STREPTOCOCCUS HEPATITIS *

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Infectious lesions of the liver do not play as important a rôle as those of a toxic nature, but they occur in considerable variety, and some of them, syphilis and tuberculosis for instance, are of considerable importance in the pathology of this organ. It is the object of this paper to present several examples of a type of infection of the liver which may not be so infrequent as examination of the literature might lead one to believe. Furthermore, its importance lies in the fact that it may throw light on certain instances of acute yellow atrophy, and on the type of cirrhosis which may follow that lesion if recovery takes place.

The degenerative and inflammatory changes of the liver that may accompany streptococcus infection with and without a septicemia vary considerably and show no one characteristic histological lesion that may be considered as specific for this organism.

ACUTE TOXIC HEPATITIS

The more common changes which are found in the liver in cases of streptococcus infection are of a degenerative and inflammatory nature and are usually ascribed to the effect of toxins circulating within the blood stream. These lesions may be distributed diffusely and uniformly throughout the liver, or they may appear quite irregularly. Such lesions as the latter have been described by Helly [1] under the name "septische Leberfleckung." This is characterized grossly by the presence of anemic-like zones throughout the liver. Histologically one sees changes in both the liver cells and endothelial cells. The former are swollen, granular, intensely stained, and frequently distended with fat. The endothelial cells are larger than normal, and show both proliferation and desquamation. The sinusoids contain less blood than the surrounding areas, and the perisinusoidal

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spaces are moderately edematous. A similar histological change may be found throughout the entire liver, and such a picture has been described by Rössle [2] as a "diffuse serous hepatitis."

In instances where the liver has been more severely injured, the liver cells in the central zones of the lobules may show dissociation necrobiosis and necrosis. The last change is not infrequently associated with an extravasation of red blood cells and an infiltration of polymorphonuclear and endothelial leucocytes.

In another group of cases, the changes within the lobule may be negligible, the outstanding lesion being almost entirely confined to the portal areas. Here one finds an acute exudative inflammatory reaction in the portal connective tissue characterized by an infiltration of polymorphonuclear leucocytes, strands of fibrin, edema and swelling of the collagen fibrils. The liver cells bordering this area may show early degenerative changes.

Occasionally one finds an almost pure lymphocytic infiltration of the portal area, a picture first described by Friedreich and von Gaffky,[3] and later spoken of by Virchow [4] as "Lymphome." Rössle regards this lesion as an inflammatory hyperplasia, in the sense of an increased resorptive activity against toxins passing from the damaged lobule into the portal areas.

Whereas we have depicted two rather distinct groups of lesions, one occurring within the lobule and the other in the portal area, we do not imply that both may not be found together — on the contrary this is a fairly common finding. However, to repeat what we have already mentioned, none of these lesions is the result of the actual presence of the streptococcus within the liver, but is due to the presence, either directly or indirectly, of a circulating toxin within the blood stream.

Acute Infectious Hepatitis

Gastou [5] in 1893, in his description of "foie infecté," was the first to point out that a diffuse, acute inflammation of the portal areas was not uncommonly associated with focal intralobular hepatitis, and in a child diagnosed clinically as having diphtheria, which terminated fatally, he demonstrated in the liver both an infiltration of the portal connective tissue and inflammatory foci (containing cocci in chains) within the lobules.

It is with this latter lesion — a lesion described recently by Landé [6] as an "acute focal necrotizing hepatitis" — that we are principally interested in this report, because we believe that in some instances, but not in all, it is the result of the actual presence of the bacteria within the liver.

In the year following Gastou's report, Babes [7] reported four cases of fulminating streptococcus septicemia showing widespread gross and microscopic degenerative and necrotic changes in the liver. In each case streptococci were obtained from the blood, and in all cases but one these organisms were demonstrable in the liver. The histological lesion which he described in three of the cases resembled acute yellow atrophy in the very early stages, showing in addition the sinusoids distended with mononuclear cells containing streptococci. The lobules were made up of trabeculae of large, swollen, granular, eosin-staining, necrotic liver cells. In the fourth case, a patient who had been jaundiced for some time, the liver grossly resembled a later stage of acute yellow atrophy. It was small, shrivelled, soft and red. Histologically much of the parenchyma had disappeared and bile ducts had begun to proliferate and extend into the lobules. Streptococci were neither demonstrable culturally nor in the fixed preparation, although they were recovered from the heart's blood and from several other organs. Babes made no attempt to explain acute yellow atrophy on an infectious basis, but thought that perhaps occasional cases might be of infectious origin. Furthermore, in explaining the absence of streptococci in the liver in the last case he believed that the organism had produced its destructive lesion, and subsequently disappeared.

Bingel,[8] in reporting the pathological findings within the liver in eight fatal cases of scarlet fever, found in two of them irregularly scattered foci of necrotic liver cells infiltrated with an inflammatory exudate. Bacteria were neither isolated nor were they seen within the lesions.

Baginsky[9] reported an interesting case of interstitial hepatitis with widespread but isolated necrosis and inflammation of the liver parenchyma occurring in a child 10 years of age. Clinically it was a picture of a generalized septicemia of ten days' duration, and streptococci were obtained from both blood culture and liver puncture. Grossly the liver was soft, grayish yellow, cloudy and swollen. Syphilis and tuberculosis, as well as such chemical poisons as alcohol

and phosphorus, were definitely ruled out. Smears made directly from the lesions within the liver at the time of the autopsy revealed streptococci. In view of this finding, even though organisms were not demonstrable within the fixed tissue preparations, the author felt that the lesions were probably infectious in origin.

Landé reported two cases of acute focal necrotizing hepatitis, and in both, the lesions varied in size and appeared as grayish yellow areas against a darker background. Microscopically the lesions varied in size from small foci scattered within lobules to much larger areas involving several lobules. These showed dissociation of both reticulum and liver cells, degeneration and necrosis of the liver cells, together with an infiltration of mononuclear leucocytes. Even in the most extensive areas, the vessels and bile ducts together with the interstitial tissue comprising the portal areas were moderately well preserved. Both cases were considered as infectious; streptococcus hemolyticus was recovered from the blood of one of these, but organisms were not demonstrated within the lesions of either.

Aschoff[10] refers to the lesions already described by Landé, and adds that similar lesions may be found in other infectious diseases as well as in streptococcus infection. Furthermore, he points out that probably many foci, often considered as pure necrosis, may be considered in this class.

Rössle, in his description of focal and acute inflammatory lesions of the liver, states that this group of lesions constitutes a relatively uncommon finding, and in autopsies in which one might anticipate these lesions, such as in cases of septicopyemias, they are usually lacking.

Thomson [11] speaks of a type of infectious jaundice in newborn children caused by the streptococcus being carried to the liver from the umbilicus and giving rise to an acute hepatitis. An interesting point which he brings out, and one which has a bearing on one of our cases, is that the umbilicus, although the primary point of infection, may show no external sign of inflammation.

Rolleston,[12] in discussing the etiology of icterus gravis, includes streptococci among the etiological agents in producing the changes within the liver, but feels that the lesion is the result of a generalized toxemia striking a liver that is already lacking in vitality, rather than the direct result of bacteria being present within the organ. He

states that various organisms have been found within the liver but none so constantly as to justify definite conclusions.

One obtains little aid in the study of these acute, non-suppurative, diffuse and focal forms of hepatitis involving the parenchyma of the liver from textbooks of pathology and medicine. Certainly one gains the impression that if streptococci reach the liver they either produce no demonstrable lesion, or an abscess results. Karsner,[13] however, does devote a paragraph to acute non-suppurative inflammation of the liver, in which he describes two types. In one the liver shows cloudly swelling, and histologically one finds an acute polymorphonuclear leucocytic exudate in the portal areas: in the second type, described as acute interstitial hepatitis in contrast to the first which he calls acute parenchymatous, one finds mononuclear leucocytes and lymphocytes instead of polymorphonuclear leucocytes.

The production of abscesses within the liver by the streptococcus is mentioned in almost all textbooks of pathology, and although not a common finding at autopsy it is one that is generally accepted as being beyond dispute. One finds in the literature isolated reports of abscess formation following streptococcus infection; perhaps among the earliest recorded cases is one by Roger [14] in 1896. The patient, a young woman 30 years of age, complained of severe abdominal pain demanding surgical interference. A large abscess was revealed in the tubo-ovarian region from which streptococci were grown in pure culture. The convalescence was poor and the patient died within a few days. An autopsy revealed abscesses in the liver in addition to the pelvic condition. Cultures taken from both sources demonstrated an organism in pure culture similar to that which was obtained a few days earlier at the operating table.

In the more recent literature mention is made by Thomson [11] of the same conditions occurring in children following infection of the umbilical vein.

Before describing the cases which we have found of this acute focal and diffuse non-suppurative type of hepatitis, we wish to consider an entirely different form of hepatitis that is essentially chronic and progressive.

Chronic Infectious Hepatitis

Suggestions of a chronic progressive inflammatory process in the liver going on to form a true cirrhosis and ascribed to streptococci colon bacilli and other bacteria are not infrequently encountered in

the literature.[15, 16, 17, 18, 19, 20, 21, 22] In fact attempts have been made to show that any and all types of cirrhosis could be explained on an infectious basis. Today, however, such an idea seems absurd. The etiological and morphological classifications of cirrhosis have been more accurately determined, and specific lesions of the liver of a chronic progressive inflammatory nature can usually be grouped among the more common and well recognized types of cirrhosis.

