CAL14(140211)

DRAFT

(prepared for the impending litigation in England and Wales in 1990)

Expert Report on

Human Immunodeficiency Virus Infection in Haemophiliacs

C.A. Ludlam

Director

Haemophilia Centre

Royal Infirmary Edinburgh

CAL14(140211)

INTRODUCTION

This report begins by outlining the very significant hardship experienced by haemophiliacs as a result of recurrent bleeding episodes prior to 1965 when effective treatment became available. The development of various therapeutic blood products and their transforming effect on the lives of patients and their families is reviewed. The report continues with a consideration of the transmission of hepatitis to patients and discusses how physicians attempted to reduce the risk.

The initial appearance of AIDS first in homosexuals and intravenous drug abusers in 1981 and subsequently in haemophiliacs in 1982 is described. The results are presented of numerous studies of haemophiliacs, undertaken both in North America and Europe, to investigate the relationship between immune changes in asymptomatic individuals and the development of AIDS.

During the period 1982-84 when there were no tests available to detect HIV the response of physicians to the confusing situation is described. The range of therapeutic options then available is reviewed. The report continues by considering how, in the Autumn of 1984 with the development

CAL14(140211)

of a specific anti-HIV antibody test and the almost simultaneous

preliminary demonstration that the AIDS virus might be heat sensitive, it

became possible to adopt a more rational policy for the treatment of

haemophiliacs. By early 1985 it became apparent that the majority of

patients had been infected by HIV during 1982 – 3 prior to its

identification.

The report concludes by presenting evidence that the sterilisation

methods adopted were mostly very effective in reducing HIV transmission

although some of initial treatment regimes did not entirely eliminate the

risk.

CAL14(140211)

BACKGROUND TO HAEMOPHILIA A AND B AND VON WILLEBRAND'S DISEASE

Haemophilia A and B are congenital bleeding disorders due to a deficiency of plasma factor VIII and IX respectively. The prevalence of haemophilia A is approximately 1:10,000 of the population whilst that of haemophilia B is only about one fifth as common. Bleeding is predominantly into large joints, e.g. knees and elbows, as well as muscles. The frequency of bleeding episodes is related to the plasma level of factor VIII/IX; those with a level of less than <2% normal are categorised as having severe haemophilia and experience frequent, often apparently spontaneous, haemorrhagic episodes which may occur once or twice a week. Individuals with 2-10% normal of factor VIII/IX have moderate haemophilia and bleed relatively infrequently; this usually being after minor trauma. Those with factor levels above 10% are described as having mild haemophilia and only bleed after major trauma or surgery.

Prior to 1965 effective treatment was not available. When bleeding occurred into a joint it became swollen and extremely painful and the patient would need to spend up to several weeks resting while the swelling gradually subsided. On occasions fresh frozen plasma was administered but this could not be given in sufficient quantity to raise the factor VIII level to stop

CAL14(140211)

bleeding because to do so would overload the circulation. Untreated

recurrent haemarthroses rapidly result in joint destruction by secondary

osteoarthrosis. When this occurs in knee joints walking becomes slow and

painful. Severe restriction of the elbow and shoulder joints makes eating,

dressing and personal toileting difficult. Mobility is further compromised

when uncontrollable bleeding occurs into muscles, e.g. calf, resulting in

necrosis with subsequent fibrosis and shortening of the muscle. When this

happens in the calf it further compromises walking because the patient can

not put his heal on the ground and has to walk on the ball of the foot.

Without adequate treatment severe haemophilia is therefore a serious

disorder resulting in great pain and distress to the patient and disruption to

his family. Previously recurrent bleeding episodes prevented attendance at

school, and most children by the age of 16 had received a very poor

education. The reduced educational attainment along with the physical

disability impaired employment prospects considerably and many were out of

work for prolonged periods. Life expectancy was shortened with a mean age

of survival of only approximately 20 years, death being due to uncontrollable

haemorrhage .

Cryoprecipitate

In 1964 a technique was described for preparing cryoprecipitate from

plasma. This simple technique for concentrating factor VIII revolutionised

CAL14(140211)

haemophilia care. When cryoprecipitate from 10-15 individual plasma

donations was combined and given to the patient it was possible to raise the

factor VIII level sufficiently to stop haemorrhage. In the UK

cryoprecipitate was prepared by Regional Blood Transfusion Centres from

locally collected plasma. During the late 1960's this treatment became

progressively available to haemophiliacs at hospitals on an out patient basis.

CAL14(140211)

Factor VIII Concentrate

During the early 1970's factor VIII concentrates manufactured by the NHS became available in very limited quantities. This was a purer preparation of factor VIII which was prepared from a pool of donor plasma, containing several hundred to several thousand donations, at the Blood Products Laboratory for England and Wales and the Protein Fractionation Centre for Scotland. It quickly became apparent that this form of treatment could be given by the patient at home resulting in a transformation in their lifestyle. The consequent demand for factor VIII concentrate, and its unavailability from NHS sources, led to importation of commercially prepared products from North America in 1973. Therapy with concentrate prevented patients with haemophilia dying prematurely and substantially improved life expectancy so that by the 1980's this was virtually normal even for individuals with severe haemophilia.

Factor IX Concentrates

Treatment of patients with Christmas disease due to factor IX deficiency, requires therapy by blood products containing factor IX. Initially this was by fresh frozen plasma. This was rather more successful clinically than using

CAL14(140211)

it to treat haemophilia A because of its longer survival time in the recipient,

than factor VIII. In the 1970's treatment with concentrates of factor IX

became available. Like factor VIII concentrates these were prepared from

large plasma pools prepared from many donors but chemically they were

quite different from factor VIII concentrates.

Hepatitis

During the early 1970's it became apparent that haemophiliacs treated with

blood products occasionally developed jaundice as a result of hepatitis and

the outbreak in Bournemouth highlighted that this could also be transmitted

by commercial imported concentrates. From 1977 onwards, studies revealed

that the from the hepatitis B virus, despite screening for HbSAg by very

sensitive third generation techniques at Blood Transfusion Centres, as well

as NANBV. It was estimated that in the UK that approximately 1% of blood

donors could transmit NANBH to patients. Thus any haemophiliac who

received more than approximately 100 donations (perhaps 5-10 treatment

episodes) of cryoprecipitate was very likely to develop hepatitis.

It was against this background that plasma fractionators attempted to

reduce the transmissibility of hepatitis viruses by Pasteurisation of factor

VIII concentrates. It had been known for a long time that heating albumen

solution at 60° for 10 hours rendered it non-infectious for hepatitis. One

commercial company, Behring in West Germany, produced very small amounts

of a factor VIII concentrate treated in this way and during studies in the early - mid 1980's it became evident that this material had a markedly reduced ability to transmit hepatitis. Other studies attempted to inactivate hepatitis viruses by heating the factor VIII concentrate in the dry state; the advantage of this method was that the loss of factor VIII was less than heating it in solution. Studies in monkeys demonstrated that dry heating at rendered the concentrate apparently free of virus when tested in primates. When this material, Haemophil T (Travenol), was given to humans during studies initiated in 1983 it resulted in patients getting hepatitis. In the same year another commercial concentrate, Factorate HT (Armour), treated in a similar way (60°C for 30 hours) also caused hepatitis in patients. Thus the initial dry heat treatment processes were not able to prevent transmission of hepatitis.

Von Willebrand's Factor

Von Willebrand's disease is a distinct disorder from haemophilia A and is due to a congenital deficiency of the von Willebrand factor. This protein acts as a carrier for factor VIII within the plasma. Patients may experience bleeding from the nose, in the gut and heavy menstrual periods. Treatment is by the use of factor VIII containing blood products which also usually contain reasonably large amounts of von Willebrand factor. Because bleeding in most patients is uncommon, treatment from the 1970's until the mid

CAL14(140211)

1980's was usually with DDAVP or cryoprecipitate. Cryoprecipitate was used

in preference to factor VIII concentrate partly because it contained a

higher concentration of von Willebrand factor and because it reduced the

risk of hepatitis transmission as patients with vWD only required an

occasional transfusion.

