BACKGROUND PAPER I

ACQUIRED IMMUNE DEFICIENCY SYNDROME (AIDS)

WHAT IS AIDS?

AIDS is a newly recognised syndrome which first became apparent in 1981 when the Centers for Disease Control at Atlanta, Georgia, USA, became aware of an increase in the occurrence of a rare tumour (Kaposi's sarcoma) and of opportunistic infections (that is, infections not usually occurring in patients with normal immunity) in promiscuous homosexual males.

SYMPTOMS

The disease comes on insidiously with non-specific symptoms such as weight loss, fever, malaise and enlarged lymph glands and there is usually considerable delay between the occurrence of the first symptoms and the onset of the illness - such as Kaposi's sarcoma - which provides the clue to the diagnosis.

WHO IS AT RISK FROM AIDS?

The disease has occurred predominantly in homosexual males but other groups such as mainline drug abusers, Haitian immigrants and haemophiliacs requiring treatment with anti-haemophilic factor concentrates (FVIII) have also been identified as being at increased risk.

IS IT CAUSED BY A VIRUS?

The cause of aids is unknown. Although medical opinion is tending to favour a virus as the agent responsible, there is no proof that this is the case. There is no means of testing for the presence of AIDS in patients or in blood or blood products such as FVIII.

LABORATORY TESTS FOR AIDS

The only consistent laboratory abnormality detected in AIDS sufferers is a reduced number of the white blood cells known as lymphocytes together with a reversal in the normal ratio of those lymphocytes known as the "helper" cells to those known as "suppressor" cells. However, this abnormality is not specific for AIDS and cannot be used to make the diagnosis. At present, the diagnosis of AIDS is based predominantly on the total clinical picture in a given case.

MORTALITY

The mortality from the established disease is high: at least 40 per cent of patients die after a variable period of months or years after contracting the disease.

IS IT TRANSMITTED IN BLOOD OR BLOOD PRODUCTS?

As yet there is no conclusive proof that AIDS is transmitted by blood as well as by homosexual contact but the evidence is suggestive that this is likely to be the case. The evidence relates to some 11 haemophiliacs in the USA and three in Spain in whom the most likely explanation for the development of AIDS was their exposure to American FVIII concentrates. There is also some evidence that AIDS has been transmitted to babies in blood transfusions.

WHAT ARE THE CONTROLS ON IMPORTING BLOOD PRODUCTS

Importation of blood products is controlled under the Medicines Act and the plasma from which the products are made has to be shown to be free from a number of diseases for which tests are available. However, in the case of AIDS, no such test is available.

AIDS IN HAEMOPHILIACS IN THE UK

There is one suspect case in Cardiff. Although CDSC states that this case meets the USA criteria for AIDS, the clinician in charge does not consider that it should be regarded as a confirmed case. There is also a possible case at Bristol Royal Infirmary but it may not meet the criteria. Further details are being sought. There is still no trace of the London case which was mentioned in the press.

MANUFACTURE OF BLOOD PRODUCTS IN THE UK.

The Blood Products Laboratory at Elstree (BPL) is being up-graded at a cost of £2 million and will, over the next three years be re-developed at a cost of £21 million. When completed, the new laboratory will be of a size capable of making England and Wales self-sufficient in blood products, including Factor VIII .

FACTOR VIII USAGE AND HOME PRODUCTION

The latest available figures for usage of Factor VIII are; 1980- 57.7 million i.u and 1981 - 65.7 million i.u. BPL at present has the capacity to produce up to 30 million i.u per year, but is at present operating below this level, (in 1981/82 it produced 22 million i.u).

PAPER II

ACTION ALREADY TAKEN BY RELEVANT AUTHORITIES OUTSIDE THE DEPARTMEMT

1. Action by Regional Transfusion Directors

At their meeting on 18 May the Regional Transfusion Directors agreed to prepare an information leaflet on AIDS which would be available to donors to read at donor sessions and could be sent to donors phoning in with enquiries. (Directors asked if the Department would pay for the printing of such a leaflet and this has been agreed with Information Division. A draft has been circulated for comment).

