ation is not clear. Recovery in $CD4^+CD45RA^+$ numbers is the consequence of thymic output (probably small in adults[4]), proliferation of $CD45RA^+$ T cells, together with reversion of primed $CD45R0^+$ T cells[5]. Reversion rates have been estimated, and, if correct, are unlikely to contribute greatly to the recovery of the $CD45RA^+$ lymphocyte count within the short period observed[6]. Proliferation of $CD4^+CD45RA^+$ cells is therefore likely to be the principal component involved in the recovery phase of the immune system following a large insult.

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Cyclosporin A

SIR — Ho *et al.*[1] and Wei *et al.*[2] draw attention to the dynamics of HIV replication *in vivo*, through close observation of the response of plasma viraemia, quantified by RNA PCR, to antiretroviral therapy. In all subjects, HIV RNA levels fell rapidly over the first 7 days of therapy at a constant rate. Reduction in viral load was associated with a prompt elevation in CD4 number, which appeared to be related to interruption of viral replication consequent to antiretroviral therapy. The rapid reduction of HIV viral load by RNA PCR and parallel CD4 increase has been observed with diverse drugs[3].

We demonstrate a novel, distinct pattern of reduction in viral load in HIV infection that is slow, sustained and associated with a parallel reduction in CD4 number. We believe this observation has implications for the pathogenesis of HIV infection.

The patient, a 36-year-old HIV-1-infected homosexual male, developed psoriasis in 1991; diverse topical and systemic agents were prescribed, without clinical benefit. By June 1993, the patient was incapacitated by psoriatic arthropathy and generalized pustular psoriasis, and 250 mg per day cyclosporin A (CyA) was given as a last resort, in the full knowledge that HIV infection may be accelerated by concomitant immunosuppression. There was a dramatic clinical response: there was a reduction of viral load of 84% ($0.87 \times \log_{10}$) over 30 weeks, which was sustained. But in contrast to the data presented in refs 1 and 2, CD4 number fell from 960 to $530 \times 10^6\ l^{-1}$ over this period. The relationship of these changes to CyA therapy was demonstrated when the patient ceased therapy about week 50–54, on account of an unrelated alcoholic hepatitis. Viral load and CD4 rose to baseline off therapy, and fell again when CyA was recommenced on week 70. No other therapy was given over this entire period.

CyA is known to inhibit T-cell activation; we believe that these data provide evidence *in vivo* for the importance of T-cell activation in permitting HIV replication. CyA reduces $CD4^+$ T-cell number, but also inhibits HIV replication by removing the host cell target. There has been speculation that there seems to be a ceiling *in vivo* for the absolute level of plasma viraemia; our observations suggest that the level of plasma viraemia may be determined by the level of availability of the activated target $CD4^+$ cell. The use of glucocorticoids to reduce T-cell activation has recently been reported, but although these lead to an increase in CD4 cells, viral load is unaltered[4].

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HO *ET AL.* REPLY — The most substantive point raised by the letters printed above concerns CD4 lymphocyte redistribution, rather than proliferation, as an explanation for the rise in CD4 cell counts following treatment with potent antiretroviral agents. Although lymphocyte re-trafficking is a plausible explanation, as pointed out by Mosier, Sprent and Tough, Dimitrov and Martin, and Phillips *et al.*, several observations collectively argue against this suggestion.

First, the elevations in CD4 cell counts were not transient, but were sustained as long as the antiviral effect was maintained, in some cases for more than 6 months. Second, in other studies, CD4 lymphocyte increases associated with viral suppression were accompanied by significant clinical improvement[1]. Third, in our recent unpublished studies, the surface-marker phenotypes of CD4 lymphocytes post-therapy differ substantially from those before treatment. In particular, our preliminary data reveal the expression of a number of activation markers on many of the CD4 lymphocytes after treatment, a finding that supports lymphocyte repopulation by cellular proliferation but argues against lymphocyte redistribution, because, as stated by Sprent and Tough, "most of the $CD4^+$ cells would be expected to display a resting rather than an activated phenotype" if the latter were true.

In reanalysing our data, Mosier found a positive correlation between the exponential slope of the CD4 lymphocyte increase and the baseline plasma level or the viral turnover rate, whereas we showed an inverse correlation with the baseline CD4 lymphocyte count[2]. These findings are fundamentally the same, as all three parameters (viral load, viral turnover rate and CD4 count) reflect the baseline disease status of the patient; they do not necessarily support the lymphocyte redistribution hypothesis. To address properly his notion that antiviral treatment liberates CD4 lymphocytes from trapping in lymphoid tissues, Mosier should instead correlate the slope (perhaps the linear slope would be more appropriate) of the CD4 lymphocyte increase with the magnitude of the antiviral effect.

Bukrinsky *et al.* are incorrect to suggest that we[1,2], Wain-Hobson[3] or Coffin[4] have stated or implied "that immunostimulatory therapies are doomed to fail". In addition, we do not understand their logic of comparing our calculated CD4 lymphocyte turnover rates with previous estimates for normal peripheral blood mononuclear cells, which are a mixture of B cells, CD8 lymphocytes, monocytes and divergent populations of CD4 lymphocytes.

Dimitrov and Martin question our estimates of the CD4 lymphocyte turnover rate based on a mathematical calculation. They suggest that if each infected lymphocyte produces 10^5 virions[5], then the particle turnover rates are simply too low, perhaps by four orders of magnitude, given our estimated number for infected cells. However, in their derivations, they did not take into consideration that many infected lymphocytes *in vivo* may be eliminated by immune responses before release of progeny virions. In essence, the "bullets" and "bodies" analogy of Ascher *et al.* suffers from the same point. Furthermore, in a recent follow-up study to determine more accurately the virion turnover rates, we have found that there are indeed more "bullets" than "bodies".

Phillips *et al.* and Lai *et al.* correctly point out that the linear (rather than exponential) slope of the CD4 lymphocyte increase does not correlate with the baseline CD4 cell count. However, the use of the linear model is based on the assumption that the CD4 lymphocytes are coming from a source such as the thymus. Based on lymphocyte phenotype studies, we now have evidence that the increase in CD4 cell counts is largely due to post-thymic lymphocyte proliferation.

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