DDAVP is a synthetic drug related to one of the body's hormones

vasopressin. Its use in patients with haemophilia and VWD was first

reported in 1977 and in the same year it was licensed for use in such

patients. When given intravenously it raises temporarily factor VIII and von

Willebrand factor levels by approximately 3-4 fold. Thus in a patient with

haemophilia A or VWD with a basal factor VIIIe or VWF of approximately

10% it could be raised to 30-50% normal for a few hours. This was often

adequate therapy to allow treatment of minor haemorrhage or for surgery.

The principal advantage of this therapy, and the main reason for its use, is

to prevent patients being exposed to blood products. If the DDAVP is given

slowly, side effects are rare and may consist of some facial flushing and

nausea. Occasionally severe reactions have been reported.

CAL14(140211)

EMERGENCE OF AIDS

In June 1981 the first case reports appeared of Pneumocystis carinii

pneumonia (PCP) and Kaposi's sarcoma (KS) in homosexual men in Los

Angeles and New York (CDC, 1981). Further publications quickly followed

and during 1982 it rapidly became apparent that PCP and KS were spreading

epidemically amongst homosexuals (CDC, 1982f; Follansbee et ale 1982;

Johnson et ale 1982). In June 1982 an increased incidence of non-

Hodgkin's lymphoma was reported in homosexual men (CDC, 1982e). In

these early days of the epidemic there was no diagnostic test for AIDS

and the definition of cases was based on clinical criteria, i.e. opportunistic

infections indicative of immune deficiency, e.g. PCP, or the presence of

specific tumours, e.g. KS. Other homosexual men were noted to have

lymphadenopathy and it became apparent that there was an association

between the presence of persistent generalised lymphadenopathy (PGL) and

the development of AIDS (CDC, 1982a). The aetiology of PGL and how it

related to AIDS remained obscure and was the subject of much

speculation. Enlargement of lymph nodes is found in response to a wide

variety of stimuli, both infectious and non-infectious e.g. drugs or immune

disorders, and can be a reflection of a vigorous immune reaction. It was

difficult to reconcile this evidence indicating an apparent active immune

state with the subsequent development of clinically profound immune

CAL14(140211)

deficiency.

The aetiology of AIDS was unknown and was the subject of much speculation. Possible causes included aberrant cytomegalovirus Infection, a mutant form of hepatitis B, recreational drugs e.g. amylnitrate, liver disease or possibly an entirely new virus. Reports of clustering of AIDS cases which appeared in mid 1982 suggested an infectious agent. An alternative hypothesis was that chronic antigen stimulation, e.g. semen deposited in the rectum, may have stimulated the immune system to cause PGLi but how this led to subsequent AIDS was obscure.

During 1982 it also became apparent that AIDS was occurring with increasing prevalence in intravenous drug abusers in the USA (CDC, 1982b).

The incidence of AIDS cases in the USA and various European countries within the general population and amongst haemophiliacs are set out in Table 1. It is pertinent to note the relatively high prevalence of AIDS in the USA compared with most countries in Western Europe in 1982-84. Although the first AIDS cases were reported in the USA in 1981 it was not until 1983 that a small number in England were identified.

CAL14(140211)

APPERANCE OF AIDS IN HAEMOPHILIACS

In July 1982 a report appeared describing 3 haemophiliacs who developed

PCP; the first had been diagnosed 10 months previously (CDC, 1982d).

These haemophiliacs denied homosexual activity or intravenous drug abuse

and this case report raised the possibility that AIDS could have been due

to an agent transmissible by factor VIII concentrate. No two patients,

however, had received the same batch of factor VIII. From this report it

was immediately clear that AIDS might be caused by factor VIII

concentrate containing a transmissible agent derived from blood donors.

As a result of these 3 cases becoming known to UK Haemophilia Reference

Centre Directors (HRCDs), the question of AIDS appearing in

haemophiliacs in Britain was raised at a HRCD Meeting on 22nd September

1982, two months after the first case report. Dr. Craske, as Chairman of

the Hepatitis Working Party, was asked at the meeting to investigate and

keep HCDs informed.

Haemophilia treaters in the United States were also quick to appreciate

that if AIDS was due to a virus it might potentially be transmitted by

factor VIII concentrates and The National Haemophilia Foundation Medical

and Scientific Advisory Committee (NHF MSAC) recommended in January

CAL14(140211)

1983 that individuals at high risk of AIDS should be excluded from blood donation. This was supported by the Public Health Service in the USA which made similar recommendations (Marx, 1983).

In December 1982 a 20 month old Californian infant who received multiple platelet transfusions was diagnosed with AIDS (CDC, 1982c). The viral aetiology of AIDS was further strengthened by a case report in May 1983 in which an additional multi-transfused infant developed AIDS (Ammann et al. 1983). The blood donors were traced and one was identified who died of AIDS 17 months after donating blood. This not only demonstrated the presence of an infectious agent, but also that the donor was infectious even when asymptomatic.

In January 1983 2 haemophiliacs were reported with PGL, although it was not certain at this stage whether this was due to an infectious blood born agent, or as a result of a immune response to the transfusion of foreign protein (Ragni et al. 1983).

In summary, evidence accumulated from June 1982 onwards that AIDS, and probably PGL, were caused by an agent that could be transmitted by blood. Although it became apparent in the latter part of 1982 that haemophiliacs may have been at risk of AIDS, this did not appear to be substantial, as by January 1983 only 8 cases out of a total haemophiliac

CAL14(140211)

population of approximately 20,000 in the USA had developed AIDS. Of

these 8 individuals, 7 had received blood components other than factor

VIII concentrate, and these might have been responsible for transmission

of the putative AIDS virus. During 1983 the total number of reported

cases in the USA increased to 21 and 1984 to 52 (Table I).

In European cases of AIDS started to be reported later than in the USA.

In the UK the first suspected case was identified in May 1983, but details

were not published until November 1983 (Daly & Scott, 1983). In other

countries within Europe few cases were reported in 1983. Of particular

interest was the observation that very few cases were recognized early in

West Germany, a country which imported a large amount of commercial

factor VIII from the USA.

CAL14(140211)

IMMUNE STUDIES IN HAEMOPHILIACS

Following the appearance of clinical immune deficiency presenting with opportunistic infections in homosexual men, studies were immediately initiated to characterise the immune abnormalities in patients with AIDS. A characteristic feature was a reduction in the blood CD4 lymphocyte numbers and decrease in CD4/CD8 ratios. Furthermore, studies in apparently well asymptomatic homosexual men also demonstrated a decrease in CD4 numbers and CD4/CD8 ratios. It was uncertain as to whether these were due to viral infection, chronic antigen stimulation or another aetiological factor. Although in a number if individuals the reduced CD4/CD8 ratio was due to a lowered CD4 count, in some it resulted from an increase in CD8 cells, and in other from both. Initially it was considered that the CD4/CD8 ratio was the most sensitive parameter of immune dysfunction and that it might be relevant clinically. In addition, other aspects of the immune system were also noted to be impaired. These included a reduction in lymphocyte response to phytohaemagglutinin and other mitogens, a reduction in natural killer cel activity, as well was increase in immunoglobulins levels.

CAL14(140211)

With this evidence of immunological abnormalities in apparently well

homosexuals and intravenous drug abusers, asymptomatic haemophiliacs

were studied after the first three cases of haemophiliac AIDS were

reported in July 1982.