The Directors further proposed to make an approach to the Medical Gay Society (an association of homosexual doctors) to enlist their help in the dissemination of information on AIDS to homosexual groups. The Society's initial reaction has been favourable.

Directors were adamant that there would be no direct questioning of donors about their sexual habits nor about the presence of symptoms such as night sweats, weight loss etc.

2. Recommendations of Haemophilia Reference Centre Directors

At their meeting on 13 May 1983, the Haemophilia Reference Centre Directors agreed that on the evidence available and because of the benefits of treatment, no restriction should be placed on the use of imported Factor VIII concentrate other than to continue with the present policy of using only NHS material for children under the age of 4 years and for mild haemophiliacs.

3. New Regulations on Donor Screening by the Food and Drugs Administration (FDA) in the USA

As from 23 March 1983, FDA regulations have required that:

i. Educational programmes be instituted for potential donors from defined high risk groups asking that they refrain from donation. (High risk groups are defined as: persons with symptoms and signs suggestive of AIDS; sexually active homosexual or bisexual men with multiple partners; Haitian immigrants, intravenous drug abusers and sexual partners of individuals at increased risk of AIDS).

ii. All plasma donors to receive information on AIDS.

iii. Plasma taken from a donor in a high-risk group should be labelled to indicate that it should only be used in the preparation of albumin, PPF, globulin or for non-injectable products. (NB: the use of such plasma for albumin, PPF etc production is extremely dubious. If an infectious agent is involved, there is no means of knowing that the heat treatment, to which these products are subjected, will inactivate it - DW).

iv. The donor's medical history should include specific questions designed to detect possible AIDS symptoms eg night sweats, unexpected weight loss etc.

v. Donors should be examined for lymphadenopathy (a limited examination to be made by "an adequately trained individual" at each donation and annually by a physician).

vi. The donor's weight should be recorded before each donation. A donor with unexplained weight loss should be referred to a physician and any plasma stored from that donor should be quarantined.

viii. Plasma from a donor known or suspected to have AIDS must be quarantined and destroyed or otherwise handled accordingly to specified procedures for bio-hazardous materials.

4. Council of Europe

Dr Gunson attended a meeting of the Council on 16-19 May. AIDS was discussed at length and Dr Gunson has sent a summary report for most of theEuropean countries. (The report from Belgium is interesting because of the preponderance of patients originating in Zaire and the suggestion in the Lancet that the disease may be caused by a variant of the African Swine Fever Virus may well be pertinent). Most countries reported additional cases following the preparation of their reports but there are veryfew cases following transfusion, even in W. Germany.

Dr Gunson reports that there is going to be a resolution put to Ministers of the Council of Europe. This has not yet been finalised but the gist is as follows:-

1. To expose the recipient to a minimum number of donations of blood in the case of transfusion of cellular and coagulation factor products.

2. To achieve national self-sufficiency in the production of coagulation factor products.

3. The avoidance of the importation of plasma and coagulation factor products from countries with high risk population.

4. To provide information to all donors so that those at risk will abstain from donating.

5. To inform all attending physicians and selected patient groups of the potential hazard and the possibilities of minimising this risk.

Dr Gunson draws attention to 1 above as indicating the probability of a greater use of cryo-precipitate in Europe since this tends to be the standard product in many European countries. This will have far-reaching implications for BPL as it would cause great difficulties to change to the production of freeze-dried cryoprecipitate. The CBLA will need to consider the interim period before completion of the new plant and the path to a solution of the problem is as yet unclear.

PAPER III

Implications for UK imports of new FDA requirements

1. Dumping

There are presumably large stocks of Factor VIII concentrates in the USA prepared before the 23 March guidelines came into force. It is possible that concentrates made from the "safer" plasma may be retained for use in the USA while the older stocks may be dumped on export markets such as the UK. MB4 advises that the manufacturers are certainly able to identify those batches of plasma collected after 24 March 1983 and are therefore able to identify batches of concentrate made from such plasma Whether or not they would be prepared to release this information is another matter.

Should we now initiate new requirements to make it mandatory for the date the plasma was collected to be on the product label?

