

## DIAGNOSTIC PROBLEMS IN HEPATIC TUBERCULOSIS

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Before the introduction of streptomycin, tuberculosis of the liver was usually fatal within 12 months,<sup>1</sup> but today a reasonably good prognosis may be expected with early and adequate antituberculous therapy. The purpose of this paper is therefore to stress the importance of hepatic tuberculosis and to discuss the difficulties which may arise in differentiating this condition from other diseases of the liver and bile ducts, and pyrexias of unknown cause.

## METHODS AND MATERIAL

From a series of 143 adult non-Whites with hepatic tuberculosis studied at Baragwanath Hospital and reported separately,<sup>2</sup> 11 Bantu cases have been selected to illustrate various aspects of the differential diagnosis. There were 9 males and 2 females in the group. Six cases were diagnosed on needle biopsy of the liver, 1 at laparotomy and 4 at autopsy. Miliary tuberculosis was present in 9 cases and local tuberculosis in 2. The histological features of tuberculosis were present in all cases. In 5 instances tubercle bacilli were demonstrated in the liver by Ziehl-Neelsen staining; in 2 no special stain was made of the liver sections but sputa were positive; in 1 a positive sputum was associated with a negative liver stain; in 1 a rectal biopsy was positive whereas the liver was negative; and in 2 cases no tubercle bacilli were demonstrated in the liver or sputa.

Results of liver flocculation tests have been omitted from the case reports as normal Bantu subjects show abnormal values due to an unexplained reversal of the albumin:globulin ratio. Serum proteins have been included, as normal values for Bantu have been calculated.<sup>3</sup>

To avoid repetition in the case reports, wherever antituberculous therapy has been mentioned, this refers to daily intramuscular injections of 1 G of streptomycin sulphate, the oral administration of 200 mg. of isoniazid *t.d.s.* and 4 G of PAS *t.d.s.*

The following are brief representative case descriptions illustrating various difficulties in differential diagnosis.

## CASE REPORTS

## A. Tuberculosis of the Liver and Cirrhosis of the Liver

## Case 1

T.M., a 45-year-old Bantu male, was admitted on 11 August 1959 complaining of vomiting of blood for 2 weeks. He had been coughing white sputum, occasionally blood-streaked, for the previous 2 months. There was no history of night sweats or weight loss or of previous tuberculosis. *On examination* he was a well-nourished male, afebrile, with a pulse rate of 72/min., and BP of 150/100 mm.Hg. The only positive findings were a tender enlarged liver (4 fingerbreadths) and splenomegaly. Two days after admission he had a small haematemesis, but his clinical condition remained good.

*Investigations.* Hb was 17.4 G/100 ml.; WBC 4,200 per cu.mm.; PI index 95%; serum bilirubin 0.7 mg./100 ml.; alkaline phosphatase 8.3 King-Armstrong units (K-A units); bromsulphalein retention 45% after 45 minutes; and total serum proteins 8.2 G per 100 ml., of which 3.7 G was albumin and 4.5 G globulin. X-ray of the chest, barium swallow and barium meal were all normal and 3 sputa were negative for tubercle bacilli. A liver biopsy performed on 22 August 1959

showed numerous epithelioid-cell granulomata. Tubercle bacilli were detected on Ziehl-Neelsen staining. On 27 August 1959 antituberculous therapy was begun and he was discharged to a clinic for further treatment. No follow-up was obtained.

*Comment.* A clinical diagnosis of cirrhosis of the liver with bleeding oesophageal varices was made in this case. Investigations revealed no evidence of extrahepatic tuberculosis, despite the history of haemoptysis.

## Case 2.

J.M., aged 60 years, was admitted on 28 April 1961 complaining of a cough productive of clear sputum for years, a dull pain in the upper abdomen, not related to meals, and occasional swelling of the ankles for 3 months. *On examination* the positive features were pyrexia of 100°F, evidence of weight loss and a tender, smooth liver edge, palpable 3 fingerbreadths below the right costal margin.

*Investigations.* Hb was 9.5 G/100 ml.; MCHC 29%; ESR (Wintrobe) 37 mm. in 1 hour; Widal was negative; serum bilirubin less than 1 mg./100 ml.; total serum proteins 5.5 G/100 ml.; of which 3.2 G was albumin and 2.6 G globulin, serum alkaline phosphatase 8 K-A units, PI 75% and the bromsulphalein retention after 45 minutes was 75%. X-ray of the chest was normal. Oesophageal varices were reported as probably being present on barium swallow. Tissue obtained on liver biopsy showed several areas of caseous necrosis and epithelioid-cell granulomata but no evidence of cirrhosis. On appropriate staining, tubercle bacilli were demonstrated. The patient responded well to antituberculous therapy and was discharged on 2 June 1961, to continue treatment at a clinic.

