DRAFT: IN STRICT CONF[redacted]

PERSONAL RECORD: PETER JONES

In 1972 I was appointed Consultant Paediatrician to the Newcastle Area Health Authority (Teaching). The major part of my responsibility was a regional commitment to the care of children and adults with haemophilia and in 1973 I took over the care of all patients in the Region on the retirement of Dr. Tom Boon, Consultant Physician at the Royal Victoria Infirmary. At the time of my appointment there was no special accommodation set aside for a Haemophilia Centre in Newcastle and patients were seen on an ad hoc basis. The adults were seen either in general outpatients by Dr. Boon or one of his junior staff or on Ward 12. Children were seen on Ward 8 or in an outpatient clinic started in the Attic Laboratory of the Department of Child Health in 1966 were I was working for my doctorate in feto-maternal bleeding. It was not until April 1974 that accommodation became available in the RVI. Prior to that date I had been working with the help of a part-time social worker, Bill Morgan, and a dentist, Rennie Porteous. In 1973 Sister Maureen Fearns was appointed and she is still employed as Clinical Nurse Specialist to the Haemophilia Centre and the Department of Haematology. In 1978 Dr. Peter Hamilton joined the staff as Consultant Haematologist and Co-Director of the Haemophilia Centre. He is presently Head of the Department of Haematology. Dr. Hamilton has maintained a special interest in hepatitis and liver disease in haemophilia.

Prior to the establishment of the Centre in 1974 most treatment had been with fresh frozen plasma or cryoprecipitate. In 1973 the government had licensed the first commercial factor VIII products for use within the United Kingdom

because there was not enough native product prepared by the Elstree Fractionation Plant. Three commercial firms were involved (Baxter Travenol: "Hemofil"; Immuno: "Kryobulin"; and Abbott, now Alpha: "Profilate"). In December 1975 I prepared a report to the Newcastle Area Health Authority on the treatment of haemophilia (JONES 1975A) In that report I pointed out that the factor VIII concentrate (termed AHG or anti-haemophilic globulin at that time) produced at Elstree was in very short supply and that this position would continue until sufficient plasma was forthcoming from the Regions and Elstree was able to process it. The report also contained the information that the doctors concerned with the treatment of haemophilia in the Northern Region had agreed that "all surgery, management of complications, and control of the home therapy programme should be the responsibility of the Newcastle Centre". This working arrangement remains the same in 1990.

In 1973 180 patients with haemophilia were known to the Newcastle Centre, 91 of them being severely affected. In 1973 it was estimated that the usage of factor VIII per severe haemophiliac was 12,500 units in the year and in 1974 16,430 units. This figure was in accord with figures from the UK Centre Directors, the MRC Working Party and figures for both Scotland and the USA, these figures ranging from 12,000 units per patient per year (UK Centre Directors prior to the institution of home therapy programmes) to 20,000 units per patient per year in the USA. A programme of home therapy had started in Newcastle in 1973 and by November 1975 43 patients were on that programme at a mean factor VIII usage of 18,796 units per patient per year. In the estimates for the following years 1976/77 it was stated that there was a waiting list for training for home therapy. There was no possibility of running the home therapy programme on NHS concentrate, and I continued to advise the relevant

authorities of the effects of the continuing shortfall. I covered most surgery with locally prepared cryoprecipitate, although I expected to have to use increasing amounts of commercial concentrate as more and more of the source product (from which cryoprecipitate is made) was needed by Elstree for fractionation.

There was a comment in this report that I was knowledgeable about potentially harmful side effects of the use of large amounts of factor VIII concentrate.

From the inception of the home therapy programme in 1973 all concentrates issued to patients have been accompanied by the relevant company data inserts which have always included warnings about hepatitis. The only exception to this was with NHS factor VIII concentrate for which there was not initially such an insert.

The start of the home therapy programme in 1973 and the opening of the Centre in 1974 should be seen in the context of the development of the principle of comprehensive care. This meant that a programme was designed to cater for all the needs of haemophilic patients and their families. The subject was addressed in an article for Community Medicine in 1972 (JONES 1972) entitled "Answering the needs of haemophilic children and their families", and in an article on "Nursing the Haemophiliac" published in the Nursing Mirror (JONES 1973).

In order to plan ahead for the needs of people with haemophilia a research assistant was employed to question all the families and seek their advice. In October 1973 the results of the survey were presented to the Second European

Meeting of the World Federation of Hemophilia in Heidelberg (JONES & LEWIS 1974); and published in more detail in Haemophilia Home Therapy (JONES 1980A)

With the establishment of comprehensive care and the understanding that sufficient factor VIII would be forthcoming from abroad for the home therapy programme, the thrust of work in the Haemophilia Centre at this time was to ensure that families were able to take advantage of the newer management techniques. I was aware of the side effects of transfusion, which were being carefully monitored through the Haemophilia Centre Directors organisation, with particular reference to the causes of death in the haemophilic community in the UK. It became a feature of the meetings of the Directors that no significant rise in death due to liver disease was reported year after year. In the mid to late 1970s it was thought that the long-term sequelae of infection with hepatitis were probably not going to be severe in the majority of patients, and certainly were outweighed by the need for quick and effective treatment with factor VIII concentrate. Despite this apparently relaxed attitude the Directors did follow up reports of morbidity in patients and continued to express their disquiet at the importation of factor VIII which had been made from the plasma of paid donors. This disquiet is shown in a series of letters to the Lancet (BIGGS 1974, DORMANDY 1974, JONES 1974A) INGRAM 1974).

Thus, in 1974 in the course of follow-up of batches of commercial concentrate which were implicated in an outbreak of jaundice in Bournemouth I became involved with correspondence with both Dr. Craske and with Dr. Holgate, the Principal Medical Officer of the Medicines Division at the DHSS. The implications of the use of commercial factor VIII concentrate were spelt out

in a paper produced by Dr. Craske, who at that time was working for the Public Health Laboratory at Poole, and the doctors in charge of the Haemophilia Centre at Bournemouth, Drs. Dilling and Stern (CRASKE ET AL 1975). In a draft paper circulated to the Directors they stated that "there seems to be a marked increase in the risk of post-transfusion hepatitis when some batches of commercial freeze dried factor VIII concentrates are used. This must be balanced against the undoubted advantage of the freeze dried product against cryoprecipitate".

In a letter to me of 23rd August 1974 (HOLGATE 1974A) Dr. Holgate mentioned current tests "which to the regret of any licensing authority fail to yield clear black and white, positive/negative answers". He went on to say that "instead, as might be expected when batches and material are obtained from pools of donors one obtains a range of antigenic content and has to select some arbitrary level from which the batch is classified as positive and not to be distributed. We may be working on too high a level at present but all this is still very much in the development stages and therefore we are extremely grateful to obtain any feedback information". Dr. Holgate later clearly sets out the dilemma when he says in his final paragraph that the Medicines Division were at that time working with a spectrum of positivity; "one could very easily say that one is not going to accept any batch with any sign of positivity at all, in which case we would probably get none at all". I replied to this letter of 18th December (JONES 1974B). This letter concerned both the question of degrees of positivity and a related worry about the health of staff responsible for giving potentially contaminated factor VIII products. Dr. Holgate replied on 2nd October (HOLGATE 1974B) and thereafter reports of putative infected batches producing jaundice in our patient

population were sent to Dr. John Craske. In June 1975 I sent a circular to my colleagues in the North of England on the implications of factor VIII concentrates and hepatitis (JONES 1975b). It is salient to later discussion that we had good knowledge both of hepatitis in the commercial concentrates and in NHS concentrates in the mid 1970s (INGLIS 1976) and in 1977: see (MAYCOCK 1977) a letter from Dr. Maycock to Dr. Murray, who was then Director of the Newcastle BTS, about hepatitis as a result of contamination of one of the Elstree batches.

As a result of the difficulties experienced in obtaining sufficient factor VIII concentrate for the treatment of haemophilia, in particular for the implementation of home therapy, I helped the Medical Correspondent of the Yorkshire Post construct a series of articles which won him the Campaigning Journalist of the Year Award for 1975. The first series of articles was published in January of that year (KING 1975). Of particular relevance to current discussion are the following observations:

1. The family described on Tuesday, 21st January 1975 are now all dead (the mother as a result of cancer, the father from a heart attack and the son Andrew from AIDS). Within the article referring to this family who had been on home therapy for a year, it is stated "with precious and expensive supplies of factor VIII concentrate nestling in the family fridge the Atkinsons have managed to put behind them a long and bitter nightmare . . . Andrew is one of the few lucky ones - one of those "rescued" by the goodwill of the Newcastle Regional Health Authority which has made money available to combat suffering from the shortage of the NHS produced factor VIII drug . . . all over Britain thousands of

haemophiliacs cannot command the same treatment".

2. "That haemophiliacs cannot get the drugs they need - although there are ample supplies - because it is too expensive to be freely prescribed on the National Health Service".

3. "As far as cryoprecipitate is concerned supply cannot meet demand. There has never been enough to go round and little has been done to reorganise the service . . . factor VIII to a haemophilia patient is literally his expectation of life, says Dr. Rosemary Biggs, Director of the world's largest Haemophilia Centre at Oxford where much of Britain's successful pioneering work was done". The differences between cryoprecipitate and concentrate are described and the question raised about why it is said to cost more to produce factor VIII in Europe than in America where donors have to be paid. The Ministry (Dr. David Owen) response is also published at the end of the first of these articles.

4. In the second article Dr. Rosemary Biggs is quoted as saying "those who treat haemophilia patients in the United Kingdom have of necessity in the past tolerated the chronic under treatment of their patients and have put much time and effort into spreading the inadequate amounts of therapeutic material thinly so that deprivation should be least damaging. Essential but non urgent operations have been and are still being postponed . . . The financial argument takes no account of the misery and anxiety attached to frequent, painful episodes of bleeding and inability to hold a normal place in school and society. In the long run it will probably be found cheaper to pay for these patients'

treatment rather than to pay for the inevitable consequences of under treatment". At the time that this was written there were sufficient supplies of commercially produced factor VIII concentrate within the United Kingdom but most Regions did not have the money to pay for it. Dr. Biggs went on "whatever solutions there may be for problems of this sort in general, some immediate solution should be found for the ridiculous impasse of, on the one hand, large available stocks of therapeutic materials locked up in stores because no-one will buy them and, on the other, patients in dire need of this material". Professor Blackburn, who was the Chairman of the Haemophilia Centre Directors, was quoted as saying "those of us in charge of haemophilic patients no longer feel we can tolerate the under-treatment of these patients. Also galling is the fact that major research in the United Kingdom, resulting in the acquisition of knowledge to treat haemophilic patients properly by modern standards cannot be fully implemented for reasons outside the control of Haemophilia Centre Directors". The article sets out the argument for properly funding the NHS to produce native material and I am quoted as saying "the majority of haemophilic patients only become physically handicapped because of inadequate treatment over the years. With adequate supplies of factor VIII concentrate there can be no excuse for this. The resources must be made available". I am also quoted as saying that I could no longer wait for the situation to improve within the National Health Service. "Faced with the dilemma he approached the Newcastle Regional Health Authority. After telling them that he felt morally and ethically obliged to provide home treatment with commercial concentrate for urgent cases, he won their backing". The article points out that Elstree and Edinburgh "receive insufficient plasma from the BTS

to produce more than a trickle of concentrate, most of which is used locally. I am quoted as saying "the answer lies in the reorganisation of the British Blood Transfusion Service. Personally I am not prepared to wait for that reorganisation or for a British product to become available in sufficient quantities. When I see my patients growing up and suffering I am convinced that home therapy is the only answer. The sooner a patient treats a bleed the sooner it stops and the less concentrate it requires". The fact that British research advances have not been properly exploited is, says Dr. Jones, "the same old British story, no money to develop anything". Dr. Biggs went on to say "I think it is absolutely scandalous. The material should be as available for British patients as anywhere in the world, especially as we were so instrumental in advancing the treatment. Of course other people used the information, what we do is published and internationally available".

In the last article Angus King compares the position in Britain in January 1975 to that in other countries. Dr. Mannucci, the Medical Director of the World Federation of Hemophilia is quoted in this final article as saying "it is simply astounding to hear that many British haemophliacs are under-treated or have no access to the most modern form of therapy (home treatment) for lack of availability through the NHS of the commercial freeze dried concentrates. To illustrate the absurdity of the situation, in my country (Italy) which started no earlier than 1968 a modern programme of haemophilia care, basically derived from that existing in the United Kingdom, the commercial freeze dried concentrates are available free of charge to all haemophiliacs covered by the social security system. The concentrates, which can be obtained at the chemists with a prescription from the Haematologist, make home treatment very

simple and easy for GPs, the patients or relatives".

Further articles followed this campaign and they are appended. Little changed and the original compaign was followed up on 13th June 1978 by Angus King (KING 1978) at which time I was Chairman of the UK Home Therapy Working Party. During my time as Chairman I produced with my colleagues in Newcastle a Handbook for Home Therapy for use by other Centres (JONES 1978A) and also a report on Haemophilia Home Therapy in the United Kingdom between 1975-76 (JONES ET AL 1978). In this article I am quoted as saying "the problem is that too little money has been invested in making the NHS self sufficient in factor VIII production in spite of assurances to the contrary . . . Even now Health Authorities throughout the country are having to rely on imported supplies of expensive, commercially produced factor VIII".

In 1977 with the help of two members of the technical staff in the Department of Haematology (Mr. Oxley and Mr. Cox) we tested all available factor VIII products in the laboratory in order to try and establish any reasons for choosing one rather than another. This study was initiated as a result of a price rise by Baxter Travenol which resulted in more expensive Hemofil, the commercial concentrate we had been using to date (JONES ET AL 1977). As a result of the in vitro work it was decided to do a small in-house study on the effects of two other concentrates on patients and they were invited to participate (JONES 1978B). The object of this study was to ensure that patients were receiving the maximum effect in terms of factor VIII rise and half life from their treatment. The work was published in summary as part of a general discussion on side effects in 1980 (JONES ET AL 1980).

Scandinavian Journal of Haematology, 24, suppl 31). It is pertinent to later published work that I remarked "a clinician should, at the very least, be aware of what he is injecting into his patients in addition to factor VIII and water".

In May 1977 a second report was prepared to the Newcastle Area Health Authority (Teaching) (JONES 1977A) It was pointed out that progress in the production of a national volunteer donor product had been slow and that the supply remained very inadequate in every Region, the quantity of Elstree product only fulfilling about 20% of the demand at the time. It was also pointed out that nationally the estimated requirements for factor VIII had remained at a minimum of 40 million units a year since 1974.

