1) Title of Project

An Epidemiological study of the Acquired Immune Deficiency Syndrome (AIDS) in patients with coagulation disorders in the U.K. and its relationship to transfusion with blood products.

2) Purpose of the Proposed Investigation

The object of this investigation will be to test the hypothesis that AIDS and the AIDS-related complex is associated with treatment with factor VIII prepared from plasma derived from commercial donors in the U.S.A.

We will undertake a retrospective study of patients treated with the batches of factor VIII concentrate received by 2 haemophilia A patients who contracted AIDS in the U.K. in 1983. The batches of U.S. commercial factor VIII received by the patients within 5 years prior to the onset of symptoms in the index cases will form the 'suspect' group of products possibly associated with transmission of a putative AIDS infective agent. Initially, follow-up will be restricted to the recipients of commercial concentrate given to the second case, who died 15 months after receiving his first transfusion of 3 batches of U.S. commercial factor VIII. Patients in Haemophilia Centres in the U.K. who were treated with these batches will be identified and followed for upto 24 months as out-patients by clinical and laboratory studies in a standardised manner. The occurrence of infections and immune dysfunction possibly related to AIDS or the 'AIDS related complex' will be studied and compared with control groups of patients who have not received those blood products used to treat the index patients. Any abnormalities found will be related to the blood product treatment records for the previous 5 years. Control groups will be chosen so as to allow for different treatment regimes and the patients who received the batches of NHS concentrate given to the 2 index patients.

The donors of cryoprecipitate used to treat one of the index patients in addition to factor VIII concentrate will be followed in collaboration with the Bristol National Blood Transfusion Service. A group of patients treated solely with NHS factor VIII will also be studied at the Oxford Haemophilia Centre. Special surveys related to: a) provide marker tests as predictors of AIDS will be carried out in collaboration with other Haemophilia Centres (see collaboration); b) cross sectional surveys to define the classes of viruses transmitted by factor VIII.

3) Background of the project

In 1981, 2 groups of investigators in New York and San Francisco reported an outbreak in bisexual men of Pneumocystis carinii pneumonia, and an aggressive form of Kaposi's sarcoma in homosexual men (1,2). A Task Force funded by the Centres for Disease Control then initiated a nationwide epidemiological study of what became known as the Acquired Immune Deficiency Syndrome (AIDS) (3). This was defined as the occurrence of biopsy proved Kaposi's sarcoma in adults under the age of 60 years and/or biopsy or culture proven opportunistic infection in previously healthy persons, which was indicative of a profound defect in cell mediated immunity. (Appendix 1)

The number of cases has increased exponentially since 1981 so that by October 1983 over 2,500 had been reported to C.D.C. Fifty per cent have been notified within the past 6 months, and the spectrum of disease has extended to include a large number of opportunistic, viral, bacterial, fungal and parasitic infections which are often multiple, are difficult to identify and are resistant to treatment. Others, such as lymphoma (4) are also now included in the definitions of this disease. While over 70% of affected patients are homosexual men, other groups of patients affected include intravenous drug abusers, (5,6), haemophiliacs (7) and Haitian immigrants to the U.S.A. (8). A similar disease has been defined in women who are sexual contacts of AIDS patients, and infants born to mothers in the high risk categories (9).

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The disease has now spread from the major cities on the East and West seaboards and includes most States in the U.S.A. and 27 Centres in Europe (10). A similar syndrome has been described in Haiti (ii) and Zaire in Africa (10), but the significance of these reports in relation to the outbreaks in the U.S.A. is not yet clear. The cumulative mortality is 41%, but the mortality in cases diagnosed in 1981 and 1982 is much higher.

Epidemiology

The cause of this 'new' syndrome is unknown, but the most widely held hypothesis is that it is caused by an infectious agent, possibly a virus, which infects human T-cells with an epidemiology and mode of spread remarkably similar to that of hepatitis B.