*Comment.* The hypochromic anaemia, hepatomegaly, hypoprothrombinaemia and report of oesophageal varices on barium swallow were suggestive of cirrhosis of the liver. There was no clinical or radiological evidence of extrahepatic tuberculosis.

## Case 3

G.K., a 30-year-old Bantu male, was admitted on 3 August 1956 complaining of weakness, loss of appetite and a cough productive of white sputum for 2 months. For the past month he had experienced a continuous burning pain in the right hypochondrium. *On examination* he was wasted and jaundiced with a pyrexia of 103°F, pulse rate of 132/min. and BP of 110/70 mm.Hg. A tender, smooth liver edge was palpable 3 fingerbreadths below the right costal margin and the spleen was palpable. Urine examination revealed bile and an excess of urobilin.

*Investigations.* Hb was 14 G/100 ml.; WBC 7,600 per cu.mm.; alkaline phosphatase 53 K-A units; total serum bilirubin 13.8 mg./100 ml., of which 12.6 mg. was direct and 1.2 mg. indirect; and the PI 62%. X-ray of the chest was normal and 2 sputa for tubercle bacilli were negative.

On 6 August 1956 the patient had an episode of epistaxis, and the antituberculous therapy together with intramuscular vitamin K and steroids were administered. There was little response and the patient died 2 weeks later.

*At postmortem examination,* tuberculous hilar lymphadenitis, local tuberculosis of the spleen and miliary tuberculosis of the lungs, liver and kidney were found. On microscopy of the liver, miliary caseous granulomata were observed and tubercle bacilli were present on Ziehl-Neelsen staining.

*Comment.* Hepatosplenomegaly, jaundice, pyrexia, epistaxis with a low PI and an excess of urobilin and bilirubin in the urine all pointed to cirrhosis of the liver as the diagnosis. The negative X-ray of the chest and the absence of extrahepatic signs of tuberculosis, made the diagnosis of hepatic tuberculosis especially difficult. Antituberculous therapy was instituted in this case because of the frequency of hepatic tuberculosis in this hospital, rather than on any distinctive clinical features. The diagnosis could only have been made confidently on liver biopsy, which was not performed because

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of the extreme jaundice. It is interesting to note the finding of miliary tuberculosis in the lungs at autopsy, although the chest X-ray was normal.

#### Case 4

A.S., a 41-year-old Bantu female, was admitted on 23 March 1960 with a history of swelling of the ankles, occasional vomiting, constipation and yellowness of the eyes for 2 months. She complained of fainting attacks for 2 days before admission. Five years previously she had suffered from a chest complaint, but had been free of symptoms for the past 2 years. For 4 years she had been a heavy drinker. *On examination* there was anaemia and jaundice, a temperature of 99.6°F, and BP of 80/60 mm.Hg. Signs of a right pleural effusion were present and crepitations were heard throughout both lung fields. Enlarged axillary and inguinal glands were present and there was minimal pitting oedema of both ankles. A firm, tender liver edge was felt only in the epigastrium and the spleen was just palpable.

*Investigations.* Hb was 10.2 G/100 ml.; WBC 7,300 per cu.mm.; serum bilirubin 2.3 mg./100 ml., of which 1.5 mg. was direct and 0.8 mg. indirect, alkaline phosphatase 13.8 K-A units, total serum protein 6.2 G/100 ml., of which 1.0 G was albumin and 5.2 G globulin and the PI was 53%. A chest X-ray showed marked elevation of both diaphragms, a right pleural effusion and widespread patchy shadowing in both lung fields. Two sputa were positive for tubercle bacilli. On 25 March 1960 the jaundice increased, purpuric spots appeared on the abdomen and a flapping tremor was noted. Antituberculous therapy was commenced and the patient lapsed into coma on 2 April 1960, with continuous twitching of the left arm. Tuberculous meningitis was suspected, but the CSF was normal.

*Postmortem examination* showed bilateral caseous tuberculosis of the lungs, a right pleural effusion and generalized tuberculous lymphadenitis. In addition the lungs, liver and spleen were the seat of a miliary spread. Sections were not stained for tubercle bacilli.