At the time of the report 65 severely affected patients from the Northern Region were on or starting home therapy, this being the total number of patients suitable or willing to participate in the programme at the time. The mean number of factor VIII units per patient per year for home therapy in 1975/76 in the Northern Region was approximately 19,000 units, compared with the national mean of approximately 25,000 units and international means ranging from 35,000 units (USA) to 129,000 units (West Germany). The paper also suggested that prophylactic therapy would be needed in the future to replace "on demand" therapy. At the time of the report 5 commercial products were available (from Travenol, Cutter, Armour, Immuno and Abbott). Within the report the question of changing patients from Hemofil to Koate was considered and a statement (which I now know to be naive) appeared (page 4, paragraph 3) "we are reluctant to expose patients to another plasma pool from a different population of paid donors. Having weathered an outbreak of serum hepatitis

with Hemofil we do not want to increase the theoretical chance of further infection". It is also interesting to appreciate from this paper the commercial outlook of big companies like Travenol who were involved in importation of blood products. As a doctor I was having to learn that blood products were regarded as simply another market commodity. For example, in answer to an attempt to try and obtain a reasonable price for factor VIII in the Northern Region, the Travenol response was to express their "willingness to meet Health Authority officials to discuss their total service to the Area (i.e. in terms of products and services in all fields of infusion therapy, urological care and haemodialysis, disposable equipment etc.) with the view to agreement of overall contract terms and cost effectiveness and savings. Hemofil could thus be viewed in the context of total expenditure/savings on Travenol products and services".

In 1979 a further report to the Health Authority (JONES 1979A) shows that prophylaxis was having an effect on the average number of factor VIII units per patient per year but that the figures were still in keeping with the United Kingdom statistics. 59% of all the concentrate being used in 1978 was imported. It was stated that the VIII usage figures for the treatment of haemophilia in the United Kingdom were still the lowest in the developed countries (about 50% of usage in the Centres in the USA and 20% of the major Centres in Germany). In view of an argument being put forward at the time, principally by people working in the Blood Transfusion Service (cf John Cash), the comment on page 2 of this report about prophylaxis is interesting "we hope that, at least in the long term, the use of prophylaxis will reduce the overall requirement for concentrate".

The report concluded "there is no hope that in the foreseeable future we will become less reliant on commercial concentrates. Dr. Lane, the new Director of the Blood Products Laboratory in Elstree, last month reported to the Haemophilia Centre Directors of the United Kingdom that, without a government investment of £25 million, it would not be possible to increase capacity". It is also salient to note that "we have deliberately revised our policy of recommending that Region only buy the most refined (high purity) products, and we now bargain for the lowest price, for any product approved by the DHSS from any manufacturer".

The question of usage of factor VIII concentrates in Newcastle is important in relation to the incidence of AIDS, because it has been suggested in some quarters that the higher incidence of AIDS originally reported from Newcastle was a direct consequence of higher use of imported factor VIII concentrates within the Region. That this is not so is presented in the appended figures which show that the rise in factor VIII usage within the Northern Region was in keeping with the rest of the United Kingdom between the years of 1969 and 1986. The figures were presented to the Regional Medical Officer on 23rd February 1988 as a historical record of the use of factor VIII preparations in the Northern Region since 1969. The request for clarification came from Dr. Donaldson as part of his response to the Member of Parliament Jim Cousins on 3rd December, 1987 (JONES 1988). (This letter also contains information pertinent to the use of heat treated factor VIII concentrates, including the argument put forward by Dr. Bird and his colleagues and the withdrawal of the Armour product (see page 64)).

In 1974 MTP Ltd. published the first edition of my book, Living with

Haemophilia. The book was written with some trepidation because it was not generally accepted at that time that patients should be given full knowledge about their disorder and its possible complications. Views about haemophilia therapy in 1974 differed widely and home therapy programmes were only just getting under way. It was therefore pleasing to find that the general reaction to the book, both in this country and abroad, was very favourable. The book won an American Journal of Nursing's Books of the Year Award, and was translated into seven languages and was one of the reasons for the award of the Macfarlane gold medal by the Haemophilia Society in 1981. Two further editions have now been written, the second edition being published in 1984, with the third scheduled for publication in May 1990, with simultaneous translations into Danish and Dutch. Publication of the book was followed by invitations to speak to people with haemophilia and their families throughout the world, and resulted in extensive travel and opportunities to keep in touch with the management of haemophilia in many countries.

Within the first edition (1974) it is pointed out (page 78) that hepatitis is one of the side effects of blood transfusion. The passage gives the generally accepted view at the time about hepatitis in that "the effect of the virus depends on its virulence and on the response of the recipient. Haemophiliacs seem to have a high response, probably developed as a result of repeated blood transfusions. Although many have the antibody, few have had severe jaundice due to serum hepatitis. In the unlikely event of jaundice affecting a haemophiliac it is obviously very important to establish the cause". The question of side effects was also addressed briefly on pages 164-166 when the genetic cloning of factor VIII was predicted. In this passage it is stated that "synthetic substitutes cut down the cost of preparation and can be

tailor-made to reduce the number of side effects, to extend activity and to ease administration". It should also be noted in view of the allegation made by the plaintiffs that there has been a lack of communication between the patient population and their doctors, that this first edition concluded with the sentence "progress cannot be one-sided; increasing knowledge and application require the understanding and mutual respect of both patients and their advisers".

In 1976 progress with home therapy was reported to the 11th Congress of the World Federation of Hemophilia in Kyoto (JONES 1976) and in that year I made a proposal to the World Federation that they adopt a standard method of following outpatients with haemophilia. This method was subsequently published as a small booklet called "WFH Medical Records and Data Collection" and many of the suggestions within it have subsequently been used by Haemophilia Centres throughout the world. With reference to the current action, this record system (page 39) was designed to take account of side effects, including lymphadenopathy and enlargement of liver or spleen, the comment being made that the items on the checklist for follow-up reflected abnormal physical findings already being reported in the severely affected multi-transfused haemophilic population. The follow-up treatment cards mentioned in this booklet (page 47) were in use in the Newcastle Haemophilia Centre from 1976 and still form the basis of follow-up of blood product usage in our patients (the "green cards"). The primary aim of presenting such a uniform approach was "to define possible long term risk of intensive multi-donor transfusion therapy, and in order to provide a background for debate on the rational use of blood product resources, particularly in developing countries without fractionation facilities" (JONES 1979).

In 1977 I wrote about current haemophilia management in a paper entitled "Development and problems in the management of haemophilia" in Seminars in Haematology (JONES 1977B). Within this article there was a section on side effects of factor VIII blood product transfusion, citing at least three separate outbreaks of hepatitis amongst haemophilic recipients since the introduction of commercial factor VIII lyophilised concentrates into the United Kingdom in 1973. The article pointed out that the incidence of hepatitis had declined following the introduction of individual donor testing. In it I stated "while we disagree with the suggestion of Craske et al that commercial concentrates be reserved for the treatment of life-threatening bleeds and to cover major surgery . . . it is our practice to restrict young children and mildly affected haemophiliacs to cryoprecipitate therapy. The article continues "more worrying than these visible outbreaks of infection, which were expected because of the large donor pools needed for source material, are the possible long term effects of frequent transfusion therapy with lyophilised concentrates. Several viruses may be involved in post-transfusion heaptitis, among them cytomegalovirus, and probably other as yet unidentified hepatitis viruses. Whether or not repeated exposure to these or other agents will result in a rising incidence of chronic liver disease remains to be seen, but the haemophilic population at risk should be regularly screened for evidence of sub-clinical abnormality".

Thus at this stage the general impression was still that exposure to factor VIII concentrate made from the plasma of paid donors was more likely to transmit infection than a volunteer donor supply. One reason for this view was that the commercial concentrates were prepared from more donors than the

volunteer concentrates (BIGGS 1976). In a report prepared by Dr. Rosemary Biggs on behalf of the MRC in 1976 she had stated "the NHS freeze-dired concentrate is an intermediate potency preparation made from pools of plasma derived at present from pools of from 200 - 750 blood donations . . . commercial factor VIII concentrate is available from several companies and each batch is derived from 1000 - 4000 litres of plasma collected by plasmapheresis from paid donors. Since about 400 mls of plasma is derived from each donor, each batch containes plasma from more than 2500 individual donors. The (commercial) material is of higher potency than the NHS concentrate".

This report also contains reference to another part of the balance that doctors concerned with haemophilia treatment have to address when they prescribe a concentrate, the question of yield. "A characteristic that must be considered is the loss of activity of the various preparations during fractionation (table 5). Naturally there is little loss during the preparation of plasma. The preparation of cryoprecipitate and NHS concentrate involves some loss of factor VIII but the loss from the NHS freeze dried concentrate is less variable than that from the preparation of cryoprecipitate. The preparation of the commercial concentrate involves more loss of activity than does that of the NHS freeze dried concentrate. Were the NHS freeze dried concentrate converted to "high potency" preparation similar to that made by commercial companies, about twice as much plasma would be required to produce a given quantity of factor VIII".

Because of this, and because there was no evidence of substantial benefit from the use of higher purity concentrates, the Haemophilia Centre Directors agreed

unanimously that they would opt for the use of intermediate purity concentrates for the treatment of the majority of patients through the 1970s and into the 1980s. The intermediate purity concentrates like that produced by the NHS were cheaper than the higher purity concentrates, but the main argument for their use was not a financial one but rather that they were equally efficacious in stopping bleeding.

Dr. Biggs' review also contained reference to the occurrence of hepatitis. She said "it was found that only 1.95% of patients who received plasma from cryoprecipitate developed jaundice. These patients were exposed to the least number of donations. 3.22% of the Oxford patients developed jaundice and these patients had been exposed to most NHS concentrate and thus to most donations. The difference between 1.95% and 3.22% is not significant and it seems that the NHS concentrate made from unpaid donors is no more likely to cause jaundice than cryoprecipitate". This observation does not appear to have taken account of the number of times a patient is exposed, i.e. it has been shown to be a misconception that commercial concentrates are more likely to transmit hepatitis than volunteer donor concentraes, or even single donor products, when the recipients <u>have already been exposed on multiple occasions</u>. Dr. Biggs alluded to this on page 13 of her draft by saying "patients undoubtedly differ in their susceptibility to viral hepatitis. Many haemophilic patients have positive blood tests for hepatitis B antibody, such patients are presumably resistant to infection with hepatitis B virus and may be resistant to other similar viruses. Patients who have received few previous infusions are more likely to be more susceptible to infection when they receive infected material since they have had little opportunity to acquire immunity".

"In 1972 commercial human factor VIII was used for the first time in the United Kingdom. This material is made from very large pools of plasma collected from paid donors, some of whom live in poor districts of the United States cities and the similar situations of other countries. It has been shown that such commercial blood is 10 times more likely to transmit hepatitis than blood collected from unpaid donations by national transfusion services. Since the introduction of commercial factor VIII its use has increased until 1974 when 13% of all material used to treat haemophilia A patients was commercial".

The article refers to Dr. Craske's work on the infective batches of commercial concentrate which he reported in 1975 (CRASKE ET AL 1975). In the figures collected during the six year period reported in this paper, it was found that the "majority of patients who had had jaundice were severely affected. This is rather surprising since one would expect the mildly affected patients to be most susceptible since they are less likely to have many antibodies. On the other hand the severely affected patients are most often exposed to infection. Of the 5 patients who died of hepatitis in the six year period, 4 had received no material other than cryoprecipitate" (my underlining).

Dr. Biggs' article concluded with a comment about the continuing shortfall in NHS material "we have the scientific and technical knowledge to make all of the factor VIII that is needed within the United Kingdom using blood that is collected in the United Kingdom. The sooner this objective of self-reliance is reached the less costly will the treatment for haemophilia A patients become. There are reasons other than cost which should encourage every effort

to have the supply of factor VIII made from United Kingdom blood. For one thing our haemophilic patients should not be dependent upon the commercial exploitation of the poorer citizens of other countries. In addition, blood from these poor citizens has a much greater chance of transmitting infection than does the blood of our own donors. In addition it must be undesirable for a major source of supply of factor VIII to be from foreign companies whose policy may be affected by political and other decisions outside the United Kingdom".

In 1976 the Newcastle Haemophilia Centre Team presented details of its work with comprehensive care to the Third European Regional Congress of the World Federation of Hemophilia (JONES ET AL 1976). It was at this conference that the then Health Minister, David Owen, made a public statement about self-sufficiency and haemophilia and expected that the UK would be self-sufficient by mid 1977 (OWEN 1976).

In his opening remarks to the Congress the Chairman of the Haemophilia Society, the Rev. Alan Tanner, reported a letter he had received from Professor Macfarlane. He had written "I go to the Haemophilia Centre in Oxford about twice a week to do a little laboratory work and also to hear all the news about current research and about my old patients. I can use inverted commas for "patients" now in many cases because modern methods have really removed them from the patient class. They are now active members of society in general. What a change from the old days!". When he opened the conference Professor Macfarlane referred to its title "Living with Haemophilia", and remarked "our patients did not live with haemophilia - at best they existed on the brink of disaster and very many of them did not, of

course, survive their childhood. Even in 1943, the expectation of life for a haemophiliac was computed - I think by an insurance company - at about 16 years. Today it cannot be very far short of the normal span. When we hear at this congress about the special arrangements and precautions that a haemophilic patient still needs, we should compare the quality of life that is now possible for him with the really dreadful disability of the crippling deformities that were inevitable only about 20 years ago".

Macfarlane's remarks about the dangers of living with haemophilia were reflected in an article in the Journal of the American Medical Association from 1970 (LEWIS 1970) on causes of death in haemophilia.

"The dramatic medical improvements since then have sprung from the slow but quite logical growth of knowlege . . . there is a long way to go; on the medical side we still hope for a preparation of clotting factors, which like insulin and diabetes, would be sufficiently active and sufficiently plentiful to keep every haemophilic patient always haemostatically normal".

Professor Ingram of St. Thomas' Hospital then gave a paper on the history of haemophilia and again quoted Professor Macfarlane, who in 1965 had written a paper on the haemostatic preparation Russell's viper venom "the main value of a historical story is that one sees how the growth of knowledge is hampered by prejudice or the failure to recognise one's own ignorance as well as by the misuse of words and the mixing up of facts and theories. Having seen that, one resolves to do better in the future".

