- and after switching to monoclonal high-purity factor VIII concentrate in HIV-infected haemophilic patients. *Thromb Haemost* 1994;72:214-7.
- 9 Seremetis SV, Aledort LM, Bergman G, Bona R, Bray G, Brettler D, *et al*. Three-year randomised study of high-purity or intermediate-purity factor VIII concentrates in symptom-free HIV-seropositive haemophiliacs: effects on immune status. *Lancet* 1993;342:700-3.
 - 10 Goedert JJ, Cohen AR, Kessler CM, Eichinger S, Seremetis SV, Rabkin CS, *et al*. Risks of immunodeficiency, AIDS and death related to purity of factor VIII concentrate. *Lancet* 1994;344:791-2.
 - 11 Bofill M, Janossy G, Lee CA, MacDonald-Burns D, Phillips AN, Sabin C, *et al*. Laboratory control values for CD4 and CD8 T lymphocytes. Implications for HIV-1 diagnosis. *Clin Exp Immunol* 1992;88:243-52.

- 12 Schulman S. Effects of factor VIII concentrates on the immune system in hemophilic patients. *Ann Hematol* 1991;63:145-51.
- 13 Madhok R, Gracie A, Lowe GD, Burnett A, Froebel K, Follett E, *et al*. Impaired cell mediated immunity in haemophilia in the absence of infection with human immunodeficiency virus. *BMJ* 1986;293:978-80.
- 14 Phillips AN, Lee CA, Elford J, Webster A, Janossy G, Timms A, *et al*. More rapid progression to AIDS in older HIV-infected people: the role of the CD4+ T-cell counts. *Journal of the Acquired Immune Deficiency Syndrome* 1991;4:970-5.

(Accepted 11 October 1995)

Commentary: non-HIV hypotheses must be studied more carefully

Peter Duesberg

Patients with haemophilia treated with commercial factor VIII and zidovudine are at risk of developing AIDS defining immunodeficiency diseases like pneumonia, candidiasis, and toxoplasmosis but not Kaposi's sarcoma or dementia. Their risk of these diseases is proportional to their lifetime dosages of factor VIII and cytotoxic DNA chain terminators like zidovudine.^{1 1a}

Haemophilia specific AIDS diseases have been explained in terms of two hypotheses. A non-infectious hypothesis holds that the long term administration of immunosuppressive foreign proteins contaminating commercial factor VIII and zidovudine causes AIDS. An infectious hypothesis holds that HIV causes AIDS.¹

Still no evidence for infection

Based on inadequate tests, Sabin *et al* reject the foreign protein-zidovudine hypothesis.² However, their data and those of others actually support the hypothesis.

Sabin *et al* claim that HIV causes AIDS because all of their haemophilic patients had antibodies against the virus. But HIV cannot be enough for AIDS because six of their 17 HIV positive patients (table 2) remained healthy for 10 years. Likewise 12 000 out of 15 000 HIV positive American haemophilic patients have remained AIDS free since 1985.^{1 3}

Sabin *et al* observe that AIDS diseases occur, if at all, only five to 10 years after the appearance of antibodies to HIV. However, "viral" AIDS should occur within weeks after infection because viruses replicate exponentially. A single infected cell produces over 100 HIV virions within 48 hours,⁴ generating 10¹⁴ viruses within two weeks after infection—enough to infect every cell in the human body. Moreover, viral AIDS should be neutralised—not caused—by the antiviral immunity that is detectable in haemophilia.

By contrast, long time periods are required to accumulate pathogenic doses of foreign proteins via transfusions.¹ Because HIV is a rare contaminant of factor VIII, it seems to be just a surrogate marker for high dosages of foreign proteins. Sabin *et al* confirm this: "Most patients with severe haemophilia—and therefore the highest users of clotting factor concentrate—were seropositive to HIV. . . ."² Thus their results support the foreign protein hypothesis.

An appropriate test of the foreign protein hypothesis would compare HIV positive patients with HIV negative patients matched for the lifetime dosage of factor VIII. By contrast, Sabin *et al* matched patients for current usage. Plainly, a 60 year old and a 14 year old would not be an appropriate match (table 1).²

The HIV hypothesis predicts the same pattern of AIDS diseases in haemophilia as in other AIDS patients, but Kaposi's sarcoma and dementia were not

observed in the haemophilic patients studied by Sabin *et al* (table 2). However, the foreign protein-zidovudine hypothesis predicts the restriction to immunodeficiency diseases observed by Sabin *et al* exactly.

