Draft: 16.10.90

STATEMENT OF DR W. G. VAN AKEN

I, **WILLIAM GERARD VAN AKEN** of 29a Van der Veerelaan, 1181 PZ Amstelveen, The Netherlands can say as follows:-

1. I have the following qualifications and experience:

Qualifications:

M.D.	Catholic University of Nijmegen, The Netherlands Faculty of Medicine, 1965.
Ph.D.	University of Amsterdam, The Netherlands, Faculty of Medicine, 1969
Internist	University Hospital "Wilhelmina Gasthuis", Amsterdam, The Netherlands, 1974.

Present Appointments:

(a) 1981 - present: Medical Director and member of the executive board, Central Laboratory of the Netherlands Red Cross Blood Transfusion Service, Amsterdam.

(b) March 1982 - present: Professor of Medicine, Department of Biomedical Technology, Technical University Twente, Enschede, The Netherlands.

(c) June 1974 - present: Member of attending staff, Department of Medicine, Academic Medical Centre, University of Amsterdam.

Positions Held:

1/66 - 11/69;	Research fellow, Central Laboratory of the Netherlands Red Cross Blood Transfusion Service.

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11/69 - 11/73; Resident in Internal Medicine, University Hospital "Wilhelmina Gasthuis" Amsterdam.

11/73 - 7/74; "Chef de Clinique", Dept. of Medicine, University Hospital, Amsterdam

7/74 - 11/75; Visiting Scientist, Ontario Heart Foundation, Dept. of Pathology, McMaster University, Hamilton, Canada.

11/75 - 1/84; "Chef de Clinique", Dept. of Medicine and consultant, Dept. of Cardiology, University Hospital, Amsterdam; Staff member, Central Laboratory of the Netherlands Red Cross Blood Transfusion Service.

2. I am a member of several national and international committees and organisations (appendix 1) and have published a number of articles and books concerning blood transfusion, coagulation, AIDS, hepatitis B and thrombosis. A selection of recent publications appears at appendix 2.

GLOSSARY

3. **Central Laboratory of the Netherlands Red Cross Blood Transfusion Service:** ("CLB") The CLB is a not-for-profit organisation founded by the Dutch government, the Netherlands Red Cross Society and the Municipality of Amsterdam in 1943.

4. **Military Blood Transfusion Service:** ("MBTS") The MBTS is the blood collection service for the Netherlands Army. It collects blood from individuals working in the army and distributes blood and blood products to the army hospitals. The CLB fractionates plasma on behalf of the MBTS for which the MBTS pay a fee. The CLB also purchase any surplus product produced by or on behalf of the MBTS.

5. **Department of Immunology:** This is a department of the University of Amsterdam which is based at the CLB and carries out research in the field of immunology.

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6. **National Council for Public Health:** A government organisation which advises the Dutch government on the scientific aspects of various health problems. One of the committee's of the Council is a committee on AIDS formed in [ ].

7. **Central Medical Blood Transfusion Commission:** A commission of the Netherlands Red Cross formed to coordinate and supervise all activities in relation to blood transfusion from collection to administration and distribution of blood products.

8. **Haemophilia Society:** The society is a patient organisation of which almost 80% of Dutch haemophiliacs are members. The society represents patients on various committees and makes representations to the government on haemophilia-related problems.

9. **Chief Inspector of Health Care:** [brief description]

HISTORY OF THE CLB

10. The CLB was formed in 1943 as a division of the Netherlands Red Cross with four objectives:

(a) the production of blood products;

(b) provision of diagnostic services to hospitals in the fields of immunohematology and blood transfusion technology;

(c) research into areas such as transfusion medicine, immunology, haematology, allergy and microbiology; and

(d) teaching and education at pre and post-doctoral level.

11. The CLB is not government funded and funding is achieved in a variety of ways including the sale of blood and blood products to hospitals throughout the Netherlands, research grants from various bodies and fees for diagnostic services.

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12. Health care in the Netherlands is based on a social welfare system with the recipients of blood and blood products receiving those products free of charge. Despite this, the CLB no receives no direct government funding and all blood and blood products produced at CLB are sold to hospitals and pharmacies throughout the Netherlands, who are funded through government run organisations.

13. The CLB collects blood and plasma through mobile clinics throughout the Netherlands. In addition it manufactures Factor VIII and IX concentrates for distribution throughout the Netherlands. CLB is the only fractionation laboratory in the Netherlands and fractionates plasma collected by the regional blood centres and the MBTS in addition to that collected directly by the CLB.

STRUCTURE OF PLASMA COLLECTION AND THE MANUFACTURE OF BLOOD PRODUCTS IN THE NETHERLANDS

14. The collection and provision of blood and blood products in the Netherlands is governed by the Law on Human Blood which was enacted, 1961. Under that law the Netherlands Red Cross is the only body authorised to collect blood in the Netherlands and the CLB is the only organisation authorised to manufacture blood products. In practice the system operates in a different manner: since 1975 the majority of blood has been collected at the 22 regional blood banks which are distributed throughout the Netherlands and which are found mainly in the larger cities and communities. These blood banks are independent not-for-profit foundations operated through the auspices of the Netherlands Red Cross and the hospitals. The regional centres collect blood in the regions in which they operate. Some of the blood is sold to the hospitals in that region for the purpose of whole blood transfusions. In addition the blood banks produce red cell concentrates which are also sold directly to the hospitals. Between 1980 and 1985 six of the blood banks also produced cryoprecipitate which was sold directly to the hospitals in that region. All the blood banks sell their surplus plasma to the CLB for the manufacture of coagulation concentrates.

12. The CLB also collects blood in the form of fresh frozen plasma for fractionation purposes through mobile clinics which operate in the smaller

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towns and rural areas where there are no regional centres. The CLB does supply some red cell concentrates to hospitals although only as a back-up service to the products provided through the regional blood banks.

13. Prior to 1985 there were a number of hospital blood banks who continued to collect blood for use within the hospital. These banks are no longer in place and since 1974 have gradually been replaced by the regional blood banks.

14. All blood is collected on a volunteer basis and donors receive no payment or any other form of remuneration for their services.

15. Currently the CLB produces heat-treated Factor VIII and IX in the form of concentrate and cryoprecipitate. These products are sold to hospitals and pharmacies throughout the Netherlands on request. The CLB does not produce DDAVP or any porcine or bovine concentrates and any hospital or haemophilia physician wishing to use these products must purchase them directly from the manufacturer.

16. In addition to the CLB product there are a number of foreign imported products licensed and available for use in the Netherlands. The hospitals and haemophilia physician have a choice as regards the products with which they treat their patients and are not obliged to purchase the CLB product. Foreign, imported concentrates are purchased directly by the hospitals from the manufacturers and the CLB are not responsible for the purchase, imputation or distribution of these products.

LICENSING IN THE NETHERLANDS

23. All blood and blood products sold in the Netherlands must be licensed prior to use. Blood and blood products are licensed by the Committee for Blood and Blood Products which is a committee of the National Council of Public Health.

