and Mollin, 1957). Hawkins and Meynell (1958) did not find significantly low levels of serum vitamin B₁₂ in their patients. Lees (1961) noted that some patients developed low serum vitamin-B₁₂ levels, and he showed that the absorption of radioactive vitamin B₁₂ improved during treatment with folic acid. The finding of a significant lowering of the level of vitamin B₁₂ in our patients would confirm the suggestion of Lees that a functional change occurs in the gut wall, for in our cases there was no indication of a dietary deficiency in vitamin B₁₂. It is possible either that anticonvulsants affect the absorption of vitamin B₁₂ *per se* or that a deficiency of folic acid impairs vitamin-B₁₂ absorption.

Summary

Haematological studies on a randomly selected group of epileptic patients on anticonvulsants have demonstrated an incidence of macrocytosis in 11% and of low serum folic-acid levels in 37%. Compared with a group of normal control subjects these patients had significantly low levels of serum folic acid and some reduction in serum vitamin B₁₂. This study confirms that the primary cause of these phenomena is the anticonvulsant therapy, but comparison with previous surveys and with a group of less well nourished subjects suggests that

an adequate diet may protect against the occurrence of macrocytosis.

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Amoebiasis—a Diagnostic Problem in Great Britain

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Most clinicians working in a large hospital in this country are unlikely to see more than one or two cases of amoebiasis a year. Between 1938 and 1964 63 patients were given a course of treatment for amoebiasis at the Radcliffe Infirmary, Oxford. In only 19 of these was the diagnosis established by the demonstration of *Entamoeba histolytica* in the stools or in biopsy specimens, but in the remainder a therapeutic trial of amoebicidal drugs was thought to be justified on clinical grounds.

In some patients amoebiasis presents little difficulty in diagnosis, as there is a history of bloody diarrhoea contracted abroad. In others the diagnosis may be missed, either because it is not considered or because the clinical features are unusual.

The present report deals with two cases of amoebic colitis and six cases of hepatic or pleuropulmonary amoebiasis seen here in recent years, all of which were a problem in diagnosis. Two were fatal, and in four others surgical procedures were carried out before the diagnosis was made.

Case 1

A man aged 34 was first seen at the ulcerative colitis clinic in November 1960 with a six-months history of diarrhoea with blood. At sigmoidoscopy the mucosa was hyperaemic and granular and a barium-enema examination was compatible with a diagnosis of ulcerative colitis. He was treated with a nightly rectal infusion of hydrocortisone hemisuccinate 100 mg., and within two weeks symptoms had regressed. In November 1962 there was a recurrence of symptoms with similar appearances at sigmoidoscopy, and a further course of local corticosteroids was given—again with improvement.

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In September 1964 he was admitted to hospital as an emergency because of massive rectal haemorrhage and fainting after two weeks of diarrhoea. Sigmoidoscopy revealed mild but definite inflammation of the rectal mucosa, and treatment with systemic and local corticosteroids was begun. Barium-enema report (Dr. K. Lumsden): "There may be some inflammatory changes in the distal colon. . . . There is a constant filling defect in the caecum which appears to be due to an intraluminal mass of 'polypoid type'." A diagnosis of ulcerative colitis with a carcinoma of the caecum was made and a right hemicolectomy performed. There were several ulcers in the caecum (one of which perforated at the operation) and a mass of granulation tissue; microscopic examination showed deep ulceration with numerous *E. histolytica* in the lamina propria. A course of emetine hydrochloride by intramuscular injection was started on the sixth post-operative day and the corticosteroids were reduced, being finally stopped one week later. When questioned the patient said that he had served with the armed Forces in Burma from 1946 to 1948 but had not had an attack of dysentery at the time.

Sigmoidoscopy three weeks after starting emetine was normal, but three months later, when he was having some looseness of the stools, the mucosa was fragile; stool examination and rectal biopsy were negative for amoebae. In the nine months that have since elapsed he has had no further bowel symptoms.

Case 2

A man aged 56 was admitted to hospital as a surgical emergency in February 1964 with a history of abdominal pain for four weeks and watery diarrhoea without blood for five days. He had lost weight and was known to have had rheumatoid arthritis for 10 years, treated with phenylbutazone. Apart from a visit to Calais in 1946 he had not been abroad. There was generalized guarding of the abdomen with rebound tenderness, most marked in the left iliac fossa. At emergency laparotomy free fluid was found in the

peritoneal cavity; the colon was distended and appeared to be gangrenous. There were perforations in the sigmoid and transverse colon. A total colectomy and ileostomy was performed, but he died on the fifth day after operation. At necropsy there were pus in the peritoneal cavity, large ulcers in the stump of the sigmoid colon and rectum, and a single small abscess in the left lobe of the liver. Histological examination of sections of the large bowel taken at operation and at necropsy showed gross mucosal destruction with *E. histolytica* in the ulcerated areas.

