stomatitis and aphthous ulceration of the buccal mucosa. The haemoglobin concentration had now fallen to 9.7 g/dl; white cell count $4.0 \times 10^9/l$ ($4000/mm^3$); erythrocyte sedimentation rate 125 mm in the first hour. Concentrations were as follows: serum albumin 17 g/l; IgG 15 g/l; IgA 7.4 g/l and IgM 0.9 g/l; serum B_{12} 455 ng/l; serum folate $1.4 \mu g/l$; red cell folate $57 \mu g/l$. Autoantibodies were not detected and the results of thyroid function tests were normal. The urine contained only a trace of albumin. Faecal fat excretion was normal, although her dietary fat intake was low at that time. Histologically, a jejunal biopsy specimen showed a trivial degree of villous shortening, consistent with folate deficiency, and a rectal biopsy specimen was normal.

In view of the continued deterioration characterised by persistent diarrhoea and hypoalbuminaemia, empirical treatment with corticotrophin was started two weeks before death. This produced an improvement in her bowel symptoms. Nevertheless, deep leg vein thrombosis supervened, which was treated with heparin, followed by a chest infection that failed to respond to antibiotics. At necropsy bronchopneumonia and small peripheral pulmonary emboli were found. Sections of jejunum showed mucosal ulceration affecting roughly half of the bowel circumference. The ulcers were lined by granulation tissue with an inflammatory infiltrate rich in lymphocytes and plasma cells. Lying apparently within the capillaries of the granulation tissue were many large cells with basophilic cytoplasm and prominent eosinophilic intranuclear inclusions. Such cells had the typical morphological features of CMV infection (figure). No histological evidence of CMV infection was found in any other organ.

Section of jejunum showing the edge of a mucosal ulcer. The intact mucosa (right) exhibits autolytic changes. Within the capillaries and venules of the granulation tissue in the ulcer are cells showing the characteristic cytomegalic and intranuclear inclusions of CMV infection (inset). (Haematoxylin and eosin. $\times 31$ (inset $\times 772$).)

Discussion

Evidence of CMV infection in the gut may be found in either the epithelial cell compartment or, as in the present case, the mucosal and submucosal capillaries and venules. These vascular lesions are associated with mucosal ulceration, presumably owing to local ischaemia.³ The lesions, whether epithelial or vascular, are invariably focal and may be missed in intestinal biopsy specimens unless many sections are examined.⁴

Presumably the hypoproteinaemia in this case, in the case reported by Tajima,³ and in some of the cases described by Levine *et al*¹ reflects serous exudation from the mucosal ulcers in the gut. The severe hypoproteinaemia and diarrhoea in our patient could not be ascribed to any lesion other than that found in the small gut at necropsy. Any causal relationship between the folate deficiency and CMV enteritis in our patient must remain speculative.

CMV enteritis should be considered, therefore, in the differential diagnosis of patients with persistent diarrhoea for which no other explanation can be found—particularly if there is concurrent hypoalbuminaemia. A rising CMV antibody titre may help in establishing

the diagnosis during life. Unfortunately, however, this information was not available in the present case.

We thank Dr C D Holdsworth for permission to report this case.

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Cryptococcosis: survival attributed to combination antifungal treatment

Cryptococcal meningitis is rare in the UK and occurs mainly as an opportunistic infection. Before the introduction of amphotericin B it was invariably fatal. Flucytosine is also effective in cryptococcal infections. Neither agent used alone is ideal, however, because of non-response, relapse, and toxicity. Medoff *et al*¹ reported in-vitro synergism of amphotericin B and flucytosine against three isolates of *Cryptococcus neoformans*. The results of treatment in a series of 20 patients were subsequently reported.²

We describe a patient who developed cryptococcosis while receiving chemotherapy for Hodgkin's disease. He would probably not have survived without combination antifungal treatment.

Case report

A 25-year-old plumber was diagnosed in June 1975 as having stage IA lymphocyte-predominant Hodgkin's disease. Staging laparotomy was not performed because he was grossly overweight. He was treated with irradiation directed to the cervical, axillary, and mediastinal lymph nodes, the "mantle" technique being used. By October his health had deteriorated. He had lost weight and developed obstructive jaundice. A lymphogram showed abnormal para-aortic nodes. Chemotherapy was started with the MOPP regimen (mustine, vincristine, procarbazine, and prednisolone). Response was good but halfway through the second cycle he developed acute streptococcal monoarthritis and septicaemia. This responded to benzylpenicillin. One week later he complained of headache and photophobia of sudden onset. Examination showed signs of meningitis. Lumbar puncture yielded purulent cerebrospinal fluid (CSF) under high pressure. Cell count was $145 \times 10^6/l$ ($145/mm^3$), protein 1.53 g/l, and glucose 0.83 mmol/l (15 mg/100 ml). CSF smears contained yeasts. *C. neoformans* was cultured from CSF and blood. Latex test result for cryptococcal antigen was positive to a titre of 1/100 in CSF and blood. Cryptococcal antibody was not detected.

Flucytosine and amphotericin B were started. Flucytosine was given by mouth, 16 g daily for four weeks, reducing to 12 g daily for nine weeks, and amphotericin B by intravenous infusion over six hours. The initial daily dose of amphotericin B (10 mg) was increased by 5 mg a day to a total of 45 mg daily, but at this dose severe rigors occurred. The same dose together with 45 mg hydrocortisone was accordingly given on alternate days and was well tolerated. Over 13 weeks he received a total of 2130 mg amphotericin. The drug was given intrathecally in doses of 0.25 mg and 0.5 mg during the first week, after which CSF smears and cultures remained negative. Three further cycles of chemotherapy were given according to schedule but with prednisolone omitted.

