Most up to date version —
actually sent to GMC.

15/4

Department of Clinical & Laboratory Haematology
Royal Infirmary of Edinburgh
Laboratories 2nd Floor
Little France Crescent
Edinburgh
EH16 4SA

Consultants
Professor C A Ludlam
Direct No: GRO-C
E-mail:
Christopher.Ludlam@GRO-C

Dr E H Horn
Direct No: GRO-C

Clinical Manager
Mr Ian King
Direct No: GRO-C

Laboratory Enquiries
Tel: 0131 242 6820/21/22

Clinic Appointments
Tel: 0131 242 6816

Fax: 0131 242 6812
Consultants Office

Date: 06.04.05
Your Ref: TCB/FPD/2003/2726
Our Ref: CAL/NS

PRIVATE AND CONFIDENTIAL
Surupa Sarkar
Investigation Officer
Fitness to Practise Directorate
GMC
5th Floor
St James's Building
79 Oxford Street
Manchester
M1 6FQ

Dear Surupa Sarkar

<u>Complaint by Mr Robert Mackie</u>

I write in reponse to your letter of 9th March offering me a further opportunity to provide comments on the issues raised by Mr Mackie as it is sometime since the GMC disclosed to me the original complaint. In our telephone conversation on 14th March 2005, you indicated to me, that contrary to usual practice, the GMC wished to review aspects of Mr Mackie's complaints about events more than 5 years ago. My original reply to the complaint of 23rd December 2003 clearly indicated that my response was confined to recent events. To assist the GMC with its assessment of the complaint, I am sending some comments on the letters from Mr Mackie dated 18th November 2003 and his further letter dated 18th January 2004, which make a variety of allegations over the past 24 years. The comments on the individual allegations are in no way to be considered a full and complete response or defence. If the GMC requires further information I would be very ready to provide this where it is available.

To aid clarity I have responded to each paragraph individually.

Letter from Mr Mackie to GMC– 18th November 2003

Para 2. In this paragraph I think Mr Mackie is referring to HIV infection in Africa. The first reports of HIV infection in Sub-Saharan Africa were published in 1985 by Tedder et al (Lancet 1 359). The first report of slim disease being due to HIV was in October 1985 (Lancet, 2, 849). I considered myself interested and well informed at this time as evidenced by my attendance at the First African Aids Conference in Brussels in 1985 because of my interest in what was being discovered in Africa. Mr Mackie may, therefore, be mistaken in recalling a conversation that he alleged with me in 1981. I do not have any recollection of such a conversation.

Para 3. Mr Mackie alleges that in 1982 that "the medical profession all over the world knew that AIDS was spread to haemophiliacs through contaminated blood". I would suggest that this is an inaccurate assessment of the situation at that time. It was in July 1982 that the first 3 haemophiliacs with pneumocystis pneumonia were reported (MMWR, 31, 365). The first case reports of pneumocystis pneumonia (now known as AIDS) were in June 1981 amongst homosexual men in Los Angeles and New York (MMWR, 30, 250 and 305). In the case report about the haemophiliacs in July 1982 it was noted that no two patients had received the same batch of factor VIII concentrate and the immune suppression was possibly due to an agent transmissible by blood products. At the time it was estimated that there were approximately 20,000 males with haemophilia in the US and the 3 individuals in the case report therefore represented a tiny fraction of the total. Over the following 12 months it was not clear to what extent the immune abnormalities detected in many haemophiliacs in the US were due to a possible latent viral infection transmissible by factor VIII concentrate, and to what extent they were an immune reaction secondary to the infusion of factor VIII concentrates per se, which in addition to factor VIII

contained many other plasma proteins, e.g. immunoglobulins (Jones, Lancet 1983, 1, 120) (AIDS Research 1983, 1, 83) (Ann Int Med, 1983, 99, 159). By the end of 1983 there was a report of 21 cases of AIDS in haemophilia in the US and 7 elsewhere in the world (MMWR, 32, 613) and 2 cases in the UK (PHLS, CDSC). Mr Mackie is therefore incorrect in his assertion about what was known in 1982.

Mr Mackie alleges that he repeatedly asked about HTLVIII/AIDS being "spread to haemophiliacs" in 1982. I have no recollections of such requests for information at this time nor is there any relevant record in his casenotes.

Para 4. Mr Mackie refers to a meeting in "late 1984" in a lecture theatre at the Royal Infirmary, Edinburgh, to which all haemophiliacs were invited. This meeting which Mr Mackie remembers attending was convened by Professor Charles Forbes (Haemophilia Director, Glasgow Royal Infirmary) and myself. My recollection is that all haemophiliacs in Scotland were invited by us to learn more about HTLVIII (now known as HIV), AIDS and haemophilia. There was a rather low turnout of about 20 – 30 individuals and some came with partners. I explained at the meeting that some individuals with haemophilia had recently been found to be anti-HTLVIII positive. These test results had been obtained in collaboration with Professor Richard Tedder at Middlesex Hospital, London who in the autumn of 1984 had established a technique for detecting anti-HTLVIII antibodies. My recollection is that his laboratory was the first laboratory in the UK to establish the technique, which was on a research basis and still under development. What was unexpected was that patients who had been treated exclusively with factor VIII derived from Scottish blood donors had become anti-HTLVIII positive, although there were no known cases of AIDS in Scotland (and therefore blood donors) at this time (see below). At the beginning of 1985 there was uncertainty about the clinical

