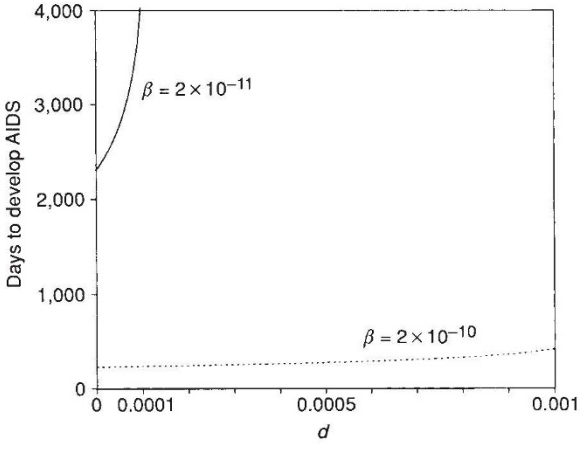
Viral burden in AIDS

SIR — Recent criticism[1] of studies of HIV infection in lymphoid tissues[2,3] claim that HIV cannot cause AIDS by a direct virus-mediated cytopathology. Sheppard *et al.*[1] state that a frequency of 1% actively infected lymph node cells is "minuscule compared to the regenerative capacity of the immune system" and that low prevalence of infected cells is "the central paradox of human immunodeficiency virus (HIV-1) infection". We show here how some simple calculations can resolve this apparent paradox.

The myth of the massive regenerative power of the human immune system seems to originate in extrapolation from mouse data[4]. Regeneration of human immune systems is probably not so rapid. Patients whose peripheral T-cell counts are halved by radiation therapy take 3–4 years to regain a normal count[5,6]. Such patients have equilibrium counts of around 2,500 cells per mm^3, and at 1,000 days post-radiotherapy their counts are around 2,000 cells per mm^3. A 'back-of-the-envelope' calculation based on these observations yields a rough estimate for the net death rate of T lymphocytes of 1 per 1,000 cells per day. (Net death rate is the difference between the proliferation rate and the death rate.) A very different estimate for this parameter (1 per 10,000 cells per day) is implied by information on the survival of lymphocytes with stable chromosome damage in the years following radiotherapy[5]. These cells pass their damage to one daughter cell on division, so the rate at which they disappear estimates their gross death rate, and hence yields an upper bound for their net death rate.

These parameters can be used in a rough calculation of the time for HIV infection to reduce the $CD4^+$ lymphocyte count to one-tenth of the uninfected level. The figure illustrates the outcome of such calculations, showing that if the net death rate of lymphocytes is around 1 per 1,000 cells per day, then all that is surprising is that with 1% of cells infected it takes so long for AIDS to develop. If, on the other hand, the net death rate is tenfold smaller, then a reduction of the population to one-tenth of its original size over about 10 years is understandable. All that is surprising is that there should be such a small difference between the proliferation rate and death rate of human peripheral $CD4^+$ cells.



AIDS incubation period as a function of the net death rate (d) of uninfected $CD4^+$ cells. Suppose that early in infection 1% of cells are actively infected and that the number of infected cells remains roughly constant during the asymptomatic phase. Suppose also that the death rate of uninfected cells is augmented by the presence of actively infected cells so that the immigration–death process describing the dynamics of uninfected cells becomes $dX/dt = \Lambda - dX - \beta XY$, where X is uninfected $CD4^+$ cells, Y is infected $CD4^+$ cells and Λ is cell immigration rate. The time taken until the $CD4^+$ count falls to one-tenth of its pre-infection value is:

$$T = \frac{1}{d+\beta Y} \ln\left[\frac{10\beta Y}{\beta Y - 9d}\right]$$

Clearly, this is defined only for $\beta Y > 9d$, and will be largest for values of β just above this value. The two lines are drawn with $\beta Y = 10d$, assuming that $Y = 5\times10^7$, that is, that an uninfected person has a $CD4^+$ count of 5×10^9 cells in total and that early in infection 1% of those are actively infected.

The calculations illustrated in the figure contain a free parameter, β, the cell-to-cell infection rate. The calculations were performed assuming that 1 in 100 cells are actively infected during the asymptomatic phase and choosing a value of β close to that which maximizes the number of days to develop AIDS. If further technological advances show that 1 in 10 cells are actively infected, exactly the same picture could be constructed by reducing the values of β by a tenth. The proportion of cells actively infected and the parameter β never appear separately. Thus to speak of a paucity of infected cells in the complete absence of quantitative information on the cell-to-cell infection rate is meaningless. In the same way, it is difficult to predict the length of the AIDS incubation period without reliable information on the normal population dynamics (and particularly the net death rate) of $CD4^+$ cells.

Populations (of cells or of animals) in which the proliferation rate is close to the death rate are particularly prone to having their density suppressed by low-prevalence infections[7]. Furthermore, as outlined above, if the net death rate is very small, one would expect such depression in population size to take place rather slowly. Thus, with certain assumptions about parameters about which very little is known, the regenerative power of the immune system, the low prevalence of HIV-infected cells, and the long time from infection to illness with AIDS form a coherent whole.

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SIR — Sheppard *et al.*[1] question work[2–6] supporting "a simple cytopathic model for AIDS pathogenesis". The arguments of Sheppard *et al.* are similar to those of other HIV iconoclasts who insist that too little HIV and too few HIV-infected cells are present to have a serious detrimental impact. It is ironic that some of the same authors[7] who dismiss the "AIDS–drug" hypothesis of Peter Duesberg appear to espouse this so-called "central paradox", a main tenet of Duesberg's case that HIV is not the cause of AIDS[8]. Like Duesberg, their arguments are based on quantitative interpretations of a single early attempt[9] to detect HIV-infected cells by *in situ* hybridization, an insensitive technique that cannot be considered quantitative, and which has since been superseded by more sensitive, quantitative assays for HIV-infected cells. Sheppard *et al.* also fail to consider work on HIV cyto-

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