TUBERCULOSIS OF THE LIVER

A STUDY OF 200 CASES

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It was previously thought that tuberculosis of the liver was a rare condition. Subsequent studies on the incidence of hepatic granulomata in tissues obtained from percutaneous needle biopsy, laparotomy and at autopsy, have shown that miliary tuberculosis of the liver is common. Miliary hepatic tubercles have been seen in acute disseminated miliary tuberculosis,[1-3] extrapulmonary tuberculosis[4, 5] and in fatal cases of pulmonary tuberculosis.[1, 6] On the other hand, local tuberculosis of the liver is rare, only 87 cases having been reported in the literature to date.

In view of the importance of hepatic tuberculosis, especially where clinical and radiological evidence of tuberculosis elsewhere is lacking, a clinical, pathological and biochemical study was made of this disease. Tuberculosis of the liver occurs in *primary* and *secondary* forms.

Secondary tuberculosis of the liver can be differentiated into:

1. *Miliary* (tubercles 0·6 - 2 mm. in diameter);
2. *Local* (lesions larger than 2 mm. in diameter)—
   (*a*) Conglomerate tubercles
   (*b*) Tuberculomata
   (*c*) Bile duct tuberculosis
   (*d*) Abscesses, and
3. *'Tuberculous cirrhosis'*(?)

MATERIAL AND METHODS

From 1955 to 1961, 200 cases of tuberculosis of the liver were studied at Baragwanath Non-European Hospital. These consisted of all cases diagnosed on biopsy and at autopsy during this period. Only the incidence, average age and type of lesion in the liver were noted in the paediatric cases (below the age of 11 years), all of which were Bantu and diagnosed at autopsy. The remaining 143 adults were studied with reference to age, sex, clinical presentation, pathology, diagnosis and differential diagnosis. There were 138 Bantu, 3 Asiatics and 2 Coloured; 83 were males and 60 females. Of these 143 cases, 114 were diagnosed at autopsy, 26 by needle biopsy and 3 at laparotomy (Table I). The author has personally followed the clinical course of 46 cases.

TABLE I. DIAGNOSIS OF HEPATIC TUBERCULOSIS

	Miliary TB	*Local TB*
Percutaneous liver biopsy	25	1
Laparotomy	2	1
Autopsy	96	18

TABLE II. INCIDENCE AND AVERAGE AGE OF CHILDREN AND ADULTS WITH HEPATIC TUBERCULOSIS (200 CASES)

	Miliary TB		*Local TB*	
	Children	*Adults*	*Children*	*Adults*
Number of cases ..	57	123	0	20
Average age	2	46	—	44

FINDINGS

Pathology

Only miliary tuberculosis of the liver was found in the paediatric cases as shown in Table II, whereas in adults miliary tuberculosis of the liver (group A) was present in 123 (86%) cases and local hepatic tuberculosis (group B) in 20 (14%).

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In all cases epithelioid granulomata, with or without Langhans-type giant cells, and/or caseation, were present in the liver. Of the 114 cases diagnosed at autopsy, 86 showed caseation in the liver and in the remaining 28 cases with hepatic granulomata and no caseation, a further 18 evidenced extrahepatic caseation, mainly in the lungs. Ziehl-Neelsen stains were performed on liver sections in only 6 autopsied patients, 5 of which were positive for tubercle bacilli. In all 29 patients diagnosed on liver biopsy, sections were stained by the Ziehl-Neelsen method and 6 were positive, 3 associated with caseating lesions. In a further 7 biopsy cases sputa were positive for tubercle bacilli and 1 other case had a positive rectal biopsy. The latter 8 cases had negative stains on liver tissue.

Associated hepatic pathology. Moderate to severe hepatic siderosis was present in 54 (47%) necropsy cases and in 8 (28%) biopsy cases, whereas fatty metamorphosis was found in 32 (28%) necropsy cases and 4 (14%) biopsy cases. Portal cirrhosis was present in 8 adults with hepatic tuberculosis, and of these 3 were chronic alcoholics, 1 was severely malnourished and 2 were associated with tuberculous peritonitis.

Site(s) of dissemination. In cases studied at autopsy, the commonest disseminating site in both groups was thought to be tuberculous lymph nodes (Table III), which were present in approximately half of the cases. In a third of cases in both groups the primary site was the lungs. A small number of cases were associated with gastro-intestinal, renal, spinal and genital foci. No primary site could be found in 6 (4·9%) cases in group A and in 2 (10%) cases in group B. In 1 additional case in the latter group, no extrahepatic tuberculosis was found. The absence of a detectable primary focus was more commonly found with local hepatic tuberculosis, probably as a result of the longer time afforded for this focus to heal. Subacute bacterial endocarditis of the mitral valve caused the disseminated miliary tuberculosis in 1 case. Where there was more than 1 possible site of dissemination, these have all been included under the various headings in Table III.

