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Dear Colleague

AIDS and haemophilia

Please find enclosed an unedited copy of the paper given at the Conference in Newcastle last week. In sending this to you I apologise for any distress caused by the suggestion that heat treatment may not always be effective. I have passed the information I have to the Department and to the Committee on the Safety of Medicines, where expert authority can decide whether any action should be taken.

I thought a great deal about whether such soft data should be presented at the Conference. My view was that because of the paucity of sero-negative cases on a variety of heat-treated materials and the time lag involved, that we could not afford to wait until sufficient "scientific" evidence was available. My decision to include the four cases in the paper was based on this view, on the strength of the personal reports I had received from reliable doctors, and on evidence that I was given in California that live virus had been found in concentrates dry-heated for short periods. The argument had been put to me that, because of the extremely low incidence of sero-positivity in blood donors tested in this country, together with heat treatment, that there is no longer any threat to haemophiliacs. I do not think this is true and felt the warning justified.

I am afraid that since I gave the paper yet another case of probable lymphoma and AIDS has presented in one of our young patients. In view of this further development I have today asked for the help of the PHLS/CDSC. I have taken this step in order to try and establish why we appear to be so vulnerable compared to the rest of the country, in the hope that the answer could prevent further cases both here and abroad in the future.

Because of the work which will be required to help this investigation, in addition to the editing of the Conference proceedings, I have decided that it would be best if I relinquished my chairmanship of the committee looking at the reorganisation of haemophilia centres, and am sending the relevant papers to Dr Forbes.

Yours sincerely

GRO-C

PETER JONES
Director

19 FEB 1986

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In 1974, in a book for the families of my patients, I wrote about the pleasures and pains of living with haemophilia. To the uninitiated the choice of the word 'pleasures' may have seemed strange then. With the advent of AIDS it probably seems even stranger now. Yet haemophilia still carries with it many of the attributes most highly prized by mankind. Among them are courage, gentleness and determination, three qualities that help people face and overcome an ever-present threat of disablement and death.

Haemophilia is an inherited disorder in which one of the clotting ingredients is either deficient or absent from the blood. In classical haemophilia or haemophilia A this ingredient is called factor VIII. In haemophilia B or Christmas disease, named after the first patient described, factor IX is affected. The severity of these two forms of haemophilia is variable, so whilst within the United Kingdom there are some 5000 people with haemophilia, only 2000 have the condition in its severest form.

Both factor VIII and factor IX are normally produced in the liver through genetic instructions inherited from the parents. Because these instructions are found on the X chromosome females (with two X chromosomes and therefore duplicate sets) do not suffer from haemophilia. It is a disorder of males.

People with haemophilia bleed no faster than anybody else; the hallmark of their disorder is prolonged oozing, often from trivial injury. The great majority of bleeds, which may occur several times a week especially in childhood, are internal into joints and muscles and the result is a very painful and crippling arthritis. Contrary to popular belief haemophiliacs do not bleed uncontrollably from scratches, small cuts or pin-pricks; the body's protective mechanisms for these insults are intact. Nor do they

bleed externally any more than other people, nose bleeds or blood in the urine being the most usual manifestations. These observations are of fundamental importance when we come to look at risk from spread of a blood borne disease. The chances of contamination of the environment and therefore from other people or someone with haemophilia are negligible.

Haemophilia has recently been cured but only by liver transplant, not a procedure to be undertaken lightly. There is however considerable hope for more appropriate cures, perhaps with easier transplant techniques or with genetic manipulation. However, these are goals for the future. At present haemophilia may be treated very simply and very effectively. All that is required is the replacement of the missing factor either when a bleed is occurring or in anticipation of bleeding, the practice of prophylaxis. Recurrent treatment is necessary because the life of the clotting factor in the blood stream, and therefore its usefulness, is finite. About half the activity disappears within 12 hours and this loss is speeded up during bleeding.

Thirty years ago the only treatment available to most patients was freshly donated blood or plasma, or fresh frozen plasma, but in 1964 a way of concentrating the factor VIII in human blood was discovered near San Francisco, and the resulting product, cryoprecipitate, revolutionised the lives of people with haemophilia. Because cryoprecipitate is a small volume product it can easily be given on an out-patient basis and its introduction freed people from the need to be admitted to hospital for most of their treatment. In the 1950's and 60's small quantities of even more potent, concentrated blood products were available. They had been developed in Oxford and Scandinavia, and indeed in 1955 a factor VIII concentrate made from pigs

