or chronic—for example, mongolism, endocrine disorders, hyperchlorhydria, chronic mastitis, chronic bronchitis, etc.

In spite of their non-specificity all precipitating events have one thing in common: they represent conditions of "cell stress" and therefore tend to reveal latent defects in organs or systems derived from abnormal genes.

Prezygotic cancers fall into two groups, depending upon whether the original mutation has occurred in a parental germ cell (*first-generation cases*) or in a more remote ancestral cell (*pedigree cases*). In first-generation cases there will be no previous family history of the cell-specific cancer or congenital defect, but the descendants of these cases may be affected. In pedigree cases there may also be a previous familial incidence of the cell-specific congenital defect or cancer—for example, intestinal polyposis, von Recklinghausen's disease, hereditary leucopenia, or retinoblastoma.

The survey data were collected by medical officers of health, and local authority health departments defrayed the cost of the field work. Financial help was also obtained from the Lady Tata Memorial Trust, the Lena Grant and Nan Williams Memorial Trust, the Medical Research Council, and the U.S.A. Public Health Department. It is a pleasure to place on record my gratitude for all this help. I also thank my colleagues, Dr. Josefine Webb, Mr. David Hewitt, Dr. Winifrid Pennybacker, and Mrs. Renate Barber, for their work on the survey records.

ADDENDUM

Since writing this paper three relevant investigations have been reported. A follow-up, in 1958, of 38,114 children who were born between 1945 and 1947 and were *x*-rayed *in utero* did not reveal an overall excess of deaths from leukaemia (Court Brown, Doll, and Hill, 1960). From unpublished data supplied by these authors it has since been ascertained that one-third of these children were born before 1950 and two-thirds during 1950–7. In the older group (aged 8–13 years at the time of the follow-up) there were 7 leukaemia deaths, or 70% more than the expected number; in the younger group (0–7 years) there were 2 leukaemia deaths, or only one-third of the expected numbers.

Doll (1960) has shown that international differences in leukaemia incidence are due mainly to lymphatic leukaemias in childhood and old age. These cases are relatively common in populations which have experienced a continuous decrease in the pneumonia death-rate since 1900—for example, Great Britain, Scandinavia, and the white population of the U.S.A.—and rare in populations which maintained a high pneumonia death-rate until 1945, when penicillin first became available—for example, Ceylon, Japan, and the coloured population of the U.S.A.

Finally, a case of lymphatic *cum* blast-cell leukaemia has been reported in a girl whose blood was found to contain 19% of foetal haemoglobin (Shuster, Jones, and Kilpatrick, 1960). A brother of this patient died in infancy of an unknown cause.

