

equally applicable, or better? Current pilot studies suggest that they probably are, provided that cheaper gene probes and methods for their labelling can be developed. This is a very important problem because as the high mortality rate in the first year of life due to malnutrition and infection is controlled in these countries, genetic diseases will pose an increasingly serious problem; there are already an estimated 700 000 severely affected children in Thailand for example.

But in a world in which millions of children die each year of starvation, the major medical application of recombinant DNA technology should be via improving world food supplies (see Dr Swaminathan's review, Dec 8) and for developing vaccines and diagnostic agents for parasitic and infectious diseases which, together with malnutrition, still look like being the main killers of the 21st century.

One of the major challenges arising from the development of biotechnology is how to persuade the governments and biotechnology industries of the developed countries that the problems of the Third World are worth tackling. Their present track records suggest that they will wish to confine their energies to diseases of western society where the financial rewards are greatest. It is sobering to reflect that if we were to develop a malaria vaccine over the next year or two it might be very difficult to find a biotechnology company to produce and market it. The first question they will ask is who will pay for the product; the answer is not obvious.

#### *Broader Implications of Human Molecular Biology*

The advent of recombinant DNA technology has raised the expectation that, as we gradually gain control over our genome, we may be able to modify the human phenotype more or less as we please. Already we have been regaled by television accounts of potential parents wandering around gene supermarkets stocking up their trolleys with genes that they would like to see expressed in their children, and fears of positive eugenics, with overtones of Nazi Germany, have been raised again—fears put into more sensible context by Professor Rose (Dec 15). There is no doubt that biological determinism is having a major impact on sociobiology and that the uncertain science which underlies this philosophy has already provided a convenient peg on which a few less balanced political groups have hung their views on how society should be regulated. But the fact is that we do not have the faintest idea about the nature of the complex interactions of genome and environment that underlie human behaviour. Indeed it is debatable whether we shall ever be able to adequately define love, greed, or jealousy, let alone the final movement of the "Jupiter" symphony, in terms of a DNA sequence. Perhaps in the long term our exploration of the human genome will provide some real insights into why we are what we are but it would be unwise to pin our hopes for the future on this expectation. In the meantime we must exploit the extraordinary medical possibilities of the new DNA technology, and try to ensure that our increasing knowledge of the human genome is not used prematurely to provide a basis for ill-conceived sociobiological theory and political extremism.

#### FURTHER READING

- Bodmer WJ. Implications of advances in genetics for the future. In: Messel H, ed. *The biological manipulation of life*. Oxford: Pergamon Press, 1981: 311-28.  
 Medawar PB. *Pluto's republic*. Oxford: Oxford University Press, 1962.  
 Rose S, Kamin LJ, Lewontin RC. *Not in our genes*. Harmondsworth: Penguin Books, 1984.  
 Vanc J, Cuatrecasas P. Genetic engineering and pharmaceuticals. *Nature* 1984; **312**: 303-05.  
 Weatherall DJ. *The new genetics and clinical practice*, 2nd ed. Oxford: Oxford University Press (in press).

## Public Health

### HTLV-III SEROPOSITIVITY IN EUROPEAN HAEMOPHILIACS EXPOSED TO FACTOR VIII CONCENTRATE IMPORTED FROM THE USA

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**Summary** 77 Scottish haemophiliacs and 22 Danish haemophiliacs were serologically tested for antibodies to human T-cell leukaemia virus III (HTLV-III). Since 1979 the Scottish patients had been treated largely with factor VIII concentrate produced in Scotland, whereas all but 2 of the Danish patients had received both locally prepared concentrate and commercial concentrate made from US donor material. 15.6% of Scottish and 59.1% of Danish haemophiliacs were antibody positive ( $p < 0.001$ ). None of 11 haemophiliacs not treated in the period 1979-84 was seropositive. 2 (6.7%) of 30 subjects who had been treated with locally produced concentrate only were antibody positive, compared with 23 (39.7%) of 58 subjects who had been treated with commercial concentrate. Among 52 users of both commercially and locally produced factor VIII concentrate, seropositivity was directly correlated with the consumption of commercial concentrate ( $p < 0.001$ ) but not locally produced material. These data indicate that European haemophiliacs were exposed to HTLV-III via some factor VIII concentrates obtained from the USA.