24. Every manufacturer who wishes to sell and distribute blood products in the Netherlands, including the CLB, must submit a licence application containing information about the product to the Committee on Blood and Blood Products. The Committee assesses each application [does it carry out any

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tests as regards safety, efficacy] etc and where appropriate, issues a licence. Licenses are granted under the Law on Human Blood which sets down the licensing regime. A licence is required for every product and must be renewed whenever the product specifications are altered in any way, for example through the introduction of a heat treatment process or a change in pool size.

25. In addition, regular inspections are preferred of all licensed premises by the Inspectorate of Pharmaceutical Drug Products in conjunction with the Governmental Control Agency. The CLB laboratory is subject to regular inspections by these bodies.

COLLECTION OF BLOOD PRODUCTS

17. Between 1980 and 1985 the total number of blood donations in blood banks increased from 580,000 to 627,000 and has gradually increased since then. See appendix []; Plasmapheresis was introduced in 1985 when 11.000 apheresis procedures for the collection of plasma were performed.

18. The total volume of fresh frozen plasma which the regional blood centres delivered to the CLB for fractionation rose from 50,000 litres in 1980 to 77,500 litres in 1985. During this period the collection of plasma by the CLB and the Military Blood Transfusion Service dropped slightly from 40,000 to 32,000 litres annually. However in total, the national collection of fresh-frozen plasma for fractionation increased between 1980 and 1985 from 90,000 litres to 110,000 litres in 1985. Since 1985 the total volume has further increased and in 1989 almost 160,000 litres was collected. These figures do not include the plasma which was used by the blood banks to produce cryoprecipitate. Three blood banks are still producing cryoprecipitate in the wet, unheated form.

CRYOPRECIPITATE

19. In 1964 Judith Pool discovered that cryoprecipitate is enriched in factor VIII and is therefore a suitable product for the treatment of haemophilia A.

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20. The CLB has produced lyophilised (dried) cryoprecipitate made from pools of 4 donations since 1987. This product is distributed to hospitals throughout the Netherlands for the treatment of haemophilia. Since 1985, all cryoprecipitate produced by the CLB has been heat-treated. In addition to the product produced at the CLB a number of the regional blood banks have also produced, since 1975 wet (=not lyophilised) cryoprecipitate which is used for the treatment of haemophilia in the regions they supply. The CLB have also continued to supply the hospitals in those regions with the dried CLB product throughout this period as many clinicians prefer to use dried rather than wet cryoprecipitate.

21. Until recently cryoprecipitate was the product of choice for the treatment of haemophiliacs in the Netherlands:- the Law of Human Blood, mandated that self-sufficiency be achieved in the Netherlands. During the 1970's and early 1980's there was a committee comprising representatives of the haemophilia physicians, the haemophilia foundation, the blood banks and the CLB which reviewed the logistics of FVIII production and use. In addition, a group representing the haemophilia physicians met approximately every 3 months to consider the amount of volunteer plasma available and the amount of FVIII that could be produced from that plasma. That group tried to influence the treatment schedule and the general strategy of haemophilia treatment in the Netherlands taking into account the desire for self-sufficiency and the corresponding wish to use the plasma in the most optimal way. In 1979 when FVIII concentrate was first introduced in the United States the CLB approached this group and enquired whether they wanted us to manufacture concentrate. At that stage, the answer was "no" and the CLB was requested to devote all its attention to the production of cryoprecipitate. Although the convennience of Factor VIII concentrate and the benefits of home treatment were recognised, haemophilia physicians considered that these factors were less important than the achievement of self-sufficiency. As a result, throughout the late 1970's and early 1980's cryoprecipitate remained the product of choice for the treatment of haemophilia in the Netherlands, as it was perceived by the haemophilia physicians that the higher yield from cryoprecipitate would enable the Netherlands to achieve a higher degree of self-sufficiency than was possible with an increased use of concentrates which had a far lower yield.

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22. By 1982 haemophiliacs, who became aware of the advantages and convenience of FVIII concentrates began to demand FVIII concentrate in increasing amounts. However by this time we were becoming aware of the possiblity that AIDS may be transmitted through blood products and therefore cryoprecipitate remained the product of choice until about 1985; as the pool size used in the production of cryoprecipitate was so small, particularly when compared with that used in the preparation of FVIII concentrates, we felt that the risk of transmission through cryoprecipitate would be much lower than for Factor VIII concentrate.

23. The annual supply of factor VIII, in the form of cryoprecipitate from the regional blood banks increased from 9 to 11 million IU of factor VIII in the period 1981 to 1985. Production at the blood banks increased as an increasing number of hospital blood banks were taken over by the regional blood banks who had better facilities available and who were therefore able to produce more cryoprecipitate. In addition, the haemophilia physicians continued to request cryoprecipitate, particularly after the development of AIDS. Since 1985, when heat-treated cryoprecipitate was introduced the production of cryoprecipitate at the regional centres has decreased and by 1989 had dropped to 4.6 million IU.

24. The production of lyophilised cryoprecipitate by the CLB during the period 1980 to 1985 was stable; between 1981 and 1984 the total amount varied between 9.4 and 10.5 million IU's, whereas in 1985 8.2 million IU's were produced. Since 1985 the production has remained stable at a level of 12.0 million IU's. Cryoprecipitate production at CLB increased after 1985 after following introduction of heat treatment. The regional blood banks did not have the technology or the funding to manufacture heated products on a large scale and therefore production at the regional centres, decreased which led to a corresponding increase in production at CLB's in order to meet the continuing demand. In addition, the regional banks are able to produce only wet cryoprecipitate whereas the CLB produces dried cryoprecipitate. The dried product is much less bulky and easier to store than the wet version. Dried cryoprecipitate may be stored and remains stable at room temperature. In addition it is easy to transport. Dried cryoprecipitate is therefore able to be used for home therapy whereas the wet product is unsuitable for home treatment. Total production of cryoprecipitate in the Netherlands remained constant until the government ordered that all products be dried and heated

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in 1987. This represents approximately [ ]% of the Factor VIII supply in the Netherlands. The use of cryoprecipitate is now diminishing and CLB has almost ceased production.

FACTOR VIII CONCENTRATE

25. Importation of factor VIII concentrate in the Netherlands was commenced in the late 1970's. Up until this time the physicians had indicated that they did not wish to use Factor VIII concentrates. However some patients, particularly those who had used concentrates during clinical trials etc indicated that they wished to use concentrates in the late 1970's. As a result the haemophilia physicians approached the CLB in 1979 with a request that the CLB import factor VIII-concentrate to satisfy the demands of those patients who wished to use it.

26. At that stage CLB did not produce any concentrates, as the haemophilia physicians had previously indicated that they did not wish us to produce concentrates. Initially we approached the Central Laboratory of the Swiss Red Cross in Bern to supply the necessary concentrate. However they were unable to supply sufficient material to meet our requirements. Subsequently we approached Baxter Travenol in the USA who were able to assist and we entered into an arrangement whereby the CLB imported the Baxter product into the Netherlands and subsequently sold the product to those hospitals and clincians who requested it. In 1981 when Baxter applied for a license for importation, other companies (e.g. Armour represented through its agent Tramedico) sued the Dutch Government for unfair competition as at that time it intended to allow only one company (Baxter) to import Factor VIII concentrate. This led to litigation which eventually resulted in the government allowing other companies to import factor VIII concentrates. Subsequently the Armour product was licensed and between 1981 and 1985 the Armour and the Baxter products were the only imported concentrates available in the Netherlands.