During the question session on the Newcastle presentations someone from

Cambridge asked "Dr. Jones, I was delighted to see the number of people you have on home treatment. One of the things that concerns me is the very high incidence of jaundice you seem to have picked up; can you account for this please?". My reply was "The questioner has just pointed out that an outbreak of hepatitis has been seen in the United Kingdom following the introduction of commercial factor VIII concentrates on which some Centres are unfortunately almost totally reliant . . . in Newcastle we saw 22 cases of hepatitis, a small proportion of which became Australia antigen positive. I think this can be explained for two reasons. First, these products were coming into virgin soil. The blood of a different population was being used for the first time in the United Kingdom to treat haemophilic patients. The second reason was that at the time that the first batches of these products were introduced into the country the sensitivity of the testing methods for the hepatitis associated surface antigen were not as sophisticated as they are now. We have not seen an episode of hepatitis in the past 9 months to one year except for one case which appeared last week. In this case, because of the relative incubation period, I think it more likely to be linked to cryoprecipitate than to our use of commercial concentrates. Hopefully the incidence of hepatitis will fall but is is worth remembering that some people would say that it is better to get a mild case of hepatitis and become immune for the future".

Later in the conference I gave a paper on the future of home therapy (JONES 1976*b*). This paper contains the arguments for using concentrate rather than cryoprecipitate (p 186) and the arguments for either controlling demand or adjusting supply (p 190-191).

In July 1979 I was invited to write an anonymous editorial for the Lancet

(ANON 1979) in which I wrote "Further work is needed to determine the lowest dose of factor VIII which is acceptable to the haemophiliac . . . and to the doctor in terms of both efficacy and safety. The safety aspect is important: although neither the British nor the Norwegian workers encountered serious side effects, the true risks of long term, intensive, multi-donor transfusion therapy remain unknown. A substantial improvement in the quality of life provided in the past decade by improved management of haemophilia, including home therapy, may be bought at the expense of shorter survival. Clearly, the continual monitoring of home therapy programmes must continue.

In 1979 I chaired a symposium on hepatitis held during the 13th Congress of the World Federation of Hemophilia in Tel Aviv, (JONES 1981). For this I had invited Professor Ari Zuckerman to define the agents responsible for hepatitis, Professor Seeff to examine the evidence for their transmission by blood products and Professor Hadziyannis to outline their effects. Finally, Professor Schimpf, who directs the Haemophilia Centre in Heidelberg, was asked to bring together the results from liver biopsies in the haemophilic population. In my overview of this symposium I said "It is evident that, although the safeguards imposed since the outbreaks of hepatitis B six years ago were welcomed the dangers of viral disease transmission inherent in intensive transfusion are far from over, and that these dangers are compounded by the use of large plasma pools from commercial sources. This is well recognised both by industry, which must continually upgrade its methods of donor collection and surveillance and by the volunteer blood donation organisations. It is perhaps less well recognised by those responsible for the finance, organisation and development of these voluntary organisations . . . although still ill defined in terms of long term effects, the risks mean

that all multi-transfused haemophiliacs must be followed closely, their general health as well as the control of their underlying disorder being monitored at regular intervals . . ."

"It is intersting to note that neither the serological nor the abnormal biopsy findings reported in haemophilia seem to match the incidence of clinically apparent disease and there has been no increase in the death rate from liver failure, even in those patients who have received numerous transfusions of commercial, large pool blood product for over a decade. So, whilst the answers to many questions will only become clear with time, perhaps the most important message to emerge from this survey is that although risks remain they are probably of less consequence than might be suggested by the literature, and are certainly outweighed by the need to treat haemophilic bleeding in the only way we know - by the rapid replacement of the relevant clotting factor".

In their papers it is interesting that none of the authors mentions heat treatment or other potential methods of viral inactivation. Professor Seeff said "at present the only means of controlling the development of post transfusion hepatitis is to continue to screen all donors for HBsAg by sensitive tests; to limit the use of blood transfusion to only essential needs; and to reduce, preferably to eliminate, dependency upon commercial blood. For the future, research is needed to develop serologic tests for identifying NANB hepatitis, to develop specific immunoglobulin products and finally to develop specific vaccines which could be given to selected high risk groups, such as patients with haemophilia".

"The high risk of hepatitis in haemophiliacs may relate to:

1. The need for plasma derivatives whose potential for infectiveness is not reduced by their method of production and

2. The need for transfusion with blood products from many thousands of donors, either in the form of individual units, or as contributors to large pools from which the plasma products are derived. Counter balancing this is the fact of high susceptibility since it is now clear that both type B and non A non B hepatitis confer homologous although not heterologous immunity".

Professor Seeff concluded that "it is probable that by the fourth decade of life, almost all persons with haemophilia A and B will have been exposed to type B and non A non B viruses. On the credit side, once the acute infection has occurred, natural immunity develops. On the debit side is the evidence 10 - 50% of persons who acquire type B or non A non B hepatitis will progress to chronic hepatitis, although the majority of such cases probably follow a benign course. The modern methods for protection against these viral diseases are limited. Ultimately, the greatest impact will come from the routine administration of the hepatitis B vaccine which is presently being evaluated and perhaps in the future from a vaccine against the virus or viruses of non A non B hepatitis".

In his paper Professor Schimpf reported on the results of biopsies and concluded that they "proved a remarkably high incidence of chronic hepatitis in haemophiliacs who are on substitution therapy. 32% of our non-selected

biopsy patients suffer from chronic persistent hepatitis, 28% from chronic active hepatitis and 3% from cirrhosis of the liver".

Thus, by the end of the decade we were in no doubt that haemophiliacs exposed to multi donor concentrates were inevitably infected with non A non B hepatitis, and that a substantial proportion of them could go on to develop chronic liver disease, although this was still not being reflected in the Oxford Returns in terms of mortality. In 1982/83 hepatitis B vaccination with the product derived from human plasma (Hep B Vax) became available and vaccination was started in Newcastle.

The early 1980s involved me in studies on improving prospects for employment of adult haemophiliacs and on further development of comprehensive care (STUART ET 1980). I was also invited to participate in the American Blood Resources Association Forum III which was held in Washington between 25th-27th February 1980. Prior to this meeting I had some knowledge of the workings of the American commercial companies because in 1975/6 I had been invited to consider applying for the post of Medical Director of Baxter Travenol who at that time had their headquarters at Costa Mesa to the south of Los Angeles. As part of the negotiations on whether to accept this post I visited their head office and their fractionation plant at Glendale in Los Angeles in 1976. Subsequently Travenol suggested that if I did not wish to take the worldwide post based in California I might be interested in becoming the European Medical Director working from Brussels. Thus it was that in 1977 the then Newcastle Area Health Authority (Teaching) gave me paid leave of absence once a week over a three month period to go to Brussels to assess the job. During this period I produced the publication "Haemophilia.Management - A Physician's

Guide to the Treatment of Haemophilia" which was published in 1979 by Transart Limited of Huntingdon, Cambs., the company for which I did subsequent work on the development of medical texts, particularly one involving Nestle who were interested in developing services for rural health workers in Malaysia. The Haemophilia Management Book contains information on desmopressin (DDAVP), a fact which may be of relevance to the current action.

I eventually decided not to take the Travenol job because, despite assurances to the contrary by the company, it would have meant losing my clinical roots in Newcastle and the continuing relationship with haemophiliacs and their families. However, it did give me further insight into the way in which companies involved in biological therapeutic materials regard their products as commodities obeying the same rules of supply and demand as with any commodity in the commercial sector (see also JOSEPHSON 1981). In this context I had become aware of the role of plasma brokers, one of whom was Thomas Hecht, who worked out of Montreal where I suspected a connection with the Head Office of the World Federation of Hemophilia which at that time was being run by Frank Schnabel, a haemophiliac who died of AIDS in 1987. The companies, with the possible exception of Armour, do not have "accredited herds" of donors but receive their plasma from plasmapheresis organisations usually within the United States of America. However, when supply becomes limited for whatever reason (for instance there has been a failure in manufacture of a particular batch with subsequent loss of plasma, or there has been a surge in demand) the source material for the commercial concentrates is available usually in the form of "cryoprecipitate paste" on the international market. The procurement and sale of cryo paste was, and to my knowledge still is, under the control of brokers like Hecht. Details of the trade have been given

in Piet Hagen's book (Blood: Gift or Merchandise, published by Alan Liss in 1982), for which I supplied some of the information.

I had further knowledge of the commercial blood industry when in 1980 I was employed as a consultant by the Revlon Health Care Group to give them an objective assessment of their plasma procuring centres which both then and now are run by an organisation called Plasma Alliance Inc., chiefly in the central United States with headquarters at Knoxville, Tennessee. The report to that company was confidential and I have no copy, but my general conclusion was that the Centres were extremely well run. The standard was certainly not in accord with the more usual public image of skid row donations in the densely populated conurbations of east and west seaboards of the United States.

I knew that both Cutter and Travenol obtained plasma in Mexico and I was told by the Chairman of the Medicines Commission in June 1981 that the source of Cutter's plasma in Mexico was known to the Commission. This knowledge was given to me in the course of a general meeting of the Commission when they were considering a licence application on behalf of Speywood Laboratories Ltd. (David Williams) who wished to import an American factor VIII called Humanate sold to them at an advantageous price by Cutter. To my memory their licence was not granted because they could not prove to the satisfaction of the commission that they were able to trace the material back to individual donors. If this was the case then the Commission must have had very detailed knowledge of plasma procurement in Mexico and presumably other developing countries in order to be assured of individual donor tracing should the need arise.

I had gone to the Plasma Forum III in 1980 prepared to give a short paper on the general management of haemophilia in the United Kingdom but in the first session of the meeting the President of Alpha Therapeutics, Tom Drees, gave a scathing report on international plasma resources and in particular on the position in Europe (DREES 1980). As a result of his remarks (which included the observation that "the United Kingdom is a disgrace to be included in that 4th world of AHF treatment and I believe that it is an indictment of what happens in a socialised system") both Dr. J. P. Allain, who was speaking before me on the position in France, and I changed the text of our papers in order to reply to Drees' comments (JONES 1980g). In this reply (pp 60-61) another thread of the arguments for and against the use of factor VIII concentrates is evident. There had been great debate through the latter part of the 1970s as to why the factor VIII consumption in the Bonn Haemophilia Centre was so high and this paper makes reference to a challenge by myself, Professor Ingram of St. Thomas' Hospital, and others, to Bonn to explain the reasons for the high dosage they prescribed for their patients and the results of this treatment in a paper in an internationally accepted medical journal. To this date the doctors involved in Bonn have not responded to that challenge, but it has been proven in law that the Centre was involved in corrupt practice during this time (JONES 1980c, HEROLD 1979 - we are trying to obtain a copy of this paper).

What was happening in West Germany was that the commercial companies were selling concentrates to those responsible for their prescription. They were then re-selling the concentrates to the patients via the hospital/university/insurance companies with an exorbitant mark-up in price, part or all of which is assumed to have gone for their private use. There was thus intense pressure to prescribe as much of the concentrate as possible

because the profits accrued from the mark-up involved were so much greater. This practice has relevance to remarks I made later about the expected incidence of HIV infection and AIDS in the West German population (Statement of Claim p 86 para 63(a)).

So disturbed was I by the revelations of Tom Drees and his colleagues at the meeting that I decided to open the question of the supply and demand for factor VIII to general debate within the medical literature, and on 21st June 1980 a letter on the subject was published by the British Medical Journal (JONES 1980c). This letter again made clear my personal commitment to the voluntary blood service and to self-sufficiency within the United Kingdom. Unfortunately the letter was muted somewhat by the concurrent publication by Dr. Tony Aronstam at Treloar College who suggested that we (ARONSTAM 1980) should explore the possibility of commercially successful private industries fractionating the material for the National Health Service. In view of the recent addendum to the Statement of Claim (83(m)B 92(f)B 94(k)A 95(h)A this observation is interesting because Dr. Aronstam has told me that he was originally employed by the plaintiffs in order to provide the historical background for their action.

During the Plasma Forum meeting transfusion associated hepatitis was addressed (OVERBY 1980) but despite the fact that this meeting was attended by representatives of all the American blood product producers (both commercial and volunteer) no reference was made to heat or other methods of viral inactivation, the whole emphasis being placed on better methods for screening out infected donors.

In 1981 I was invited to write the Leader, "Post Transfusion Hepatitis" in the British Medical Journal (ANON 1981) referred to as Appendix I, 97(at) p128 in the Statement of Claim under anonymous authorship. In this article I said that attention had been focussed on 3 practices: the risks of collecting plasma from paid as opposed to volunteer donors; the optimum size of the plasma pool and attempts at removing the several viruses of hepatitis from blood products.

I pointed out that although the risks of viral contamination "are certainly increased if plasma is obtained by plasmapheresis of paid donors . . . the sensitivity of testing for hepatitis B has been improved so that incidence in patients given multiple transfusions is about the same from either paid or volunteer sources . . ." and I quoted the papers already referred to at the Israeli conference in 1980 (REFS to Seeff & Co; see JONES 1981). I also referred to the US Veterans Administration studies which had shown that post transfusion hepatitis rates dropped from 25.7% to 8.1% when volunteer as opposed to commercial blood was used, i.e. with "commercial blood excluded the incidence of hepatitis is lowered by 75%". However, this statement carried the rider that the figures referred to non haemophilic (i.e. not multi-transfused) patients in the United States.

With regard to the size of donor pool I referred to a study (LEVINE ET AL 1977) which suggested that there was no correlation between biochemical abnormality and the use of concentrate or cryoprecipitate, and pointed out that in the study reported by Stirling and his colleagues (STIRLING ET AL 1981) the results had not been sufficiently clear-cut for the authors to recommend the limitation in prescription of blood products for home treatment. This was also discussed in (LEVINE ET AL 1976).

The question of small pool concentrates was also addressed by Dr. Biggs in 1978 (BIGGS 1978) and of liver function abnormalities with cryoprecipitate by Counts in 1977 (COUNTS 1977).

In the last paragraph of this Leader I referred to the question of heat treatment, this reference being the one quoted in the Statement of Claim. I said ". . . is it likely that the recipients of multiple transfusions can be immunised, or that the threat of hepatitis can be removed from donated blood entirely? Immunisation against hepatitis B is certainly a possibility, but, in the absence of specific markers for non A non B hepatitis overall protection against hepatitis appears remote. A more likely possibility is that hepatitis free blood products will become available, 3 recent reports suggesting that viral contamination may be removed by specific processing by chemicals, ultra violet light or heating. If this or similar studies prove that hepatitis free products are commercially practicable a major and very welcome advance will have been made - but one that will also present yet another, and probably expensive, challenge to the under-funded and fragmented service in Britain".

