

## DRAFT MINUTES

## MEETING ON THE INFECTIOUS HAZARDS OF BLOOD PRODUCTS

NIBSC, February 9th, 1984

In introducing the meeting, Dr. Smith (NIBSC) welcomed participants, and explained that NIBSC was not the Licensing Authority in the U.K., but the Institute gave scientific advice to the Licensing Authority and the Committee on Safety of Medicines. The meeting had been called to examine the infectious hazards of blood and blood products, with particular reference to hepatitis and the acquired immune deficiency syndrome (AIDS).

In surveying the sources and use of Factor VIII concentrates in the U.K., Dr. Thomas (NIBSC) pointed out that the mean age at death of haemophiliacs had risen from 37 years in 1962 to virtually normal in 1984, and similar changes had occurred in the United States. The undoubted therapeutic benefit of Factor VIII concentrates was clouded by a well recognised side-effect, namely hepatitis, and also, more recently, by AIDS. It has been shown that the first exposure to concentrate, from whatever source, is associated with a hundred per cent infectivity with non-A, non-B hepatitis. The most recent information available indicates that 21 haemophiliac patients in the United States and 11 in Europe (2 in the U.K.) have contracted AIDS, presumably through transfusion of Factor VIII concentrates.

A recent report from the CDC, Atlanta, has also identified 31 cases of AIDS in the U.S. who have been recipients of a blood transfusion

within the past five years. Dr. Thomas suggested that there were three questions which the meeting should consider 1) Can AIDS be caused by transmission of an infectious agent in blood or blood products? 2) Can virus inactivation methods, such as heat treatment, reduce the risk of transmission of hepatitis and/or AIDS? 3) Are the steps currently being taken by transfusion centres and manufacturers of blood products adequate to minimise the risks?

In discussion, Dr. Cash (SNBTS, Edinburgh) pointed out that, in Scotland, there were a number of patients who had never received commercial concentrates; they were being kept under observation. Dr. Thomas pointed out that a recent study from Glasgow, (Brit.Med.J., 287: 1091, 1983) had found similar immunological changes in patients who had received blood products prepared by the Scottish National Blood Transfusion Service, as compared with those who had received commercial concentrates.

Dr. Craske (PHLS, Manchester) described the incidence of jaundice in U.K. haemophiliac patients from 1969 to 1979. Apart from a period in the mid-1970s when the incidence of jaundice rose to five per cent, the incidence has mostly been around two per cent per year. The incidence of hepatitis B has declined and, although serum markers are still seen, these are not usually associated with symptoms. On the other hand, non-A, non-B hepatitis (NANB) is very prevalent in the haemophilic population. In a prospective study, all nine patients with no previous exposure developed NANB from a single infusion (7 NHS, 2 commercial concentrates), as did eight out of 15 patients who had previously received concentrates. Some 30 to 40 per cent of U.K. haemophiliacs have abnormal liver function tests, indicative of possible chronic liver

damage but, in fact, only two patients have died of liver disease in the past 10 years. Two haemophiliacs have contracted AIDS in the United Kingdom, and one of these patients has died (Lancet 2: 1190, 1983). One of the U.K. AIDS patients received nine different batches of Factor VIII concentrate and a total of 231 patients who were given concentrate from one or more of these batches are being followed up - so far none has developed AIDS.

In the discussion that followed, it was pointed out that the pool sizes used by the commercial fractionators ranged from 1,000 to 10,000 litres of plasma, though sometimes the pools were combined at the cryo-precipitate stage, giving a possible maximum of 20,000 litres of plasma equivalent. The average volume collected from plasmapheresis donors was 680 ml, with a minimum pool size of around 1500 donors and a maximum of around 30,000 donors. The maximum pool size used by the NHS producers is 1000 kg of cryoprecipitate, incorporating material from about 5,000 donors. <sup>PLASMA</sup>

