COUNCIL OF EUROPE

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**EUROPEAN HEALTH COMMITTEE**

26TH MEETING

Strasbourg, 20 - 24 November 1989

**COMMITTEE OF EXPERTS ON BLOOD TRANSFUSION AND IMMUNOHAEMATOLOGY**

12TH MEETING

Liège, 23 - 26 May 1989

# MEETING REPORT

Forty years
Council of Europe
Quarante ans
Conseil de l'Europe

21.675
03.4

## LIST OF ITEMS SUBMITTED TO THE CDSP

The CDSP is requested to :

1. TAKE NOTE that the guidelines on Cellular Products will be finalised in 1990, i.e. one year ahead of schedule (see item 4.1) *;

2. APPROVE the setting up of a working group to study legal responsibility of Blood Transfusion Centers (see item 4.1 and Addendum II to this document);

3. APPROVE the participation of a paid expert from Spain in the SP-R-GS*;

4. APPROVE for publication in Vox Sanguinis, the SP-HM consensus opinion on Cytomegalovirus and Bone Marrow Transplantation, on a Minimum Acceptable Haemoglobin Level and on the use of fibronectin (see item 5.3, 9.1, 9.1.2 and Appendix IV);

5. APPROVE the draft recommendation on Plasma products and European self-sufficiency and the publication of the report on the same subject (see item 13.1, Addendum I to this document and SP-HM (89) 13.1 rev);

6. APPROVE the questionnaire on Legal Aspects of HIV infection in relation to transfusion (see item 15 and Appendix VI);

7. APPROVE the holding of a special SP-HM Bureau meeting in Brussels on 3-4 October to discuss technical cooperation with the EEC (item 23.4) and, in the light of developments within the Council of Europe, cooperation with Eastern European countries (item 3.3)*;

8. TAKE NOTE of the report as a whole.

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* Items marked with an asterisk were already taken note of or approved by the CDSP at their June 1989 meeting.

**OPENING OF THE MEETING**

Dr. H. Heistø (Norway), past-chairman of the Committee, opened the meeting and stressed that following Finland's recent accession to the Council of Europe as the 23rd member State, Dr. Leikola was to be welcomed as a new member of the Committee.

He then welcomed Dr. Brüster (Federal Republic of Germany), Dr. Schiff (Australia) and Dr. Lopez (WHO) who were attending a session of this Committee for the first time (for list of participants, see Apendix I).

1. **ELECTION OF THE CHAIRMAN, VICE-CHAIRMAN, MEMBERS OF THE BUREAU**

On a proposal by Dr. Genetet (France), Prof. André (Belgium) was unanimously elected chairman of the meeting. Prof. Van Aken (Netherlands) then proposed that Prof. Mandalaki (Greece) be elected vice-chairman. On a proposal by Dr. Heistø (Norway), Prof. Barbolla (Spain) was appointed as a new member of the Bureau.

Prof. André welcomed delegates to Liège and, speaking in the name of the Committee, thanked Dr. Heistø for his excellent chairmanship. He also took the opportunity to thank Mrs. Sacré-Bastien from the Belgian Ministry of Health for her support and help in organising the present meeting.

2. **ADOPTION OF THE REVISED DRAFT AGENDA**

Mrs. V. Boltho Massarelli (Secretariat) introduced the new agenda which had been agreed upon during the special meeting of the Bureau (Strasbourg, 28 September 1988). The Bureau had thought it useful to have a coordinator for every section in the agenda. His role would be to coordinate the work carried out by the rapporteurs, to assist the chairman in the development of the discussion and the Secretariat with the drafting of the report. He would especially be entrusted with the drafting of conclusions for each item of the section of the Agenda (drafting of recommendations or consensus opinions, proposal for further consideration by the Committee or for deletion from the agenda, etc.).

She then proposed that item 24 be subdivided as follows :

- 24 : Cooperation with Blood Transfusion Services
- 24.1 : of European non-members States
- 24.2 : of developing countries

and that a new item 25 "Miscellaneous" be added to the Agenda.

Prof. André added that a hearing with Dr. Poplavsky from his Institute would take place on Thursday afternoon to discuss a proposal to institute a post transfusion surveillance system.

Conclusion

The Committee approved the draft agenda as set out in Appendix II.

3. **DECISIONS OF COUNCIL OF EUROPE BODIES**

3.1 SP-HM Bureau

Mrs. V. Boltho Massarelli (Secretariat) summarised further conclusions reached during the special meeting of the Bureau as follows :

- agreement to increase collaboration with Group of Experts 6B of the European Pharmacopoeia Commission,

- agreement to use the funds still available following the Symposium on Blood Transfusion for fellowships to be given to South European countries,

- choice of the subject "Clinical trials" for the 1990 Coordinated Research Programme on Blood Transfusion.

3.2 European Health Committee (June/Nov 1988)

The Secretariat informed the Committee that the CDSP had approved all the items submitted to it by the SP-HM.

3.3 Committee of Ministers (October 1988/March 1989)

The Secretariat informed the Committee that the Council of Europe had celebrated its 40th anniversary on 5th May 1989 and had adopted a recommendation on the future role of the Council of Europe. The recommendation highlighted three main fields of action :

- Human Rights
- European cultural identity
- Social challenges

The Committee of Ministers had stressed the need for increased transparency and for closer cooperation with the EEC, the European non-member States (Eastern countries) and the Parliamentary Assembly. It was suggested that the SP-HM entrusted the Bureau with terms of reference enabling it to formulate proposals for these new orientations.

Conclusions

The SP-HM expressed its satisfaction as to these developments and entrusted the Bureau with the task of formulating in collaboration with the Secretariat proposals for concrete projects of cooperation for the years 1990-91 with :

- the EEC,
- the Parliamentary Assembly of the Council of Europe,
- European non-member States

with a view to expanding the respect and support of the ethical principles upheld by the SP-HM , the free circulation of products, the availability of rare products, transfusion safety and staff training.