27. The CLB has manufactured factor VIII-concentrate (intermediate purity;spec. act. 1-2 IU/mg) since 1981. The CLB developed its own method of fractionation on the basis of the published literature and through knowledge acquired from contacts in the fractionation industry. **[Brief description of the process ie. precipitation - glycine purification]**

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28. Between 1981 and 1985 the production of factor VIII concentrate CLB increased from 3.4 million IU to 11.4 million IU. During this period cryo remained the preferred product of treatment and there was only a gradual increase in the use of concentrate. Currently, the CLB produces 21 million IU per annum which accounts for 51% of the annual demand. See appendix . In 1984 and 1985 one regional blood bank manufactured 100,000 - 200,000 IU of factor VIII concentrate which was sold locally.

29. As can be seen from table 1 (appendix), the volume of imported factor VIII (mostly from U.S. companies) was initially slightly higher in 1981 and 1982 (6.0 to 7.0 million IU) than in the period between 1983 and 1985 (3.7, 3.5, 4.02 million IU) when less concentrate was imported. The reason for this is that the haemophilia physicians advised their patients not to use imported products after it became known that AIDS may be transmitted through blood products.

FACTOR IX CONCENTRATE

30. Factor IX concentrate was introduced in the Netherlands in [ ]. The Netherlands is self-sufficient in Factor IX concentrate and all Factor IX used in the Netherlands is produced by the CLB. Heat-treated Factor IX was first introduced in July 1985. The product is called prothrombin complex or 4-clotting factor concentrate since it contains, in addition to factor IX, clotting factors II, VII and X. It is distributed in lyophilised form. This is a product developed by CLB using a DEAE cellulose chromatography process.

31. Factor IX concentrate is used for the treatment and prevention of bleeding episodes in patients with haemophilia B and for the treatment of bleeding in patients with an overdosage of coumarins (oral anticoagulants), severe liver disease with coagulation abnormalities and in patients with congenital deficiencies of coagulation factor II, VII and X.

32. Between 1970 and 1985 one blood bank (Groningen) imported some Factor IX, although the volume is not known. Although the Netherlands is self-sufficient in Factor IX the Groningen centre chose to import the product rather than using the CLB product.

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33. The annual volume of Factor IX produced by the CLB is relatively constant at 9 - 10.5 million IU of which approximately 50% is used for the treatment of haemophilia B.

ALTERNATIVE METHODS OF TREATMENT

34. Other methods of treatment such as DDAVP and animal concentrates such as bovine concentrate are not manufactured at the CLB. These products are imported by the hospitals who require them on an individual basis and the CLB is not responsible for their purchase or distribution. At some time in the early 1980's the CLB was responsible for the importation of bovine concentrates. However that practice was stopped in around 1985 as the amount of product required was so low that it did not seem feasible for us to continue importing it.

SELF-SUFFICIENCY OF BLOOD PRODUCTS

35. Self-sufficiency should be considered in conjunction with a system of voluntary, non-remunerated blood donation. A working definition of self-sufficiency which was recently proposed by Dr. Leikola of the Finnish Red Cross to the Council of Europe (still informal) reads as follows:

> "The satisfaction of the appropriate clinical demands of a population for products derived from human blood or human plasma, by the provision of sufficient quantities of suitable quality from within that population".

36. The Netherlands has had a policy of self-sufficiency since 1961 when the Law on Human Blood was enacted.

37. There is ample evidence to demonstrate that blood and plasma products derived from paid donors are less safe than blood and plasma products from non-paid donors. However data tends to demonstrate that NANBH is just as frequent in patients treated only with products produced from volunteer plasma as it is in those patients treated with commercial products. While patients treated with commercial products may contract NANBH earlier than patients receiving only volunteer products or cryoprecipitate, as the amount

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of product received and therefore the number of donors a patient is exposed to increases, so does the probability of contracting NANBH with the result so that eventually, all patients will contract the disease.

38. In the period 1970 to 1985 the risk of transmission of hepatitis B and NANBH by cellular and plasma products was significantly increased in products derived from paid donors; when post-transfusion AIDS become known, it was demonstrated in various studies that commercial plasma products prepared from paid donors carried a higher risk for AIDS transmission than plasma products prepared from non-remunerated donations. In fact, it was this aspect that led the European Commission to formulate in the recent EEC-directive 89/381 (appendix) that member countries should take appropriate measures to ensure that, after 1992, only blood from non-remunerated blood donors is used in the EEC.

39. [In the Netherlands, where prior to 1985 most of the patients were treated with cryopeciptate produced from local volunteer plasma, the rate of seroconversion among haemophiliacs is [13%]. The rate of seroconversion amongst severe haemophiliacs is [18%]. There are no material differences between the rate of seroconversion amongst patients with haemophilia A and those with haemophilia B. - You will check this information.]

40. The achievement of self-sufficiency requires adequate starting material, production facilities and the know-how to process plasma products. Most of the debate and discussion about self-sufficiency is focused on the question of the quantity of source plasma. If plasma can be contract-fractionated abroad and the methods and product specifications satisfy the requirements of the national authorities as well as the users of products, national self-sufficiency can be fulfilled even without local fractionation establishments.

41. The limiting factor for achieving quantitative self-sufficiency is the product that is most consumed in relation to its yield from the starting material. All other products prepared from the same plasma are then in surplus. Whereas albumin was the scarcity product in the early seventies, factor VIII has been the driving force for blood and plasma collection during the last ten years. This change was largely caused by the increased usage of factor VIII by haemophiliacs and by the decreased recovery of factor VIII

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from the original plasma due to the change from the relatively impure cryoprecipitate to factor VIII concentrates of higher specific activity.

42. Advantages of Self-Sufficiency.

42.1. The major advantage of self-sufficiency is improved safety: prevention of the transmission of diseases by plasma products depends on the selection of donors, the sensitivity of screening tests and the virus inactivation methods which are applied during the manufacture of plasma products. The latter two measures, although beneficial, carry some limitations. For example, screening techniques are dependent on the "open-window" phase during which a donor may be infective but not sufficiently so for a positive test result. The effectiveness of virus inactivation methods depends on the breadth of disease which the method is effective against. For example, while heating may inactivate most viruses there may be some viruses which are heat insensitive. Nevertheless, in combination with a well-defined and healthy donor population these provide optimal safety guarantees.

42.2. Self-sufficiency of blood products guarantees that the spread of diseases like AIDS and post-transfusion hepatitis (hepatitis B, non-A, non-B hepatitis and other as yet unknown diseases in the future) which in the early stages after they become known are not detectable by laboratory tests, through the use of these products, remains local and is not spread to many other countries. While there may be exceptions to this, for example in some instances, surplus products, which are exported may carry disease, in the majority of cases, plasma which is collected and retained within one region will limit the spread of disease.

42.3. A further argument in favour of self-sufficiency is the optimal use of donor blood. Whole blood is collected for the provision of cellular blood components in hospitals with the plasma used either as fresh-frozen plasma for transfusion or fractionated into albumin, gammaglobulins and clotting factor concentrates. Plasmapheresis may be used to produce greater amounts of plasma in circumstances where a need for plasma exists. Importation of plasma competes with this system and may lead to donor demotivation when excesses of certain

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products arise. This may then lead to shortages of cellular blood products. For example, if donors are aware that only a small portion of their donation is to be used, with the remainder disposed of they may refrain from continuing to donate.