In considering current views on the aetiology of AIDS, Dr. Tedder (Middlesex Hospital, London) pointed out that AIDS is manifested as a profound deficiency of both cellular and humoral immune systems. One possible explanation is that the occurrence of AIDS in recipients of blood and blood products is due to a filterable agent, presumably a virus. Another possible explanation is an overwhelming of the immune system by repeated infusion of foreign (and possibly altered) proteins. He suggested that the true explanation may lie between the two extremes, namely that there may be a transmissible agent, which only becomes infective when certain conditions are met in the host. Various candidate viruses have been considered as putative AIDS agents, such as cytomegalo-

virus, Epstein-Barr virus, and human T-cell leukaemia virus. One possibility referred to by Dr. Tedder was that AIDS may be caused by a zoonotic infection, for example by an agent such as the African swine fever virus.

In discussion, it was pointed out that immunological suppression could be a factor in the blood transfusion-related cases. For example, transfusion modified the immune response of patients prior to kidney grafting. Dr. Schild (NIBSC) referred to the possible importance of genetic susceptibility, and suggested that HLA typing might be useful. Dr. Smith asked how certain was the diagnosis of AIDS? For example, most people currently use the CDC criteria for diagnosing AIDS, but how do patients with lymphadenopathy fit in?

Dr. Petricianni (FDA, Bethesda, MD) outlined the current strategies adopted by the FDA for the identification and exclusion of high-risk donors. Four strategies have been considered: 1) voluntary limitation by high-risk groups; 2) exclusion of high-risk donors; 3) laboratory testing and 4) a combination of the above. Currently, there are no specific laboratory tests that are able to identify a possible AIDS carrier. Although anti-hepatitis B core antibody is positive in more than 90 per cent of AIDS cases, it is also positive in approximately five per cent of normal individuals. The approach adopted by the Office of Biologics since March, 1983, was for plasma collecting centres to give information to each donor on AIDS, to encourage self-exclusion, and to examine donors for lymphadenopathy. The New York Blood Center had introduced an additional option, allowing donors to indicate privately that their blood should be used only for research purposes.

Long-term research on AIDS and transfusion in the United States had

focussed on three areas: 1) investigating the immunological changes seen after exposure to blood and blood products; 2) development of animal models for transmission of AIDS by blood products; 3) development of laboratory tests for carriers of AIDS. Dr. Tyrrell (CRC, Harrow) asked about testing for the unusual interferons recently described in patients with AIDS. Such tests were being considered, but Ms. Carr (Alpha Therapeutics, Los Angeles) commented that such tests would not be easy to develop on a large scale.

Dr. H. Eibl (Immuno, Vienna) asked what would happen to the hepatitis status of Factor VIII concentrates if all donors with antibodies to hepatitis B were screened out. Dr. Rodell (Armour, Kankakee, IL) pointed out that current Factor VIII concentrates contained little antibody to hepatitis B. Dr. Tedder said that two to three per cent of donors at the North London Blood Transfusion Centre were positive for hepatitis B core antibody.

Dr. M. Eibl (University of Vienna) reported on work in which several in vitro test systems had been applied to blood samples from haemophiliac patients in comparison with normal controls, and also in comparison with samples from patients with immunosuppression. Lymphocytes from haemophiliacs were less responsive than controls to antigen stimuli, and 30-40 per cent did not respond at all. She also mentioned that serum from some haemophiliacs prevented antigen uptake by normal macrophages. Dr. McClelland (SNBTS, Edinburgh) commented that the presence of immune complexes could influence these tests in vitro, and Dr. Eibl agreed that they could.