The results that emerged during 1983 and 1984 demonstrated a range of

immune disturbances similar to those observed in other risk groups

(Weintrub et al 1982, Ragni et al 1983, Jones et al 1983, Lederman et ale

1983; Menitove et ale 1983; Ratnoff et ale 1983; Luban et ale 1983;

Goldsmith et ale 1983; Lancet Editoria, 1983; Landay et ale 1983; Ludlam

et ale 1983; Ceuppens et ale 1984; Rickard et ale 1983; deShazo et ale

1983; Lechner et ale 1983; Eyster et ale 1983; Tsoukas et ale 1983;

Gervais et .al. 1983; Aznar et ale 1984; Carr et ale 1984; Moffat et ale

1985; Luban et ale 1982). A reduction in CD4 counts, CD4/CD8 ratio and

other immune abnormalities was observed in asymptomatic haemophiliacs.

These were similar to those observed in apparently well homosexuals and

intravenous drugs abusers.

There was much speculation as to the cause of the immune abnormalities

in haemophiliacs. The following are some of the possibilities that were

considered.

1)   Immune disturbance could have been a previously undescribed feature of

CAL14(140211)

haemophilia. Subsequent studies have not substantiated this possibility.

2) Chronic liver disease in non haemophiliacs is associated with changes in the immune system. Many haemophiliacs have hepatitis due to transmission of hepatitis viruses by transfusion. The immune disturbances observed in haemophiliacs may therefore have been due to liver disease.

3) Blood products given for the treatment of haemophilia contain large amounts of plasma proteins other than factor VIII/IX which constitutes less than 1% of the total protein. The other constituents include fibrinogen, fibronectin, immunoglobulin and many additional proteins derived from the starting plasma. The evidence for the immune abnormality being due to blood products and not a virus are:

a. Many haemophiliacs exposed to blood products had abnormal immunity. Immune changes were observed in recipients of both factor VIII/IX concentrate as well as cryoprecipitate. Although some studies indicated that cryoprecipitate use was associated with less immune disturbance, this was almost certainly because patients receiving cryoprecipitate were moderate and mild haemophiliacs who only required occasional treatment compared with concentrate users who tended to be clinically severe haemophiliacs requiring frequent injections.

b. Recipients of factor IX concentrates had fewer abnormalities than those

CAL14(140211)

treated with factor VIII. The manufacture of these two concentrates is quite different. Factor VIII is much less pure and contains considerably more extraneous protein which might be responsible for the greater immune disturbance.

c.   Studies in haemophiliacs treated exclusively in 1983 by blood products manufactured from local blood donors in AIDS free areas, e.g. Scotland, demonstrated that the patients had similar immune abnormalities compared with patients treated with commercial concentrations manufactured in North America.

d.   Some haemophiliacs who had received massive doses of factor VIII concentrate and other blood products apparently had normal immune function. If a putative AIDS virus was present in even a minority of batches of factor VIII/IX concentrate then patients in receipt of these very large doses would have been expected to be infected and demonstrate the reduced CD4 cell count numbers characteristic of individuals in other risk groups for AIDS.

e.   In patients who had received factor VIII/IX concentrate there was no relationship between the degree of CD4 concentration or CD4/CD8 ratios and the total annual use of the concentrate. This argued in favour of an

CAL14(140211)

"all" or nothing response to factor VIII/IX concentrate infusion, with some patients being more susceptible to immune change following only small amounts of concentrate.

f.   If AIDS was due to a virus transmitted by blood products, why had so few patients with haemophilia out of many tens of thousands developed AIDS in 1983. (It was not proved until later, when anti-HIV testing became available, that the latency between infection and the development of AIDS could be many years.)

4.   The immune changes could have been due to a putative AIDS virus. The evidence for this was :

a.   AIDS was only reported in haemophiliacs who had received blood products.

b.   Some factor VIII concentrate users were reported as having more immune abnormalities than recipients of cryoprecipitate. As concentrate is manufactured from plasma pools derived from 5-25,000 donors it was possible that if a single plasma donation was infected with a putative AIDS virus it could contaminate the whole batch of factor VIII derived from the pool of source plasma.

c.   AIDS cases in haemophiliacs were only initially reported amongst patients who had received factor VIII/IX which had been manufactured from

CAL14(140211)

plasma collected in countries where AIDS was prevalent.

d.   Other blood products, e.g. platelets, had been implicated in the

transmission of AIDS and by implication factor VIII/IX concentrates

might also be infectious.

e.   Amongst intravenous drug abusers it was likely that the putative virus had

spread through blood contamination of shared needles and syringes.

f.   The clinical epidemiology of AIDS was very similar to hepatitis B virus, a

virus known to be transmitted by blood products.

Of the four principal possible causes for immune modulation in

haemophilias there was general agreement that it was due, at least in

part, to the extraneous non-factor VIII proteins in the concentrates.

Some of the immune disturbance might in addition be due to the presence

of a putative AIDS virus in some patients.

The reason why it was possible that both the extraneous proteins and the

putative AIDS virus gave rise to similar immunological changes is because

the immune system only has a limited repertoire of responses when

challenged by foreign substances. The interpretation was further

complicated because either blood products directly, or secondary to

transfusion induced viral liver damage, might cause immune modification

such that individuals became more susceptible to infection when exposed

CAL14(140211)

to new viruses. From this it followed that those individuals with the

greatest immune disturbance were more likely to have become infected by

a putative virus which would have further damaged the immune system.

By the end of 1984 when anti-HIV testing became available it became

clear that the immune changes in haemophiliacs were found in both anti-

HIV negative and positive patients. Thus the presence of immune

abnormalities did not equate with HIV infection as many anti-HIV

negative patients had profound alterations due to extraneous proteins in

the concentrates and possibly the presence of liver disease. Following

infection with HIV it was observed during 1985-86 that the immune

system gradually declined further as patients developed AIDS.

CAL14(140211)

TREATMENT POLICY 1982 – 1984

PRIOR TO IDENTIFICAITON OF AIDS VIRUS

(a)   BACKGROUND AND OPTIONS

By mid 1983 it was reasonable to assume that AIDS could have been

caused by transfusion of a virus, but with only 7 cases in

haemophiliacs being reported world wide by January 1983 and 28 by

the end of the year, should treatment policies have been modified?

At this time within Europe and North America the majority of

individuals with severe haemophilia were on home treatment with

factor VIII/IX concentrates. Their lifestyle and quality of life had

been transformed during the previous 10 years by the availability of

home therapy (vide supra). Was it then appropriate to change

therapy throughout the UK because a few haemophiliacs had

developed AIDS in the USA? Apart from these few cases of AIDS,

the only other evidence to suggest that haemophiliacs might be

infected by an AIDS virus were the reduced CD4 counts and

CD4/CD8 ratios and other immune abnormalities. As set out above,

however, there was much evidence to demonstrate that such changes

were not related to a putative AIDS virus.

During 1983 the argument for change in policy was that the putative

CAL14(140211)

AIDS virus behaved epidemiologically identically to hepatitis B and would therefore be spread very quickly by factor VIII/IX concentrates because each batch was prepared from several hundred, to many thousand, individual plasma donations. This argument assumed that the virus was not inactivated during processing of the plasma and would be present in a concentration that would infect the majority of recipients. The alternative explanation was that the putative virus was not very infectious, was partially inactivated during preparation of the concentrates, and that only a minority of haemophiliacs were infected and that the immune changes in the majority of haemophiliacs were due to transfusion of foreign proteins.

Prior to the Autumn of 1984 when anti-HIV testing became available and the heat sensitivity of the virus was demonstrated, how should Haemophilia Directors in the UK have responded to the available knowledge? During 1983 and 1984 only two haemophiliacs amongst 5,000 haemophilias had been reported in the UK. Given the great uncertainty about the cause of the immune changes in the haemophiliacs, what would have been a reasonable course of action to adopt?