43. Disadvantages of Self-Sufficiency

43.1. It has been argued that self-sufficiency may lead to shortages of essential products when blood centres collect whole blood in sufficient quantities for the supply of red cell concentrates but are unable to supplement the plasma volume with aphorises material.

43.2. Lack of competition is another argument which is used to disfavour self-sufficiency of plasma products. For example, the cost of plasma products (as well as other blood products) is said to be higher in countries which are self-sufficient. This is attributed to the (smaller) size of the organisations or production facilities and the costs of developments and patent rights (licenses).

44. Current experience in Europe has shown that national self-sufficiency in countries with a population of more than four million is feasible (Scotland, Finland, Sweden, Belgium, the Netherlands). In fact, a population between 5 and 15 million may be more or less ideal in terms of a national or supranational blood programme which is self-sufficient; larger countries are sometimes quite heterogenous with remarkable regional differences (e.g. West-Germany) with the result that the organisational framework may be complicated and difficult to manage.

SELF-SUFFICIENCY IN THE NETHERLANDS

45. I consider that today and between 1981 and 1895 the Netherlands was self-sufficient in both Factor VIII and Factor IX. During this period CLB together with the blood banks producing cryoprecipitate supplied approximately 90% of the annual demand for Factor VIII. The remainder of the demand was met by importing factor VIII concentrate from foreign commercial manufacturers in varying amounts, ranging from 10 - 20% of the annual demand. See table 1 (appendix). Although the Netherlands was using imported concentrates during this period and continues to do so, the use of imported

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products arises, in my opinion, through choice and not out of necessity. Hospitals and haemophilic physicians in the Netherlands have a choice whether to use cryoprecipitate or concentrates and whether to use local or imported products. Some hospitals choose to use imported products for a number of reasons such as price etc. The fact that this happens does not detract from the fact that the Netherlands produces sufficient plasma to meet the annual requirement for Factor VIII and Factor IX and has the necessary infra-structure to fractionate and produce sufficient product. Although we do not produce sufficient plasma to provide only high purity, lyophilised Factor VIII concentrate we nevertheless have the ability to product sufficient product to meet the annual demand for Factor VIII.

46. Self-sufficiency in the Netherlands is regarded as the ability to supply sufficient product to both treat and prevent bleeding episodes both in hospitals and through home treatment. Although some directors of blood banks in the Netherlands (as well as in other places) have at times disputed the increasing use of factor VIII products and have argued that haemophiliacs should be more restrictive with the application of plasma products, the CLB has only used clinically accepted guidelines, ie those accepted and adopted by haemophilia clinicians, to plan the production of factor VIII and factor IX concentrates. Since 1979, regular meetings have taken place between representatives of blood banks, the CLB, the haemophilia society and physicians treating haemophiliacs, at which the logistics of and requirements for factor VIII-products are discussed and arrangements for the optimal supply made. In addition, the Haemophilia Society have organised repeated surveys among patients to make inquiries about the usage of factor VIII.

RESPONSE TO THE AIDS CRISIS

47. During 1981 the first scientific reports of patients with AIDS in the United States appeared. At that stage the disease was reported in promiscuous, homosexual men. Later the appearance of the syndrome in IV drug abusers and Haitian immigrants was reported.

48. In May 1982, during a symposium at the University Hospital in Rotterdam, the first report of a patient with AIDS in the Netherlands was reported. Dr. Curran from the CDC and head of the US AIDS task force

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presented an overview of "fatal diseases in promiscuous homosexuals" at the conference.

49. In August 1982 the chairman of the Haemophilia Association contacted the Netherlands Red Cross Committee on blood transfusion and the CLB to report on recent articles in the press which mentioned the possible association between AIDS and blood transfusion.

50. In September 1982 the Head of the Department of Infectious Diseases wrote to all physicians and others working in public health care reporting on the rapid increase in the number of patients with Kaposi's Sarcoma, opportunistic infections and decreased immunity in the United States. Doctors in the Netherlands were requested to report any patients with these abnormalities to the Department of Infectious Diseases.

51. In November 1982, the CLB learned through informal contacts with scientists in the USA of the possibility that AIDS might be transmitted by blood transfusion. At that time there was a great deal of controversy about the evidence that such transmission of the disease through blood products was real; the evidence available at that time and until 1984 was epidemiological evidence mainly on small groups. On this evidence it was not clear whether a virus was responsible for the disease and a number of other theories were touted including the possibility that it was a combination of a virus in conjunction with other viruses such as hepatitis. Some influential experts in blood transfusion in the USA refused to accept that transmission through blood products could occur.

52. In November/December 1982, the CLB became aware of the reported appearance of AIDS amongst haemophiliacs in the United States following a visit to the CDC in Atlanta by the head of the Department of Infectious Diseases, Public Health, Amsterdam. In addition, in November 1982, I received a copy of a pre-print of an article submitted by J Lederman to the New England Journal of Medicine which reported immune changes in haemophiliacs after transfusion with plasma products.

53. Shortly thereafter and as a result of the growing evidence that AIDS might be transmitted through blood and blood products, the Executive Board of the CLB, concerned that the disease may also be present in the Dutch donor

population and/or in concentrates imported from the United States, organised a meeting with representatives of the Haemophilia Society, the haemophilia physicians and the government to consider the measures which might be taken to prevent the spread of AIDS among haemophiliacs in the Netherlands. That meeting took place during November.

54. During the meeting it was decided to start a clinical trial in Dutch haemophiliacs to determine whether there were any immune changes and, if so, the nature and incidence of the reported immune changes after treatment with various clotting factor concentrates and cryoprecipitate. **[You are to check whether this study took place and if, so, send me the results of that study]**

55. In December 1982, an "emergency" plan was devised by the CLB to increase the production of small pool cryoprecipitate as factor VIII concentrate was considered to be less safe because of the much larger plasma pools used. Although we had not at that stage seen the US reports indicating that treatment with cryopecipiate may be safer, we decided on a theoretical basis that it may be safer to treat our patients with cryopecipiate where the number of donations in a pool was considerably lower than the number used during the manufacture of FVIII concentrates. The plan, which went so far as to eliminate the production and importation of FVIII altogether was subsequently implemented although not to the extent we originally intended. Although, the usage of concentrate diminished, the demand continued as the patients were reluctant to switch back to treatment with cryopecipiate. By that time it would have been difficult for the CLB to switch back to producing only cryopecipiate especially at short notice; there was a large volume of plasma already in production and it would have taken some time for this material to be phased out. In addition, production of cryopecipiate requires additional staff who would in turn have required training in the various procedures involved.

