THE LANCET

Blood Transfusion, Haemophilia, and AIDS

THERE are new anxieties concerning the acquired immunodeficiency syndrome (AIDS), especially in its relation to blood transfusion and the use of plasma derivatives. The role of blood and its products in the transmission of the syndrome is being clarified by the detection of the putative virus called lymphadenopathy-associated virus (LAV) by the ench group[1] and human T cell lymphotropic virus ...f (HTLV III) by the American group.[2] The evidence that HTLV III is the cause of AIDS includes its demonstration in tissues, the high incidence of antibodies to it in patients, and the development of AIDS in infants of apparently healthy antibody-positive mothers. The last observation suggests that the antibodies are not necessarily protective; and in fact they are not neutralising in the presence or absence of complement.[3] In the UK, antibodies to HTLV III were found in less than 1 in 1000 of the general population whereas they were present in almost all the AIDS patients and in about 20% of homosexual males.[4] Although four Australian premature infants contracted the disease from one donation,[5] the chance of AIDS developing after ordinary blood transfusion is very low. About 100 transfusion-associated cases have occurred in the USA, where some three to four million transfusions are given annually—a risk over the past three years of about 1 in 100 000 transfusions. owever, the Australian experience illustrates both the risk to the premature immune system and one danger of divided donations.

What has been gained from the virological advances reported in 1984? The main immediate spin-off will be the large-scale development of antibody tests to exclude donors who are HTLV III antibody positive. Already five American commercial firms are competing to provide test kits, and there are confident predictions of success despite a high rate of false positives at present. Clearly, even a true positive test is not diagnostic of AIDS since most people who seroconvert have not acquired the disease. Neither does a positive test necessarily indicate protection or exclude the carrier state, since the antibodies are not neutralising. Presumably also donors may be infective before seroconversion occurs, so that tests for viral antigens will be needed to complete the screen. On p 1418 of this issue Dr Salahuddin and colleagues report on four such antibody-negative carriers. One was the wife of an AIDS patient and another the wife of a patient with AIDS-related complex, and these observations are very pertinent to haemophiliacs at risk. Nevertheless, HTLV III antibody screening and more rigorous donor selection should exclude most of the donors who constitute a risk. The chance of contracting AIDS from ordinary blood transfusion is therefore very small indeed and should become even less as donors are effectively screened. To limit blood donation to females is unnecessary and impracticable.

What of the risk in haemophiliacs? Fifty-two haemophilia-associated cases of AIDS have been reported in the USA (including two in haemophilia B patients and two in patients with other clotting disorders[6]) and three in the UK. The overall prevalence of AIDS in treated American haemophiliacs is about twice that in Europe,[7] but in countries that use factor VIII concentrate from the USA the incidence is likely to increase. Thus Gürtler et al[8] in Germany reported a steadily rising incidence of HTLV III antibody in stored samples from their healthy haemophilic population, from 0% before 1980 to 53% in 1984. In the UK, 32% of healthy haemophiliacs were found to be antibody positive[4] compared with 72% in the USA.[9] In a later American study 94% of treated symptomless patients with haemophilia A were found to be positive during 1984.[10] Since the prevalence of HTLV III antibody in the donor population in the UK is extremely low,[4] the virus was presumably acquired mainly via American concentrate. On p 1444 of this issue Dr Melbye and co-workers provide evidence for this notion. They report that, of Scottish haemophilic patients treated at one centre with domestic factor VIII concentrate only and who had not travelled abroad, none were HTLV III antibody positive whereas in other patients positivity correlated with exposure to American commercial concentrate. However, the prevalence of HTLV III infection in homosexuals and others seems to be increasing rapidly in countries outside the USA[11] and contamination of local blood products must only be a