REFERENCES

Anderson, R. C. (1951). *Amer. J. Dis. Child.*, **81**, 313.
—— and Hermann, H. W. (1955). *J. Amer. med. Ass.*, **158**, 652.
Ardashnikov, S. N. (1947). *Brit. med. J.*, **2**, 955.
Cobb, S., Miller, M., and Wald, N. (1959). *J. chron. Dis.*, **9**, 385.
Court Brown, W. M., and Doll, R. (1957). M.R.C. *Spec. Rep. Ser. med. Res. Coun. (Lond.)*, 295. H.M.S.O., London.
—— —— and Hill, A. B. (1960). *Brit. med. J.*, **2**, 1539.
Cramblett, H. G., Friedman, J. L., and Najjar, S. (1958). *New Engl. J. Med.*, **259**, 727.
Cronkite, E. P., Moloney, W., and Bond, V. P. (1960). *Amer. J. Med.*, **28**, 673.
Debré, R., Bernard, J., and Buhot, S. (1951). *Bull. Soc. Méd. Hôp. Paris*, **67**, 183.
De Vries, A., Peketh, L., and Joshua, H. (1958). *Acta med. Orient. (Tel-Aviv)*, **17**, 26.
Doll, R. (1960). Communication to the British Society of Haematology, London, November 19.
Ford, D. D., Paterson, J. C. S., and Treuting, W. L. (1959). *J. Nat. Cancer Inst.*, **22**, 1093.
Guasch, J. (1954). *Sang*, **25**, 384.
Hemmes, G. D. (1957). *Geneesk. Bl.*, **48**, No. 9, p. 1.
Hewitt, D. (1955). *Brit. J. prev. soc. Med.*, **9**, 81.
Hornbaker, J. H. (1942). *Amer. J. med. Sci.*, **203**, 322.
Jelke, H. (1940). *Acta paediat. (Uppsala)*, **27**, 87, 137.
Lejeune, J., Gautier, M., and Turpin, R. (1959). *C.R. Acad. Sci. (Paris)*, **248**, 602
Mittwoch, U. (1957). *J. ment. defic. Res.*, **1**, 26.
Polhemus, D. W., and Koch, R. (1959). *Pediatrics*, **23**, 453.
Razis, D. V., Diamond, H. D., and Craver, L. F. (1959). *Ann. intern. Med.*, **51**, 933.
Registrar-General (1940–59). *Statistical Review of England and Wales*. H.M.S.O., London.
Reilly, E. B., Rapaport, S. I., Karr, N. W., Mills, H., and Carpenter, G. E. (1952). *Arch. intern. Med.*, **90**, 87.
Riel, L. (1948). *Kinderärztl Pax.*, **16**, 148.
Rous, P., and Kidd, J. G. (1941). *J. exp. Med.*, **73**, 365.
Salaman, M. H. (1958). *Brit. med. Bull.*, **14**, 116.
Shuster, S., Jones, J. H., and Kilpatrick, G. S. (1960). *Brit. med. J.*, **2**, 1556.
Stewart, A., Webb, J., and Hewitt, D. (1958). Ibid., **1**, 1495.
Turpin, R., and Bernyer, G. (1947). *Rev. Hémat.*, **2**, 189.
Videbaek, A. (1947). *Heredity in Human Leukemia and its Relation to Cancer*. Busch, Copenhagen; Lewis, London.
Weller, C V. (1941). *Cancer Res.*, **1**, 517.
Yoffey, J. M., Thomas, D. B., and Russell, P. M. (1960). *J. Anat. (Lond.)*, **94**, 576.

CHRONIC DIFFUSE NON-SUPPURATIVE AMOEBIC HEPATITIS

BY

T. DOXIADES, M.D.

Professor and Director of the First Medical Clinic, Evangelismos Hospital, Athens

N. CANDREVIOTIS, M.D.

Assistant Professor and Director of the Pathological Department, Evangelismos Hospital, Athens

M. TILIAKOS

AND

I. POLYMEROPOULOS

[WITH SPECIAL PLATE]

Amoebic hepatitis, well known in its acute form, is considered to be the early (pre-suppurative) stage of the solitary abscess or multiple abscesses of the liver (Lichtman, 1949; Seneca, 1956). Chronic lesions of the liver interstitium and parenchyma have been described as occurring in chronic abscess of the liver and in chronic amoebic colitis (Chatgidakis, 1953; Seneca, 1956). In the former condition fibrosis and thickening of the portal tracts have been observed. In the latter, fat degeneration or necrosis of the liver cells, hyperplasia of the connective tissue of the portal spaces with inflammatory infiltrations by lymphocytes and monocytes, as well as regeneration of the liver cells, have been reported (Lichtman, 1949; Seneca, 1956). These lesions are considered to be due to toxic substances produced by amoebae or other bacteria in chronic colitis (Lichtman, 1949).

Cases of chronic hepatitis due to the presence of amoebae in the liver without a localized abscess have not yet been published. The purpose of this paper is to present such a case.