TABLE III. POSSIBLE SITE(S) OF DISSEMINATION OF HEPATIC TUBERCULOSIS

	Miliary TB	*Local TB*
Lymph nodes	56	10
GIT	6	2
Kidney	5	2
Female genitalia	4	0
Lung	38	8
Spine	6	2
Mitral valve	1	0
Unknown	6	2
(Liver only organ affected)	0	1

Clinical Features

The clinical features are set out in Tables II and IV. The average age in the paediatric cases was 2 years, but it is noteworthy that the average age in group A was 46 years and 44 years in group B. Approximately one-third of cases in group A and one-quarter in group B had no symptoms or signs or radiological evidence of pulmonary tuberculosis. Night sweats were common to both groups, anorexia and weight loss usual, and pyrexia of variable severity, almost universal. Of the 4 cases with no pyrexia, 3 were close to termination on admission. Abdominal pain unrelated to meals was a presenting symptom in about half of the cases in both groups. As compared to generalized abdominal pain, upper abdominal pain was about twice as common in group A and about 3 times as common in group B. Tuberculous peritonitis contributed to the pain in 12 cases with miliary hepatic tuberculosis and 1 case with local hepatic tuberculosis, but in these cases generalized abdominal pain was invariably present. In about one-half of the cases in both groups there was a disturbance of bowel habit, diarrhoea being about twice as common as constipation.

TABLE IV. CLINICAL FEATURES OF HEPATIC TUBERCULOSIS

	Miliary TB	*Local TB*
Symptoms/Signs of pulmonary disease	79	15
Night sweats	48	6
Weight loss	104	15
Bowels: Normal	60	9
Constipated	21	4
Diarrhoea	42	7
Anorexia	65	11
Abdominal pain: Generalized	25	3
Upper	40 } 65 (53%)	10 } 13 (65%)
Peritonitis	12	1
Pyrexia	121	18
Hepatomegaly: Tender	42	12
Non-tender	45 } 87 (71%)	7 } 19 (95%)
Splenomegaly	39	11
Jaundice	21 (3 Haemolytic, 1 cirrhosis, 5 biochemical)	10 (1 Cirrhosis, 1 AC hepatic necrosis, 4 biochemical)

Hepatomegaly was present in 71% of cases in group A and 95% in group B. Hepatic tenderness was present in about half the cases in both groups. Splenomegaly was present in approximately one-third of cases in group A and half of the cases in group B. In group A, 21 cases were jaundiced. Of these, 16 (13%) were clinically jaundiced, 3 of which were associated with haemolysis and 1 with cirrhosis. The incidence of jaundice was higher in group B, in which 10 (50%) cases were jaundiced. Six of these were detected clinically, 1 of which was associated with cirrhosis and 1 with acute massive hepatic necrosis. Three of the clinically jaundiced cases were found to have tuberculous glands in the porta hepatis at necropsy. Of these 3, 2 had the highest and second highest bilirubin levels recorded (13·8 and 7·2 mg./100 ml.). The third had only mild hyperbilirubinaemia (3·8 mg./100 ml.). Seven of the 29 patients diagnosed on liver biopsy died while in hospital, the other 22 being discharged to clinics to continue antituberculous therapy. Of the 7 that died, 6 were clinically jaundiced preterminally, and of the 8 patients that were clinically jaundiced in the group of 29 cases, 6 (75%) died.

One patient in group B showed hypoglycaemia, but this could be accounted for by the associated acute massive hepatic necrosis. One patient in group A developed hypoglycaemia and autopsy revealed a massive miliary tuberculosis of the liver to an extent seldom seen, where almost the entire liver was replaced by tubercles. There was no evidence of any other disease in the liver, or of tuberculosis in the thyroid, adrenal glands or gastro-intestinal tract, but the pituitary was not examined. Severe liver dysfunction was the probable explanation for the hypoglycaemia.

Biochemical Tests

In the 23 jaundiced patients with tuberculosis of the liver, all were found to have both excessive urobilin and bilirubin in the urine, whereas in 11 non-jaundiced patients, all were found to have an excess of urobilin only (Table V).

Serum bilirubin and alkaline phosphatase. In 17 patients where liver biopsies yielded granulomata, serum-bilirubin and alkaline-phosphatase estimations were done. In 6 of these, the serum bilirubins were normal and the serum-alkaline-phosphatase levels raised (range 15 - 96 King-Armstrong units). In a further 5 patients the serum bilirubins ranged between 1·3 and 3·6 mg./100 ml., where the serum-alkaline-phosphatase levels ranged between 28·6 and 200 K-A units. In the remaining 6 cases the serum-alkaline-phosphatase levels were normal, whereas hyperbilirubinaemia occurred in 2. In the 123 cases in group A, 25 serum-alkaline-phosphatase estimations were performed and of these 18 (72%) were raised. Of the latter, 6 were associated with normal serum-bilirubin estimations. In 11 of the remaining 12 patients, the serum-bilirubin levels ranged between 1·3 and 4·5 mg./100 ml. and the serum-alkaline-phosphatase levels between 13·8 and 200 K-A units, approximately half the latter being above 30 K-A units. Increased serum-alkaline-phosphatase levels were found in 7 of 8 (87·5%) cases in group B. Of these 7 cases, 4 had normal serum bilirubins, whereas 3 had levels between 2·3 and 5·8 mg./100 ml., where the corresponding range of serum-alkaline-phosphatase levels was 24·2 to 51 K-A units. The highest serum-alkaline-phosphatase level recorded in group A was 200 K-A units, the serum bilirubin being 2·9 mg./100 ml. and 52 K-A units in group B, where the serum bilirubin was 0·6 mg./100 ml. The average serum-alkaline-phosphatase in group A was 43·8 K-A units and 32·3 K-A units in group B.