Siredey [23] in 1886 described lesions in the liver both degenerative and inflammatory in nature in cases of diphtheria and scarlet fever, and believed that the inflammatory reaction may become chronic and account for certain instances of sclerosis found in later years. He also remarked that patients with an alcoholic history are predisposed to inflammatory lesions within the liver, stating that the alcohol may lower the vitality of the cells, making them more susceptible to infection.

A year later Mogk [24] reported a case of cirrhosis occurring in a young child who, eight weeks before death, suffered a very severe attack of scarlet fever. The liver at autopsy showed irregular areas of necrosis, an inflammatory exudate and a proliferation of connective tissue. The most interesting finding in this case, however, was that chains of streptococci were demonstrated within the more recent lesions.

At a pathological meeting several years later this case of Mogk's was thoroughly discussed by Schlichthorst [25] who, admitting the probability that the changes in the liver were part of the infectious disease, found it difficult to believe that streptococci could persist in the liver for so many weeks.

Henoch [26] was convinced of the important rôle infectious diseases play in the etiology of cirrhosis of the liver. He observed in the very severe cases of measles and scarlet fever signs and symptoms indicative of pathology within the liver. These lesions, he pointed out, could either completely disappear with full restoration of the liver, or could persist long after the acute infection, as an interstitial hepatitis. Histologically he found in such cases a moderate hepatosis, proliferation of the portal connective tissue and dilatation of the small ducts, and looked upon this form of hepatitis as being quite capable of developing into a true cirrhosis.

Folger [27] reported an unusual case of hypertrophic cirrhosis of the liver in a child who had been jaundiced for weeks. The liver was

definitely cirrhotic, and showed advanced sclerosis and a massive production of small bile ducts. Streptococci were demonstrable in the liver and other organs, but were accepted by Folger with considerable doubt as having any direct bearing on the lesion within the liver.

Bingel [8] firmly believed that certain cases of cirrhosis in children, alcohol and syphilis being excluded, could be directly linked up with changes in the liver which may occur in severe epidemics of scarlet fever. He reported a case in a young child, 9 years of age, who had recently suffered a very severe angina, probably of scarlet fever origin, accompanied by pain in the right upper quadrant. The convalescence was poor and seven months later jaundice appeared, together with gastric distress and fever. A few days later the child died. The liver was uniformly firm, sclerotic and irregularly lobulated. Microscopically it resembled somewhat the alcoholic type of cirrhosis, but in addition the fibrosis extended quite often between groups of liver cells. There was a reconstruction of the liver parenchyma, marked increase in connective tissue and a somewhat irregularly distributed, small, round cell infiltration.

Very recently Moon [28] reported two cases showing a progressive type of cirrhosis which he considered as being infectious in origin. One of these occurred in a patient, aged 12 years, who had been diagnosed clinically as having "Banti's disease." The spleen and liver were of about equal size, each weighing just under 1000 gm. The liver, which was firm and nodular, was diagnosed as atrophic cirrhosis. Histologically a section stained for bacteria showed cocci in pairs throughout this organ. The autopsy unfortunately was done a considerable number of hours postmortem; thereby lessening to some extent the importance attributed to these organisms within the liver. The second case was in a boy 14 years of age. The family history is worthy of note in that several of the children had already died from cirrhosis of the liver. This child's spleen and liver were large, and in addition he showed marked anemia, moderate leucopenia, increasing ascites and shortly before death a slight degree of jaundice. No clinical diagnosis was made. At autopsy the liver was large, firm, and showed a hobnail granular surface. Sections of liver tissue showed cocci in areas of more recent degeneration and necrosis, and in addition a pure culture of streptococcus hemolyticus was obtained from the liver at the time of the autopsy.

An attempt to ascribe certain chronic inflammatory lesions of the liver to streptococci, acting locally, is of course open to criticism even where the organism may be demonstrable within the lesions of the liver, since such a bacteriological finding could occur in a terminal bacteremia. Cases assumed to be the result of streptococcus infection, purely on the basis of a clinical history — such cases in which the organisms are not demonstrable, the supposition being that they have died and disappeared — are subject to even greater criticism and can be accepted only with reserve.

Healed Infectious Hepatitis

The last point which we must now consider is the gross and histological changes which one may find in the healed stages of these acute and chronic inflammatory processes within the liver. Where the acute lesions are small there is evidence to show that there is probably complete structural and functional restoration; yet as Rössle says, "we know too little about the fate of these small areas of necrosis and the associated liver changes that may appear with various infectious diseases." The large areas in which all of the liver cells in one or more lobules have been destroyed probably show incomplete regeneration, and heal by sclerosis. Such healed lesions are characterized by the presence of one or more rather sharply circumscribed and irregularly distributed areas composed of connective tissue, bile ducts and regenerated liver tissue; the latter in some cases is entirely absent. This picture, though usually focal in distribution, resembles very closely the healed stage of true acute yellow atrophy of non-infectious origin.

Apropos of this, is an unusual case of cirrhosis, reported several years ago by Rössle,[29] occurring in an elderly male. The liver was quite normal, except for a single isolated area of sclerosis about the size of the palm of the hand lying on the anterior surface of the right lobe. This was irregular, yellowish brown and extended into the liver several finger breadths. Sections from different parts of the liver were carefully examined histologically and except in the areas of sclerosis showed no noteworthy change. The lesion itself showed definite cirrhosis, with reconstruction of the remaining liver parenchyma, increase in connective tissue and bile ducts and a small round cell infiltration. No visible explanation was found for this rather

rare occurrence and the author suggested that it was probably a type of cirrhosis that could be explained on the basis of an embolic toxic-infectious process.

Material for Study

The material which forms the basis for this work was obtained from several of the larger hospitals of Boston, and the cases which are reported below have been selected from several thousand autopsies. We have included only those cases of streptococcus hepatitis which can best be explained as the result of the actual presence of the organism within the liver, and the five cases selected are fairly representative of the types of pathology one may encounter. We have purposely omitted those showing the more common and well recognized degenerative and inflammatory changes so often seen in instances of generalized toxemia of streptococcus origin.

We have considered the lesions in the liver as occurring in three rather characteristic forms: the acute stage with necrosis of liver cells accompanied by a cellular exudate; a chronic lesion showing degeneration and necrosis on the one hand and active proliferation of liver cells, bile ducts and connective tissue on the other; and lastly the healed stage, from which all signs of an active inflammatory reaction have disappeared. As examples of the acute lesion three cases are fully reported. The remaining two cases represent the chronic and healed lesions. We are quite aware of the criticism that may be directed against these latter cases, and for this reason they are presented not as definitely proved examples of what the streptococcus can do, but only as possibilities that may result when the process becomes chronic, and lastly when it has entirely healed.

Case Reports

Case 1. (C. H. A. 28–30), an apparently healthy, white male infant, aged 8 days, developed an abscess near the right wrist. Two days later this was incised and drained. On the third day after the operation the child suddenly developed difficulty in breathing, cried almost continually, and passed five loose green stools during that night. The following morning he was admitted to the hospital dangerously ill. In addition to the lesion on the wrist, an examination revealed signs of bronchopneumonia, a distended abdomen and a protruding umbilicus covered with a pigmented crust. Death occurred a few hours after admission, and an autopsy was performed one and a half hours postmortem.

The peritoneal cavity contained an excess of amber-colored fluid in which were clumps of thick, white, purulent material. Smears of this revealed chains of

streptococci. The wall of the umbilical vein was thickened and the lumen contained pus.

The liver, weight 179 gm., was enlarged and smooth. The sinus venosus was patent, though the wall was thickened and surrounded by a wide area of necrotic tissue extending from the wall into the liver substance. Smaller areas, yellowish red and varying in size from a pinhead to 1 cm. in diameter, were scattered throughout the liver.

The spleen, weight 38 gm., was large, soft and of the septic type.

No noteworthy lesions were found in the heart, lungs and other viscera. The bacteriological examination from both peritoneal cavity and liver was positive for streptococcus hemolyticus.

Anatomical Diagnoses: Acute infectious hepatitis; acute peritonitis; pyophlebitis of the umbilical vein; cellulitis of the right wrist and omphalitis.

Histological Examination

The umbilical vein shows an inflammatory reaction with a fibrinous thrombus attached to its inner surface, and an infiltration of endothelial leucocytes, lymphocytes and plasma cells in its wall.

Within the liver some of the branches of the portal vein are distended with endothelial leucocytes containing numerous streptococci, together with fibrin, polymorphonuclear leucocytes and free streptococci. Many of the smallest branches of the portal vein contain endothelial leucocytes with many streptococci within them.

The liver lobules show scattered foci of hematopoiesis. The outstanding lesion present consists of necrotic liver cells occurring singly and in small groups. They extend to the portal vessels and to the central veins but are most numerous in the intermediate zones. Some lobules show many more of these lesions than others. The necrotic cells tend to stain deeply with eosin and the nuclei are more or less pyknotic. Others have lost their nuclei and are being surrounded or invaded by endothelial leucocytes. In certain areas which may involve one or more complete lobules, all of the liver cells have disappeared, leaving only the stroma infiltrated with numerous endothelial leucocytes. There is no evidence in any of the lobules of a toxic central necrosis, and no abscesses are present.

