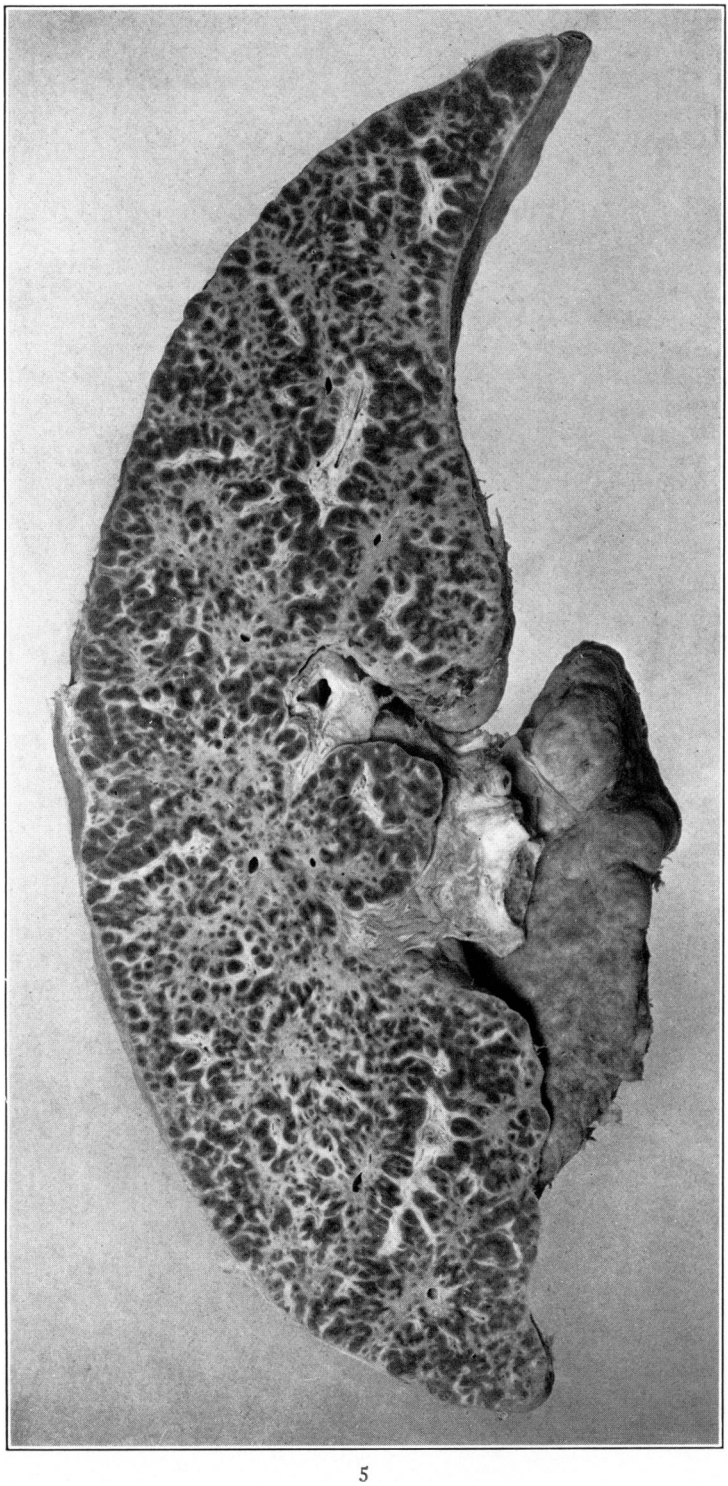
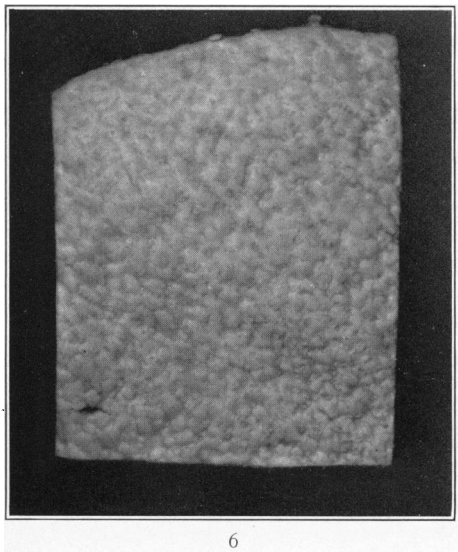