significance of an anti-HTLVIII positive results, except that it was evidence that the individual had been exposed to the virus. It was unclear whether the individual was still infected or had cleared the virus (as is common for most viral infections). In early 1985 only a relatively small number of haemophiliacs worldwide had developed AIDS and therefore an anti-HTLVIII result was not necessarily indicative of a high likelihood of developing AIDS. Professor Forbes and I indicated that it would be prudent to assume that anti-HTLVIII positive individuals harboured the virus and that it might therefore be transmitted sexually. As it was unclear whether or not patients testing anti-HTLVIII negative might still harbour the virus we advised all patients to use condoms to reduce the risk of sexual spread to partners. This advice was sent to patients' GPs (for Mr Mackie, Dr Love) and an information sheet was sent to each patient irrespective of their anti-HTLVIII test result (Appendix 1 and 2). You will see that in both these we recommended use of condoms. Mr Mackie was therefore given in January 1985 the most up-to-date information about the then current knowledge about HTLVIII and the possible implications of having a positive antibody result.
Mr Mackie is correct in recalling that at the meeting I and Professor Forbes asked that all those who wished to talk about their own circumstances further, and/or to learn the result of the anti-HTLVIII test, should telephone their Haemophilia Centre to make an appointment. During the succeeding months patients requested a consultation and I personally met with all those who wished to know more.

At the open meeting for patients we did our best to answer all questions as openly and honestly as we could, given the limited knowledge at the time. I deny the allegation that I told a colleague "just to ignore him (Mr Mackie), he is a troublemaker".

Para 5. After the open meeting for patients in January 1985 Mr Mackie did not request a consultation with me. My recollection is that I invited

him some considerable time later to come and see me for a consultation, because he had not been to enquire of his anti-HTLVIII status. I think this may have been during the period in 1987 – 88. I did so at this time because he had not been to enquire about his anti HTLVIII status (see Para 7 below). His statement in this paragraph is incorrect.

Para 6. Mr Mackie reports that a blood sample was requested from Mrs Mackie in 1985/6 and that she was uncertain of the purpose despite apparently being told it was for genetic purposes. I think it extremely likely that we would have told her why we were seeking a blood sample. As evidence of our open policy with patients I even wrote to her in 1986 seeking her consent to use this blood sample for some research we were undertaking in hepatitis. You see that she signed the letter to give her consent (Appendix 3). A further blood sample was taken in 1989 when she had requested an anti HIV test and I wrote with the result (Appendix 4).

Para 7. Mr Mackie refers to the consultation I asked him to attend. (see para 5 above). I remember Mr Mackie was accompanied by his wife, but I was keen to have a private conversation with Mr Mackie, because I wished to discuss whether or not he would wish to know his HTLVIII status. I had a duty of confidentiality towards Mr Mackie and I could not presume that he would want his wife to necessarily know of his antibody positive status and therefore I asked him to consider how he would like our consultation to proceed. My recollection is that I did leave the room for a few minutes to allow Mr and Mrs Mackie to consider the situation in private. As Mr Mackie was adamant that his wife should continue to be present, the consultation proceeded and it emerged that he wished to know his anti-HTLVIII result. Part of my responsibility in the consultation was to ascertain whether he may have had other risk factors for HIV infection or might potentially pass it to other individuals.

In 1987/1989 I think it unlikely I would have assessed the risk of him dying of AIDS as being similar to my dying of a heart attack, as it was becoming clear by 1987 that individuals who were anti-HTLVIII positive were developing AIDS.

Para 8/9. In the letter from Dr Devlin, on my behalf, of 30th January 2004 he provided evidence from Mr Mackie's case notes that not only had Mr Mackie been told of his hepatitis C status in 1993, but that he was also seen by the hepatologist Professor Peter Hayes. In addition further investigations were arranged which were cancelled by Mrs Mackie and he failed to attend a follow up appointment (Appendix 7).

Para 11. I note Mr Mackie alleges that it took 87 days for him to receive a copy of his medical notes. This does seem longer than it should have taken, but there are 6 thick volumes of casenotes and all the individual reports etc had to be photocopied and the complete records had to be scrutinised to ensure there was no evidence about third parties in the records

Para 12. Mr Mackie states that a full "AIDS Study" was carried out in March/April 1983. The background to this research project was to investigate the immune status of haemophiliacs in Edinburgh who had been treated exclusively with factor VIII concentrate prepared from Scottish blood donors. The reason for undertaking this project was that immune abnormalities had been reported in many haemophiliacs without AIDS in the United States. These might have been due to either a putative virus for AIDS, or a secondary immune "reaction" to the infusion of proteins in the factor VIII concentrates, or to another viral infection or hepatitis. As there were no known cases of AIDS in Scotland in 1983 I hypothesised that the chance of local haemophiliacs being infected by a putative AIDS virus was small. Subsequent studies when anti-HTLVIII testing

became available proved that most patients were not infected until 1984. Our study demonstrated similar immune abnormalities in Edinburgh patients to those in US patients and this was therefore evidence that the immune changes in the North American patients may have been due to the clotting factor concentrates per se, and that they were not necessarily solely due to infection with a putative virus (Carr, Lancet, 1, 1431).

The above research project was part of a more extensive research programme into infections transmitted by clotting factor concentrate. For example I had published a study, with colleagues on hepatitis B infection in haemophiliacs (Stirling et al J Clin Path, 1983, 36, 577). The "AIDS Study" referred to above used serum samples for measurement of total immunoglobulin levels, $\beta 2$ microglobulin and samples were also assessed for CD4 and CD8 lymphocyte counts. At this time in 1983 there was no blood test to detect the putative virus of AIDS and therefore no such investigation could be undertaken.

Mr Mackie seroconverted to HIV between March and August 1984, almost certainly from a batch of Scottish National Blood Transfusion factor VIII concentrate (batch 023110090).