The most noticeable feature in the sections stained by the Gram-Weigert method is the presence of large numbers of streptococci, chiefly in the endothelial cells lining the sinusoids, but also to some extent within the vessels. In the areas where all the liver cells have been killed off and have disappeared, the stroma is infiltrated with endothelial leucocytes containing fairly numerous streptococci.

In this case the necrosis of the liver cells and the inflammatory reaction are evidently due to the direct action of the toxin liberated by the organisms present in the lesion. This toxin has destroyed the more highly specialized liver cells, leaving the endothelial cells and fibroblasts relatively uninjured.

If the child had overcome this infection and lived, the streptococci and necrotic liver cells would have been removed and the histological picture would then suggest a rather late stage of acute yellow atrophy. In many places only the stroma and portal vessels would have remained, whereas in areas where liver cells had escaped necrosis, regeneration would have occurred. The end result would have been a cirrhosis corresponding to that so often seen following acute toxic hepatitis.

CASE 2. (U 25–23), a female infant who had suffered a prolonged and difficult delivery and died on the fifth day after birth. A postmortem examination disclosed a hemorrhage into the cerebellar fossa, with extension down the spinal canal and out into the loose tissue of the neck.

The liver, weight 150 gm., was normal in size, shape and consistence and dark reddish brown. On the upper surface of the right lobe were two round areas, one 3 cm. in diameter and the other 2 cm. Both were slightly depressed beneath the normal surface, and yellowish brown.

On section these depressed areas were seen to extend about 1.5 cm. into the liver parenchyma. Their yellowish brown cut surfaces were striated with dark red lines suggesting distended capillaries. In consistence, these areas were distinctly softer than the surrounding tissue.

A culture from the heart's blood yielded streptococcus hemolyticus in pure culture.

Anatomical Diagnoses: Infratentorial hemorrhage into cerebellar fossa. Focal necrosis of liver.

HISTOLOGICAL EXAMINATION

Sections from the greater portion of the liver show a few small foci of hematopoiesis but nothing abnormal beyond the presence of small and medium sized fat droplets in some of the liver cells. There is no toxic central necrosis. The two lesions described in the gross examination show a very different condition. Necrosis of liver cells is extensive and in many of the lobules all of them have been killed. In other lobules they remain around central or portal vessels, or are scattered in small groups within the lobule. Masses of necrotic cells are still present and are slowly being invaded and surrounded by endothelial leucocytes and gradually dissolved. The terminal bile

ducts in the portal systems are prominent, but they have not yet begun to grow toward the centers of the lobules. Around them are a few polymorphonuclear leucocytes, eosinophiles and lymphocytes.

Examination for organisms in the fixed preparations, especially for streptococci, was entirely negative.

The decidedly focal character of the two lesions present in the liver strongly suggests that they are of infectious rather than toxic origin. The lesion is in the reparative stage and the causal agent has been destroyed and removed. There remain two foci showing the early healing stages of acute yellow atrophy. In time these would have terminated in areas of sclerosis.

CASE 3. (B. C. H. 01–46), a white female, aged 20 years, was operated on Feb. 2, 1901 and the left ovary removed. On March 16, about six weeks later, at a second operation the right ovary and tube were excised and a diagnosis of acute purulent salpingitis made. Death occurred a week after this second operation and at the postmortem examination made twelve hours later, acute salpingitis of the left tube, a pelvic abscess, and a localized peritonitis of the pelvis were found.

The liver, weight 2320 gm., was much enlarged, smooth and mottled yellowish brown. On section the middle portions of the lobules were yellow and surrounded by narrow red zones.

Cultures from the heart's blood, spleen, kidneys and liver showed a streptococcus.

Anatomical Diagnoses: Pelvic peritonitis, septicemia.

HISTOLOGICAL EXAMINATION

Many of the liver cells contain small to medium sized fat vacuoles; occasionally single large vacuoles are present. Necrosis of liver cells is extensive and diffuse and involves an irregular zone about each portal area from two to ten cells in width, but as a rule leaves one or two rows of cells adjacent to the portal area comparatively uninjured. Viewed in relation to the central vein of the lobule it could be called a zonal necrosis involving principally the periphery of the lobule. Occasionally the necrosis reaches the portal connective tissue, less often it extends here and there to the central vein. There is no evidence anywhere of a toxic central necrosis, even in its earliest stages. The cytoplasm of the necrotic cells is finely granular and strongly eosinophilic. In an occasional normal liver cell adjoining the necrotic zone a mitotic figure can be found. In one section three were grouped closely together.

The necrotic cells are surrounded and to some extent invaded by polymorphonuclear and endothelial leucocytes. The former often collect in considerable numbers but no abscesses are found. They are present also in the portal connective tissue together with endothelial cells and lymphocytes. Here and there branches of the portal vein are distended with clots, evidently of postmortem origin, consisting of fibrin, polymorphonuclear and endothelial leucocytes. Inspissated bile is present in some of the bile capillaries near the central vein.

A striking feature of this lesion is the presence of masses of streptococci most often within and adjoining the zones of necrotic liver cells. They are found in endothelial cells lining the sinusoids and also in the vessels, extending along them and often filling them.

In this liver we have a lesion uniformly distributed in every lobule, in close relation to the portal areas but occasionally reaching the central vein. This uniformity of distribution would suggest a toxic origin. On the other hand, the numerous clumps of cocci situated in the endothelial cells and in the sinusoids adjoining the affected liver cells strongly favor the view that, in part at least, they bear a causal relationship to the necrotic cells.

The clinical history of this case resembles very closely the case reported by Roger [14] in 1896. In his case, however, the pathological anatomy differed in that the liver was riddled with abscesses.

There is another explanation for this zonal necrosis based on experimental work done by Opie [30] which will be discussed more fully below. He found that by producing a bacteremia in an animal whose liver he had previously injured, he invariably produced a rather characteristic midzonal form of necrosis. Certainly the more common severe lesion caused by the streptococcus toxin is a central necrosis, and of that there is not the slightest evidence in this liver.

CASE 4. (P. M. H. 970, M 1153), a white male, 56 years of age, was operated upon for appendicitis and made an uneventful recovery. Ten months later the gall-bladder containing two concretions was removed. The liver was reported to be small and a piece was excised which histologically showed nothing abnormal. Seven weeks later the patient developed chills and fever which persisted for a month. Jaundice later appeared; and finally ascites developed which required tapping on two occasions. At this time the liver was observed to be definitely enlarged. The patient's condition progressed gradually and eight and a half months after the operation on the gall-bladder he died with an extensive cirrhosis of the liver.

At autopsy the tissues were all deeply jaundiced, the abdomen was distended and the peritoneal cavity contained 6000 cc. of slightly cloudy yellowish fluid containing flakes of fibrin.

The liver, weight 1920 gm., extended 1 cm. below the costal margin. Old adhesions joined the anterior surface of the liver to the under surface of the diaphragm. The left lobe was reduced to a small scarred puckered mass of connective tissue lying to the left of the coronary ligament, which, when sectioned, revealed scar tissue, blood vessels and large bile ducts.

The right lobe was yellowish in color with a fairly nodular surface. It cut with increased resistance, exposing on the fresh surfaces nodules of deep golden yellow which changed to green on exposure to air.

The remaining viscera, with the exception of the spleen which was enlarged and rather lax and weighed 400 gm., showed no noteworthy changes.

Anatomical Diagnoses: Cirrhosis of the liver, peritonitis, ascites and jaundice.

Histological Examination

The liver presents a most unusual appearance. The original lobular architecture is almost entirely replaced by wide interlacing tracts of proliferating bile ducts and connective tissue which isolate small nodules of liver cells composed partly of remnants of former lobules together with regenerated trabeculae showing no orderly structure. These young bile ducts form a most intricate meshwork of channels among themselves, often encircling small groups of liver cells. The bile ducts are definitely abnormal, resembling somewhat the structures seen in primary bile duct tumors. The cells and nuclei are parallel with the lumina, both are distinctly elongated, instead of being rather cuboidal with the nuclei at right angles to the lumina. Occasional clusters of streptococci can be found among the liver cells, some are extracellular, others intracellular, apparently within the cytoplasm of endothelial cells lining the sinusoids. In other fields are small groups of degenerating and necrotic liver cells which are infiltrated with polymorphonuclear and endothelial leucocytes. The interstitial tissue is increased, especially about the new formed bile ducts and also, although to a lesser degree, among the regenerated liver cells. The stroma everywhere is infiltrated with neutrophilic leucocytes, endothelial leucocytes, lymphocytes, occasional eosinophiles and nests of plasma cells.

The striking feature of this case is the extraordinary number of bile ducts present. They are so prominent that they suggest the possibility of a tumor but evidently are not. Small patches of a somewhat similar bile duct formation occur in other forms of cirr-

hosis such as the pigment and syphilitic types, but to nothing like the extent and amount present in this case.

In the relatively common type of toxic cirrhosis following acute yellow atrophy, the bile ducts at the periphery of each lobule grow for a certain distance toward the center and then stop. In the adult they do not produce liver cells and they do not extend indefinitely.

The history of this case strongly suggests infection of the liver. "Seven weeks after cholecystectomy the patient had chills and fever which persisted for a month. After two months he became jaundiced, and one month later developed ascites. He died from cirrhosis of the liver eight and a half months after the operation of cholecystectomy."

