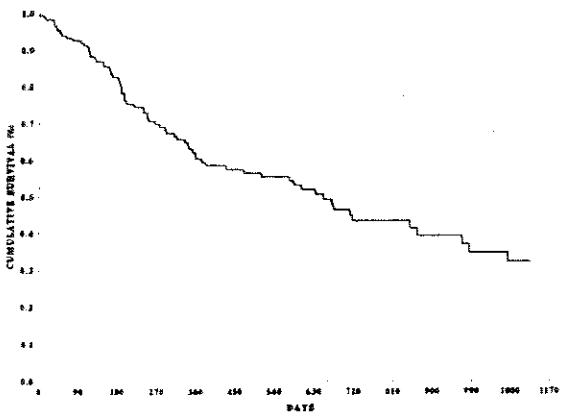

Cumulative probability of freedom from AIDS (expressed as survival) among 161 homosexual men with CD4 count below 200/μl.

our cohort study in Amsterdam. Since 1984, blood samples from these men have been collected every 3 months. 108 (67%) of the 161 men with at least one CD4 count below 200/μl were symptom-free (CDC class II and III) at the time of their first low CD4 sample. In 60% of these 161 men AIDS did not develop within 360 days of the first CD4 count below 200/μl. After 720 days of follow-up 43%, and after 1080 days 32%, did not have AIDS (figure). The median interval between the first low CD4 count and the development of AIDS was 651 days (95% confidence interval 429–865 days).

We conclude that a considerable proportion of HIV-infected individuals with a CD4 count below 200/μl will not be diagnosed with AIDS for several years because they are symptomless and will not seek health care. As a result the completeness of future AIDS surveillance data will be difficult to assess, which makes the study of trends in the AIDS epidemic nearly impossible. Our data show that a considerable proportion of HIV-infected persons with a CD4 count below 200/μl live for a long time without having to experience the negative psychological and social consequences of being labelled as an AIDS patient.

Although we recognise that the current AIDS definition does not cover the total burden of HIV disease, we agree with the position taken by the European Centre for the Epidemiological Monitoring of AIDS not to adopt the proposed expansion for the surveillance of AIDS for countries of the European Community and Norway, Sweden, and Switzerland. It would be better to institute an additional surveillance system for severe HIV-related immunodeficiency, while leaving the current AIDS case definition intact.

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Changes in thiols and glutamate as consequence of simian immunodeficiency virus infection

SIR,—Dr Eck and his colleagues (Aug 10, p 346) intravenously inoculated 21 macaques with $SIV_{ac251/32H}$ containing 1, 10, or 100 MID_{50}. 2 macaques were inoculated with blood (volume not stated) from an $SIV_{mac251/32H}$ infected macaque with symptoms. 18 non-inoculated macaques were used as controls. Infection of inoculated monkeys was shown by viraemia and by seroconversion, these events being preceded by a decrease in acid-soluble thiol and a rise in glutamate. Eck et al conclude that "the early rise in plasma glutamate and fall in cysteine levels may have an important role in the pathogenesis of AIDS" (a view we agree with[1,2]) and that these changes are "at least in this model, a direct and early consequence of the retroviral infection", an interpretation we find difficult to accept.

SIV_{mac251} was obtained by simple ultracentrifugation (non-density gradient) or by passing supernatant through filters. Neither guarantees isolation of pure retrovirus. Much of the material found in HIV preparations, even when obtained by double banding in density gradients, is non-viral, presumably cellular.[3] According to Montagnier's group, HIV "isolates" obtained by filtration contain microorganisms as large as mycoplasmas (and these may be a co-factor in the development of AIDS).[4] Can we be sure that the decrease in thiol observed by Eck et al was caused by SIV_{ac251} rather than by the non-viral components of the inoculation? Some of the non-viral components may have been of non-simian (human) origin. The original SIV_{mac251} was "isolated" from HUT78 cells. The preparation with which monkey 32H was inoculated was obtained from H9 cell cultures. H9 is nothing more than a clone of HUT78, a malignant cell line from a patient with mature T4-cell leukaemia/lymphoma. HUT78 (H9) cells being malignant should be relatively oxidised.[5] Furthermore if, as generally accepted, that patient's disease was caused by HTLV-I, HUT78 (H9) co-cultures (and thus the inoculated material) would have at least one other retrovirus; and if HTLV-I does cause malignancy, it should, like all other carcinogens and mitogens,[5] be an oxidising agent. Also SIV_{mac251} was isolated from monkey 32H, from co-cultures stimulated with phytohaemagglutinin, an oxidising agent. Furthermore, the decrease in acid-soluble sulphydryl groups (cysteine) preceded the viraemia.

Because preparation of the inoculum entailed a variety of oxidative procedures and because the isolation methods are not specific for SIV, several oxidised products apart from SIV would have been injected into these macaques. Any of these could have induced oxidative stress. Ambiguity could have been largely avoided if extra controls had been injected with materials, prepared in exactly the same way as those for the test animals, from sick but non-SIV-infected macaques.

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*** This letter has been shown to Professor Dröge, whose reply follows.—ED. L.

SIR,—Dr Papadopulos-Eleopulos and colleagues wonder if our virus preparations might have been obtained from an infected T-cell line and contained cellular components. The dysregulation of plasma aminoacid levels might thus have been caused by a non-viral contaminant rather than by the retroviral infection itself. This possibility seems very unlikely because our virus preparations were diluted at least 100-fold and HIV-infected individuals show a similar dysregulation of aminoacid levels. And in view of the small amount of inoculated material we also consider it very unlikely that contamination by oxidised products in our virus preparations might have produced the profound decrease of plasma cysteine or the increase in glutamate.