*Comment.* Generalized tuberculosis and cirrhosis with liver failure were suspected in this case, but autopsy revealed no evidence of cirrhosis.

#### Case 5

S.Q., a 49-year-old Bantu male, admitted on 26 April 1957, complained of generalized abdominal pain with frequent stools containing blood and mucus and a non-productive cough for 3 weeks. He was a heavy drinker up till the time of his illness. *On examination* the positive features were pyrexia of 99°F,

emaciation, jaundice, clubbing, ascites, atrophic testes, ankle oedema and an enlarged firm liver, palpable 2 fingerbreadths below the right costal margin.

*Investigations.* Hb was 16.2 G/100 ml.; WBC 9,600 per cu.mm.; serum bilirubin 5.2 mg./100 ml.; of which 4.8 mg. was direct and 0.4 mg. indirect; and the PI was 48%. The Widal test was negative; *B. typhosus* was not isolated from bile cultures, a fresh bed-pan stool was negative for amoebae and no pathogens were found on stool culture. X-ray of the chest showed miliary mottling throughout both lung fields. Peritoneal paracentesis yielded blood-stained fluid, and treatment with intravenous fluids, vitamin K and antituberculous therapy was begun. The patient became comatose on 29 April 1957 and a blood-sugar estimation at that time was 60 mg./100 ml. and his CSF was normal. Death occurred after 3 days of coma, a large bed sore developing over the sacrum, terminally.

*Autopsy finding.* Tuberculous peritonitis of the plastic type, miliary tuberculosis of the liver, tuberculous tracheo-bronchial and hilar lymph nodes and a nodular hyperplastic cirrhosis were present at autopsy. Sections were not stained for tubercle bacilli.

*Comment.* Evidence of pulmonary and peritoneal tuberculosis, together with jaundice, hepatomegaly, atrophic testes, ankle oedema, clubbing and terminal coma with a normal CSF suggested the possibility of both cirrhosis and hepatic tuberculosis in this case.

### B. Tuberculosis of the Liver and Liver Abscess

#### Case 6

K.N., a 42-year-old Bantu male, was admitted on 7 April 1960 with a history of dysentery and weight loss for 2 months and a pleuritic pain in the right chest with a cough, productive of sputum mixed with blood for 2 days. *On examination* he was somewhat thin and dyspnoeic, the temperature was 103°F, pulse rate 132/min. and BP 135/95 mm.Hg. There were signs of consolidation at the right base and the liver was 3 fingerbreadths enlarged and extremely tender. On proctoscopy a large ulcer was observed on the posterior wall of the rectum and a biopsy specimen was taken from this site.

*Investigations.* The Hb was 13.1 G/100 ml.; WBC 4,200 per cu.mm.; total serum bilirubin 0.6 mg./100 ml.; alkaline phosphatase 8 K-A units; PI 100%; repeated stool examinations for parasites were negative and sputa examinations for tubercle bacilli were negative on 2 occasions. X-ray of the chest on 8 April 1960 (Fig. 1) showed consolidation at the right base with early breakdown, and fluoroscopy showed a raised immobile right diaphragm.