Other liver-function tests. Bromsulphalein tests were only performed in 6 cases and the retention of dye ranged from 35 to 90%. Three serum-cholesterol estimations were done and, of these, 2 were decreased and 1 increased. The serum albumin was abnormally low in 35 out of 37 cases and the serum globulin was elevated in about half of these cases. Normal Bantu subjects have been found to have abnormally low serum albumins and raised serum globulins by White standards,[7] and these have been taken into account. In 18 of 30 cases, the prothrombin index was below 80% and was low in all cases in group B. Liver flocculation tests were not analysed in view of the abnormal serum proteins.

DISCUSSION

1. *Pathology*

Tuberculosis in the liver is always secondary to tuberculosis elsewhere, except where infection is carried from

TABLE V. LABORATORY FINDINGS IN HEPATIC TUBERCULOSIS

Test	*Miliary TB*			*Local TB*		
	No. abn.	*Range*	*Aver.*	*No. abn.*	*Range*	*Aver.*
1. Blood						
S. albumin (G %)	28/30	0·7—2·58 (Normal 2·8—3·6)	2·1	7/7	1·1—2·7	1·8
S. globulin (G %)	15/30	1·7—6·3 (Normal 2·7—4·2)	4·0	3/7	2·7—4·8	3·9
Alk. phosphatase (K–A units %)	18/25	15—200	43·8	7/8	20—52	32·3
Cholesterol (mg. %)	2/5↓ 1↑	70—364				
PI	13/25↓ 80%	Lowest 45%	65%	5/5	Lowest 58%	65%
BSP	6/6	35—90%				
Bilirubin (mg. %)	21	1·4—13·8	3·8	10/20	2·3—5·8	4·1
2. Urine						
Urobilin & bilirubin in jaundiced patients	16/16			7/7		
Urobilin in non-jaundiced patients	7/7			3/3		

a diseased placenta to the foetus along the umbilical lymphatics or blood vessels.[8] 'Primary hepatic tuberculosis' is used in the sense that a tuberculous lesion in the liver may result from tubercle bacilli gaining access to the portal vein from a microscopic or small tuberculous focus in the bowel; subsequent healing taking place at the site of entry and leaving no trace of it. To satisfy a diagnosis of 'primary hepatic tuberculosis', the liver lesion should be the only tuberculous focus in the body or the principal and oldest lesion.[9] It can thus only be diagnosed on a full postmortem examination. One case in group B satisfied the former criterion and 2 cases in group B the latter.

Miliary hepatic tuberculosis (Figs. 4 and 6). Miliary tubercles range in size from 0·6 to 2mm. in diameter.[10] Where resistance to the tubercle bacilli is high, these consist of epithelioid granulomata, with or without Langhans-type giant cells; where resistance is low, the cellular infiltrate is replaced by a mass of caseation. In the former case tubercle bacilli are not commonly found, whereas they are frequently found in great numbers in association with caseous lesions. According to Popper and Schaffner,[10] tubercle bacilli are rarely identified in pathological preparations of liver tissue, except in children. Diagnosis must therefore be based on the histological appearance or on the culturing of the organism from a needle-biopsy specimen.[11, 12] In the presence of hepatic caseation, positive Ziehl-Neelsen stains for tubercle bacilli were found in 5 of 6 cases diagnosed at autopsy in this