The options were to:

CAL14(140211)

a) <u>Stop treatment of all bleeding episodes</u> During the 1970's and early 1980's death from haemorrhage was still the commonest cause of death in haemophiliacs. If all treatment had been stopped then there would, without a doubt, have been increased mortality from haemorrhage (Johnson et al. 1985). Furthermore the disruption to patients' lives, and to that of their families, along with the pain and misery of recurrent haemarthroses and other serious bleeds would have made this option unacceptable to patients in 1983-84 (Ratnoff et al. 1985).

b)   <u>Revert to cryoprecipitate therapy.</u> This would have been theoretically possible, but both in the UK and USA plasma collection was directed to factor VIII/IX concentrate manufacture (because of the high demand for this product)

and away from cryoprecipitate. To have reversed this policy would have required patients to abandon come off home treatment and to receive cryoprecipitate in hospital. This too would have led to great disruption to the patient's life and experience in the USA suggests that such a policy would not have been acceptable to patients (Ratnoff et al. 1985).

Cryoprecipitate has many disadvantages for treating haemophiliacs.

It is a product of low purity resulting in a high incidence of unpleasant and occasionally potentially fatal allergic side effects. Storage has to be in a deep freeze at -20 °c and after thawing 10 – 15 individuals' donations need to be pooled before infusion. The factor VIII content is very variable. For these reasons it was unacceptable for home therapy. It was acceptable treatment for clinically mild haemophiliacs because they were treated in hospital as therapy was required infrequently and reactions were uncommon. The only known advantage of using this product compared to factor VIII concentrate was for infrequently transfused patients, e.g. mild haemophiliacs, because it carried a lower risk of hepatitis. When a patient received more than 100 – 200 donations i.e. 10 – 20 life time infusions, non-A non-B hepatitis was likely to be transmitted.

Similarly, although cryoprecipitate may protect the population of haemophiliacs from viral infection e.g. HBV or NANBV, the extent to which it does so depends upon the prevalence of the virus in the donor population. In some European countries e.g. Sweden and Belgium, cryoprecipitate had been used extensively for many years prior to 1982 and in these countries prevalence of HIV infection in haemophiliacs is low. But in other parts of the world where cryoprecipitate has been exclusively used, a high percentage has

CAL14(140211)

become infected because the HIV was silently present in many

donors (Gjerset et ale 1985).

Even if a decision had been made to revert to establishment of a

major cryoprecipitate manufacturing capacity within Blood

Transfusion Centres. This in itself would have needed immediate

substantial space and investment for equipment and the employment

and training of further personnel. More blood donors would have to

have been recruited or a facility to Plasmapheresis donors would

have had to have been established.

c. Stop importation of commercially by manufactured factor VIII

and rely on NHS factor VIII and cryoprecipitate.

In 1983/84 approximately 60% of all treatment products in the UK were

imported (Fig. 1). This commercial concentrate could have to have

been replaced by the manufacture of cryoprecipitate by local Blood

Transfusion Centres because the Blood Products Laboratory at

Elstree was working near maximum capacity and could not have

manufactured more factor VIII concentrate. Some of the

difficulties of increasing cryoprecipitate production are outlined

above.

The success of this option in reducing HIV infection would depend on

CAL14(140211)

the HIV prevalence amongst blood donors. In 1983/84 it was

appreciated that, despite presumed infection by a putative virus,

donors could still feel entirely well. It was therefore impossible

accurately to assess the prevalence of this possible virus in a

particular population (e.g. the HIV outbreak in the Summer of 1983

in Edinburgh was completely silent clinically and was only discovered

in 1985 when anti-HIV tests became available).

In some parts of the world commercial factor VIII/IX concentrates

are not used, partly to prevent importation of foreign viruses.

Australia is one such country and it was claimed that its

haemophiliacs were free of HIV in 1983. Unfortunately it was not

appreciated at that time that a significant number of infected

homosexuals had contaminated the plasma pools from which factor

VIII/IX was manufactured (Rickard et ale 1983).

d)   <u>Develop virus reduced factor VIII/IX concentrates.</u>

In early 1983 there was merely epidemiological evidence that AIDS

was caused by a virus and therefore to embark on a heat, or other

treatment, process of concentrates would have been inappropriate.

There was a real fear that heated factor VIII concentrates might

be hazardous. Heating might have destroyed a putative virus, but

CAL14(140211)

experience demonstrated that it did not prevent transmission of

hepatitis. The principal anxiety about heat treatment was that it

might denature either factor VIII or any of the other proteins and

cause serious, potentially fatal, reactions in the haemophiliacs.

Additionally many patients might have developed antibodies to the

partially denatured factor VIII which would have made further

therapy almost ineffective.

Thus the failure to prevent hepatitis transmission by heating, the

absence of an identified AIDS virus, and the potentially hazardous

results of heat treatment of factor VIII concentrates might render

hazardous, meant that the option to heat treat all factor VIII just

incase AIDS was caused by a heat sensitive virus was not attractive.

e.   <u>Try to ensure that individuals in high risk groups did not donate</u>

<u>blood and continue to use factor VIII concentrates.</u>

A policy was adopted by the American Association of Blood Bank

Committee on Transfusion Transmitted Diseases in January 1983 and

by the Regional Transfusion Centres in England and Wales to

persuade donors in high risk groups to refrain from donating. The

NHS MSAC reiterated in January 1983 their original advice of

November 1982 that high risk donors should be excluded.

(b) CONSIDERATION OF TREATMENT OPTIONS IN THE UK

Following the first case reports in July 1982 of three haemophiliacs with AIDS, urgent and very serious consideration was given, both in the UK and internationally, as to whether there should be a change in treatment policy for haemophiliacs. In 1982 there was speculation that there might be a virus causing AIDS, but all the decisions about therapy for haemophiliacs had to be made in the absence of a blood test to identify individuals exposed to the virus, which only became available in the Autumn of 1984. It was presumed that there was a latent asymptomatic period between infection and the development of AIDS, but that this could extend for 10 or more years was not appreciated. Nothing was known about whether the manufacturing process for factor VIII/IX concentrates might have inactivated the virus. It was not until late September 1984 that a single publication demonstrated the heat sensitivity of HIV (Levy et al. 1984) and supported by a further independent report (CDC, 1984).

Decisions had to be made on very limited data during 1983-84 when the only information available related to knowledge of the immune abnormalities in haemophiliacs, that there might be a responsible virus and that a very tiny percentage of haemophiliacs had developed AIDS.

During the first quarter of 1983 there was debate in Editorials in several leading medical journals about whether there should be any change in therapeutic practice. An Editorial in the New England Journal of Medicine wondered whether it would be prudent to switch from concentrate to cryoprecipitate (Desforges, 1983). In the Annals of Internal Medicine Editorial in March 1983 the author indicated that he had reduced surgery and switched a few patients from factor VIII concentrate to cryoprecipitate (White & Lesesne, 1983. Both these North American Editorials in advocating a change to cryoprecipitate were bringing American therapy more into line with existing UK practice where it was common practice to give cryoprecipitate to mild or infrequently transfused patients. Also in March an Editorial in The Lancet considered whether the T cell abnormalities in haemophiliacs were the submerged part of a large viral iceberg, but if so, the author wondered why so few haemophiliacs in West Germany, where a large amount of American factor VIII concentrate was used, had ~ not developed AIDS (Lancet Editorial 1983). The Editorial concluded there was no strong argument for a change in treatment policy.

In March 1983, as there did not appear to be any haemophiliacs with AIDS in Britain, the HRCD's organised a survey to try and identify

CAL14(140211)

AID cases amongst British haemophiliacs.

A special meeting of the Reference Centre Directors on the 13th May 1983, was called to consider the AIDS issue because it became known that a haemophiliac in the UK might have developed AIDS. At that time there were thought to be about 10 cases of non-haemophilia AIDS in the UK which were mainly concentrated in London. It was agreed that Dr. Craske would draw up a form for reporting any further cases that might be diagnosed.