Case control studies in the U.S.A. suggest that sexual transmission is the mode of transmission between homosexual men. The risk factors most highly correlated with AIDS patients include a large number of sexual partners, use of drugs to heighten sexual experience, exposure to faecal material as part of sexual practices, and a past history of syphilis, hepatitis A infection, and other sexually transmitted diseases (12). There is also evidence of case clustering in homosexual men (13).

Parenteral transmission is suggested by cases that have been described in parenteral drug abusers, and haemophiliacs receiving factor VIII and IX concentrates (5,7). C.D.C. Atlanta has collected 31 cases of AIDS possibly related to blood transfusion (37), and this is supported by the report (15) of an infant with AIDS who was transfused with platelets obtained from a donor who later died of AIDS. A similar disease has also been described in infants borne to Haitian women, drug addicts or the sexual partners of male AIDS patients (16). Therefore, the evidence suggests the cause is an infective agent transmittable by the sexual, parenteral and perinatal routes. Current evidence suggests an incubation period of between 10 months and 45 months related to blood transfusion (37).

There is a possibility that transmission of this disease by blood and blood products may become a serious problem. In the U.K. the disease is still rare even in the homosexual community but widespread transmission could occur by transfusion, particularly via large pool blood products unless precautions are taken to exclude donors from the already identified high risk group for AIDS. Since there is no test for the disease, the use of surrogate tests (e.g., anti-HB_c or anti-treponemal antibodies) is under investigation by transfusion services in the U.S.A. and elsewhere.

AIDS in Haemophiliacs with blood coagulation disorders

The incidence in haemophiliacs is at present low, being approximately 0.8 - 1.00/1,000 patients at risk (17). Up to November 30th 1983, 19 patients with haemophilia A and 2 with haemophilia B had been identified as cases of AIDS. Of these, one was diagnosed in 1981, 8 in 1982 and 12 so far in 1983. Two patients are known to have other risk factors for AIDS (18). Seven other patients have so far been notified to C.D.C. from Europe as suffering from AIDS. No cases of Kaposi's sarcoma have occurred in the haemophilia A and B transfusion related cases so far. The commonest opportunistic infection has been Pneumocystis carinii (in 20 of 21 cases in the U.S.A.). The same is true of the European cases. Retrospective surveys have failed to establish any patient with AIDS-like disease in the U.S.A. before 8 September 1983. Several patients with haemophilia have been reported as suffering from unexplained illnesses possibly related to AIDS, which do not fit the C.D.C. criteria for an AIDS, including

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lymphadenopathy (19), thrombocytopenic purpura (20) and Burkitt's lymphoma (21), fever, weight loss, etc. This is known as the AIDS related complex and its relationship to the main syndrome is at present not known. Other special features of AIDS in haemophilia are:-

a) The distribution of cases of AIDS in haemophiliacs in the U.S.A. was different from that in homosexuals. Cases identified in Ohio and Georgia for instance were the first cases of the disease to be reported in these States and had had no contact with other high risk subjects (22).

b) The age distribution (10-70) of the patients is far wider than for homosexuals.

c) So far no batches or brands of factor VIII or XII have been identified as being associated with the acquisition of AIDS. Of the 21 cases so far reported in the U.S.A., no common batch of these products has been received by any of these patients. The same is also true of both the cases identified in the U.K. The transfusion records of the U.K. cases have been compared with those of the U.S. cases at C.D.C. Atlanta with similar results.

Commercial factor VIII is made from plasma obtained from paid donors in the U.S.A. The precise details of pooling and pool size is a commercial secret, but it is known that pool sizes can vary from 2,000 to 20,000, and that each donor can contribute several litres per pool by contributing several weekly donations to the same plasma pool. The number of donations per pool size, therefore, is probably not much different from that used for NHS factor VIII (3-7,000 donations) where each donation is approximately 250mls of plasma (38). However, the total volume of plasma may be much larger and the dilution factor for any virus contaminated donation when added to this pool will be similar in both products, probably of the order of 10^{-3} to 10^{-4}.