1. 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; i: 753–57
2. Popovic M, Sarngadharan MG, Read E, Gallo RC. Detection, isolation and continuous production of cytopathic retroviruses (HTLV III) from patients with AIDS and pre-AIDS *Science* 1984, **224**: 497–500.
3. Laurence J, Brun-Vezinet R, Schutzer SE, et al. Lymphadenopathy-associated viral antibody in AIDS: Immune correlations and definition of a carrier state *N Engl J Med* 1984; **311**: 1269–73.
4. Cheingsong-Popov RC, 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.
5. O'Duffy JF, Isles AF. Transfusion-induced AIDS in four premature babies *Lancet* 1984; ii: 1346
6. Centers for Disease Control Update Acquired immunodeficiency syndrome (AIDS) in persons with hemophilia. *MMWR* 1984; **33**: 589–91.
7. Bloom AL Acquired immunodeficiency syndrome and other possible immunological disorders in European haemophiliacs *Lancet* 1984, i. 1452–55
8. Gürtler LG, Wernicke D, Eberle J, Zoulek G, Deinhardt F, Schramm W Increase in prevalence of anti-HTLV III in haemophiliacs. *Lancet* 1984, ii: 1275–76.
9. Ramsay RB, Palmer EL, McDougal JS, et al. Antibody to lymphadenopathy-associated virus in haemophiliacs with and without AIDS. *Lancet* 1984; ii 397–98.
10. Kitchen LW, Barin F, Sullivan JC, et al Aetiology of AIDS-antibodies to human T-cell leukaemia virus (type III) in haemophiliacs *Nature* 1984, **312**: 367–69
11. Public Health Laboratory Service. Communicable Disease Report, 1984, no 48 (unpublished).

matter of time. Dr Melbye's findings must be reconciled with previous observations that this particular Scottish haemophilia population still exhibited the abnormal lymphocyte subsets seen in other haemophilic populations at risk.[12] These observations together with the relative lack of Kaposi's sarcoma in transfusion-associated and haemophilia-associated AIDS are consistent with suggestions[8] that the pathogenesis of AIDS involves something more than infection with HTLV III.

In the medium term, blood-donor selection by publicity, more searching questions at donor sessions, and serological testing should go some way towards exclusion of at-risk groups. However, experience with hepatitis B suggests that additional measures will be needed, because with products that are pooled from over 5000 donations even one HTLV III infected donation has contaminated a whole batch. Since HTLV III is relatively heat-labile,[6] heat treatment of concentrates (as developed for serum hepatitis) is a step that could rapidly be introduced. Alcohol precipitation and pasteurisation are used successfully for sterilisation of albumin, but treatment of protein to retain complex functions such as those of blood coagulation is more difficult. β-propiolactone and ultraviolet light have been used successfully to sterilise factor IX with regard to hepatitis[13] but these techniques inactivate factor VIII for therapeutic use and their effectiveness against LAV is unproven.[14] Dry heat, designed to conserve about 85% of the factor VIII, has been used for the first generation of heat-treated concentrates. In the UK unheated large-pool concentrates, even those prepared from voluntary donations, have transmitted non-A, non-B hepatitis,[15] and we learn that a first-generation dry heated concentrate has also transmitted the disease (Mannucci PM, unpublished). There are no published data concerning the transmission of hepatitis by concentrates heated in solution in the presence of stabilisers but the loss of factor VIII (and hence the cost) is probably much increased. Thus although dry heat shows promise of inactivating HTLV III in factor VIII concentrates, such concentrates are not necessarily sterile. Their clinical efficacy vis-à-vis AIDS and seroconversion remains to be studied in previously unexposed patients. Meanwhile the serious nature of AIDS justifies a pragmatic approach, and it is reasonable to switch to heat-treated factor VIII concentrate for haemophilia A. The position regarding heat-treatment of factor IX concentrate is less clear. HTLV III antibody and lymphocyte changes in haemophilia B seem to be less common than in haemophilia A[10,16] although AIDS is still occurring.[7] The effect of heat treatment on thrombogenicity of factor IX concentrate is unknown, but heat-treated factor IX is available commercially.

The National Hemophilia Foundation of the USA has lately examined the options, including the possible use of pharmacological means of raising factor VIII such as desmopressin (DDAVP).[17] Cryoprecipitate (or fresh frozen plasma for haemophilia B) prepared from a small number of donors is recommended for the treatment of children under 4 years of age and newly diagnosed patients but the large volumes have proved troublesome in small children. In the UK heated domestic concentrate should be more acceptable, though it may still involve a risk of non-A, non-B hepatitis. DDAVP is effective only in mildly affected patients with haemophilia A and von Willebrand's disease[17] but is an attractive option in this group who are at high risk of infection from concentrates. Extensive use of frozen cryoprecipitate prepared from selected plasma exchange donations, as suggested by McLeod and Scott,[18] is probably impracticable on a large scale and the material would not be as acceptable for home treatment as dried standardised heated concentrates. The aim of plasma fractionators should thus be to prepare factor concentrates from non-infected donors and to ensure sterility before use. For England and Wales a new blood products factory should be in operation in 1986 and Scotland is already self-sufficient, but the ability to provide all the products needed will depend upon increasing the supply of plasma at regional level. This will demand a reassessment of regional financing for plasma procurement, a requirement made all the more urgent by the AIDS crisis. Meanwhile, additional funds will be needed to purchase heat-treated concentrate. It would be indefensible to allow prescription and home use of material known to be at risk from HTLV III when apparently safer preparations are available.