Unfortunately the liver was not cultured at the time of the autopsy. The chains of cocci seen in the stained sections may represent simply a terminal bacteremia, or, and what seems to us not improbable, they may have been present in the liver for weeks, possibly having gained entrance to the organ at the time of the cholecystectomy. There seems to be no other way to explain it. It would mean a chronic lesion due to a streptococcus of moderate virulence causing widespread, but not extensive and rapid necrosis.

CASE 5. (B. C. H. 98–211), a young woman who died of pernicious anemia. The immediate clinical history is irrelevant insofar as it has no bearing on an old healed inflammatory process which was found within the liver.

The liver was of normal size and color, but revealed both beneath the capsule and on the cut surface minute grayish areas suggesting small scars.

HISTOLOGICAL EXAMINATION

These small scar-like areas consisted of contracted lobules containing numerous bile ducts but no liver cells. They strongly suggest healed patches of acute yellow atrophy and so far as can be determined from their size, shape, isolation and distribution, are much more likely to have been of infectious than of toxic origin. The lesions at first suggested multiple adenomas of bile duct derivation, but careful study of them later disclosed the contracted lobular arrangement with the portal vessels still evident.

REPORT OF EXPERIMENTAL WORK

If we are willing to postulate that streptococci acting locally can produce a definite inflammatory reaction in the liver with degeneration and necrosis of the parenchyma, then one might ask what experimental evidence we have to substantiate such a claim. Furthermore, can we assume in certain cases of streptococcus infection in which one finds inflammatory foci within the liver, but no organisms, that such lesions are actually infectious in origin, only the organisms have been rapidly killed and removed?

We have employed rabbits in our experimental work, but there are certain dangers in attempting to correlate pathological lesions produced in lower animals with those seen in man, in that we have here two biological systems of quite different constitution. The problem becomes still more complicated when we add to these a third living organism — namely an organism so complex and variable as the streptococcus. In attempting, therefore, to answer these two questions, namely, can streptococci produce similar changes in animals, and how long may the organisms survive within these lesions, we report the results of our work with considerable reserve.

Among the earliest investigators in this field of research was Wyssokowitsch [31] who as early as 1886 showed that the endothelial cells of the liver were capable of phagocytosis and would take up bacteria that were injected into the circulating blood.

Many years later this work of Wyssokowitsch's was repeated by Nathan,[32] using not alone bacteria, but collargol and other substances as well. He verified the earlier work on phagocytosis by the Kupffer cells, and demonstrated an active proliferation of these cells followed by a desquamation into the circulating blood.

Roger [14] in 1896, after isolating a streptococcus from abscesses within the liver, made an emulsion with saline and injected this subcutaneously and intravenously into rabbits, but produced no marked demonstrable reaction.

Weaver [33] in 1900 produced a type of cirrhosis in guinea pigs by inoculating a strain of *B. coli* into the portal vein. This type of cirrhosis was characterized by an increase in bile ducts and perilobular connective tissue. His results indicate how critical one must be in interpreting the results obtained in lower animals, because the same organism produced absolutely no lesions in rabbits.

A year later Hektoen [34] reported certain results, confirming the work of Weaver. He produced a similar lesion, using a second organism belonging to the *B. diphtheria* group, and was able to demonstrate the organisms within the early lesions.

As far as we can determine from a review of the literature, Opie [30] was the first to attempt to produce lesions experimentally within the liver by injecting streptococci. When he injected a suspension of streptococci intravenously into dogs, the only appreciable change he found in the liver was a slight deposition of fat within the liver cells. However, if he first inoculated dogs with a small amount of chloroform or phosphorus — an amount which he previously determined to be incapable of producing destructive lesions within the liver — and then followed this a few days later with an intravenous injection of streptococci, he invariably produced extensive midzonal and central necrosis — a type of lesion resembling that of acute yellow atrophy. He explained these lesions on the basis of a combined intoxication, making no attempt to link up the changes with the presence of organisms within the liver.

Recently Moon [28] in an attempt to substantiate his claim that a strain of streptococcus hemolyticus, which he had isolated from the liver of a young child with cirrhosis was the causative agent in this disease, injected a suspension subcutaneously and intraperitoneally into rabbits and produced degenerative lesions in the liver in which he demonstrated the organisms.

Regarding the second question relative to the period of survival of organisms within inflammatory lesions in the liver, some information is to be found in a report by Schwarz.[35] This worker injected into mice an organism of the diphtheroid group which he had isolated from a child's liver. He killed these mice at intervals of one to seven days following the injection. After twenty-four hours the liver was riddled with minute inflammatory foci teeming with organisms; as the interval of time increased, the number of organisms diminished, and after seven days he was unable to demonstrate organisms within the lesion.

Kyes [36] studied the fate of pneumococci after intravenous inoculation into the pigeon, which is naturally resistant to this organism. He made careful studies of various organs and found that the organisms were quickly removed from the circulating blood and localized within the endothelial cells of both spleen and liver. In addition he

showed that at the end of one hundred and twelve hours the cocci were completely destroyed.

We began our experimental work using a group of guinea pigs, but because the livers of these animals were practically refractory to infection, it was necessary to select rabbits, which proved to be more satisfactory.

A pure culture of streptococcus hemolyticus which had been isolated from the throat of a patient with scarlet fever was used throughout the experiments. On blood agar the colonies were quite typical, being small, gray and opaque and surrounded by a wide clear ring of hemolysis.

A saline suspension was made from a growth on blood agar slants as we wished to inject the organism as free from toxin as possible. The quantity injected varied from 3 to 4 cc. of a moderately heavy uniform suspension.

As a control, an equal quantity of a similar suspension that had been heated to 60° C for one hour, and proved sterile, was introduced into the rabbit's liver under precisely the same conditions. These animals lived and showed neither gross nor histological lesions within the liver.

The operating technique was simplified as much as possible. The abdomen was shaved and using asceptic precautions a small opening was made into the peritoneal cavity. A loop of the small intestine was drawn through the opening, thereby exposing branches of the mesenteric artery and portal vein. The vein was freed for about 1 cm. from the surrounding fat and connective tissue and ligated at the distal end of this exposed section. A second ligature was loosely tied about the vein proximal to the first. The next step was to inject the organisms into the vein, and for this a small Luer syringe with a No. 24 gauge needle proved most suitable. Just before withdrawing the needle the proximal ligature was tightly tied. The intestines were replaced and the abdominal wall closed with a double row of continuous sutures.

The first rabbit died after eighteen hours, the second after twenty. The third, which made a good recovery and appeared quite healthy, was killed at the end of forty-eight hours. The fourth rabbit also made a good recovery but was killed after five days.

Blood cultures taken from the ear veins of these animals at the end of twelve hours showed streptococci in pure culture. Further cultures taken after forty-eight and seventy-two hours were negative.

The autopsy blood cultures from the first and second rabbits, which had died at the end of eighteen and twenty hours respectively, were sterile. Cultures taken directly from the liver in both cases yielded a few typical colonies on a blood agar plate. Smears made from scrapings of the freshly cut surfaces of both livers, showed in addition to liver cells, chains of cocci and many polymorphonuclear leucocytes. A blood culture taken from the third rabbit at the time of the autopsy forty-eight hours after the injection was sterile, while only three colonies were grown on a blood agar plate after being heavily streaked with a swab that had been inserted deeply into the liver parenchyma. A smear made directly from the liver at this time showed liver cells, cellular débris, polymorphonuclear and endothelial leucocytes, and a few poorly stained and questionable clusters of organisms suggesting streptococci.

The fourth rabbit, from which sterile blood cultures had been obtained at forty-eight and seventy-two hours after the injection, was autopsied at the end of five days. Cultures taken from the heart, and liver, as well as smears from the latter organ revealed no streptococci.

In summing up our bacteriological results we find that at twenty-four hours living organisms had to a great extent disappeared from the circulating blood and the liver; at forty-eight hours the number of viable streptococci in the liver was practically negligible, and lastly at the end of five days all cultures from different sources, as well as smears taken directly from the liver showed no trace of streptococci.

The rapidity with which streptococci have been destroyed in the liver may largely explain some of the histological characteristics of the lesions, and particularly the fact which has been previously stressed in this paper that it has often been quite impossible to demonstrate organisms histologically in the lesions.

Gross Examination: Within the first twenty-four hours there was little to suggest any severe injury to the liver. The organ was normal in size, the capsule smooth and the cut surface uniformly congested and rather soft. In the forty-eight hour animal, small areas beneath the capsule showed up as a yellowish stippling or a very fine network of delicate lines that were slightly raised above the surrounding liver tissue. The cut surface varied considerably in different lobes; some areas showed simply congestion, edema, and a loss of the finer mark-

ings, other areas were traversed by thin yellow lines, and still others were mottled with small yellowish foci which varied in size and contour. After five days, the liver was normal in size, moderately firm and dark reddish brown. The surface was smooth, except for three yellowish depressed areas, each about 2 to 3 mm. in diameter.

Microscopic Examination: In Rabbit 1, dead at the end of eighteen hours, one finds chains of cocci up to a dozen or more in many of the endothelial cells lining the sinusoids. The reaction to these consists in an accumulation of polymorphonuclear and endothelial leucocytes, together with small clumps of fibrin within the vessels. Where leucocytes have clustered in adjoining sinusoids, the isolated liver cells often show necrobiotic changes and necrosis. Such lesions are found in any part of the lobule, even adjoining the hepatic vein, but they occur most abundantly at the periphery of the lobules close to the portal vessels. These peripheral lesions may suggest in their extent and distribution, small zones of infarction, but the inflammatory reaction which is uniformly distributed throughout this damaged area differentiates them clearly from bland areas of infarction.