At the meeting treatment recommendations were drawn up and circulated to all Haemophilia Centres on 24th June 1983. The advice was in line with what was current practice at many Haemophilia Centres at the time. The advice was that for patients with haemophilia A treatment should be as follows:

1. DDAVP for minor lesions in patients with mild disease or von Willebrand's disease.

2. Avoid factor VIII concentrates in patients who had not previously received concentrates because of the known risk of hepatitis transmission.

3. For children and mildly affected patients and patients not previously exposed to commercial concentrates use NHS factor VIII

CAL14(140211)

concentrates or cryoprecipitate.

4.   Patients who had previously received factor VIII concentrate could

continue on such concentrates.

NHS factor IX concentrate (as there was less reason to suspect this

product of transmitting a putative AIDS virus).

The circular stated that there was no evidence to suggest that the

process involved in the preparation of "hepatitis reduced" factor

VIII concentrates (Haemofil T and Factorate HT) would inactivate

any other hypothetical virus.

At this time the NHF MASC recommended the continued use of

clotting factor concentrates for patients who had previously

received them to treat bleeding episodes.

In June 1983 Dr. Craske wrote to all HCDs indicating that a

haemophiliac in the UK may possibly have developed AIDS. Reporting

forms were distributed to all Haemophilia Centres.

During the remainder of 1983 and 1984 the number diagnosed with

AIDS in the USA and Europe increased, but they were still only a

very small percentage of the total haemophiliac population. At each

subsequent meeting of Haemophilia Centre Directors the topic was

discussed.

CAL14(140211)

CAL14(140211)

INDENTIFICATION OF VIRUS CAUSING AIDS IN

HAEMOPHILIACS

In May 1983 a retrovirus was cultured by French workers from a patient

with PGL (Barre-Sinoussi.et.al. 1983) and a year later in April 1984 the

same group isolated live virus from two brothers with haemphilia B, one

having AIDS and the other being asymptomatic (Vilmer et al. 1984). Gallo

and colleagues published results indicating culture of HIV from two AIDS

patients in May 1984 (Popovic et al. 1984.). Other workers identified an

antibody in patients with AIDS which cross reacted with HTVL I)virus

causing T-cell leukaemia) and in February 1984 5/59 haemophiliacs were

found positive by this cross reactivity test indicating that they might

have been exposed to an HTLV I like virus (Kreiss et al. 1984)

By mid 1984,) techniques had been developed to detect anti-HIV

antibodies. The results of testing haemophiliacs were published in the

summer and autumn of 1984; viz July 64% of Danish positive (Ramsey et

ale 1984). A study of haemophiliacs in London published in September

indicated that 34% of haemophiliacs were anti-HIV positive (Cheingsong-

Popov et ale 1984). A further study from the USA indicated that 65% of

haemophiliacs were anti HIV positive (Kitchen et al. 1984). Thus by the

Autumn of 1984 it was clear that many haemophiliacs had been exposed to

HIV, although it was not clear whether the presence of specific

CAL14(140211)

antibodies reflected exposure to HIV and the development of protective immunity, or whether the patients were actively infected. By the end of 1984 in the USA 52 patients had developed AIDS out of a total of at least 20,000 and in the UK only two were reported as developing AIDS out of a total of approximately 5,000 patients.

The other major development in the Autumn of 1984 was the report in September that a murine retrovirus was heat sensitive and that heating of freeze dried factor VIII at *68°* centigrade destroyed the virus (Levy et al. 1984). An additional report of studies at Cutter Laboratories demonstrated the heat sensitivity of HIV (CDC, 1984).

In the USA the NHF MSAC issued further "Recommendations Concerning AIDS and the Treatment of Haemophilia" on October 13th 1984. These reiterated the previous advice of using cryoprecipitate for infants and children and newly identified patients with haemophilia etc. Other patients should receive heat treated concentrates, although it is stated that there was only scant evidence for the efficacy of heating to inactivate HIV.

Although this advice was issued in October 1984 the transition to the exclusive use of heat treated factor VIII in the USA took until about June 1985.

TREATMENT POLICY AFTER THE IDENTIFICATION OF THE AIDS VIRUS

Although the initial ifying a possible AIDS virus appeared in May 1983 (Barre-Sinossi et al. 1983), it was not until the confirmatory report of May 1984 (Popovic et al. 1984) extent of haemophiliacs' became apparent. Furthermore with the early demonstration of the heat sensitivity of HIV it became possible for haemophilia treaters to offer advice on treatment based on a sound scientific basis.

As stated above in the discussion on hepatitis, small amounts of dry heated factor VIII were available in the UK as part of an international multi-centre trial (Hemofil T) and also for treating 3 patients (Factorate HT). Both these products resulted in a high transmission rate of hepatitis and they were therefore quickly withdrawn from further trial. Thus although these products when used in primates were apparently free of hepatitis viruses, they still caused hepatitis in humans. Because of this disappointing result further heat treated concentrates were not assessed in patients although manufacturers contained research. By December 1984 it was clear that many haemophiliacs had been exposed to HIV, that the virus appeared to be heat sensitive and it was possible

CAL14(140211)

to heat treat factor VIII. HRCD's met on December 10th 1984 to

reconsider again the situation in the UK.

By December 1984 it was clear that at least two batches of NHS factor

VIII, one in England, in Scotland, had been contaminated by HIV and had

result infection of patients. At that time it appeared that the risk of an

anti-HIV positive individual developing AIDS was approximately 1%. The

presence of cleaned from the body by the immune system, as is the case

for most viral infections, or whether patients might harbour the virus.

From a few anti-HIV positive patients it had been possible to isolate live

virus, but how common this was remained unknown for some time. It was

therefore agreed that any haemophiliac who was anti-HIV positive

should be considered potentially infected and infectious.

It was agreed after considerable discussion at the HRCD's that heat

treated concentrate should be used in preference to non-heated factor

VIII concentrates. The ideal product would have been an NHS heat

treated concentrate and there was considerable discussion as to

whether it was better to use heat treated commercial in preference to

non-heated NHS concentrate. The problem of funding the conversion to

a much more expensive heat treated commercial product was also

considered. The legal aspects of changing to an unlicensed heat treated

product were also reviewed. It was known that commercial manufactures

CAL14(140211)

were seeking CSM license variations.

The Blood Products Laboratory at Elstree, was to have some NHS factor VIII available in the Spring of 1985, but production of the new heat treated factor VIII concentrate 8Y would not be available until the Autumn. When considering which product to use it had to be borne in mind that there were other risks than HIV associated with commercial concentrate, e.g. hepatitis.

An advisory document dated 14th December 1984 was drawn up and circularised to all Haemophilia Centres in the UK. It recommended that patients with haemophilia A should be treated as follows:

1. New patients, children and patients not previously treated with concentrate should received cryoprecipitate or heat treated NHS factor VIII concentrate or cryoprecipitate.

2. Patients with severe or moderate haemophilia previously treated with concentrate should receive heat treated NHS or commercial concentrate.

3. DDAVP should be considered for treating patients with mild haemophilia A or VWD.

For patients with haemophilia B treatment should be as follows:

CAL14(140211)

1. Patients with mild disease should receive fresh frozen plasma or NHS

    factor IX concentrate.

2. New patients and those not previously treated with concentrates should

    receive fresh frozen plasma (and NHS factor IX concentrate only if

    essential).

3. Patients with severe or moderate deficiency previously exposed to NHS

    factor IX concentrate should continue to receive this product.

The document stated that there was uncertainty as to whether heated

US factor VIII was safer than non-heated NHS and that some directors

might wish to continue using non-heated NHS material until heat treated

NHS factor VIII was available. Advice was given about trying to obtain

additional funds and directors were invited to let the Chairman or

Secretary of the HeDs know if there were difficulties.

It was recommended that all patients should be anti-HIV tested

although it was acknowledged that testing facilities were not generally

available and additional DHSS resources were urgently needed.