Mr Mackie enquires about the entry, which he considers there should be in the casenotes, in 1987 when I saw him and his wife for counselling (para 7 above). The probable reason for its absence is that at that time we were very keen to avoid having information in the patients' hospital casenotes indicating their anti-HTLVIII status and a record of what we considered to be very confidential counselling meetings. At this time there was great concern about HIV and confidentiality and about the difficulties in getting diagnostic tests and therapeutic procedures carried out on infected

patients. Records from such counselling sessions were kept brief and held in separate files. With the move from the old RIE in Edinburgh to our new hospital last year, it was our intention that all records were amalgamated into the hospital casenotes. I have searched Mr Mackie's extensive records and cannot find a record of this counselling event.

Para 13. Although Mr Mackie alleges that I knew that factor VIII carried HIV in 1982, this is incorrect, as it was not until 1984 that it became clear that AIDS was likely to be due to HTLVIII infection. A misunderstanding may have arisen because of the words 'AIDS study' on the haematology request forms, which accompanied Mr Mackie's letter of 18th November 2003. In this study we were investigating the immune function of haemophiliacs not their virological status because at this time there were no tests for HTLVIII or HIV. Details of the immune tests we carried out in 1983 are given in paragraph 12 above. Until November 1984, in patients treated with factor VIII manufactured from blood donors in Scotland, it was considered that the risk of HTLVIII infection was low.

Para 14. Patients in Edinburgh were treated in line with Haemophilia Centre Doctors Organisation (UKHCDO) guidance, which was issued in May 1983 and December 1984 (Appendix 5 and 6). Mr Mackie clearly knew he was at risk of HTLVIII infection as a result of attending the patients' meeting in December 1984, but only learnt in 1987 of his status as a result of my invitation to meet with me (see para 7 above). In January 1985 he received the patient information leaflet, which recommended that all haemophiliacs used condoms to reduce the risk of sexual transmission (Appendix 2)

Para 15. Mr Mackie enquires about "an informal Lothian Region AIDS Group". There were two AIDS groups with which I was associated.

The first was a small group of clinicians, including Genito-Urinary Medicine and Infectious Disease physicians, Virologists and Public Health Physicians who were keen to investigate possible HTLVIII infection in "at risk groups" in Edinburgh in early 1985. Anti-HTLVIII tests were only available in London initially in late 1984 (Professor Richard Tedder, see above) and we were keen to establish laboratory anti-HTLVIII testing in Edinburgh. This group pioneered HIV studies in Edinburgh, which was at the forefront of UK and international research.

The second group was the "Lothian AIDS Advisory Group" which I chaired. This was a group of concerned health care staff who met over a period of about 5 years to try to ensure that there were appropriate and safe arrangements so that patients at risk of HIV could receive appropriate investigation and treatment in hospitals in Edinburgh. This was in response to staff anxieties about their perceived risk of infection in treating these patients. This committee developed guidelines early to ensure appropriate arrangements and these were available long before any national guidelines were available.

Para 16. Mr Mackie refers to 18 haemophiliacs who contracted HIV from a batch of factor VIII concentrate. When Professor Tedder setup the initial anti-HTLVIII test in his laboratory, he generously agreed to test serum samples from some of our Edinburgh haemophiliacs who had been treated exclusively with Scottish National Blood Transfusion manufactured factor VIII concentrate, prepared from blood donors in Scotland. Our expectation was that the Edinburgh haemophiliacs would test negative (for reasons given above) and we were saddened to learn that a number tested positive. As we keep very detailed transfusion records on our patients we were readily able to identify that many of those who were anti-HTLVIII positive had received the same single batch of concentrate. So far as I recall this was a first indication that the UK blood supply had become

contaminated with HTLVIII. These data, along with other concerns, lead to an important meeting, which I attended, between UK Haemophilia Reference Centre Directors and the Blood Transfusion Service on 10th December 1984. This made recommendations about future treatment of those with haemophilia (Appendix 6). From the above you will see that it was not possible to have informed Mr Mackie before he became anti-HTLVIII positive and that he had the opportunity to learn of his status in January 1985, if he had so wished.

Para 17. Mr Mackie states that he could not find any information in his casenotes regarding being tested for AIDS or hepatitis C. In my letter to Mr Mackie dated 14th March 2003 (penultimate paragraph)(disclosed by Mr Mackie to GMC) I indicate that the HIV records were kept separate to maintain confidentiality. His HCV status is set out in records, which were in his casenotes in 1993 (letter to GMC of 23rd December 2003 refers). Mr Mackie states that I do "not have any stored serum samples before 1992"; I think Mr Mackie has misinterpreted paragraph 4 of my letter dated 14th March to him. In this I state that it is "likely that you became infected with hepatitis C early in your life, when you were initially treated with blood products. As we do not have any stored serum samples from that time we are unable to accurately estimate when you became infected". It is likely that Mr Mackie became infected in the first few years of his life.

Para 18. Mr Mackie reports a request to me about Mrs Mackie's hepatitis C status. It is unclear to what this refers, although Mr Mackie knew of his hepatitis C status in 1993 (see above).