In Rabbit 2, dead at the end of twenty hours, streptococci are more difficult to find. The lesions are more numerous and a little larger. Many of the necrotic liver cells have already disappeared, and their places are occupied by minute islet-like collections of endothelial leucocytes.

In Rabbit 3, killed forty-eight hours after the injection, numerous large and small lesions are present. Some nearly equal the size of a lobule. These large lesions are composed of necrotic liver cells among which polymorphonuclear and endothelial leucocytes are invading and digesting the cellular débris. At the periphery of these lesions the necrotic liver cells have largely disappeared, and here accumulations of endothelial leucocytes are more prominent than centrally where the polymorphonuclear leucocytes are in greater evidence. The smaller lesions represent a later stage in this reparative process, and are merely nests of endothelial leucocytes which have removed the dead liver cells. A very few streptococci can still be found in a few of the lesions.

In Rabbit 4, killed after five days, only small lesions are present. They consist of accumulations of endothelial leucocytes and signify a late stage of repair. Either the lesions were originally very small,

or neighboring liver cells have regenerated and replaced those that were destroyed.

In summarizing these histological lesions we find that they are essentially destructive and focal in character, and in none of the livers was there a suggestion of a lesion uniformly limited to the central zones of all lobules such as is seen in toxic hepatitis resulting from chemical intoxication or severe bacterial toxemias. In other words we are dealing with a pathological condition of the liver in which the injury is the result of the immediate presence of the organisms within the lesions themselves.

Pathological Physiology

Before entering into a general discussion of inflammatory lesions within the liver, it seems not at all irrelevant at this point to say a word about the pathological physiology of the liver in cases of streptococcus infection. Since this organ constitutes the largest gland of internal metabolism within the body and is directly or indirectly involved in the metabolism of proteins, fats and carbohydrates, any alteration in function of the liver cell, with or without histological signs, might be considered as sufficient to interfere with the metabolism of any one or all of these substances. We shall not go into this phase of the problem fully, but merely mention a few of the important functional changes which at times are manifested as clinical signs and symptoms.

Hildebrandt [37] in 1910, made the observation that many cases of scarlet fever showed an appreciable increase in the urobilin content of the urine. Such patients may show no trace of jaundice and no demonstrable bilirubinuria. He considered two possibilities in explaining this urobilinuria: first and more important as the result of a functional insufficiency on the part of the liver cell, and secondly, though probably merely as a contributory factor, by the increased destruction of red blood cells. He reported the findings in one liver from one case which terminated fatally. This organ was large, swollen and edematous, and microscopically revealed scattered patches of necrosis. He described these changes as a form of "parenchymatous hepatitis," and quoted Litter who believed that in instances where destruction was more widespread the liver would simulate the picture of acute yellow atrophy and the patient would

show corresponding clinical signs and symptoms, with jaundice and increased bilirubin in the circulating blood.

Schelenz [38] several years later followed up this work of Hildebrandt, and reported that the liver would appear to be more severely affected in some epidemics of scarlet fever than in others. This simulates an observation which has been made repeatedly in regard to inflammatory lesions of the kidney complicating scarlet fever. This investigator reported a fatal case of scarlet fever in a young child who showed a very high urobilin excretion. The liver parenchyma revealed a slight degenerative change, and a diffuse interstitial hepatitis.

In cases of streptococcus infection there are usually no constant clinical signs and symptoms referable to functional or morphological changes within the liver. That is, the liver is involved to such a slight degree as to be clinically unrecognizable.

Where the liver is damaged it is probable that the secretion of urobilin is not the only functional alteration of secretion that occurs in the more severe infections. Smyth and Whipple [39] have demonstrated the marked influence that mild chloroform poisoning has on bile salt secretion. Dogs, which had received small doses of chloroform, did not show the slightest clinical indisposition, and yet the bile salt secretion was greatly reduced. Microscopic examination of the livers at this time showed only very slight degenerative changes within the liver cells in the central zones of the lobules.

Whipple and Smith [40] have indicated that an important function of the liver cell is to group together the animo acids to join the precursors of hemoglobin which in turn are utilized by the marrow cells in turning out the finished red blood cells into the circulation. This function of the liver cell, like that of bile salt secretion and the secretion of urobilin and bilirubin, is diminished in liver cells showing slight degenerative changes and would therefore probably be altered in streptococcus hepatitis.

Discussion

One of the most interesting characteristics of the liver is the resistance it shows to infection. Indeed how often at autopsy one sees acute suppurative inflammatory lesions in different parts of the body, severe septicemias and septicopyemias, diffuse inflammatory

reactions within the gastro-intestinal tract, sloughing tumors and ragged ulcers — and yet the liver apparently unharmed. Certainly we may say that the manner in which the liver handles massive infection is scarcely to be seen in any other organ in the body. This very fact, namely the rarity of inflammatory lesions within the liver, coupled with the rather unusual character of these lesions when they do occur, makes the study of this organ one of the most interesting problems in general pathology.

What structures are to be found in the liver which are not common to most organs which may play an important rôle in preventing inflammations from gaining a foothold? Certainly the most important factor is the presence of a very highly developed and healthy system of endothelial cells. But it is not alone the mesenchymal portion of the liver that is bound up with this protective mechanism, it is definitely supported by the integrity of the liver cells and a very rich blood supply. But after all, this protection has its limits: we see this in the occasional colon infection extending out from the terminal bile ducts, in the metastatic abscesses following suppurative phlebitis of the portal vein, in the amebic and actinomyces infections, and also in tuberculosis, syphilis, typhoid and others, and lastly, as we have attempted to point out in this paper, we see this occasionally in streptococcus infection.

We have presented the lesions found in five different livers. Two of the three acute cases showed a rather acute inflammatory reaction with degeneration, necrosis of liver cells and an active cellular infiltration in which streptococci were demonstrable within the lesions.

The remaining two livers contain very unusual lesions which may be considered distinctly puzzling. One of these is probably a variety of a chronic lesion due to the immediate presence of streptococci within the liver, whereas the other may perhaps be considered a healed type of lesion due to a similar organism.

These five cases, two of them certainly and perhaps all, due to the immediate presence and action of streptococci, are presented for the purpose of calling attention to these pathological processes which might be overlooked or misinterpreted.

In our short series of experiments we have attempted — with certain reservations — to correlate lesions which may be produced in animals with lesions found in man. Lastly, in regard to the survival period of streptococci within the animal liver, considerable

light is thrown on the interpretation of the rarity with which one can demonstrate organisms within the lesions in man.

It should be pointed out clearly that absolutely no attempt has been made to explain cirrhosis of the liver in its broad sense, as a chronic or healed inflammatory lesion of infectious origin. On the contrary, the points that are particularly emphasized are first that an acute inflammation can occur in the liver as a result of the actual presence of streptococci within this organ; and second, that with extensive destruction of liver cells, followed by a reparative proliferation of connective tissue and bile ducts, wide tracts of sclerosis can be produced, giving a picture which resembles in many respects the healed stages of acute yellow atrophy.

Summary

1. The more common inflammatory changes in the liver in cases of streptococcus infection with and without a septicemia are described.

2. Emphasis is laid on a less common lesion of which three cases are given in detail. This is characterized by focal or diffuse areas of liver tissue showing necrobiotic changes and necrosis, infiltrated with an inflammatory exudate. A Gram-Weigert stain shows streptococci in large numbers in the lesions of two of these livers.

3. The similarity of this lesion to the histological picture at times encountered in acute yellow atrophy is discussed, and the suggestion is made that a careful bacteriological search of the liver in the fixed preparation together with a culture of the liver at the time of the autopsy might reveal bacteria within the lesions more commonly than is suspected — particularly in those cases of so-called acute yellow atrophy showing a very irregular distribution of the lesion — a condition that is extremely difficult to explain purely on the basis of a circulating toxin in the blood.

4. Another case is described with a chronic inflammatory reaction within the liver, showing on the one hand degeneration, necrosis, exudation and bacteria, and on the other a very active proliferation of bile ducts and connective tissue. This case is presented more for discussion than as a proved case of chronic progressive cirrhosis of infectious origin.

5. The last point that is considered is the histological and gross changes which one may find in the healed stage of these acute and chronic inflammatory lesions.

6. The second part of the paper is devoted to the results of experimental work. A streptococcus obtained from an early case of scarlet fever, was injected free of toxin into one of the radicles of the portal veins of both guinea pigs and rabbits. The animals were killed at varying intervals, and the lesions produced, together with the results of bacteriological studies, are fully described and compared with the lesions seen in human cases.

