AIDS/HIV Infection in haemophilia Patients:
Historical Development

1980 (Sept.) — Establishment that viral-induced immunodeficiency resulted in specific T lymphocyte subset profiles (J. Immun. 125; 3 : 1269).

1981 (June/ July) — Initial reports of Pneumocystis pneumonia and Kaposi's sarcoma in homosexual men in Los Angeles and New York (MMWR 30; (21) 250 and 350).)

1981 (Dec.) — Pneumocystis cases identified as cellular immune dysfunction (Gottlieb, NEJM, 305, 24, 1425 and 1431).

1982 (May) — PGL (Persistent Generalised Lymphadenopathy) reported among gay men (MMWR 31 (19) 249).

1982 (June) — Report of cluster of Kaposi's sarcoma and Pneumocystis carinii pneumonia among homosexual residents of Los Angeles and Orange Counties, California. Key report indicating possible infectious cause of AIDS. (MMWR 31 (23) 305).

First report of undifferentiated non-Hodgkins lymphoma among homosexual males in the U.S. (MMWR 31 (21) 277). Associated relationship with Kaposi's sarcoma, opportunistic infections and cellular immune dysfunction.

1982 (July) — Case reports of homosexuals and drug-addicts with Pneumocystis pneumonia, presenting initially in October 1981. (Masur, NEJM, 305: 24, 1431).

The Editorial implied that immune suppression similar to homosexuals with Pneumocystis demonstrated in 3 patients with haemophilia and could have been due to an agent(s) transmissible by blood products. No two patients were known to have received concentrate from the same factor VIII batches (MMWR 31; (27) 365).

During 1982 it became apparent that fatal Pneumocystis and Kaposi's sarcoma were spreading epidemically in homosexual populations Follansbee Ann. Int. Med.: 96: 705; Johnson, JAMA, 247: 1739). Homosexuals were confirmed to be at risk of PGL (MMWR, 31 (27) 249) which possibly reflected an underlying immune disorder or a pre-AIDS syndrome. Non-Hodgkins _ lymphoma was also confirmed in homosexual men and was considered to be due to an infectious agent. (MMWR 31 (27), 277).

1982 (August) Scientific update on clinical and laboratory manifestations of AIDS. Discussion as to viral aetiology or to recurrent antigenic stimulation causing immune system paralysis. In the context of AIDS in haemophilia, inference as to a possible beneficial effect of high purity concentrates (Science, 217, 618).

1982 (Sept.) AIDS diagnosed in Drug Addicts (MMWR 31, (27) 507). As many addicts use contaminated needles, the concept of a blood borne infectious agent(s) was raised.

1982 (Oct). Report of opportunistic infections in female drug abusers - initial communications of community acquired cellular immunodeficiency. (Masur - Ann. Int. Med. 97(4) 533).

1982 (Nov) Medical and Scientific Advisory Council of NHF circulate letter on their deliberations re exclusion of high risk groups from blood donations (meeting 3.10.82).

1982 (Dec.) American Society of Haematology Meeting. Altered T cell immunity in haemophilics receiving frequent factor VIII administration. Discussion of possible causes. (Weintraub - Blood 60, Suppl. 1, 224a.

Report of cryptosporidiosis in a haemophiliac with AIDS (Eyster, Blood, 60, Suppl. 1, 211a). Haemophilic children and adolescents have normal cellular and humoral immunity but continued surveillance advocated (Luban, Blood, 60, Suppl. 1, 216a).

1982 (Dec.)

√B An additional 4 cases of AIDS in haemophilia described. No common batches of factor VIII concentrate identified (MMWR 31 (27) 644).

* First case of transfusion-associated AIDS in California in 20-month old infant with multiple platelet transfusions derived from the blood of a man subsequently found to have AIDS (MMWR, 31 (48) 652). This is a key report supporting the likelihood of AIDS transmission through blood or blood derivatives, and sexually. In this respect similar to hepatitis B virus infection. Latent period from infection to symptoms 2 months to 2 years. √B

Public Health service recommendations - high risk groups should refrain from donating blood. AIDS reported in haemophiliacs and children (Marx - Science 219, 42 (2).