T. DOXIADES *ET AL.*: NON-SUPPURATIVE AMOEBIC HEPATITIS

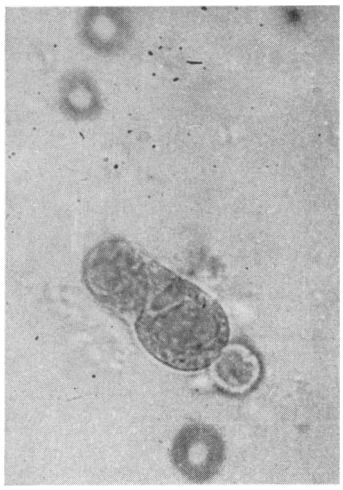

FIG. 1

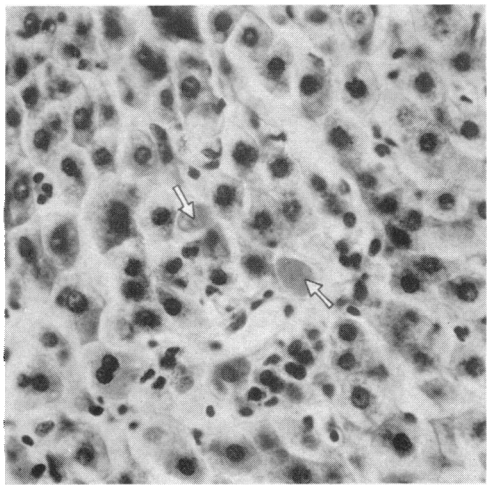

FIG. 2

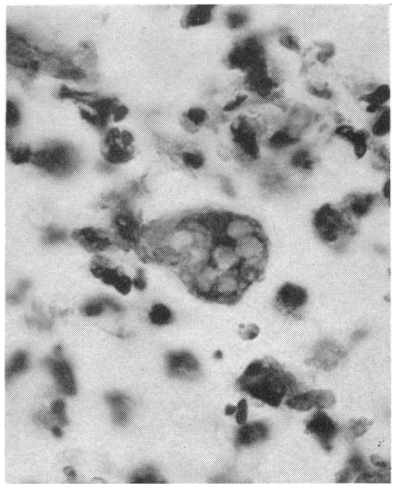

FIG. 3

FIG. 1.—*Entamoeba histolytica* in ascitic fluid.

FIG. 2.—First needle biopsy of liver. *Entamoebae histolyticae* (arrowed) among liver cells with vacuoles in cytoplasm; slight inflammatory infiltration.

FIG. 3.—*Entamoeba histolytica* in liver abscess produced experimentally in guinea-pig.

FIG. 4.—Surgical liver biopsy. Amoebic granuloma of liver. Two *Entamoebae histolyticae* (arrowed) with vacuoles in cytoplasm.

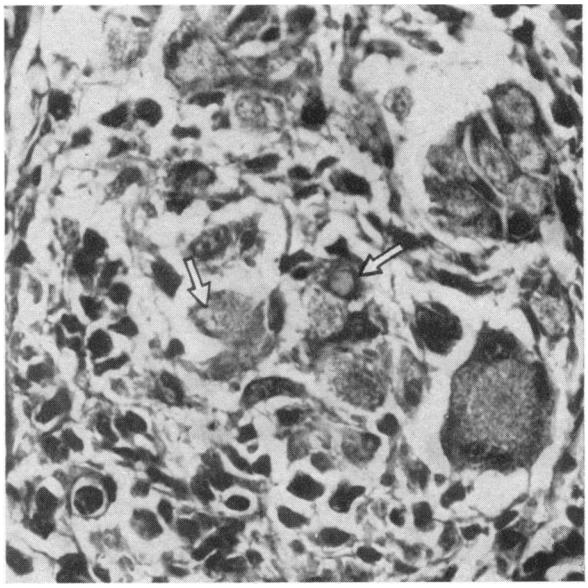

FIG. 4

H. M. ASKENASY *ET AL.*: CHRONIC OSTEOMYELITIS OF BASE OF SKULL

FIG. 1.—Necropsy specimen from Case 1. Disease process has destroyed floor of sella turcica and invaded hypophysis.