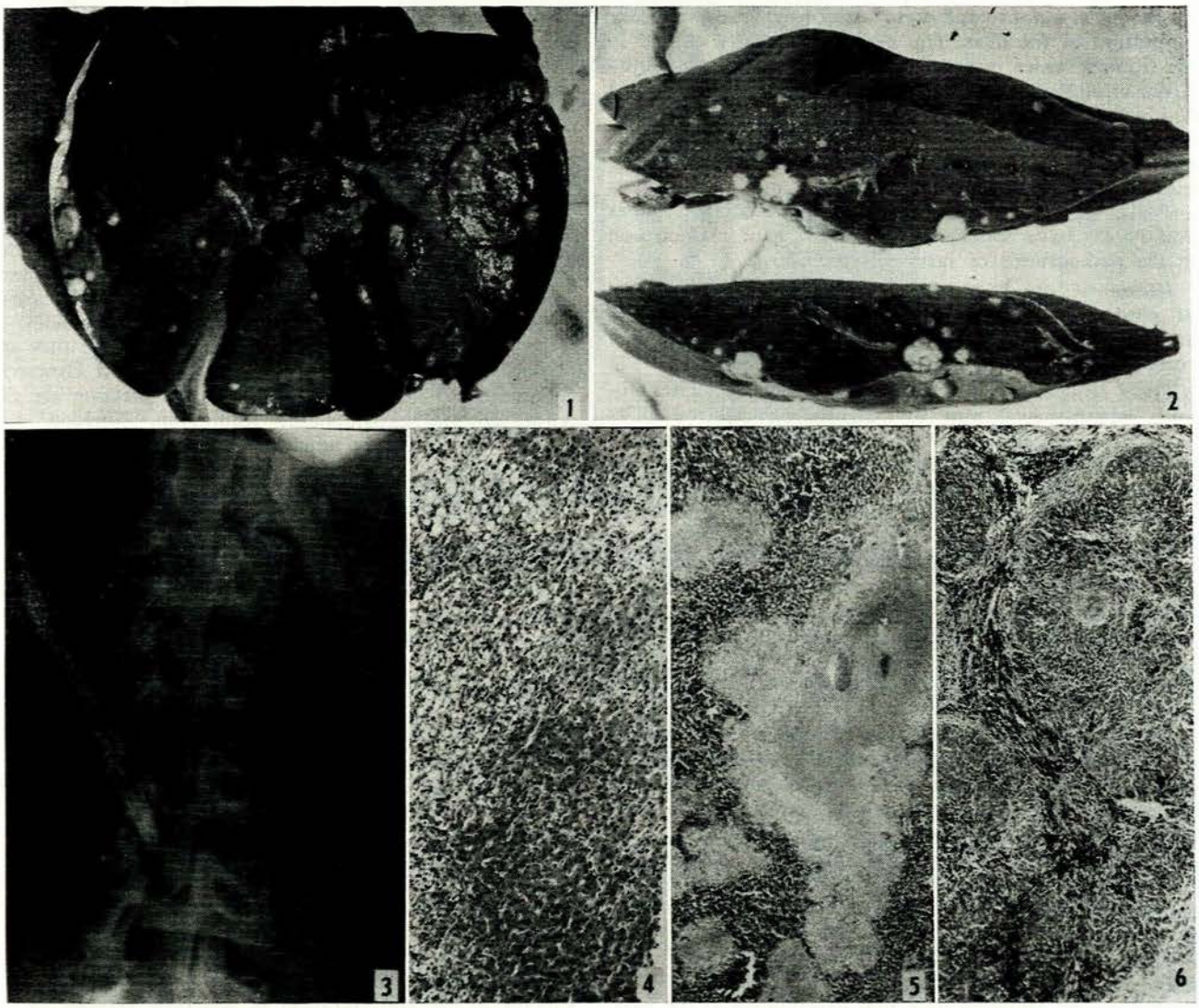

Fig. 1. Inferior surface of the liver showing multiple tuberculomata.
Fig. 2. Cross-section of liver showing tuberculomata and conglomerate tubercles.
Fig. 3. Radiograph of the abdomen showing dye inserted in a fistulous track from liver to skin following liver biopsy. Hepatic calcification is seen in the left lobe of the liver.
Fig. 4. Marked fatty metamorphosis with 2 miliary tubercles on the left (H. & E. × 120).
Fig. 5. Caseous local tuberculosis (H. & E. × 30).
Fig. 6. Cirrhosis, siderosis and 2 miliary tubercles (H. & E. × 30).

study, and in 3 of 4 cases diagnosed on biopsy. Of the remaining 25 cases with epithelioid granulomata without caseation diagnosed on biopsy, only 2 were positive for tubercle bacilli.

Popper and Schaffner[10] have described a number of changes which may occur in the liver during the course of miliary tuberculosis. The commonest of these are irregular areas of focal necrosis and portal inflammation resembling infective hepatitis. Kupffer-cell proliferation, leading to a decrease in the sinusoidal diameter and liver-cell compression with necrosis, epithelioid cell tubercles surrounded by Langhans-type giant cells, miliary caseation and fatty metamorphosis are the other abnormalities described.

Associated hepatic fatty metamorphosis (Fig. 4). Of the present cases with hepatic tuberculosis, 32 (28%) diagnosed at autopsy and 4 (14%) on biopsy, showed fatty infiltration of the liver. The incidence of fatty change in the autopsy cases is exactly the same as that found by Arora *et al.*,[13] similar to the findings of Korn *et al.*[5] (30%) and higher than that of Seife *et al.*[14] (20%). Compared with cases diagnosed at autopsy, biopsy specimens showed half the incidence of fatty change. Possible explanations for this may be that the latter cases had less advanced tuberculosis and also that the biopsies were not representative. Jones and Peck[15] have commented on the role of malnutrition in the pathogenesis of fatty metamorphosis.

Haemosiderosis of the liver (Fig. 6). The high incidence of moderate to severe hepatic siderosis found both at autopsy and on biopsy is not surprising, as this is a common finding in healthy Bantu.[16]

Local hepatic tuberculosis (Figs. 1, 2 and 5). Granulomata larger than 2 mm. in diameter are referred to as local tuberculosis. Conglomerate tubercles may result from the survival, extension and coalescence of tubercles, whereas granulomata which enlarge and develop fibrous capsules are known as tuberculomata. Bile-duct tuberculosis results from the ulceration of tubercles into bile ducts from adjacent liver tissue.[17] Tuberculous abscesses consist of caseous material usually containing an abundance of tubercle bacilli, as they are usually associated with a low resistance. In group B there were 2 cases with conglomerate tubercles, 17 with tuberculomata and 1 with a tuberculous abscess. No convincing cases of bile-duct tuberculosis were seen.