1983 (January)

√Blood-borne agent in AIDS (Science News 123, 8(1)).

AABB Committee on Transfusion Transmitted Diseases 06.01.83 - recommendations for blood bank practice.

√B Reports of 2 cases of AIDS in female sexual partners of i.v. drug addicts with AIDS. (MMWR, 31, 697).

Spread of AIDS sparks new health concern (Marx-Science 219, 271, 07.01.83).
AIDS reported to have caused 8 haemophilic deaths in 1982.

Abnormal T4/T8 ratios in haemophiliacs treated with cryoprecipitate and concentrates. Five haemophilics with autoimmune thrombocytopenia purpura reported, 3/4 patients with abnormal T4/T8 ratios. (Menitove NEJM 308, 2, 83).

New evidence suggests that AIDS is transmitted in donor blood (Marx-Medical World News - 10.01.83, p.8).

AIDS. At this time it was unclear whether such individuals were likely to get AIDS, but this study indicated that in the absence of opportunistic infections the presentation of PGL may represent a prodromal phase or forme fruste of AIDS. (Ragni - Lancet i, 213).

Ban on gay men as blood donors urged; Haemophilia Foundation action (see document 14.1.83) L.A. Times v 102 Section 1 p3. 18.01.83.

Haemophilia Unit is cautioned. N.Y. Times v 132 p.10 - 19.01.82.

Impaired cell mediated immunity reported in haemophilia patients and found to be significantly abnormal in those receiving lyophylized concentrates (Lederman-NEJM, 308, 2, 79).

Reports of low T4 and T4/T8 ratios in severe haemophilia - concluded that underlying cause may be transfusion associated, possibly as a response to antigenic load. None of the patients studied had clinical features of AIDS (Jones - Lancet i, 120).

Editorial in NEJM questioning whether it would be prudent to switch to cryoprecipitate (Desforges - NEJM, 308, 94).

Medical and Scientific Advisory Council to National Haemophilia Foundation. Recommendations to prevent AIDS in patients with haemophilia - 14.01.83. High risk donors should refrain from giving blood particularly when plasma used for high donor pool non-inactivated blood products. NHF recommendation that new patients should be given cryoprecipitate as long as possible, but patients already using factor VIII concentrates should continue to do so. Similar guidelines for factor IX deficient patients recommending use of fresh frozen plasma (American Med. News. 04/02/89).

1983 (Feb.)

Statement in the Haemophilia Bulletin that heat treated factor VIII from plasma pools (homosexual donations eliminated) would not be on the market until March/April 1983 and will be more expensive. No heat treated factor IX available (Haemophilia Bulletin Jan. 1983).

Further report of ITP in haemophilic patients receiving factor VIII concentrates. In 3 of 4 patients studied, there was evidence of impaired cell mediated immunity (Ratnoff - NEJM, 308, 8, 439).

Health officials seek ways to halt AIDS (Science) - recommended introduction of 'surrogate' testing of blood donations and exclusion of high risk group donors.

1983 (March)

Prevention of AIDS: report on Inter-Agency Recommendations for blood collection agencies (HHS News - 04.03.83 and FDA - 24.03.83).

Case reports of 3 haemophiliacs with AIDS (Elliot - Ann Int. Med. 98, 290; Poon - Ann. Int. Med., 98, 287; Davis - Ann. Int. Med., 98, 284). Further report of immune abnormalities (low T4, T4/T8 ratios decreased, T8 increased) observed in asymptomatic children and adolescents with haemophilia (Luban - Lancet, i, 503). It was unclear whether these abnormalities were due to "latent AIDS" caused by transmissible agent or whether they were the result of factor VIII concentrate per se.

In major report on T lymphocyte subpopulation abnormalities in apparently healthy patients with haemophilia', it was stated that there was insufficient evidence to advocate a change in therapeutic practices (Goldsmith - Ann. Int. Med., 98, 294).

However, Editorial in Ann. Int. Med. discusses dilemma of how to treat haemophiliacs; author recommended the stop gap of reduced elective surgery, reduction in concentrate dose and switching a few patients from factor VIII concentrate to cryoprecipitate. (White - Ann. Int. Med., 98, 403).