The HIV hypothesis predicts sexual transmission of AIDS. However, in the United States the wives of 15 000 HIV positive haemophilic men have only the normal background prevalence of AIDS defining diseases.^{1 5}

Strong temporal evidence

HIV is now said to cause AIDS 10 years after infection, and infections by transfusions were stopped in 1985. Hence AIDS in patients with haemophilia should have peaked long before 1995. Instead, cases declined until 1986¹ and then sharply increased from 1987 both in the United States and in Britain when zidovudine and other drugs were introduced as treatment for and prophylaxis against HIV infection and AIDS.^{6 7}

Zidovudine kills all growing cells, particularly fast growing blood cells, and therefore must cause immunodeficiency. Even the manufacturer acknowledges, "It is often difficult to distinguish adverse events possibly associated with zidovudine administration from underlying signs of HIV disease."⁸ An epidemiological study cited by Sabin *et al* directly confirms that zidovudine treated HIV positive haemophilic patients have a 4.5-fold higher annual AIDS rate and a 2.4-fold higher annual death rate than untreated controls.⁹ This explains why the morbidity of American⁶ and British⁷ patients with haemophilia has sharply increased since 1987, when most HIV positive haemophilic patients began zidovudine.^{1 1a} Sabin *et al* confirm the zidovudine hypothesis, as "all nine HIV positive patients with AIDS received zidovudine" in addition to the "toxic" pentamidine,¹⁰ co-trimoxazole, and fluconazole.²

The foreign protein hypothesis predicts that AIDS in patients with haemophilia can be prevented if not cured by using factor VIII that is free of foreign protein. Sabin *et al* endorse this: "These concentrates seem to preserve the immune system. . . ." Indeed, not only were the immune systems of HIV "positive" haemophilic patients treated with pure factor VIII and no zidovudine "preserved" but their T cells increased by up to a quarter over three years—despite the presence of the hypothetical T cell killer HIV.^{11 12}

Conclusion

The foreign protein-zidovudine hypothesis provides biochemically plausible candidates for pathogenicity—that is, large amounts of foreign proteins transfused over decades and DNA chain terminators prescribed

indefinitely such as zidovudine. With a daily dose of 500 mg zidovudine a person receives 2×10^{20} molecules, or 2×10^6 for every human cell, every day for the rest of his life. By contrast, after 11 years of research the HIV hypothesis has yet to identify a single molecule that could be pathogenic.¹³ In view of this and the complete failure of the HIV hypothesis to produce public health benefits, non-HIV hypotheses must be studied more carefully.

- 1 Duesberg P. Foreign-protein-mediated immunodeficiency in hemophiliacs with and without HIV. *Genetica* 1995;95:51-70.
- 1a Duesberg P. Is HIV the cause of AIDS? *Lancet* 1995;346:1371-2.
- 2 Sabin CA, Pasi KJ, Phillips AN, Lilley P, Boffill M, Lee CA. Comparison of immunodeficiency and AIDS defining conditions in HIV negative and HIV positive men with haemophilia A. *BMJ* 1996;312:207-10.
- 3 Centers for Disease Control and Prevention. US HIV and AIDS cases reported through December 1994. *HIV/AIDS Surveillance Report* 1994;6:1-39.
- 4 Ho D. Quantification of human immunodeficiency virus in the blood. *N Engl J Med* 1990;322:1467.
- 5 Kreiss JK, Kasper CK, Fahey JL, Weaver M, Visscher BR, Stewart JA, et al.

- Nontransmission of T-cell subset abnormalities from hemophiliacs to their spouses. *JAMA* 1984;251:1450-4.
- 6 Chorba TL, Holman RC, Strine TW, Clarke MJ, Evatt BL. Changes in longevity and causes of death among persons with hemophilia A. *Am J Hematol* 1994;45:112-21.
- 7 Darby SC, Ewart DW, Giangrande PLF, Dolin PJ, Spooner RJD, Rizza CR, et al. Mortality before and after HIV infection in the complete UK population of haemophiliacs. *Nature* 1995;377:79-82.
- 8 Retrovir. In: *Physicians' desk reference*. Oradell, New Jersey: Medical Economics Data Protection Company, 1994:742-6.
- 9 Goedert JJ, Cohen AR, Kessler CM, Eichinger S, Seremetis SV, Rabkin CS, et al. Risks of immunodeficiency, AIDS, and death related to purity of factor VIII concentrate. *Lancet* 1994;344:791-2.
- 10 Stedman TL, et al. Pentamidine isethionate. In: *Stedman's medical dictionary*. Baltimore: Williams and Wilkins, 1982:1049-50.
- 11 De Biasi R, Rocino A, Miraglia E, Mastrullo L, Quirino AA. The impact of a very high purity of factor VIII concentrate on the immune system of human immunodeficiency virus-infected hemophiliacs: a randomized, prospective, two-year comparison with an intermediate purity concentrate. *Blood* 1991;78:1919-22.
- 12 Seremetis SV, Aledort LM, Bergman GE, Bona R, Bray G, Brettler D, et al. Three-year randomised study of high-purity or intermediate-purity factor VIII concentrates in symptom-free HIV-seropositive haemophiliacs: effects on immune status. *Lancet* 1993;342:700-3.
- 13 Cohen J. Researchers air alternative views on how HIV kills cells. *Science* 1995;269:1044-5.