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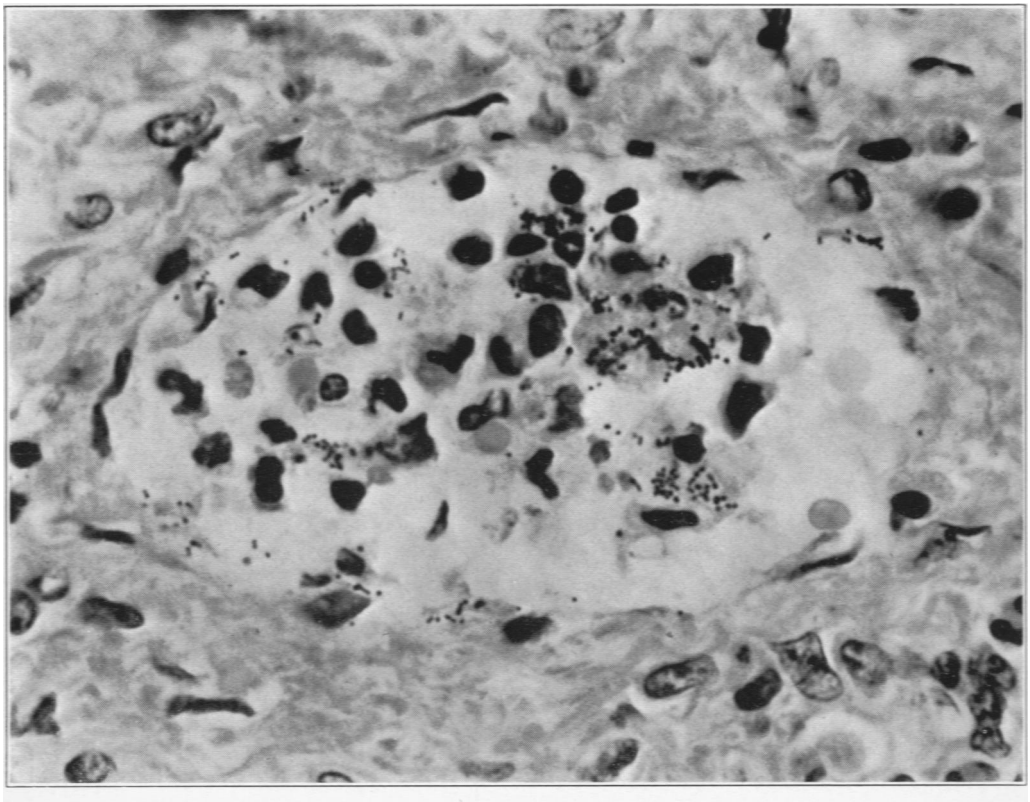
DESCRIPTION OF PLATES

PLATE 55

FIG. 1. Case 1. Masses of streptococci, largely in endothelial leucocytes, within a portal vein. × 1000.

FIG. 2. Case 1. The sinusoids of the liver contain numerous streptococci of which many are included in the lining endothelial cells and in endothelial leucocytes filling the vessels. × 1000.



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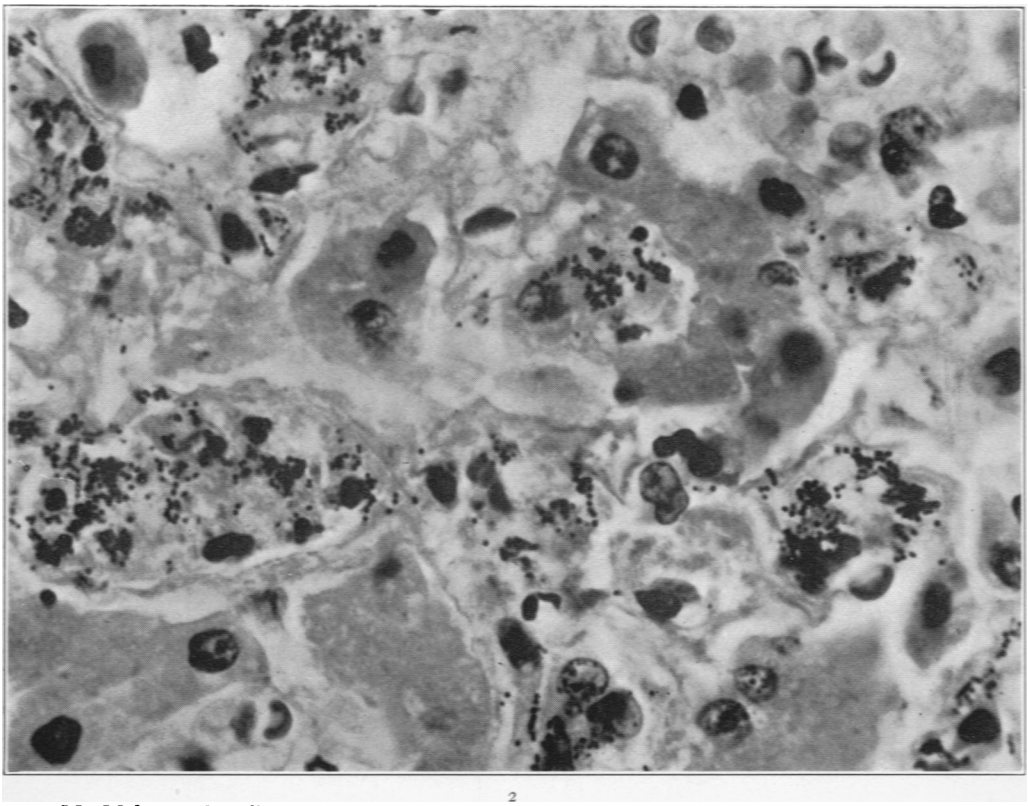


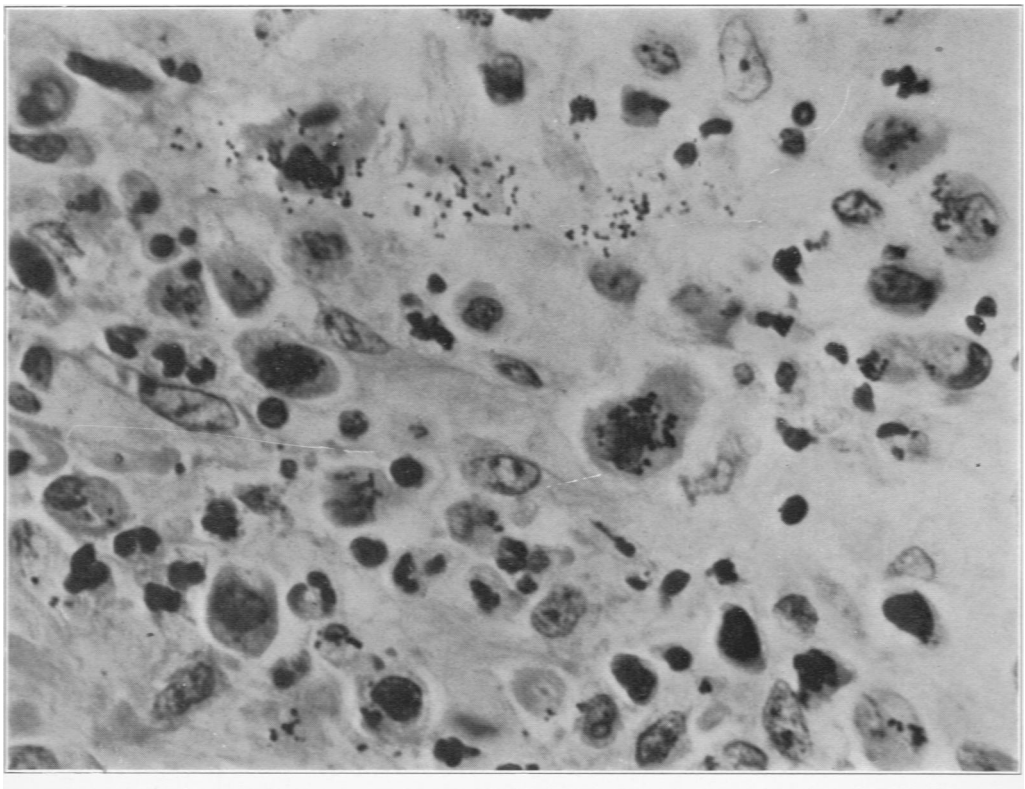
2

MacMahon and Mallory Streptococcus Hepatitis

PLATE 56

FIG. 3. Case 1. An area in a lobule where the necrotic liver cells have to a large extent disappeared. Streptococci are still persistent in moderate numbers, largely in endothelial leucocytes. × 1000.

FIG. 4. Case 2. The edge of one of the two areas of necrosis involving many lobules. All of the liver cells have been killed and are being removed by the action of leucocytes. Only the bile ducts and stroma persist. The adjoining liver tissue is uninjured. × 40.