## A. SAFETY OF BLOOD TRANSFUSION

## 4. QUALITY ASSURANCE IN BLOOD TRANSFUSION SERVICES

Coordinator : Prof HEINIGER

4.1 Report by the Select Committee on Quality Assurance

Prof. E. Freiesleben (Denmark) presented the report from the meeting (SP-HM (89) 4.1) and the document "Draft Guidelines for the preparation, use and quality control of cellular blood components" (SP-HM (89) 4.1 Addendum), which had been approved by the Select Committee at its 12th meeting. He asked the SP-HM to take note of the conclusions following each item in the report, and particularly of the list of items prepared by the Secretariat on page 2 of the report. The SP-HM was especially requested to decide and undertake appropriate action on three items:

- microbiological safety considerations for staff in blood transfusion practice,

- definition of liability in connection with the terms "accident" and "side effects",
- proposal to invite Spain to participate in the Committee.

Prof. Freiesleben pointed out a few other items of actual interest : the interesting and promising Austrian experience with Neopterin testing of blood donors as an acute phase marker of infections transmissible by blood transfusion, resulting in an acceptable loss of donations with elevated values. Also Dr. Högman's (Sweden) progress report on storage of platelets for transfusion in plasma-poor synthetic media ; furthermore the acceptability of validated sterile connecting devices for transfer of blood and its components between previously independent blood packs, to make a "functionally closed" system. Finally, new aspects of cooling down donor blood after donation. Prof. Freiesleben asked the SP-HM to approve the draft Guidelines in the Addendum and to adopt the meeting report and the item on "Future work" of the Select Committee. In this connection Dr. Leikola (Finland) mentioned that the Council of Europe Quality Control booklet had become an important reference source for most countries in Europe.

During the discussion it appeared that none of the members had any experience with neopterin screening of blood donors, and had no further remarks on the use of sterile connecting devices. The Select Committee was encouraged to continue the work on proper cooling down of donor blood after collection. Following a lengthy discussion on the problem of liability in connection with accidents and side-effects in treatment with blood products, it was agreed that this was an important matter of great urgency that should be dealt with by a group of members of the SP-HM in collaboration with one or more selected legal experts.

Conclusions

i. The SP-HM thanked the Select Committee for its excellent work and adopted the proposed guidelines (Addendum) in principle. Comments, if any, could be submitted by members to the Secretariat before the end of September 1989. Final editing before publication would be dealt with by the following delegates of the Select Committee : Dr Habibi, Dr Högman, Dr Wagstaff, Dr Walsh and Prof. Freiesleben. The SP-HM instructed the Secretariat to print the Guidelines in loose-leaf form to enable continuing updating.

ii. The Committtee commissioned the Secretariat to assemble at the earliest possible convenience a working party composed of members of SP-HM and legal experts to study the questions related to liability in transfusion medicine and to formulate a proposal to the SP-HM. The working party would be entrusted with the terms of reference set out in Appendix III revised by the SP-HM Bureau, see Addendum II to this report.

iii. The SP-HM instructed the Secretariat to transmit the guidelines to Group 6B of the European Pharmacopoeia, for information.

iv. The SP-HM warmly welcomed Spanish participation in the Select Committee.

v. The SP-HM adopted the meeting report as a whole and its item on future work.

4.2 Safety of plastic blood transfusion equipment

Prof. Genetet (France) pointed out that the problem of safety of plastic equipment was resolved and that this item could be deleted from the agenda. He proposed that the issue on safety of equipment be focused on filters. Prof. Van Aken (Netherlands) stressed the problem of external contamination of blood bags and proposed that an item on this subject be included in the agenda.

Conclusions

i. Current item 4.2 of the agenda would be replaced by : "Quality control and safety of leucocyte filter devices".

ii. A new item 4.3 would be included in the agenda as follows : "Prevention of external contamination of blood bags".

4.3 Quality control of the selection of donors

Further to a suggestion of the Secretariat, the Committee

- concluded that the Select Committee on Quality Assurance should review this item in the light of the relevant chapter in the Quality Control Report and report back to the SP-HM, Prof. Genetet being in charge of this item.

## 5. CONTROL OF TRANSFUSION-ASSOCIATED INFECTIOUS DISEASES

Coordinator : Dr. GUNSON

### 5.1 Aids

#### 5.1.1 General aspects and epidemiology

Dr. Gunson (United Kingdom) opened the discussion on this topic, asking Mrs Hoppe (USA) to summarise the current situation in the USA.

She said that there were no dramatic changes overall in the USA HIV epidemic, although in some cities the proportion of new cases had shifted significantly to a predominance of drug users.

It was believed that the HIV antibody screening tests and donor selection procedures were effective in assuring safe blood products, but it was acknowledged that perhaps as many as 1/40,000 donors may transmit HIV infection in spite of current efforts.

The possible utility of HIV antigen tests to further increase the safety of transfusion products was under study. To date, about 400.000 blood donors in the USA have been screened without finding a single confirmed positive HIV antigen test in donors having negative HIV antibody tests. The improvement of donor exclusion procedures was being studied by the American Research Institute under contract for the government (FDA). A large proportion of HIV-antibody positive blood donors were males (ages 30-40), at least for 80 per cent of whom could be identified retrospectively drug abuse or homosexual contacts as risk factors; they however failed to reveal that they were not suitable donors until confronted with positive HIV antibody test results.

Therefore more effective methods of communication were being studied hoping to make freely available by 1990 model materials to assist in educating donors about HIV infection and assuring that those with risk factors refrain from donation. Preliminary results suggested that :

- the message must be more clear and simple,
- pictures and direct questions were both helpful in eliciting correct responses from donors at risk.

The improved materials will be field-tested in several blood centers and the most effective models will be widely distributed for adoption by any interested.

The problem of HIV infection world-wide was summarised by Dr Lopez (WHO) who said that there were considerable differences of HIV prevalence between and within individual regions of the developing world. In certain parts of Africa for instance, the prevalence of HIV infection was very high and may be up to 15% in the general population. In other areas eg. in Nigeria, prevalence has been reported as being relatively low, in the region of 0.2%. In these areas risk of spread of HIV was a real possibility not only for HIV1, but also for HIV2. In general, blood transfusion was carried out extensively even in peripheral hospitals. However even though HIV screening facilities may be available, blood transfusion with screened blood was not always possible because of inability to store blood, lack of refrigeration facilities, problems with reagent supplies and equipment failure. There were major organisational problems, and lack of policies for Blood Transfusion Services.