56. In January 1983 the CLB organised a discussion between representatives of blood banks, the Inspector of Health Care, the Amsterdam Health Care Service, the haemophilia society, the responsible physicians and the homosexual community about donor selection, particularly the exclusion of high-risk donors. At that time we were aware of measures being adopted in the United States to exclude high risk donors. However the government representatives and the homosexuals were not supportive of the suggestion

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that homosexuals be asked to self-exclude and there was no consensus reached at the meeting as regards donor screening or exclusion. In March and April 1983 further meetings were held at which agreement was reached as regards donor screening. As a result, a brochure was produced for use in all the blood centres, including the regional blood banks, asking high-risk donors to self-exclude. The brochure which was produced in collaboration with the representatives of the homosexuals asked donors in high risk groups to refrain from donating blood and was distributed in the blood banks from June 1983. The high risk groups identified were: male homosexuals with numerous, anonymous contacts, intravenous drug abusers, Haitian immigrants and haemophiliacs. **[You will send me a copy of the brochure and any subsequent brochures that were issued]**

57. The chairman of the group of haemophilia physicians attended these meetings and through him, the physicians were informed of the developments and information we had concerning AIDS, at about the same time, ie January 1983 the physicians treating haemophiliacs decided to inform patients with haemophilia about the potential risk for AIDS after treatment with clotting factor concentrates. A number of recommendations were distributed to physicians and patients by the haemophilia physicians including:

(i) preference should be given to factor VIII concentrate prepared from plasma collected in the Netherlands instead of commercial clotting factor concentrates;

(ii) Haemophiliacs below the age of 4 years, patients with less severe forms of haemophilia (ie mild haemophiliacs) and newly diagnosed patients were advised to use cryoprecipitate instead of factor VIII concentrate.

(iii) **[Recommendations concerning the use of DDAVP]**

The recommendations of the group of physicians treating haemophiliacs were published in the "Netherlands Tijdschrift voor Geneeskunde" (similar to the British Journal of Medicine) which has about 30,000 subscribers.

58. From the end of 1982 onwards the CLB, through myself and the Scientific Director kept in touch with the developments and reports on AIDS throughout

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the world. Representatives from the Netherlands attended a symposium on AIDS in New York in March 1983 where there was a great deal of discussion on the question whether AIDS was transmitted through blood and blood products. In March 1983 during a visit to the United States I noticed that many scientists had reservations concerning the possible link between Factor VIII concentrates and AIDS. Although there had been several reports of the development of AIDS in US haemophiliacs the immune abnormalities in haemophiliacs were not identical to those in other AIDS patients and although opportunistic infections had occurred in haemophiliacs there were no reports of Kaposi's Sarcoma which was a common feature in other cases. In addition the T4/T8 abnormalities were different in haemophiliacs who had an increase in T8 cells but no decrease in T4 cells.

59. At the biannual meeting of the Haemophilia Society in 1983 representatives of the CLB informed the haemophiliac patients about the possible risk of transmission of AIDS through blood products. A parent of one haemophiliac, who happened to be a reporter for one of the national newspapers (Trouw) obtained relevant information on AIDS and the transmission by blood at a very early stage of the AIDS epidemic. As is described already earlier, officials of the government, the health care inspection and the national blood transfusion organisation were informed on several occasions.

60. In several issues of the CLB-Bulletin, a periodical which is sent to almost 10,000 persons involved in blood transfusion, haematology, paediatrics, internal medicine, anaesthesiology, pharmacy and clinical chemistry in the Netherlands, the most recent information concerning AIDS was regularly included. Two review articles in the "Nederlands Tijdschrift voor Geneeskunde", written by the medical director of the CLB, addressed the topic of post-transfusion AIDS. **[May we have copies of these articles.]**

61. In April, 1983 the CLB became the first organisation in the Netherlands to organise a symposium on AIDS. During the symposium the risks for recipients of blood products were specifically reviewed. After the first International AIDS-conference in the USA in March 1983 the CLB organised a symposium to inform Dutch experts about the findings reported during the meeting in the USA. During the symposition the results of the first clinical trial on the T4/T8 ratio in Dutch haemophilics were presented. These

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indicated that patients receiving commercial concentrates had lower ratios than those treated with cryopeoptate and CLB concentrate.

62. In May 1983, Montagnier published an article in Science (appendix), in which he reported the isolation of a virus belonging to the group of retroviruses which he thought to be responsible for causing AIDS. I did not see this article at the time it was published although I became aware of it later in the year. Montagnier's results were viewed with some scepticism at the time although I recall we discussed the possible implications of his findings with regard to the inactivation of the virus in blood products, particularly the fact that retroviruses were known to be sensitive to heat.

63. Montagnier's findings were confirmed by Gallo in May 1984 when he reported the discovery of the HIV virus. Gallo was able to culture the virus in large quantities which enabled the development of test kits. The first developmental test kits became available in the Netherlands in November 1985.

64. In [ ] it was reported that the wife of a haemophiliac, who himself revealed no other risk factors for AIDS, had developed symptoms of AIDS. She died shortly afterwards and the diagnosis of AIDS was made. It was later demonstrated that her husband was seropositive.

65. In [[another patient with haemophilia was report to have AIDS.

INTRODUCTION OF HEAT TREATMENT

66. CLB first became aware of the existence of heat-treated Factor VIII concentrates in July 1982 when Baxter/Travenol (Hyland) introduced a heat-treated factor VIII concentrate during a one day Symposium for physicians treating haemophiliacs in the Netherlands. At that time only the reduced hepatitis risk was mentioned with Baxter's claiming that the product reduced the risk of transmitting NANBH. Inactivation of other viruses, including AIDS was not mentioned which is not surprising as at that time the development of AIDS in haemophiliacs had not been reported.

67. In February 1983 Baxter's distributed a brochure concerning Hemofil-T in which they put forward heat treatment as the best method of obtaining

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maximum protection against hepatitis. The brochure emphasised a report showing that heat treatment inactivated NANBH in plasma although there was no clinical data in the brochure. Subsequently in February 1983, Baxter distributed a "position letter" concerning AIDS in which it pointed out that only a small percentage of AIDS patients in the United States were haemophiliacs and that there were no reported cases amongst European haemophiliacs. The letter stated that the greatest problem for haemophiliacs is NANBH. (appendix). **[May we have copies of the brochure and the letter?]**

68. In May (or somewhere around that time) 1983 Hemofil-T, the Baxter heat-treated product was registered in the Netherlands and a number of the haemophilia clinicians began using the product on their patients shortly thereafter. At that time the product was introduced for the purpose of combatting NANBH.

69. CLB did not introduce heat-treated concentrate in the Netherlands either following the symposium in 1982 or after Hemofil-T was licensed in 1983. Although Baxter's claimed that their product was safer than non heat-treated products since it was alleged to inactivate NANBH, some experts were critical of the evidence for this claim particularly as Baxter's did not produce any clinical data to substantiate it. In addition, there was a concern that heat treatment might increase the risk of the development of Factor VIII inhibitors which could have serious consequences for haemophiliac patients. As a result of the above the CLB did not give any consideration to the introduction of a heat-treated product in 1983 and nor was it under any pressure from the haemophilia clinicians or their patients to do so. **When the CLB did eventually introduce a heat-treated product it was at our own initiative and without any pressure or order to do so.**

70. There were some risks perceived in importing and using factor VIII concentrate manufactured using plasma from commercial donors by companies in the United States. Before 1983 we were mainly concerned about the increased risk of NANBH transmission in relation to the use of commercial factor VIII and factor IX concentrates. In addition, since the screening of blood donations for hepatitis B antigen does not give absolute guarantees that all carriers of the hepatitis B virus have been excluded, it was taken into account that the risk of transmission of HBV virus was also higher in commercial concentrates than for products derived from non-remunerated

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donations. At that time we were routinely vaccinating patients against HBV and also adding anti-HBV immunoglobulin to the concentrate during fractionation. We were not taking any steps to alleviate the risk of NANBH.

