Cirrhosis of the Liver in Northern India

A Clinicopathologic Study

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Introduction

Cirrhosis of the liver is known to be a common condition in India.[1] Its morphology and morphogenesis, however, are not entirely clear, due partly to lack of uniformity in the criteria used for distinguishing the various anatomical types. This is evident from a recent careful study in which it has been reported that, contrary to previous reports, the majority of cases of cirrhosis in Eastern India (Calcutta area) belong to the post-necrotic variety.[2]

Autopsy studies alone, unaided by sequential clinical studies before death, are of limited value. At autopsy the process is seen in its end-stages, and a single anatomical type of cirrhosis may be produced by more than one etiological factor. Autopsy studies in India suffer from the further disadvantage that they are most often made on unclaimed bodies belonging to the destitute class and are therefore unrepresentative. In a progressive, continuing process like cirrhosis, a combined clinical and pathological study at various stages of the disease is likely to be of value. This is attempted in the present study. It should be noted that the cirrhosis of infancy and early childhood seen with characteristic frequency in India[3] is not included in this study.

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Material, Method, and Scope of Study

The present communication deals with 46 adult patients admitted to the Institute Hospital with established clinical features of portal hypertension, such as splenomegaly, ascites, and engorged abdominal veins. The presence of portal hypertension was established in each case by the demonstration of esophageal varices, of collaterals on splenovenography and/or the presence of a portal pressure, measured as splenic pulp pressure, of 15 mm. of Hg or more. The normal range of splenic pulp pressure under similar conditions with the same baseline was 6-10 mm. Hg. In none of these cases was there any evidence of extrahepatic obstruction on splenoportal venography. The mode of onset and clinical evolution of the cases was studied in detail, and they were followed up for a period of about 2 years from the date of admission with established portal hypertension.

Liver biopsies using the Vim-Silverman needle were performed successfully at least once in each case. In 10 cases, adequate biopsies were obtained on 2 or more occasions at intervals ranging from one to 12 months. During the period of study 6 of these cases came to autopsy, and in 2 additional cases, an open wedge biopsy of the liver was obtained at laparotomy. All this material was fixed in buffered neutral 10% formalin and paraffin sections were made for various staining procedures. Hematoxylin and eosin, periodic acid-Schiff, and Gomori's reticulin stains were used as a routine.[4]

From an evaluation of the past history, the mode of onset, clinical progression, and termination of the present illness the cases could be grouped into 3 distinct types. In the account below the broad clinical features of these types and their points of distinction are described followed by the pathological anatomy of the liver in each type.

Results

The disease was seen most commonly in persons between 20 and 50 years of age, and men were more commonly affected than women (Fig. 1). Most of the patients belonged to the working class, and their nutrition in this part of the country was considered to be fair. Their daily calorie intake was of the order of about 2,200 to 2,600 with a protein intake of about 50 to 100 gm. They came, in the main, from the rural surroundings of Delhi.

Description of Clinical Types

TYPE I (Jaundice Type).—Thirteen out of 46 cases in the present series belonged to this type. All cases gave a definite history of onset of the illness with an acute attack of jaundice. In 8 of them, the illness progressed with recurring jaundice and in an average period of one year from the onset had led to an established clinical picture of cirrhosis, with ascites, splenomegaly, and abdominal vein prominence. In the remaining 5 cases the jaundice cleared completely, and, after a variable asymptomatic period of a few weeks to a few months, it recurred again and their subsequent behavior was similar to that of the above-mentioned 8 cases. Jaundice was a prominent feature of the illness in this type. All except one showed ascites which was moderately severe in a majority of the cases (9 out of 13), quite severe in 2 cases, and mild in one. The spleen was palpable in all cases except one and measured on the average 5.2 cm. from the costal margin. Endocrine disturbances characteristic of cirrhosis developed prominently in this type in comparison with the other types, 6 out of 13 cases showing one or another manifestation. The manifestations consisted of gynecomastia (2 cases), spider angiomata (4 cases), palmar erythema (2 cases), and scanty pubic and axillary hair (3 cases). Hematemesis occurred while the patients were under our care in 4 cases, in one of which it proved fatal. Splenovenography revealed that the portal and splenic veins were normal in size and free from any block, but all cases showed collaterals (Fig. 2).