'Tuberculous cirrhosis'. That tuberculosis gives rise to cirrhosis has not been convincingly proved. Kern and Gold[18] rate tuberculosis of the liver as the second most important factor in the causation of cirrhosis of the liver; the first being alcohol. Lorentz[19] found tuberculosis as the chief finding in 16 of 111 cases of cirrhosis. Seife *et al.*[14] biopsied the livers of 70 pulmonary tuberculotics and found cirrhosis in 13. Evidence in favour of tuberculosis as a cause of cirrhosis is the fact that other granulomatous diseases such as brucellosis[20, 21] and sarcoidosis[22] have been reported to lead to cirrhosis. On the other hand Rolleston and McNee[23] state that tuberculosis in the liver, or some other part of the body, may result in fibrosis of the liver, but that a true cirrhosis does not occur. Furthermore they add that, where tuberculosis and cirrhosis coexist, the cirrhosis usually predates the tuberculosis, the latter resulting from malnutrition or some defect in immune mechanisms. Mouisset and Bonnamour[24] believe that cirrhosis in tuberculous patients is nearly always due to concomitant alcoholism. Kaufmann[25] states that cirrhosis of the liver is found more frequently when associated with tuberculosis in sites other than the liver. This is suggested by the work of Burack and Hollister[26] who found that 40% of patients with tuberculous peritonitis have alcoholic cirrhosis. In the present series, 8 cases had both hepatic tuberculosis and cirrhosis (Fig. 6). Of these 2 had associated tuberculous peritonitis, 3 were chronic alcoholics and 1 had severe malnutrition. The incidence of cirrhosis in these patients (5·6%) was less than half the incidence of cirrhosis in consecutive necropsies performed on adults in this hospital (12%).[27] It is therefore unlikely that hepatic tuberculosis was the cause of the cirrhosis in these cases.

Site(s) and mode of dissemination. The primary site of dissemination of tuberculosis to the liver in both groups was thought to be lymph glands in approximately half of the cases and the lungs in one-third of cases. In a few cases lymphadenopathy and chronic lung lesions were both present. A primary site was less often found in group B than in group A and probably resulted from the longer time afforded for this focus to heal.

Rolleston[28] believes that in adults acute miliary tuberculosis of the liver results from dissemination through the hepatic artery and that chronic tuberculosis of the liver is caused by infection carried along the portal vein from gastro-intestinal or glandular foci. Miliary hepatic tubercles are nearly always situated inside the lobules, in contrast to the local forms of tuberculosis, where they are mainly in the portal regions. Rosenkranz and Howard[29] believe that the 2 important avenues of infection are the portal vein and the lymphatics. Kaufmann,[25] Sheldon[30] and Morris[31] emphasize the importance of the lymphatics in the development of tuberculous liver abscesses, which they state are usually secondary to tuberculous peritonitis. It has not been satisfactorily demonstrated that ascending infection along the bile ducts occurs.

In a pathological analysis of 297 cases of acute generalized miliary tuberculosis, Auerbach[32] found that caseous lymph nodes were invariably present and therefore concluded that the lymphovenous circulation was the route of miliary dissemination. Chronic pulmonary tuberculosis was associated in 64·3% of these cases.

Variations in local tissue reaction to tuberculosis. Although no tissue is exempt from tuberculous infection, the inherent ability of different organs to resist infection by the tubercle bacillus varies a great deal. Resistance is low in lung, kidney, fallopian tube, intestine, epididymis, prostate, adrenal, bone, skin, eye and lymph node; whereas resistance is high in skeletal muscle, liver and spleen. In miliary tuberculosis, lesions are more numerous in the liver and spleen than in the fallopian tube and kidney, but progression of the miliary tubercles to form extensive granulomata are far more common in the latter. The main factor which is said to influence the survival of the tubercle bacillus is the concentration of available oxygen in the organ. Where the oxygen concentration is high, as in the lung, multiplication of tubercle bacilli will be great, but where it is lower, as in the liver, survival will be less.[33]

2. *Incidence of Hepatic Tubercles in Various Forms of Tuberculosis*

(a) *Miliary*. In autopsies performed on patients dying

from pulmonary tuberculosis, hepatic granulomata have been found in from 50 to 80% of cases.[1, 6] Where miliary tuberculosis was the cause of death, Torrey[1] found hepatic granulomata in 100% of cases and where pulmonary and extrapulmonary tuberculosis were both present, Lorentz[19] found granulomata in 99% of cases. Liver biopsy yielded granulomata in miliary tuberculosis in from 25·3 to 100% of cases,[2, 3] in chronic pulmonary tuberculosis in 20·3%[34] and in extrapulmonary tuberculosis in from 40 - 80% of cases.[4, 5] According to Korn *et al.*[5] the variation in the reported incidence of granulomata on liver biopsy may be due to varying severity of the disease, the modifying effects of antituberculous therapy, different criteria for defining granulomata and the varying number of sections per biopsy employed by different authors.