Despite the general recommendation to use heat treated factor VIII

concentrates there was considerable hesitation in the minds of some

Haemophilia Directors that the heating process might denature proteins,

including factor VIII. This could result in potentially serious immune

reactions when given to haemophiliacs (vide supra). The other real

anxiety was that denatured proteins might stimulate the immune system

of the recipient resulting in increased susceptibility to infection or

enhanced replication of the virus if the individual was already infected

(Bird et al. 1985). The decision therefore to use heat treated

concentrates was finely balanced and was taken in the light of the

limited knowledge available.

During the early part of 1985 it became clear that there were no

immediately obvious severe side effects of using heated concentrates

and the balance of opinion swung unambiguously towards the use of

heated concentrates.

The first clinical evidence that a dry/heated factor VIII concentrate

had a reduced risk of HIV transmission was published in February 1985.

No sero conversions in 18 patients treated with Haemophil T were

observed (Rouzioux et al. 1985). Also published in the same month was a

small study from London indicating that 9 of 15 haemophiliacs treated

with unheated commercial factor VIII were anti-HIV positive whereas

13 patients who received only unheated NHS produced products were all

anti-HIV negative

(Machin et al. 1985). These findings were very similar to a study

CAL14(140211)

reported from Glasgow again demonstrating the relative safety of

unheated NHS, compared to unheated commercial concentrates (Madhok

et al. 1985).

At the end of 1984 and beginning of 1985 several studies reported that

smaller users of factor VIII concentrate were at lower risk of being

anti-HIV positive. Several reports also indicated that patients treated

with cryoprecipitate were at much lower risk of becoming anti-HIV

positive (Koerper et al. 1985; Machin et al. 1985). This in part may be due

to cryoprecipitate being given relatively infrequently to mild or moderate

haemophiliacs who had fewer bleeds than individuals with severe

haemophilia who were treated with concentrate. A study published in

1986 from Seattle where all patients had been treated predominantly

with cryoprecipitate demonstrated a high anti-HIV prevalence (Gjerset

et al. 1985). Thus it was demonstrated that the chance of becoming

infected with HIV was related to the prevalence of HIV in the donor

population and frequency of transfusion.

In response to the Recommendations sent by Haemophilia Reference

Centre Directors in December 1984, many treaters in the UK changed to

using heat treated concentrates. In England and Wales this was initially

commercial concentrate, as the only material available, but in the Spring

a small amount of heat treated NHS material was released by the Blood

CAL14(140211)

Products Laboratory. From late 1984 onwards there were reasonable supplies of commercial heat treated concentrate available from several manufactures. Initially this was issued on a named patient basis, as Profilate HT and Haemophil T did not receive CSM licenses until February 1985 and Factorate in March.

In February 1985 it was reported that a UK patient with haemophilia B treated exclusively with NHS factor IX concentrate had become anti-HIV positive. As a result some Haemophilia Directors opted to treat patients with commercial heat treated factor IX concentrate instead of unheated NHS material.

The transition towards use of heat treated concentrate in the UK was monitored in April by a survey conducted by Professor Bloom the USA and UK. Thus by mid 1983 when major changes in therapeutic practice were being considered many of the patients had already been infected by HIV.

During the period 1985-88 viral safety studies were reported on further concentrates viral inactivated by heat either in the dry, or wet state or vapour treated. The studies assessed transmission of HBV, NANBV and HIV. Transmission of HBV was observed in one study but it was not possible in many others because the patients had received prior

CAL14(140211)

immunisation with hepatitis B vaccine. The NANBV was harder to

inactivate and initial studies at temperatures up to 68°C in the dry state

failed to prevent transmission as did a heptane slurry technique. The use

of either higher temperatures (80°C) in the dry state, pasteurisation at

60°C in solution or treatment with solvent and detergent effectively

prevented NANBV transmission.

HIV transmission has been reported from dry 60°C heated concentrate.

Other individual reports of HIV infection from concentrates heated

below 80°C from both anti-HIV screened and unscreened blood have led

to the abandonment of the lower temperature dry heat treatment

regimes.

There is now substantial evidence that factor VIII/IX concentrates

prepared from anti-HIV screened plasma and heat treated wither at

80°C in the dry, 60°C in the wet, or in the presence of solvent and

detergent have a negligible chance of transmitting HIV and NANBH.

Ammann, A.J., Cowan, M.J., Wara, D.W., Weintrub, P., Dritz, S., Goldman, H. & Perkins, H.A. (1983) Acquired immunodeficiency in an infant: possible transmission by means of blood products. Lancet, **1**, 956-958.

Aznar, J.A., Jorquera, J.I., Carbonell, F., Sanchez-Cuenca, J.M., Trenor, A., De Andres Medina, R., Carmona, E. & Gonzalez-Molina, A. (1984) Immunological studies of haemophilic patients with inhibitors treated with Factor VIII concentrates in a protocol to induce immunotolerance letter. Thromb. Haemost., **52**, 212-213.

Barre-Sinoussi, F., Chermann, J.C., Rey, F., Nugeyre, M.T., Chamaret, S., Gruest, J., Dauguet, C., Axler-Blin, C., VezinetBrun, F., Rouzioux, C., Rozenbaum, W. & Montagnier, L. (1983) Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). Science, **220**, 868-871.

Bird, A.G., Codd, A.A. & Collins, A. (1985) Haemophilia and AIDS letter. Lancet, **1**, 162-163.

Bloom, A.L., Forbes, C.D. & Rizza, C.R. (1985) HTLV-III, haemophilia, and blood transfusion letter. Br. Med. J. [Clin. Res]., **290**, 1901-1902.

CAL14(140211)

Carr, R., Veitch, S.E., Edmond, E., Peutherer, J.F., Prescott, R.J., Steel, C.M. & Ludlam, C.A. (1984) Abnormalities of circulating lymphocyte subsets in haemophiliacs in an AIDS-free population. Lancet, **1**, 1431-1434.

CDC (1981) Pneumocystis Pneumonia - Los Angeles. mmwr, **30**, 250252.

CDC (1982a) Persistent, generalized lymphadenopathy among homosexual males. mmwr, **31**, 249-252.

CDC (1982b) Update on Acquired Immune Deficiency Syndrome (AIDS) United States. MMWR., **31**, 507-514.

CDC (1982c) Possible transfusion-associated acquired immune deficiency syndrome (AIDS) - California. mmwr, **31**, 652-654.

CDC (1982d) Pneumocystis carinii pneumonia among persons with hemophilia A. mmwr, **31**, 365-367.

CDC (1982e) Diffuse, undifferentiated non-Hodgkin's lymphoma among homosexual males - United States. mmwr, **31**, 277-279.

CDC (1982f) A cluster of Kaposi's sarcoma and pneumocystis carinii pneumonia among homosexual male residents of Los Angeles and Orange Countries, California. mmwr, **31**, 305-307.

CAL14(140211)

CDC (1984) Update: acquired immunodeficiency syndrome (AIDS) in

persons with hemophilia. MMWR., **33**, 589-591.

K., Stevens, E., The, A.L., Vanham, G., Vermylen, C. & Verstraete, M. (1984) Immunological alterations in haemophiliacs treated with lyophilized Factor VIII cryoprecipitate from volunteer donors. Thromb. Haemost., **51,** 207-211.

Cheingsong-Popov, R., Weiss, R.A., Dalgleish, A., Tedder, R.S., Shanson, D.C., Jeffries, D.J., Ferns, R.B., Briggs, E.M., Weller, I.V., Mitton, S. & et aI, (1984) Prevalence of antibody to human T-Iymphotropic virus type III in AIDS and AIDS-risk patients in Britain. Lancet, **2,** 477-480.

Daly, H.M. & Scott, G.L. (1983) Fatal AIDS in a haemophiliac in the UK letter. Lancet, **2,** 1190-1190.