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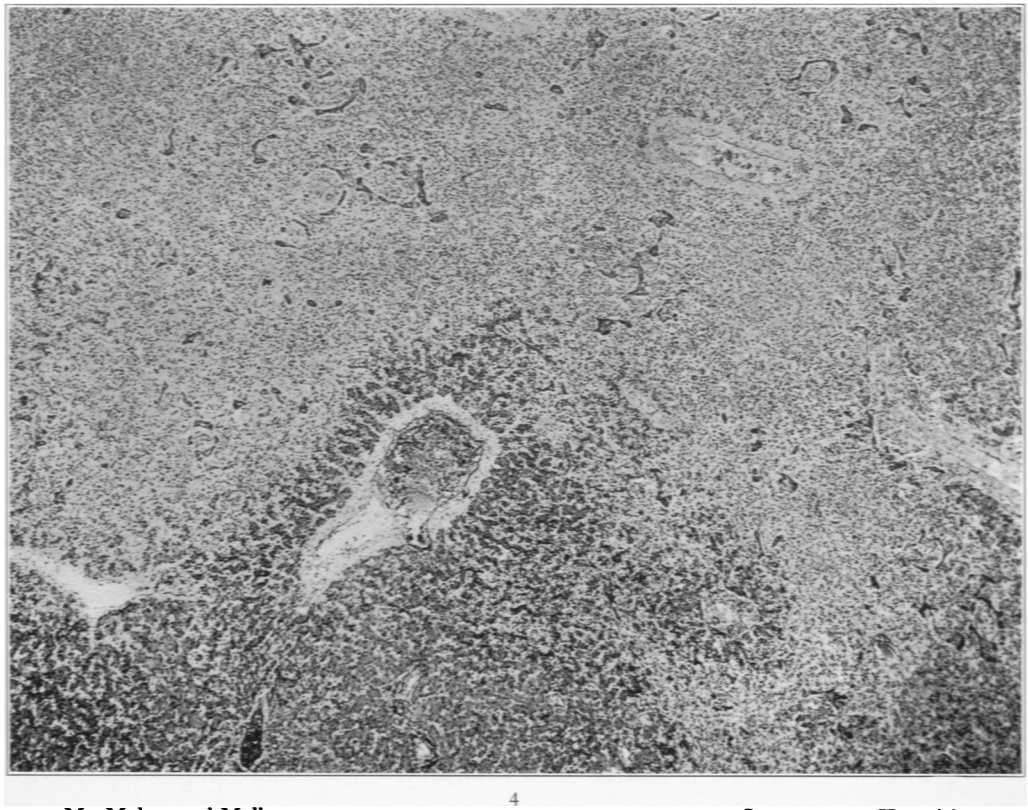


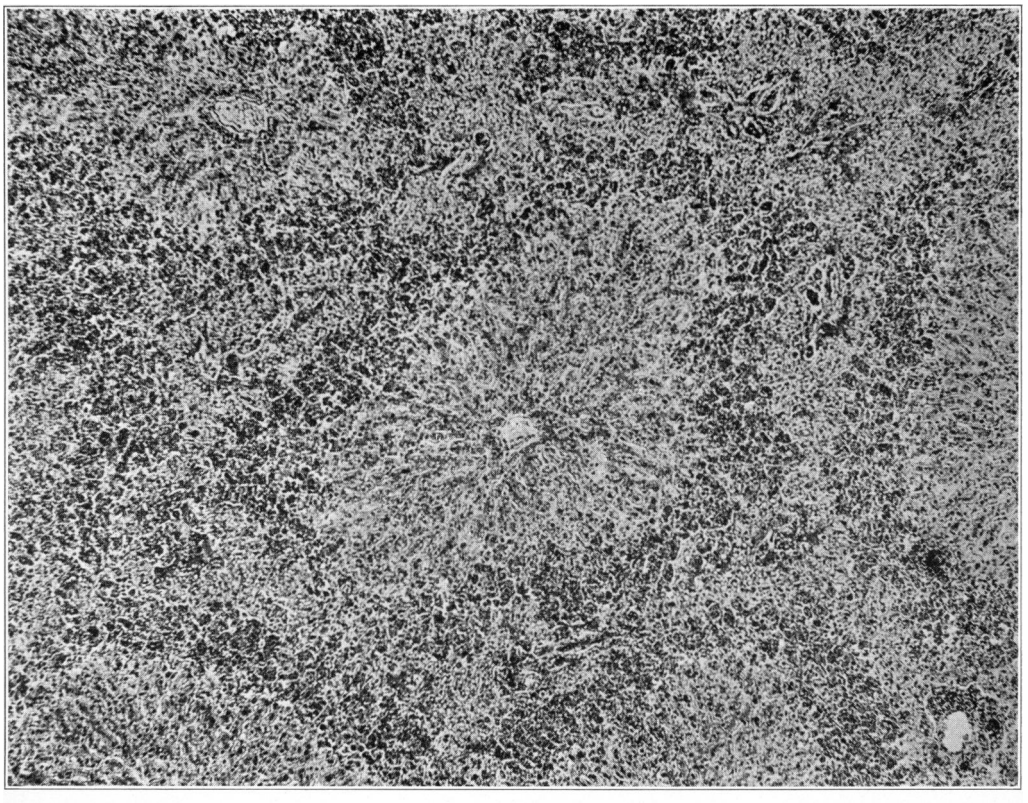
4

MacMahon and Mallory Streptococcus Hepatitis

PLATE 57

FIG. 5. Case 3. The liver cells are necrotic in the peripheries of the lobules, presenting in places a zonal arrangement. × 60.

FIG. 6. Case 3. A high power view of a small area in the necrotic zone. The nuclei of the liver cells have mostly disappeared. The sinusoids contain large clumps of streptococci. × 1000.



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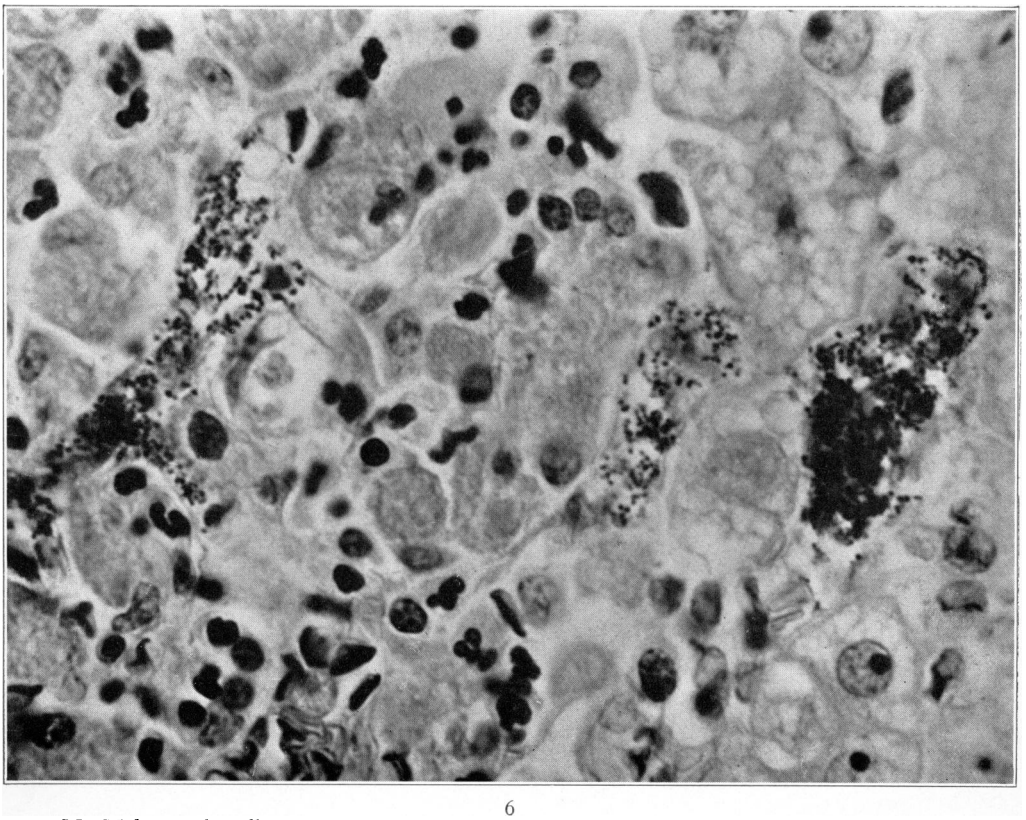


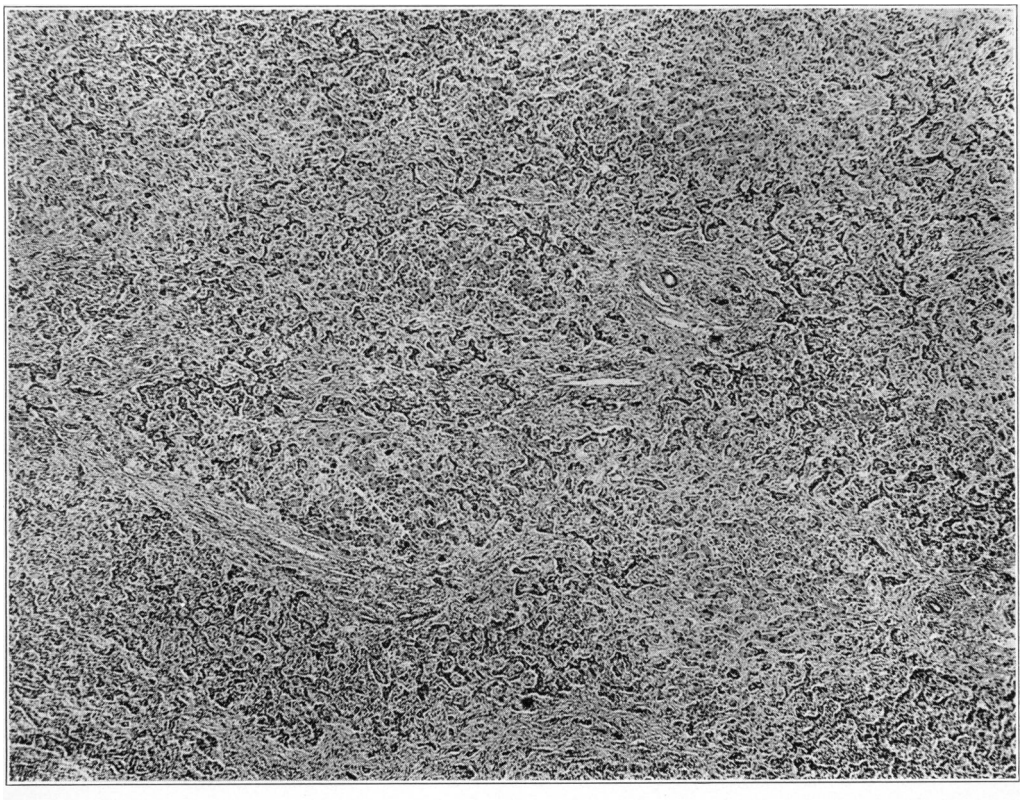
6

MacMahon and Mallory Streptococcus Hepatitis

PLATE 58

FIG. 7. Case 4. A low power view showing the extensive formation of bile ducts. An occasional portal area can be made out. × 50.