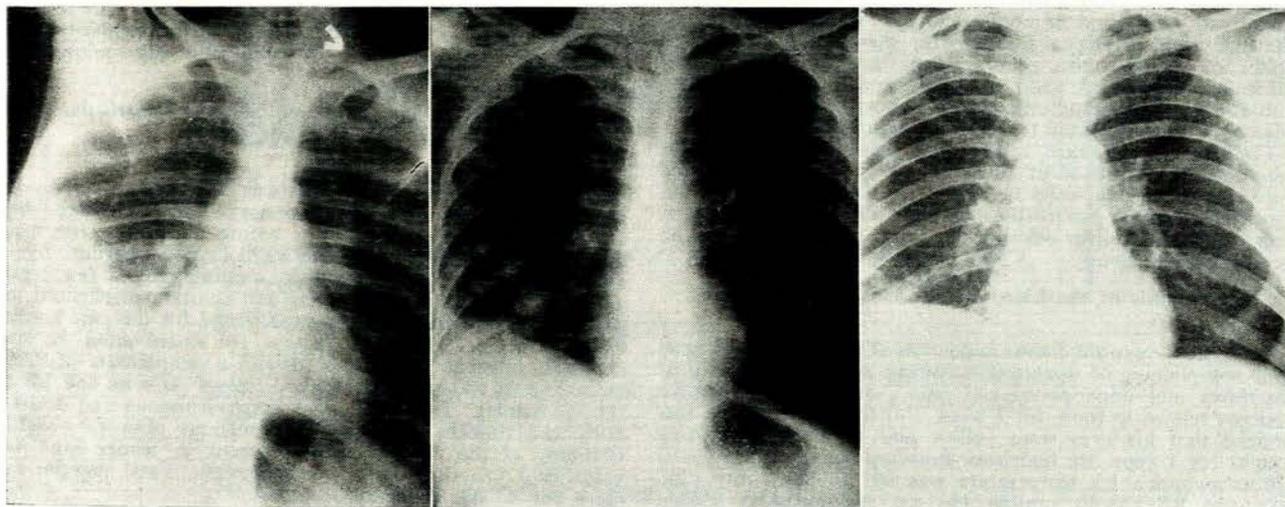


Fig. 1.

Fig. 2.

Fig. 3.

Fig. 1. Case 6. X-ray of chest on 8 April 1960, showing consolidation at the right base with early breakdown. Fig. 2. Same Case. X-ray of chest on 20 April 1960, showing elevation of the right diaphragm and a lung abscess in the right lower lobe. Fig. 3. Same Case. X-ray of chest on 1 June 1960, showing residual scarring at the right base.

**Progress.** A diagnosis of amoebic colitis, and liver abscess with extension into the right lung was made and treatment with emetine hydrochloride, tetracycline and diodoquin commenced. A week after admission, the report on the rectal biopsy was received, epithelioid granulomata together with numerous tubercle bacilli being found. The liver was needed to exclude an amoebic abscess but no pus was obtained. At the same time a biopsy of the liver was taken. Anti-amoebic therapy was stopped and antituberculous therapy substituted. The liver biopsy showed epithelioid-cell granulomata, giant cells of the Langhans type, but no tubercle bacilli. On 20 April 1960 repeat X-ray examination of the chest showed an abscess cavity in the posterior segment of the right lower lobe, with the elevation of the right diaphragm persisting (Fig. 2). By 28 April 1960 the liver tenderness, dysentery and pyrexia had all settled and he was transferred to a hospital for tuberculous. One month later his chest X-ray showed residual scarring at the right base (Fig. 3) and 4 months later he had gained 12 lb. in weight and was discharged to continue anti-tuberculous therapy as an outpatient.

**Comment.** Clinically, this case was virtually indistinguishable from amoebiasis, the diagnosis of hepatic tuberculosis first being suggested on rectal biopsy and confirmed on liver biopsy.

#### Case 7

S.N., a 29-year-old Bantu female, was admitted on 24 January 1959 with a history of weight loss, constipation, increasing abdominal pain and swelling and a cough productive of white sputum for 1 month. *On examination* the positive features were pyrexia of 103°F, a tender liver edge felt 3 fingerbreadths below the right costal margin, splenomegaly, ascites and crepitations at the right base. Paracentesis of the abdomen yielded heavily blood-stained fluid which was negative for tubercle bacilli and organisms on culture.

**Investigations.** Hb was 11.8 G/100 ml.; WBC 1,700 per cu.mm. (neutrophils 60%, monocytes 1%, lymphocytes 39%); platelet count 300,000 per cu.mm.; serum bilirubin 0.7 mg./100 ml.; serum alkaline phosphatase 22 K-A units; PI 74% and repeated stool examinations negative for parasites. Repeat white cell counts were 1,000 cu.mm. (1 week later) and 4,600 (3 weeks later). Sputa for tubercle bacilli were positive on 2 occasions and X-ray of the chest on 24 January 1959 showed bronchopneumonic changes in the right middle and lower zones with slight elevation of the right diaphragm. Repeat X-ray examination on 5 March 1959 showed an extensive opacity obscuring the right lower zone. In the lateral view the right diaphragm was seen to be markedly elevated, the appearance suggesting a liver abscess. On fluoroscopy, the right dome was raised and immobile and attempts at aspiration of the liver yielded no pus. Liver biopsy showed the presence of epithelioid granulomata, giant cells of the Langhans type, but no tubercle bacilli. A good clinical response was obtained on antituberculous therapy and the patient was discharged on 28 March 1959, to continue treatment as an outpatient.

**Comment.** Pulmonary tuberculosis was confirmed in this case and the presence of blood-stained peritoneal fluid and hepatosplenomegaly were suggestive of disseminated tuberculosis. The clinical picture together with radiological investigation pointed to a liver abscess, but this was not confirmed on needling of the liver.