The low incidence of AIDS in haemophilia A patients could therefore be explained by one of the following hypotheses:-

1) A low titre of virus in the contaminated plasma donation producing a low contamination rate for each bottle of factor VIII concentrate, e.g., 1% with a low infective dose by the intravenous route for men. Most recipients of an infected batch would remain uninfected after transfusion.

2) A high titre of virus with a high infective dose required for the severe illness in man; minor immune defects could be caused by exposure to a smaller dose of virus. Most of the recipients of a contaminated batch would be uninfected, but a lower proportion than in (1).

3) A high titre of virus, with a high ratio of symptomless to symptomatic infection for the virus in an analogous manner to poliovirus infection, e.g., less than 1/1,000. A high proportion of recipients would be infected. One result of this may be a higher incidence of AIDS in sexual contacts of infected recipients of factor VIII concentrate with an AIDS related virus. There is as yet no evidence of this.

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4) As for 2) or 3) but with a genetic factor would also be required to produce a severe illness, or 2 or more infections acting synergistically.

5) The severe and mild or the AIDS complex forms of AIDS are carried by serologically distinct viruses. Promiscuous homosexuals suffer from a higher incidence of multiple infections as a result of sexually transmitted disease, and this high risk group are most likely to be the source of infected plasma donations. Both these viruses would be present in factor VIII at a low titre.

AIDS related to transfusion of whole blood or platelets

In addition to the cases already recorded, C.D.C., Atlanta has investigated 31 cases of AIDS possibly related to transfusion in non-haemophiliac patients. So far, 7 have been completed and in each case a donor who was a 'high risk' category for AIDS has been identified. However, the evidence is as yet circumstantial. Prospective studies of patients who received blood or platelet donations from 'high risk' donors are also underway, but no information as to the outcome is as yet available.

Immunology

A high proportion of AIDS patients have changes in their peripheral blood lymphocyte populations and an altered response to tests of immune function. These appear to reflect the pronounced defect in cell mediated immunity (CMI) which is characteristic of the syndrome (23). There is anergy to intradermal injections of common skin test antigens such as candidin, and an impaired transformation of lymphocytes after stimulation by mitogens such as phytohaemagglutinin in vitro. The most consistent finding is a profound lymphopenia associated with an absolute decrease in T-helper cells in the peripheral blood, with a relative increase in T-suppressor cells and an inverted T-helper/suppressor ratio. There is also evidence of an increase in B-lymphocyte response with hypergammaglobulinaemia (24), and the presence of circulating B cells in the peripheral blood which spontaneously produce immunoglobulin in vitro. In some patients circulating immune complexes can be demonstrated. The relationship of these changes to the alterations in T-cell functions in the AIDS syndrome is at present unknown.

A reversed T-helper/suppressor ratio associated with a normal lymphocyte count with an increase in absolute number of T-suppressor cells, has been found in healthy homosexual men, in patients with persistent lymphadenopathy (24) and in haemophiliacs regularly treated with factor VIII concentrate (26). In haemophiliacs the only related factor seems to be treatment with factor VIII. The degree of alteration of the T-helper/suppressor ratio in the peripheral blood is correlated with the lifetime treatment load of concentrate the patient has received (27). Similar changes in T-cell subsets in the peripheral blood have been described after treatment with factor VIII concentrate prepared from volunteer plasma donations. The latter changes are probably unrelated to the occurrence of AIDS in haemophilia A patients (28).

The presence of acid labile α-interferon in the serum of some patients in the prodromal and severe phases of AIDS has prompted the suggestion that this can be used as a surrogate test for identifying patients at a high risk of contracting the disease (29).

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Virology

Immunosuppression is a characteristic feature of some virus infections in animals and man. AIDS could be due to the cumulative effect of simultaneous virus infections which could differ in different patient groups, or could be due to one agent which is transmitted to all groups.