Editorial Lancet - Are T cell abnormalities the submerged part of iceberg of which AIDS is the tip? Cites, Desforges - NEJM Editorial in January and White - Ann. Int. Med., 93, 403 for proposal to switch from concentrate to cryoprecipitate (Lancet i, 745). Writer commented that if there is an iceberg why W. German haemophiliacs have not developed AIDS (heavy uses of U.S. concentrate). No strong argument for change of treatment policy consistent with Goldsmith - Inn. Int. Med., 98: 294.

(March) 1983 Start of International Multicentre Clinical Trial in Europe of first American Heat Treated Factor VIII concentrate (Hemofil T). Aim to study:- NANB transmission in previously untreated haemophilic patients.

1983 (April) Hypothesis that alloantigens in factor VIII concentrate induce immune changes which make individuals more susceptible to infection by a transmissible agent (Shankey - AIDS Research 1, 83).

1983 (May) Multiple transfusions in an infant with Rhesus disease led to opportunistic infection by 14 months of age. One of the donors died of AIDS 17 months after donation. Key Report indicating that AIDS in the infant derived from a transmissible agent in the transfused blood which was NOT CMV, EBV or HBV (Ammann, Lancet, i, 956).

Retrovirus cultured by French workers from patients with PGL. This is first report of virus to be known as LAV (lymphadenopathy associated virus) later as HTLVIII and HIV1. (Barre-Sinoussi - Science, 220, 868). This is a key report since the virus grew in CD4 cells for 7 days and produced a cytopathic effect on healthy cells. The presence of reverse transcriptase was demonstrated in the culture supernatant implying that the agent in all likelihood would be a retrovirus, and thus conceivably heat sensitive.

Other workers noted an antibody in patients with AIDS which cross-reacted with HTLV1 (HTLV-MA; membrane associated antigen) (Essex, Science, 220, 869).

Further report of immune abnormalities in haemophiliacs. Of interest is the observation of an increase in T8 numbers. Immunity was noted to be normal in individuals treated only with cryoprecipitate (Landay - JCI, 71, 1500).

Reports on disordered immune regulation in haemophiliacs not exposed to commercial factor VIII suggested that antigenic overload could explain T4/T8 observations (Ludlam - Lancet i, 1226).

1983 (June)

General recommendations on treatment policy sent out by Reference Centre Directors' to all Haemophilia Centre Directors in U.K.

Immune alterations in haemophiliacs treated with lyophylized factor VIII cryoprecipitate from voluntary donors in Belgium (Ceuppens - Thromb. Haemostas. 51(2); 207).

BPL Elstree Research Programme for the production of 8Y instigated - specific development to eliminate NANB hepatitis.

1983 (July) /B

Absence of AIDS in Australian haemophiliacs possibly due to treatment with domestic concentrate since import of commercial factor VIII prohibited; all factor VIII manufactured from local volunteer donor blood. (Rickard et al - Lancet ii, 50).

1983 (August)

Report of immune abnormalities in asymptomatic haemophiliacs (de Shazo - Ann. Int. Med., 99, 159), but still not clear whether these were due to latent infection with AIDS virus or due to factor VIII concentrate itself.

Lymphadenopathy associated with T cell alterations in concentrate treated haemophiliacs (Lechner - Thromb. Haemostas., 50(2), 552).

1983 (Sept.)

Raised interferon levels reported in haemophiliacs as in homosexuals. This was suggestive that haemophiliacs might be latently infected with an AIDS virus (Eyster - NEJM, 309, 585).

1983 (Oct.)

Immune abnormalities in haemophiliacs similar to those in AIDS patients. Those with severe haemophilia had greater degree of abnormality than those with mild form of haemophilia (Tsoukas - Can. Med. Assoc. J., 129, 713).

No immunological abnormalities reported in 5 patients receiving massive concentrate therapy with high dose immunetolerance regimes for inhibitor treatment (Aznar - Thromb. Haemostas. 52(2), 213).

U.S. National Haemophilia Foundation Recommendations issued 22.10.83.

Four haemophiliacs described with PGL like syndrome (Gervais - AIDS Research 1, 197).

1983 (Nov.) √B First U.K. AIDS case in haemophilia reported (Daly - Lancet ii, 1190).