Response to Mr Mackie's letter of 21st November 2003

Paragraphs 2-6	The questions raised in these paragraphs are similar to ones raised in Mr Mackie's letter of 18th November and have been answered above
Paragraph 7	Anti-HTLVIII testing only became available on a research basis in two laboratories in the UK during the second half of 1984 (see Appendix 6) and therefore haemophiliacs in England could not have known before this time their anti-HTLVIII status. Haemophiliacs in Scotland were some of the first to be tested in the UK and the results were available for those who wished to know them.
Paragraph 8	It was not known that factor VIII was 'infected with HIV' in 1982 nor the extent to which haemophiliacs were infected. It was therefore not possible to offer reasoned advice about sexual transmission. It was known that factor VIII could transmit hepatitis at this time. No test for hepatitis C became available until 1990 and therefore it was not possible to assess its transmissibility sexually until after this date.
Paragraph 9	I do not think it is true that SNBTS 'isolated HIV' in 1983.
Paragraph 10	Factor VIII manufactured from blood donors in Scotland was thought to have a lower risk of potentially being infected with a putative AIDS virus (subsequently reported by Melbye, (Lancet, 1984, 1444) because there were no know cases of AIDS in Scotland in 1984. No-one decided in 1984 that factor VIII was free from contamination. By this date the number of known AIDS cases amongst haemophiliacs worldwide was small and only reported from a limited number of countries.

Paragraph 11 The 'informal Lothian region AIDS group' is described above.

Paragraph 12 I have always tried to be open and honest and to give patients the available information. The difficulty we all faced in the early 1980s was that as HIV and AIDS were evolving, it was only possible to give information about this viral infection as the facts became apparent from the intensive research efforts we, and very many others, were making to try to understand, prevent and treat infection.

As further background information the GMC might find it helpful to know of some of my activities during the 1980's in relation to the safety of blood products. Over the 10 year period from 1982 I published about 30 papers in relation to hepatitis B, hepatitis C and HIV infection in haemophilia in studies funded by the MRC, Wellcome Trust and Scottish Office. My activities in this field were therefore at the forefront of knowledge internationally during this decade.

As further evidence of my commitment to blood safety I would draw your attention to my following activities:

1. During the early 1980s I worked strenuously at a national level to ensure, so far as possible that haemophiliacs in Edinburgh only received treatment in blood products manufactured from Scottish blood donors. This was in an attempt to reduce the risk of a variety of viral infections – at that time notably hepatitis viruses.
2. UKHCDO Hepatitis Working Party, Member from 1980 – this investigated hepatitis in haemophilia and complied national guidelines for its management.
3. UKHCDO Reference Centre Directors Committee, Member since 1980 (and Chairman 1996-1999) – this national committee considered in

detail issues related to blood safety and complied the guidelines issues in June 1983 and December 1984.

4. Coagulation Factor Working Party for Scotland, Chairman 1987 – to date. This committee was established by the Scottish Home and Health Department to promote good communications between Haemophilia Directors, the Scottish National Blood Transfusion Service and the Scottish Office in matters related to safety and efficacy of therapeutic clotting factor concentrates.
5. Lothian AIDS Advisory Group, Chairman from 1985
6. Expert in Haemophilia and HIV Infection to English Health Authorities in relation to HIV litigation (1989 onwards) (Mr Simon Pearl of Davies, Arnold and Cooper, London).

I hope that the above information and the accompanying appendices will help the Case Examiners to assess the allegations.

Yours sincerely

Christopher A Ludlam
Professor of Haematology and Coagulation Medicine
Director of Haemophilia & Thrombosis Centre

Appendices

1. Copy of advice sheet for adult patients and families.
2. Copy of letter to Dr Love (GP).
3. Letter of 27th January 1986 signed by Mrs Mackie.
4. Letter of 3rd March 1989 to Mrs Mackie with HIV result.
5. Copy of UKHCDO Guidance on Acquired immune deficiency syndrome, May 83.
6. Copy of UKHCDO AIDS Advisory Document, December 1984.
7. Copy of letter of 27th May from Dr Peter Hayes and copy of clinical entry in case notes.

(1)

ADVICE SHEET FOR ADULT PATIENTS AND FAMILIES

ACQUIRED IMMUNE DEFICIENCY (AIDS)

We hope you will find this fact-sheet useful and that the information in it will complement that given by your Haemophilia Centre Director. It is important that you understand a little about this very new disease and its implications for people with haemophilia. As you will appreciate, the pace of research is moving very fast and we will be in touch with you and your family as further information becomes available. If however, you have any major anxieties in the meantime please do not hesitate to phone your Centre Director for a personal appointment (Glasgow 041-552-3535 Ext. GRO-C; Edinburgh 031-229-2477 Ext. GRO-C).

1. What is AIDS?

This is a new disease, probably due to a virus which harms the immune system of the person affected. The result is that they have a reduced ability to combat infections.

2. Where did it come from?

The evidence suggests that the original virus has come from Africa (Zaire or Chad) and been transported to Haiti and then to the USA. In haemophilia, the evidence is that it has been transmitted by blood products and is now therefore present in most countries of the world. It is still however an extremely rare disorder - and has affected only 3 haemophilic patients in the U.K.

3. Who does it affect?

The majority of people affected are homosexuals or their male (and female) partners. There is clear evidence of sexual transmission in this group and the virus has been found in semen. In addition some females with many sexual partners have acquired the infection sexually. Intravenous drug abusers, haemophiliacs and blood transfusion patients are probably infected by blood borne transmission. In this way transmission of the disease resembles hepatitis B.

4. Why does immunity alter?

Our immune system, which fights infection, is extremely complex and involves certain cells and antibodies in our blood. The virus attacks one cell type (lymphocytes) which play a key role in the body's defences. Some of these cells are called helper or T_4 cells. It is likely that, at routine visits patients will have the numbers of these cells counted. It is only if there is a major destruction of these cells that immunity is significantly reduced.

5. How does AIDS affect patients?

As immunity is suppressed, the patient becomes liable to infections of all kinds especially to bacterial infections which previously were not powerful enough to penetrate the body's defences. Pneumonia is also common, but this, of course, can be treated. Fungal infection such as thrush may occur, and we normally live happily with these organisms in our bodies which only get out of control with loss of immunity. Again effective anti-fungal agents are available. Other viruses may also appear, e.g. herpes simplex ("cold sore" virus). This will spread locally as the body cannot mount its normal immune defence. Anti-viral agents are now in use and new and more effective ones are being developed.