These developments re-emphasise the need for adequately staffed centralised haemophilia facilities at which management and follow-up can rigidly be controlled; perhaps decentralisation has already gone too far. The safety considerations extend beyond haemophilia. All blood products must be reassessed in the light of these events. Hyperimmune globulin for hepatitis B and cytomegalovirus infection is derived from an AIDS-risk population but the preparative procedures used for this, for ordinary immunoglobulin, and for antithrombin III may well inactivate HTLV III. On the other hand, plasminogen, fibrinogen, and other pooled blood and human tissue products must be regarded as potential hazards until

12. Froebel KS, Madhok R, Forbes CD, et al. Immunological abnormalities in haemophilia: are they caused by American factor VIII concentrate? *Br Med J* 1983, 287: 1091–93
13. Heinrich D, Kottschke R, Berthold H. Clinical evaluation of the hepatitis safety of β-propiolactone/ultraviolet treated factor IX concentrate (PPSB). *Thrombosis Res* 1982, 28: 75–83
14. Spire B, Barré-Sinoussi F, Montagnier L, Chermann JC Inactivation of lymphadenopathy associated virus by chemical disinfectants. *Lancet* 1984; ii: 899–901
15. Fletcher ML, Trowell JM, Craske J, Pavier K, Rizza CR Non A-non B hepatitis after transfusion of factor VIII in infrequently treated patients. *Br Med J* 1984; 287: 1754–57.
16. Moffat EH, Bloom AL, Jones J, Matthews N, Newcombe R. A study of cell mediated and humoral immunity in haemophilia and related disorders. *Br J Haematol* (in press)
17. Mannucci PM, Ruggeri ZM, Paretti FI, Capitanio A. 1-deamino-8-D arginine vasopressin: a new pharmacological approach to the management of haemophilia and von Willebrand's disease. *Lancet* 1977; i: 869–72.
18. McLeod BC, Scott JP. Use of "single donor" factor VIII from plasma exchange donation. *JAMA* 1984; 252: 2726–29

proved otherwise. Ethical questions are raised by HTLV antibody testing of blood donors and haemophiliacs. An unenviable task will be the counselling of people with positive results—a task made all the more necessary by the detection of virus in semen and saliva and the findings reported by Dr Salahuddin and colleagues in this issue.

Although the AIDS crisis is worsening, silver linings can be discerned in the clouds. The main causal virus seems to have been identified and, although there will be difficulties (eg, because of the lack of total protection by antibody), a vaccine will probably be developed. In addition several drugs active against reverse transcriptase, the virus, or serious secondary pathogens such as cytomegalovirus are under study including suramin, inosine pranobex, phosphonoformate, and ribavirin,[19-22] as well as immunorestorative agents. Meanwhile we must not forget that by far the commonest cause of haemophilic death is bleeding.

Q Fever: Antigens and Vaccines

Q FEVER is a disease of worldwide importance,[1] most notably as an occupational hazard in people exposed to infected cattle, sheep, or goats.[2] Nevertheless, the frequency of clinical Q fever in certain occupational groups varies from place to place, and unexplained outbreaks sometimes occur in the general population.[3] These sporadic outbreaks are presumably the result of airborne infection from an unrecognised source; exposure to infected milk from cows or goats may also be responsible for some cases.[4] On p 1447 of this issue Dr Kosatsky describes a Q fever outbreak in which the parturient family cat was a probable source of infection.

While Q fever vaccines have been available for some years, prophylaxis has been largely restricted to laboratory workers. Vaccination is commonly held to be effective but has a reputation for causing unpleasant reactions.[5] Early Q fever vaccines (Smadel vaccines) given to laboratory workers in the 1940s and 1950s undoubtedly caused some local and systemic reactions but a clear distinction was not always made between trivial effects at the inoculation site (eg, erythema, transient induration, tenderness) and more serious complications such as persistent masses, abscesses, and fistulas. Benenson[6] then reported that serious reactions were related to frequency of revaccination, and he also showed that local reactions were more apt to arise when Q fever complement fixing (CF) antibody was present before injection. Prevaccination screening for immunity or hypersensitivity was subsequently introduced.[7] Diluted vaccine was inoculated intradermally and only non-reactors were vaccinated, with the result that the frequency of reactions diminished. Development of modern, inactivated, whole-cell Q fever vaccines stems from the discovery by Stoker and Fiset[8] of antigenic phase variation in *Coxiella burneti*. When the organism is isolated from infected animals or man it has a surface antigen (phase 1) with some important biological properties.[9] If an isolate is passaged serially in chick embryo yolk sac, phase 1 organisms are gradually replaced by organisms lacking phase 1 antigen (phase 2). Inactivated vaccines made from purified *C burneti* in phase 1 are much more potent than comparable phase 2 vaccines.[10]