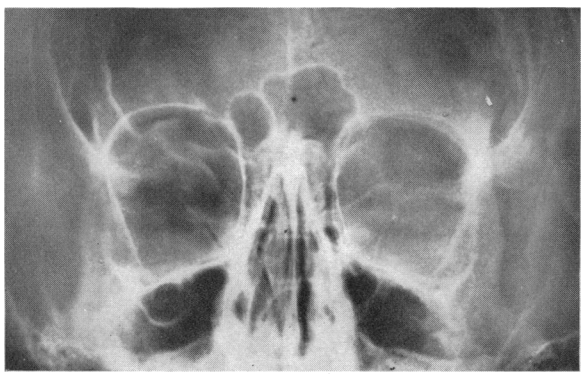

FIG. 2.—Case 2. Radiograph showing destruction of left orbital roof.

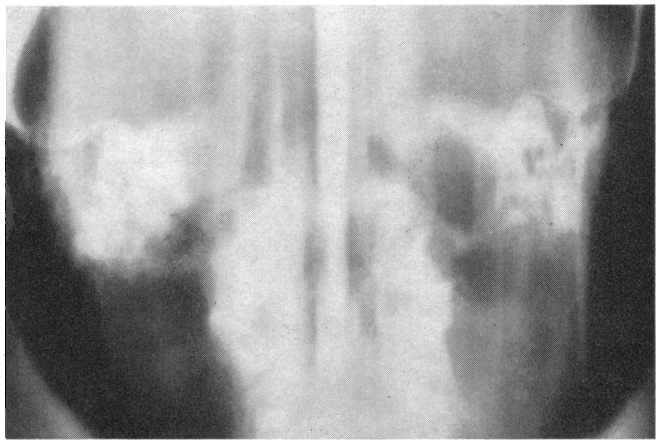

FIG. 3.—Case 3. Tomogram showing bony defect in left pyramid.

Case Report

A 32-year-old woman was admitted to the Evangelismos Hospital because of pain on the right side of the thorax and low-degree pyrexia. Since early childhood she had complained of periodic episodes of abdominal distress, distension, generalized abdominal pain, and diarrhoea with blood and mucus in the stools. In 1941–2, during the German occupation, these symptoms became worse, and oedema of the legs also appeared, due probably to malnutrition. Six months before her admission to hospital her condition had deteriorated and there was pain in the chest. Physical examination showed a malnourished woman with oedema of the face and both legs as well as abdominal distension. There was dullness to percussion on the right side of the thorax. Pleural puncture yielded 3 ml. of slightly turbid fluid. The liver was enlarged six finger breadths below the costal margin and tender on palpation. The spleen was not palpable. The other organs and systems yielded no abnormal findings.

The results of laboratory investigations were as follows. Blood examination: R.B.C. 4,300,000 per c.mm.; Hb 13.2 mg. per 100 ml.; haematocrit 40; W.B.C. 10,600 per c.mm.; E.S.R. 16 mm. in one hour. Urine analysis and liver function tests negative. Total serum protein 3.10 mg. per 100 ml. (albumin 2.15 mg., globulin 0.95 mg.). Blood sugar 88 mg., blood urea 20 mg., and blood cholesterol 150 mg. per 100 ml. Serum chlorides 480 mg., sodium 300 mg., and potassium 20 mg. per 100 ml. Wassermann and Kahn reactions negative. Pleural fluid: Rivalta reaction negative; albumin 0.12 mg. per 100 ml.; a few red cells and lymphocytes (80%) seen on microscopical examination; culture for bacteria negative. Examination of stools for parasites negative. Mantoux skin test negative 1:100,000. *X*-ray examination showed effusion on the right side. Gall-bladder series, barium enema, and pyelography negative. The electrocardiogram was within normal limits.