(b) *Local.* Whereas miliary tuberculosis of the liver is common, only 87 cases of local hepatic tuberculosis have previously been reported in the literature. This number does not include Geraghty's series of 43 cases of hepatic tuberculosis[35] and Korn *et al.*'s series of 24 cases[5] as they did not state the number of local forms which they observed. Morris[31] in 1930 reviewed 11 cases of local hepatic tuberculosis, adding 1 case of his own. He located only 1 case by sending questionnaires to several pathologists and to tuberculosis hospitals with a total bed capacity of 11,455 in various parts of America. Local hepatic tuberculosis is most common in association with tuberculous ulceration of the intestine and in 1858, Bristowe,[36] on examining 167 autopsy cases with tuberculous ulceration of the bowel, found tuberculous cavitation in the liver in 12.

3. *Clinical Features*

Age. The first striking observation was that the average age in both groups lay in the fourth decade. This differs from the more usual finding that both miliary and local hepatic tuberculosis are uncommon in adults.

Symptoms. Two important presenting symptoms were abdominal pain and altered bowel habits. Approximately half of the cases in both groups presented with abdominal pain. The commonest situation of this pain was in the upper abdomen and, being unrelated to meals, was probably due to hepatic enlargement. Less frequently the complaint was of generalized abdominal pain and it is significant that half of these cases in group A and a third in group B, were found to have associated tuberculous peritonitis. Of the cases in both groups with a disturbance of bowel habit, diarrhoea was about twice as common as constipation. Most descriptions of the clinical features of miliary tuberculosis stress the rarity of diarrhoea.

Signs. Miliary tuberculosis has been divided into 3 classical clinical presentations—typhoid, meningeal and pulmonary. Mixed types also occur. As hepatic symptoms and signs dominated the clinical picture in so many cases in the present series, it is suggested that this constitutes a fourth group—hepatic.

Hepatomegaly was the most striking and constant physical sign in tuberculosis of the liver and was present in 71% of miliary cases and 95% of local cases. Tenderness on palpation of the liver was noted in approximately half the cases in both groups. It is noteworthy that most standard textbooks make no mention of the presence of hepatomegaly or tenderness over the liver area in clinical descriptions of generalized miliary tuberculosis. Gold *et al.*[37] state that there are usually no symptoms or signs referable to the liver in miliary or local hepatic tuberculosis, but that variable degrees of liver enlargement may occasionally be present. On the other hand Lichtman[38] states that the liver is uniformly enlarged and tender in miliary tuberculosis, right-heart failure contributing to the enlargement and tenderness in some fatal cases. Arora *et al.*[13] noted that hepatomegaly was twice as common in abdominal tuberculosis as compared to pulmonary tuberculosis. Morris[31] stated in 1930 that all authors were agreed that local tuberculosis of the liver was not diagnosed clinically as the condition gave rise to no clinical phenomena. Cleve *et al.*[39] believe that when the liver is principally or exclusively involved by tuberculosis, hepatic symptoms and signs are usually prominent. To describe such cases they used the term 'atypical' tuberculosis of the liver. Fistulae on the abdominal wall, either spontaneous or postoperative, or following liver biopsy, are suggestive of hepatic tuberculosis.[37, 40] One of the present cases described, developed a fistula overlying the liver following a liver biopsy (Fig. 3). The hepatic friction rub described by Bockus[41] has not been found to be helpful in view of its non-specificity. Splenomegaly was present in about a third of cases in group A and half of the cases in group B. In some cases the spleen was markedly enlarged and painful and in 2 cases reached as far down as the pelvis. Gelfand[42] has stated that the spleen is usually larger in Bantu with miliary tuberculosis than in Whites.

In the present study, clinical jaundice was noted in 22 (15·4%) cases and biochemical hyperbilirubinaemia in a further 9 cases. A search of the literature has shown only 45 previous cases of clinical jaundice in association with tuberculosis of the liver. On the other hand, mild hyperbilirubinaemia in the absence of clinical jaundice is common. Warthin[43] reported the presence of jaundice in 80% of his cases of acute generalized miliary tuberculosis and in a similar percentage of cases of chronic pulmonary tuberculosis with terminal miliary spread. His observations have not been confirmed by other workers. At the Phipp's Institute, Cruice[44] found 7 cases with clinical jaundice out of a total of 1,748 cases with pulmonary tuberculosis. Autopsies performed on 570 of these cases showed local hepatic tuberculosis in 2 and miliary tuberculosis of the liver in 1. The rarity of jaundice in tuberculous abscess of the liver has been stressed by Geraghty[35] but has been seen by Thayer,[45] Maximowitsch,[46] Sheldon,[30] Warthin[47] and Rosenkranz and Howard.[29] Where tuberculosis of the liver is accompanied by jaundice, a correct diagnosis is more likely to be made than in its absence, as attention is more readily directed to the liver and biliary system.

The present findings show that tuberculous glands in the porta hepatis are usually associated with the higher bilirubin levels, but not necessarily so. Furthermore, local forms of hepatic tuberculosis more commonly cause jaundice than miliary lesions. According to Popper and Schaffner[10] fatty metamorphosis in the liver may cause jaundice, in the absence of any other liver pathology, and may have contributed to the jaundice in some of these cases. Tuberculosis in the form of pulmonary, miliary and hilar lymphadenopathy may all cause haemolytic jaundice,[49-51] but in none of the reports of hepatic tuberculosis

accompanied by jaundice in the literature, was haemolysis investigated as a possible cause of the icterus. Of the cases with hepatic tuberculosis and jaundice described here, a haemolytic process was found in 3. Although multiple transient episodes of jaundice have not been noted here, such cases have been described in the literature. At least 2 of these, however, were found to have double pathologies, as in the case of De Crespigny and Cleland[48] (hepatic tuberculosis and hepatic hydatid disease) and Maximowitsch[46] (hepatic tuberculosis and chronic cholecystitis). Double liver pathology was noted in 3 of the present cases with clinical jaundice.