Desforges, J.F. (1983) AIDS and preventive treatment in hemophilia editorial. N. Engl. J. Med., **308,** 94-95.

deShazo, R.D., Andes, W.A., Nordberg, J., Newton, J., Daul, C. & Bozelka, B. (1983) An immunologic evaluation of hemophiliac patients and their wives. Relationships to the acquired immunodeficiency syndrome. Ann. Intern. Med., **99,** 159-164.

Evatt, B.L., Gomperts, E.D., Coincidental appearance hemophiliacs and

the onset Med., **312,** 483-486.

McDougal, J.S. & Ramsey, R.B. (1985) of LAV/HTLV-III antibodies in

of the AIDS epidemic. N. Engl. J.

Eyster, M.E., Goedert, J.J., Poon, M.C. & Preble, *D. T. (1983)* Acid-

labile alpha interferon. A possible preclinical marker for the acquired

immunodeficiency syndrome in hemophilia. N. Engl. J. Med., **309,**

583-586.

Felding, P., Nilsson, LM., Hansson, B.G. & Biberfeld, G. (1985) Absence

of antibodies to LAV/HTLV-III in haemophiliacs treated with heat-

treated factor VIII concentrate of American origin letter. Lancet,

2, 832-833.

Follansbee, S.E., Busch, D.F., Wofsy, C.B., Coleman, D.L., Gullet, J.,

Aurigemma, G.P., Ross, T., Hadley, W.K. & Drew, W.L. (1982) An

outbreak of Pneumocystis carinii pneumonia in homosexual men. Ann.

Intern. Med., **96,** 705-713.

Gervais, F., Tsoukas, C., Fuks, A. & Shuster, J. (1983) Natural history

of the AIDS related complex in hemophilia-- relationships to Epstein

Barr virus. AIDS Res., **1,** 197-209.

Gjerset, G.F., McGrady, G., Counts, R.B., Martin, P.J., Jason, J.,

CAL14(140211)

Kennedy, S., Evatt, B. & Hansen, J.A. (1985) LYIDphadenopathy-associated virus antibodies and T cells in hemophiliacs treated with cryoprecipitate or concentrate. Blood., **66**, 718-720.

Goedert, J.J., Sarngadharan, M.G., Eyster, M.E., Weiss, S.H., Bodner, A.J., Gallo, R.C. & Blattner, W.A. (1985) Antibodies reactive with human T cell leukemia viruses in the serum of hemophiliacs receiving factor VIII concentrate. Blood., **65**, 492495.

Goldsmith, J.C., Moseley, P.L., Monick, M., Brady, M. & Hunninghake, G.W. (1983) T-Iymphocyte subpopulation abnormalities in apparently healthy patients with hemophilia. Ann. Intern. Med., **98,** 294-296.

Johnson, R., Horwitz, S.N. & Frost, P. (1982) Disseminated Kaposi's sarcoma in a homosexual man. JAMA, **247,** 1739-1741.

Johnson, R.E., Lawrence, D.N., Evatt, B.L., Bregman, D.J., Zyla, L.D., Curran, J.W., Aledort, L.M., Eyster, M.E., Brownstein, A.P. & Carman, C.J. (1985) Acquired immunodeficiency syndrome among patients attending hemophilia treatment centers and mortality experience of hemophiliacs in the united States. Am. J. Epidemiol., **121,** 797-810.

Jones, P., Proctor, S., Dickinson, A. & George, S. (1983) Altered immunology in haemophilia letter. Lancet, **1,** 120-121.

Kitchen, L.W., Barin, F., Sullivan, J.L., McLane, M.F., Brettler, D.B., Levine, P.H. & Essex, M. (1984) Aetiology of AIDS--antibodies to human T-cell leukaemia virus (type III) in haemophiliacs. Nature, **312,** 367-369.

Koerper, M.A., Kaminsky, L.S. & Levy, J.A. (1985) Differential prevalence of antibody to AIDS-associated retrovirus in

haemophiliacs treated with Factor VIII concentrate versus cryoprecipitate: recovery of infectious virus letter. Lancet, **1**, 275-275.

Kreiss, J.K., Lawrence, D.N., Kasper, C.K., Goldstein, A.L., Naylor, P.H., McLane, M.F., Lee, T.H. & Essex, M. (1984) Antibody to human T-cell leukemia virus membrane antigens, beta 2microglobulin levels, and thymosin alpha 1 levels in hemophiliacs and their spouses. Ann. Intern. Med., **100**, 178-182.

Lancet Editorial (1983) Acquired immunodeficiency in haemophilia. Lancet, **1**, 745-745.

Landay, A., Poon, M.C., Abo, T., Stagno, S., Lurie, A. & Cooper, M. D. (1983) Immunologic studies in asymptomatic hemophilia patients. Relationship to acquired immune deficiency syndrome (AIDS). J. Clin. Invest., **71**, 1500-1504.

Lechner, K., Niessner, H., Bettelheim, P., Deutsch, E., Fasching, I., Fuhrmann, M., Hinterberger, W., Korninger, C., Neumann, E., Liszka, K. & et aI, (1983) T-cell alterations in hemophiliacs treated with commercial clotting factor concentrates. Thromb. Haemost., **50**, 552-556.

Lederman, M.M., Ratnoff, O.D., Scillian, J.J., Jones, P.K. & Schacter,

CAL14(140211)

B. (1983) Impaired cell-mediated immunity in patients with classic

hemophilia. N. Engl. J. Med., **308,** 79-83.

Levy, J.A., Mitra, G. & Mozen, M.M. (1984) Recovery and inactivation

of infectious retroviruses from factor VIII concentration. Lancet, **2,**

722-723.

Luban, N.L., Kelleher, J.F., Jr. & Reaman, G.H. (1983) Altered distribution of T-Iymphocyte subpopulations in children and adolescents with haemophilia. Lancet, 1, 503-505.

Luban, N.L.C., Kelleher, J.F. & Reaman, G.H. (1982) Investigation of immune status in children and adolescents with hemophilia. Blood., 60 supple 1, 216a-216a.

Ludlam, C.A., Carr, R., Veitch, S.E. & Steel, C.M. (1983) Disordered immune regulation in haemophiliacs not exposed to commercial factor VIII letter. Lancet, 1, 1226-1226.

Machin, S.J., McVerry, B.A., Cheingsong-Popov, R. & Tedder, R.S. (1985) Seroconversion for HTLV-III since 1980 in British haemophiliacs letter. Lancet, 1, 336-336.

Madhok, R., Melbye, M., Lowe, G.D., Forbes, C.D., Froebel, K.S., Bodner, A.J. & Biggar, R.J. (1985) HTLV-III antibody in sequential plasma samples: from haemophiliacs 1974-84 letter. Lancet, 1, 524-525.

Marx, J.L. (1983) Spread of AIDS sparks new health concern news. Science, 219, 42-43.

Melbye, M., Biggar, R.J., Chermann, J.C., Montagnier, L., Stenbjerg, S. &

Ebbesen, P. (1984) High prevalence of lymphadenopathy virus (LAV) in European haemophiliacs letter. Lancet, 2, 40-41.

Me nit O v e , J. E ., As t e r, R . H ., Cas per, J. T ., La u e r, S. J ., Gottschall, J.L., Williams, J.E., Gill, J.C., Wheeler, D.V., Piaskowski, V., Kirchner, P. & Montgomery, R.R. (1983) Tlymphocyte subpopulations in patients with classic hemophilia treated with cryoprecipitate and lyophilized concentrates. N. Engl. J. Med., 308, 83-86.

Moffat, E.H., Bloom, A.L., Jones, J., Matthews, N. & Newcombe, R.G. (1985) A study of cell mediated and humoral immunity in haemophilia and related disorders. Br. J. Haematol., 61, 157-167.