71. The first circumstantial evidence that the AIDS-agent (at that time not yet identified) might be sensitive to heat, was mentioned in 1983 when Montagnier published an article in Science that he had isolated a virus which belonged to the group of retroviruses, which he thought to be responsible for causing AIDS. At that time we discussed the implications of his findings at the CLB as we were aware that retroviruses were generally sensitive to heat.

72. At around the same time it became known that surveillance studies among AIDS-patients indicated that previous albumin administration was not involved in the transmission of AIDS. This led some people to the hypothesis that the AIDS-agent was heat-sensitive.

73. In early 1984 we heard the first rumours that virus may be heat-sensitive. Subsequently in the summer of 1984 the CLB held discussions with Baxter/Travenol concerning the possibility of obtaining a licence from Baxter to manufacture heat-treated factor VIII-concentrate using the process developed by Baxter. This resulted in an agreement in August 1984 which was immediately followed by the transfer of know-how to the CLB.

74. In September 1984 Levy et al (Cutter) published evidence about the heat sensitivity of murine retroviruses which we accepted as further evidence that the virus causing AIDS was also probably heat labile. (appendix)

75. The Centre of Disease Control in the USA reported in the October 26 1984 issue of Morbidity and Mortality Weekly report that the AIDS-agent is sensitive to heat-treatment. (appendix)

76. In October 1984 developmental work for the production of factor VIII concentrate, which was heated in the lyophilised state, was started at the CLB. In addition, in December 1984 research on the heat inactivation of factor IX (prothrombincomplex-concentrate) was commenced. In January 1985 we decided that heated lyophilised cryoprecipitate should also be developed in the CLB; we were aware that if we only produced heat-treated concentrates

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we would quickly soon experience logistical problems because of the low yield we were obtaining through the heat-treatment process. Heated cryoprecipitate was developed to overcome this problems. Initially the yield from the heat treated concentrate was 150 IU per kilo. This subsequently increased to 200 IU although it has slipped to 180 IU following the implementation in [ ] of a controlled pore glass chromatography process ("PEG"). At about the same time further evidence for the heat-sensitivity of the AIDS-virus was provided by Spire et al. (appendix)

77. Clinical trials with heat-treated factor VIII concentrate manufactured at the CLB were performed in April/May 1985. These trials were performed on a small scale using 10 patients in one centre. The trials were directed to the clinical tolerance and Factor VIII recovery and its half-life in patients with haemophilia A. Comparative studies using non heat-treated Factor VIII were also conducted concerning the in vivo half-life, ie measuring the FVIII activity in the patient over a period of time to establish the period after infusion for which the level of concentrate remained at least 50% of the normal level. After the successful completion of these trials which showed that the half life was the same as for non-heated product, that there were no additional side effects, no drop in blood pressure or rise in temperature and that the product halted bleeding, the product was immediately registered and released for distribution in June 1985. Distribution began immediately to all hospitals and pharmacies and there was no interim or phase-in period during which the product was only available on a named patient/special request basis.

78. Clinical trials with heat-treated factor IX started in June 1985 and were finished in August of that same year after which also this product was registered and introduced on the market.

79. Heat-treated cryoprecipitate was clinically evaluated during August and September 1985 and after registration it was introduced for the treatment of haemophilia A in December 1985.

80. Our initial work into heat-treatment of clotting factor concentrates was carried out at a time that there was, certainly in the beginning, only scanty and circumstantial evidence about the efficacy of this method of inactivation with regard to HIV. At the time we entered into the licensing

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agreement with Baxter's HIV had not been proven to be heat labile and thereafter, the developmental work/research carried out at CLB was performed largely in isolation. We were working in isolation and very limited co-operation or sharing of information took place with the other manufacturers. In particular, we were uncertain as regards the use of stabilising agents which had to be added or to be left out of the product during the heating process to prevent degradation or modification of the factor VIII and factor IX as we feared that the use of such stabilising substances could, at least in theory, also lead to stabilisation of the virus(es) and consequently diminish the efficacy of heat treatment.

81. In 1985 we were heat-treating Factor VIII concentrate using the method we had obtained under license from Baxter. Although we were still fractionating using the method developed at CBL we were heating under the same conditions as Baxter, using the same additives as Baxter to protect the product during the heating process.

82. After the CLB entered into the licensing agreement with Baxter all our efforts were directed to inactivating the AIDS-agent (HIV) in plasma products. This was possible because the Department of Immunology was able within a short period of time to culture the virus in sufficient quantities to perform virus spiking experiments. As model viruses, we used phage X174, which was available at CLB and canine parvovirus which was provided by a firm called Duphar in Weesp. As a result we were able to perform the required virus-spiking experiments which enabled us to determine the extent of virus-inactivation in each of the individual steps taken in the preparation of plasma products. The Central Laboratory of the Swiss Red Cross in Bern has followed the same policy although most of their experiments were undertaken in close collaboration with the Institute Pasteur in Paris.

83. Under to the license which the CLB obtained through Baxter/Travenol the lyophilised factor VIII concentrate was heated for 72 hours at 60°C. The results of virus-spiking experiments performed at the CLB, in which known amounts of AIDS-virus were added to the product before inactivation and residual virus was determined afterwards, largely confirmed what at that time or later was published by other groups. This data showed that heat-treatment at 60°C for 72h reduced the virus-titer by a factor of 10.000 to 100.000 (4 to 5 logs) and in addition of 1 log reduction was obtained during

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lyophilisation. A log is the degree of infectivity in the starting pool. At that time the available evidence suggested that a 5 log reduction in infectivity during fractionation and heating would be sufficient to prevent the transmission of HIV. Similar results as regards the reduction of infectivity were obtained when factor IX concentrate and cryoprecipitate were used. Since the introduction of the CPG process a greater reduction has been achieved.

84. Heat-treated products have been available in the Netherlands since 1983. In 1987, the Dutch government ordered that only dried, heated products may be licensed and used in the Netherlands. Prior to 1985 the only products licensed and used were the Baxter product and Armour's product. The Baxter product was heated in the same way as the CLB factor VIII concentrate, although the product from Armour was heated for only 30 hours at 60°C. The Armour product was later shown to be less safe; in [ ] the group in the Academic Medical Center in Amsterdam wrote to the Lancet reporting that seroconversion (for AIDS) had occurred in a patient who was treated only with Armour concentrate. (appendix) Since then, two or three similar reports from other centres have appeared in the literature.

85. As described in paragraph [ ] above, heating for only 30 hours at 60°C (in combination with the use of non-screened plasma from remunerated donors) proved to be ineffective in eradicating HIV.

86. A longitudinal study among patients with haemophilia A and B in the Netherlands, performed in [ ] after the introduction of heat-treated factor VIII concentrate and cryoprecipitate, showed that there were no seroconversions during the two year length of the study which was conducted using patients who had received both local and imported product. [you will send me the results from the study] It should be noted that by that time all donations in the Netherlands were screened for antibodies to HIV and seropositive plasma was excluded from fractionation.