The references to heat treating came from a paper presented by Schwinn and his colleagues at the First International Haemophilia Conference which took place in Bonn in 1980. A short version of this paper, of which only the abstract was quoted in my Leader, subsequently appeared in Suppl I, vol 10 of Haemostasis (1981) and is appended (SCHWINN ET AL 1980) (HEIMBURGER ET AL 1981).

Thus in July 1981, at about the time that AIDS was being recognised for the

first time in the United States, the question of heat treating concentrates in order to remove viral contamination was in its infancy. To my knowledge the only company working along these lines and producing sufficient factor VIII concentrate for clinical use was Behringwerke in West Germany, but the production of this product was so small that none was made available for use within the United Kingdom.

The question of heat treatment has been addressed in Dr. Rizza's statement in answer to the questionnaire (para 92(as)) in which he says "from the late 1970s onwards it was known that the producers of factor VIII were investigating different procedures to try to reduce the risk of transmission of hepatitis by large pool factor concentrates. One of the methods under investigation was heat treatment of factor VIII. From 1981 and 1982 protocols were developed by different companies to study the safety and efficacy of these products in trials in different countries. These trials were aimed at loking at the safety of heat treated concentrates vis-a-vis transmission of hepatitis. These studies on efficacy and safety continued as the heat treated products became more widely available during 1984 and 1985".

The question is further considered in his answer to para 92(ac) "in vitro evidence of the efficacy of heat treatment in destroying HIV in factor concentrates did not become available until autumn 1984. These were in vitro tests and there is no evidence of studies carried out in human beings or animals" and in 92(m) when in answer to the question "why did you not use heat treated factor VIII or IX from 1980 because of the risk of hepatitis?" Dr. Rizza answers "because in the first place the material was in very short supply and secondly the evidence for efficacy of heat treatment was slow in

accumulating as the studies had to be carried out in previously untransfused patients who were very few in number".

The question of the doubts about the efficacy of heat treatment is addressed later in this personal account in the context of first reports of sero-conversions using one of the commercial dry heated products in 1986.

In 1982 I was asked to write another Leader for the BMJ. At this time their policy had changed and the leading article termed "Blood donors with a history of jaundice" is signed (JONES 1982A).

It was published on 25th September 1982 and concerned the sensitivity of testing for hepatitis B and the use of large pool concentrates and the problem of non A non B viral contamination. I pointed out that the diagnosis of non A non B was important because the infection "may progress to chronic liver disease". Using Australian experience I quoted the suggestion that surrogate testing of donors using liver function tests may reduce the incidence of hepatitis and said "the present risk of developing disordered liver function after transfusion of volunteer HBsAg negative blood is about 10% and the risks rise with the number of donations transfused".

At about this time, of course, we were becoming aware of a new disease called AIDS in the United States which had first been described in 1981. In the summer of 1982 the first haemophilia cases of immunodeficiency were described but the immediate description escaped my attention because, like most of my colleagues, I do not subscribe to the American Morbidity and Mortality Weekly Report (MMWR). However, that concerning haemophilia was brought to our

attention by Professor Bloom at a meeting of the Haemophilia Reference Centre Directors in September 1982 when Dr. John Craske was to look at the question of British haemophiliacs being involved.

In September 1982 I attended a conference in Potsdam, where I was invited to give a paper on side effects of transfusion therapy (JONES 1982). My invitation was from Professor Remde; sadly he died before publishing the proceedings. No reference to AIDS was made in this paper, although at the end the question of immunological deficit is addressed very briefly. Ironically, the small section on patients being frightened by reports of blood donation by drug addicts was added to the original text before presentation (page 7).

It was a further year before the first haemophiliac with AIDS was described in the United Kingdom, and in the interval there was much debate about whether we may be seeing the same disease process in our patients as was being reported increasingly in the male homosexual and intravenous drug abuse groups in the United States. At that time those surveying the disease in the United States were still questioning whether or not an infectious agent was the primary cause of the disorder. As the evidence involving haemophilia grew and in particular with the appearance of cases which could only be linked by blood transfusion, the evidence for an infectious agent increased. The thinking at this time is set out in my letters regarding the Mail on Sunday and the Press Council, which package has been forwarded already.

In January 1983 (JONES 1983) I wrote with colleagues to the Lancet reporting that we had found alterations in immunology in haemophilic patients which might be associated with AIDS.

Later that month (Lancet 29 January) an AIDS-like syndrome was reported in two haemophiliacs in Pittsburgh (RAGNI 1983). In their discussion the authors suggested "the presence of this AIDS-like syndrom in haemophiliacs suggests the possibility of transmission by an infectious agent through blood products".

In March 1983 (ANON 1983α) I was asked to write an unsigned leading article for the Lancet which appeared under the heading "Acquired immunodeficiency syndrome in haemophilia" in the 2nd April issue. This article referred back to a Leader (not written by me) of 22nd January 1983 (ANON 1983β). This Leader had included the words "finally the syndrome may well be transmissible: women may acquire AIDS from their male partners; and the disease has developed in haemophiliacs after factor VIII administration, in a child after blood transfusion, and in 4 infants whose mothers either had or were at risk of AIDS". The earlier article also reviewed some of the putative causes for the new syndrome saying ". . . several risk factors seem to be important. Amongst the homosexual population promiscuity was a common but not constant finding. Similarly, abuse of sexual stimulants such as amyl nitrate was associated with an increased risk in some but not all studies. This was of interest in view of the potential muta-genicity of these substances and their possible effects on T lymphocytes . . . several herpes simplex virus infections have been described in AIDS and virologists have commented also on the widespread sero-positivity for Epstein Barr virus and cytomegalovirus".

". . . Can these confusing clues be assembled into a single hypothesis? . . . If the syndrome does prove to be transmissible, this will strengthen suspicion

that the immune depression is due to an infective agent. Such an agent may be entirely novel . . . or, more likely, a wolf currently in sheep's clothing. In view of the roles of CMV, EBV and "human T leukaemia lymphoma virus" in human cancer, a search for a retrovirus or similar agent in AIDS might be rewarding".

"Meanwhile, clinicians dealing with these patients - particularly patients with a lymphocyte wasting syndrome - face many difficulties. How often and how aggressively should they be investigated? Is cotrimoxazole prophylaxis worthwhile? Can they be blood donors? Need they be nursed in isolation? What advice should be given about sexual intercourse? Satisfactory answers await the unravelling of this mystery; at present the most compelling question is why now?"

In my article of 2nd April I quoted advice from the Centers for Disease Control that "sexual contact with known AIDS patients should be avoided; that homosexual males should limit the number of their partners; and that steps should be taken to exclude high risk subjects from blood or plasmapheresis panels - a precaution already adopted by some of the commercial organisations collecting and processing blood products". I cited the March issue of Annals of Internal Medicine in which cases of AIDS in haemophilia were described and remarked on an editorial in that journal suggesting that "T cell population abnormalities commonly seen in haemophilia may be the submerged part of an iceberg of which AIDS is the clinically obvious "tip"". In this editorial the authors recognised that "AIDS has developed in only a few out of many haemophiliacs receiving large pool factor VIII concentrates, and they have pre-disposing factors", citing in particular repeated attacks from hepatitis

virus as possible precursors. I went on to say "because of the (limited) evidence that cryoprecipitate is free of the "transmissible" agent and that the greater the exposure to concentrates the greater the risk, these workers have adopted a series of preventive measures in their own haemophilia practice. Elective surgical procedures have been cancelled, doses of factor VIII reduced, and where possible patients switched from concentrate to cryoprecipitate therapy. An editorial in New England Journal of Medicine goes further. On the strength of 5 reported haemophilic cases Desforges (DESFORGES 1983) suggests that it is time to consider giving up home therapy programmes which are reliant on factor VIII concentrates "even though we may not have enough evidence to demand such a radical change"".

"Two aspects of this surge of interest in an as yet unexplained syndrome must at this stage be clearly separated. Firstly, the finding of alterations in lymphocyte populations although reported as common may not be causally related. Secondly, the recognition of disease in a few haemophiliacs does not necessarily reflect the tip of an iceberg. Of course we can expect to see side effects from transfusion therapy with plasma collected from many thousands of donors but if the explanation of AIDS were that easy, even allowing for a transmissible agent introduced in the late 1970s and with a long incubation period, the syndrome would surely have affected greater numbers of either American or West German recipients who have received far more factor VIII concentrate transfusions of United States origin than have haemophiliacs in other developed countries. The links suggested by the American workers must be regarded as not proven. Whilst careful surveillance must continue the reported cases do not constitute a strong argument for a change in treatment policy".

These latter views were the subject of comment in a Health Services article on 6th May 1983 (Statement of Claim page 41 para 63(a)).

Discussion about possible aetiology of AIDS in haemophilia continued in 1983 and was referred to in articles in the Annals of Internal Medicine (ELLIOTT ET AL 1983, POON ET AL 1983, DAVIS ET AL 1983). They were referred to in an editorial in Annals written by White and Lesesne (WHITE ET AL 1983), in which liver disease as a possible aetiological factor was discussed.

In June 1983 the question of AIDS and haemophilia was discussed at a special session of the World Federation of Hemophilia Meeting in Stockholm, at which the Americans presented the data on their cases. From memory, the conclusions of this workshop were that:

1. Whatever was happening in the haemophilia population did not preclude continuing replacement therapy for the treatment of haemophilia.

2. That patients should be followed up rigorously with particular attention to any immunological defects, the recommendation at that time being that the T4/T8 ratio be monitored as the primary indication that something was amiss and that

3. Thought should be given to treating children and mildly affected haemophiliacs who require blood product with single volunteer donor products rather than concentrates. In the case of haemophilia A patients not requiring blood product treatment but requiring haemostatic

cover should be given DDAVP.

In general, the tone of this meeting was optimistic because so few patients seemed to be ill. In retrospect this is because nobody at that time fully appreciated the very long incubation period during which the immune status of infected people gradually wanes before they present with overt disease. But also in retrospect by that time most patients had already been infected, and in any case anti-viral methods of treating the large quantities of blood product required could not have been implemented.

Just prior to the Stockholm meeting I was asked by the periodical The Health Services to write a general article on the economics of the blood supply (JONES 1983). I understood this was an article intended for the general reader but it has some importance in that it is mentioned in the Statement of Claim (page 42 para 63(d)). In that article I stated that "because of previously inadequate planning and lack of proper funding, at least half of the factor VIII concentrate used in Britain has to be imported from the United States . . . Mention has already been made of the hepatitis risk. With the exception of some albumin products, every transfusion carries this risk, in spite of sensitive testing to each individual donor unit of blood whether in this country or in the United States. Occasional outbreaks of hepatitis B still occur, but more worrying is the incidence of liver damage following presumed viral attack with non-A non-B agents for which no specific markers have yet been identified.

"Naturally, people who need frequent replacement therapy - haemophiliacs for example - are most at risk. Recently another, seemingly new disorder, has

been in the headlines. Acquired immune deficiency syndrome (AIDS) in which the body's defence mechanisms fail, has appeared in predominantly homosexual male communities in New York and California. The syndrome may be fatal with patients dying of overwhelming infection or cancer. Because some people with haemophilia have contracted a disorder similar to AIDS the suggestion has been made that the agent responsible is probably a virus which can be transmitted through blood products. The evidence for this is by no means clear and no special precautions, other than careful follow-up, have been suggested for patients in this country".

The Statement of Claim fails to quote the next paragraph in my article: "Nevertheless, the publicity has increased pressure on Health Ministers to ensure that Britain becomes self-sufficient in factor VIII as soon as possible, since the risk of contamination by infectious agents is thought to be higher in imported blood products. It has also boosted interest in the possibility that genetic engineering techniques could lead to production of pure factor VIII in the laboratory".

Later in the year I was asked by the British Medical Journal to prepare a Leader on AIDS and hepatitis. This appeared under the heading "Acquired immunodeficiency syndrome, hepatitis and haemophilia" on 10th December 1983 (JONES 1983c). Within this article I said "people with haemophilia, their families and their doctors are threatened by the deluge of speculation about the possible side effects of treatment with blood products. Two topics hold their attention: the risk of contracting the acquired immunodeficiency syndrome (AIDS) and the risk of developing hepatitis and subsequent chronic liver disease". After considering the definition of AIDS proposed by the

Centers for Disease Control in Atlanta, I said "for epidemiological purposes this definition is wide; it does not suggest a single aetiological agent, merely a similar response, or lack of it, to injury. It is important to recognise this in view of the difficulty in classifying the different disorders concerned and the current reaction of the media to announcements of "new" cases. Until diagnostic markers for the disorder are found terms like "confirmed AIDS" are unhelpful in defining what may well be a multi-factorial disorder".

At the time that this article was written 1% of patients notified to the Centers for diseae Control as fulfilling the disease criteria were haemophiliacs and a further 1% recipients of blood products. Of the estimated 20,000 people with haemophilia A in the United States 17 cases of AIDS had been reported, two of whom had other risk factors for the syndrome. In Britain with 4592 people with haemophilia A, known to the Haemophilia Centre Directors, two cases of AIDS had been reported. I said "thus the reported incidence of AIDS in the two countries is about 0.8 per thousand haemophiliacs. If all disorders of cellular immunity, thrombocytopenia and lymphopenia are classed as cases of AIDS, this figure may be an under-estimate but it does help to put the risks into perspective".

With regard to liver disease I pointed out that "despite increased sensitivity of testing for hepatitis B virus and the screening of donors this virus remains a hazard of blood transfusion, especially in the large pool concentrates prepared for haemophilia treatment. Most post-transfusion hepatitis is now, however, associated with non-A non-B agents, presumably viral. As with the B virus, non-A non-B hepatitis has been more prevalent in

blood from paid rather than volunteer donors".

"So, in Britain where imported commercial cncentrates accounted for 60% of the total factor VIII used in 1980, what risk is there of serious harm from haemophilia treatment? Part of the answer is given by Fletcher and her colleagues (reported in the same issue of the BMJ). In a study of 30 patients given a transfusion of factor VIII concentrate 4 had developed chronic unsuspected liver disease, 17 developed hepatitis, and only 2, who had received cryoprecipitate, remain unscathed. 12 of 19 patients who received only National Health Service concentrate prepared from volunteer donor plasma, and all 5 patients who received a commercial concentrate, developed hepatitis (my underlining). Although the results were influenced by previous transfusions, the striking finding was that hepatitis developed in all 9 patients who had not previously received factor VIII concentrate. The authors suggest that the size of the pool of National Health Service concentrate (over 3500 donors a batch) has been increased to a point where the benefit conferred by the use of volunteer donor plasma might have been lost (my underlining) . . . despite these gloomy figures, the mortality from liver disease remains low, and only two British haemophiliacs died from hepatitis between 1974 and 1980".