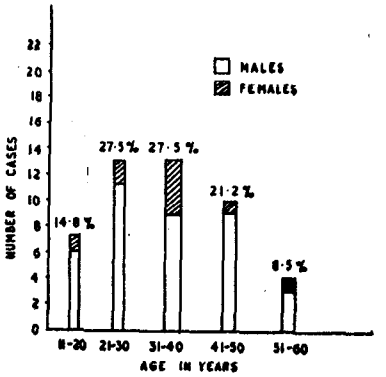

Fig. 1.—Age and sex distribution of cases.

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Fig. 2. — Splenoportal venogram showing normal-sized splenic and portal veins and distorted intrahepatic vascular pattern. Retrograde flow into the coronary, short gastric and inferior mesenteric veins are visualized (Type I case).

Temporary improvement could be obtained in most cases by appropriate therapy, but despite this the course of the disease was one of progressive deterioration and the commonest mode of termination was hepatic coma. Six out of the 7 patients that died in this group during the 2 years' follow-up study had this mode of termination, and, as already stated, the remaining patient died of hematemesis. The average total duration of the illness from its inception to death in the fatal cases was 21.5 months. Of the 5 patients that are alive, the average duration of the illness was 22.5 months. One case could not be followed.

Type II (Ascitic Type).—This type consisted of 17 out of 46 cases. Unlike Type I, the onset in this type was insidious with vague abdominal symptoms, and the first concrete sign was ascites. In a majority of them the ascites was severe. In contrast to Type I, jaundice was either inconspicuous or did not occur at all at any stage of the disease. The spleen was palpable in all but 2 cases and measured on the average 4.7 cm. below the costal margin. Endocrine disturbances developed, but with less frequency than in Type I, 3 out of 17 cases showing one or another of these disturbances. Gynecomastia and spider angioma were present in one, scanty pubic and axillary hair in 2 cases. Hematemesis occurred in 4 cases, in 2 of which it proved fatal. On splenovenography there was no block in the extrahepatic portal bed, and the portal and splenic vein showed no dilatation except in one case. Although many cases could be temporarily improved on appropriate therapy, the disease on the whole followed a relentless downhill course, rapid formation of ascites being the most prominent feature, and the condition terminated most often in hepatic coma as in Type I. Out of 8 patients that died during the 2 years' period of study, in 5 death was due to hepatic coma, in 2 to hematemesis, and in one to superimposed hepatoma. The total duration of the illness was on the average 14 months. In the remaining 9 patients that are alive, the average duration of the illness was 22 months, similar to Type I.

Type III (Splenomegalic Type).—This type consisted of 16 cases. While Type I and Type II have considerable overlap in their features including the pathological changes in the liver (see below), this type was unique and quite distinctive. The onset was vague, and splenomegaly was the first feature noted by the patient and remained dominant throughout the illness. It was followed by ascites after a relatively long latent period. The average duration of illness at the time of admission in this type was of the order of about 8 years in marked contrast to the other types. The spleen was very markedly enlarged and measured on the average about 9

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Fig. 3.—Splenoportal venogram showing markedly dilated splenic and portal veins with normal intrahepatic vascular pattern. Retrograde flow into coronary and short gastric veins can be visualized (Type III case).

cm. from the costal margin. Ascites was mild in a majority of the cases. Jaundice was also not a feature at any stage of the disease. Endocrine disturbances were least conspicuous, being present in only one out of 16 cases, a patient with gynecomastia. Hematemesis was also uncommon; it was present in 2 cases in one of which it proved to be fatal. On splenovenography, in contrast to the other types, the portal and splenic veins showed marked dilatation in a majority of the cases (Fig. 3). There was no demonstrable obstruction to the extrahepatic portal bed. The prognosis in this type proved to be much more favorable than in the others. There was only one death attributable to hepatic coma during the 2 year period of observation, one due to hematemesis, and in 3 others, the death was attributable to operative procedures. In the 2 patients that died a natural death, the total duration of the illness was 132 and 44 months.

Appropriate therapeutic measures brought about prompt relief of symptoms in a majority of the cases. There was no progressive deterioration in the manner observed in Types I and II, and the average duration of the illness of the surviving cases is 123 months.