#### C. Tuberculosis of the Liver and Carcinoma of the Liver

##### Case 8

W.F., a 42-year-old Bantu male, was admitted on 15 August 1960 complaining of weakness, numbness of the legs, vomiting, diarrhoea and upper-abdominal pain, which was cramp-like and not related to food, for 1 week. For the past month it was noticed that his eyes were yellow and he had been losing weight for 1 year. He had been drinking heavily for 4 years. *On examination* his temperature was 101°F, pulse rate 120/min. and BP 120/80 mm.Hg. He was malnourished, wasted and jaundiced. Crepitations were heard in the right axilla and a pleural rub over the left base. The liver was 3 fingerbreadths enlarged with an irregular, tender, firm mass in the left lobe. Moderate splenomegaly was present and signs of peripheral neuritis were noted in the legs.

**Investigations.** Hb was 17.5 G/100 ml.; WBC 9,500 per cu.mm.; PI 94%; total serum bilirubin 3.5 mg./100 ml., of which 2.2 mg. was direct and 1.3 mg. indirect; alkaline phosphatase 35.5 K-A units, total serum proteins 6.2 G/100 ml., of which 1.7 G was albumin and 4.5 G globulin, and the urine contained a moderate excess of urobilin and bilirubin. A chest X-ray showed a probable tuberculous lesion of doubtful activity at the right apex. Liver biopsy showed several epithelioid granulomata, 1 of which contained a Langhans-type giant cell. Although acid-fast bacilli were not observed, the features were suggestive of tuberculosis.

**Progress.** Antituberculous therapy was commenced and the patient was discharged on 24 September 1960, to continue further treatment as an outpatient. The hepatomegaly and hepatic mass were moderately decreased in size at that time. On 5 May 1961 the patient was seen again. The liver edge was just palpable and non-tender and the spleen impalpable. The serum bilirubin was 0.7 mg./100 ml.; alkaline phosphatase 8.6 K-A units; total serum protein 8.4 G/100 ml., of which 3.2 G was albumin and 5.2 G globulin. The X-ray of the chest was now clear.

**Comment.** The abdominal signs were highly suggestive of cirrhosis with superimposed hepatoma but the chest radiograph raised the suspicion of tuberculosis.

##### Case 9

G.N., a 34-year-old Bantu male, was admitted on 15 June 1955 with a 17 months' history of having noticed a hard epigastric mass which was intermittently painful. A month before admission he had suffered from diarrhoea, which cleared up after taking medicines given to him by a private doctor. *On examination* he was jaundiced with a temperature of 100°F, pulse rate of 92/min. and BP of 120/80 mm.Hg. The liver was enlarged to 2 fingerbreadths below the right costal margin with a nodular mass attached to the right lobe.

**Investigations.** Hb was 12.6 G/100 ml.; WBC 7,600/cu.mm.; total serum bilirubin 5.2 mg./100 ml.; and alkaline phosphatase 41 K-A units. X-ray of the chest was normal, but the straight X-ray of the abdomen showed a calcified opacity in the right hypochondrium. At laparotomy there was a mass measuring approximately 12 cm. in diameter in the liver, which was thought to be a primary carcinoma. Histological examination of the biopsy specimen revealed a large area of coagulative necrosis surrounded by endothelioid and chronic inflammatory cells (Fig. 4). The Ziehl-Neelsen stain was positive for tubercle bacilli. Antituberculous therapy was commenced and the patient was discharged on 15 July 1955, to continue treatment at a clinic. No follow-up was obtained.

**Comment.** The finding of a nodular mass in the liver was suggestive of a neoplasm and at laparotomy the clinical impression was believed to have been confirmed. No clinical or radiological evidence of extrahepatic tuberculosis was detected.

#### D. Tuberculosis of the Liver and Surgical Obstructive Jaundice

##### Case 10

I.N., a 27-year-old Bantu male, was admitted on 18 November 1960. He was a known pulmonary tuberculous, who had stopped his treatment 3 months before admission. His main complaint was of pain in the right hypochondrium for 3 months. Sometimes it was colicky, lasting only a few hours and at other times it was nagging and constant throughout the day. The cough which he had experienced for the past 5 years was still present but unproductive. *On examination*, he was cachectic, anaemic and jaundiced with a temperature of 99°F, pulse rate of 120/min., respiratory rate of 30/min. and BP of 100/70 mm.Hg. The lungs were emphysematous and crepitations and rhonchi were heard throughout both lung fields. Clubbing of the fingernails was present. A tender liver was palpable 4 fingerbreadths below the right costal margin, but there was no splenomegaly or ascites.