This case of fulminating amoebic colitis in a patient who had not been in the tropics is most unusual and will be reported in detail elsewhere (D. Essenhigh and R. Carter, in preparation).

Case 3

A man aged 34 was admitted to hospital in December 1962 for investigation of pain in the right upper quadrant of the abdomen for six weeks, which radiated to the right shoulder-blade. He had lost nearly 2 stones (12.7 kg.) in weight, and had anorexia, nausea, and dark urine. He had been in the armed Forces in Egypt in 1947. There was tenderness under the right rib margin and fever (99.8° F.; 37.7° C.). Investigations two weeks before admission: Hb 11.2 g./100 ml.; plasma bilirubin 0.2 mg./100 ml.; alkaline phosphatase 13 K.A. units; flocculation tests negative. X-ray examination: raised right diaphragm was reduced movement on screening. Cholecystogram: no gall-bladder function.

A tentative diagnosis of cholecystitis was made and a laparotomy performed. An abscess on the superior aspect of the right lobe of the liver was found and "anchovy-sauce" pus aspirated. The gall-bladder was normal. The haemoglobin on the day after operation was 9.5 g./100 ml. Cysts of *E. histolytica* were observed in the stools, and a full course of emetine hydrochloride, chloroquine, di-iodohydroxyquinoline (Diodoquin), and tetracycline was given. He made a good recovery and no further aspirations were required.

Case 4

A man aged 30 who had arrived in this country from Pakistan 15 months previously was admitted to a medical ward in July 1963 for investigation of headache, fever, and malaise which he had noticed for two weeks. He ran an intermittent pyrexia up to 101° F. (38.3° C.) and there was tender enlargement of the liver to one to two fingerbreadths below the right costal margin. Investigations: Hb 13.5 g./100 ml.; W.B.C. 10,300/c.mm., neutrophil leucocytosis; E.S.R. 85 mm. X-ray examination: chest normal. Cholecystogram: no gall-bladder function. Liver-function tests: plasma bilirubin 0.3 mg./100 ml., alkaline phosphatase 14 K.A. units, S.G.P.T. 210. Plasma proteins: total 6.6 g./100 ml., albumin 3.5 g./100 ml. Liver biopsy unsuccessful.

The symptoms improved and the pyrexia settled after six weeks without specific treatment and he was discharged with the diagnosis of chronic cholecystitis. When seen as an out-patient he was well apart from tenderness over the liver, but he subsequently became pyrexial and was readmitted to hospital on 9 November. The liver was enlarged to four fingerbreadths below the right costal margin and was extremely tender, with bulging of the right lower chest laterally, intercostal tenderness, and a pericardial friction rub. Investigations: Hb 9.6 g./100 ml.; W.B.C. 12,100/c.mm., neutrophil leucocytosis. X-ray examination of chest: raised right diaphragm. Liver-function tests: plasma bilirubin 0.6 mg./100 ml., alkaline phosphatase 34 K.A. units, S.G.P.T. 48 units. Plasma proteins: total 7.7 g./100 ml., albumin 2.9 g./100 ml.

A diagnosis of amoebic liver abscess was made and 2 pints of pus aspirated through the lateral chest wall at the point of maximum intercostal tenderness. The liver shrank considerably and by the following day the pericardial friction rub was no longer audible and he was afebrile. A full course of emetine hydrochloride, chloroquine, di-iodohydroxyquinoline, and tetracycline was given and a further 400 ml. of pus aspirated 13 days after admission. He made a good recovery, and when seen one year later was well.

Case 5

A man aged 50 was admitted to hospital as an emergency in November 1963 with a four-months history of an influenza-like

illness with shivering, sweating, and pain under the right costal margin, which recently had radiated to the right shoulder. He had a dry cough and had lost 2½ stones (15.9 kg.) in weight. He had served with the armed Forces in South Africa and India from 1943 to 1945 but had not had dysentery.

While under observation in hospital he ran a pyrexia up to 102° F. (38.9° C.) with rigors and sweating. There was tender enlargement of the liver to three fingerbreadths beneath the right costal margin. Investigations: 9.9 g./100 ml.; E.S.R. 110 mm.; W.B.C. 13,000/c.mm.; alkaline phosphatase 31 and 46 K.A. units; serum bilirubin 0.2 mg./100 ml.; S.G.P.T. 21 units. X-ray examination of chest: markedly raised right diaphragm with pleural reaction. A liver biopsy was attempted and thick blood-stained fluid aspirated. The needle was withdrawn. Twelve hours later signs of peritonitis developed and a laparotomy revealed a diffuse odourless turbid peritonitis, which was drained.