Pathologic Anatomy

Before presenting the results, it is desirable to set down the criteria used in the interpretation of the biopsy and autopsy specimens and the precise meaning of the nomenclature used. The diagnosis of cirrhosis was made if the criteria laid down by the Board for Classification and Nomenclature of Cirrhosis of the Liver of the Pan American Congress of Gastroenterology (1956) were satisfied. In both biopsy and autopsy specimens, portal and postnecrotic cirrhosis were recognized according to the criteria of Smetana.[5] A further subdivision of postnecrotic cirrhosis was attempted into broad- and fine-band types. If there was evidence of broad fibrous bands with collapse, stromal condensation, and approximation of several portal canals as the major pathological process, it was designated broad-band type of postnecrotic cirrhosis.[6] If, on the other hand, the fibrous bands were fine for the most part, it was designated as fine-band type of postnecrotic cirrhosis.[7] While this subdivision of postnecrotic cirrhosis was made in all the autopsies, it was not always feasible on needle biopsies. However, if there was evidence in needle biopsies of broad scars with approximation of portal canals, a probable diagnosis of broad-band type of postnecrotic cirrhosis was made. In the cases that came to autopsy such an interpretation on the basis of the needle biopsy was found to be corroborated. In many needle biopsies the cirrhosis had to be left unclassified.

Picture in Type I.—Twelve out of 13 cases showed cirrhosis on biopsy, in 4 of which it

Fig. 4.—Persistent hepatitis with portal scarring and portal and intralobular infiltrates; liver biopsy in a Type I case. Hematoxylin and eosin; reduced about 25% from mag. × 100.

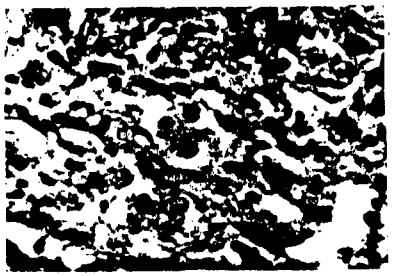

Fig. 5.—Higher magnification of the specimen in Figure 4 to show the diffuse hepatitis, reminiscent of viral hepatitis. Reduced about 25% from mag. × 475.

was confirmed at autopsy (Table). The remaining case showed persistent hepatitis with much scarring, not amounting to cirrhosis (Figs. 4 and 5). Five out of the 12 cases of cirrhosis also showed evidence of persistent hepatitis in the form of focal degeneration and necrosis of liver cells, intralobular cellular infiltrates, moderately severe mononuclear infiltrates in the fibrous bands, and extension of the inflammatory exudate from the fibrous bands into the surrounding liver parenchyma and into the portal canals contained within the multilobulated pseudolobules. In a few cases the degenerating liver cells showed hyaline and acidophil body formation. In the remaining cases of cirrhosis, the picture was quiescent with clearly demarcated pseudolobules sharply separated from the fibrous bands. The liver parenchyma in the pseudolobules was of the regenerative type with 2-cell-thick liver cords; bile, hemosiderin, and lipofuchsin pigments were variably present.

Histologic Features of the Liver in the 3 Clinical Types

Hist. Features	No. Showing the Hist. Features in Each Type		
	Type I	Type II	Type III
Cirrhosis	12	9	—
Postnecrotic	9	8	—
Portal	1	—	—
Unclassified	2	1	—
Persistent hepatitis with scarring	1	2	—
Portal scarring only	—	5	11
Minimal nonspecific changes	—	1	5
Fatty change	—	—	—
Total	13	17	16

In 9 of the 12 cases of cirrhosis, the cirrhosis was of the postnecrotic variety; in 2 it could not be classified (both biopsies), and in one it was portal. Of the postnecrotic group, the majority (7 out of 9) showed evidence of broad-band formation with considerable collapse as the major pathological process (Figs. 6, 7, and 8). In one case, broad and fine bands were equally prominent, producing a mixed type of postnecrotic cirrhosis (Figs. 9 and 10). In the last case the picture was predominantly one of fine-band type of postnecrotic cirrhosis corresponding to Gall's posthepatitic variety.[7]

Picture in Type II.—Out of 17 cases, definite evidence of cirrhosis was present in 9

Fig. 6.—Postnecrotic cirrhosis, postcollapse type (Steiner) showing a broad band with collapse and stromal condensation; autopsy specimen in a Type I case. Hematoxylin and eosin; reduced about 25% from mag. × 35.