6. What is the virus?

The virus probably responsible is called Human T-cell Lymphotropic Virus (HTLV III). Its main action is to reduce the effectiveness of a particular cell (T_4 cells) in the immune process. Exposure to the virus results in the body making an antibody (HTLV III Ab) to the virus protein and this is now used as a marker of exposure to the virus. These tests are now available and will be carried out on your routine visits to your centre. About half the patients in England and about ten per cent in Scotland have had exposure and are HTLV III Ab-positive.

7. What are the implications?

The implications of a positive HTLV-III Ab test are not known. All we can say for certain is that the positive test means that the person has been exposed to the virus proteins. It would seem reasonable now for all patients who have had concentrates, no matter from which source, to take simple measures to limit the possible spread of infection. These should include -

(a) You should make up and handle your own bottles of concentrate. Great care must be taken not to contaminate work surfaces with spilled concentrate. Care must be taken with used needles and syringes and these must be returned (in "Cinbins") for disposal in the Centre. Any spillage of material should be washed up with a solution of a household disinfectant. Hands should be washed in ordinary soap and water and garments splashed with concentrate should be washed as normal in your washing machine with a hot rinse. After use the work surface should be washed with a household disinfectant such as Milton. It is better not to use a place on which food is prepared.

(b) If anyone in the family wishes to help prepare concentrates and injections they should wear gloves and disposable plastic aprons (provided). Both these measures (a) and (b) should be used routinely.

(c) As sexual intercourse has been shown to be involved in the spread of the disease the wearing of a condom (sheath) during intercourse. You should abstain from rectal or oral sex. Also if you wish to consider having a baby you should discuss this with your haemophilia Director in advance.

(d) All relatives living in the same house with the family should refrain from giving blood. This is a simple precaution only.

(e) The problem of dental care will also have to be organised and further advice will be given about this.

It is to be EMPHASISED that these are only simple precautions for you and your family. No changes need occur in your day-to-day life with friends, neighbours, at school or at work.

8. So what is being done?!

As of now, all factor VIII concentrate is being heat-treated to destroy the virus. You will be given heat treated factor VIII as soon as possible.

In addition, the Transfusion Service is making every effort to ensure people who have a greater than average risk of exposure to AIDS do not donate and all donors are required to sign that they are not in a high risk group. Also we hope that in the near future it will be possible to test all blood donations for the presence of HTLV III antibody. These measures will effectively remove sources of virus from the donor pool.

In the next few years we hope to have available a new preparation of factor VIII which is made by genetic engineering. This will not involve blood products and therefore cannot be a source of infection. Already test batches are being prepared so it is only a matter of time and we predict that supplies will be available in the next four years.

9. Reassurance

We realise how worried some of you may be and this is the reason that we have called a series of meetings of patients and relatives. We will keep you informed of all new developments. If anyone wishes a further discussion please phone your Centre Director for a private chat. Bring your spouse if you wish.

Remember that you must continue to treat yourself with the concentrates as the risks are much greater of bleeding than of contracting the rare disease of AIDS.

THE ROYAL INFIRMARY OF EDINBURGH

HAEMATOLOGY DEPARTMENT

DR. A. C. PARKER (Ext. GRO-C)
DR. C. A. LUDLAM (Ext. GRO-C)

Senior Chief M.L.S.O.
MR. P. F. J. NEWMAN (Ext. GRO-C)

LAURISTON PLACE
EDINBURGH EH3 9YW

Telephone: 031-229 2477

Your Ref.:
Our Ref.: CAL/PMS

31st January, 1985

Dear Dr Lane.

Acquired Immune Deficiency Syndrome (AIDS) in Haemophilia

You will be aware from both the medical and popular press that patients with haemophilia are at risk of developing AIDS as a result of the transmission of the HTLV III virus in factor VIII and factor IX concentrates. To date there have only been three cases of AIDS in British haemophiliacs and the chance of any individual patient developing the disorder, based on our present information is very small, probably less than 1:1000. From serological studies of patients in the United Kingdom, including Edinburgh, it is clear that many haemophiliacs have antibodies to the HTLV III virus. The presence of antibody, however, does not necessarily confer immunity and such patients may be capable of transmitting the virus both by semen and blood. Like Hepatitis B, needlestick incidents are capable of transmitting the virus. It is therefore particularly important that the same precautions are observed as for hepatitis B positive patients. Needles and syringes should be disposed of appropriately. Samples should be sent to laboratories double wrapped in "high risk" bags, again as for hepatitis B.

I write to let you know that I have circularised your patient with an information sheet about AIDS. If you would like a copy I would be delighted to forward one to you. The chief recommendations are:

1. Patients should mix up and inject their factor VIII/IX concentrates with care and should dispose of all the syringes and needles into the Cinbins we provide.

2. A barrier contraceptive, i.e. condom sheath, should be used during sexual intercourse. We are issuing such contraceptives free to individuals from the Haemophilia Centre, when they come for treatment or collect their home therapy.

Apart from these recommendations it is important that patients lifestyles continue as previously. The HTLV III virus is not passed between individuals by ordinary social contact and the patient's family and friends should be strongly reassured.

All Scottish factor VIII concentrates are now being heat treated under conditions that are believed to kill the HTLV III virus. Thus Scottish factor VIII no longer transmits the AIDS virus. We hope that heat treated factor IX will be available in the near future.