**Investigations.** Hb was 10.6 G/100 ml.; WBC 5,800/cu.mm.; ESR (Wintrobe) 36 mm. in 1 hour; PI 59%; total serum protein 4.7 G/100 ml., of which 2.1 G was albumin and 2.6 G globulin; total serum bilirubin 7.2 mg./100 ml., of which 5.8 mg. was direct and 1.4 mg. indirect; alkaline phosphatase

38 K-A units; and the urine contained bilirubin and urobilin. X-ray of the chest showed extensive patchy consolidation in the right middle and lower lobes and consolidation and cavitation in the left upper lobe. Sputa for tubercle bacilli were positive on 2 occasions. Despite antituberculous therapy and steroids, the patient died 4 days after admission.

*Postmortem examination* showed extensive bilateral pulmonary tuberculosis and foci of caseous tuberculosis up to 5 cm. in diameter in the liver (Fig. 5) and spleen. The lymph nodes

are lacking, needle biopsy of the liver is an essential investigation.

#### DISCUSSION

The 4 conditions most likely to cause difficulty in the differential diagnosis of hepatic tuberculosis are cirrhosis, carcinoma of the liver, liver abscess and 'PUO'.

When a patient with pulmonary or extrapulmonary tuberculosis presents with hepatomegaly or hepatosplenomegaly, it may be difficult if not impossible to determine whether this is due to cirrhosis, tuberculosis of the liver, or both conditions. That tuberculosis of the liver can cause cirrhosis has been stressed by some authors<sup>4-6</sup> and denied by others.<sup>7-10</sup> Hepatic tuberculosis and cirrhosis may both be accompanied by ascites, and then the possibility of tuberculous peritonitis must be borne in mind. Even when cirrhosis has been proved on liver biopsy, ascites should be investigated to exclude tuberculous peritonitis. Burack and Hollister<sup>11</sup> found a complicating tuberculous peritonitis in about 40% of cases with alcoholic cirrhosis.

Cases 1, 3 and 4 had hepatosplenomegaly and cases 2 and 5 hepatomegaly only. Additional features suggestive of cirrhosis were haematemesis in case 1; hypochromic anaemia, hypoprothrombinaemia and a report of oesophageal varices on barium swallow in case 2; jaundice and epistaxis in association with hypoprothrombinaemia in case 3; anaemia, jaundice, purpura, flapping tremor, ankle oedema, hypoprothrombinaemia and hypoalbuminaemia with terminal coma in case 4; and jaundice, clubbing, ascites, ankle oedema, atrophic testes, hypoprothrombinaemia and terminal coma in case 5. Cases 1-3 were diagnosed clinically as cirrhosis and cases 4 and 5 as hepatic tuberculosis plus cirrhosis, only case 5 having both conditions. In cases 1-3 there was no clinical or radiological evidence of extrahepatic tuberculosis. Liver biopsy was diagnostic in cases 1 and 2, but was not performed in case 3 because of marked jaundice. Autopsies were performed in cases 3-5. Antituberculous therapy was instituted following the liver biopsy reports in cases 1 and 2 and soon after admission in cases 4 and 5 owing to the presence of extrahepatic tuberculosis. Case 3 was treated empirically with antituberculous drugs, as hepatic tuberculosis could not be excluded. Sheldon<sup>12</sup> diagnosed cirrhosis in an 11-year-old boy with a nodular hepatomegaly, splenomegaly and jaundice, where postmortem examination showed tuberculous abscesses of the liver. Massive tuberculosis of the liver was found in Cruice's case,<sup>13</sup> where a clinical picture of hepatosplenomegaly, pyrexia, purpura and jaundice simulated cirrhosis with liver failure.

A history of dysentery and weight loss, the finding of pyrexia, tender hepatomegaly, rectal ulceration, right basal pulmonary consolidation with abscess formation and an immobile right diaphragm on fluoroscopy in case 6, illustrates how closely the clinical picture of amoebic colitis and liver abscess can be simulated by tuberculosis. This presentation is probably not uncommon in patients with tuberculous ulceration of the intestine as Bristowe<sup>14</sup> found that 7.2% of such cases had local tuberculosis of the liver at necropsy. Thayer<sup>15</sup> diagnosed amoebic colitis and liver abscess in a 49-year-old Coloured woman, who presented with pyrexia, dysentery and hepatomegaly. At autopsy tuberculous nodules measuring up to 1 cm. in diameter