1983 (Dec.) Total of 21 cases of AIDS in haemophilia in U.S. (19 haemophilia A; 2 haemophilia B) and 7 from outside U.S. (MMWR, 32, (47) 613). Infectious cause suggested from epidemiological evidence. Donor pools 2000-20000 donations.

1984 (Jan.) √B Wife of haemophiliac reported with AIDS - first evidence of heterosexual transmission in haemophilia (Pitchenik - Ann. Int. Med., 100, 62).

1984 (Feb.) Study demonstrating 5/39 haemophiliacs positive for HTLV-MA (HTLV1) and that B2 microglobulin and thymosin levels were increased in haemophiliacs (Kreiss - Ann. Int. Med., 100, 178). This study demonstrated antibodies to HTLV1 which we now know are against HIV but cross-react with HTLV1 i.e. they were false positives. This represented early evidence that some haemophiliacs were infected with a latent virus.

1984 (March) Serological evidence of human T cell leukaemia virus infection of donors in transfusion associated AIDS. (Jaffe - Science 223, 1309).

1984 (April) √B LAV(HIV) isolated as live virus from two haemophilia B patients - one having AIDS the other asymptomatic (Vilmer - Lancet i, 497). Key article indicating new infective retroviral agent with an envelope structure. Further support for the concept that the viral agent should be thermolabile.

SCIENTIFIC STATE OF THE ART ESTABLISHED HERE

Ratnoff in published lecture, reviews his experience of immune disturbances and AIDS cases. Although acknowledging the benefits of factor VIII concentrates he wondered whether it would not have been prudent to use cryoprecipitate. He stated that his hospital had recently banned the use of factor VIII concentrates except for severe life-threatening bleeding (Ratnoff - J. Lab. Clin. Med., 103, 653).

1984 (June)

Gallo et al, report 100% AIDS patients have antibodies to HTLVIII (HIV) (Safai - Lancet, i, 1438).

French workers publish antibody prevalence in homosexuals to LAV (HIV1) in 75% of PGL, 38% AIDS and 18% healthy homosexuals (Brun-Vezinet - Lancet i, 1253).

Editorial accepted that AIDS is transmitted by blood products. 1/1000 U.S.A. haemophiliacs had AIDS but 50% had immune abnormalities (B.M.J., 288, 1782). Key document since state of the scientific art formally declared.

Survey of European haemophiliacs revealed that 11/13,000 had AIDS and 179 had evidence of immune abnormalities. (Bloom - Lancet i, 1452).

Edinburgh study of haemophiliacs in an apparently AIDS free area treated with factor VIII manufactured from locally collected blood demonstrated immune abnormalities comparable to U.S. haemophiliacs, and who could be latently infected with AIDS virus (Carr - Lancet i, 1431.

AIDS - New disease in Haemophiliacs affecting older aged individuals, high concentrate users. However, clotting factor concentrate use has dramatically reduced haemophilia mortality since 1970 (Johnston - Am. J. Epidem., 121, 797).

CLINICAL STATE OF THE ART ESTABLISHED ABOUT HERE
ALL EFFORTS SHOULD HAVE BEEN MADE AT THIS STAGE TO SECURE HEAT TREATED PRODUCTS FOR HAEMOPHILIA A AND B PATIENTS.

1984 (July)

American heat treated factor VIII concentrates available on a named patient basis in U.K.

Selective growth of a LAV in CD4 lymphocytes of healthy carrier noted (Klatxmann - Science, 225, 59-67).

Study of Danish haemophiliacs 14/22 (64%) anti HIV positive; most had received U.S. commercial factor VIII. Implication that commercially available untreated cryoprecipitate products should be considered contaminated (Melbye - Lancet ii, 40).

AIDS reported in haemophiliacs treated only with cryoprecipitate (Can. Med. Assoc. J., 131, 45).

1984 (August)

Behring's pasteurised factor VIII concentrate received full licence through DHSS.

A third group report ARV (AIDS Related Virus) from San Francisco patients - later found to be identical to HIV1 (Levy - Science, 225, 840).