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was developed. Unfortunately this product has so far not proved to be effective for a long period of time, although it is of great value in the treatment of some of the complications of haemophilia. In this country, as a result of a government decision to allow importation of human blood products for the first time in 1973, freeze dried (or lyophilised) concentrate became readily available, the products coming principally from manufacturers in the United States. Within the last two years the genetic structures of both factor VIII and factor IX have been discovered, and there is hope that within the next five years genetically engineered or recombinant DNA factor VIII and IX concentrates will be available to the haemophilic population. Until they are the health and life of this population is still dependant entirely on the donation of human plasma. Without the help of donors haemophiliacs are lost. It is vital to them, and of course to countless others, that healthy donors continue to come forward from the community. Donors must be continually reassured, beyond question, that there is no risk of contracting any disease, let alone AIDS, by donating their blood or plasma.

In order to make clotting factor concentrate up to 30,000 donations of plasma might be used. The more refined the product the greater the loss of biological activity occurring during manufacture and thus the more source material needed and the greater the likelihood of viral contamination. The commonest complication of this massive exposure is viral hepatitis, and abnormal liver function tests, and cases of cirrhosis, are seen in every haemophilic population studied. However, when in July 1982 the Centers for Disease Control reported unusual opportunistic infections in three men with haemophilia, the possibility of a viral aetiology was thought less likely than an immune response to the constant barrage of

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extraneous denatured protein involved in treatment. However in December 1982 the first case that linked AIDS and blood transfusion directly was reported and this, together with further reports of AIDS in haemophiliacs, proved without doubt that the disease appearing in haemophilia was essentially the same as that affecting the other risk groups.

Recently the United Kingdom Haemophilia Centre Directors have tested a substantial proportion of the haemophilic population of the UK. Their results show that overall 44% of the people with haemophilia A are anti-HTLV III Positive. This figure rises to 59% in the severely affected population. The percentage of infected people remains low in those with haemophilia B, or von Willebrand's disease, another, unusually mild, bleeding disorder. In these disorders the percentage affected lies between 5-6%.

In this country it is usual to treat small children with cryoprecipitate collected from volunteer donors in the National Blood Transfusion Service. As families learn when and how to treat bleeds freeze dried concentrates are introduced so that children can be put onto home therapy and not have to come to hospital. This practice is reflected in the Table. The anti-HTLV III status of the children examined by the Haemophilia Centre Directors is low in children below the age of five (12%) and then rises through 35% for the 5-9 year old group to a peak of 68% in those entering their teens.

The reason for this increase is apparent in the next table. Only 1% of the anti-HTLV III positive people examined by the Directors had received only cryoprecipitate. 10% had received only National Health Service concentrate, indicating that before individual donor testing the AIDS related virus was a contaminant of our volunteer blood donation system.

Sixty per cent of the factor VIII used within the United Kingdom is imported from the United States, and the evidence that this was the principal vehicle for the transmission of AIDS to our haemophilic population is overwhelming.

We still do not know with precision what the future holds for our antibody positive haemophiliacs. Present figures suggest that the chances of developing overt AIDS lie between 1% and 5%. To date 135 cases have been reported to CDC and 11 to CDSC in this country. Although no child in the United Kingdom has developed AIDS we will undoubtedly see this happen in the near future. Within this region in our population of 143 multi-transfused patients we have reported 3 cases fulfilling the CDC definition of AIDS. In retrospect and with HTLV III testing a further 2 haemophilic men have died with AIDS. We now have to report a further 2 cases, diagnosed within the past month.

To date the majority of haemophiliacs who have developed AIDS have contracted and died from opportunistic infections. These latest cases, however, have lymphomas, one of the lower jaw, and one of the gastro-intestinal tract.

So we are now seeing malignancy in the haemophilic as well as the other risk groups. In addition my colleague Dr Dietrich in Los Angeles tells me that 3 cases of Kaposi's sarcoma are now known in haemophiliacs without other risk factors in the United States - one of the liver, one of the gastro-intestinal tract and one presenting as a small skin lesion in the axilla.

Although the average incubation period from infection to development of the full-blown syndrome is generally accepted as about 29 months recent

evidence from blood transfusion cases in the States suggests that it may be longer. For these cases the 'best guess' is presently four years with a long tail-off during which activation of the disease by unknown co-factors may occur. Given that a cohort of 15 of our patients have proved to be negative for HTLV III antibody on blood samples stored down in 1982, and have subsequently sero-converted to positive, we are, at best, at peak prevalence only now.