87. Although there was initially evidence from animal (chimpanzees) studies carried out by Hollinger and Purcell and described in a patent application by Armour, that the heat-treatment was also sufficient to inactivate non-A, non-B hepatitis virus(es), in mid 1985 (tab), Colombo et al (Italy) published a prospective study in which was it concluded that heating of lyophilised

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clotting factor concentrates at [ ] for [ ] hours was not sufficient to inactivate non-A, non-B hepatitis virus(es) (appendix).

88. After heat-treated product was introduced there was no attempt to withdraw non-heated product from stock. So far as I am able to recall the CLB timed the introduction of heat-treated concentrate to coincide with the exhaustion of existing stocks of the non-heated product. We did not seriously consider retro-heating any of the existing stock as we were uncertain of the effects that retro-heating may have on the product. I do not know what the hospitals or pharmacies did with any non-heated product they had in stock at the time the heat-treated product was introduced.

89. In [ ], following the introduction of heat-treated concentrates and heat-treated cryoprecipitate, the haemophiliacs were informed that, where possible non heat-treated products should no longer be used.

90. The CLB no longer produces heat-treated FVIII concentrate under license from Baxter and since [ ] has produced a pasteurised product which is also effective against NANBH.

91. In addition to the CLB product, a number of the commercial manufacturers, have obtained licenses for their products. The products which have been licensed at various times include: Hemofil T, Factorate (Armour), Hemate-P (Behringwerke), Hemofil-M, and Monoclate-P which has only recently been introduced. Some of these licenses are no longer in effect either because the authorities reviewed their previous decision (see Armour product) or the company replaced the product by another factor VIII concentrate (e.g. Baxter). Behringwerke have submitted a heat-treated factor IX concentrate for licensing.

ALTERNATIVE METHODS OF VIRUS INACTIVATION

92. Since 1982 CLB has carried out immune neutralisation, i.e. the addition of specific antibodies to hepatitis B to the product during fractionation as a means of eliminating the risk of hepatitis following the infusion of Factor VIII concentrates. **[expand on the development and use of this method. For example when and where was it developed, at which stage of production are the antibodies added etc.]** It has been demonstrated in animal studies

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(chimpanzees) that this is effective to reduce/eliminate the transmission of HBV.

93. In other European countries methods of chemical/physical inactivation by beta-propiolactone and U.V., irradiation have been developed (Biotest, Germany). Chemical inactivation by solvent/detergent mixtures, as propagated and pioneered by Horowitz in the New York Blood Centre was also studied and developed at a later stage. The Biotest product has never been used or considered by the CLB. We have recently started using the Horowitz method in the fractionation of FIX concentrates.

94. Gamma irradiation was studied in the Netherlands in 1987 by the CLB who conducted a study using this method of inactivation. In addition we have considered pasteurisation (in the liquid state) of factor VIII. This method of pasteurisation was developed in 1987 at CLB and after clinical trials was registered and has been available since 1990. In addition work has been carried out on the solvent/detergent treatment of prothrombin complex concentrate since 1988 and we expect to begin distributing this product in 1990.

TESTING

95. In the Netherlands testing of blood donors for hepatitis B antigen started in about 1972 and became mandatory in about 1973 under the Law of Human Blood.

96. The CLB is responsible for the screening of plasma derived from the donations collected during the campaigns of its own mobile teams as well as for the screening of plasma collected by the Military Blood Transfusion Service. The CLB screens plasma collected by its mobile teams for HBV and HIV. Testing for HCV has been introduced at one centre on a trial basis and will be introduced at all clinics after 1 November 1990.

97. Plasma delivered by the regional blood banks to the CLB for fractionation is tested at the blood banks for the presence of antibodies to HIV and hepatitis B-antigen. Testing for HCV has not been introduced although it will probably follow shortly after the introduction of HCV

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testing at the CLB clinics. Except for apheresis plasma, plasma delivered by the blood banks is derived from whole blood donations, from which cellular blood components are prepared. These concentrates may only be released for distribution to the hospitals after they have been found negative. The blood banks supply the CLB with a list of the results of the screening tests performed on the individual donations from which the plasma is sent to the CLB.

98. Plasma received at CLB for fractionation is not retested and there are no tests conducted on either the start pool or at any stage during the fractionation process. The final products are tested although I have doubts as to the efficacy and value of these tests.

99. The first experimental test kits for HIV were available in the Netherlands in November 1984.

100. In the last part of 1984 and the beginning of 1985 CLB performed a comparative study of several test kits for the detection of antibodies to HIV. The CLB did not develop its own test for the virus and the tests we were evaluating were those produced by other companies. Most of the evaluations were carried out by the National Institute of Health with the CLB acting as a reference centre. [Explain] The evaluations were carried out to determine sensitivity and specificity of each test before it could be licensed and used for regular screening.

101. Surrogate testing was not introduced although it was contemplated for some time before anti-HIV testing became possible. Experience with some of these surrogate tests in the USA indicated a low sensitivity and specificity which were considered not suitable for use in the screening of blood donations. In any event we were not under any pressure from the haemophilia society to introduce any form of surrogate testing.

102. The routine screening for antibodies to HIV in the plasma of donors who attended the mobile campaigns of the CLB, was started in March 1985. During the following months (April till July 1985) the regional blood banks introduced routine screening of all their blood donors. Initially donors were not informed that testing was performed and seropositive donors were not informed of the results.

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103. It was decided both by the National Council of Public Health and the Central Medical Blood Transfusion Commission of the Netherlands Red Cross not to announce that the screening of blood donors was mandatory or to inform donors about the (positive) result of the anti-HIV testing, until the organisation of "alternative testing facilities" was more or less ready. The Dutch authorities have never required/directed mandatory testing of all donations and testing was implemented on a voluntary basis by the blood banks. Although there was some concern as regards the introduction of testing without informing the donors we decided that our primary responsibility was to the recipients of the products and not to the donors. Although we appreciated that there may later be problems as regards those donors who tested positive and were not immediately informed, or felt there was be a greater danger in announcing that testing was being carried out without first ensuring that alternate test sites were available. After the alternate test sites were introduced and the announcement made that we were testing for HIV, all donors who had tested positive since the intial introdution of screening were informed of the results.

104. Alternate test sites at Public Health Laboratories were established by December 1985 and consequently in the beginning of 1986, it was decided [by who] to start informing all seropositive (i.e. Western Blot confirmed) donors. The Director of the relevant blood bank is responsible for informing the donors if they have tested positive.

105. Tests from a number of different manufacturers have been used. These include Abbott (USA), Welcome (UK) and Organon (the Netherlands). At a later time also test reagents from companies like Dupont (USA) have been used.

108. The timing of the introduction of testing in the Netherlands was governed by:

(i) the availability of sufficient reliable test kits for the screening test; both the sensitivity and the specificity of the method(s) were considered when a selection was made;

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(ii) "alternative test facilities" (i.e. outside the blood banks). These were necessary in order to prevent persons belonging to any of the risk groups, using the blood banks to determine their individual sero-status; in view of the length of the "open window" period of the HIV-infection, a considerable risk would be taken when such donors were included. This factor only affect the introduction of the screening tests for blood donations to the extent that the information about the test result was passed to the donors.