Both Cytomegalovirus (CMV) and Epstein Barr Virus (EBV) have been implicated in this syndrome. CMV has been suggested as the cause of Kaposi's sarcoma (30). Immunosuppression is associated with primary CMV infection (31) and there is a high prevalence of antibody in homosexual men. EBV is associated with 2 human tumours and primary infection is associated with immunosuppression. High titres of antibodies to both viruses have been found in homosexual men with AIDS (32), but this probably reflects reactivation of latent virus infection associated with AIDS. There is no evidence that viruses of the Herpes group are transmitted by factor VIII (33), though reactivation of EBV was found in one of the haemophiliacs with AIDS in England (34).

Retroviruses have also been suggested as the cause of AIDS, as these are known to cause a variety of immune disorders and other diseases. Isolations of viruses related to human T-cell leukaemia virus (HTLV) have been made from American and French patients, and pro-viral DNA homologous to HTLV RNA have been found in peripheral blood lymphocytes in 25% of AIDS patients but not in healthy contacts (35,36). However, a survey of HTLV infection related to blood transfusion in Japan has shown that infection is only transmitted by fresh blood or platelet transfusions and not by fresh frozen plasma (37).

This suggests that HTLV is probably not related to AIDS in haemophiliacs, but a different retrovirus with different characteristics might be involved. The isolations of these viruses in some patients may be examples of reactivation of latent virus disease.

Two cases of AIDS out of the 27 cases reported to CDSC have occurred in Haemophilia A patients in the U.K. The first (case A/1) contracted oesophageal candidiasis in March 1983 followed by Pneumocystis carinii pneumonia in October 1983. This responded to therapy with septrin and he is now on a small maintenance dose of the drug. He is a severe haemophiliac aged 21 years who received several batches of U.S. commercial factor VIII between 1978 and 1983. Nine were transfused between 1.1.80 and 1.5.83. The complete transfusion records are available since 1976. The second patient (case A/4) was a 57 year old mildly affected patient who had 2% VIII. He had received only cryoprecipitate since 1973 and only one batch of NHS concentrate in 1978. He required treatment infrequently, approximately 2-6,000 factor VIII units per year. In December 1981 he underwent a herniorrhaphy and was transfused with 3 batches of commercial factor VIII made from plasma of U.S. origin. No commercial products were given subsequently up to his death from Pneumocystis carinii pneumonia in August 1983. He had become a carrier of hepatitis B virus in September 1983, and developed fever, weight loss and oral candidiasis in the Spring of 1983. He was suspected to have AIDS, but a diagnosis was not made until a few days before his death. The diagnosis of Pneumocystis carinii pneumonia was confirmed at post mortem. No batch of factor VIII was common to these 2 patients.

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Plan of Investigation

The results of investigation of cases of AIDS in haemophiliacs in the U.S.A. has shown that the incidence of the disease is low (0.8-1.0/1,000 patients at risk). The transfusion records of Haemophilia Centres in the U.S.A. are poor (37), but what evidence there is has failed to identify one common batch of factor VIII between any 2 AIDS cases. The incidence of AIDS in the U.K. outside the homosexual community in London in the U.K., is as yet low. The occurrence of mild forms of immunosuppression and cases of AIDS or AIDS-related diseases in haemophiliacs is likely to be related to transfusion with commercial blood products.

For several years, I have carried out a surveillance scheme for factor VIII and IX associated hepatitis on behalf of the U.K. Haemophilia Centre Directors. A register of patients with coagulation disorders is held at Oxford, and most Haemophilia Centres have transfusion records for the past 10 years for most of their patients. In March 1983, we set up a reporting system for cases of AIDS and related disorders in U.K. patients with coagulation disorders. So far 2 cases of AIDS and 2 cases of the lymphadenopathy syndrome have been reported, and 3 patients with autoimmune thrombocytopenia. (Appendix 2)

With the co-operation of the manufacturers of commercial factor VIII and the Blood Products Laboratory of the N.B.T.S., we have identified all the Haemophilia Centres where the commercial blood products given to the 2 cases of AIDS were used. A register of patients who have also received these batches is being compiled. Each batch was used to treat 60 - 70 patients. There are 14 batches of commercial concentrate (9 given to case A/1 and 5 given to case A/4) being followed up, but initially the batches related to case A/4 will be studied. There also exists a significant number of patients who have not received these products.