In a study of U.S. haemophiliacs 72% anti-LAV (HIV1) positive as assessed by the presence of antibodies to p25 and p41. T cell numbers in peripheral blood present in equivalent numbers in anti-LAV positive and negative patients. This provided further evidence that factor VIII per se modulates the immune system. Large users of factor VIII were more likely to be anti-LAV positive and that LAV was transmitted by some blood products (Ramsay - Lancet ii, 397).

1984 (Sept.)

London study of anti-HTLVIII reported the following positivity rates AIDS 97%; homosexuals 59%; haemophiliacs 34%; I.V. Drug users 1.5% (Cheingsong-Popov - Lancet ii, 477).

3B First report that murine retroviruses were heat sensitive, and that heating freeze dried factor VIII spiked with virus to 68°C over 48 hours reduced viral titres from 8 logs to 2 infection particles/ml. (Levy, Lancet, ii, 733).

1984
(Oct.)

Additional formally unpublished report that Cutter Laboratories had demonstrated heat sensitivity of HIV presumably in blood coagulation factor concentrates (MMWR, 33, 589).

Medical and Scientific Advisory Council of National haemophilia Foundation of U.S. "Recommendations Concerning AIDS and the Treatment of Haemophilia", October 13th (JAMA, 252, 19; 2679 - leads from the MMWR 33, (42) 1984).

1. Cryoprecipitate for infants and children less than 4 years and for newly identified patients never previously treated with factor VIII.

2. Fresh frozen plasma to be used in factor IX deficient patients in some categories.

3. DDAVP when possible for mild and moderate haemophiliacs.

4. All other patients should received heat treated concentrates although only scant evidence for the efficiency of viral inactivation and safety.

5. Stringent evaluation of possible delays in elective surgical procedures.

1984
(Nov.)

A study of U.S. haemophiliacs reported that 65% are anti-HTLVIII positive. At this stage it was not clear whether all individuals who were antibody positive were infected with HTLVIII or whether, in some, the virus had been cleared from the body as happens with most viral infections and the presence of antibody merely denoted previous infection (Kitchen - Nature, 312, 367).

Thermolability of AIDS virus reported - 5 logs of virus heated at 68°C and after 24 hours virus undetectable (JAMA, 252, 19, 2679).

American heat treated factor IX concentrates available in the U.K. on a named patient basis.

1984
(Dec.)

SNBTS introduced heat treated factor VIII concentrate.

Scotland reported that only 16% of haemophiliacs were anti-HTLVIII positive compared to 59% Danes who had been treated with U.S. commercial

blood product therapy during 1979-84, none were anti-HTLVII positive. Only 2 of 7 patients treated with locally produced Scottish factor VIII concentrates were anti-HTLVIII positive. Higher prevalence of seropositivity in those who were large users of factor VIII concentrate (Melbye - Lancet, ii, 1444).

Lancet Editorial - makes similar recommendations to NHF (Lancet, ii, 1433).

Another study of U.S. haemophiliacs demonstrated 30/54 cases anti-HTLVIII positive with 20/21 patients with PGL being positive. 50% of anti-HTLVIII negative patients had evidence of immune dysfunction by skin testing (Tsoukas - NEJM, 311, 1514) indicating immunosuppressive effect of concentrate alone or possibly by other viruses, at that time undetectable, but not related to HTLV III.

Haemophilia Centre Directors' Organisation distributed out AIDS Advisory Document to all U.K. Haemophilia Centre Directors. Document discussed the various options for treatment and gave general recommendation for use of heated concentrates.

1985 (Jan.)

Reservations expressed by Bird et al (Lancet - i, 162) about effect of heated concentrates on immune system, and that such material might provide development of anti-factor VIII inhibitors, and promote HTLVIII infection by stimulating immune system of patient with partially heat denatured protein.

Child of haemophiliac developed AIDS due to heterosexual transmission to wife and vertically from mother to son. (Ragni - Lancet i, 133).

U.S. Blood Collection Agencies Statement on strengthening donor screening - recommend anti-HTLVIII screening (MMWR 34.1).

Reply to criticism by Bird of heat treating factor VIII stated that immune abnormality in many haemophiliacs may be due to infusions of foreign proteins and that on current evidence only a minority of patients will get AIDS (Lancet i, 225). Bloom also replied to Bird's letter stating that at least two batches of NHS concentrate had transmitted HIV and urging use of heat treated concentrate (Lancet i, 336). No mention made of heat treated factor IX concentrate.