A diagnosis of amoebic liver abscess was made and a course of emetine hydrochloride, chloroquine, and di-iodohydroxyquinoline with penicillin and streptomycin given. One month later 700 ml. of "anchovy-sauce" pus was aspirated through the right lower chest and the liver decreased considerably in size. He made an uneventful recovery and has remained well since.

Case 6

A man aged 67 was admitted to hospital in May 1957 with a five-months history of pain in the right chest and upper abdomen; loss of weight 2½ stones (15.9 kg.). He had served abroad in the first world war. On examination he looked ill and was febrile (100° F.; 37.8° C.), with marked tenderness in the right hypochondrium and an enlarged liver. Investigations: Hb 14.5 g./100 ml.; W.B.C. 17,500/c.mm., neutrophil leucocytosis. X-ray examination: raised right diaphragm. Cholecystogram: no gall-bladder function. Bronchoscopy: normal. Plasma bilirubin 0.3 mg./100 ml.; alkaline phosphatase 13 K.A. units. Plasma proteins: total 7.1 g./100 ml., albumin 2.1 g./100 ml.

A definite diagnosis was not established, but it was assumed that he had secondary carcinomatous deposits in the liver. There was steady deterioration in his condition, with coma and death one month after admission. At necropsy the liver weighed 3,500 g., was fluctuant, and consisted of a small margin of hepatic tissue around a huge abscess. The gall-bladder was natural. A diagnosis of a pyogenic abscess of the liver was made but no source of infection found.

Because of the clinical resemblance to the cases reported above, histological sections of the wall of the abscess were examined again and numerous *E. histolytica* were seen, which stained strongly with periodic acid Schiff.

Case 7

A man aged 33 was admitted to hospital in April 1959 with a history of fever, headache, and rigors for three months, and pains under both costal margins and at the right shoulder-tip aggravated by deep-breathing for three days. He had never been abroad. There was slight tenderness over the liver, diminished air entry, with crepitations at the right base and fever (100.8° F.; 38.2° C.). Investigations: Hb 13.2 g./100 ml.; W.B.C. 14,000/c.mm., neutrophil leucocytosis. X-ray examination of chest: some increased markings just above the right costophrenic angle. Cholecystogram: no gall-bladder function. Plasma bilirubin 0.7 mg./100 ml., flocculation tests negative. Repeated examination of fresh stools for parasites were negative. Liver biopsy: foci of lymphocytes and small numbers of eosinophils.

He continued to run a fever, at times with rigors, despite treatment with oxytetracycline 1 g. daily, and was extensively investigated. In the seventh week after admission his temperature rose to 104° F. (40° C.). He coughed up odourless purulent sputum described as having the appearance of anchovy sauce, and a chest x-ray film showed a lung abscess at the right base occupying most of the lower lobe, which was collapsed. Hb 10.8 g./100 ml., W.B.C. 23,000/c.mm. Treatment with emetine hydrochloride 1 gr. (65 mg.) daily intramuscularly was begun. The temperature fell within 48 hours and by the end of the week he was afebrile. Chloroquine was given in addition and he made a good recovery. Ulceration of the rectum was found at sigmoidoscopy during convalescence but amoebae were not seen.

Case 8

A man aged 47 was admitted to hospital in February 1961, having had a febrile illness for three weeks with right-sided chest pain aggravated by breathing and a cough productive of thick blood-stained sputum for three days. He had served in North Africa during the second world war but had not had dysentery. On examination he looked ill, was confused, breathless, and cyanosed, and had a temperature of 102° F. (38.9° C.). Diminished air entry, dullness to percussion, bronchial breathing, and crepitations at the right base were present. A portable chest x-ray film showed collapse and consolidation at the right base. A diagnosis of right basal pneumonia was made. Treatment with intramuscular penicillin and streptomycin was begun, but at the end of a week he was still very ill with a high fever. The chest was aspirated and 13 oz. (270 ml.) of reddish-brown fluid obtained. Amoebae were found in a warm specimen of sputum examined under a microscope. He was treated with emetine hydrochloride intramuscularly, and within 72 hours the temperature settled.

Investigations: Hb 12.1 g./100 ml.; W.B.C. 10,000/c.mm.; E.S.R. 73 mm. Plasma bilirubin 0.2 mg./100 ml., alkaline phosphatase 19 K.A. units, S.G.P.T. 66 units. X-ray examination of chest: raised right diaphragm and pleural effusion. His temperature settled, but convalescence was complicated by a pulmonary embolus.