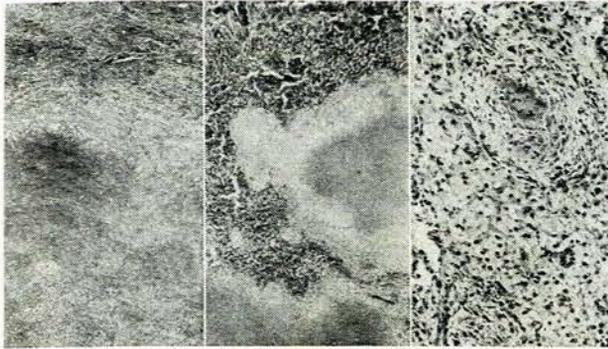


Fig. 4.

Fig. 5.

Fig. 6.

Fig. 4. Case 9. Section of hepatic tuberculoma biopsied at laparotomy. (H. & E. x 30.)

Fig. 5. Case 10. Caseous local tuberculosis of the liver. (H. & E. x 30.)

Fig. 6. Case 11. Section of liver biopsy showing 2 granulomata, 1 with central caseation. (H. & E. x 190.)

in the porta hepatis were markedly enlarged and caseous. Histological examination of the liver, spleen, lungs and lymph nodes confirmed the diagnosis of caseous tuberculosis. No Ziehl-Neelsen stains were performed.

*Comment.* A known pulmonary tuberculous presented with pain in the right hypochondrium and incomplete biliary obstruction. The chances were great that this was due to either hepatic tuberculosis, or glands in the porta hepatis, or both, but a surgical cause for the obstruction could not be excluded.

#### E. Tuberculosis of the Liver and Pyrexia of Unknown Origin Case 11

J.W., a 46-year-old Bantu male, was admitted on 27 August 1958 complaining of generalized joint pains, night sweats, constipation, headache and occasional cough, productive of white sputum for 3 weeks. On examination he was a well-nourished male with no anaemia, cyanosis or jaundice. His temperature was 103°F, pulse rate 80/min. and BP 110/70 mm.Hg. Scattered rhonchi were heard in both lungs and the liver was enlarged to 2 fingerbreadths below the costal margin, but was not tender. There was no objective evidence of arthritis.

*Investigations.* Hb was 13.4 G/100 ml.; WBC 11,800/cu.mm. (neutrophils 71%, monocytes 1% and lymphocytes 28%); ESR (Wintrobe) 32 mm. in 1 hour; PI 75%; serum bilirubin 1.1 mg./100 ml.; serum alkaline phosphatase 11 K-A units; malarial smears negative; blood and bile cultures negative; Widal, brucella and Weil-Felix agglutinations negative; Paul-Bunnell test negative; cerebrospinal fluid normal; stool examinations negative for parasites; chest X-ray normal; and 2 sputa were negative for tubercle bacilli. Liver biopsy showed epithelioid cell granulomata with central caseation (Fig. 6), Langhans-type giant cells and acid-fast bacilli on Ziehl-Neelsen staining. On 3 September 1958 antituberculous therapy was commenced and the patient was discharged to a clinic for further treatment on 22 October 1958, when he was afebrile and the liver still enlarged. No follow-up was obtained.

*Comment.* A tentative clinical diagnosis of typhoid fever was made in this case because of the history of headache and constipation, the finding of high temperature with relative bradycardia and rhonchi on auscultation of the chest, but investigations for typhoid were negative. In such a case of pyrexia of unknown origin, where signs of extrahepatic tuber-

were found in the liver. In case 7 the finding of a tender hepatomegaly and immobile right diaphragm on fluoroscopy raised the suspicion of a liver abscess. Extrahepatic tuberculosis was present in cases 6 (rectal) and 7 (pulmonary). In both instances liver biopsy was diagnostic and antituberculous therapy instituted.