#### INTRODUCTION

HAEMOPHILIACS are at increased risk of the acquired immunodeficiency syndrome (AIDS).<sup>1,2</sup> In the United States this risk group comprises 1% of all diagnosed cases of AIDS, whereas in Europe, at the beginning of 1984, 8 (2.5%) of 314 cases had been reported among haemophiliacs.<sup>3</sup> AIDS is believed to be transmitted via the clotting-factor preparations used by these patients,<sup>4-6</sup> and antibodies to the probable causal agent(s), human T-cell leukaemia virus III (HTLV-III) or lymphadenopathy-associated virus, have been sought in haemophiliacs. Initial prevalence studies revealed a high prevalence of antibodies to these viruses in European<sup>7</sup> and American haemophiliacs<sup>8</sup> (and Goedert JJ, Sarngadharan MG, Eyster ME, et al, unpublished). We have compared HTLV-III antibody prevalences in two populations of haemophiliacs—Scottish patients who mainly use factor VIII concentrate of local origin, and Danish patients who use both imported and locally manufactured concentrates.

#### MATERIALS AND METHODS

Blood was taken from Danish haemophiliacs in Aarhus, during routine health evaluation in April, 1984, and plasma was kept at  $-70^{\circ}\text{C}$  until testing. Detailed information was available on the

amount and origin of factor VIII or IX used by each patient since 1979. Similar data were obtained on Scottish haemophiliacs enrolled in the Regional Haemophilia Reference Centre, Glasgow. Blood was taken from these patients between December, 1983, and July, 1984.

Antibody to HTLV-III was measured by an enzyme-linked immunosorbent assay<sup>9</sup> in which disrupted whole virus (HTLV-III-H9)<sup>10</sup> was the substrate. Samples were run in duplicate and a known negative control was run eight times on each microtitre plate, the results for each being averaged. Sample results were compared with negative control results through the ratio of the two values.<sup>11</sup> Antibody was recorded as present if the ratio between sample and background was  $>5.0$ , and as borderline if the ratio was between 3.0 and 5.0. Tests for significance ( $\chi^2$  squared and Wilcoxon-Mann-Whitney W test<sup>12,13</sup>) compare antibody-positive with antibody-negative persons, persons with borderline ratios being excluded.

## RESULTS

### Patient with AIDS

A 35-year-old Scottish haemophilia A patient with no other AIDS risk factors had since 1979 been treated exclusively with US manufactured factor VIII concentrate in high dosage. In his last 7 months, he had malaise, anorexia, weight loss, intermittent fever, lymphadenopathy, and night sweats. There were persistent herpetic lesions of the lips and oral cavity, and also candidiasis of the mouth and anus. Lately he complained of dysphagia and central sternal pain. He was HTLV-III seropositive, lymphopenic, and moderately thrombocytopenic, and had reduced responses to several mitogens. T helper cell numbers were reduced, as was the helper/suppressor ratio (May, 1984, 0.64; July, 1984, 0.29). In September, 1984, he was admitted to hospital with streptococcal septicaemia and he died in late October with *Pneumocystis carinii* pneumonia.

### Healthy Haemophiliacs

22 Danish haemophiliacs (mean age, 22.8 yr, range 12-46) and 77 Scottish haemophiliacs (mean 34.9 yr, range 13-72) were enrolled. 12 (57%) of 21 Danish haemophilia A patients had antibodies against HTLV-III, as did a single haemophilia B patient (total, 59% positive; table 1). Between 1979 and 1984 antibody-positive subjects with haemophilia A had received significantly ( $p < 0.05$ ) larger quantities of factor