The article continued "the commercial companies in the United States acted responsibly and quickly to exclude high risk donors, and similar action has now been taken in Britain, but in the absence of diagnostic serological markers putative agents of AIDS or non A non B hepatitis cannot be excluded from donor plasma. So what further measures can be taken to lessen the potential risks of AIDS and hepatitis? Studies in animals suggest that heat treatment might reduce transmission of non-A non-B hepatitis, and the

manufacturers of factor VIII concentrate are poised to introduce heat treated preparations although this may double the cost of treatment to the British market. It is too early to evaluate the effects of the new manufacturing processes, including the use of heat which differ among companies, but protection is known not to be absolute (my underlining). At least six patients on the study have developed abnormal liver function test results after transfusion. There is no evidence that any product, commercial or volunteer, is free from the risk of transmitting AIDS. Patients with haemophilia B (factor IX deficiency) do not appear to develop AIDS despite multiple transfusions. This may simply be because haemophilia B is rare, but it might reflect a difference in the way factor IX concentrate is manufactured. Possibly what we are seeing among haemophiliacs is an entirely different disorder from that described in homosexuals - that is one due to repeated antigenic challenge over many years rather than to a transmissible agent".

"The median expectation of life of patients with severe haemophilia in Britain was estimated as near normal in 1980 in contrast to 37 years in 1962. This increase in longevity and the improved quality of life are due entirely to the widespread introduction of factor VIII concentrates and comprehensive care. When AIDS was first linked with haemophilia and the extent of the problem in the United States was unknown, some Centres curtailed planned surgery and home treatment. Nevertheless, most have now reverted to their routine programmes and throughout the world the opinion of the majority is that the risk of haemorrhage and its complications far outweighs the risk of developing AIDS or chronic liver disease" (my underlining).

"For the moment, however, it seems sensible to treat very young severely affected children with cryoprecipitate rather than with concentrates. Alternative methods of raising factor VIII activity with Desmopressin (DDAVP), Danazol or perhaps the new porcine material should be used in mildly affected haemophiliacs, people with von Willebrand's disease and carriers of these disorders. There may be a case for long term prophylaxis with cotrimoxazole in those haemophiliacs presenting with lymphopenia and unexplained fever or wasting because all the deaths to date have been associated with infection from pneumocystis carinii. Prophylaxis against this organism is effective and its suppression may buy time for the patient with AIDS. There is no evidence of casual transmission to health care staff, although the Americans recommend the adoption of similar precautions to those already in use for hepatitis B when handling specimens from suspected cases. The most important precaution of all, however, is to maintain a high level of surveillance of the haemophilic population".

On 6th June 1983, John Craske wrote to the Haemophilia Centre Directors about the surveillance of haemophilia A patients suspected to have AIDS.

"The transfusion records of the American haemophilia A patients are far from complete, and as many of their patients have received more intensive treatment than is usual in the UK, they have been unable to identify any suspect batch or brand of factor VIII concentrate. This means that although there is substantial evidence linking AIDS with factor VIII concentrate, this is not strong enough to make any recommendations to the Licensing Authority in the UK regarding the restrictions of the importation of such products manufactured from donor plasma obtained in the USA". In this letter Dr. Craske also says

"we can find as yet no evidence for the existence of a second case of AIDS as was recently reported in the press" (cf Mail on Sunday).

In November 1983 the first fatal case of AIDS was reported in a haemophiliac in the United Kingdom (DALY ET AL 1983).

In 1983 and 1984 the putative agent responsible for AIDS was discovered in France and America, the French virus being termed the lymphadenopathy associated virus (LAV) and the American virus the human T-cell lymphotropic virus type III (HTLV III). Later these viruses were shown to be virtually identical and by international agreement the causative agent of AIDS was named the human immunodeficiency virus. A similar virus discovered later has been named HIV 2. It was HIV 1 which infected the haemophilic patients. However, it was not until 1984 that a test to identify this virus was developed.

It is important to realise that it was not until mid 1984 that the strength of the aetiological link between HTLV III and AIDS was being reported (SAFAI ET AL 1984). Similarly, the link between LAV, AIDS and its association with haemophilia was still unclear in mid 1984 (MELBYE 1984) although warning noises were being made and the question of LAV transmission by blood products was gaining support (RANSEY 1984). Despite the apparent clarity of these arguments in retrospect, doubts still remained until HIV antibody testing became widespread, for instance in a New England Journal of Medicine December 1984. Questions were still being raised as to whether we were dealing with a single aetiological agent (HTLV III) (TSOUKAS ET AL 1984).

Also in December 1984 the link between HTLV III, sero-positivity in European

haemophiliacs and imported factor VIII concentrate was proposed (MELNYK 1984).

By the autumn of 1984 the test had become available to Dr. Richard Tedder at the Middlesex Hospital in London and he kindly agreed to look at the Newcastle haemophilic cohort pending the development of the test at the Public Health Laboratory Service laboratories at Newastle General Hospital (Dr. Arthur Codd). In relation to some of the questions which are being asked of the litigants it is extremely important to understand that at the time testing began (October 1984) we did not know with any certainty:

1. Whether the disease was contagious.

2. Whether whole families might be infected.

3. Whether members of staff might be infected.

4. The number of patients who might be infected.

5. What infection meant in terms of development of overt disease.

6. What the incubation period was.

7. Whether infection was naturally cured by the future development of immunity in the patient.

At the time the increasingly vociferous debates on matters of counselling,

insurance, travel, segregation etc. were not a feature in the United Kingdom. I therefore took the pragmatic decision that we should test everybody who might be infected should the disease be contagious, i.e. spread by day to day social and staff:patient contact and formal consent was not a feature of the initial run of testing. In part this was because I had no idea of what we were going to find and did not want to alarm patients (or staff) prematurely, and in part because we needed to make sure that as far as possible that the tests were accurate. So when Dr. Tedder began to test the patients he was also evaluating the method in his own laboratory in comparison with others, and we later extended this early quality control to matched samples between Dr. Tedder's laboratory and at Dr. Codd's laboratory in Newcastle.

Two things then happened. Firstly, I was able to compile a list of patients who were HTLV III antibody positive on Dr. Tedder's testing and a list of both patients, family members and staff who were HTLV III antibody negative. The good news that staff were uninfected was reported by Dr. Hamilton and I in the Lancet on 26th January 1985 (JONES ET AL 1985a). Later in that year (in the Lancet 22 June 1985) (JONES ET AL 1985b) we were also able to report on contaminated laboratory reagents, this report leading to a general warning to laboratories by the DHSS. Secondly, meetings had to be arranged both with individual patients and with groups of patients and their families in order that they could be as fully informed as possible about the current state of knowledge. It would have been impossible to do this without knowledge of the state of infection in the patient cohort and the lack of infection in casual contacts.

The first general article that I wrote for patients in the Northern Region was

in the Haemophilia Society Spring Newsletter of 1983 (JONES 1983b). This piece was written at around the time that my complaint had been made to the Press Council about the Mail on Sunday (forwarded) and I think demonstrates the openness with which patients were approached about the disease. Throughout the history of the development of knowledge all the patients have been kept fully informed and no facts, however unpalatable, have been hidden. As a corollary, of course, they have also been kept informed about the many myths associated with HIV infection. Throughout they have also been aware that the Centre has continued to run an open door policy, and that they or anybody they know who has been worried, have been able to come and talk to a member of staff in private at any time.

The short piece in the Newsletter is also notable because it contains (second paragraph) one of the premises that I and the other members of staff have followed from the beginning of the epidemic. That is that we would regard anybody who became infected with HIV, no matter what the aetiology of the infection was, on the same standing. In other words there was to be no discrimination and that everybody would be helped equally. This attitude was later to become a feature of the campaign for recompense which was run largely by the Newcastle Haemophilia Centre working with the national Haemophilia Society, and resulted in the formation of the Macfarlane Trust with a £10 million ex gratia payment by the Government (JONES 1987a), and also referred to in a letter (JONES 1986a) and an article in the Times of 9 October (JONES 1987b) and a Leader in the British Medical Journal of 17 October 1987 (JONES 1987c).

In the context of the development of public awareness about AIDS in the United Kingdom this attitude was of immense importance and I believe that it helped

prevent much of the bigotry which has been apparent in America. Both our attitudes and those of the national Haemophilia Society in the planning of the recompense campaign could easily have focussed on the "innocent victim" nature of HIV infection in haemophilia, and a punitive attitude to homosexuals in particular, and to intravenous drug abusers. The clean nature of the campaign, and indeed the present campaign for the Government to settle out of court, has been remarked upon by people in authority and has, I am sure, stood the relatively small haemophilia community in good stead, both in this country and abroad.

On 2nd August 1983 I met Clive Jenkins, the General Secretary of ASTMS at his invitation to discuss AIDS. Following this meeting ASTMS Health and Safety Officer, Sheila McKechnie, wrote to me about self-sufficiency and I replied on 29th September 1983 (JONES 1983).

In October 1983 (JONES 1983) I wrote to patients individually about an invitation to attend a Haemophilia Society weekend seminar in Newcastle. Several patients had already applied to attend this seminar but because of the growing evidence of HIV infection in the haemophilic population I wanted to ensure that as many of our families as possible attended. This was not simply a matter of imparting information. One of the strengths of our work with haemophilia over the years has been the ease with which patients and their families have been able to talk about their troubles amongst themselves, and in the autumn of 1983 it was becoming apparent that this easy communication was beginning to falter because people were unsure and fearful. So the letter encouraged people to come and tell us what they wanted in terms of general haemophilia follow-up, and also gave them an opportunity to ask any questions

that they wanted about the side effects of treatment.

In the second edition of Living with Haemophilia (1984) further consideration was given to the question of side effects (JONES 1984[b]). By now the difference was known between hepatitis B and non-A non-B and these conditions are both considered together with the recommendation that people at risk should be vaccinated against hepatitis B. On page 90 in a short section on hepatitis non-A non-B it is stated "the incubation periods for these agents appear to be short, in some cases only a matter of days. There is evidence that haemophiliacs have multiple episodes of NANB hepatitis, most going unnoticed, although the first attack is sometimes accompanied by the appearance of jaundice. The NANB agents are important because, as with hepatitis B, infection they cause can lead on to chronic liver disease. No way of protecting recipients from NANB hepatitis is known. Manufacturers are trying the effects of heat and chemicals on blood products, but no foolproof method of inactivating NANB viruses has been found. Vaccination is not yet possible" (my underlining).

On page 91 reference is made to AIDS. In the course of the discussion, which was written in the autumn of 1983, it is stated "because haemophiliacs have developed immune deficiency, and because of the fact homosexuals have donated their blood plasma, it has been assumed that whatever it is that causes AIDS is being spread from blood transfusion. This assumption has been developed into a theory that a virus with a very long incubation period is responsible. At this stage we do not know if these assumptions are justified. Immune deficiency in a few haemophiliacs may be the result of repeated exposure to proteins and other antigens in blood products, and nothing whatsoever to do

with what is happening in the homosexual community. However, as a precaution checks have been introduced to exclude people in the high risk groups from giving blood".

"What should people with haemophilia do? The answer is straightforward: they should continue to treat their bleeds as quickly and as effectively as possible. Without treatment haemophilia cripples and kills. Hopefully, by the time this description of AIDS appears in print we will know some of the answers to the questions it poses to patients and their doctors. One of these is likely to be that, if there is an infectious agent in blood, its attack rate is very small and that only a few people will have trouble with it. The story of AIDS has many similarities to that of hepatitis B and, as we have seen, hepatitis B can be controlled".

In November 1984 an invited article on the management of haemophilia was published in the Archives of Disease in Childhood (JONES 1984b). In that article I said "Despite intensive research the aetiological agents of non-A non-B hepatitis remain elusive. They are present in all blood products used for the treatment of haemostatic disorders, including the newer heat treated concentrates. Because non A non-B hepatitis is, however, more common after exposure to large donor pool concentrates there is a case for trying to maintain young (pre-school) children on voluntarily donated cryoprecipitate. Despite recent publicity on the human T cell lymphotrophic retrovirus type III the definitive cause of AIDS has yet to be established with certainty. If the syndrome is spread by blood transfusion (and the evidence that this is so remains sparse) identification of the agent responsible should lead to appropriate screening tests. For the present, the same provisions as for

hepatitis should apply to children, and parents should be reassured that, at least in the haemophilic population, AIDS is a relatively minor problem affecting only 1 in 1000 patients: only two adult cases of haemophilia and AIDS are known in the United Kingdom, and they were reported over a year ago. If the problems of non-A non-B hepatitis and AIDS can be laid to rest there is a strong case for introducing prophylaxis, perhaps on a weekly basis, very early in childhood.

Another problem of relevance to the treatment of children has been the discovery of immune disorders in up to 10% of the haemophilic population. Thus we have seen idiopathic thrombocytopenic purpura and acquired haemolytic anaemia in otherwise well children in Newcastle. Non-specific lymphadenopathy has to date been confined to our adult patients. The emergence of these disorders in addition to the recurrent abnormalities of liver function make it obligatory that every child receiving blood products from whatever source is followed up rigorously at minimum intervals of six months".

Things were going fairly smoothly until November 1984 when one event precipitated an intense public debate about haemophilia and AIDS. The event was the death of GRO-A a patient who divided his loyalties between the Glasgow Haemophilia Centre and the Newcastle Haemophilia Centre. GRO-A was a severely affected haemophilia A patient. He was the first patient that I diagnosed with AIDS and when he presented with pneumocystis carinii pneumonia in May of 1984, in order to avoid any hysteria which was then likely from the local ambulance authorities and possibly from the media, I took him in my own car to the infectious diseases ward at Newcastle General Hospital (at that time ambulance men would have kitted themselves out in full

biological protection clothing in order to do this).

GRO-A recovered from this infection and subsequently returned to Glasgow where he again became ill and was admitted to the Ruchhill Hospital where he died on GRO-A 1984. We had no immediate knowledge of his death until we were phoned by a representative of the press. I was later told in confidence that the link between GRO-A AIDS and Newcastle had been deliberately leaked in order to divert attention from the growing problem with AIDS in Scotland to south of the border. If this was deliberate policy then it had its effect because from that time Newcastle became the focus for media interest in the disease and the infection of haemophiliacs in the United Kingdom with up to 40 calls a day at peaks of interest. A special office and secretary were assigned by the administration of the hospital in order to enable me to cope with the enquiries.