If we take a 60% prevalence rate from the Haemophilia Centre Directors survey we can expect around 5000 severely affected haemophiliacs in the United States and 1200 in the United Kingdom to be anti-HTLV III positive. These people cannot stop treating their haemophilia, because the major cause of morbidity and mortality remains bleeding and its complications. In the United States the appearance of AIDS did initially cause a fall of around

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20% in the amount of factor VIII and factor IX concentrate used, and a similar phenomenon is now occurring in this country. However, in the United States the usage has now returned to previous levels. In part this is due to confidence in the sensitivity of testing of individual blood donations for anti-HTLV III and the exclusion of donors in the high risk groups, and in part to the introduction of concentrates which have been subjected to heat during manufacture. It has been known for many years that heating destroys viruses in blood products and indeed albumin, which is pasteurised and which is used principally for the treatment of shock and burns, transmits neither hepatitis nor AIDS. Heating was not applied to the factor concentrates before 1984 because it results in a further loss of activity and therefore the need for more plasma and more donors, with a subsequent increase in both exposure to extraneous material and cost.

Laboratory experiments show that the AIDS related virus does not like heat and is readily destroyed. Most manufacturers now use heat during the preparation of the concentrates, although chemical methods of viral inactivation are also being studied. Whatever method is used complete AIDS inactivation cannot yet be guaranteed, hence the enormous importance of discouraging people in high risk groups from donating and continuing to check individual donations by the most sensitive test available. Only time and careful follow-up will tell us how effective introduction of the more expensive heat treated materials have been. To date I know of four possible break-throughs. Three are known to CDC and have been described to me by Dr Peter Levine as being probable sero-conversion to anti-HTLV III positivity in one case and possible sero-conversion in two others. The fourth case is about to be reported by Dr Brederweld from the Netherlands

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and is perhaps the most convincing. This patient is known to be in no other risk group, and was sero-negative when started on heat treated material, becoming positive after almost a year's treatment. This takes him well past the known incubation period between infection and sero-conversion.

Given that haemophilia has to be treated the alternatives now available lie between a reliance on heat treated concentrate perhaps with adjustments in terms of type and length of heating, and tested cryoprecipitate for haemophilia A, or fresh frozen plasma for minor bleeds in haemophilia B. In the case of mildly or moderately affected patients with haemophilia A or those with von Willebrand's disease the alternative to blood product is DDAVP, or Desmopressin, which carries no risk whatsoever from either hepatitis or AIDS, but is useless in severe haemophilia.

The impact of AIDS on the haemophilic population is enormous. Within the past 20 years people with haemophilia have learnt to lead almost normal lives. They hold down normal jobs, go to normal schools, follow normal careers and participate in most sporting activities. Families have been assured of the normal growth and development of their affected children and the children have grown and thrived in healthy competition with their non-haemophilic peers.

AIDS has changed all that. Haemophiliacs now demand a response from the medical and para-medical professions like that forthcoming 20 years ago when concentrates first became generally available. They need formal medical, dental, nursing and social care of the highest quality. They need facilities for repeated and confidential counselling. They require information

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and advice about topics as diverse as prognosis, heterosexual spread, their relationship with other risk groups and the increasing claims of alternative medicine. And in helping them their carers also need help. Our nurses and social workers and physiotherapists and laboratory workers must be protected as they mourn the loss of patients well known to them for years.

At present the most important and positive help we can give is to emphasise that AIDS is not spread by casual contact. People caring for those with haemophilia, whether it be in the hospital, in the home, in the school, in the place of work, in the swimming pool, on the sports field or on holiday, have nothing to fear. In the many studies made of casual medical, household, and environmental contact there have been no cases of transmission. To emphasise this we have tested 79 hospital staff, most of them working every day with blood and many of them working with overt AIDS, and all are anti-HTLV III negative.

This and other incontraventible scientific evidence has allowed the health and education authorities in both the United States and this country to issue guidelines about the schooling of infected children. The draft document recently referred for discussion in the United Kingdom by the DHSS and DES is particularly welcome because it addresses itself both to the privacy and integrity of the individual child and his or her family, and to all the vagaries of a boisterous and healthy school life where parents and teachers may have questions of concern. It is worth quoting parts of these documents, because upon them depends in part the future of the 500 or so haemophilic children likely to be anti-HTLV III positive in the United Kingdom, as well as their peers born to mothers infected for other reasons.

"Infected children should be allowed to attend school freely and be treated in the same way as other pupils". (UK)

"These children should be allowed to attend school and after-school day-care and to be placed in a foster home in an unrestricted setting". (USA)

"Persons involved in the care and education of infected children should respect the child's right to privacy, including maintaining confidential records". (USA)

"The basis of any teaching (about AIDS) offered should be the presentation of straightforward, factual information about the virus and about modes of transmission of infection in order to balance the incomplete and inaccurate impression which pupils may have gained from other sources". (UK)

It cannot be pretended that the question of confidentiality is always an easy one. School and clinic doctors need to know the antibody status of children because live vaccines, including polio and BCG may be dangerous to them and are contra-indicated, and those children with symptoms of immunodeficiency are at especial risk from contact with the common infectious fevers of childhood, including measles.