TABLE 1—HTLV-III SEROPOSITIVITY IN HEALTHY SCOTTISH AND DANISH HAEMOPHILIACS

	Total tested	HTLV-III antibody positive (%)
<i>Scotland:</i>		
No treatment	11	0 (0.0)
Local	28	2 (7.1)
Commercial	4	1 (25.0)
Both	34	9 (26.5)
Total	77	12 (15.6)
<i>Denmark:</i>		
Local	2	0 (0.0)
Commercial	1	1 (100.0)
Both	19	12 (63.2)
Total	22	13 (59.1)
<i>Both countries:</i>		
No treatment	11	0 (0.0)
Local	30	2 (6.7)
Commercial	5	2 (40.0)
Both	57*	21 (39.6)
Total	99	25 (25.3)

\*Detailed information on use of factor VIII concentrate missing on 1 subject (see figure).

TABLE 2—MEAN UNITS OF LOCAL AND COMMERCIAL FACTOR VIII CONCENTRATE USED BY SEROPOSITIVE AND SERONEGATIVE HAEMOPHILIA A PATIENTS, 1979-84

	HTLV-III antibody		
	Positive	Negative	p*
<i>Scottish</i>			
Local	202.700	98.700	$>0.05$
Commercial	144.900	9.100	$<0.001$
<i>Danish</i>			
Local	195.500	144.200	$>0.05$
Commercial	498.800	83.800	$<0.05$

\*Wilcoxon-Mann-Whitney (W) test.

TABLE 3 HTLV-III SEROPOSITIVITY IN HEALTHY HAEMOPHILIA A AND B PATIENTS

	Total tested	HTLV-III positive (%)
<i>Scotland</i>		
Haemophilia A	62	11 (17.7)
Haemophilia B	15	1 (6.7)
<i>Denmark</i>		
Haemophilia A	21	12 (57.1)
Haemophilia B	1	1 (100.0)

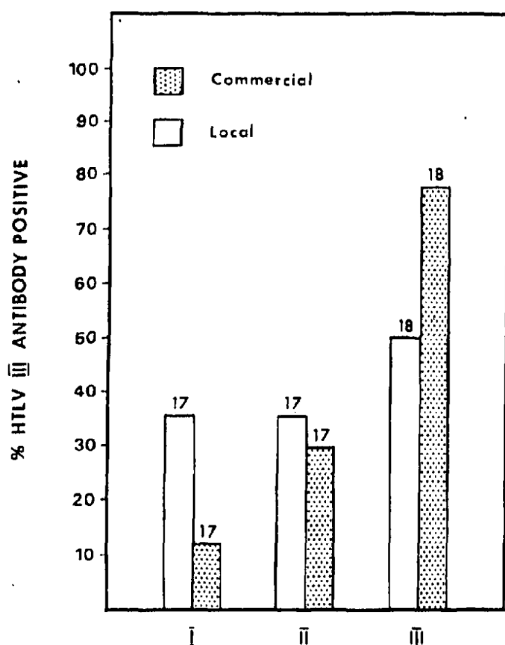
VIII concentrate made from US donor material (mean 498.8 units) than antibody-negative subjects (mean 83.8 units). There was no statistical difference between the amounts of locally manufactured concentrate used in the two groups (table 2). The 2 subjects who had not received factor concentrate made from US donor material in the period 1979-84 were both seronegative, whereas the seropositive haemophilia B patient had used only US manufactured factor IX concentrate.

In Scotland, 11 (18%) of 62 haemophilia A patients and 1 (7%) of 15 haemophilia B patients were HTLV-III positive (tables 1 and 3). All but 2 of the seropositive subjects were known to have received commercial factor concentrate in the period 1979-84: one had travelled yearly throughout Europe and could have received unrecorded treatment; the other was a citizen of Pakistan who often visited his home country. Seropositive haemophilia patients had received more commercial clotting factor concentrate than seronegative subjects ( $p < 0.001$ ), whereas there was no statistical difference between the two groups in use of local products.