Fig. 7.—Section stained with hematoxylin and eosin from the same specimen as in Figure 6 to show the structure of a multilobulated nodule. Reduced about 25% from mag. × 35.

only, in 2 of which the diagnosis was confirmed subsequently at autopsy (Table). Five out of these 9 cases belonged to the postnecrotic variety, 3 of which were of the broad-band collapse type. One case could not be placed either in the broad- or the fine-band groups, and one belonged to the mixed variety. In the remaining 2 cases which showed cirrhosis (all biopsies), the anatomical type could not be identified with certainty. Two other cases in this series showed persistent hepatitis with considerable scarring, not amounting to cirrhosis, and in 4 others there were either portal or intralobular scars of varying sizes without distortion of the lobular architecture. In one case no significant pathological lesions were found in the liver. As already stated, one of the cases with postnecrotic broad-band type of cirrhosis also had an associated hepatocellular carcinoma.

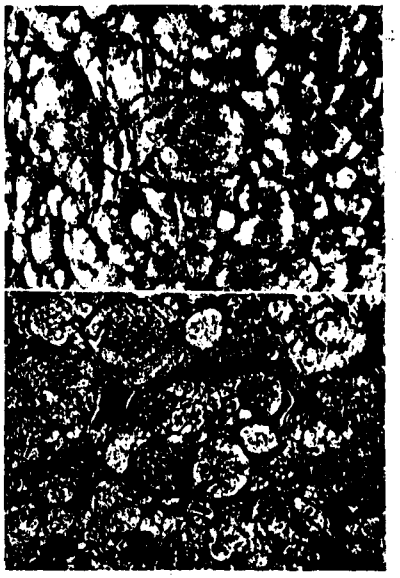

Fig. 8.—*A*, close-up view of the gross external and *B*, cut surfaces of the specimen of liver whose microscopic features are shown in Figures 6 and 7. The extreme variation in the size of the regenerating nodules and depressed scars are characteristic of postnecrotic cirrhosis (Gall), postcollapse cirrhosis (Steiner).

Picture in Type III.—The pathological picture in this type was totally different from that in Types I and II. Out of 16 cases, there

Fig. 9.—Postnecrotic cirrhosis showing a broad band of collapse from a Type I case which showed a mixture of broad and fine bands. Hematoxylin and eosin; reduced about 25% from mag. × 35.

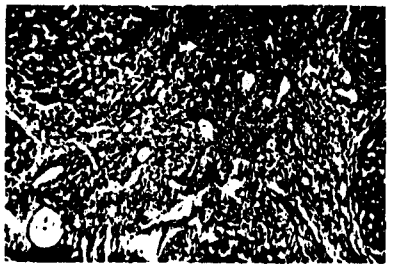

Fig. 10.—Same specimen as in Figure 9 showing another area with fine bands. Broad and fine bands were equally prominent in this case. Gomori's reticulin; reduced about 25% from mag. × 35.

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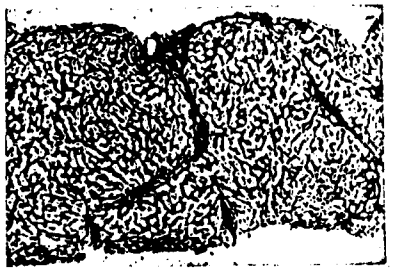

Fig. 11.—Liver biopsy from a Type III case showing portal scars, tendency to pseudolobulation but no cirrhosis. Gomori's reticulin; reduced about 25% from mag. × 35.

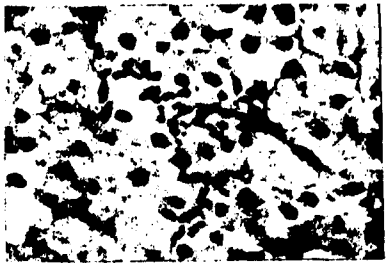

Fig. 12.—Liver biopsy from a Type III case showing focal necrosis in the lobule with mononuclear satellitosis of individual liver cells. Hematoxylin and eosin; reduced about 25% from mag. × 475.

was not a single case that showed unequivocal evidence of cirrhosis (Table). The majority (11 out of 16 cases) showed varying degrees of portal and intralobular scarring, in 2 of which it was quite marked but not sufficient enough to distort the liver as in cirrhosis (Fig. 11). The remaining 5 cases showed minimal nonspecific changes in the form of mild inflammatory infiltrates in the lobule and focal degenerative changes in the liver parenchyma (Fig. 12). The general picture in this type can be summarized as one of mild nonspecific prolonged injury to the liver, the reaction of the liver being one of focal degeneration, focal inflammatory-cell collections, mild endothelial reaction, and varying degrees of portal and intralobular scarring.