In the known low prevalence areas of South East Asia, recent research findings had become a source of concern. In Thailand, surveillance reports indicated a considerable increase of HIV prevalence in the drug addict population from less than 1% a few years ago, to 40% in recent times. In India, increase in prevalence had become evident in certain groups of blood donors over the last few years. Transfusion induced HIV infection was therefore a real risk at least in some areas. The decision to screen blood for HIV was made in Thailand in 1987. In India a decision has been made recently to introduce the screening of blood for HIV in a stepwise manner, commencing in large metropolitan areas first and then extending this to other major centres subsequently. Logistic high costs of reagents and organisational problems also affect implementing universal HIV screening tests in the large countries. Malaysia had instituted 100% HIV screening programme of all donated blood. In Sri Lanka, also a low prevalence area, progressive screening of donors for HIV was being instituted.

In South America, prevalence was known to be higher than in Asia. However, the provision of HIV negative blood transfusion was difficult to achieve, mainly because of problems related to the coordination of services, collection of data on transfusion practice and implementation of government policies and regulations.

HTLV-I needed to be considered in many areas. In some areas of the Caribbean prevalence figures were reported to be 7% of the general population. A similar incidence was also found in parts of Asia, eg. Papua, New Guinea.

Mrs. Boltho Massarelli (Secretariat) commented on the report by the WHO on the Surveillance on Aids in Europe to December 1988. The highest rates for Aids in Europe were found in Switzerland (106.4 per million), France (101.7 per million) and Denmark (70.2 per million). The increase in the number of reported cases since December 1987 had been 87%, but within this figure there had been an increase of 147% in cases amongst drug users and a fall to 67% in cases amongst homosexual/bisexual men. Also the numbers in haemophilia and transfused patients had fallen during the period 1987-1988.

Mrs Boltho Massarelli (Secretariat) pointed out that there were discrepancies between the statistics provided by WHO and this Committee with respect to HIV seropositivity of blood donations in some countries. A check was made with the representative from each country and it appeared that the same reporting agency had provided the data for both WHO and to Dr Gunson (United Kingdom) who had acted on behalf of the Committee in this matter.

Mrs Boltho Massarelli (Secretariat) also reported that at a recent WHO meeting in Moscow, there was considerable debate concerning the ways in which epidemiological surveys on HIV prevalence were to be conducted. Ethical aspects of anonymous unlinked screening were considered and the value of using

blood donation/donor studies for extrapolation to give information representative of the population as a whole. It was generally agreed that blood donors were not representative of the population as a whole but Mrs Boltho Massarelli had promised to raise the question whether information could be determined on the demography of blood donors including such information as gender, age, socio-economic class, and geographical location (urban or rural).

The topic of HIV infection as a whole was opened for general discussion and the following matters were raised. Dr Habibi (ISBT) said that despite the steady decline in the rate of seropositivity among blood donations experienced in most countries over the last 3 years, several challenges continued to preoccupy the blood transfusion community :

i. The proportion of HIV infected first time donors remained dramatically high.

ii. Over 80% of the seropositive donors had risk behaviours and should have refrained from donating blood.

iii. According to a look back programme conducted in Paris, 25% of previous donations of donors found out one year later to be seropositive had turned out to transmit HIV to recipients despite negative serological status at the time of donation.

iv. According to a mathematical simulation study carried out in Paris HIV infected but seronegative individuals donating blood during the window period could represent up to 20 - 30 % of the total number of infected donors.

All these lines of evidence were causes of concern and once again stressed the need for more effective mobilisation and policies of information and education of the public in general and of prospective blood donors in particular.

Prof. Heiniger (Switzerland) informed the Committee that in Switzerland no HIV positive first time donors have been found in the last two quarters possibly due to an intensive Aids information campaign which discourages risk groups to donate. In the military donors in 1986/1987, a 3-6 times higher prevalence of HIV-1 positivity than in the civilian population was found. Donations excluded for transfusion by the donor were checked : of more than 20,000 such donations, so far none was HIV-1 positive.

Dr Högman (Sweden) gave information about transfusion transmitted HIV (TTHIV) infection in Sweden. Homosexual men happened to be over-represented as blood donors in comparison to the general population in the early 1980s. This caused 85 recognised cases of TTHIV infections. Of these, information was available for 74, 2 patients receiving their infections in 1980 and 81, respectively 13 in 1982, 21 in 1983, 27 in 1984, 11 in 1985, no patient in 1986, 1987 and 1988. Donor testing started in May-June 1985. Testing together with other measures which have been taken, thus seemed to have been very effective in preventing TTHIV so far. The computerised registration of transfusion recipients had been of great help in exploring the situation.

Dr. Britten (LRCS) noted that HIV-2 had appeared in Mozambique, including refugees from Mozambique in Malawi. He asked, in the light of significantly higher prevalence of HIV in military personnel vis-à-vis the general public, whether the Swiss Red Cross had considered discontinuing blood collection from the military. He raised the issue of pessimistic projections for window-phenomenon testing failures (1:40-100 thousand (Hoppe); 25% of all infected donors (Habibi)) vs. optimistic observations on actual transmission (Högman: 0 transmission in Sweden in 1986-87-88, 450,000 donations p. year.)

Prof. Van Aken (Netherlands) informed the Committee about the discussions in the Netherlands concerning anonymous testing for HIV. After a thorough analysis of the various studies concerning the prevalence of HIV in his country, concern had been expressed about the lack of information on the spread of HIV infection outside the known risk groups. Although some experts objected, the National Health Council had advised the Minister of Health to perform a study in persons admitted to hospital, pregnant women and newborns taking into account that testing should be anonymous without explicit previous consent. This advice was however not followed by the Minister since it was considered that such data were not required for the time being.

Furthermore, Prof. Van Aken stressed the limitations of data from blood donors to evaluate the prevalence in the general population.