The identification of all patients transfused with these suspect batches of factor VIII gives us a unique opportunity in the U.K. to test the hypothesis that AIDS is transmitted by blood products, and that the cases of minor immune dysfunction (AIDS-related complex) which have also been identified are also causally related to specific batches or brands of factor VIII.

Initial Assessment of Contacts

a) Haemophiliacs Each Haemophilia Centre Director where the 'suspect' batches of factor VIII were used has been contacted and asked to supply a list of patients who received transfusions of the suspect batches of commercial factor VIII, and also the names of patients treated with the batches of NHS factor VIII used to treat cases A/1 and A/4 in the period under study.

The details will be included in a register of patients stored at Manchester PHL on a microcomputer purchased for the purpose with the aid of a grant from the Haemophilia Society. Details will include name, date of birth, Haemophilia Centre, National Registration Number, diagnosis, and level of factor VIII, date(s) of transfusion of blood products and the total quantity of factor VIII in units used for each batch. This will enable the total population of patients transfused with each batch of factor VIII to be identified. So far 194 patients in 12 Haemophilia Centres have been identified as having received one or more batches of commercial factor VIII transfused to case A/1 between 1.1.80 and 1.3.83. The latest information regarding the incubation period of transfusion related AIDS is that it varies between 10 and 43 months.

This means that the blood products given to case A/1 between 1.1.78 and 1.3.83. will have to be included in the survey (37). The patients who received the batches of concentrate given to case A/4 will also be identified. The total number of patients in the 'suspect' group for both AIDS patients will, therefore, approach 400. An equal number may have received the batche of NHS factor VIII transfused to the 2 AIDS patients during the at risk period.

b) Blood Donors The donors who gave plasma used in the cryoprecipitate given to case A/4 since 1.1.80 will be traced as far as possible with the help of Dr. Ian Frazer, Director, National Blood Transfusion Service, Bristol. In addition, recipients of other donations by the same donors will be traced as far as possible. Enquiries will be limited to checks to establish that they are well and not suffering from illness possibly related to AIDS. Permission will be obtained to contact the original donors 3 years after their transfusion. This will take the form of a standard letter to their general practitioner. The serum specimen from the latest donation of each donor will be stored at -70°C for future use if further investigation is required.

Clinical Assessment

Each Haemophilia Centre Director will be asked to review patients who have received the suspect commercial factor VIII batches and the batches of NHS factor given to the 2 AIDS patients at 3 monthly intervals until four years have elapsed since the last transfusion of any batch of concentrate under study. The batches related to case A/1 were transfused between October 1979 and March 1981. The follow up may therefore last from one year to eighteen months, with the possible extension to two years for the contacts of case A/4, where the products were transfused in 1981 and 1982. Patients will undergo a clinical examination designed to exclude symptoms and signs associated with AIDS, e.g., weight loss, breathlessness, malaise, diarrhoea, dysphasia, enlarged lymph nodes, and spleen and liver as defined by the C.D.C. criteria (see appendix I). Any suggestive symptoms will be investigated. Care will be taken not to indicate to the patient that they are suspected of contracting AIDS (but the fact that they have received a blood product used to treat one of the 2 known cases of AIDS will be communicated to the patient, if thought advisable by the Haemophilia Centre Director).

Transfusion Records

Complete transfusion records for the past 10 years, or as much that there is available will be reviewed, and kept with documents related to the project at each participating Haemophilia Centre. Care will be taken to exclude other high risk factors for AIDS such as drug addiction, homosexuality, or recent visits to the Caribbean, Africa or the U.S.A.