A retrospective study using frozen serum samples from haemophiliacs in California and Georgia indicated that the first LAV positive sample was in 1978 but that most patients seroconverted in 1982/3. By the end of 1984, 85% of patients were positive. The interpretation of anti-HIV positive results unknown : is it an immune reaction, or had virus been neutralised and the individual no longer infected, or does live virus co-exist with specific antibody transfused from the bottles of factor VIII concentrate (Evatt - NEJM, 312, 483).

1985
(Feb.)

Absence of antibodies to AIDS virus in previously untreated haemophiliacs treated with heat treated factor VIII concentrates during 1982-84. Comparative study of heated vs unheated Hemofil T (U.S. product) (Rouzious - Lancet i, 271). Key report since it demonstrated the first published information on heat treated concentrates compared to unheated concentrates in previously untreated patients.

Use of cryoprecipitate reported to be associated with lower risk of ARV (HIV) positivity. Users of > 300 U/kg/year - i.e. large users of concentrate 26/26 positive while only 2/6 cryoprecipitate users were positive. Virus cultured from one patient demonstrating that at least one patient had active infection (Koerper - Lancet i, 275). This report demonstrated coexistence of virus and its specific antibody.

All U.S. importers of commercial factor VIII concentrates receive full licences through DHSS.

Study of haemophiliacs in U.K.; 9 of 15 treated with commercial and NHS concentrate seroconverted 1982-84 whereas 13 moderate and mild haemophiliacs treated with NHS and cryoprecipitate were all negative in September 1984 (Machin - Lancet i, 336).

Study from New York of T4 numbers in haemophiliacs using concentrates compared to transfusion dependent B-thalassaemics and sickle cell patients. No patient had AIDS. T4 numbers less in haemophiliacs. Concluded that this is due to immune suppression and AIDS agent. No anti-HTLVIII data on patients (Jason - JAMA, 253, 1140).

90% of patients with severe haemophilia who had been frequently treated were anti-HTLVIII

treated with factor IX, volunteer plasma or cryoprecipitate (Goedert - NEJM, 65, 492).

Report from Dr. Craske, Chairman of the AIDS Surveillance Working Party of the U.K. Haemophilia Centre Directors - clear evidence that a small but significant number of factor IX deficient patients treated exclusively with NHS material were HTLV III antibody positive. On the basis of these figures a significant contamination of the domestic plasma supply could be inferred, particularly since lower doses of concentrate were generally administered to factor IX deficient patients compared to factor VIII dosages in haemophiliacs, and that the NHS factor IX manufacturing process was considered to confer some degree of viral inactivation.

1985
(March) First ELISA test for anti-HTLVIII licensed by FDA in U.S.

Introduction of donor self-exclusion pamphlets into B.T.S.

Glasgow haemophiliacs who had received commercial concentrate seroconverted 1981-83 (Madhok - Lancet i, 524).

Case report of haemophiliac heterosexual contact who may have become infected by anal intercourse.

Letter by Ratnoff listing morbidity and mortality due to AIDS or AIDS like syndromes in his patients. Commented that it is curious that only 5 of 84 haemophiliacs have opted for cryoprecipitate therapy (Ratnoff - Ann. Int. Med., 103, 412.).

1985
(April) Cryoprecipitate usage associated with lower rate of anti-HIV positivity, 2 of 11 were anti-HIV positive (McGrady - AIDS Conference Atlanta).

In a study of U.K. haemophiliacs 28 of 52 were anti-HTLVIII positive and the chance of positivity was related to amount of factor VIII concentrate usage. None of 11 NHS factor VIII concentrate users were positive although two recipients of NHS factor IX concentrate had seroconverted.

Reduction in T4 cell numbers was similar in anti-HTLVIII negative and positive individuals (Moffat - Brit. J. Haem. 61, 157).

A further study reported similar reduction in T4 and T4/T8 in severe haemophiliacs treated with concentrates as in mild haemophiliacs and von Willebrand's disease patients treated with cryoprecipitate or plasma.