This is obviously an anxious time for your patient. If you would like to discuss any of the points I have raised further, I would be delighted to hear from you by telephone or letter.

With best wishes,
Yours sicnerely,

C.A.Ludlam
Director, Haemophilia Centre

(3)

THE ROYAL INFIRMARY OF EDINBURGH

HAEMATOLOGY DEPARTMENT

DR. A. C. PARKER (Ext. GRO-C)
DR. C. A. LUDLAM (Ext. GRO-C)

Senior Chief M.L.S.O.
MR. P. F. J. NEWMAN (Ext. GRO-C)

LAURISTON PLACE
EDINBURGH EH3 9YW

Telephone: 031-229 2477

Your Ref.:
Our Ref.:

27th January, 1986

Mr. R. MacKie,
GRO-C

Dear Mr. Mackie,

As you will know factor VIII and IX concentrates may cause hepatitis in individuals with haemophilia. Very occasionally, the hepatitis is transmitted to other members of the family. We believe this to be a very rare occurrence. We would however like to investigate local families to find out how commonly this occurs.

You may remember you very kindly arranged for some member(s) of your family to come to the Haemophilia Centre a little while ago to let us have a blood sample. We have kept this sample in the deep freeze and I write to ask if you would be agreeable to us testing this for evidence of previous infection by hepatitis virus. This will save members of your family coming up to the Haemophilia Centre again.

Before testing the samples from our deep freeze I should like to seek approval of those members of your family who kindly donated samples. If you are agreeable, I should be grateful if you could ask the individuals listed below to sign opposite their names to indicate their willingness to have their blood samples tested. Please could a parent sign against a child's name to give consent.

Name	Signature	Date
Alice MacKie,	GRO-C	13/2/86

If you would like to discuss the project further I would be delighted to hear from you. I enclose a stamped addressed envelope for your reply.

With best wishes,
Yours sincerely,

GRO-C

C.A.Ludlam
Director Haemophilia Centre

THE ROYAL INFIRMARY OF EDINBURGH

COPY OF DOCTORS LETTER

NUMBER

NAME

(6)

M15

Mrs. Alison Mackie,

GRO-C

2CAL.EM01
3rd March, 1989.

Dear Mrs. Mackie,

I write to let you know that the antibody test to HIV for yourself and your son, Robert, were both negative on the sample that we collected on 20th February.

You may recall that there was the possibility of vaccinating your son against tuberculosis and I am writing to Dr. Sudlow to ask him about this further.

I shall be in touch with you as soon as I have had a reply.

With Best Wishes,

Yours sincerely,

C.A. Ludlam
Consultant Haematologist

Reference Centre (5) 1

OXFORDSHIRE AREA HEALTH AUTHORITY (TEACHING)

OXFORD HAEMOPHILIA CENTRE

Tel: Oxford (0865) 64841
Ext. GRO-C

Churchill Hospital,
Headington,
Oxford OX3 7LJ.

24th June, 1983.

Dear Dr. Ludlam,

Acquired Immune Deficiency Syndrome

A Meeting of Reference Centre Directors was held on May 13th, 1983 to discuss this problem in haemophilia, its implications and our recommendations. So far one possible case has been reported to our organisation. This patient (A/1) conforms to the definition published by the CDC in Atlanta, Georgia but cannot be considered as a definite case. We are not aware of any other definable patients amongst the U.K. haemophilic population.

At the above mentioned meeting on May 13th the following general recommendations were agreed.

1. For mildly affected patients with haemophilia A or von Willebrand's disease and minor lesions, treatment with DDAVP should be considered. Because of the increased risk of transmitting hepatitis by means of large pool concentrates in such patients; this is in any case the usual practice of many Directors.

2. For treatment of children and mildly affected patients or patients unexposed to imported concentrates many Directors already reserve supplies of NHS concentrates (cryoprecipitate or freeze-dried) and it would be circumspect to continue this policy.

It was agreed that there is as yet insufficient evidence to warrant restriction of the use of imported concentrates in other patients in view of the immense benefits of therapy but the situation will be constantly reviewed. Following the meeting on 13th May, the Licensing Authority was asked to consider any implications for us of the revised recommendations of the American Food and Drug Administration which were made on March 24th, 1983 to American plasma collecting agencies.

Two additional points have been drawn to our attention since the meeting of May 13th.

1. The first concerns the treatment of patients with haemophilia B. The evidence to incriminate factor IX concentrates in AIDS is even less than with factor VIII and it seems logical to continue to use our normal supplies of NHS concentrate.

2. Another point concerns the proposed trials of "hepatitis reduced" factor VIII concentrates. There is no evidence that the processes involved in the manufacture of these inactivate any other hypothetical viruses. However it is

still important that the effectiveness of imported "hepatitis reduced" concentrates vis-à-vis hepatitis is subjected to formal clinical trials in mild haemophiliacs notwithstanding our general recommendations above. Directors are urged not to use these concentrates randomly on a "named patient" basis.

If you have any other queries or suggestions please write to us or telephone.

Yours sincerely,

GRO-C

A.L. Bloom
Chairman, Haemophilia Centre Directors Organisation

GRO-C

C.R. Rizza
Secretary, Haemophilia Centre Directors Organisation

Dr. C. Ludlam,
The Royal Infirmary,
Edinburgh.

Dec 1984

6

HAEMOPHILIA CENTRE DIRECTORS ORGANISATION

AIDS Advisory Document

At a recent meeting of Reference Centre Directors the following observations were discussed and recommendations made in consultation with Drs. Richard Lane, John Cash, Harold Gunson, Phillip Mortimer, Richard Tedder, John Craske and others.