Discussion

The present report emphasizes some of the difficulties which may be encountered in the diagnosis of amoebiasis in this country. The serious consequences of delay in diagnosis are apparent from the fact that two patients died and four had surgical operations before the diagnosis was made.

In Case 1 the symptoms of amoebic colitis were severe despite a prolonged latent period of nearly 20 years since infection, and perforation of the colon was imminent at the time of operation. The second patient had never visited an endemic area but presented with fulminating amoebic colitis, from which he died. Though the majority of patients with amoebic colitis seen at this hospital give a history of a recent visit to an endemic area, severe and even fatal disease may occasionally occur in the absence of such a history. The factors influencing invasiveness of amoebae are poorly understood (Wilmot, 1962), but it is possible that corticosteroid treatment (Mody, 1959; McAllister, 1962), as in Case 1, and chronic rheumatoid arthritis or its treatment with phenylbutazone, as in Case 2, may have pre-disposed to the development of severe infection.

None of the patients with hepatic or pleuropulmonary amoebiasis gave a history of dysentery. One (Case 7) had never been abroad, and with the exception of Case 4 the time interval since infection was over 15 years in the remainder. Hepatic amoebiasis in the absence of intestinal symptoms and a prolonged interval since the time of infection are well recognized (Manson-Bahr, 1943; Paulley, 1961; Wilmot, 1962), and amoebic abscess of the liver or lung has previously been noted in patients who have never lived in an endemic area (Saundby and Miller, 1909; Conan *et al.*, 1950; Paulley, 1961).

The first patient was seen repeatedly over a period of three years with sigmoidoscopic appearances which were indistinguishable from those seen in haemorrhagic proctitis. Though it is possible that this patient had both disorders, it underlines the difficulty which experienced observers may have in distinguishing amoebic colitis from ulcerative colitis or Crohn's disease of the colon and supports the suggestion of McAllister (1962) that biopsy and stool specimens should be taken from all cases of idiopathic ulcerative colitis and examined for *E. histolytica*.

Though the absence of a history of recent exposure to infection in an endemic area makes the diagnosis of a sporadic case of hepatic or pleuropulmonary amoebiasis difficult, certain well-recognized clinical features of the disease are usually present. Pain over the liver, often referred to the right shoulder, fever, malaise, and loss of weight were present in all the cases

reported here. A normocytic normochromic anaemia was often found in the more chronic cases, a feature emphasized by Lamont and Pooler (1958), and leucocytosis was not invariable. A markedly raised E.S.R. was usual. Elevation of the right diaphragm was seen on x-ray films of the chest in all the patients with liver abscess and is an important sign which should lead to the diagnosis being suspected (Lamont and Pooler, 1958), but was absent initially in Case 4. Failure of gall-bladder function assessed by cholecystography was a further radiological sign which was observed in all four patients in whom the investigation was done, and sometimes led to the erroneous diagnosis of cholecystitis. The plasma alkaline-phosphatase level was raised above the upper limit of normal of 13 King-Armstrong units in several of the cases reported here. A raised plasma alkaline phosphatase in association with a normal plasma bilirubin and normal or moderate elevation of the S.G.P.T. may be of value in arousing suspicion of a space-occupying lesion in the liver, but the extent to which tests of hepatic function are disturbed in liver abscess is variable and the pattern is not diagnostic (Brem, 1955; Powell, 1959).

Cases 7 and 8 failed to respond to treatment with antibiotics for right basal pneumonia, and pleuropulmonary amoebiasis was suspected when dark blood-stained pus was coughed up or aspirated from the chest. Both showed features which suggest that the chest pathology followed the rupture of an amoebic liver abscess through the diaphragm.

Though the clinical features of amoebic abscess of the liver and lung may be sufficiently characteristic to warrant the use of amoebicidal drugs without demonstrating the parasite, early diagnosis rather than a diagnosis by exclusion or by chance is necessary to avoid considerable morbidity or death. In search of a method of early diagnosis attempts have been made to develop serological tests for infection with *E. histolytica*, but these have been hampered by technical difficulties, particularly in producing a pure antigen. In a recent report a high incidence of positive reactions was obtained with sera from patients with invasive amoebiasis by means of a gel-diffusion technique, whereas the incidence was extremely low among healthy controls in a non-endemic area (Maddison *et al.*, 1965a, 1965b). It is possible that serological tests may be helpful in the early diagnosis of sporadic cases of amoebiasis, the need for which is emphasized by the present report.

Summary

Two cases of amoebic colitis and six cases of hepatic or pleuropulmonary amoebiasis are described to illustrate the problems which may arise in the diagnosis of the condition in a general hospital in this country.

In two patients the diagnosis was made after death and in three others after surgical operations. Clinical features which may be of value in diagnosis are briefly discussed.

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