Jaundice appearing during the course of hepatic tuberculosis was of poor prognostic significance, being associated with a mortality rate of 75% in cases diagnosed on liver biopsy.

DIAGNOSIS

It is important to bear in mind the possibility of tuberculosis of the liver in any case of hepatomegaly or pyrexia of unknown origin, as the condition responds well to early and adequate antituberculous therapy. Isoniazid and para-aminosalicylic acid, steroids in the severely ill,[52] and streptomycin, have all been used successfully. The US Veteran Administration in a cooperative study reported over 90% survival in an adequately treated group of miliary tuberculosis.[53]

The clue to the diagnosis of hepatic tuberculosis in most cases, is the *presence of tuberculosis elsewhere*. Where such evidence is lacking, a correct diagnosis may be extremely difficult and in the past has usually been made either at autopsy or laparotomy and occasionally by liver biopsy.

Biochemical tests. These are very useful in screening patients for tuberculosis of the liver. A highly suggestive pattern is that of a raised serum-alkaline-phosphatase level in the presence of a normal serum bilirubin or a moderate or markedly raised serum-alkaline-phosphatase with only mild hyperbilirubinaemia. In group A there were 11 of 25 (44%) cases with such a combination of findings and 5 out of 8 (75·5%) in group B. The majority (10 out of 11) of these cases in group A and 1 case in group B were diagnosed on liver biopsy. The average serum-alkaline-phosphatase in group A was 43·8 K-A units and 32·3 K-A units in group B. It is concluded therefore, that whereas local tuberculosis of the liver causes a more consistently raised serum-alkaline-phosphatase than miliary hepatic tuberculosis, the higher levels are not usually associated with the larger granulomata on liver biopsy. It is possible that these specimens were not representative, the needle missing the larger tuberculous lesions. Furthermore, high alkaline-phosphatase levels may be a measure of the extent of the granulomata, rather than the size of the individual lesions in some cases.

The cause of the raised alkaline phosphatase in the presence of a normal bilirubin has not been satisfactorily explained and has been observed experimentally by ligation of a portion of the intrahepatic bile ducts.[54] The degree of obstruction caused by the tuberculous lesion determines whether the test will be revealing and hence a normal test does not exclude hepatic disease.

These biochemical findings are not specific for hepatic tuberculosis, but may occur in other 'space-occupying lesions within the liver'[54] such as metastatic carcinoma, liver abscess, echinococcosis, amyloidosis, granulomata of varying aetiology and also in active cirrhosis.[55] Serum-alkaline-phosphatase levels may drop with improvement in the clinical condition, as in 1 case where the level dropped from 200 to 98 K-A units in 10 months and another from 96 to 17 K-A units in 2 years. In none of these cases was bone tuberculosis detected clinically or radiologically and this was not thought to be a factor in the production of the raised serum-alkaline-phosphatase levels.

The bromsulphalein test (BSP) will also show biliary obstruction before a rise in serum bilirubin, as it is a loading test which is a sensitive index of hepatic function and excretory ability. Too few BSP tests were done in this study to draw any conclusions. Korn *et al.*[5] demonstrated impaired BSP excretion in 85·7% of 50 cases of extrapulmonary tuberculosis and a raised serum-alkaline-phosphatase in 40·9%. Hyperbilirubinaemia was present in 25% of these cases, 3 of which were clinically jaundiced. Using both the serum-alkaline-phosphatase estimation and BSP test in combination, Brem[54] showed abnormality of at least 1 test in 100% of 13 non-icteric cases with intrahepatic lesions.

Serum-albumin levels were consistently low in the present cases (94·5%) and the serum globulin was raised in 48·6%. Korn *et al.*[5] found hypoalbuminaemia in 50% and hyperglobulinaemia in 75% of their cases. In the present study the prothrombin index was below 80% in 60% of cases. Hypoprothrombinaemia has been noted in 30% of patients with chronic pulmonary tuberculosis.[56] According to Seife *et al.*[14] subnormal cholesterol levels closely parallel the clinical course of pulmonary tuberculosis and may be due to malnutrition. As a diagnostic test in hepatic tuberculosis it is of very limited value.