POOL SIZE

106. Calculations on the effect of pool size on the risk of contamination/infectivity of HIV have been made, taking into account various estimates on the prevalence of HIV-carriers in the donor population. **[who carried out these studies and when]** From the results of these studies **[do you have the results]** it was evident that a significant correlation existed between the pool size and the risk of HIV-transmission. The risk was significantly lower when small pool cryoprecipitate was considered.

107. Estimates were also made for various pool sizes. These demonstrated that only when the pool size of plasma for the production of factor VIII and factor IX concentrate was very much reduced, was the risk of HIV transmission markedly reduced. However, regular production of these products would then need to be changed and clinical studies of the products from such production methods would have to be performed. Inactivation of the AIDS-agent(s) was considered to be more successful and feasible as a means of reducing the risk of transmitting AIDS thorough blood products than reducing the pool size. One of the problems in reducing the pool size was that we would have had to obtain a new license for our product which would also have required clinical trials. We knew that we would have to undergo a similar procedure when we introduce an inactivation method and in the circumstances decided that we would only go through this process once and that on balance, virus inactivation was more feasible and, in the long term likely to be more successful in inactivity or reducing the risk of virus transmission than a reduction in pool size. In addition, our calculations showed that in order for a reduction in pool size to be of any great effect, the pool had to be

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reduced so greatly that it would not have been possible to produce a commercially viable product.

108. Similar studies/calculations regarding NANBH have not been made; it should be noted that at that time reliable information regarding the prevalence of this disease in the donor population was still lacking in the Netherlands.

109. As far as the relationship between hepatitis B and pool size is concerned, it should be kept in mind that the CLB used anti-hepatitis B immunoglobulin, which is added to the products during the manufacturing process, to eliminate the transmission of hepatitis B virus. The efficacy of this measure was previously demonstrated in chimpanzee studies.

110. According to information provided by Dr J Over, head of New Product Development at CLB, the pool size for the production of factor VIII-concentrate prepared in the CLB was 700 kilograms (ie 2800 donations) in the period between 1979 and (approximately) 1986 and 1500 kg. during the period 1986 till mid 1988; at present this volume varies between more than 2000 and 4000 litres per lot.

111. For factor IX the pool size varied from 400 kg to 600 kg till mid 1988. Since then the volume has varied between 1000 and 2000 kg.

POSITION IN THE REST OF EUROPE

112. **Self-sufficiency**

In 1988 the Expert Committee on Blood Transfusion and Immunohematology of the Council of Europe conducted a coordinated research programme in blood transfusion entitled "Procurement and proper use of human plasma and their relevance for national blood transfusion programmes". A questionnaire was sent to all member countries asking for data from 1980, 1983 and 1986. From this information the following can be concluded.

(i) National blood transfusion services are responsible for country-wide blood supply in England and Wales, France, Ireland, Malta and Scotland, whereas the Red Cross plays virtually the same role

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in Austria, Belgium, Finland, Luxemburg, the Netherlands and Switzerland. Denmark, Cyprus and Sweden have an exclusive hospital-based transfusion network. In the following countries a mixed system exists: Federal Republic of Germany, Turkey, Italy, Norway, Portugal and Spain.

(ii) In 1980 and 1983 self-sufficiency was largely achieved in countries such as France, Belgium and Finland. In these countries, where only not-for-profit organisations are allowed to collect blood, importation of blood products was not allowed (Belgium) or not attractive for commercial companies as the local organization (Finland) had close ties with the clinicians. In Franch importation is only possible through the CNTS in Paris, which is itself a producer of plasma products. The consumption of factor VIII in these countries is, however, similar to that in most other European countries.

113. **Introduction of Heat treatment**

113.1. Heat treatment was introduced into Belgium at about the same time as it was introduced in the Netherlands. (Dr. Vermylen, [who is he], personal communication)

113.2. In Finland **[to be completed]**

113.3. **any other countries**

114. **Method of Heat treatment**

114.1. The Central Laboratory of the Swiss Red Cross is Bern, the CNTS in Paris, various regional transfusion centres in France, the Blood Transfusion Service of the Finnish Red Cross, the fractionation centres in Brussels and Leuven and the Blutspendedienst of the German Red Cross all adopted a process which involved heating at 60°C for 72h.

114.2. Some of the commercial fractionators in Europe used different methods: Biotest developed a process using beta-

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propriolactone and ultraviolet irradiation; Behringwerke used a method of pasteurisation of Factor VIII in the fluid state. Kabi, in Sweden heat-treated under the same conditions as CLB.

115. **Testing**

115.1. In most countries the same factors as described above, influenced the timing of the introduction and the nature of the HIV-screening. There was also some dispute in some organisations that a reliable and standarized confirmatory test should be available before the screening of anti-HIV could be introduced [**Was this a factor in the Netherlands?**]. Otherwise, it would be problematic to informed seropositive donors only on the basis of the result of screening test which carry a inherently limited specificity.

115.2. To my knowledge and information, the situation in countries such as Finland, Switzerland, Belgium, France and Sweden is similar to that in the Netherlands so far as the introduction of testing for HIV is concerned.

115.3. In May, 1985, at a meeting of the Committee of Experts on Blood Transfusion and Immunohematology of the Council of Europe, the measures with regard to anti-HIV testing in the various member countries were reviewed. The following information was available at the meeting:

- it was not clear when screening would be introduced in France although the CNTS in Paris had performed a comparative study of three different screening methods although the results were not available at that time;

- anti-HIV screening had been introduced by some of the larger blood centres in Germany, for example Frankfurt, although it was not known how much of the total donor population was involved or when screening would be introduced nation-wide although mandatory testing was expected to be introduced in the second half of 1985;

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- in Ireland, Greece, Spain, Austria and Norway it was not clear when routine screening for anti-HIV would begin.

- Belgium introduced routine screening on 1 April 1985, Switzerland on 1 June 1985;

- Finland were waiting for the results of the screening of the first 10,000 donations before a decision on routine screening would be taken.

115.4. In September 1985, the Committee of Ministers of the Council of Europe recommended that the governments of the member states "where they are considering, in the light of the national situation, the introduction of screening procedures for the presence of AIDS markers in blood donors, take all the necessary steps and measures to ensure that donors are aware that their blood may be tested for the presence of AIDS markers, if a reliable method of evaluating the specificity of the screening test is available this is applied to confirm a positive test.....".

115.5. In 1986, at a meeting of the Council of Experts it was reported that routine screening for antibodies to HIV had been instituted in all member countries except Spain where it was not mandatory although it was performed in some regions.

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Table 1: Usage of factor VIII (in million units) in the Netherlands from 1981 to 1985.

	1981	1982	1983	1984	1985
cryo blood banks	9.2	9.1	10.6	11.9	11.0
cryo CLB	10.5	9.4	9.7	10.0	8.2
factor VIII conc. CLB	3.4	8.8	12.0	11.7	11.4
imported factor VIII	6.1	7.0	3.7	3.5	4.0
Total usage	29.2	34.3	36.0	37.1	34.6
Usage per million inhab.	2.1	2.3	2.5	2.6	2.3

(according to data provided by the "College van de Bloedtransfusie", 1990)

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