2. Should we accept only 'post 24 March' products? Would there be adequate supplies? MB4 advise that all FVIII concentrates are subject to full "Stop Orders", which require the manufacturers to submit protocols and samples from every batch they propose to sell in the UK, to Dr Duncan Thomas's department at NIBSC. The content of an individual manufacturer's protocol is very much a matter for agreement between Dr Thomas and the company. Date of plasma collection is thought not to be a requirement at present, but probably could become so if it were thought desirable. The Licensing Authority would then, on the advice of Dr Thomas, be able to reject those batches which did not comply.

The practical and legal aspects of this suggestion would, of course, have to be checked beforehand, but even the threat of such action might be sufficient to persuade the manufacturers to comply voluntarily. There are probably large stocks of FVIII waiting for batch clearance by NIBSC and this almost certainly includes material made from pre 24 March plasma.

3. Possibility of obtaining concentrates from plasma which does not come from "epidemic" centres

Plasma taken from high risk donors has to be labelled as such but the products derived therefrom do not. MB4 advise that exclusion of suspect plasma could only be achieved by voluntary action by the companies themselves, since although the source of all plasma is known to the manufacturers, unless they take a specific decision to segregate the plasma on geographical grounds, it is likely that the huge pools employed would contain everything available. Travenol have closed down their downtown New York City Plasmapheresis Centre and they and the other three companies may be giving thought to doing the same thing to centres in San Francisco, Florida, etc.

4. Could we obtain from sources other than the USA sufficient material derived from European plasma to supply up to 30 million i.u. of FVIII concentrate should it prove necessary to withdraw some or all of the American products? MB4 advise that the European manufacturers would have no chance at all of producing this amount from European plasma, for sale in the United Kingdom. The Swiss are said to have a small surplus of "home grown" concentrate but the amounts involved are nothing like 30 million i.u.

However, Dr Gunson has discussed the situation with Dr Hassig, Director of the Swiss Red Cross Blood Transfusion Service and it would appear that Switzerland has no surplus either of plasma or of products.

PAPER IV

Implications of the introduction of heat-treated Factor VIII concentrates

A number of commercial manufacturers of Factor VIII are hoping to introduce Factor VIII concentrates which have undergone an additional heat-treatment step which is designed to reduce viral infectivity. Although originally aimed at reducing the risk of transmission of hepatitis, it is now being suggested that heat-treated concentrates might also reduce the risk of the transmission of AIDS.

As far as is known, there have been no controlled clinical trials to substantiate a reduced hepatitis risk from the heat-treated concentrates and nor, of course, is there any information on the transmission of AIDS. Nevertheless, should they be licensed for use in this country, it seems more than likely that there will be a heavy clinical demand for them. Not only would this have cost implications for the NHS, since the heat treatment substantially reduces the yield of Factor VIII per litre of plasma and therefore increases production costs, but the BPL may find itself obliged to manufacture heat-treated concentrates for which up to 60% more plasma might be needed simply to produce the current output of Factor VIII.

Clearly, there is a need for a controlled clinical trial of heat-treated concentrates in respect of hepatitis infectivity. However, such a trial could pose ethical problems at the present time. In earlier discussions on a protocol for such a clinical trial, Haemophilia Centre Directors had been of the opinion that a meaningful trial could only be conducted in patients who had not previously been trated with Factor VIII ie newly diagnosed mild haemophiliacs. However, this is a particular group of patients for whom the Directors have recommended that only NHS material should be used.

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PAPER VI

Implications of AIDS for production of FVIII at BPL

1. BPL manufactures an intermediate purity FVIII concentrate.

2. This year BPL will process approximately 130,000 litres of fresh plasma (FFP) to produce approximately 26 million i.u. FVIII. There is capacity in the existing factory to process approximately 150,000 litres of plasma (30 million i.u. FVIII).

3. Regional Transfusion Centres produce a variable quantity of single-donor cryoprecipitated FVIII. On average, each Region produces about 10,000 bags of cryoprecipitate (equivalent to approximately 1 m i.u. FVIII) per Region. One or two Regions have traditionally produced rather more cryoprecipitate than the majority - say 17-19,000 bags.