Dr Habibi pointed out that, although knowledge about the epidemiologic features of seropositive donors was important, the collection of scientifically reliable data was extremely difficult in practical terms and required preestablished plans, manpower and equipment. These prerequisites were seldom met by the transfusion network or by public health administrations in most countries. He thus believed that the most satisfactory solution remained well conducted pilot studies covering a limited population area rather than a whole country.

Prof. Mandalaki (Greece) considered that blood donors in Greece were fairly representative of the population since 60% were friends or relatives of patients. On another aspect of the discussion she reported that the National Aids Committee in Greece had issued rules against routine screening of the population for anti-HIV. This also applied to Army recruits.

Dr Carbonnel Uberos (Spain) commented that there had been an increase in HIV seropositive drug users in both Spain and Italy.

Conclusion

Dr Gunson (United Kingdom) summarised the matters raised in the discussion pointing out that while the Committee was not asked to express an opinion regarding routine (anonymous) screening of the population, it should concentrate on matters concerning HIV and blood donors. With respect to the demography of blood donors, he reported that a study analysing gender, age, period since last donation and blood group of 1 in 200 of the donors in the UK during the first half of 1987 had just been completed. This showed that overall there was no sex difference from the general population but the age range, as might be expected was not the same as in the population. This study was important in that HIV seroprevalence could be related to the donor population rather than to the population as a whole.

Education of donors was a vitally important aspect in protecting the blood supply. The remarks made by Mrs Hoppe (USA) were very relevant in this respect and the outcome of the studies undertaken in the USA would be an important contribution in this area.

5.1.2 Screening of donors : HIV 1 infection

With respect to the statistics presented to the Committee, Dr Gunson commented that he had sent the tables giving the data to each member country since he was not sufficiently confident to publish these without receiving confirmation that they were correct. Some representatives had altered their data at the meeting and Dr Gunson asked that positive confirmation should be obtained from each country even if the data was correct. He was willing to discuss the discrepancies with a representative of WHO and with Dr Perrault who was compiling statistics for the ISBT to present to the forthcoming International Aids Conference.

Mrs. Boltho Massarelli (Secretariat) proposed, and it was accepted, that Dr. Gunson should be contacted by 15 June 1989. Any country not responding by that date would be omitted from the report.

Conclusion

A brief review of the results of the questionnaire was given and the principal matters of interest were that :

- the incidence of HIV seropositive blood donations had fallen since 1985 and the rates for first-time donors had remained fairly constant (although there were difficulties in defining this group of donors as Prof. Freiesleben (Denmark) pointed out);

- the sex distribution for confirmed HIV seropositives was approximately 4 males to 1 female and the majority of donors were under 40 years of age. The principal risk behaviours for seropositive donors were still homo- or bisexuality and intravenous drug use. Relatively few seropositive donors had no declared risk activity.

- with respect to performance of the tests there were clearly differences in initial and repeatable reactive rates which had implications for blood centres in that such donations had to be put into quarantine until confirmatory tests had been performed. Because of the time involved they were often lost for use and sometimes subsequent donations also reacted similarly. Those donations which could not be confirmed as HIV positive, yet remained repeatedly positive, caused problems since it was difficult to counsel the donor.

- HIV 2 infection

Dr Gunson stated that, in general, it appeared that routine screening for anti-HIV 2 in blood donations was not justified but that selective screening of donors who had visited countries where there was a significant prevalence of HIV 2 infection was recommended. However, he asked the representative from Portugal whether routine screening was taking place in that country.

Dr Simao Dos Reis (Portugal) replied that there was no obligation to perform routine screening but it was being done, and that the seropositivity rate in blood donations for HIV 2 equalled that of HIV 1. Proposals for the introduction of routine screening were being considered.

Dr Habibi (ISBT) commented that there was no new data on HIV 2 infection since that reported to the Select Committee on Automation and Quality control. He drew attention to current evaluation of combined anti-HIV 1/HIV 2 test kits.

Conclusion

Dr Gunson (United Kingdom) concluded the discussion by saying that the situation with respect to HIV 2 infection in relation to blood transfusion should be monitored and that it would be interesting to see the results of the evaluation of the combined anti-HIV 1/HIV 2 tests, since it was important not to compromise the sensitivity and specificity for the detection of anti-HIV 1.

- Anti-HTLV I screening

Dr Gunson introduced this subject by reporting the results of a survey he had carried out. In only three European countries had studies been carried out to-date : Netherlands (1 positive out of 20,000 donations), U.K. (3 positives in 6,900 donations, some of which had been selected from Afro-Caribbean donors) and Finland (0 positives out of 1,800 donations).

Mrs Hoppe (USA) reporting on the status of anti-HTLV I testing of blood donations in the USA said that HTLV I testing had been routinely performed on all blood donations (cellular products) in the USA since December 1988; a survey of test results on approximately 400,000 representative volunteer donors (Hawai excluded) during the first 4 months of testing indicated the following :

- there are significant differences among geographic regions, the incidence of confirmed positive tests varying at least 5-fold ;

- the overall average of confirmed positive (RIPA and Western Blot) is about 0.02 per cent with both Abbott and Dupont tests (no data for CPI), but the numbers of initial reactive samples vary significantly among the 3 licensed tests (Abbott, Dupont, Cellular Products, Inc.);

- there appears to be some excess of females (55%) in the confirmed positive group as compared to the percentage of female donors (41%). Most of these can identify sex contacts with a drug abuser as a risk factor when retrospective questioning is done.

The possible cause of discrepancies in detecting positive results among the 3 licensed tests is being aggressively investigated ; it is not known at this time to what extent the differences can be attributed to variation in specificity for HTLV II.

Conclusion

Dr Gunson concluded the discussion by stating that this matter would have to be carefully reviewed during the next year as a result of the USA experience.