Mosseler, J., Schimpf, K., Auerswald, G., Bayer, H., Schneider, J. & Hunsmann, G. (1985) Inability of pasteurised factor VIII preparations to induce antibodies to HTLV-III after long-term treatment letter. Lancet, 1, 1111-1111.

Petricciani, J.C., McDougal, J.S. & Evatt, B.L. (1985) Case for concluding that heat-treated, licensed anti-haemophilic factor is free from HTLV-III letter. Lancet, 2, 890-891.

Popovic, M., Sarngadharan, M.G., Read, E. & Gallo, R.C. (1984) Detection, isolation, and continuous production of cytopathic retroviruses (HTLV-III) from patients with AIDS and pre-AIDS. Science, 224, 497-500.

Ragni, M.V., Lewis, J.H., Spero, J.A. & Bontempo, F.A. (1983) Acquired-immunodeficiency-like syndrome in two haemophiliacs. Lancet, 1, 213-214.

Ramsey, R.B., Palmer, E.L., McDougal, J.S., Kalyanaraman, V.S., Jackson, D.W., Chorba, T.L., Holman, R.C. & Evatt, B.L. (1984) Antibody to lymphadenopathy-associated virus in haemophiliacs with and without AIDS letter. Lancet, 2, 397-398.

Ratnoff, O.D., Menitove, J.E., Aster, R.H. & Lederman, M.M. (1983) Coincident classic hemophilia and "idiopathic" thrombocytopenic purpura in patients under treatment with concentrates of antihemophilic factor (factor VIII). N. Engl. J. Med., 308, 439-442.

Ratnoff, O.D., Lederman, M.M., Krill, C., Jr., Pass, L.M. & Ross, C.E. (1985) Hemophilia and the acquired immunodeficiency syndrome letter. Ann. Intern. Med., 102, 412-412.

Rickard, K.A., Joshua, D.E., Campbell, J., Wearne, A., Hodgson, J. & Kronenberg, H. (1983) Absence of AIDS in haemophiliacs in Australia treated from an entirely voluntary blood donor system letter. Lancet, 2, 50-51.

Rouzioux, C., Chamaret, S., Montagnier, L., Carnelli, V., Rolland, G. & Mannucci, P.M. (1985) Absence of antibodies to AIDS virus in haemophiliacs treated-with heat-treated Factor VIII concentrate

CAL14(140211)

letter. Lancet, **1,** 271-272.

Tsoukas, C., Gervais, F., Fuks, A., Guttmann, R.D., Strawczynski, H., Shuster, J. & Gold, P. (1983) Immunologic dysfunction in patients with classic hemophilia receiving lyophilized factor VIII concentrates and cryoprecipitate. Can. Med. Assoc. J., **129,** 713-717.

van den Berg, W., ten Cate, J.W., Breederveld, C. & Goudsmit, J. (1986) Seroconversion to HTLV-III haemophiliac given heat-treated factor VIII concentrate letter. Lancet, **1,** 803-804.

Vilmer, E., Barre-Sinoussi, F., Rouzioux, C., Gazengel, C., Brun, F.V., Dauguet, C., Fischer, A., Manigne, P., Chermann, J.C., Griscelli, C. & et aI, (1984) Isolation of new lymphotropic retrovirus from two siblings with haemophilia B, one with AIDS. Lancet, **1,** 753-757.

Weintrub, P., Ammann, A.J., Abrams, D.I., Shuman, M.A., Addiego Jr, J.E., Cowan, M.J. & Koerper, M.A. (1982) Altered T-cell immunity in hemophiliacs receiving frequent factor VIII concentrate. Blood., **60 supple 1,** 224a.

White, G.C. & Lesesne, H.R. (1983) Hemophilia, hepatitis, and the acquired immunodeficiency syndrome. Ann. Intern. Med., **98,** 403404.

White, G.C., Matthews, T.J., Weinhold, K.J., Haynes, B.F., Cromartie,

CAL14(140211)

H.L., McMillan, C.W. & Bolognesi, D.P. (1986) HTLV-III seroconversion associated with heat-treated factor VIII concentrate letter. Lancet, **1**, 611-612.

(Year Quarter)	1981				1982				1983				1984				1985			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
UK Total								9			14	24	31		42	54	108		206	241
Haemophilia													2			2			6	
Europe Total											153	267			391	421	762	940		1226
Haemophilia											1				8	12	17	27		39
USA Total			5	108		355	593				1641	1972	2753	3000	4918		6993	10,000		13,000
Haemophilia				4			3	7		1%		2%	1%			52	65			

NOTES: In UK by November 1984 65/90 (70%) AIDS - London
3/90 AIDS - Scotland

Summary of AIDS cases in USA, Europe and UK by totals and Haemophiliacs 1981-1985
(Sources, WHO Weekly Epidemiological Record, Morbidity and Mortality Weekly Report, Communicable
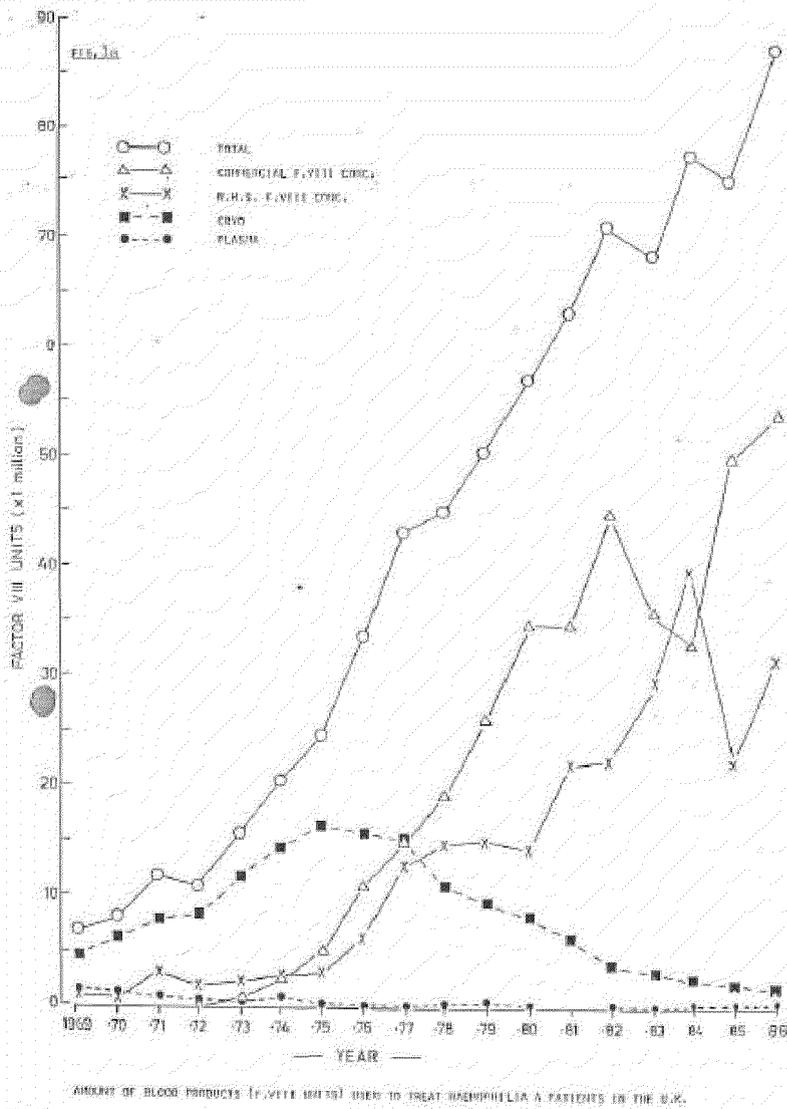Disease Reports, and Report by Dr. M. McEvoy for CDSC to DHSS - November 1984)

TABLE 1

CAL14(140211)

Figure 1

Factor VIII concentrate use in UK 1969-1986