(JONES 1984C) is a letter sent to colleagues in the Region, with a copy to Professor Arthur Bloom, who was at that time Chairman of the Haemophilia Centre Directors. A copy of the press release referred to in this letter is appended (JONES 1984D).

In the week prior to this letter the first details of the response of the American National Hemophilia Foundation to the haemophilia problem had become known and reference is made to the statements in the penultimate paragraph.

My immediate concern was to inform the patients and their families what was happening and on 16th November 1984 (JONES 1984E) I wrote to the Chairman of the Northern Branch of the Haemophilia Society about current knowledge of

AIDS. The state of knowledge at that time was reassuring to everybody because it suggested that, whatever the AIDS virus was, it was of low infectivity. However naive this particular observation might be in retrospect, the fact that the evidence also showed that the disease was not contagious has stood the test of time. Within this letter is an open invitation for people to discuss any questions relating to the problem either individually or in meetings.

Data on how factor VIII and IX concentrates may be made safe from HIV was accumulating rapidly towards the end of 1984. Most of the preliminary data came from the United States and was disseminated via the National Hemophilia Foundation Medical and Scientific Advisory Council. (We have written to obtain the Medical Bulletins prior to 13th October 1984).

Medical Bulletin 9 (NATIONAL HEMOPHILIA FOUNDATION 1983) 22nd October 1983, did not contain heat treatment in its recommendations for physicians treating patients with haemophilia. It did, however, recommend to factor VIII concentrate manufacturers (part 28) that "efforts should be continued to expedite the development of processing methods that will inactivate viruses potentially present in factor VIII concentrates. While heat treated products offer certain theoretical advantages, the data are insufficient at this time to assess their efficacy or to recommend that the presently licensed heat treated products be used instead of standard factor VIII concentrate, either for modification of the risk of hepatitis or AIDS. For this reason prospective studies of the efficacy and safety of modified products are strongly encouraged".

In the light of this it is interesting to recall the state of knowledge in the UK in 1983: from a record of the DHSS Medicines Division 13th July 1983 (agenda for discussion on AIDS in relation to licenced blood products, section A factor VIII and other clotting factors):

1. Aetiology, current possibilities, Dr. Mortimer "An infectious cause seems likely and a single new agent could be responsible. Repeated exposure to, or reactivation of, known viruses cannot be excluded, although posible agents have been proposed, e.g. CMV, EBV, HTLV, their relationship to the disease appears very uncertain. The infectivity of the supposed agent appears to be low, requiring for transmission intimate contact or introduction into the body tissues".

2. Epidemiology, Dr. Galbraith "Recipients of clotting factor concentrates are at risk. The degree of risk cannot yet be quantified. The risk appears to be greatest from products derived from the blood of homosexuals and IV drug abusers resident in areas of high incidence and in those who repeatedly receive concentrates in high dosage".

3. Possible scientific approaches to avoiding or reducing the presence of viruses in clotting factor preparations.

Treatment of blood products with heat or chemicals. Dr. Fowler "Although the value of such measures in respect of unidentified agents can be proven only by long term epidemiological studies, they are likely on general grounds to reduce infectious hazards but may not eliminate them".

4. Consideration of the different operational possibilities for reducing the risks from clotting factor preparations.

(i) To withdraw factor VIII and IX concentrates, i.e. use only cryoprecipitate for treatment. Professor Bloom "this step cannot at present be recommended.

(a) It is probably impossible to satisfy UK needs in this way.

(b) Even if needs could be satisfied it would involve a major re-think of UK policy for preparing blood products.

(c) The level of risk at present does not justify serious consideration of this solution".

(ii) Withdraw US preparations from the UK market. Dr. Fowler "Impracticable on grounds of supply".

(iii) Use US blood products as sparingly as possible. Professor Bloom "The uncertain balance of risk benefit considerations in various categories of patient are to be finely balanced to justify action via licensing: the matter should be left to clinical judgement".

(iv) Promote UK self-sufficiency in supply of concentrate. Dr. Fowler "This is highly desirable since it should reduce risk appreciably, although not completely".

(v) Use UK blood products only if the source plasma was collected after the new regulations were introduced (23rd March 1983). Note it is known that US manufacturers have stocks of pre-March plasma and that the US Office of Biologics is to consider this matter on 19th July. Dr. Fowler "This should be adopted as soon as practicable even though its value may be limited".

(vi) Use products treated by heat or other inactivation methods. Note: Hyland are now licenced in the USA for heat treated factor VIII and Armour is shortly to apply for a US licence. The cost of these products are apparently at least double that of untreated material. Dr. Fowler "This is desirable, but is impracticable at present, since no such products are yet available in the UK. This development could, however, be encouraged, notwithstanding the cost penalty".

When these products become available in the UK should licences for non-heat treated factor VIII from the USA and/or elsewhere be continued? Dr. Fowler "When these become available the quantity that can be supplied should be established and the advisability of this step re-examined in the light of this information and on up to date knowledge of AIDS at the time".

The Committee examined hepatitis B vaccine, immunoglobulin and albumin and concluded that although there was no evidence of risk and no action was presently justified, the position with regard to these agents should be

closely observed.

In Medical Bulletin 15 for 13th October 1984 (NATIONAL HEMOPHILIA FOUNDATION 1984A) it was recommended that "cryoprecipitate be used to treat newborn infants and children under the age of 4, and newly identified patients never treated with factor VIII concentrates. Secondly, Desmopresson should be used whenever possible (my underlining) in patients with mild or moderate haemophilia A and thirdly (and of chief import with regard to the Statement of Claim) "We do not yet have sufficient data of scientific nature to know with certainty that viral attenuated (heat treated) coagulation factor concentrates should now be universally adopted. However, very preliminary data do suggest that HTLV III is heat sensitive. Further, we do not know whether haemophiliacs who are positive for antibody to HTLV III have been exposed to living virus capable of causing AIDS, or have developed effective immunity against AIDS".

"Because heat treated products appear to have no increase in untoward effects attributable to the heat treatment, we now recommend that treaters using coagulation factor concentrates should strongly consider changing to heat treated products with the understanding that the protection against AIDS is yet to be proven . . ." (my underlining).

This document also contains recommendations to factor VIII concentrate manufacturers and section (e) may be relevant to arguments about safety of blood products at this time. (e) refers to the previous withdrawal of lots of clotting factor concentrate known to have contained plasma from a donor confirmed as having AIDS (see Medical Bulletin 10 January 24, 1984 (NATIONAL

HEMOPHILIA FOUNDATION 1984β). The decision to do this caused considerable disquiet because although it seemed eminently sensible as evidence grew that many, if not most, lots would be contaminated, it was thought that there would simply not be enough factor VIII or IX concentrates left to treat the primary bleeding disorder. The dilemma was only resolved with the development of viral inactivation, including heat (see Medical Bulletin 22, 8 May 1985 (NATIONAL HEMOPHILIA FOUNDATION 1985c).

On 14th February 1985 the Medical and Scientific Advisory Committee made further recommendations with regard to heat treatment, this being finalised in Medical Bulletin 21 which was issued on 12th April 1985 (NATIONAL HEMOPHILIA FOUNDATION 1985E). Before looking at these recommendations it is worth noting that throughout the time period covering the development of viral inactivation one recommendation remained unchanged, both in America and the United Kingdom. In Bulletin 21, it was that "the Medical and Scientific Advisory Committee re-affirms its position that PATIENTS CONTINUE TREATING BLEEDING EPISODES WITH CLOTTING FACTOR AS PRESCRIBED BY THEIR PHYSICIANS AS THE RISKS OF WITHHOLDING TREATMENT FAR OUTWEIGH THE RISKS OF TREATMENT".

The revised recommendations for 14th February 1985 were that physicians treating patients with haemophilia:

(a) "In view of the accumulating evidence for the heat sensitivity of HTLV III and the apparent lack of untoward effects attributable to the heat treatment, we recommend that physicians should strongly consider prescribing heat treated coagulation factor concentrates for the treatment of patients with severe haemophilia with the understanding that protection against AIDS is yet to be

proven".

"It is recognised that we do not know whether haemophiliacs who are positive for antibody to HTLV III have been exposed to living virus capable of causing AIDS or if they have developed effective immunity against AIDS. In order to develop a secure scientific basis for such practice we again urge a prospective national study of the use of heat treated materials in patients not previously exposed to pooled blood products. The Medical and Scientific Advisory Council will continue to review its position on heat treated products as more complete studies become available".

The document affirmed that new and mildly affected patients should be treated with cryoprecipitate or plasma and also emphasised "that hepatitis B vaccination is essential". In addition the text contains the words "moreover, as the transmission of non-A non-B hepatitis may be greater with these products, even if heat treated . . ."

In an AIDS Update leaflet published in March 1985 intended for patients and families and headed "this report is based on the most current information available" the question of heat treatment was covered in Section 22: "Do heat treated products offer protection from AIDS?" "It is not known for certain if the heat treatment of concentrates has eliminated their potential to transmit AIDS. It is, however, becoming apparent that some viruses are heat sensitive. There is now preliminary evidence that HTLV III is quite sensitive to the heat treatment processes used to treat concentrate".

"For this reason the National Hemophilia Foundation's Medical and Scientific

Advisory Council has recommended that heat treated concentrate should be strongly considered for patients now on factor VIII concentrate. The same advice has been given for the recently released heat treated factor IX concentrate. The Center for Disease Control in Atlanta has endorsed these views (NATIONAL HEMOPHILIA FOUNDATION 1985c).

These questions were being considered at the same time as individual donor screening was getting under way in the United States. My view was (and remains) that the UK BTS should have followed the American lead immediately and introduced individual donor testing rather than waiting from March to October 1985 and I voiced this view on the BBC programme This Week Next Week (JONES 1985a). This view is at variance with that pleaded on page 52 of the Health Authority's Defence.

By November 1985 (Medical Bulletin 32 (NATIONAL HEMOPHILIA FOUNDATION 1985b) the Medical and Scientific Advisory Committee was feeling confident enough to extend the use of "heat treated or otherwise viral attenuated factor VIII and factor IX" to groups other than the patients who had already received multiple transfusions. Recommendation 18 was that the heat treated materials "may be the perfect products for the treatment of patients in groups for which it was previously recommended that cryoprecipitate or plasma would be used, i.e. new or mildly affected patients". However, it was still emphasised that hepatitis B vaccination was essential and that transmission of non-A non-B hepatitis may be increased.

In a memorandum dated 29th March 1984 Drs. Bloom, Craske and Rizza addressed all UK Haemophilia Centre Directors and quoted "clinical trials have only been

completed on one product, the Hemofil HT factor VIII, which is prepared using a dry heat method. The results indicated that there was still a 63% attack rate of non-A non-B hepatitis on first exposure to this product in patients who have not received factor VIII concentrate previously" (my underlining). The memo listed the products currently availble (Armour, Cutter, Travenol (dry heat) and Alpha (wet heat)) and stated that a heated NHS factor VIII should shortly be available from Edinburgh and a second from Elstree available later in the year. In view of the suggestion in the Statement of Claim that we should have been using a German product from the late 1970s, the following statement is appropriate "a heated preparation manufactured by Behringwerke, the German pharmaceutical company. This is heated at 60°C for a period known to inactivate hepatitis B in the preparation. The problem is that the yield of factor VIII coagulation activity is considerably reduced, so that the cost is likely to be at least four-fold higher ?40p per unit. Trials have been carried out in Germany, but no published information is available. At least 30 patients have been studied".

We started to use heat treated material in Newcastle in December 1984, at the time of the UK Directors Advisory Document Issued by Professor Bloom as Chairman (Health Authority's Defence page 43). Details of the availability of material are given in (RIZZA 1988). Whilst it might have been thought that a prescription for heat treated material would be a straightforward affair, principally because of costing the District Administrator, Mr. Chris Spry, and the Chairman of the Hospital Medical Committee, Dr. C. B. Henderson, called together an ad hoc group to consider the use of heat treated factor VIII concentrate. A draft of the report of this group is appended (AD HOC GROUP 1984).

Although not reported disquiet was expressed by Dr. Bird at this meeting about the rationale of switching all haemophiliacs to heat treated material and this disquiet was communicated to Dr. Collins, Director of the Regional Blood Transfusion Service and to Dr. Arthur Codd, Consultant Virologist at the PHLS in Newcastle and stated in the letter to Professor Rawlins in his capacity as Chairman of the Ad Hoc Group on 28th December, 1984 (BIRD ET AL 1984). Professor Rawlins decided not to act on the request in this letter, and Dr. Bird and his colleagues wrote to the Lancet (BIRD ET AL 1985) expressing their reservations. This letter is of considerable import in view of the suggestion made in the Statement of Claim that an earlier switch to heat treated material could have been seen to eliminate or virtually eliminate risks of viral transmission. Dr. Bird is an immunologist of repute and the letter of 19th January 1985 represents a state of the art response to the Lancet editorial 22/29 December 1984 (ANON 1984) in which the argument for switching everybody to heat treated factor VIII and probably factor IX was put forward. The letter stresses doubt as to the efficacy of heat treatment (para 5) and recommends that sero-negative individuals should only receive cryoprecipitate.

Points raised in Dr. Bird's letter were replied to by Professor Bloom on 9 February 1985 (BLOOM 1985).

A decision to implement the prescription of heat treated concentrates to haemophilia patients in Newcastle was not followed by <u>immediate</u> implementation for all patients, i.e. I did not initiate an immediate recall of products, a substantial quantity of which were already in patients' homes. I made this decision because I assumed that patients had already been exposed to the

batches that they had available for home therapy, and I did not think that the available evidence warranted the fear that such a quick recall would invoke.

In addition, we were at the time checking the antibody status of the patients and knew that sero-conversions had already occurred - it was therefore thought probable that everybody who had been exposed was already infected (KADHOK ET AL 1985). It should also be remembered that there was still doubt about the switch to heat treatment in everybody, i.e. although it was recommended it was not an absolute requirement.

The patients were, however, kept fully informed. In November 1984 the question of heat treatment had been discussed at a general meeting to which all patients were invited in Newcastle. I also sent a letter to colleagues concerned with haemophilia care in the Northern Region and wrote to the patients' family doctors (JONES 1984). This document contains my decision to discontinue use of non-heat treated NHS concentrates, both VIII and IX. This meant that, for the first time, we had to use commercial IX concentrate in Newcastle, and continued to do so until NHS IX (heat treated) became available. Instead patients were switched to heat treated material if they presented for treatment either as outpatients or as inpatients at the Haemophilia Centre or when they came to stock up on their home therapy supplies. As a result all patients were being issued with heat treated factor VIII by mid 1985. Details for individual patients are presently being determined in the computer analysis and will be given in the replies to individual Statements of Claim.