5.1.3 Safety of blood and blood products

Prof. Van Aken presented a brief synopsis of recent developments. The risk of post-transfusion AIDS due to cellular blood components was highly dependant on the selection of blood donors, the self-exclusion procedure of blood donors and the accuracy and sensitivity of screening for antibodies to HIV. Routine screening of donor blood for HIV-antigens had been considered in some countries but had not been instituted. Removal of viral agents, such as HIV, by filtration of cellular blood components was presently being investigated by various groups. The results of such studies might help in deciding if and to what extent filtration should be instituted. This subject was rather complicated since the efficacy of virus removal might be different for cell-bound agents versus free virus material and virus material released by fragmentation of blood cells (leucocytes). The present data (from the US) indicated that the risk of HIV transmission varies from 1:40,000 to 1:00,000.

Concerning the removal and/or inactivation of HIV, as well as other viruses present in plasma components a variety of physical and chemical methods was now used and their efficacy had been tested clinically. Both pasteurisation and solvent/detergents (INBP/cholase/and BBP/UV irradiation provided safe products with regard to transmission of HIV, NANB hepatitis and hepatitis B. In addition, "dry heating" of factor VIII/IX concentrates under certain conditions inactivates HIV. Heating at 80°C for 72 hours has demonstrated in one country (UK) to inactivate NANB-hepatitis virus. Removal of virus material by chromatography, notably immune affinity added to the inactivation. Irradiation alone, although effectively inactivating various viruses, caused significant loss of biological activity, and was therefore not practical. As to further developments in this area the following points appeared relevant :

- longer follow-up and larger numbers of patients were needed before definite statements concerning efficacy of each of these methods could be made;

- the potential toxicity of certain ingredients, such as certain solvents present in the final product, needed to be examined;

- combination of various inactivation methods (eg. physical and chemical) might offer garantees for the inactivation of different types of viruses;

- further improvements reducing the loss of biological activity, would be beneficial.

Conclusion

It was apparent according to Dr Gunson that there were considerable developments in this field which merited careful monitoring : the recommendations of the Committee concerning NANB hepatitis during the past two years were confirmed namely that each country must assess the incidence of transfusion transmitted NANB hepatitis and decide whether surrogate tests be justified and subsequently which anti-HCV testing to introduce.

5.1.4 Aids and haemophilia

Prof. Mandalaki (Greece) summarised her documents saying that Haemophiliacs. a group of patients who contracted Aids very early after the beginning of the epidemic (even in Europe due to imported commercial F. VIII or IX concentrates) should be followed-up regularly. The prevalence of HIV 1 infection and Aids cases in European haemophiliacs showed a wide range ; it was very low in Finland and Belgium and very high (60-70%) in F.R.G., Ireland and Spain.

According to the study of the seroconversion working group organised by NCI and to the study in the Athens Haemophilia Centre (Laikon Hospital), haemophiliacs who have seroconverted progress to Aids more slowly than homosexuals. Age at the time of seroconvertion (above 50 years) is a statistically significant variable for progression to advanced immune disfunction or Aids. There were also problems in relation to substitution therapy ; the introduction of high purity concentrates, using monoclonal anti-bodies techniques had led to a shortage of F.VIII supplies and to a marked elevation of treatment costs especially in the USA and in those European countries which covered their needs through imported concentrates.

Conclusion

The whole issues of self-sufficiency in the EEC and Council of Europe areas supplies of F.VIII and evaluation of different procedures of fractionation should be considered without delay. A small working group of experts in both transfusion medicine and haemophilia care consisting of Prof. Mandalaki (Greece), Dr. Faber (Luxembourg), Prof Van Aken (Netherlands) and Prof. Heiniger (Switzerland) was requested to put forward proposals for study.

5.2 Hepatitis

Coordinator : Prof. VAN AKEN

5.2.1 Hepatitis B-virus

Prof. Van Aken told the Committee that in his opinion no new developments concerning the screening of donors had occured. The safety of products with regard to hepatitis B had already been discussed (althought not explicitly for hepatitis B) under the previous item of the agenda.

5.2.2 NANB hepatitis - testing of blood for indirect evidence of infectivity

Dr Gunson (United Kingdom) reported on the results of the questionnaire which he had circulated to member countries. Of the 10 countries who had replied, 4 were routinely performing ALT tests on blood donations (Federal Republic of Germany, France, Malta and Switzerland) while France was also performing routinely anti-HBc tests. In Ireland, there was some selective ALT testing of donations.

Dr Leikola and Prof. Van Aken then reported about recent developments with regard to the development of a test for antibodies to HCV and the preliminary results in patients with NANB hepatitis. Dr Leikola mentioned that epidemiological studies were currently going on in Europe about the new HCV. The anti-HCV test by Ortho/Chiron was being used in these studies. The preliminary results would be discussed at the end of June 1989, and final results available in September-October 1989.

Conclusion : Pro memoria.

5.3 Cytomegalovirus

Coordinator : Prof. HEINIGER

Prof. Heiniger (Switzerland) introduced his paper on CMV and asked delegations to consider the recommendation contained therein.

Conclusion

It was agreed that the recommendation

- would be inserted in the guidelines for the preparation, use and quality control of blood components,
- would be transmitted to the Committee of Experts on organ transplantation
- would be published in Vox Sanguinis as a consensus opinion of the SP-HM after approval by the CDSP.

5.4 Malaria

Coordinator : Prof. GENETET

Prof Genetet (France) presented the results of his questionnaire concerning the incidence of post-transfusion malaria from which he concluded that the situation was stationary with no particular problems in 1988.

Conclusion : Pro memoria.

5.5 Pre-donation testing

Dr Leikola (Finland) asked the participants whether predonation testing, in addition to haemoglobin determination, was done in their countries. Predonation testing included tests carried out prior to the donation itself as a prerequisite for donation acceptance. He mentioned that predonation testing was now under discussion. Dr Högman mentioned that in his country there was an old practice to call new donors first for tests and only later for donation, when tests were repeated.

Conclusion

It was decided that this item should be included in the agenda. Dr. Leikola promised to report on the subject, based on data from different countries.