Splenectomy was done in 3 cases, and the histological picture in the spleen resembled so-called early fibrocongestive splenic enlargement. There was no evidence of infection with malaria or kala-azar.

Comment

The description given here relates to the clinical material seen in North India and diagnosed on clinical grounds as cirrhosis of the liver. These cases have ascites, splenomegaly, prominent abdominal veins, dilated collateral vascular channels between the portal and systemic circulation, and elevated portal pressures. And yet from the point of view of their evolution and natural history, they seem to fall into 3 clinical types. The situation is somewhat reminiscent of "chronic nephritis" of earlier times and nephrotic syndrome of more recent times.

Of the 3 types, Type III stands out clearly as a distinct entity, and we would like to emphasize its existence and its natural history. It commences with splenomegaly which persists and increases throughout the course of the disease. It runs an indolent course extending over several years, developing in the course of time various manifestations of portal hypertension. The liver shows nonspecific changes during the greater part of the illness with more or less fibrous scarring, but there is no evidence that cirrhosis eventually develops with lobular distortion and nodular regeneration.

These are the cases that have been labeled in the past as "tropical splenomegaly," Banti's syndrome, and some have masqueraded as cirrhosis. A malarial etiology has been advocated for such cases.[9] Some of our cases do give a past history of malaria. However, histological examination of the liver and spleen in these does not show evidence of malarial parasites or pigment. Furthermore, the interruption of transmission of malaria through antimalarial operations has been continuously in progress in this part of the country for over 10 years, and, under these conditions, it is unlikely that the splenomegaly is attributable to malarial infection.

The fact that the bulk of Type III cases develop undoubted portal hypertension in the

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course of the disease with mild nonspecific reactive changes in the liver calls for comment. In the absence of obstruction in the extrahepatic portal bed and of established cirrhotic changes in the liver, the mechanism of portal hypertension is difficult to explain. Similar cases have been reported from outside India,[9,10] and it seems probable that long-continued splenomegaly may in its wake bring about circulatory changes in the portal bed, leading to portal hypertension.

There are several overlapping and distinguishing features between Type I and Type II cases, in the manner of Ellis's nephritic types. In their mode of onset, presence or absence of jaundice and severity of ascites, the 2 types are fairly distinct. In their pace of progression, therapeutic response, and pathological alterations in the liver, there is a considerable overlap and the distinction becomes blurred. Anatomical evidence of cirrhosis was present in a majority of the cases of both types, and postnecrotic cirrhosis was the commonest variety in both. On comparing the 2 series, however, certain differences become apparent (Table). While all but one case of Type I series showed anatomical cirrhosis, it was present in just over one-half of the cases of Type II series. Among these, the postnecrotic variety was more common in Type I than in Type II. Nearly one-half of Type II cases did not show cirrhosis but only varying degrees of scarring; there was only one case of this nature in Type I series. These differences are of course relative and cannot be applied in the analysis of individual cases. They, however, indicate a difference either in the injurious agent or in its dose or in tissue reaction to injury.

It is hardly likely that the same etiological factor is at work in all the 3 types. Type III must in any case be considered distinctive. Of the hepatotoxic agents, the hepatitis viruses have been receiving much attention in recent years. Both postnecrotic [11] and portal cirrhosis [12] have been reported as following viral hepatitis. It has even been stated that a nonicteric attack of hepatitis can progress to cirrhosis.[13] The possibility that the Type I and Type II cases are the result of viral hepatitis of icteric and nonicteric varieties, respectively, must be considered. The clinical and histological features of Type I cases are certainly compatible with the known sequences of unresolved viral hepatitis progressing to cirrhosis. But as the disease progresses, histological features become more and more nonspecific, and we have no way of knowing that the Type I and Type II pictures are not the sequelae of some other form of "toxic" hepatitis.

Our data in the Delhi area suggest that the cirrhosis here is predominantly of the postnecrotic variety. We have no evidence that malnutrition plays a primary role. Fatty change was conspicuous by its absence at any stage in any of the 3 types. The patients were obviously not malnourished. In a series of 300 medicolegal autopsies in this area, 15 cases belonging to the destitute class were found to have severe and extensive fatty change in the liver, but none of these showed excessive fibrosis or cirrhosis.[14]

In the cases presented here, alcohol can be eliminated as an etiological factor. Siderosis is rare. Malaria has not been a health problem in this area for well over 10 years. Bilharziasis does not occur. The significance of native medicines, indigenous herbs, toxins from vegetable sources, and metallic intoxication from the use of metal utensils is unknown.