As shown in table 1, 40% of subjects receiving commercial factor concentrate either alone or in combination with local products had antibodies against HTLV-III, compared with 6.7% of those recorded as receiving only local products. HTLV-III seropositivity was more common in persons more exposed to commercially produced factor VIII (figure). The proportion with antibody rose from 11.8% among subjects in the bottom third of commercial product use to 29.4% in the middle third and 77.8% in the top third (trend analysis,  $p < 0.001$ ). In contrast, no significant difference in seropositivity was observed between groups classified according to their use of locally produced factor VIII concentrate.

## DISCUSSION

Since 1982, almost all treatment in Glasgow has been with locally produced factor concentrate. Therefore exposure to the HTLV-III antigen is likely to have taken place among Scottish patients before then. In line with this observation are data from another study showing that some American haemophiliacs were infected as far back as in 1979 (Goedert JJ, unpublished). Clinical AIDS in an American citizen can



Percentage HTLV-III seropositivity among 52 haemophiliacs distributed into thirds according to use of both commercially and locally produced factor VIII concentrate.

Number of subjects tested is at top of each column. Use: I=lowest, II=middle, III=highest. Trend analysis: local, not significant; commercial,  $p < 0.001$ .

be traced back to 1978;<sup>3</sup> so the virus must have been present in the United States before this date. In 1981, 9% of Danish homosexual men had antibodies against HTLV-III and seropositivity was most strongly correlated with travel to the United States and especially to New York City.<sup>14</sup> These and other<sup>3,15</sup> observations suggest that, in terms of prevalence of HTLV-III antibodies and incidence of AIDS, European homosexuals are 1–2 years behind those in the United States. However, the prevalence rates of HTLV-III antibodies in Danish haemophiliacs are similar to those in American haemophiliacs, probably because of the use of US plasma products. Furthermore, the estimated incidence of AIDS among American haemophiliacs, 1–2 per thousand, is very close to that in European haemophiliacs (1 per thousand).<sup>16</sup>

Our findings suggest that HTLV-III was distributed through haemophilic populations by factor VIII concentrate made from US donor material. Although a high proportion of patients exposed to such products were seropositive, the effects on their health remain to be clarified. Both HTLV-III and lymphadenopathy-associated virus have been isolated from haemophiliacs with AIDS.<sup>17,18</sup> Furthermore, mouse type C retroviruses have proved to withstand the procedures used for factor VIII concentration;<sup>19</sup> however, lymphadenopathy-associated virus is labile under certain circumstances.<sup>20</sup> In addition, most factor preparations are stored for months at 4°C before use, and this might inactivate the virus while preserving its immunogenicity.

People in groups at high risk of AIDS are now asked to exclude themselves as donors; this should reduce the risk

from future batches of factor concentrates. However, until viral contamination can be completely eliminated it seems desirable to treat newly diagnosed haemophilic children with concentrates from donors living in low-risk areas.