FIG. 8. Case 4. Marked formation of bile ducts. Only small islands of liver cells are present. × 60.



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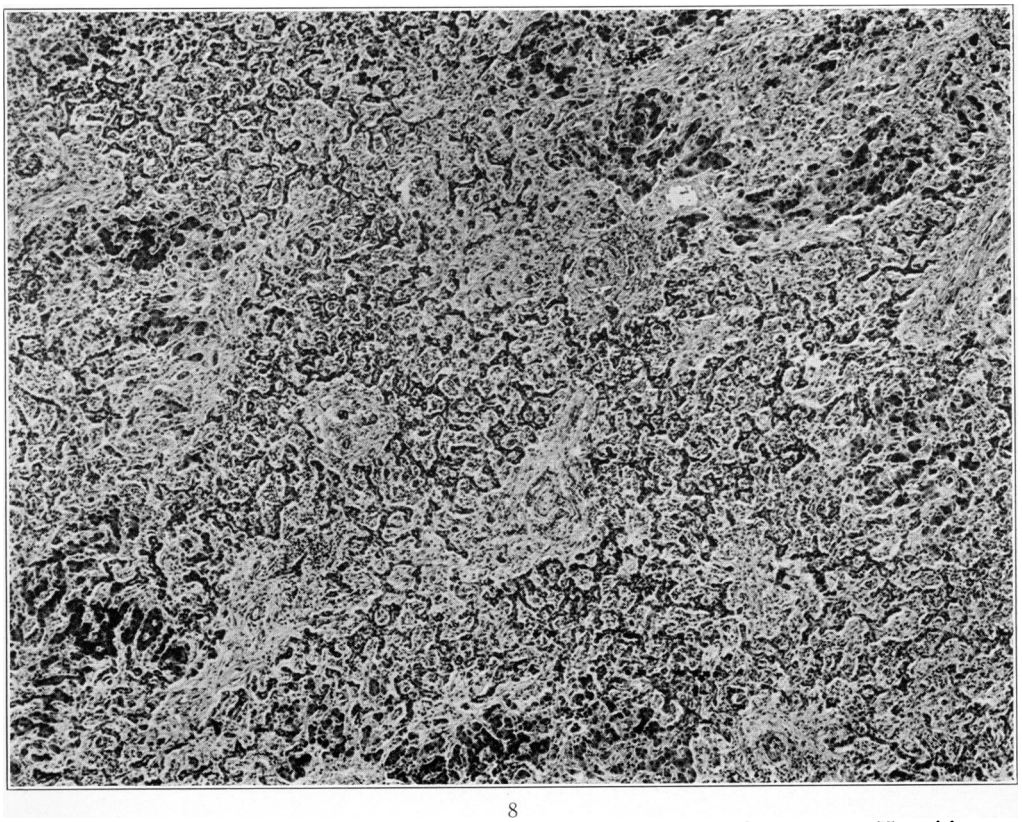


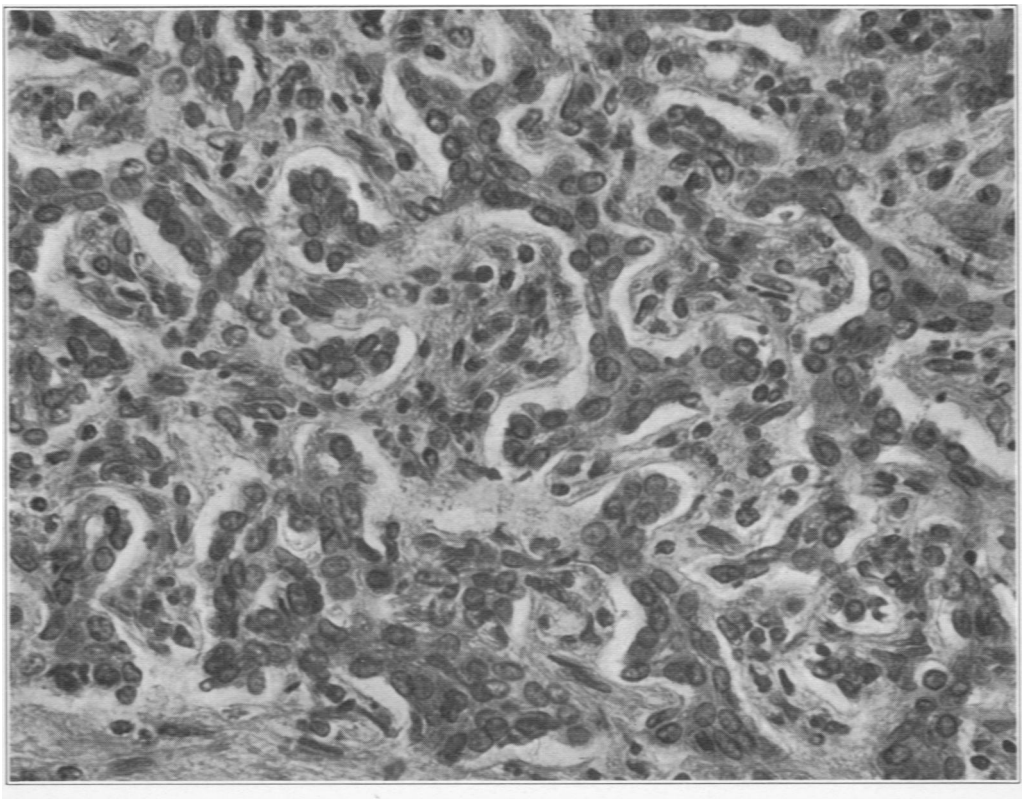
8

MacMahon and Mallory Streptococcus Hepatitis

Plate 59

Fig. 9. Case 4. High power view of network of bile ducts. The stroma is fairly abundant. × 500.

Fig. 10. Case 4. Masses of streptococci mostly contained within endothelial cells lining the sinusoids. × 1000.



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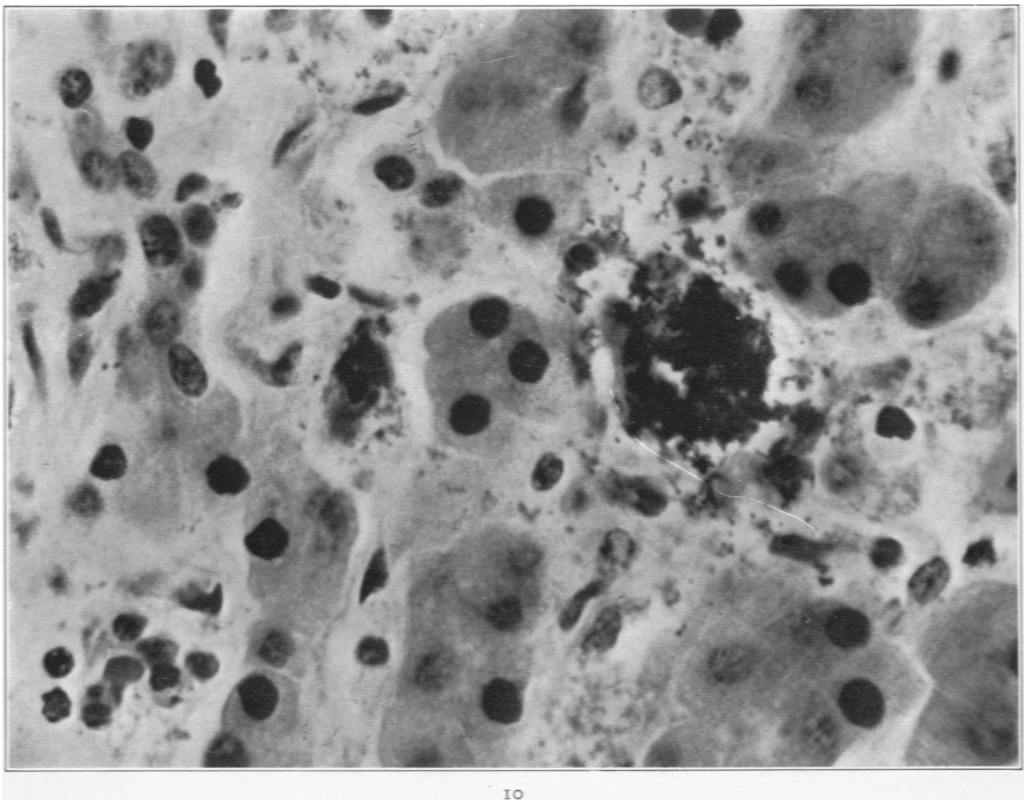

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MacMahon and Mallory Streptococcus Hepatitis