## 6. POST-TRANSFUSION SAFETY

Coordinator : Prof GENETET

### 6.1 Clinical aspects of immune suppression by blood transfusion: report by the working group

Prof. Van Aken presented his report on the possible relation between perioperative blood transfusion and cancer recurrence. The clinical and experimental information which was presented already at previous meetings of this Committee, has been supplemented with an analysis of some important factors relative to blood transfusion, such as the volume and type of blood products, as well as the time of transfusion in relation to surgery. He concluded that although a deleterious effect of blood transfusion on the prognosis of patients with certain types of tumours was suggested by several investigators, it was still premature to have definite conclusions regarding such a risk. The methodological weaknesses of retrospective studies could also be held responsible for some of the observed differences. The definitive resolution of this issue would require further prospective randomized studies using standard red cell concentrates or transfusions which were thought not to induce a state of immunosuppression. Such studies were currently underway. Prof. Van Aken proposed therefore to await the results of these investigations before recommendations were made by the Committee.

Prof. Genetet stressed that the difficulty in obtaining serious scientific data was the most relevant problem. This was the case both from the experimental as well as clinical angle. Prospective studies were required that would extend over several years. In the end they would provide answers to the following questions :

i. can the risk of recurrence of certain cancers (should it really exist), in particular colono-rectal cancers, be explained solely by transfusion (this indeed was the essential question) ?

ii. can the different parameters such as surgical procedures, additional therapies, age of the patient, stage of development of the tumour, immune status of the patient at the time of surgery, be computerised?

iii. is there any risk that other cancers develop than those reported in the U.S. and Canadian studies?

iv. is there "a general risk" (linked to transfusion) of an immune system depression or modification in transfused patients for reasons other than cancer? If there is a risk, the different responsible agents should be identified in whole blood, plasma, etc. (eg. Blumber's work in Rochester).

Conclusion

The question to-day seemed to be less disquieting than it was several years ago (the post-transfusion immunological risk seemed to have evolved towards a viral risk). It was agreed that for scientific reasons this question should remain on the agenda of the SP-HM as one of its "topical" issues.

### 6.2 Monitoring safety of blood transfusion

Prof. André recalled that the origin of the project came from the Study Group having prepared Rec. (88) 4. He then introduced Dr. J.L. POPLAVSKY (Belgium) who had helped him in preparing a plan of work for a prospective study on transfusion safety.

In his intervention, Dr Poplavsky stressed that :

- the ever-increasing variety of therapeutic substances of human origin which were used and the diversity of fields of medicine concerned added to the complexity of a discipline which was widening all the time;

- clinicians had to be induced to take account of all the potential adverse effects associated with the different acts involved in transfusion, if the development of transfusion therapy was to go on developing satisfactorily.

The setting up of a post-transfusion monitoring procedure might :

i. produce objective statistics permitting an assessment of real risks;

ii. reveal any weak points in the system;

iii. lead to some harmonisation of precautions based on a corpus of objective conclusions;

iv. bring about closer collaboration between hospital doctors and doctors in transfusion services, which might make it possible to define more objective rules determining the indications for a transfusion.

He then explained the various cards, protocols and questionnaires drawn up.

Conclusion

After a general discussion the SP-HM thanked Dr Poplavsky and welcomed the offer by Prof. André, Prof. Van Aken and Dr. Carbonell to set up pilot projects on the basis of the plan of work and to report back in 1990.

## B. NEW DEVELOPMENTS

## 7. CELLULAR PRODUCTS

Coordinator : Dr. HÖGMAN

### 7.1 Preservation of blood cells

Dr Högman (Sweden) gave a report on the preservation of blood cells. He emphasised the advantages of additive solutions for red cell storage, giving improved quality of the red cells with respect to post transfusion survival as well as better flow properties, and higher yield of plasma which could be used to meet the increasing demand for Factor VIII. Recent studies indicated that the commonly used plasticiser (di-ethylhexyl-phthalate DEHP) after splitting into the mono-ester form, could be toxic for certain heart tissues. The clinical implications of these experimental studies were yet not clear, however. New plastic materials without these effects were under study.

The beneficial effects of mixing red cells during liquid storage was mentioned as well as recent attempts to reduce the virus contents in cellular products and the usefulness of automated procedures. Concerning the preparation and storage of platelets, special emphasis was put on leucocyte contamination as the likely cause of refractoriness to platelet transfusion.

New techniques had been developed which reduced the leucocyte contamination in the platelet concentrate as well as possibilities to achieve further and substantial reduction by leucocyte filters. The recent development in the preparation of platelets from buffy-coats was also mentioned and the possibility to obtain pooled preparations under sterile conditions using sterile connecting devices.

In the discussion, Dr Habibi (ISBT) brought up the question of quality assurance when leucocyte filters were used in direct connection with transfusion. In his reply Dr Högman emphasised the importance of establishing for these procedures appropriate rules in the development of which the transfusion services should take an active part. It was mentioned, also, that removal of leucocytes in direct relation to the blood component production had the advantage of reducing the formation of leucocyte fragments.

Dr Van Aken mentioned that studies in his laboratory had shown considerably lowered concentration of DEHP in the extracellular fluid of SAG-M red cell units than in whole blood and plasma. This was confirmed by Dr Högman who mentioned, however, that the plasticiser apparently combined with the lipid membrane of red cells. If this had any negative consequences was unknown, the positive effects being improved storage properties.

Dr Britten asked, in the light of difficulties with techniques of bedside filtration to deplete leucocytes, whether the stage had been reached when it should be recommended to deplete leucocytes from all products to be issued for transfusion. Prof. Van Aken also mentioned that much of the acidification of the medium at platelet storage was caused by leucocyte contamination and that removal of leucocytes before storage reduced this problem.

Conclusions : Pro memoria.

7.2 Platelets

Dr Engelfriet (Netherlands) gave a report of the activities of the ISBT-ICSH Working Party on Platelet Serology. A workshop was being held for the evaluation of new techniques in which isolated glycoproteins were used. These techniques use either glycoproteins isolated by chemical means, or glycoproteins isolated by proteins of glycoprotein complexes such as GP IIb/IIIa. These new techniques were considered to be important because it was now certain that the older techniques such as immunofluorescence test were insufficiently sensitive to detect all clinically important platelet allo- or auto-antibodies. There were indications that the new techniques were more sensitive. Furthermore, antibodies of other specificities such as anti-HLA, did not interfere. Results of these studies might be available in 1990. A proposal for an international uniform nomenclature for platelet specific antigens was under discussion. Probably the system to which these antigens belong will be called : HPA = human platelet antigen system.