Liver biopsy by needle biopsy or laparotomy is the most reliable method of diagnosing hepatic tuberculosis. A positive specimen is most likely to be obtained where preliminary biochemical tests have shown partial biliary obstruction and particularly in cases of acute disseminated miliary tuberculosis. Of the cases diagnosed on liver biopsy, 20 of the 29 were found in the final 2 years of this study owing to increased awareness of the condition. The 2 main indications for liver biopsy were pyrexia of unknown origin and hepatomegaly or hepatosplenomegaly of uncertain cause. In 9 cases there was no pulmonary or extrahepatic evidence of tuberculosis. In a further 3 cases there was no evidence of pulmonary tuberculosis, but hilar glands, epididymal thickening and peritonitis respectively, lent support to the tuberculous aetiology. Pulmonary disease and hepatomegaly or hepatosplenomegaly were present in 10 additional cases, but no definite diagnosis had been made. In the remaining 7 cases with pulmonary disease, positive sputa for tubercle bacilli were obtained and the biopsies were performed to exclude cirrhosis, carcinoma, amoebiasis and other concomitant liver diseases. The finding of fatty metamorphosis on liver biopsy necessitates the exclusion of a tuberculous infection especially pulmonary, intestinal or hepatic. A negative needle biopsy of the liver does not exclude hepatic tuberculosis and where the condition is strongly suspected the diagnosis may be confirmed on liver biopsy performed at laparotomy.

Radiology. Hepatic calcification on straight X-ray of the abdomen may aid diagnosis[57] and was present in 2 of the present cases (Fig. 3).

DIFFERENTIAL DIAGNOSIS

Tuberculosis of the liver may present as 'PUO', or closely resemble other diseases affecting the liver, notably cirrhosis, carcinoma, amoebic hepatitis and liver abscess. In the absence of associated stigmata such as palmar erythema, spider naevi, caput medusae and oesophageal varices, it is especially difficult to determine whether a patient has cirrhosis of the liver or hepatic tuberculosis. Ascites may be a sign of cirrhosis or tuberculous peritonitis. Hepatomegaly or hepatosplenomegaly due to tuberculosis of the liver may simulate carcinoma of the liver, especially as splenomegaly is often present in the latter condition, because of pre-existing cirrhosis with portal hypertension. Tuberculosis of the gastro-intestinal tract with diarrhoea or dysentery and tender hepatomegaly may mimic amoebic colitis with complicating liver involvement. A detailed account of the differential diagnosis of hepatic tuberculosis is discussed in a separate paper.[58]

SUMMARY

200 cases of hepatic tuberculosis, 57 in children under the age of 11 years and 143 in adults, have been studied in South African non-Whites. The age, sex, clinical presentation, pathology, diagnosis and differential diagnosis were studied in the adults, whereas only the age, incidence and pathology were noted in the paediatric cases.

Only miliary tuberculosis of the liver was found in the paediatric cases whereas 86% of the adult cases were miliary (group A) and 14% local hepatic tuberculosis (group B). The diagnosis was confirmed on liver biopsy in 29 cases and at autopsy in 171.

The commonest sites of dissemination of tuberculosis to the liver in order of frequency were lymph nodes and the lungs. So-called 'primary hepatic tuberculosis' was seen in 3 cases.

Fatty metamorphosis of the liver commonly accompanied hepatic tuberculosis and this finding on liver biopsy necessitates the exclusion of a tuberculous infection particularly intestinal, pulmonary and hepatic. That tuberculosis of the liver is a cause of cirrhosis has not been substantiated by this study.

Miliary tuberculosis may present in 4 clinical forms: typhoid, pulmonary, meningeal and hepatic. Mixed forms are common.

The average age in group A was 46 years and 44 years in group B. In both groups about a half of the cases presented with abdominal pain unrelated to meals and mainly in the upper abdomen and in the remainder of the cases there was a disturbance in bowel habit, particularly diarrhoea.

Hepatomegaly occurred in 71% of cases in group A and in 95% in group B and was associated with tenderness on palpation in about half of the cases in both groups. Splenomegaly was found in about one-third of cases in group A and in about a half in group B.

Clinically jaundice was present in 13% and 30% of groups A and B respectively. Haemolysis contributed to the jaundice in 3 miliary cases. Tuberculous glands in the porta hepatis were usually associated with the higher bilirubin levels, but not necessarily so. Local hepatic tuberculosis more commonly caused jaundice than miliary tuberculosis of the liver. Jaundice appearing during the course of hepatic tuberculosis was of poor prognostic significance.

The combination of a raised serum-alkaline-phosphatase level in the presence of a normal serum bilirubin or of moderate or marked elevation of serum-alkaline phosphatase with mild hyperbilirubinaemia is suggestive of hepatic tuberculosis and was observed in 44% of cases in group A and in 75·5% of cases in group B. Whereas in local hepatic tuberculosis serum-alkaline-phosphatase levels were more consistently raised than in miliary hepatic tuberculosis, the height of the level may have been a measure of the extent and/or size of the lesions.

Hypoalbuminaemia, hyperglobulinaemia and hypoprothrombinaemia were common findings in tuberculosis of the liver.

Liver biopsy is essential for the diagnosis of hepatic tuberculosis and the main indications for its use were pyrexia of unknown origin and hepatomegaly of uncertain cause. The need for liver biopsy was borne out by the finding that approximately one-third of cases in group A and one-quarter in group B had no symptoms or signs or radiological evidence of pulmonary tuberculosis. Furthermore, of the 29 cases diagnosed on liver biopsy, 9 had no clinical or radiological evidence of pulmonary or extrahepatic tuberculosis.

Hepatic tuberculosis may present as 'PUO' or closely simulate cirrhosis, carcinoma of the liver, amoebic hepatitis or liver abscess.

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