Side effects of treatment were few. Hypokalaemia developed after two weeks but was adequately controlled with potassium supplements or amiloride 10 mg daily. Renal function was otherwise normal. The haemoglobin concentration tended to fall gradually, requiring blood transfusion on two occasions. Serum alkaline phosphatase and γ -glutamyltransferase concentrations rose three weeks after starting treatment but returned to normal after treatment was stopped. Results of further examinations of CSF during and after treatment were normal.

The patient remained well without any treatment for 18 months. Examination of CSF after 14 months showed a lymphocyte count of $26 \times 10^6/l$ and a protein concentration of 0.81 g/l, but a search failed to disclose any crypto-

cocci. A raised protein concentration has been recorded up to five years after successful treatment.³ We think that the cryptococcal infection was eradicated.

Comment

The results of treatment of cryptococcal infections with a combination of amphotericin B and flucytosine have been reported.^{2,4} A retrospective study of 111 patients with cryptococcal meningitis treated with amphotericin alone enumerated factors associated with a fatal outcome or relapse.³ Of relevance to our patient was the finding that no patient with a positive blood culture was cured with amphotericin alone; indeed, patients with a positive blood culture usually died during treatment. Our patient had six of the seven factors that have been found to correlate with a fatal outcome—namely, a positive CSF Indian-ink smear, a high CSF pressure, a low CSF glucose concentration, absence of anticryptococcal antibody, a high antigen titre, and underlying lymphoreticular malignancy.

The survival of this patient, who had a positive blood culture at the time of diagnosis, is somewhat remarkable. It can probably be attributed to early diagnosis and to treatment with combination antifungal agents. In retrospect a smaller dose of amphotericin might have been as effective. Utz *et al*² used 20 mg daily and suggested that early diagnosis and institution of treatment may be more efficacious than larger doses or longer courses of treatment.

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Failure of aspirin to prevent postoperative deep vein thrombosis in patients undergoing total hip replacement

Venous thromboembolism is a frequent and well-recognised complication of total hip replacement. The role of aspirin in preventing deep venous thrombosis (DVT) after this operation is controversial. Some authors claim that aspirin exerts no antithrombotic effect,^{1,2} while others report a reduction in the incidence of DVT and pulmonary embolism.³ This study aimed at assessing the effect of aspirin in a group of consecutive patients undergoing total hip replacement.

Patients, methods, and results

Thirty consecutive patients (18 men, 12 women) admitted for total hip replacement were studied for postoperative DVT using the ¹²⁵I-fibrinogen uptake test⁴ and ascending venography,⁴ screening for DVT being carried out daily using the former. Venography was performed on the operated leg between the 14th and 16th postoperative day, unless an isotopic thrombus was detected earlier, in which case venography was carried out at that time.

Venography was performed in the contralateral limb only if the result of the fibrinogen uptake test was positive. Each patient received 600 mg of soluble aspirin twice daily, starting the day before operation, until discharge from hospital. Aspirin was discontinued only if a patient developed DVT which required anticoagulant treatment.

The mean age of the patients was 65 (SD $\pm$ 7.7). On established criteria 13 were considered to be at high risk from DVT; three patients undergoing revision surgery were included in this group. DVT was demonstrated by venography in 24 patients. It occurred in the operated limb in 11, the contralateral limb in four, and both limbs in nine. Femoral vein thrombosis occurred in 13 patients and was extensive in four. DVT was demonstrated by venography in 15 patients before the 9th postoperative day, and between the 10th and 16th postoperative days in the remaining nine. One patient developed troublesome wound bleeding on the 3rd postoperative day. There were no other local or systemic complications attributable to aspirin. In those patients (13) considered to be at high risk, DVT was detected in nine, of whom two developed extensive femoral thrombus.

Discussion

This study shows that aspirin failed to protect patients from thromboembolism after total hip replacement. The diagnosis in every case was based on venography, generally accepted to be the most accurate method for detecting DVT. Hence undoubtedly the high incidence of detected DVT (80%) reflects the true frequency of this complication in this group.

Two other published trials^{1,2} have also concluded that aspirin is ineffective for preventing DVT after this operation. In both, the diagnosis of DVT was based entirely on the results of the fibrinogen uptake test. Nevertheless, when assessed by venography this test is inaccurate for detecting DVT after hip replacement, and thus the results of these two trials are open to criticism. In contrast, a further study,³ in which DVT was assessed by venography carried out between seven and 10 days after surgery, reported that only 36% of patients receiving aspirin prophylaxis developed this complication, and that no patient sustained an extensive femoral vein thrombosis. The striking difference in the incidence of DVT between the patients reported by Harris *et al*³ and those in our study cannot be entirely explained either by the timing of venography or by the exclusion of high risk patients from the former study. Clearly the substantial difference in results of these two studies warrants further investigation.

We conclude, on the basis of a venographically controlled study, that for patients undergoing total hip replacement, prophylaxis against DVT using aspirin in a dose of 600 mg twice daily is ineffective.

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Correction

Antithrombin III deficiency . . .

We regret that in the case report by Dr O H B Gyde and others (11 March, p 621) the antithrombin III levels should have read: (0.07 g/l compared with the normal range in serum of 0.20-0.35 g/l) . . ., and seven were found to have low antithrombin III concentrations (0.07-0.10 g/l).