Interest in vaccine prophylaxis for certain occupational groups was rekindled in the 1970s by outbreaks of Q fever in research institutes and medical schools where pregnant sheep were used as laboratory animals, and more recently by sharp increases in Q fever in Australian abattoirs that had started slaughtering feral goats. On p 1411 Professor Marmion and his colleagues report the results of a South Australian trial with low dose (30 μg) inactivated, whole cell, Henzerling strain phase 1 vaccine in more than 1600 abattoir workers. Seroconversion of 50–60% was achieved, as judged by antibody tests of medium sensitivity, and no cases of Q fever were observed in vaccinated subjects who had time to acquire immunity after vaccination before they were exposed to natural infection.

This evidence of protection is encouraging but several questions remain unanswered. How long does protection last and are booster doses required? Single-dose vaccination regimens have been used in staff at the Rocky Mountain Laboratory for many years with no Q fever cases among vaccinees, suggesting that immunity is long-lasting. In abattoirs or other high-risk environments, protection given initially to the new recruit by vaccine might well be boosted by periodic natural exposure, without clinical illness; longer term investigations are needed to verify this. It is important to establish which markers are valid indicators of immunity after vaccination. Antibody tests vary considerably in sensitivity, and this complicates their use as an index of vaccine efficacy. Moreover, immunity does not depend on antibody alone;[6,11] there are strong indications that the outcome of *C burneti*/macrophage interactions is central to the pathogenesis of Q fever and to immunity to the

19. Mitsuya H, Popovic M, Yarchoan R, Matsushita S, Gallo RC, Broder S. Suramin protection of T cells in vitro against infectivity and cytopathic effect of HTLV III *Science* 1984; **226**: 172–74.
20. Tsang KY, Fudenberg HH, Koopmann W, et al. Effect of isoprinosine on the interleukin 2 (IL-2) production and Tac antigen bearing lymphocytes in vitro in patients with acquired immunodeficiency syndrome (AIDS). *Clin Res* 1984; **32**: 36A
21. Wahren B, Oberg B Inhibition of cytomegalovirus late antigens by phosphonoformate. *Intervirol* 1979; **12**: 335–39.
22. McCormick JB, Getchell J, Mitchell S, Hicks DR. Ribavirin suppresses replication of lymphadenopathy-associated virus in cultures of human adult T lymphocytes. *Lancet* 1984; ii: 1367–69.
1. Berge TO, Lennette EH. World distribution of Q fever: human, animal and arthropod infection. *Am J Hyg* 1953, **57**: 125–43.
2. Derrick EH. The epidemiology of Q fever: a review. *Med J Aust* 1953; i: 245–53.
3. Salmon MM, Howells B, Glencross EJG, Evans AD, Palmer SR. Q fever in an urban area. *Lancet* 1982; i: 1002–04.
4. Marmion BP, Stoker MGP. Epidemiology of Q fever in Great Britain. *Br Med J* 1958; ii: 809–16.
5. Derrick EH. The query fever. *Queensland Health* 1964; i: 1–20.
6. Benenson AS. Q fever vaccine: efficacy and present status. In: Smadel J, ed Symposium on Q fever. Washington: Walter Reed Army Institute of Research, 1959: 47–60.
7. Lackman DB, Bell EJ, Bell JF, Picken EG. Intradermal sensitivity testing in man with a purified vaccine for Q fever. *Am J Public Health* 1962; **52**: 87–91
8. Stoker MGP, Fiset P. Phase variation of the Nine Mile and other strains of *Rickettsia burneti*. *Can J Microbiol* 1956; **2**: 310–21.
9. Baca OG, Paretsky D. Q fever and *Coxiella burnetii*: a model for host parasite interactions. *Microbiol Rev* 1983; **47**: 127–49
10. Ormsbee RA, Bell EJ, Lackman DB, Tallent G. The influence of phase on the protective potency of Q fever vaccine. *J Immunol* 1964, **92**: 404–12.
11. Fiset P Review of status of Q fever vaccine and vaccine studies Commission on Rickettsial Diseases of the Armed Forces Epidemiological Board, 1970