Defective viruses and AIDS

SIR—Robin Weiss¹ and others²⁻⁵ have recently discussed the possibility that replication-defective viruses play a role in AIDS. Defective viruses may complement the host range and virulence of non-defective viruses with variant alleles of common genes or with unique genes⁶. Accordingly, defective human immunodeficiency virus (HIV) with variant *gag* or *env* genes could complement the host range and virulence of conventional HIV to generate a pathogenic virus complex^{1,2}. This notion is inspired primarily by feline and murine defective helper-virus complexes, which in animals a few weeks after experimental infection at high multiplicity, cause viraemia and some of the diseases that are now included in acquired immunodeficiency syndrome³⁻⁴.

If these animal systems were good models for AIDS, they would predict that humans develop AIDS soon after infection, carry high titres of the defective pathogen and helper HIV in primary lesions, and transmit AIDS with a latency of weeks or months. Furthermore, asymptomatic carriers of HIV should be protected against AIDS, and could in fact transmit a protective live vaccine. Yet none of these predictions is confirmed⁷. I suggest that even if a defective pathogenic virus arose in a human or in an animal outside the laboratory, it would not survive under natural conditions of transmission, and hence would not be relevant for the AIDS epidemic for the following reasons.

First, as the defective virus is unable to replicate on its own, pathogenicity of the complex would depend on double infection, and would thus be unstable. It is for this reason that defective viruses survive only on passage at high multiplicity of infection. Classical examples are the defective von Magnus influenza virus⁸ and the defective Bryan 'high titre' strain of Rous sarcoma virus^{9,10}. Indeed, a few passages at low multiplicity — termed biological cloning — are the orthodox method to rid virus stocks of defective variants. Because natural virus transmission is almost always based on low multiplicity of infection — perhaps often initiated by only one infectious unit — none of these experimentally generated virus complexes could survive in nature. This would be particularly true for HIV, whose titres *in vivo* are too low to be measured directly⁷.

Second, even in the rare cases where both a defective and a non-defective HIV were transmitted naturally or via a doubly infected cell to the same cell of a susceptible host, or if the defective version arose *de novo*, virus spread within the host would discriminate against the defective

component of the virus complex. As the helper virus is autonomous, it can out-replicate the defective virus by single infection, shifting the balance in favour of the non-pathogenic helper virus. Moreover, helper virus-infected cells would further discriminate against the defective pathogen by interference¹¹. Because the defective virus is packaged (pseudotyped) by the envelope proteins of the non-defective HIV, it would be either entirely (if it lacks *env*) or partially (if it lacks *gag*) excluded from all helper virus-infected cells.

Finally, all infections by non-defective HIV alone would further discriminate against natural transmission of the virus complex by antiviral immunity. Indeed, it was induction of interference and immunity against defective pathogenic retroviruses that earned non-defective helper viruses the term resistance-inducing factors¹¹. Even on simultaneous infection, the range of the hypothetical defective AIDS pathogen would be restricted by the same

antiviral immunity that restricts its helper virus⁹. In other words, a positive 'AIDS test' of an asymptomatic person, which detects antibody to HIV, should be considered a certificate of vaccination rather than a prognosis for death.

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- Weiss, R.A. *Nature* **338**, 458 (1989).
- Haas, M. *Cancer Res.* **49**, 2184–2187 (1989).
- Aziz, D.C., Hanna, Z. & Jolicoeur, P. *Nature* **338**, 505–508 (1989).
- Overbaugh, J., Donahue, P.R., Quackenbush, S.L., Hoover, E.A. & Mullins, J.I. *Science* **239**, 906–910 (1988).
- Lusso, P. *et al.* *Nature* **337**, 370–373 (1989).
- Weiss, R., Teich, N., Varmus, H. & Coffin, J. *RNA Tumor Viruses* (Cold Spring Harbor Laboratory, New York, 1985).
- Duesberg, P.H. *Proc. natn. Acad. Sci. U.S.A.* **86**, 755–764 (1989).
- Duesberg, P.H. *Proc. natn. Acad. Sci. U.S.A.* **59**, 930–937 (1968).
- Shimizu, T. & Rubin, H. *J. natn. Cancer Inst.* **33**, 79–91 (1964).
- Gross, L. *Oncogenic Viruses* (Pergamon, Oxford 1970).
- Rubin, H., Fanshier, L., Corneliuss, A. & Hughes, W.F. *Virology* **17**, 143–156 (1962).

Sulphate aerosols and climate

SIR—I proposed¹ that anthropogenic SO₂ emissions serve as a surrogate for enhanced marine dimethyl-sulphide (DMS) emissions to test the hypothesis of Charlson *et al.*² that marine DMS emissions regulate global cloud albedo and mean temperature by enhancing the number density of aerosol sulphate particles that serve as cloud condensation nuclei (CCN). I concluded that no influence of anthropogenic SO₂ emissions (confined predominantly to the Northern Hemisphere (NH)) of magnitude consistent with the sensitivities postulated in ref. 2 was found in inter-hemisphere comparisons either of present cloud contribution to planetary albedo or of 100-year temperature trends. None of the authors of the letters^{3,7,15,20} commenting on my paper, has come to grips with the fact that a major perturbation in emissions (tripling of NH gaseous sulphur emissions) should, if the hypothesis² is correct, have resulted in major perturbations of cloud contribution to albedo and mean temperature, neither of which is evident. By focusing on the trees of my argument, they have failed to perceive the forest.

Ghan *et al.*³ suggest that in continental air there may be an overabundance of CCN compared with over the ocean, making this air insensitive to incremental CCN derived from anthropogenic SO₂. In fact, the high concentrations of CCN commonly present in continental and continentally-influenced air may be due largely to human activity. There is abundant evidence (for example, refs 4,5) that the presence of anthropogenic sulphate greatly increases cloud droplet number densities in the continental air into which

it is emitted and in continentally-influenced air. While a nonlinear relation between cloud droplet and aerosol particle number density is evident, droplet number density is drastically enhanced in air influenced by industrial emissions relative to background continental air. Moreover, as air containing high CCN concentrations is diluted by mixing with cleaner air, the efficiency of the nuclei in nucleating cloud droplets would be expected to increase^{5,6}. A decreased efficiency at CCN concentrations of 1,000 or more per cm³ should not therefore be viewed as invalidating my argument.

A major premise of my article was that aerosol sulphate persists sufficiently long in the atmosphere for industrial SO₂, whose emissions are highly localized, to exert an influence throughout much of the NH marine atmosphere. I am surprised that Charlson *et al.*⁷ question this. Elsewhere Lovelock⁸ has taken it for granted in support of the assertion that tropospheric air in the NH and Southern Hemisphere (SH) does not freely mix, "as any observer travelling on a ship through tropical regions will readily perceive from the difference in clarity of the skies between the clean Southern and relatively dirty Northern hemispheres".

Charlson *et al.* question the suitability of the data presented in Table 2 of my paper to support the claim of widespread NH influence of anthropogenic sulphate, citing concern over comparing total non-sea-salt sulphate (n.s.s. SO₄²⁻) with fine (below ~1 µm, sub-µm) n.s.s. SO₄²⁻. Although I share this concern, I note that only 3 of the 11 SH data sets cited were for the sub-µm fraction, and that these measurements were explicitly compared with NH measurements that obtained much greater concentrations using the