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#### REFERENCES

- Centers for Disease Control. *Pneumocystis carinii* pneumonia among persons with hemophilia A. *MMWR* 1982; 31: 365–67.
- Marmor M. Risk factors. In: Ebbesen P, Biggar RJ, Melbye M, eds. *AIDS: a basic guide for clinicians*. Copenhagen/Philadelphia: Munksgaard/Saunders, 1984. 46–47.
- Melbye M, Biggar RJ, Ebbesen P. Epidemiology. Europe and Africa. In: Ebbesen P, Biggar RJ, Melbye M, eds. *AIDS: a basic guide for clinicians*. Copenhagen/Philadelphia: Munksgaard/Saunders, 1984. 29–41.
- Lederer MM, RatnofOD, Seilhan JJ, Jones PK, Schacter H. Impaired cell-mediated immunity in patients with classic hemophilia. *N Engl J Med* 1983; 308: 79–83.
- Menitsky JE, Aster RH, Casper JT, et al. T-lymphocyte subpopulations in patients with classic hemophilia treated with cryoprecipitate and lyophilized concentrates. *N Engl J Med* 1983; 308: 83–86.
- Froebel KS, Madhok R, Forbes CD, Lennie SE, Lowe GDO, Sturrock RD. Immunological abnormalities in haemophilia: are they caused by American factor VIII concentrate? *Br Med J* 1983; 287: 1091–93.
- Melbye M, Biggar RJ, Chermann JC, Montagnier L, Stenborg S, Ebbesen P. High prevalence of lymphadenopathy virus (LAV) in European haemophiliacs. *Lancet* 1984; ii: 40–41.
- Ramsey RB, Palmer EL, McDougal JS, et al. Antibody to lymphadenopathy-associated virus in haemophiliacs with and without AIDS. *Lancet* 1984; ii: 397–98.
- Saxinger C, Gallo RC. Methods in laboratory investigation. Application of the indirect enzyme-linked immunosorbent assay microtest to the detection and surveillance of human T-cell leukemia lymphoma virus. *Lab Invest* 1984; 49: 371–77.
- Popovic M, Saragadharan MG, Read E, Gallo RC. Detection, isolation, and continuous production of cytopathic retrovirus (HTLV-III) from patients with AIDS and pre-AIDS. *Science* 1984; 224: 497–500.
- Saragadharan MG, Popovic M, Bruch L, Schupbach J, Gallo RC. Antibodies reactive with human T-lymphotropic retroviruses (HTLV-III) in the serum of patients with AIDS. *Science* 1984; 224: 506–08.
- Wonnacott TH, Wonnacott RJ. Nonparametric statistics. In: Wonnacott TH, Wonnacott RJ, eds. *Introductory statistics for business and economics*, 2nd ed. Santa Barbara: Wiley, 1977. 481–500.
- Goldstein A. *Biostatistics: An introductory text*. New York: Macmillan, 1965. 114–17.
- Melbye M, Biggar RJ, Ebbesen P, et al. Seroepidemiology of HTLV-III in Danish homosexual men. Prevalence, transmission, and disease outcome. *Br Med J* 1984; 289: 573–75.
- Cheingsong-Popov R, Weiss RA, Dalgleish A, et al. Prevalence of antibody to human T-lymphotropic virus type III in AIDS and AIDS-risk patients in Britain. *Lancet* 1984; ii: 477–80.
- Bloom AL. Acquired immunodeficiency syndrome and other possible immunological disorders in European haemophiliacs. *Lancet* 1984; ii: 1452–55.
- Gallo RC, Salahuddin SZ, Popovic M, et al. Frequent detection and isolation of cytopathic retroviruses (HTLV-III) from patients with AIDS and at risk for AIDS. *Science* 1984; 224: 500–03.
- Vilmer E, Barré-Sinoussi F, Rouzioux C, et al. Isolation of new lymphotropic retrovirus from two siblings with haemophilia B, one with AIDS. *Lancet* 1984; ii: 753–57.
- Levy JA, Mitra G, Mozen MM. Recovery and inactivation of infectious retroviruses added to factor VIII concentrate. *Lancet* 1984; ii: 722–23.
- Spire B, Barré-Sinoussi, Montagnier L, Chermann JC. Inactivation of lymphadenopathy associated virus by chemical disinfectants. *Lancet* 1984; ii: 896–901.

“Viewing medicine as a battle too often reduces the patient to an object—a fragile boat, a rudderless frigate, a hapless barge of statistical misfortune tossed upon the stormy seas of illness. The doctor, in turn, views his responsibilities as a naval skirmish—a confrontation to be prepared for, fought, and won. The patient in this perspective is entirely passive. He hopes only to be saved. The doctor sends in his armada and tries to occupy disease’s strategic islands; or occasionally he has to retreat. What he does not do is relate well to his patient. The family of the patient is also relegated to the role of helpless bystander. . . . With distressing regularity, families are excluded from any substantive involvement with the physician. . . . They hover compliantly in the background while physicians, medicine’s gladiators, unsheath their swords and do battle with disease. What a waste of powerful, and potentially healing, resources!”—DAVID E. REISER and DAVID H. ROSEN. *Medicine as a human experience*. Baltimore: University Park Press, 1984: 139.