Since no clinical improvement was noted after administration of streptomycin (1 g. daily for 23 days) a chronic amoebic colitis was suspected on the basis of the patient's history. Chloroquine diphosphate (500 mg. daily for four days and 250 mg. for one day) was given. During the first two days of therapy the patient's condition deteriorated; the temperature rose to 39.2° C. (102.6° F.) and the right pleural cavity filled with fluid. This was confirmed fluoroscopically. Examination of the pleural fluid showed: Rivalta reaction negative; albumin 0.10 mg. per 100 ml.; polymorphonuclear cells 80%. No parasites or neoplastic cells were detected and no bacteria were cultured.

The chloroquine was stopped and emetine hydrochloride (60 mg. daily for 10 days) given subcutaneously. Four days later the patient felt much better. The temperature dropped from 39.2° C. (102.6° F.) to 36.5° C. (97.7° F.). The right-sided pain became much less intense and the pleural fluid almost disappeared. The liver was reduced to normal size. After eight days' intermission the treatment was repeated for four days. The patient felt quite well and was discharged.

Second Admission

Four and a half months later she was readmitted because of recurrence of symptoms. A generalized oedema appeared, with ascites and abdominal distension. The liver was again enlarged six finger breadths below the right costal margin. The laboratory data were found to be similar to those of the previous admission. An abdominal paracentesis was performed, and examination of the ascitic fluid revealed: Rivalta reaction negative; albumin 0.5 mg. per 100 ml.; lymphocytes 80%; a few red cells. Culture of the fluid for bacteria was negative. Some formations with the features of *Entamoeba histolytica* were seen in the ascitic fluid (Special Plate, Fig. 1). Proctosigmoidoscopy revealed marked hyperaemia of the sigmoid area up to 25 cm., with small superficial ulcerations of the mucosa. A rectal smear from the ulcerations did not reveal amoebae or other parasites. A liver specimen taken by needle biopsy showed the following histological appearances. The liver parenchyma was well preserved. The outline of the liver cells was sharply demarcated, the cytoplasm finely granular and well preserved. The nuclei were easily visible, with fine chromatin granules. The interlobular connective-tissue spaces showed, in some areas, inflammatory cellular infiltrations of lymphocytes, monocytes, and some polymorphonuclear leucocytes. Similar inflammatory infiltrations were also seen in the dilated interlobular capillaries. In one area two formations were observed among the liver cells showing the morphological features of *E. histolytica* with large vacuoles in the cytoplasm (Special Plate, Fig. 2).

Animal experiments were carried out by injection of 2 3, and 5 ml. of ascitic fluid respectively into the portal vein of three guinea-pigs; 4 ml. of ascitic fluid were also directly injected into the liver parenchyma of another guinea-pig. The animals were killed 17 days later. In the last guinea-pig an abscess of the liver 2×2 cm. in diameter was found, in which some *E. histolyticae* were detected histologically (Special Plate, Fig. 3). In the other three animals no liver abscess had developed.

The patient was put on a high-calorie diet plus a multivitamin preparation, and anti-amoebic therapy was continued with emetine, 60 mg. daily for 10 days. After eight days' intermission 250 mg. of chloroquine daily was given. The patient's general condition promptly improved and the oedema of the legs and the ascites rapidly lessened.

Sixteen days after the end of this course of therapy a second needle biopsy of the liver showed the same picture as the first biopsy. In this specimen *E. histolytica* was found in an inflammatory area of the interlobular connective tissue.

Three months after the second admission and one month after the second biopsy—that is, on October 31, 1958—exploratory laparotomy was performed. The peritoneum was normal in appearance and no ascitic fluid or adhesions were found. The liver was normal in consistency and size. No evidence of any abscess was seen. The colon was intact. Two small specimens were taken from both liver lobes for pathological examination.