Loss of weight, anorexia, nodular hepatomegaly, splenomegaly, jaundice and disproportionately raised alkaline phosphatase in comparison with the serum bilirubin<sup>16</sup> occur in both hepatic tuberculosis and carcinoma of the liver. Splenomegaly is commonly found in Bantu with carcinoma of the liver, due to the concomitant cirrhosis and portal hypertension. In case 8 the only clue to the diagnosis was a right apical shadow of doubtful activity on X-ray of the chest. There was no extrahepatic evidence of tuberculosis in case 9 and a hepatic tuberculoma was consequently macroscopically misdiagnosed as carcinoma at laparotomy, an error which has previously been reported.<sup>17</sup> Hepatic calcification, which was present in this case, may be found in carcinoma of the liver and in miliary or local hepatic tuberculosis. Other lesions which also calcify in the liver are hydatid cysts, lymphangiomas, haemangiomas, gummata and abscesses.<sup>18</sup> After the diagnosis was made on liver biopsy in cases 8 and 9, antituberculous therapy was instituted. Gold *et al.*<sup>19</sup> diagnosed gastro-intestinal malignancy with hepatic metastases in a 44-year-old Negro who presented with anorexia, weight loss, intermittent diarrhoea, jaundice and nodular hepatomegaly. Hepatic tuberculosis was found on liver biopsy.

A picture of obstructive jaundice in tuberculous may be caused by hepatic tuberculosis<sup>20</sup> or glands in the porta hepatis, or by an unrelated surgical condition or both, as in the cases of Maximowitsch (tuberculous liver abscess and chronic cholecystitis)<sup>17</sup> and De Crespigny and Cleland (tuberculosis of the liver and hydatid disease of the liver and gallbladder).<sup>21</sup> In case 10, pain in the right hypochondrium was accompanied by a moderate rise in the serum bilirubin and a high serum alkaline phosphatase, simulating surgical obstructive jaundice.

When there is no evidence of extrahepatic tuberculosis, hepatic tuberculosis can present as 'PUO' and often closely resembles typhoid fever as in case 11. Headache, cough, weakness, epistaxis, abdominal pain, change in bowel habits, pyrexia, depressed sensorium, jaundice, anaemia, rhonchi in the chest, hepatosplenomegaly and leukopenia are common to both conditions. The final diagnosis is made on blood culture and agglutination tests in typhoid and on liver biopsy (as in case 11) in hepatic tuberculosis. Herrell and Simpson<sup>22</sup> diagnosed a solitary tuberculoma at laparotomy, where 'PUO' had been present intermittently for 6 years. Diagnosis was made on liver biopsy by Mansuy and Seiferth<sup>23</sup> in 5 cases of miliary tuberculosis, where there was no radiological or bacteriological evidence of tuberculosis, pyrexia being the presenting feature in 2 of them.

#### General Features

The average age of the 11 cases described was 40 years. Only 1 patient was afebrile, the temperature ranging between 99 and 103°F, in the other 10. Hepatomegaly was present in all cases, 9 being tender and 2 non-tender. Splenomegaly was present in 5 cases and jaundice in 6.

The finding of a normal serum bilirubin with a raised serum alkaline phosphatase and/or abnormal bromsulphalein retention or mild hyperbilirubinaemia in the presence of moderate or marked elevation in the serum alkaline phosphatase is suggestive of hepatic tuberculosis or other 'space-occupying lesions within the liver'.<sup>16</sup> In cases 8 and 9, the serum bilirubins and alkaline phosphatases were 3.5 and 5.2 mg./100 ml., and 35.5 and 41 K-A units respectively; in cases 1 and 2, where the serum bilirubin and alkaline phosphatase levels were normal, abnormal degrees of bromsulphalein retention were present. In case 8 the biochemical abnormalities returned to normal after 9 months of antituberculous therapy. In 6 of the 11 cases there was radiological evidence of lung disease. Of these 6 cases, 3 showed active pulmonary tuberculosis confirmed on sputa examination (cases 4, 7 and 10), 1 had a lesion of doubtful activity with negative sputa (case 8), 1 had miliary tuberculosis with no sputa available (case 5) and in 1 a lung abscess was present with negative sputa (case 6). It is noteworthy that in 5 cases there was no clinical or radiological evidence of extrahepatic tuberculosis (cases 1, 2, 3, 9 and 11). Of the latter cases, liver biopsy was diagnostic in 4 and the remaining case was not biopsied because of marked jaundice. The need for liver biopsy as a diagnostic measure in all cases of unexplained hepatomegaly or fever is thus stressed.

#### SUMMARY

The 3 most important diseases of the liver which may be simulated by hepatic tuberculosis are cirrhosis, carcinoma of the liver and liver abscess.

Hepatic tuberculosis may present as 'PUO', or resemble surgical obstructive jaundice.

Eleven cases are described, illustrating various difficulties in differential diagnosis.

In 5 of the 11 cases there was no clinical or radiological evidence of extrahepatic tuberculosis. The need for liver biopsy in cases with unexplained hepatomegaly or pyrexia is therefore stressed.

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