Dr. Ashworth (Cutter, Berkeley, CA) described collection procedures at plasmapheresis centres used by the four main U.S. companies. There

are some 340 plasmapheresis stations in 42 states, employing 6,000 people. Approximately a third of these centres are owned by the companies, and the rest supply plasma under contract. All plasmapheresis stations in the United States are licensed by the FDA, as is the centre in Belize. Dr. Ashworth described the donor records in detail, including questions intended to identify and exclude AIDS carriers. A detailed system exists which allows easy identification of product batches that contain material from a particular donor. Some companies are now avoiding taking plasma from centres in high risk areas of the United States, although he pointed out that not all donors who contracted AIDS lived in these areas. For example, both Cutter and Alpha Therapeutics have each had one donor who was later shown to have developed AIDS; in both cases, the donors were from Texas, which is considered a low risk area.

In discussion, Dr. Cash commented that paid donors are perhaps less likely to be truthful about their activities than volunteer donors. Dr. Rodell disputed this, and pointed out that in three of the four instances of blood donors contracting AIDS, leading to subsequent withdrawal of product, the donors were in fact non-paid volunteers. Furthermore, the payment to plasmapheresis donors probably sufficed only to cover their expenses.

Dr. McClelland (SNBTS, Edinburgh) presented data which suggested that the risk of transmitting NANB hepatitis by blood transfusion was 1 in 100, for hepatitis B, 1 in > 10,000 transfusions, and for transmitting AIDS, approximately 1 in a million. However, for haemophiliacs the risks were much greater because of the large number of donors to whom they were exposed. The policies adopted in Scotland to minimise the risk of trans-

mission of infection were explained. The three main strategies were 1) avoidance of high risk communities (such as prisons, known homosexual areas, etc.); 2) detection of clinical abnormalities by examination and careful questioning; 3) exclusion of the high risk donor, or his blood, always allowing an 'escape route' for the donor who is deemed unsuitable. Dr. McClelland pointed out that it is essential to have well established and well documented procedures in order to carry out these fairly simple strategies. It is also essential to have personnel at the local transfusion centres who can understand and accept the necessary training.

In discussion, Dr. H. Eibl commented that it was insufficient to ask a donor if he had jaundice during the previous 12 months, since some individuals could be carriers for several years. He also said that a study carried out in Europe indicated that there was no difference in the incidence of hepatitis B surface antigen in paid and volunteer donors. There was some discussion about the interval between collection of blood and processing of plasma. Dr. Rodell gave the following figures for the U.S. industry: collecting, testing, shipping - 7-14 days; transport - 1-14 days; pooling and processing - 20-90 days from date of collection.

Dr. Lane (BPL, Elstree) summarized fractionation and processing methods adopted to minimise infectious hazards. The incidence of hepatitis B surface antigen is 1 in 500 new donors, but fell to 1 in > 13,000 among previous donors. The laboratory test for hepatitis B surface antigen is a very effective screening procedure, but positive blood occasionally slips through the screen, usually because of technical errors in the performance of the test. Hepatitis virus may be present in all the various Cohn fractions. However, in Fraction V it is inactivated by the pasteurisation process, and in Fraction II (IgG for I.M. injec-

tion) neutralisation by antibodies could well be important, since extensive use has demonstrated the non-infectivity of this fraction. However, the recent occurrence of non-A, non-B hepatitis from intravenous IgG prepared at Elstree suggests that fractionation methodology may also play an important role in producing a noninfective product. Since the nature of the putative AIDS agent is unknown, it must not be assumed that IgG is incapable of transmitting AIDS.

Dr. Lane discussed three main options to reduce the risks of transmitting an infectious agent: 1) exclusion of source plasma; 2) exclusion of the virus by selective fractionation - for example, new methods such as affinity chromatography or virus binding; 3) inactivation of the virus by physical or chemical means. The third approach is currently the area of most active development, but it should be recognised that such processes may induce formation of neoantigens, with consequent toxicity or enhanced immune suppression. Of the range of products currently manufactured, most can be pasteurised with dry heat and some, like Factor IX and antithrombin III, can be pasteurised by wet heat without unacceptable loss of activity.