Summary

The clinical features and pathological anatomy of a consecutive series of 46 cases with established signs of portal hypertension and clinically diagnosed as cirrhosis of the liver form the subject matter of this study. Cases showing extrahepatic obstruction on splenoportal venography were excluded.

The clinical material was not a homogeneous entity. From a study of the mode of onset and clinical picture, the cases could be classified into 3 clinical types.

The clinical and pathological features of each type are presented and discussed. Type III emerges as a unique and distinct group in which splenomegaly is the initial and dominating feature throughout the illness, while

the liver shows mild, nonspecific changes with no evidence of progression to cirrhosis. Type I and Type II cases show progressive liver changes with cirrhosis in the majority. There are overlapping as well as distinguishing features between these 2 types.

Cirrhosis, when present, was most commonly of the postnecrotic variety; it was unclassifiable in some biopsies; portal cirrhosis was rare.

The features of each type and probable etiological factors have been discussed.

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Histoplasma Endocarditis

Report on a Patient Treated with Amphotericin B, with Review of Amphotericin B Therapy for Histoplasmosis

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The primary purposes of this paper are: (1) to report a case of progressive, fatal histoplasmosis treated with amphotericin B in which the predominant lesion was that of vegetative endocarditis, (2) to discuss briefly the clinical entity of histoplasmosis with particular reference to endocardial involvement, and (3) to review amphotericin B therapy for histoplasmosis and Histoplasma endocarditis. One other case of Histoplasma endocarditis found at the Mayo Clinic was that reported by Broders and associates in 1943.[1]

Clinical Features of Histoplasmosis

Histoplasmosis infects various organ systems, but particularly the respiratory and gastrointestinal tracts. Lesions of the throat and nasopharynx are often present. Productive cough, loss of weight, anemia, leukopenia, sweats, fatigue, chest pain, fever, and chills were listed as the chief clinical manifestations by Vivian and associates reporting on 20 cases seen at the Mayo Clinic.[24] Hepatosplenomegaly was a frequent finding.

The most common type of the disease is a benign, self-limiting, and apparently asymptomatic pulmonary infection with excellent prognosis. Three other types of the disease may be found. The first, acute pulmonary nonfatal histoplasmosis, is characterized by an influenza-like syndrome affecting children and adults alike. The x-ray findings may range from that of a small single nodule in the lung with hilar adenopathy to that of a large number of miliary lesions. Bronchopneumonic infiltrates may be seen. Rarely the disease may progress with dissemination, fever, lymphadenopathy, and hepatosplenomegaly. The chest roentgenogram may not show any abnormality during this stage. A spontaneous remission of the disease after a duration of 6 to 8 weeks may occur, but the disease may develop into the second type, that of fatal progressive disseminated histoplasmosis.

This second type of histoplasmosis is characterized either by slow progressive disease lasting months to years or by a fulminating rapidly fatal disease with wide dissemination. Involvement of the skin and mucous membrane is frequent. It is often a concomitant finding among people suffering from tuberculosis, Hodgkin's disease, chronic leukemia, or similar disease of the reticuloendothelial system.

The third type of the disease is chronic progressive pulmonary cavitary histoplasmosis. This type closely resembles reinfection tuberculosis and is a problem of extreme importance in the country's tuberculosis sanatoria.[26] The disease may be symptomatically mild and is characterized by exacerbations and remissions. Hemoptysis is rare. Roentgenograms may show apical fibrotic infiltration progressing to cavitation. Calcified hilar areas are frequently found. Relapses are common. Progressive cavitation of the lungs usually causes a fatal termination of the disease, with symptoms of increasing respiratory distress, unless treated surgically and with amphotericin B.

Report of a Case

A 50-year-old white male bartender first entered the Mayo Clinic on Oct. 25, 1956. Diagnoses of duodenal ulcer, inactive rheumatic heart disease with mitral stenosis, and mild congestive heart failure

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Fellow in Medicine (Dr. Palmer); Section of Medicine (Dr. Geraci); Fellow in Pathology (Dr. Thomas); Mayo Clinic and Mayo Foundation.