Because the ulcers worsened and became very painful, foscarnet had to be discontinued and replaced by ganciclovir. The lesions disappeared within 2 weeks. Ophthalmological examination revealed recurrence of CMV retinitis during ganciclovir therapy, and foscarnet was given again, with an induction schedule of 12 g per day. Oral and oesophageal ulceration recurred within 4 days. Worsening led to discontinuation of therapy after 14 days. The lesions healed within 3 weeks.

The simultaneous use of other drugs is an unlikely explanation for the oral ulceration, although such lesions could be compatible with a diagnosis of fixed drug eruption to cotrimoxazole.[4] The histopathology of fixed drug eruption, however, is different from the findings in our patient. Our case did not have penile ulceration. In such cases, repeated exposure of the glans to small quantities of urine containing high concentrations of foscarnet, causing local irritation, is a possible mechanism. For oral ulceration, mechanisms are unknown. Crystallised foscarnet deposition in arterioles and capillaries could explain some of the drug's adverse effects such as ulceration.[5] The delay of occurrence, healing after treatment interruption, relapse with reintroduction, and absence of other causes suggest that these ulcerations were foscarnet-related.

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Possible role of *Rochalimaea henselae* in pathogenesis of AIDS encephalopathy

SIR,—Dr Regnery and colleagues (June 13, p 1443) report that 88% of patients with suspected cat-scratch disease (CSD) had serum antibody titres of 64 or more to *Rochalimaea henselae* by immunofluorescence assay (IFA). We confirmed and extended these observations with a standard enzyme immunoassay (EIA) with whole *R henselae* as antigen for detection of *R henselae* reactive antibodies. *R henselae* was cultured on tryptic soy agar with 5% sheep blood and harvested on the 10th day in sterile phosphate buffered saline. This suspension was fixed in 3·7% formalin for 1 h and used as antigen for ELISA.

EIA cutoff (mean + 3 SD) was established in 80 serum samples from healthy adults. EIA values were expressed in arbitrary units with a standard curve ranging from 0 to 100 units with a cutoff of 12 (around 0·250 optical density). In a direct comparison with serum samples from biopsy-proven cases of CSD, bacillary angiomatosis, and peliosis hepatis, EIA proved 5-fold to 10-fold more sensitive than IFA (EIA values ranged from 50–100 with an average of 71 units). The specificity of EIA was ascertained by testing serum samples with high antibody titres to *Brucella abortus* (10), *Rickettsia typhi* (9), *Rickettsia rickettsii* (9), *Afipia felis* (2), *Borrelia burgdorferi* (10), *Yersinia pestis* (8), *Chlamydia trachomatis* (5), cytomegalovirus (5), rubella (4), antinuclear antibodies (10), antiphospholipid antibodies (10), and IgM rheumatoid factor (5). None of these samples showed crossreactivity with *R henselae* antigen by EIA.

Because *R henselae* is associated with CSD and has been isolated from patients with bacillary angiomatosis, peliosis hepatis, and fever of unknown origin with AIDS[1-3] and because of the well-defined spectrum of encephalopathy in CSD,[4] we investigated the possibility that *R henselae* might contribute to the encephalopthy of AIDS. To determine the frequency of *R henselae* antibodies in serum and cerebrospinal fluid (CSF) of HIV-positive patients with suspected central nervous system involvement, we analysed by EIA 50 paired serum and CSF specimens from HIV-positive patients for IgG *R henselae* reactive antibodies. 16 paired serum and CSF specimens from multiple sclerosis patients were controls. 32% (16/50) and 24% (12/50) of HIV-positive samples showed raised concentrations of IgG *R henselae* reactive antibodies in serum and CSF, respectively (EIA values ranged from 15 to 60 with an average of 35 units): none of the controls had high titres of *R henselae* antibodies.

To see if IgG *R henselae* reactive antibodies in the CSF of HIV-positive patients were produced locally or were present in serum because of blood-brain barrier (BBB) damage, the IgG *R henselae* reactive antibody index was calculated in these patients. Total IgG in paired serum and CSF samples was mesured by nephelometry and the specimens were adjusted to the same concentration. Diluted specimens were tested by EIA for *R henselae* IgG antibodies. Antibody index was calculated by the ratio of *R henselae* reactive IgG in CSF to that in serum. An antibody index of 1·5 or greater is regarded as strong evidence of local (intra-BBB) production of organism-specific antibodies and is generally thought to reflect continuing central nervous system infection by the organism being evaluated.[5] All (12/12) *R henselae* reactive CSF specimens had an *R henselae* antibody index of 2 or greater; these 12 also had raised HIV antibody indices. 5 patients with increased HIV antibody indices were CSF-negative for *R henselae* antibodies. The specificity of the increased *R henselae* antibody indices is indicated by the finding that none of these 12 patients had raised adenovirus antibody indices.

CSD in its atypical form can be associated with various central nervous system findings. In our specimens, raised *R henselae* antibody indices demonstrated intrathecal production of antibody, which is consistent with *R henselae* infection of the cental nervous system. The possibility that central nervous system *R henselae* infection in AIDS plays a part in the pathogenesis of AIDS-associated central nervous system disease, including AIDS encephalopathy, is being investigated.

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Clinically diagnosed AIDS cases without evident association with HIV type 1 and 2 infections in Ghana

SIR,—The latest international conference on AIDS in Amsterdam seems to have provoked dispute about the aetiology of the disease: is AIDS truly caused by HIV?