The complete family history, particularly for current and past sexual partners in the past 5 years will be noted as far as possible, and it is planned to carry out a limited survey of household contacts.

Laboratory Investigations

These will include haemoglobin, E.S.R., W.B.C., and differential counts, absolute lymphocyte count, platelet count, total IgG, IgA and IgM antibody levels, direct Coombs test, liver function tests.

Serological tests

20mls of clotted blood will be collected for serological investigation. Half of this serum obtained will be used for tests in the local laboratory. The rest will be frozen at -40°C or as low a temperature as is possible. This will be sent to Dr. Craske at the Public Health Laboratory, Withington Hospital, Manchester. This will form part of a collection of sera to be used to assess marker tests for putative AIDS related agents or surrogate tests to identify high risk individuals, e.g., the possible use of an α-interferon as a predictor for the developments of AIDS in a patient, and the prevalence of antibodies to human T-cell leukaemia virus (in collaboration with Dr. Richard Tedder, Dept. of Virology, Middlesex Hospital Medical School, and his colleagues). Dr. P.P. Mortimer (Virus Reference Laboratory, Central Public Health Laboratory, Colindale) will also carry out studies of the prevalence of human serum parvovirus infection.

Virology

Studies in AIDS patients suggest that they have a higher incidence of virus shedding, e.g., for Cytomegalovirus and Herpes Simplex virus in throat and urine specimens; Adenoviruses and Coronavirus particles in the faeces. One homosexual with lymphadenopathy investigated in this laboratory has been found to be excreting coronavirus in his faeces. An increased prevalence of virus excretion may be indicative of minor degrees of immunosuppression.

At the local hospital laboratory:

a) Isolation: (1) a throat swab and urine for virus isolation using secondary baboon kidney and human fibroblast cultures.

(2) A specimen of faeces for virus isolation and, if possible, electron microscopy.

b) Serology at the local hospital laboratory.

Hepatitis B surface antigen (anti-HAV, anti-HB$_s$ and anti-HB$_c$ (if possible), CMV (CFT), Herpes Simplex (CFT), Mumps, Adenovirus, R.S.V. (CFT's), Toxoplasma (dye test or immunofluorescence) or the local reference laboratory. Rubella (radial immune haemolysis or HI).

*(see below)

Bacteriology

1) Throat swab will be examined for the presence of Candida and cultured to elucidate the predominant bacterial flora.

2) Faeces will be examined if diarrhoea is present. Parasites, cysts and ova will also be sought.

3) Lymph Node Biopsy will be carried out if any patient presents with persistent lymphadenopathy as defined in the appendix. Half will be sent for histology after fixation and electron microscopy and half cultured for bacterial and viral pathogens, including Mycobacterium. Other investigations such as chest x-ray will be carried out if thought appropriate

*Serology: **It is suggested that where there is no suspicion of AIDS or an AIDS-related illness, tests for Hepatitis B, CMV etc., should be performed every 6 months after the initial serum. Blood should be taken when the patient is seen at the next 3 monthly visit and this serum specimen divided into 2 parts, one should be stored locally and the second sent to Dr. Craske at Manchester PHL. Further tests on these specimens can be done as clinically indicated.**

Special Studies

The minimum investigations for all the patients will include - blood count, total immunoglobulins, liver function tests, hepatitis B screen and platelet and direct Coombs tests and complement fixation tests carried out in the local laboratory. Sera will be stored at Manchester PHL and the patients investigated further if clinically indicated.

Special studies at certain Haemophilia Centres will include phenotyping or peripheral blood mononuclear cells for total T-cells (T3); helper (T4); and suppressor (T8) subsets.

Immunological screen Exposure to skin test antigens; candida, tetanus, streptodornase, streptokinase. In vitro transformation tests with mitogens using lymphocytes from peripheral blood, e.g., phytohaemagglutinin.