Review of haemophilia and AIDS by Levine - outline major clinical benefits of factor VIII concentrate therapy. Stated that AIDS cases in haemophilia had attained 1% and considered that the attack rate had reached a peak, and that only a minority of infected patients would get AIDS (Levine - Ann. Int. Med. 103, 723).

April 1985 ✓ Introduction of NHS heated intermediate purity factor VIII concentrate - 68°C for 24 hrs.

1985 (May)

Further report that heat treatment (Behring) prevents HTLVIIII transmissibility (Mosseler - Lancet, i, 1111).

1985 (June)

✓B Bloom et al. on behalf of U.K. Haemophilia Centre Directors advocated use of heat treated concentrates instead of non-heated NHS product or cryoprecipitate because of rising prevalence of HIV in community. Urge the early introduction of anti-HTLVIII screening of all donations by blood transfusion services (Bloom - BMJ, 290 1901).

In this report, survey results from U.K. Haemophilia Centres in April 1985 demonstrated a high proportion of centres using unheated NHS VIII and IX, and the authors somewhat belatedly admit that the safety of cryoprecipitate and unheated UK blood products could no longer be assumed. The continued usage of unheated concentrates explained on the basis of 'clearing of existing stock' and on financial grounds.

Follow-up information by Dr. Craske to the U.K. Haemophilia Centre Directors concerning seropositive factor IX deficient patients. Dr. Craske urged for the immediate transition of therapy to heat treated factor IX. ✓

1985 (Sept.)

✓ Introduction of NHS superheated factor VIII concentrate (8Y) - 80°C for 72 hrs.

Survey of Newcastle haemophiliacs treated with commercial and NHS factor VIII. Of 99 haemophilia A patients, 76 were anti-HTLVIII positive; 1 of 3

positive. Two patients with basal factor VIII 5-10% given concentrate rather than cryoprecipitate were positive. Patient with mild haemophilia A given concentrate for major bleed became anti-HTLVIII positive. Of 36 heterosexual contacts 3 were anti-HTLVIII positive.

Anti-HTLVIII positivity compared between concentrate and cryoprecipitate users in Seattle.

In 1983, concentrate users 65% and cryoprecipitate users 31% HTLV III antibody positive, and in 1984 77% and 40% respectively were positive. Calculated that the risk of seroconversion from 1981 to 1984 3.9 times higher using concentrate compared to cryoprecipitate (Gjerset - 66, 718, Blood).

1985 (Oct.)

Anti-HTLVIII screening introduced simultaneously by all transfusion centres in U.K. Report that heating freeze dried factor VIII at 60°C for 30 hours (Armour) does not transmit HTLVIII (Felding - Lancet ii, 832).

Letter to Lancet considered that heating at 60°C for 10 hours should be adequate to kill 20 logs of HIV in lyophilised factor VIII concentrate. This apparent degree of virus kill should be more than adequate to prevent HIV transmission. (Petricciani - Lancet ii, 890).

1985 (Nov.)

Introduction of NHS super heat treated factor IX concentrate - 80°C for 72 hrs.
Data presented to demonstrate that in plasma exposed to ethanol in the cold (as conducted in plasma fractionation by some manufacturers to prepare factor VIII concentrate) there was a substantial virucidal effect (Piszkiewicz - Lancet ii, 1188).

1986 (March)

Seroconversion of haemophiliac receiving dry heat treated factor VIII concentrate (White - Lancet i, 611). Report complicated by previous history of drug abuse. This report raised the question that at least one of the then current dry heat treated concentrates could not be considered to be entirely safe.

1986
(April)

Further seroconversion of 2 patients receiving heat treated factor VIII concentrates. One patient reported as definite. Heated concentrate was started Jan. 1984 but showed a positive test in 1985, which in view of HIV latency could imply that patient became infected from non-heated material (Vanden Berg - Lancet i, 803).

Absence of seroconversion in 17 Dutch haemophilics receiving Hemofil T after 28 months of follow-up (Van der Meer - BMJ, 292, 1049).

1986
(Oct).

Voluntary withdrawal of Factorate HT (Armour) from U.K. market on the basis of seroconversions to HIV (case studies subsequently reported).