Dr Laurence and colleagues (Aug 1, p 273) report 5 AIDS or AIDS-related complex (ARC) cases from New York City, none of which had serological evidence of HIV type 1 and 2 infections. Taking into account preceding descriptions of AIDS patients without evidence of known HIV infections,[1-3] and your recent correspondence (Aug 22, p 484 and Sept 5, pp 607–09) the number of potential so-called HIV-negative cases seems to be increasing. The cause of these immunodeficient disorders should be urgently clarified. Our group has been investigating the epidemiology of HIV in Ghana for several years, and has encountered patients whose serological status was negative or indeterminate.[4]

In 1990, blood samples were collected from 227 Ghanaian AIDS patients diagnosed by WHO clinical criteria in Africa. On the basis of multiple laboratory diagnostic tests, they were classified into five serological categories: 48 were only HIV-1 positive, 17 only HIV-2 positive, 11 dual positive, 16 indeterminate, and 135 seronegative.

The techniques used were enzyme-linked immunosorbent assay (ELISA), particle agglutination, indirect fluorescent assay (IFA), western blot, and mono-epitope ELISA. 11 samples with dual reactivity were interpreted as double infection with HIV-1 and HIV-2, or a single infection with antigenetical cross-reactivity with the other. 16 indeterminate specimens showed some reactivity with HIV-1 and HIV-2 by IFA. Nonetheless, they did not show specific bands on western blotting with HIV-1 and HIV-2 infected cells as antigens, whereas the positive samples clearly revealed typical *gag*, *pol*, and *env* bands of each virus. The result by mono-epitope ELISA for differentiating the viral type was also negative. Virus isolation from peripheral blood cells was attempted, with negative results. We therefore assume that there might be unknown agents (viruses) which are antigenetically different from any known type of HIV, since in west African countries there is a unique circulating collection of various HIV strains. In fact, we have previously isolated from a Ghanaian patient with ARC a highly divergent strain of HIV-2 that is genomically equidistant from a simian immunodeficiency virus of sooty mangabeys (SIV_{sm}) and that of rhesus macaques (SIV_{mac}).[5] Gao et al[6] have lately reported human infection in Liberia by genetically diverse HIV-2 strains that are more closely related to SIV_{sm}/SIV_{mac}. Thus, there is a possibility that some AIDS cases in this region might be caused by viruses that cannot be detected by the current HIV laboratory assay system.

Our attention is now focused on the considerably large number of the seronegative group (135/227, 59%) who were clinically diagnosed as having AIDS. All the patients had three major signs: weight loss, prolonged diarrhoea, and chronic fever. Many of them also had other AIDS-associated signs, such as lymphadenopathy, tuberculosis, dermatological diseases, and neurological disorders, though CD4 cells were not counted because of insufficient facilities. We believe that many patients of this group were perhaps improperly diagnosed and had other unidentified diseases. Even if that is true, the number is still more than negligible. In relation to the AIDS cases in the USA without evidence of known retroviral infection, our African cases are especially intriguing. The existence of other agents causing AIDS-like syndromes might be possible among these so-called HIV-negative cases. Further searching for such novel aetiological agents of the disease should be continued.

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Prevention of cisplatin-induced emesis

SIR,—Dr Egros and colleagues (Sept 5, p 619) challenge the conclusions of our study (July 11, p 96) that ondansetron plus dexamethasone is more effective than metoclopramide plus dexamethasone plus diphenhydramine in the prevention of cisplatin-induced emesis, mainly because we did not use the best therapeutic scheme for metoclopramide. They claim that a continuous infusion preceded by a loading dose has proved a more efficacious regimen[1,2] than the intermittent infusion schedule of metoclopramide chosen by us.

Egros et al have raised an old and much discussed difficulty about the best schedule of administration of high-dose metoclopramide in the prevention of cisplatin-induced emesis. Five of seven comparative trials,[3–7] including the most recent,[6,7] indicate that intermittent infusion is as efficacious as continuous infusion. In fact, intermittent infusion became the method of choice of the most important groups in antiemetic research. Also noteworthy is the evidence that a single high dose of metoclopramide (4 mg/kg) infused in 15 minutes before chemotherapy can protect from cisplatin-induced nausea and vomiting similar to a repeated bolus regimen (3 mg/kg × 2).[8] Furthermore, Egros and colleagues misinterpret the results of Warrington's study[1] cited in support of their claims. This work did not show complete protection from vomiting (zero emetic episodes) in 82% of patients treated by continuous infusion, but did show a major response ($\leq$2 emetic episodes). A similar response rate has been achieved in other studies by intermittent bolus injection of metoclopramide.[8,9]

We believe that we used one of the best antiemetic combination therapies that included metoclopramide in an appropriate schedule and dose by comparison with ondansetron plus dexamethasone, and our results clearly showed the superiority of the ondansetron treatment. Furthermore, we think that future research should not be directed to the evaluation of the methods of metoclopramide administration but rather to other important, still unsolved difficulties—ie, identification of the best 5-HT3 antagonists, evaluation of efficacy during subsequent cycles of chemotherapy, and study of more efficacious strategies to prevent delayed emesis from cisplatin.

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Urticaria and angioedema induced by low-molecular-weight heparin

SIR,—Unfractionated heparin (UFH) and low-molecular-weight heparins (LMWH) are glycosaminoglycan chains of alternating residues of D-glucosamine and a uronic acid, either gluconic acid or iduronic acid.[1] LMWHs are potent thromboprophylactic agents, and have the advantage over UFH of daily administration and reduced risk of bleeding.[2] Allergic reactions due to LMWHs are rare, and skin eruptions and angioedema have not been associated with these agents. We report widespread urticaria and angioedema in association with LMWH (enoxaparin).