Conclusion

Due to ongoing discussion, no definite conclusion could be reached for the time being.

8. **PLASMA PRODUCTS**

Coordinator : Dr. FABER

8.1 Clinical use of intravenous gammaglobulin

Prof. Heiniger (Switzerland) informed the Committee that the use of IVIG had been increasing substantially during the last few years although the registered, scientifically documented indications had remained the same. This increase was probably due to the perception by physicians that IVIG "do no harm, even if they don't help".

The primary indications presently accepted were :

- primary, hereditary immunodeficiencies
- secondary, acquired immunodeficiencies
- ITP
- Kawasaki syndrome

The following indications were at an experimental stage :

i. Prophylaxis of infections in multiple myeloma, lymphoproliferative disorders, posttraumatic and postoperative immunodeficiencies, burns
ii. Prophylaxis of infections in pre-term neonates
iii. Prophylaxis of CMV interstitial pneumonia transplant recipients
iv. Adjuvant therapy in sepsis and septic shock,
v. Immunodiseases : autoimmune and aplastic anaemia, neutropenia, myasthenia gravis, Guillian-Barré Syndrome, autoantibodies against Factor VIII.

Safety of IVIG

Past and ongoing studies document that the presently registered preparations produced in large quantities are safe :

i. no cases of transmission of HIV have been reported,
ii. no cases of hepatitis B have been reported,
iii. five cases of documented NANB hepatitis transmission have been reported : the products involved were either at an experimental stage of development (pilot plant) or produced in very small batches.

Based on this record, IVIG could be declared as safe, not transmitting presently known diseases.

Conclusion

Intravenous gammaglobulins demand had considerably increased, mainly due to higher doses used in therapy and to more numerous clinical indications for this product. With respect to the security of this product, it was considered to be safe because no cases of transmission of HIV or HB had been reported and only very few cases of HNANB had been recorded in exceptional cases in relation with local products from small scale production.

8.2 Wound-healing and haemostatic products of human origin

It was recalled that wound-healing products had some classical indications in ENT surgery, dental procedures and reconstructive surgery but no new development were to be reported.

## 9. HAEMOTHERAPY

Coordinator : Prof. LUNDSGAARD-HANSEN

9.1 Anaesthesiology, surgery, intensive care

Prof. Lundsgaard Hansen informed the Committee about a controlled trial with purified fibronectin for the prophylaxis and treatment of sepsis in severely injured patients done at the Department of Surgery in Augusta/GA, the complete data now being printed in the Annals of Surgery. The authors had concluded that their data suggested that exogenous Fn repletion in states of deficiency does not alter the clinical course, the development of sepsis, or septic mortality".

These conclusions confirmed those emanating from the only other controlled-prospective study of purified Fn in septic (peritonities) patients as well as with the results of controlled studies with cryoprecipitates. Thus, all of the controlled studies published till now had failed to confirm the claims-based on anecdotal data-of Dr T Saba in Albany/N.Y. He felt that the time had thus come for the Committee to express the consensus that there was no solid scientific evidence for a prophylactic or therapeutic value of fibronectin in septic states.

Conclusion

The Committee endorsed this proposal as its consensus opinion (see Appendix IV). It suggested its approval by the CDSP for publication in Vox Sanguinis.

9.2 Minimum acceptable haemoglobin level

Prof. Lundgaard-Hansen summarised the contents of the paper on a "minimum acceptable haemoglobin level", as well as the conclusions which he considered appropriate on the basis of the data contained therein. In his opinion, the essential point was that a simple, generally valid "acceptable minimum haemoglobin level II did not exist. The adequate haemoglobin level is a decidedly individual matter and should be dealt with as such. A computer programme, now in print, should be helpful in this context.

Prof. Freiesleben, Dr. Heistø and Prof. Van Aken supported these conclusions and welcomed what might at any rate be an approach evaluating this problem.

Conclusion:

Prof. Lundgaard-Hansen edited the conclusions as contained in his paper which were accepted by the Committee as its consensus opinion and it was proposed to publish them in Vox Sanguinis after approval by the CDSP.

9.3 Internal medicine, haematology, oncology, paediatrics, neonatology

Prof. Van Aken informed the Committee that in his opinion, considering the developments since 1988, most of the topics falling under item 9.2 were covered by other participants.

## 10. MOLECULAR BIOLOGY IN BLOOD TRANSFUSION

Coordinator : Dr. LEIKOLA

10.1 Molecular genetics in transfusion medicine and exchange of DNA probes

Dr Jensson gave a report on molecular genetics in transfusion medicine and exchange of DNA probes stressing that molecular biology techniques acquired in the past in laboratories of hospital and blood transfusion services were mainly connected with analyses of DNA variations of genetic diseases and genetic markers. Such activities had made the laboratories more capable of using the rapid advance made recently in molecular virology. Because of increasing possibilities in the field, the exchange of probes, restriction enzymes and DNA primers should be extended to viral markers of transfusion-transmitted diseases.

Conclusion

Transfusion experts should closely follow the rapid development in the field, and aspects of molecular biology should be increasingly included in blood transfusion training courses.

The Secretariat was asked to contact the European Molecular Biology Organisation (EMBO) for further information on the training activities of this Organisation. Because of the highly technical nature of the field, the SP-HM might organise a hearing in the future with pertinent experts.

10.2 In vitro production of antibodies

Prof. Genetet reported on the present status of monoclonal antibodies produced in vitro. He emphasised the fact that even routine reagents tend to be more and more produced in vitro, and that it was important for the transfusion centers to be aware of these new possibilities. He went on to describe separately in his report the monoclonal antibodies against red blood cells, against complement components, against lymphocytes, granulocytes, monocytes and platelets, as well as against the Major Histocompatibility Complex (MHC).