Background

1. In U.S.A. There are over 6,000 cases of AIDS including 52 haemophiliacs.

   In U.K. There have been 102 cases with three reported haemophiliacs. No doubt other cases are developing in the haemophilic population.

2. Tests for HTLV III antibody are available for haemophiliacs via:
   Dr. Phillip Mortimer
   Central Public Health Laboratory Service
   175 Colindale Avenue
   Colindale, London NW9 5HT.

   Dr. Richard Tedder,
   Department of Virology
   School of Pathology,
   The Middlesex Hospital Medical School,
   Riding House Street,
   London W1P 7LD.

   Antibody positivity probably correlates with exposure to imported concentrates but there have been two notable recent episodes concerning U.K. concentrates.

3. Antibody tests indicate prior infection but do not imply immunity as antibodies may not be neutralising. Infective carriers can be antibody positive and there may also be a variable period of antigen positivity before seroconversion occurs.

   Antibody positive persons should therefore be considered at risk of transmitting or developing AIDS but antibody negativity does not exclude infectivity.

General Precautions

Donors

(a) the BTS is making increased efforts to ensure exclusion of donors at risk by questionnaires or leaflets or both.

(b) HTLV antibody tests either commercial or home grown should become available during 1985 but cannot be instantaneously implemented. Equipment, space and staff may be needed at Regional Transfusion Centres.

It seems probable that HTLV III has been incorporated into at least one BPL and one Scottish batch of factor VIII. Recipients are being followed up.

Concentrates

Factor VIII. Evidence is accruing that HTLV is heat labile but the data from "spiked" concentrate is entirely related to U.S. concentrates and is minimal. It seems that in concentrates HTLV III is inactivated by dry heat at 68°C for 24 hours. It is unlikely that this process completely inactivates Non A Non B hepatitis . Loss of yield is 15% for dry heat. Wet heat with stabilisers is probably more effective but evidence is lacking and loss of yield is up to 50%. Of current products heat treated Koate HT and Factorate HT are dry heated and sell at 12p a unit. Travenol Hemofil T is dry heat treated and sells at 15p a unit. Alpha Profilate (heated) is wet-treated (14p a unit). Immuno also have heated preparations.

Factor IX Profilnine (heated) (Alpha), heated Konyne (Cutter) and Immuno (heated Prothromplex) are available at prices up to 20p a unit but the effects on efficacy and thrombogenicity are unpublished. Since AIDS and laboratory changes seem (controversially) to be less common in Christmas disease than haemophilia A no firm recommendation can be given on heated factor IX.

Heated Feiba is also available from Immuno at 30p a unit but is probably not cost-effective.

BPL Factor VIII BPL can dry heat 30% of its output available from January 30th, 1985 and the rest in two months time when two more ovens are installed to supplement the existing one. The process produces an acceptablein vitro product but extensive clinical trials have not been undertaken.

Edinburgh From now on all Scottish factor VIII will be dry heated to supply Scotland and N. Ireland.

Options in probable decreasing order of safety from AIDS for Haemophilia A

1. Heated U.K. concentrate (note: still NANB hepatitis risk)
2. Single donor cryo. or FFP
3. Heated imported conc. (note: still NANB hepatitis risk)
4. Unheated U.K. conc.
5. Unheated imported conc - almost certain to be contaminated.

Note: Heated concentrates may still transmit hepatitis. Some of the distinctions e.g. between 3 and 4 are debatable and the long-term effects (e.g. immunogenicty) of using heated plasma proteins in this way are unknown. Even pasteurised albumin is not given as frequently to individuals as will be factor VIII.

RECOMMENDATIONS

1. Concentrate is still needed; bleeding is the commonest cause of disability and death.

2. Use DDAVP in mild Haemophilia A and vWd if possible.

For Haemophilia A needing blood products

(a) "Virgin" Patients those not previously exposed to concentrate, and childre use cryo or heated NHS factor VIII (if available).

(b) Severe and Moderate haemophiliacs previously treated with factor VIII use heat treated NHS factor VIII, if available or heat treated US commercial.

4) Haemophilia B

(a) Mild Christmas Fresh frozen plasma if possible (otherwise NHS Factor IX.

(b) "Virgin" Patients and those not previously exposed to concentrate use fresh frozen plasma (or NHS factor IX concentrate if essential)

(c) Severe and Moderate Christmas Disease previously exposed to factor IX concentrate continue to use NHS factor IX.

In individual patients there may need to be a choice. In general heated concentrate appears to be the recommendation of virologists consulted but individual Directors may wish to make up their own minds. This is particularly true of unheated NHS material. The evidence that heated U.S. factor VIII is safer than unheated NHS is debatable and some Directorsmay wish to continue using unheated NHS material until all supplies are heated. This is valid for carefully selected patients but must be on individual decision based on the assumption that some batches of NHS materials will be contaminated with HTLVIII. The argument that HTLV III positive patients have already beeninfected and could receive unheated American material is probablyscientifically true but this material would pose an additional risk to staff and families and its continued use would pose logistic problems.

Supplies

It seems that as from January 30th, 1985 a limited supply of BPL heat treated British factor VIII will be available. Preference will be given (a) to treat patients defined in recommendation 3a above and possibly (b) to those willing to participate in clinical trials.

NOTES

1. The Blood Products Laboratory cannot take back for reissue unused unheated concentrate. Do not ask your BTS to order more of this than you are willing to use because this would prejudice supplies of heated material later in the year.

2. If the bill for heated commercial concentrate is heavy at first it can be put to your Authority that increasedsupplies of heat treated BPL material could be available later in the Summer asstockpiled unheated material at BPL is heated.