Histologically, the parenchyma in these specimens showed the same picture as the previous liver biopsies. In addition, small inflammatory foci of lymphocytes, histiocytes, a few polymorphonuclear leucocytes, and several large cells with large nuclei poor in chromatin arranged in small groups, were found in some interlobular spaces. There were some giant cells with multiple nuclei arranged in the periphery. A few *E. histolyticae* were also found in these foci. There was no evidence of necrosis. These formations in the interlobular spaces constitute granulomas (amoebic granulomas) (Special Plate, Fig. 4).

Discussion

The liver findings in this case are indicative of a chronic non-suppurative amoebic hepatitis. It must be considered that the disease began at the time when the patient presented the diarrhoeic syndrome with blood and mucus in the stools. The fact that no amoebae or other parasites were found in the stools on several examinations cannot be held to exclude amoebic hepatitis, because it is well known that "in a great number of cases of amoebic abscess of the liver in autopsies no bowel lesions can be demonstrated." Chatgidakis (1953) found that, of 87 cases of amoebic abscess studied at necropsy, 24 (27.6%) had no intestinal lesions. Similar conclusions are reached by Danker (1947) as well as by Gharpura and Saldanha (1931).

The ascites was probably due to the chronic stage of the liver amoebiasis aggravated by malnutrition. The appearance of *E. histolytica* in the ascitic fluid is difficult

to explain on the basis of only one case. Nevertheless, it *is* possible for *E. histolytica* to reach the ascitic fluid by the blood or lymphatic circulation or by infiltration of the peritoneum.

The striking improvement in the patient's condition after anti-amoebic therapy also confirms the nature of the disease. The therapeutic test often gives the only valid evidence of amoebic disease. In explaining why no abscess developed in the liver during the long course of the disease it must be remembered that many different factors are related to the formation of the lesions of hepatic amoebiasis. Seneca (1956) mentioned that liver lesions produced by malaria, syphilis, alcohol, malnutrition, or trauma may predispose to the development of liver abscess. It must also be assumed that the majority of amoebae do not survive in the liver when the organ is intact.

Summary

An unusual case of chronic non-suppurative diffuse amoebic hepatitis has been described. *Entamoeba histolytica* was found in needle and surgical liver biopsies as well as in a liver abscess which developed in an experimental animal after injection of ascitic fluid. The mechanism of the disease process is discussed.

REFERENCES

Chatgidakis, C. B. (1953). *S. Afr. J. clin. Sci.*, **4**, 230.
Danker, D. D. (1947). Cited by Chatgidakis, *loc. cit.*
Gharpura, P. V., and Saldanha, J. L. (1931). Cited by Chatgidakis, *loc. cit.*
Lichtman, S. S. (1949). *Diseases of the Liver, Gall Bladder, and Bile Ducts*, 2nd ed., pp. 767–75. Lea and Febiger, Philadelphia.
Seneca, H. (1956). *Amer. J. dig. Dis.*, N.S. **1**, 250.

AMOEBIC LIVER ABSCESS IN GREAT BRITAIN

BY

J. W. PAULLEY, M.D., F.R.C.P.

Physician to the Ipswich Hospitals

It has been variously stated that the carrier rate for *Entamoeba histolytica* cysts in the faeces of groups of people who have never been out of Great Britain ranges between 1.6% (Morton *et al.*, 1951), 2.7% (Dobell, 1921), and 4.7% (Matthews and Smith, 1919). As Morton *et al.* pointed out, considerable differences are likely to arise from the methods used and the criteria adopted, notably pathogenicity tests, there still being some doubt about the pathogenicity of small race strains. With increasing travel, and the effect of infected personnel returning from two world wars, the indigenous carrier rate may be expected to rise; for example, Morton *et al.* found a rate of 8.8% in airmen returning from overseas. The same authors recorded three instances of clinical dysentery in patients who had never been abroad.