Because at the time that this schedule was circulated there was such a paucity

of information about AIDS and how to respond to it in the UK, with the help of my colleagues I extended it and in February 1985 published via the Haemophilia Centre a booklet entitled "AIDS and the Blood". This booklet was given freely to the National Haemophilia Society for distribution and was the first patient orientated information to be given wide dissemination in the United Kingdom (JONES 1985A). As such it also became the first source of basic information to the media and was widely and enthusiastically reviewed. The text in whole or in part subsequently appeared in many other publications and was translated into Portuguese in 1985 and Italian in 1986. All my own patients received a copy soon after publication.

In February 1985 another leading article on AIDS appeared in the British Medical Journal. This article drew attention both to the problems associated with blood transfusion and to the difficulties being experienced by the male homosexual community who were being blamed in some quarters for the spread of the disease via transfusion (LEACH 1985). Drawing on a paper by Dr. K. M. De Cock (DE COCK 1984) in which a connection between the occurrence of AIDS in Africa and the United States had been postulated, I suggested another link in the story and cited knowledge I had of the procurement of plasma from Africa (JONES 1985B). This letter provoked a response from the Chief Medical Officer (ACHESON 1985) who said that under the Medicines Act "Information about sources of plasma is provided to the Licensing Authority in confidence by the companies concerned. I can, however, assure Dr. Jones and those concerned with this issue that on the basis of that information we are satisfied that none of the plasma covered by current (my underlining) UK licences comes from areas where AIDS is known to be endemic". This statement is in fact untrue because plasma was coming from endemic areas in the United States at the time.

The letter goes on to mention British self-sufficiency.

My letter also provoked a response from industry (REILLY 1985). When Robert W. Reilly "a national spokesman for the American plasmapheresis industry", wrote on 20th July 1985 in defence of the American position, the BMJ asked me to reply at the same time (JONES 1985c)

Dr. Reilly stated "US manufacturers must be licensed by the US Food an Drug Administration. As such they are restrained as to their sources of plasma, and it can easily be verified that they did not rely on plasma from Africa . . ." Reilly obviously chose his words carefully because his letter did not state that plasma from outwith the United States was, or had been used, or that the rules governing manufacturers within the United States were not applicable outwith that country. In my reply I drew attention to the long-standing contract between a multi-national company (which I knew to be Baxter Travenol/Hyland) and a plasmapheresis centre in Lesotho in Africa and the facilities run by at least two companies in Mexico (which I knew to be Hyland and Cutter).

These letters were followed by a string of mostly telephoned comments from around the world by people seeking to establish the initial spread of AIDS. Unfortunately we did not keep a record of all these calls but one of them did result in a meeting at Heathrow Airport in 1985. The gist of this meeting, and of some of the phone calls which came from the United States, fell into a familiar pattern which was that government sources in the United States had prior knowledge of what we now know as HIV infection. There were suggestions that the virus had actually been manufactured or developed in the US

biological warfare programme. These suggestions have been publicly refuted as speculative myth on many occasions, but some of our correspondents cited information from the records of the Central Intelligence Agency which they had obtained via the American Freedom of Information Act, only to find that large sections of the record had been deleted. One of the correspondents, a professional journalist, had followed the story through to the Congo and what he claimed were human experiments in the 1970s. Both at Heathrow and by telephone as late as 1989 I was told to be extremely careful and not to continue publicly any suggestion that there had been prior knowledge of the putative agent which we now know as HIV, or that any government agencies either in this country or in America might be implicated. Any written suggestions were consigned to a "rubbish" file in the Haemophilia Centre (our Nut file!).

Another warning, this time personal, was given to me as a result of the initial letter (JONES 1985A). At the First International Conference on AIDS which was held in Atlanta between 14th - 17th April 1985 I was paged to meet a Dr. Louis Greenberg in the foyer. When I met him Dr. Greenberg was talking to a medical journalist (I think from Nature). He took me aside and told me that as a result of the words "It may be very pertinent to the epidemiology of AIDS that plasmapheresis centres supplying companies directly, or through the services of brokers working principally from Zurich and Montreal, were situated in exactly the areas now known to be endemic for Kaposi's sarcoma and other AIDS-related diseases", GRO-D with whom he worked in the brokering business in Montreal, had considered taking legal action against me for defamation. Instead he had decided to send Dr. Greenberg with the verbal warning that if he made anything further of this matter he would "ruin my

career". Dr. Greenberg also said that I should write to Mr. GRO-D withdrawing my statement and apologising. My reply was that it was Mr. GRO-D s perfect right to question the validity of the statement but that he should do so through the professionally accepted route, i.e. writing a letter to the BMJ. Nothing more was heard of the matter. GRO-D is still in the business having acquired further blood resource companies in the United States. He is currently supplying plasma to Europe for the manufacture of solvent detergent product.

Pertinent to the question of the international plasma trade the following documents are appended (PAPERS CONFIDENTIAL TO DR. JONES: 1, 2, & 3). It should be noted that they are highly confidential and that I have been told that No. 1 can be traced back to the person who gave it to me.

Most of the background knowledge was obtained in the course of my work with middle management who, in the 1970s, frequently moved between companies. The major companies concerned were Baxter Travenol; Armour, which went through a number of acquisitions and at one stage was under Revlon, the cosmetics and health care group; Abbott, later Alpha, which is now a subsidiary of the Green Cross Corporation in Japan; and Cutter, a subsidiary of Miles Laboratories. The other company in the field at the relevant time was Immuno which produced Kryobulin; because I did not use their product on grounds of cost I had little to do with this company directly.

Knowledge of the trade initially came from Brian Steer, then the British Manager for Travenol. It was Steer who piloted the introduction of Hemofil into the United Kingdom in the early 1970s and who is referred to in the first

paragraph of confidential paper No. 2. Robert Taub later became a friend and associate (he appears as an author in Supplement to the Scandinavian Journal of Haematology which we wrote together in Madrid in 1980 (JONES ET AL 1980). Other information came from Piet Hagen, the author of "Blood - Gift or Merchandise".

Confidential paper No. 1 refers to the illegal importation of plasma to the United Kingdom and is of especial importance with regard to possible connection with AIDS. It cites the source of this plasma as being outwith the United States, e.g. Lesotho and Berlize. Obviously the information contained in this in-house document, which originated on 2nd February 1979, could be highly damaging. If possible its contents should be checked against the Medicine Commission records referred to by Dr. Acheson in his letter (ACHESON 1985). If the source of the plasma is not named in the product licences at that time, then the information in this document clearly opens the whole question of accuracy in the British records, and the failure of the licensing authorities to adequately monitor the safety of the blood supply at times relevant to the present action.

Confidential paper No. 2 refers to a meeting in September in 1979. It is a memo which I dictated to my secretary on my return from the meeting at which it had been suggested that I might wish to work as a consultant for the Revlon Health Care Group. The outcome of this meeting was that I visited the United States in a consultant capacity to Revlon in 1980. My task was to inspect and prepare a report on the plasmapheresis facilities run by Plasma Alliance Inc. of Knoxville, with particular emphasis on whether they complied with the Food and Drug Administration regulations (they did in all but minor respects and as an independent observer I was favourably impressed). I also was given the

opportunity to visit the fractionation plant at Kankakee in Illinois where I was taken through the manufacturing process by Fred Feldman, who is still associated with the company.

Confidential paper No. 3 refers to a telephone call from Robert Taub in 1985 following the "African connection" letter in the BMJ. This letter contains further information about the importation of plasma from Africa. The crux of the matter is contained in the statements on page 2 of this report (paras 2 and 3) which demonstrate how the commercial companies got round the FDA regulations. This was very simple because all they had to do was to collect and process plasma not collected in the United States outwith the country. The only safeguards other than those imposed by the companies themselves were the importation controls of individual states and confidential paper No. 1 suggests that these were wholly inadequate.

In the course of a World Federation of Hemophilia Meeting in Milan in 1986, it was suggested that plasma was still coming from under-developed countries and the involvement of a Spanish company, Landerlan, was raised, one delegate suggesting that they were still receiving plasma from Uganda. I wrote to Frank Schnabel about this and his reply is appended (SCHNABEL 1986).

The question of control of plasma supplies has already been addressed in the draft reply to the Statement of Claim (page 4) which is quoted here:

"As a result of meetings with the Department of Health in the early 1970s commercial concentrates were made available from 1973. Initially these were supplied by Travenol (now Baxter Health Care) in the form of a concentrate

called Hemofil. This, like the other commercial concentrates, was prepared from plasma of paid donors. Control of this manufacture within the United States was initially by the Division of Biologics Standards and was governed by a Public Health Service Act and a Federal Food Drug and Cosmetic Act until 2nd May 1972 when the Food and Drug Administration took over. At the time of the National Heart and Lung Institute's Report (volume 2 Regulation of the Nation's Blood Resource 20th June 1972) it was estimated that the Federal Government of the USA had control of only 63% of the blood fractions being manufactured. So, when plasma was collected from paid donors in the United States, this collection was only partially under legislative control, and this control was proving difficult to monitor. In addition within the legislation there was allowance for "short supplies" which were not regularly inspected. This allowance was included within the legislation to allow the procurement of materials from sources outwith the usual suppliers of the manufacturers which were meant to be routinely vouched for by the manufacturers (who were meant to list them), and several of them were outwith the United States. Many are listed in volume 2 of the NHLI Report and they include firms in the Caribbean, Central and Latin America, Spain, India and South Africa. Later evidence suggests that other countries than those listed were involved in supply of plasma to the United States, particular examples being Mexico and Nicaragua".

Knowledge of the importation of plasma from developing countries was widespread in the early 1970s and was referred to in Bulletin No. 9 of the World Federation of Hemophilia (special issue on blood transfusion and plasmapheresis) which was published in June 1975 just before the 10th Congress of the World Federation of Hemophilia in Helsinki which I attended as Chairman of an orthopaedic and surgical session. See paper by J. P. Soulier, who was

the Head of the French Blood Transfusion Service (SOULIER 1975), Rosemary Biggs (BIGGS 1975), who was then Director of the Oxford Haemophilia Centre, Katherine Dormandy (DORMANDY 1975), who was then Director of the Royal Free Haemophilia Centre, and Jack O'Riordan (O'RIORDAN 1975), who was then Head of the Irish Blood Transfusion Service.

In February 1985, following the publication of AIDS and the Blood, it was clear that there was an urgent need to continue the dissemination of factual knowledge about AIDS, but no-one in authority seemed to be doing much about it, although the Director of the Public Health Laboratory Service, Dr. Spence Galbraith, Miss Weller the Chief Nurse, and Dr. Alison Smithies, then responsible for blood products in the DHSS, visited New York after the Atlanta meeting. I joined them in several of their discussions and later went to see how infected children were cared for in New Jersey. Draft notes remain of these visits (JONES 1985D). Later in 1985 I approached the DHSS with the idea of holding the first conference on AIDS in the United Kingdom in early 1986. The Department quickly came up with the necessary funding and as a result the first AIDS Conference was held in February 1986 in Newcastle. Prior to the conference I visited San Francisco General Hospital to talk to Dr. Paul Volberding and his colleagues about the conference, at which he was one of the prime speakers. I also visited voluntary associations in San Francisco, including the Shanti Project, and later used this as a template for a recommendation to the DHSS that they fund a pilot project on AIDS and the community in Newcastle; this proposal was later implemented as the Community Support Centre. The proceedings were published later in the year (JONES 1986B). As part of this conference I presented the available data on haemophilia (JONES 1986C). Some of the facts given in this presentation had

previously been published in the British Medical Journal (JONES ET AL 1985C) which detailed our experience in Newcastle. Within the presentation (pp 106-107) I raised the question of the efficacy of heat treatment and reported that Drs. Brederveld and Levine had seen patients who they thought had sero-converted whilst on heat treated material. These remarks provoked an immediate response from the Chief Medical Officer (who had opened the meeting), who was no doubt trying to give public assurance about the blood supply. Unfortunately Dr. Acheson's response had the effect of blunting the thrust of the argument that heat treatment may not be a guarantee of safe blood product, and subsequent sero-conversions occurred in patients on the same blood product that had been reported by Dr. Brederveld to be of questionable safety (Armour Factorate heated to 60° for 30 hours).

The controversy echoed my knowledge that nobody has yet been able to find HIV in any factor concentrate, and that all work into product safety has had to be performed either by spiking concentrates with HIV and following viral inactivation using the most sensitive methods now available, or by using surrogate viruses and showing their removal. Thus it is clear that the amount of HIV which must have contaminated the factor VIII and factor IX concentrates in order to produce the epidemiological picture in the haemophilic population was so small that it is undetectable by present methods. It follows that demonstration of so-called "log kill" following spiking experiments can never lead to the conclusion that traces of virus capable of infection had been removed.

Therefore the proof of complete removal of HIV depends entirely on epidemiology, which in the haemophilic population requires repeated testing

for sero-conversion of cohorts of HIV sero-negative patients. Since dry heated materials (with the exception of the British BPL products from Elstree and Edinburgh), were removed from the market by the manufacturers the epidemiology has looked extremely encouraging. However, it has been calculated that up to 30 times more exposure with volunteer donor products is needed in comparison with the paid donor or commercial products. This is because the likelihood of an infected person donating plasma is around 30 times more likely in the case of paid donors (who are more likely to come from populations with far higher rates of infection) than occur in, for instance, this country.

The real test of any system would come when a donor presents shortly after infection, is highly viraemic, and is sero-negative because he or she has not yet developed sufficient detectable antibody (this is the case of the "window" in which there is no known method of detecting infectious donors). The heavy load of virus donated would, with knowledge of the spiking experiments referred to above, be virtually removed by all the methods currently in use, including dry heating at 80°C for 72 hours, but there must remain the possibility that the trace left would be (a) undetectable by present methods of testing either the individual donation or the pooled product and (b) capable of infecting recipients. A similar position applies with regard to hepatitis B and hepatitis C, where most of the presently available products have been shown to transmit despite negative testing. One of the difficulties in all this is that the pooling together of hundreds of thousands of donations dilutes out the infected dose making it harder to detect. This is why, in the case of hepatitis B, patients are still vaccinated.