Papadopulos-Eleopulos et al suggest, correctly, that ambiguity could largely have been avoided if additional control animals had been injected with SIV-free inocula. To cut experimentation on primates to a minimum we compromised on that point. However, we do agree with Papadopulos-Eleopulos and colleagues on the

basic interpretation that a distorted balance of oxidants and antioxidants may play a key part in the immunopathology of HIV/SIV infection.

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SIR,—Dr Eck and colleagues report an early rise in plasma glutamate and a fall in cysteine after infection with SIV in rhesus monkeys and conclude that similar metabolic changes might have an important role in the pathogenesis of AIDS. Other studies have suggested abnormalities of folate metabolism in AIDS,[1,2] methylation abnormalities that may account for some of the CNS lesions in HIV infection,[3] vitamin B_{12} malabsorption in HIV progression, and brain methyltransferase inhibition in early brain involvement in HIV-positive patients.[5] Two of our HIV-positive patients who are being managed with parenteral vitamin B_{12} and magnesium sulphate have improved clinically and are not following the typical course of AIDS progression. Our rationale for this approach is the suggested importance of folate, magnesium, and vitamin B_{12} in folate-dependent methyl-group transfer.

Unfortunately, most effort directed at the treatment or understanding of AIDS is targeted on viruses, antiviral agents, vaccines, and immunology. Methylation abnormalities, which, if corrected, might affect disease progression favourably, have been neglected.

Indeed a publication prepared by the American Academy of Family Physicians and supported by two pharmaceutical companies gives the impression that the pathophysiology of HIV infection is well understood, and that the treatment of HIV-induced disease is zidovudine (or zidovudine-like drugs soon to be released).[6] It also suggests that symptom-free HIV-infected patients be given potent anti-cancer regimens (multiple zidovudine-like drugs).

A more rational approach should include study of treatments, such as metabolic management, that might prevent progression of the disease while the search for a definitive vaccine continues.[7] A concerted effort should be made to elucidate other areas of the pathophysiology of AIDS progression before toxic drugs become standard medical care in AIDS, so making it difficult, if not impossible, to study far less toxic modalities scientifically.

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Recovery from fulminant infection with *Mycoplasma fermentans* (incognitus strain) in non-immunocompromised host

SIR,—In 1989 Lo et al[1] described a virus-like agent in six non-AIDs patients who died with a fulminant febrile illness. This agent was later identified as a mycoplasma, tentatively referred to as "*Mycoplasma incognitus*",[2] and it is probably a unique strain within *M fermentans*.

A 28-year-old man was admitted with a 7-day history of fever, vomiting, diarrhoea, abdominal pain, an abdominal rash, shortness of breath, and deteriorating mental status. He had scleral icterus, subconjunctival haemorrhage, and suffusion. There were bibasilar râles, and the liver was palpable 6 cm below the right costal margin. There were two large erythematous macular lesions over the lower chest and abdomen. There were no focal neurological findings. His white blood cell count was 1700/μl with toxic granulations on peripheral blood smear. Total bilirubin was 198 μmol/l and aminotransferases were abnormal. An abdominal ultrasound scan indicated hepatomegaly and a small right pleural effusion.

Electronmicroscopy of bone marrow biopsy which immunostained positive for *M fermentans* (incognitus).

Clusters of mycoplasma-like structures are identified, with electron-dense filamentous forms (arrows), some with branching (thick arrow) and some with less electron-dense pleomorphic structures (open arrows). Unit membrane, but no cell wall, identified on surface of these structures. Many spherical mycoplasma-like particles also noted (insert). Bar represents 200 nm

On admission imipenem, gentamicin, and vancomycin were given intravenously. 2 days later penicillin G was substituted because of a suspicion of leptospirosis, and intravenous penicillin was administered for 14 days. The packed cell volume fell to 0·25 and the total bilirubin rose to 265 μmol/l. Hypoxia necessitated mechanical respiratory assistance and total parenteral alimentation was initiated. When congestive heart failure and ascites developed an endomyocardial biopsy was done, revealing an acutely dilated cardiomyopathy with lymphocytosis within the endocardium but no necrosis of the myocardium. Liver biopsy revealed bileduct proliferation and a bone marrow aspirate and biopsy showed reactive, hypercellular marrow. An extensive search for bacteria, fungi, and viruses revealed no pathogens and serological tests for mycoplasma were negative. A cold agglutinin titre was 1024.

Bone marrow biopsy material was sent to S. C. L. and probed by antibodies specific for *M fermentans* (incognitus). Reactions were strongly positive intracellularly and extracellularly. Positive areas were retrieved and examined by transmission electron microscopy,[3] and mycoplasma-like structures were identified (figure).

M fermentans (incognitus) has been associated with acute fatal disease in six previously healthy young adults who had no evidence of HIV infection or immunosuppression.[1] They presented with fever, nausea, vomiting, diarrhoea, and myalgia and had at first been treated with oral antibiotics for presumptive atypical pneumonia. They died 7–50 days from the onset of illness. *M fermentans* (incognitus) was demonstrated in liver, bone marrow, spleen, and lymph nodes. The patient described here seems to be a survivor from a similar fulminant infection.