4. The more cryoprecipitate a Region produces, the less plasma it can send to BPL for FVIII concentrate production.

5. The major advantage of cryoprecipitate is that each bag comes from a single donor. Although an episode of bleeding may require a total of, say, 100 bags of cryoprecipitate (equal to 100 donors), every vial of FVIII concentrate is derived from a pool of plasma from 500 (PFL, Oxford) to 3,000 (commercial) donors. The pool size for BPL is approximately 1-1,500 donations. Exposure to fewer donors is thought to reduce the risk of infection to those receiving cryoprecipitate rather than concentrate.

6. There is some evidence from the USA to suggest that asymptomatic haemophiliacs who had been treated with FVIII concentrates were more likely than those treated with cryoprecipitate to have abnormal ratios of T-helper and suppressor lymphocytes, suggesting some disordered state of immunity in the patients receiving FVIII concentrate but not in those treated with cryoprecipitate. These results (N Eng J Med 1983, 308, 83-86) must be interpreted with caution. In particular, it should be noted that the cryoprecipitate was derived from volunteer plasma whereas the concentrate came from paid plasmapheresis donors. Nevertheless, the signed leading article in the same edition of the journal (pp 94-95) advocates the need to consider a change to a greater use of cryoprecipitate "even though we may not have enough evidence to demand such a radical change". It should also be noted that in Dr Gunson's summary of the Council of Europe Meeting on AIDS, he discerned a trend towards encouraging the greater use of cryoprecipitate in Europe (see paper II p. 4).

7. There are a number of disadvantages to cryoprecipitate as therapy for haemophilia, particularly for home treatment.

   i) It has to be stored deep frozen (concentrate can be stored in a domestic refrigerator).

   ii) It is messy to make up and inject and there is more difficulty preventing contamination during thawing and pooling.

   iii) Considerable volumes may be needed requiring i.v. infusion rather than injection.

   iv) It frequently causes allergic reactions.

   v) It is more difficult to calculate the dose required as the number of units of FVIII per bag is not known accurately.

8. In certain European countries a freeze-dried (rather than frozen) cryoprecipitated FVIII product is manufactured. Such material can be stored in a domestic refrigerator. There is little advantage in terms of donor exposure where the national product (as in Belgium) is large-pool freeze-dried cryoprecipitate. Small-pool (say 12 donor-pool) freeze dried cryprecipitates suffer high losses of product during quality control procedures and may be expensive to produce. No country has yet used repeated plasmapheresis of "accredited" donors to produce a moderate pool-size product (say 500 donations) from a smaller number of donors (say 50), thus combining the production advantages of a larger pool with a smaller donor exposure.

9. At present, haemophilia centre directors in the UK are not advocating a change in the pattern of treatment of haemophiliacs which would require increased production of cryoprecipitates. However, this could well change if a haemophiliac who had received only BPL concentrate were found to have developed AIDS.

10. If there were to be a significantly increased demand for cryoprecipitate, this would pose major operational and financial problems for RTCs and would reduce significantly - or even totally - the amount of plasma sent to BPL. The alternative to single donor cryoprecipitate produced in RTCs would be for BPL to change to small-pool freeze-dried cryoprecipitate production. The operational problems posed by such a switch in technology would be immense and it is doubtful whether it could be undertaken in the existing facilities. Moreover, the design brief for the redeveloped BPL would have to be totally re-worked to plan for the changed requirements.

11. The preceeding paragraph describes a worst-case situation. Nevertheless, the demand for cryoprecipitate could well increase to a certain extent and we need to know what contingency plans the CBLA has - or is in the process of developing - to deal either with a reduction in the supply of plasma to BPL or with conversion of part of its manufacturing out-put to freeze-dried cryoprecipitate.

12. Ascertaining the views of the CBLA could be either by

    i) a specially convened DHSS/CBLA meeting, or

    ii) Dr Harris could ask for it to be dealt with as an agenda item, for which DHSS could provide a paper.

Diana Walford
Med SEB
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