Subsequent to the conference an article appeared in New Scientist on 20th February, 1986 (CONNOR 1986) which detailed the choices open for haemophilia treatment at that time. As a result of the controversy I sent details of the cases that I knew about to the Committee of Safety of Medicines, and Armour subsequently withdrew their product at the Committee's suggestion in October 1986, when a representative of the Committee was kind enough to phone me to tell me of this decision before it became public knowledge. Prior to this I had had correspondence with both the Committee and with the Armour Pharmaceutical Company, papers being referenced under (CORRESPONDENCE WITH COMMITTEE OF SAFETY OF MEDICINES & ARMOUR PHARMACEUTICAL COMPANY). It emerged during the course of this correspondence that some of the product was not being individually donor tested. Unfortunately the withdrawal was too late to save further sero-conversions in Birmingham, which was referred to in a letter from the Director of Clinical Sciencies at Armour on 27th February 1987.

The company were also in trouble in the United States having had to withdraw lots of heat treated factor VIII which had been unscreened for antibody (NATIONAL HEMOPHILIA FOUNDATION 1986). Furthermore, the late withdrawal of product elsewhere in the world was later implicated in sero-conversions in Canada which are presently the subject of legal action (INWOOD 1989).

It is possible that the initial, presumptive safety of products following viral inactivation was more because of the introduction of individual donor testing and therefore the exclusion of HIV positive donors, than through the viral inactivation steps themselves.

On 17th February, 1986 I wrote to all my colleagues in the United Kingdom and

sent them an unedited copy of the paper I had given at the Conference. The purpose of this was to keep them as up to date as I could on the controversy as to whether heat treatment was as effective in removing viral contamination from factor VIII and IX concentrates as had been suggested (JONES 1986D).

Thereafter my time has been devoted to the follow-up and treatment of the Newcastle patient cohort, including those infected with HIV, their families, and where appropriate their sexual partners. All patients have continued to attend for follow-up and no patient has refused to be treated by me as a result of their iatrogenic infection. After the initial spell during which we felt we had to allow our patients to be nursed in the Infectious Diseases Ward at Newcastle General Hospital, Dr. Hamilton and I made the decision that we were sufficiently experienced in dealing with opportunistic infections and malignancies to revert to all in-patient therapy being carried out at the RVI. I continue to be involved in clinical research, both with regard to the management of haemophilia and to the management of AIDS and its related diseases. The Centre is participating in the Medical Research Council Concorde I Trial of Zidovudine, and an application is before the Ethical Committee for participation in a second MRC trial into the compassionate use of Dideoxyinosine (ddI).

I remain one of the four DHSS appointed Trustees for the Macfarlane Trust,

which was established two years ago to administer ex gratia payments by government to HIV infected haemophiliacs and their families.

I have read the amended Statement of Claim and the Health Authority Defence and will comment on both in more detail in the future. At present it would appear that my views differ from those expressed in the Health Authority Defence in only two aspects. Firstly, with regard to the government failure to implement changes in the blood transfusion service for the use of volunteer donor plasma in the 1970s and secondly, with regard to the implementation of HIV antibody testing in 1985. If the question of self-sufficiency becomes an issue in court then I believe that the consensus view of witnesses from the Haemophilia Centres will be in accord with my own.

The following is a broader summary of the main points in my evidence.

SUMMARY

1. AIDS was a new and entirely unexpected disease.

2. Its link with blood transfusion only became established in late 1982.

3. Testing for infection only became possible in late 1984.

4. Methods of viral inactivation on a large scale were not possible until after the infection of most, if not all, of the haemophilic population exposed.

5. Heat treated materials were not available in the United Kingdom prior to late 1984.

6. If heat treatment had been explored thoroughly in the late 1970s there is a possibility that it would have been discontinued or at least radically modified because we now know that it does not prevent the transmission of all hepatitis B or other infections.

7. Individual donor testing probably had as much to do with the safety of blood products developed as a result of HIV infection as viral inactivation steps.

8. There was no alternative but to continue to treat the underlying bleeding disorder.

9. There was a need to assess each individual patient on his or her own merits. All recommendations for use of particular blood products between 1982 and the present day are made on this basis.

10. No human blood product can be guaranteed to be completely safe.

11. The British Government were at fault by holding back the development of a national Blood Transfusion Service and the central procurement and processing of volunteer donor plasma in the 1970s, despite assurances to the contrary.

12. Although the evidence will show that the chances of multi-transfused patients becoming infected with hepatitis are the same for volunteer and paid donor plasma products, all the evidence is that there would have been less likelihood of patients receiving volunteer donor products becoming infected with HIV before individual donor testing and viral inactivation procedures got under way.

13. There is evidence that the procedures for licensing plasma products in the late 1970s and early 1980s were inadequate and there is some evidence that plasma products from questionable sources were imported to this country without the knowledge of the authorities.

Notes on the Rome meeting "Factor VIII concentrates and the treatment of haemophilia. State of the Art in 1990" (18/19 January)

Dr. Lou Aledort (New York) stressed the universally accepted statement "no human blood product can be guaranteed to be completely safe". This statement headed one of the main debates of the meeting. The other debate concerned the question of whether or not we should be using high purity rather than intermediate purity products. In general the high purity products require more exposure to foreign proteins, and therefore antigens, than the low purity products and there is an argument that future epidemiology will show that these additives are harmful and capable of producing long-term side effects. High purity products are both more expensive than intermediate purity products and, because the loss of yield is greater, they require more donations per batch. Therefore, if viral inactivation steps do not work there is more likelihood of infection.

John Cash (Scotland) spoke about his fears about the use of solvents and detergents in the manufacture of most products now in use in Europe, and of his concern about the exposure to animal proteins, particularly murine antigens, in the manufacture of the monoclonal products and indeed in the present products produced by recombinant DNA technology. He questioned the scientific evidence that purity mattered and stressed that if physicians wanted an increase in purity it had to fit the pattern of both availability and safety "do not introduce new things to patients until you are sure".

Dr. Kernoff from the Royal Free Hospital in London stressed that he would only now use licensed products because he was not willing to become involved in

further problems of litigation! In prescribing unlicensed products each doctor was taking an individual choice which he would have to defend if anything went wrong. The only licensed products available in the United Kingdom were commercial, Monoclate P (which had just received its licence); Humate P (the Behringwerke product which remains in too short supply to prescribe); Alpha Profilate; Cutter Koate HT and the Speywood porcine product. NHS 8Y was still not licensed but hid behind Crown immunity. None of the other products being discussed at the Conference were licensed in the United Kingdom. He pointed out that in terms of cost one should not simply look at the cost per international unit of factor VIII or IX but at the specific activity in terms of international units per mg (a higher specific activity probably - but debatably - being better for treatment purposes.

The example he gave was a comparison between 8Y and Monoclate. 8Y has a specific activity of between 2 and 5 international units per mg, whilst Monoclate has 10 times these values at 20 - 50 international units per mg, yet in terms of pricing 8Y costs the equivalent of 40 US cents per international unit and Monoclate twice (rather than 10 times) as much at 72 cents per international unit.

There was a suggestion that CD4 cell counts were more stable with increasing purity concentrates (although the consensus of opinion was against the use of high purity concentrates for HIV positive patients, on the assumption that their immune systems would be less challenged by the massive antigenic components of intermediate purity concentrates. Evidence produced by Drs. Brettler and Levine from Worcester, Massachusetts when they followed patients on Monoclate, was too scanty.

Against the use of intermediate purity concentrates was Dr. Harold Roberts who prefaced his remarks by saying that haemophiliacs needed only factor VIII or factor IX. He suggested that the use of intermediate purity products and the continuation of on demand rather than prophylactic therapy was the equivalent of "striving for mediocrity" and said that both HIV positive and HIV negative patients should receive the same treatment and this should be of the highest quality "in case there is a cure".

He suggested that recombinant DNA technology, not human plasma, was the future for factor VIII production, especially in developing countries and said that not to follow this route revealed "poverty in the mind". (Incidentally, during his talk he referred to the use of plasma collected in Africa). Dr. Roberts had been an exponent in 1979 for heated concentrates but had found it very difficult to sell this, especially because the Centers for Disease Control thought that the cause of AIDS was unlikely to be a virus until at least 1983. The recombinant product which was, of course, preferable to heated concentrates of human origin could not be used until March 1987, following the rapid development from the discovery of the factor VIII gene through to expression of recombinant product by Chinese hamster ovarian cells. The phase I study of the Hyland product had started in Dr. Roberts' unit in Chapel Hill with two patients in 1987 and a phase II trial was now under way, having recruited 54 severely affected patients (40 of whom were HIV positive).

Dr. Brettler in her argument for using high purity concentrates for HIV positive patients, said that factor VIII concentrates had been shown to have a "mild" effect on the immune system. Four parameters showed change:

1. CD8 counts tended to rise.

2. The CD4 and CD8 ratio tended to fall.

3. Lymphocyte mitogen responses tended to fall.

4. The CD4 count tended to fall.

It is also pertinent to any discussion on safety that both the recombinant products and the monoclonal products are reconstituted in human albumin. Albumin has always been pasteurised and the epidemiology suggests that it is extremely safe, but the same arguments could be used for this product as for the factor VIII and IX concentrates, espcially in view of the fact that long-term follow-up after the use of albumin is unlikely and anyway rates of exposure are extremely small (the most common use of albumin is to correct low blood volume in cases of shock).

Dr. Aledort reported that because of the difficulty in knowing whether anti-viral measures work there had been a trend to apply more than one method to the concentrates. For instance, chromatography (whether by hydrophobic interaction, the use of polyelectrolytes or the use of affinity chromatography) had shown that viral removal was not complete. So another step had had to be added to manufacture. Depending on the product the second step was either partitioning in the case of gammaglobulins, ultra-filtration (which had been thought to be only of use for cells but was now possible for viruses without clogging up the cellulose layers of the filters) or physical, including the use of heat and solvents. Other physical methods which had been explored were the use of ionising radiation from a cobalt 60 source, or UV light. Biochemical and chemical methods included immune neutralisation, the

use of ethanol, the use of solvent detergent techniques and the use of beta propiolactone or other chemicals. A recent development had been the use of light pulses - a spin-off from the "star wars" programme in the United States. It relied on photosensitivity and an interaction between UV light and various drugs or dyes (cf psoriasis treatment). To date it had been shown that pulsed light of low intensity might be capable of clearing virus from cellular blood products. Lastly, there was the possibility of removing viruses by monoclonal antibodies.

There were potential difficulties with all these methods and there may be other viruses which have to be removed from products as well as the murine virus from mouse antibodies used in the preparation of monoclonal products. Dr. Aledort cited hanta virus, lymphocytic chorio-meningitic virus, reo virus type 3 and sendai virus. He also reminded the audience that stabilisers added to products during manufacture to stabilise factor VIII protein to heat or other methods were also capable of stabilising viruses.

Dr. Mannucci gave a list of products now available on the market (appended) and reported on the number of sero-conversions that had occurred since viral inactivation methods had been introduced. Of 125 reports of sero-conversion worldwide 22 met the strict criteria of the Centres for Disease Control. Of these 5 were the result of the use of a concentrate heated at 60° for 30 hours (this would have been Armour). 10 implicated this product but the product had not been used exclusively, and 7 implicated other products. Of the 7 one patient had sero-converted after a product heated at 60° for 24 hours, one patient after exposure to blood product heated at 60° for 72 hours, one patient after Alpha Profilate which had been heated at 60° for 20 hours with the addition of heptane, and one patient after another Alpha product heated at

68° for 72 hours with heptane. The remaining three patients of the 7 had received 3 or more products.

In the prospective study which had started in November 1985 by CDC (Dr. Dale Lawrence) 1489 HIV negative patients, using over 100 million units, had been followed without sero-conversion. In 1989 these figures had suggested that there was a chance of sero-conversion of less than one case per 4000 treated patients per year of therapy with presently available concentrates.

However, post-transfusion hepatitis was still occurring. To date 181 patients had been studied prospectively in a previously untreated patient study fulfilling the criteria of the International Committee on Thrombosis and Haemostasis. Nine patients of the 181 had developed post transfusion hepatitis, giving an attack rate of 5%. Hepatitis had been reported in a range of products, including Behring, New York Blood, British BPL, Bio-Transfusion, Hyland Monoclate, Armour Monoclate, Immuno Hot Steam and AIMA (solvent detergent). Alpha heat and heptane products had transmitted to 5 cases and Immuno hot steam (made in Italy) to 4 cases. The discovery of hepatitis C and the development of the antibody test should help to reduce post transfusion hepatitis but there had been a suggestion that there was also a non B non C virus without a fatty envelope and which could therefore be resistant to solvent detergent. One of the difficulties in applying the hepatitis C test would be in the prolonged interval between hepatitis C infection and the appearance of the antibody which on average was 22 weeks (range 10 - 39 weeks). There is an analogy here with HIV infection. Answering the question of why heat treated material had not been made generally available in 1979, Professor Mannucci stressed that although it seemed easy to say this in retrospect, at the time there was not sufficient

evidence for manufacturers to apply heat generally and that heating had been considered to be potentially dangerous. (In any case prior to HIV infection heat would have been shown not to be completely effective in preventing hepatitis transmission and might therefore easily have been abandoned in favour of other methods). "There is no progress without mistakes".

Finally, the application of polymerase chain reaction (PCR) testing was mentioned briefly, only to say that the state of the art was as yet imprecise and that positive results may simply be picking up parts of the virus which were non-infective. The technology was "not yet established". Having said that there was one anecdotal report that a fourth generation monoclonal product had been found to be PCR positive.

IN CONFIDENCE

ADDENDUM TO DRAFT OF PERSONAL RECORD

EUROBLOOD

On my visit to New York of May 1985 I met with Dr. Pindyck, the Vice President of the New York Blood Center (310 East 67th Street, New York 10021). Dr. Pindyck was the Vice President of the Center and had responsibility for the Euroblood programme. This was started in 1973 with the object of importing red cell concentrates from Swiss, German and Belgian Red Cross because of the shortage of red cells for medical and surgical programmes in New York city, which does not have enough volunteer donors and has to support nine medical schools. One of the leading European members of Euroblood was Professor Hassig. The Euroblood programme is referred to on p 142-143 of Hagen's book, "Blood: Gift or Merchandise". He cites an import of 200,000 units of red cells per year, accounting for one third of the New York metropolitan area red cell supply.

The New York Center is a non-profit blood bank with a distinguished Board of Directors, including doctors concerned with haemophilia care, in particular Dr. Margaret Hilgartner, and the importation of red cells perfectly legal and under FDA inspection. However, there is verbal evidence that Professor Hassig has a foot in both camps supplying red cells to New York and plasma for commercial fractionation via the Lessine plant of Baxter Travenol.

I have added this addendum to show that the supply of blood products is more complex than the commercial factor VIII market with predominant supply from the United States to other countries. If necessary I can obtain further information from the New York Blood Center on the Euroblood programme.

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