Manson-Bahr (1943), in an extensive review of the literature, quotes seven authenticated cases of amoebiasis arising indigenously in the British Isles. Four of these had abscesses of the liver (Saundby and Miller, 1909; Wenyon, 1916; Simpson, 1926; Gilroy, 1928), and in a personal communication in 1959 Air Vice-Marshal Sir Aubrey Rumball has told me of a further case. In France, Garin and Lépine (1924) recorded 208 cases of indigenous amoebiasis, two of them with liver abscesses.

Case 1

A youth of 18 was admitted to hospital on March 31, 1959. A diagnosis of retrocaecal appendicitis had been made, but at laparotomy the appendix was normal, and a manual search had failed to reveal any abnormality in the paracolic or subdiaphragmatic areas. The white-cell count was 22,400 (polymorphs 90%), and urine examination negative. A pre-operative film showed the right diaphragm to be raised with some paracardiac collapse of the right lower lobe. "Crystamycin" 1 ampoule b.d. was prescribed. The next day he was transferred by the surgeon to my care; though very ill, he was able to give the following history.

At school early in February, 1959, he had "influenza," but afterwards never felt really well. Three weeks later he had further pyrexia, which was also thought to be influenza, and with it he had pain in the right lower chest posteriorly. Shortly before admission he had severe pain in the right upper abdomen. Movement and breathing caused the pain to be intense, and lying down gave him pain in the right shoulder-tip. His temperature was 103° F. (39.4° C.) and pulse 112; his tongue was dry and furred when the surgeon saw him. A provisional diagnosis was made of retrocaecal appendix with a leak into Morison's pouch.

The patient had always lived in the United Kingdom, apart from one holiday in Dinard and one in Brunswick. His father had spent a year in Palestine, but the patient had not been in touch with him for 12 years. He had once spent a few weeks' holiday with an aunt who had lived in India.

Examination on the day after his laparotomy (April 1) revealed a very toxic patient experiencing very severe pain over the right lower ribs on movement or breathing deeply. Lying on his left side exacerbated the pain. He was tender to percussion over the right lower chest and on palpation subcostally. A further antero-posterior chest film and a lateral view showed that the whole diaphragm was raised, but especially anteriorly.

A tentative diagnosis of non-specific abscess of the liver was made in the absence of residence in the tropics or subtropics. Penicillin was increased to two mega units t.d.s., and chloramphenicol, 500 mg. q.i.d., was added. By April 2 his temperature had fallen to 101° F. (38.3° C.), but his condition had deteriorated and he was having repeated drenching sweats. The pain in the right subcostal area increased, and any movement exhausted him. On the morning of April 4 he was weaker and had had two rigors during the night. His condition was grave, and occasioned great anxiety. Emetine hydrochloride was initiated, 1 gr. (65 mg.) intramuscularly daily. Rigors and sweats ceased from that time, and 18 hours after his first injection he was less tender, and 36 hours later he was asking for food for the first time, and was able to turn in bed. He made an uninterrupted recovery and was afebrile by April 9. He had emetine for six days, and then chloroquine by mouth for three weeks. At the time of writing he was very fit, but his diaphragm was still elevated.

Case 2

A Pole aged 44, who had lived most of his life in Paris before the war and had never been further south than Marseilles, where he had once spent a three-months holiday, developed pneumonia and a right pleural effusion in 1943 while serving with the Polish forces in Scotland. The effusion took several months to resolve. In 1946 he was admitted to the Middlesex Hospital with a recurrence of pain and signs of effusion in the right lower chest, a raised diaphragm, fever, and leucocytosis. He failed to respond to penicillin and sulphonamides. He spoke little English, but on being approached with a sigmoidoscope to search for amoebic ulceration he announced that he was "very small." This was confirmed by the finding of a rectal stricture. With the aid of an interpreter there emerged a story of diarrhoea and what sounded like a mucosal slough while in Paris before the war. I carried out exploratory