PLATE 17

FIGS. 6, 7 and 8. Healed obstructive and infectious cirrhosis from a man 40 years of age. Weight of liver 2495 gm. Jaundice, esophageal varices. The lesion is very evenly distributed throughout the liver. The surface is granular. The photomicrograph shows that the lesion is situated around the portal vessels. The even distribution of the lesion, in contrast to that seen in Fig. 5, is probably due to the bile stasis which enabled the infecting agent to spread uniformly throughout all the dilated bile ducts. × 50.



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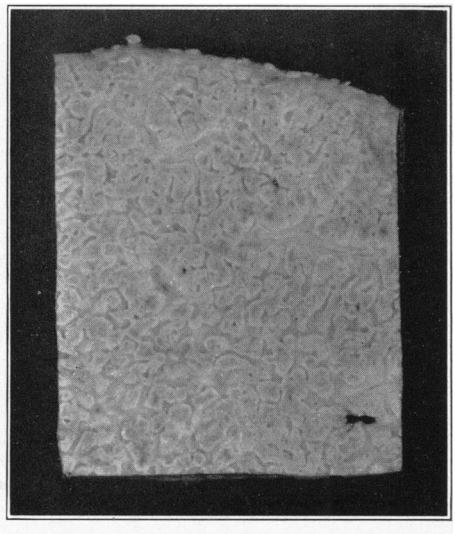

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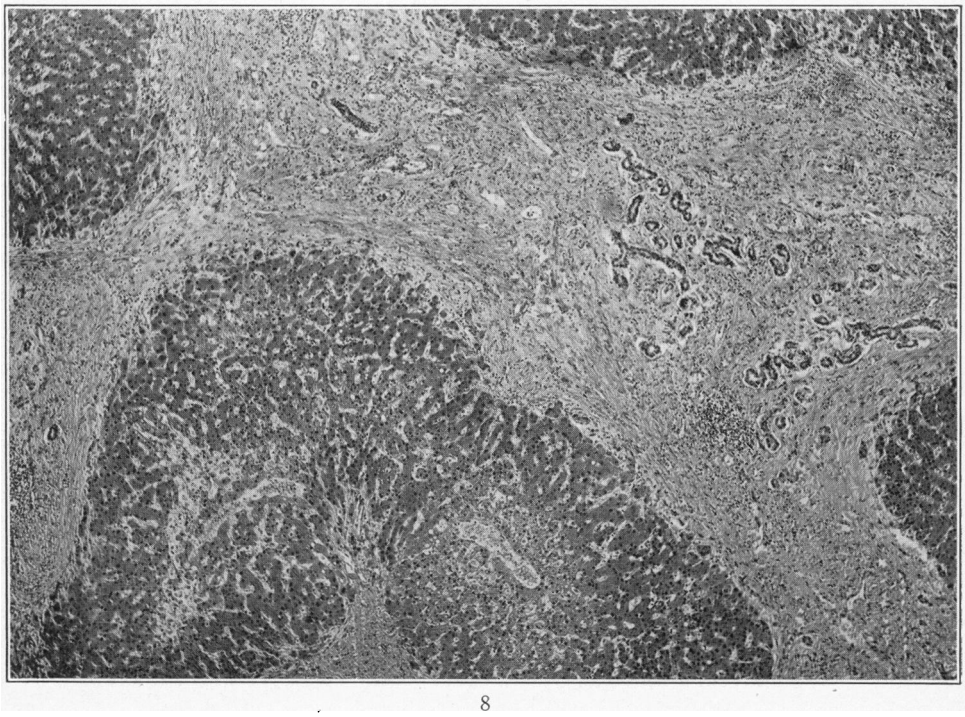

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