One of the most distasteful aspects of the work of those of us working with people at risk is having to counsel that there is a risk of transmitting the virus sexually to loved ones. In the context of haemophilia this usually means heterosexual spread. In our cohort of patients reported in the British Medical Journal in September, we noted that three female sexual partners of haemophiliacs were also anti-HTLV III positive. The table shows that these three women were the partners of three sero-positive men. We have also tested a further 33 sexual partners who have proved to be negative although the males are positive. Nine partners of sero-

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negative males have also proved to be negative. Detailed investigation has shown no risk factors other than normal vaginal intercourse in two of the three positive cases, all of whom have voluntarily allowed repeated testing. One of the cases fulfils the CDC criteria for AIDS and has pneumocystis carinii pneumonia. She had previously received blood transfusions and until we have cleared all the donors we cannot be certain of a sexual cause for her infection. Another lady has delivered a child who is also sero-positive, demonstrating both the horizontal and vertical transmission of the virus. These figures, although small, are in keeping with other studies outwith Africa which suggest that there is a 10% risk of heterosexual transmission. Because of them we have no option but to advise those at risk that sexual intercourse be protected by sheath together with a lubricant. Until we both know more about the disease and have a vaccine for their partners those at risk have to think carefully about having children. Such advice obviously has a very sad and profound effect, which depends in part on the age of the patient. I am particularly concerned about our youngsters and their psycho-sexual development during adolescence, both because of the bleak future of so called "safe", but not perhaps so enjoyable, sex and because of the knowledge that at present both marriage and parenthood might be at stake because of the result of a laboratory test. Not unexpectedly our advice will not always be heeded, indeed it would be inhuman if it was. It is of great importance that we ensure that people who decide not to heed it are not made to feel wrong or guilty by their decision; censure will only add another burden to their disrupted lives.

Distortions that may occur in psycho-sexual development may be echoed in distorted body image in these patients. Certainly in the days before

there was effective treatment for haemophilia severely affected patients frequently grew to regard themselves as handicapped, and in some cases adopted a sick role, becoming chronic invalids. Once again the haemophiliac is in danger of falling prey to the many facets of a single disease. He has been referred to as "the innocent victim", a term I do not personally like because the adjective 'innocent' implies that somebody else is guilty, and I cannot condone differentiation by sexuality any more than I can differentiation by race, or class, or colour, or creed. However, there are major differences between the perception of AIDS in the haemophilic and the ~~homosexual~~ gay population. The haemophiliac has to have a diagnostic label in order to receive treatment should he be injured or need surgery. Because of this need for treatment coupled with the need to ensure the safety of staff dealing with blood and body fluids the haemophiliac's anti-HTLV III status must be known. The ~~homosexual's~~ gays decisions to be known as gay and/or to have the test is optional, unless of course he elects to try to donate blood. Because both patient and doctors know the result of the haemophiliac's test so will insurance companies, and people with a positive test now find that decisions about insurance are postponed; in other words their chances of obtaining life insurance or mortgage endowment have been lost. A haemophiliac's sexual partner will in most cases know that he has haemophilia and will therefore also know the results of the test. Indeed there is a medical reason for the partner to know. Although this reason is ~~even more~~ as necessary in the ~~homosexual~~ gay population the decision to tell remains purely voluntary. Children with haemophilia are affected and the attitudes of those who work in schools and places of employment may also be affected, and the public now acquaint the diagnosis of haemophilia with the diagnosis of AIDS. The final vestige of confidentiality, and because of an insensitive response by the media, the privacy and dignity of affected haemophilic

families is stripped away shortly after death by the decision of the Coroners Society to submit all cases to public inquest. Whilst I cannot, especially as the prescribing doctor, argue against the fact that death from AIDS contracted via haemophilia treatment is misadventure, I do question the concurrent need for personal publicity. Because they are identified so readily those with haemophilia already perceive themselves as guineapigs for the study of the epidemiology and treatment of AIDS. We must try to find some way both to protect them and their families and to compensate them for our failure as a society to deliver safe therapeutic material. Watching the advent and unfolding of AIDS in the haemophilic population is like watching a slow Aberfan - the engulfing of a generation because we, as a country, did not act in time.