Response: Arguments contradict the "foreign protein-zidovudine" hypothesis

Caroline A Sabin, Andrew N Phillips, Christine A Lee

In 1991 Duesberg challenged researchers to provide either data on "controlled epidemiologic studies comparing matched hemophiliacs, with and without HIV, or epidemiological evidence that the mortality of hemophiliacs is increased by HIV."¹ We and Darby *et al* have provided that evidence.^{2,3} Duesberg's commentary⁴ requires further comment.

HIV may be enough to cause AIDS

It is incorrect to conclude that HIV is not sufficient to cause AIDS simply because some of the infected patients in our study had not developed AIDS by 10 years after seroconversion. Only longer term follow up studies will finally establish whether all HIV positive patients would, given enough time, ultimately develop AIDS. In the United States around 3800 haemophilic patients have reportedly developed AIDS out of 9000 who have been infected⁵ (World Federation of Hemophilia, personal communication, 1995), a far higher proportion than that quoted by Duesberg in arguments against the HIV hypothesis.

Duesberg's foreign protein-zidovudine hypothesis predicts that haemophilic patients will not develop non-immunodeficiency diseases such as dementia. Given the low prevalence of some of the 26 different AIDS defining conditions it would not be expected that we should witness all conditions among our 17 patients. However, dementia is well documented in HIV positive haemophilic patients and occurs with a similar prevalence to that in other exposure categories (Xen Santas, Centers for Disease Control, personal communication, 1995). Among all 111 HIV positive haemophilic patients at this hospital, dementia occurred in six.

Duesberg points out that lifetime usage of concentrate may be expected to be different between a 60 year old and a 14 year old (our pair 3). Unfortunately, lifetime usage of concentrate was not available in these patients and therefore usage patterns over 10 years were used. However, it is important to remember that clotting factor concentrate was introduced in our centre in 1978 on average, so that age differences in the pairs may suggest larger differences in lifetime usage than actually existed. Even when the analysis was restricted to pairs in whom the HIV positive patient was younger than or the same age as the HIV negative

patient (eight pairs) the results remained similar: four of eight HIV positive patients developed AIDS defining diseases compared with none of the eight HIV negative patients. Furthermore, since 1980 none of 400 HIV negative haemophilic patients registered at this hospital has developed AIDS despite having received clotting factor concentrates on average since 1978, and CD4 counts in these patients have been similar to those of HIV negative heterosexual subjects.⁶

Contrary to Duesberg's assertion, sexual transmission of AIDS has been observed at our centre. At the Royal Free Hospital sexual transmission of HIV to partners with no other risk factors for HIV has occurred in three cases. Of these infected partners, one developed AIDS and died (the haemophilic partner of this patient also died with AIDS), one was symptomatic with a CD4 count of zero but remained AIDS free, and the third remained asymptomatic but with a CD4 count of $0.2 \times 10^9/l$. No wives of any other haemophilic patients at our centre have developed AIDS.

Patients are given zidovudine because they are ill

It is not true that most British haemophilic patients infected with HIV have been given zidovudine since 1987. Initially patients were given zidovudine after the development of AIDS. Subsequently, since around 1989, patients have been given zidovudine once their CD4 count has fallen below $0.2 \times 10^9/l$ or after the development of symptomatic disease. Similar recommendations are made for pentamidine or co-trimoxazole as prophylaxis against *Pneumocystis carinii* pneumonia. Consequently, by the time patients begin zidovudine and pentamidine they have low CD4 cell counts and are usually symptomatic.

Observational studies often show that patients given zidovudine have a worse prognosis than untreated patients.⁷ Patients receiving zidovudine are selectively treated because they are ill. The interpretation of findings from these studies should not therefore be that zidovudine increases the risk of AIDS. Of the nine patients developing AIDS in our study, seven received zidovudine only after an initial AIDS diagnosis when immunological deterioration had already occurred. There is no possibility, therefore, that either

HIV Research Unit,
Department of Public
Health, Royal Free
Hospital School of
Medicine, London
NW3 2PF

Caroline A Sabin, lecturer in
epidemiology and medical
statistics

Andrew N Phillips, reader in
epidemiology and biostatistics

Haemophilia Centre and
Haemostasis Unit,
Department of
Haematology, Royal Free
Hospital and School of
Medicine, London
NW3 2PF

Christine A Lee, director
haemophilia centre

Correspondence to:
Dr Sabin.