Virological studies E.B. virus antibodies (Manchester PHL) Immunofluorescence to capsid antigen; Paul Bunnell. CMV antibodies (Manchester PHL) IgG antibodies by an ELISA test. Antibodies to HTLV-type 1. (Dr. Richard Tedder). Serum parvovirus antibodies (Dr. P.P. Mortimer) Specimen of buffy coat urine and throat swab will be stored at -70°C from selected patients.

The Centres where these studies will be carried out are:-

1) The London Hospital, London. Dr. Brian Colvin. Studies on suspect patients.

2) St. Thomas' Hospital, London. Dr. Geoffrey Savidge. Studies on suspect patients.

3) The University Hospital of Wales. Professor Arthur Bloom. Studies on suspect patients.

4) Churchill Hospital, Oxford. Dr. C.R. Rizza. Studies on suspect patients treated with NHS factor VIII only.

Controls

a) Patient controls who received the batches of NHS factor VIII given to case A/1 or A/4.

b) Local or Haemophilia Centre Controls. Directors of Haemophilia Centres will be asked to select from their patients control patients who have not received any batch of factor given to the suspect or patient controls under study. Informed consent will be required for this part of the investigation. Selection will be random as far as possible, but matching for age, severity of coagulation defect and quantity of factor VIII received will be carried out. One should be selected for each patient in the suspect group per Haemophilia Centre.

c) Patients treated with only NHS factor VIII A group of these patients is under study at the Oxford Haemophilia Centre. These will be evaluated prospectively according to the protocol.

Results The results of the 3 monthly follow-up will be reported to each Haemophilia Centre Director locally who will consider what further investigations are necessary if indicated. The results will be on the forms provided for the purpose from Oxford and returned to Miss Spooner at Oxford with a copy retained for the Director's use. At intervals, the forms will be sent to Dr. Craske at Manchester, who will enter the information on the microcomputer. Sera will be sent to Dr. Craske at Manchester so that a series of sera from a representative sample of patients will be obtained.

Sample size The total number of patients followed will depend upon the distribution of patients in British Haemophilia Centres and the total number at risk for each treatment episode. The first state of identifying the patients at risk is underway and will be complete in 4-5 months. It is estimated that the sample size with control patients will approach 1,200.

In the event of any patient developing symptoms or signs suggestive of AIDS, then the clinical and laboratory investigations will be carried out by the consultant having clinical charge for that patient as medical problems indicate, except that whenever possible specimens of serum will be obtained at appropriate intervals and stored at -40°C for future investigation, and specimens of buffy coat stored in liquid nitrogen.

Analysis of Results

The incidence of AIDS related symptoms and signs and laboratory markers related to patients who will have received each batch and brand of factor VIII will be determined and compared with that in the control group.

Particular attention will be paid to minor differences in antibody prevalence, virus shedding and the presence of hepatitis B surface antigen as indicators of mild degrees of immunosuppression which may be related to subclinical infection with a putative AIDS related virus, e.g., titres of EBV antibodies, CMV antibodies and prevalence of virus shedding, e.g., Herpes Simplex and Varicella Zoster, CMV, presence of candida species and symptoms of oral candidiasis, shedding of adenoviruses and faecal coronavirus.

Follow up of household contacts

The report of Pneumocystis carinii pneumonia (P.C.P.) in the wife of a haemophiliac who himself died of P.C.P. (14) raises the question as to what the risk is of sexual partners of haemophiliacs contracting AIDS. There is no evidence that non-sexual household contacts are at risk from casual contact..

The spouses of haemophilia A patients in the suspect groups will be identified. Serum specimens and a minimum investigation will be carried out on spouses of patients who develop early features suggestive of AIDS or the AIDS related complex. A group of relatives is under observation at Oxford as part of a prospective study of non-A, non-B hepatitis, and this will serve as a control group.

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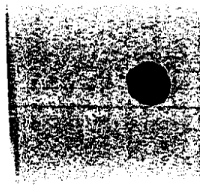

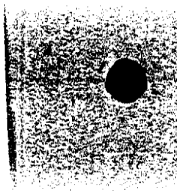

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USEFUL FOR RESEARCH AND NOT FOR IDENTIFYING PATIENTS AT RISK

Working definition developed by NIH AIDS working group in collaboration with CDC and clinical investigators in US.