Dr. Schild (NIBSC) referred to the wide variety and characteristics of the many viruses that may be present in plasma. There are large differences in the overall virus size and shape, and also in the size and characteristics of the genome. These differences contribute towards the varying effectiveness of inactivation by the common chemical methods. For example, 8-molar urea is very effective in inactivating most viruses. Pepsin is also effective, except for the polio viruses. Formalin is not very good for inactivating double-stranded DNA viruses. However, these three processes, when applied sequentially, as in the MSD hepatitis B



vaccine, inactivate all known viruses. Almost 50 batches of hepatitis B vaccine have now been used in man, involving some 5,000,000 doses to over 1,000,000 recipients. So far there has been no evidence of AIDS or other infectious hazards developing in recipients as a consequence of vaccination. He reminded the audience that hepatitis B surface antigen can now be made by recombinant DNA technology, and such a product is likely to be available within the next few years.

Dr. Snape (BPL, Elstree) said that the ideal laboratory test for infective hazards should be specific and capable of detecting concentrations below the infective level. No such tests exist yet for AIDS and NANB, but the radioimmunoassay for hepatitis B surface antigen almost satisfies these requirements, being able to detect 0.1 - 0.5 ng/ml of antigen. Laboratory tests are usually applied to the screening of donors, but they can also be used on the final product, and in research and development. Screening of donors for serum alanine aminotransferase (ALT) levels has been considered in the United States, but is not used in the United Kingdom. Regarding the transmission of AIDS, the current approaches in the U.K. were to attempt to exclude high risk donors, to exclude plasma with a positive test for syphilis, and to quarantine plasma for 3-6 months to allow for retrospective evaluation.

Following the formal presentations, the discussion focussed on four main issues:-

1. What should be done about blood products made from plasma pools when one of the donors to that pool subsequently develops AIDS? This has already happened to U.S. manufacturers, leading to withdrawal of the affected batches. Dr. Thomas asked Dr. Petricianni whether the FDA had

specifically requested the manufacturer to withdraw batches that had been made from an affected pool. Dr. Petricianni replied that no formal instruction had been issued by the FDA, but the withdrawal had taken place as a result of informal discussion and agreement. The general feeling of the meeting was that if the diagnosis of AIDS in a donor is definite, then products prepared from pools to which the donor had contributed should be withdrawn. If a donor is found to have symptoms and signs, such as lymphadenopathy, which were associated with incipient AIDS, but were neither diagnostic nor specific for the condition, the recall of material to which the subject had previously contributed plasma was not justified. It was recognised that the scientific rationale for this course of action left much to be desired, but that no other action could be taken which would not imperil the supply of Factor VIII.

2. As far as laboratory tests for screening for AIDS are concerned, it was generally agreed that, on present evidence, only the test for hepatitis B core antibody was thought likely to be of value. However, there was no general agreement that such testing for core antibody should be part of the routine screening carried out on all donors.

3. There was much discussion about the optimal size of plasma pools, but no agreement that reduction of pool size would be either a practicable or a successful way to reduce the transmission of either hepatitis or AIDS.

4. The MSD hepatitis vaccine licensed in the U.K. was regarded as safe, having been exposed to three separate virus inactivation steps.

5. The safety of the specific immunoglobulins was discussed. The specific immunoglobulin preparations for intramuscular use, such as those for hepatitis B and CMV, must be regarded as potentially capable of trans-

mitting AIDS. These immunoglobulins were prepared from plasma collected from high risk donors and, unlike hepatitis B vaccine, no specific viral inactivation procedures are carried out during production. However, there is currently no evidence to suggest transmission of AIDS by specific immunoglobulins and, consequently, no reason to justify changes in their recommended use.

6. Continued research was clearly necessary. For example, the capacity of the various fractionation steps to inactivate viruses, and the effects on the properties of various blood products of these and other procedures to inactivate viruses, were areas requiring study.

In closing the meeting, Dr. Smith thanked the participants for their attendance, particularly those who had come a long distance to take part in the meeting.