pathogenesis indicating that direct cytopathic effects of HIV are adequate to explain the $CD4^+$ T-cell depletion which is the hallmark of AIDS.

Sheppard et al.[1] state that "In a cytopathic model, the rate of $CD4^+$ cell loss would be determined by the number of actively infected cells, and even a frequency of one per 100 lymph node cells (based on 1/10 infected and 90 per cent latent) is still minuscule compared to the regenerative capacity of the immune system". But the regenerative capacity of the human immune system has not been measured, particularly in AIDS patients. Components of the immune system, such as the lymph nodes, may not have infinite capacity for self-renewal. When HIV kills cells responsive to certain antigens there may not be mechanisms to restore them or to re-educate other cells to respond to these antigens. Furthermore, Sheppard et al. grossly underestimate the effects of acute HIV cytopathology on $CD4^+$ cell depletion. In cell culture experiments, for every cell persistently infected with HIV there are typically 10–20 cells killed[10,11]. In vivo, most $CD4^+$ cells dying after HIV infection will be rapidly engulfed by scavenger cells such as macrophages. Thus, in vivo (as opposed to in vitro) the actively infected cells at any cross-section in time represent only a fraction of cells dying from the acute cytopathic effects of HIV. Moreover, Sheppard et al. conclude that active HIV infection is required to compromise cell viability, but this is not supported by available data. Cells persistently infected by HIV do not have the same viability as uninfected cells. Typically, HIV-infected T-lymphoblastoid cells are only 95% viable whereas uninfected cells are greater than 99% viable[10].

The second point made by Sheppard et al. is that the high levels of plasma virus observed by Piatak et al.[4] were about 99.9% non-culturable, which Sheppard et al. believe does not support the cytopathic model. But the fact that most HIV virions present in the circulation no longer seem to be infectious is not an argument against the HIV hypothesis. HIV is not known as a stable virus, so it comes as no surprise that most plasma virus is not culturable. However, in the microenvironment of the lymph node or elsewhere, newly released and intact HIV could do substantive damage before entering the circulation. Moreover, direct toxic and immunosuppressive effects of inactivated HIV or HIV proteins are well documented[11-14]. In fact, there may be far more virion equivalents of HIV proteins present in the circulation than genomic RNA. It is not unusual to find thousands of picograms of the major HIV capsid protein p24 per ml of serum and elsewhere in HIV-infected people. Dividing Avogadro's number by the molecular mass of p24 and assuming approximately 1,000 p24 molecules per HIV virion gives an estimate of 2.5×10^4 particles per pg p24. The highest number of virion RNA equivalents of HIV measured by Piatak et al. (1.09×10^7) is an order of magnitude lower than estimates based on the 5,406 pg p24 protein per ml present in this patient (1.35×10^8 virion equivalents).

Finally, the recent data[2-4] may indeed explain the relative ineffectiveness of AIDS therapy with nucleoside analogues, but for reasons opposite to those suggested by Sheppard et al. Their suggestion that the ineffectiveness of AZT and related drugs in treatment of HIV disease is due to the slow dissemination of the infected cell burden is contrary to the fact that even early after infection there is already a massive infection of the lymph nodes and elsewhere[2,3]. It has been known for years that AZT does not affect HIV production from already infected cells (except as a result of drug cytotoxicity), explaining the high levels of plasma virus even in the presence of the drugs. Furthermore, nucleoside analogues that block the reverse transcriptase step do not block early interactions of HIV with $CD4^+$ cells. These early membrane interactions can be deleterious to cells even if further steps in HIV replication are blocked[12,15]. Thus, inactivated or defective HIV or structural proteins of the virus released from cells infected before drug therapy can be cytotoxic even in the presence of nucleoside analogues.

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Which source of mercury pollution?

SIR — Nriagu[1] concludes that the Spanish American silver mines were partly responsible for the high global background concentrations of mercury now being reported. Although there is no doubt that the atmosphere is the main pathway for the global distribution of heavy metals, I disagree with Nriagu's conclusion.

The total natural input of mercury to the atmosphere ranges from 25,000 to 50,000 tonnes per yr (ref. 2), the main source being continental degassing. In addition, the contemporary anthropogenic input of mercury to the atmosphere falls in the average range of 3,560 to 13,000 tonnes per yr (refs 2, 3), the main source being burning of fossil fuels. The residence time of mercury in the atmosphere has been estimated as 5.7 yr (ref. 2). After atmospheric transport, most of the mercury from natural and anthropogenic inputs goes to the oceans through precipitation and fluvial transport. Thus, the open oceans are the primary global reservoirs and accumulators of mercury. The average concentration of mercury in unpolluted sea water has been reported to be 0.1 p.p.b. (refs 4, 5), the total amount of mercury in the oceans ranging from 41 million to 135 million tonnes[4-7]. This is about 200–700 times Nriagu's estimate of the cumulative loss of mercury in Central and South America between 1570 and 1900. And because mercury binds tightly to many organic and inorganic materials, a fraction of that total amount settles to the bottom of the ocean every year.

Thus the contribution of the Spanish American silver mines to the high background concentrations of mercury in the global environment is negligible. Moreover, owing to the relatively long time since the mines were operational, it is probable that most of the mercury lost during the refining of silver via the *patio* process is now in the open oceans. After all, the cumulative input of mercury to the atmosphere from the combustion of fossil fuels since global industrialization is surely much higher than that from the refining of silver and gold so far (including the gold rush in California in the past century and the present gold rush in Amazonia).

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