3. Funding will need to be negotiated at local level although strong representations are being made to DHSS for central funding if needed. Please inform the Chairman (Prof A.L. Bloom) and Secretary (Dr. C.R Rizza) if you are experiencing difficulties. They cannot promise individual help but the information will be useful.

4. The need for elective surgery etc., should be assessed in the light of supplies of heated concentrate.

ANTIBODY TESTING

It is recommended that patients be HTLV III Ab tested.

Test should be repeated if positive.

Ab positive people should be informed, reassured and counselled regarding transmission to spouses etc., including the possible use of barrier contraception. This seems to be the most practical method available. Facilities are only available at present for HTLV III Ab studies on contacts as part of organised projects. Please note that sample bottles of serum must be leak-proof. The Laboratory Directors would prefer to liase with a small number of haemophilia doctors. Thus where possible samples should be chanelled through Reference Centres or the nearest large Haemophilia Centre from where suitable sample bottles may be obtained.

ORDINARY LABORATORY TESTING

Samples from patients with AIDS or PGL will be subject to the regulations promulgated by the AdvisoryCommittee on Dangerous Pathogens. Although very restrictive draft instructions have been circulated in an unauthorised fashion in various quarters we were assured that the definitive document is less so. Careful safety auditing of laboratory procedures is recommended. The recommendations apply to AIDS and high suspect patients. The rules for samples from healthy HTLV III Ab positive patients have not been specifically addressed but presumably these are also potentially dangerous.

CLINICAL

Plastic aprons could be used for preparing and administering all treatments (including home treatment). Home treatment procedures should be reviewed. Use of butterfly needles may be safer than ordinary syringe and needle as the risk of 'walk on' injury is reduced.

In the wards patients with AIDS or high risk thereof should be nursed in single rooms. Gloves and aprons should be worn by nurses when carrying out practical procedures. In general hepatitis B-like precautions should be taken. HTLV III Ab pos. patients should be dealt with for Dental care as for hep. BAg pos. In case of needle injuries virological advice from PHLS at Colindale should be obtained after applying the usual first aid measures. Aerosols and casual contacts do not constitute a risk and there is no need to isolate routinely HTLV III Ab positive patients.

STAFF

HTLV III Ab testing of staff is not recommended routinely but it could be useful to have organised studies in certain larger centres.

These recommendations will obviously need to be modified in the light of rapidly changing experience.

December 14th, 1984

(7)

LOTHIAN HEALTH BOARD

Royal Infirmary of Edinburgh *and Associated Hospitals*

Lauriston Place Edinburgh EH3 9YW Telephone 031-229 2477
Fax 031-228 2189

HAEMATOLOGY DEPARTMENT

Dr A.C. Parker
Dr C.A. Ludlam
Senior Chief MLSO's
Mrs F. Turner
Mr I. Abbott

Dr C A Ludlam
Consultant Haematologist
Royal Infirmary of Edinburgh

Your Ref
Our Ref PH/IGH/290650
Date 27 May 1993
Enquiries to (Dic. 25.5.93)
Ext. No. GRO-C

Dear Dr Ludlam

ROBERT MACKIE, GRO-C

I saw this man in the Haemophilia Centre with you today and we discussed potential Interferon treatment for his hepatitis C. Presently he is keeping generally well and there were no stigmata of chronic liver disease. He has not had an upper G.I. endoscopy in the past and we thought initially that it would be reasonable for this to be undertaken to see if he has oesophageal varices or not. He agreed to have this done next Tuesday, although he is very keen to be discharged in the evening thereafter. If there are no varices present, I would have thought that the next most appropriate step would be for him to have a laparoscopy and liver biopsy, but he wanted to think about this. We will be able to see him again in the clinic after his endoscopy to discuss this further.

Kind regards.

Yours sincerely

GRO-C

Dr Peter Hayes
Senior Lecturer

cc G.P.

DATE

, Advise FVIII 6 bottles bd 1.5
4 bottles bd 2.5

GRO-C

See 3.5

5.93 Says took 6 bottles bd. + feels much the same/
Had run out of Rx. + so none today so far!
o/e (R) buttock - soft, some tenderness mid. haematoma
SLR 50° no neuro. def.
Cont. FVIII 6 bottles b.d.

GRO-C

Seen by Dr Lindlan Knees (R) 10 - 100° (buttock bleed)
(L) 5 - 110°
recent bleeds knees R > L - (L) knee 'gives way'
XRay knees → Orthop Clinic June '93
Discussion re Hep. C. ~~agrees~~ to V/S Abdo.
decline endoscopy

Lab to check anti HBsAb result
(Was anti-C +ve, & anti HBsAb +ve on 15.9.92)

25/5/93 Blood for - autoAbs, anti nuclear factor, SMA, mito,
- Igs (G, A & M), FBC, LFTs, α1 antitrypsin, caeruloplas-
- αFP ~~serum~~ to store. T cells.

THE ROYAL INFIRMARY OF EDINBURGH

O.P. CLINICAL NOTES

NUMBER

NAME MACKIE Robert

M2

DATE	SHEET No.
25.5.93	Joint Clinic - Dr Lindsay / Dr Hayes
	PH No jaundice No GI symp. Alcohol. few beers at times - can go weeks ± no alcohol.
	Abdo
	Advice 1. ENDOSCOPY 2. LAPAROSCOPY (+ biopsy) / indicated 3. INTERFERON
	Pt. agreed to endoscopy.
25/5/93	Bed booked ± endoscopy sec.
27/5/93	Patients wife rang to inform us that he was cancelling his endoscopy for next wk Pt
	~~DNA~~ CAL. To be sent a further Tues appt
22.6.93	DNA - Liver Clinic
26-7-93 ~~12.6.93~~	Blood taken for inhibitor.