To satisfy the definition, a person must have any two (or more) signs/symptoms and any two (or more) abnormal laboratory values.

I. Clinical signs/symptoms: chronic condition present for 3 months or longer, unexplained.

1. Lymphadenopathy ≥ 1 cm 2 non-inguinal sites.
2. Weight loss ≥ 7 kg (15 lbs) or ≥ 1=% normal body weight.
3. Fever ≥ 38°C, intermittent or continuous.
4. Diarrhoea.
5. Fatigue/Malaise.
6. Night sweats.

II. Laboratory Studies

1. Decreases members of T-helper cells.
2. Decreased ratio of T-helper : T-suppressor lymphocytes.
3. Anemia or leukopenia or thrompbocytopenia or lymphopenia.
4. Increased serum globulin levels.
5. Decreased blastogenic response of lymphocytes to mitogens.
6. Cutaneous anergy to multiple skin-test antigens.
7. Increased levels of circulating immune complexes.

APPENDIX 2

4C

U.K. HAEMOPHILIA DIRECTORS AIDS SURVEILLANCE

Symptoms/signs or illness possibly related to AIDS or the AIDS-related complex

Please report patients who fit the criteria as indicated below. The conditions reported should be those where an association with AIDS is possible and where there is no alternative explanation to account for the presence of the condition, and all common causes have been excluded. In categories a) and b) please report patients who have any 2 features in a) + 2 features in b). In group c) only one criterion is necessary.

a) Clinical signs/symptoms: chronic condition for 3 months or longer.

1 Lymphadenopathy > 1cm enlargement in any 2 non-inguinal sites

2 Weight loss unexplained >7kg (15 lbs) or > 10% of normal body weight.

3 Fever >38^{o}C, intermittent or continuous.

4 Diarrhoea; chronic a) specific pathogens/cause identified b) no specific cause found.

5 Fatigue/malaise

6 Night sweats

b) Laboratory studies

1 Decreased members of T-helper cells

2 Anaemia or leucopenia (<4300/mm^3) or lymphopenia (<1500/mm^3)*

3 Increased serum globulin levels (IgM, IgA or IgG) *

4 Decreased helper/suppressor ratios (only if associated with decrease in T-helper cells in a patient treated within the past month with factor VIII or IX)

5 Decreased blastogenic responses of lymphocytes to mitogens

6 Cutaneous anergy to multiple skin-test antigens

7 The presence of immune complexes in serum

c) Other conditions which do not conform to the C.D.C. definition of AIDS but which may be related to the syndrome.

1 Thrombocytopenia (<100,000 mm^3) + idiopathic/autoimmune thrombocytopenic purpura.

2 Autoimmune haemolytic anaemia

3 Nephrotic syndrome

4 Candida infection a) colon-rectal b) oral/pharyngeal
(oesophageal candida indicating AIDS)

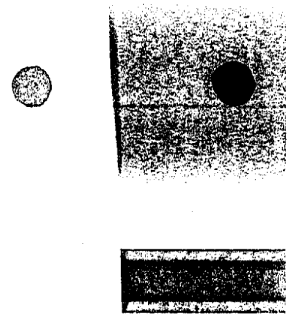
5 Amoebiasis/persistent

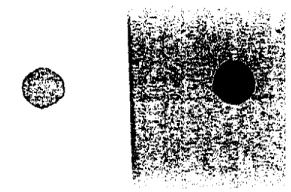
6 Varicella-zoster a) localised b) generalised

7 Non-Hodgkins lymphoma; lymphoma of the central nervous system

8 Diabetes - insulin dependent or recent onset.

9 Encephalitis, peripheral neuropathy or Guillain-Barre syndrome





*Observations made on 2 separate occasions over a period of one month