Conclusion

A close follow-up of this field was of prime importance to the SP-HM. The item should remain on the agenda. Prof. Genetet was asked to report on the latest developments at the next meeting.

10.3 In vitro production of plasma proteins and haematopoietic hormones

Prof. Van Aken reported on recombinant proteins important for transfusion experts. Because of the dominant importance of Factor VIII, he limited his report to this protein.

The isolation of CDNA clones of Factor VIII and of von Willebrand Factor and the in vitro expression of these proteins had opened the possibility to produce synthetic Factor VIII for clinical use and to study the structure - function relationships of these haemostatic factors. At present biologically active "full length" recombinant factor VIII was tested clinically in restricted numbers of haemophilia A patients. The first report about the one year home-treatment of haemophiliacs with recombinant Factor VIII indicated that this product behaved similarly to plasma-derived Factor VIII and no untoward effects had been observed.

Conclusion

Recombinant Factor VIII preparations would probably be in the market within a few years time, and they were biologically as active as the preparations of human origin. Some concerns however were expressed, namely that the production might be more expensive than originally expected. Because of theoretical possibilities of viral contamination of cell lines, safety issues remained important when regulatory authorities were to consider licensing these products. It seemed likely that, in the future, both human and recombinant products would be on the market, and that the ultimate outcome would depend mainly on economic aspects, especially if the yield of plasma F. VIII could be increased substantially.

11. **APHERESIS**

Coordinator : Prof. MANDALAKI

11.1 Plasma procurement by cell separators

Dr Walsh declared that plasma collection by apheresis was now an integral part of many countries' self-sufficiency programme. It was likely that platelets would be increasingly collected in combination with plasma particularly if there was a reduced requirement for red cell transfusion. A

report on the hazards and defects had been presented at the select Committee of Experts on Quality Assurance in March in Innsbrück by Dr Wagstaff. This report emphasised the requirement for continued monitoring of this new procedure which had been introduced with very little control and at best ad hoc local or national guidelines.

Conclusion

At the suggestion of the chairman a working party consisting of Dr. Walsh, Prof. Heiniger, Prof. Genetet and Prof. Mandalaki was established to examine and advise the Committee on developments in this field.

11.2 Therapeutic aspects of apheresis

Prof. Mandalaki said that therapeutic apheresis had been applied for various disorders, especially in the fields of neurology, dermatology, nephrology and especially haematology. According to the experience of the plasmapheresis unit of the 2nd Tr. Center of Athens, results are excellent in TTP (92% remission rate) pemphigus and Guillaine Barré (100% remission rate) myasthenia gravis, Rh alloimmunisation and F. VIII inhibitor.

Prof. Genetet introduced his paper mentioning that the techniques of apheresis originally developed for removing granulocytes from healthy donors for transfusion purposes were being used in an increasingly varied range of therapeutic indications. Plasma exchanges, the modern equivalent of blood-letting, led the field in this connection. However, in recent years other applications have developed, particularly in onco-haematoloy.

Technological developments in relation to plasma exchanges were also reported by Prof. Genetet. As a replacement fluid, fresh frozen plasma had, except in special cases, been replaced by albumin, which is much better tolerated. Centrifugation and filtration were still the two techniques used for plasma isolation. Cascade filtration systems had been developed, which enabled selective retention of molecules with a particular molecular weight and reinjection into the patient of his own plasma from which toxic substances had been removed. Immunoabsorption (another great hope from the point of view of selective purification) had become truly operational on a routine basis only in the area of hypercholesterolaemia. Thermofiltration allowed for better albumin-lipoprotein separation than double filtration and was no longer necessary to compensate for protein losses. Clinical results of the use of Eppolyvynil - alcohol with tryptophan residues which appeared to have a particular affinity for acetyl-choline receptor antibodies (Ac anti-RACH) in cases of myasthenia were quoted.

Cell-removal techniques of the lymphapheresis type had been put forward in association or alternation with plasma exchanges for certain diseases with an immunological component (disseminated lupus erythematosis, rhumatoid polyarthritis).

Over the past ten years, their number had greatly diminished. The selection had taken place following clinical trials carried out on the basis of national protocols.

Conclusion

It was concluded that apheresis in blood donors would gain an importance in the future because of :

- the need for plasma self-sufficiency relying on plasmapheresis programmes ;
- increasing need for platelets to treat patients suffering from malignant haemopathic disorders undergoing intensive chemiotherapy.

In addition to the favourable effect on a large number of diseases, therapeutic apheresis also offered interesting indications for the treatment of cancers.

It was decided to maintain the item on the agenda and that Prof. Genetet, Dr. Walsh, Prof. Mandalaki, Prof. Heiniger would report at the next meeting.

11.3 LAK cells

Prof. Genetet recalled that immunotherapy, which was based on hyperstimulation of the immune system or on the replacement of defective reactions, had since long raised hopes in the treatment of cancer. In 1985, Rosenberg presented the 1st clinical results of adoptive immunotherapy, in the form of an injection of a high dose of IL2 combined with autologous LAK (lymphokine activated killer) cells manufactured ex-vivo from mononuclear cells and taken from the peripheral blood and cultured in the presence of IL2. These results triggered off a wave of enthusiasm in the world of immunology and cancerology and several teams were currently working on this subject. The problem of obtaining a sufficient quantity of IL2 seemed to have been solved by the manufacture of human IL2 by means of genetic recombinant techniques.

Toxicity: the main complication of the treatment was linked to a syndrome called "capillary leakage" ranging from a mere gain in weight to pulmonary and cerebral oedema requiring intubation. This complication, which was found in 60% to 80% of patients, was due to IL2. The other side-effects observed were: fever, skin lesions, nausea, vomiting, diarrhoea.

The future: one of the possibilities was to re-inject TIL (tumours infiltrating lymphocytes). These lymphocytes were obtained by dissecting tumours, having enzymes digest them and culturing them in the presence of IL2. One of the major drawbacks of this technique was its complexity and cost. Another possibility had been envisaged based on the principle that LAK cells are very close to NK cells, which are also NHK1 + CD 3 cells existing naturally in peripheral blood.

Conclusion

Thanks to progress in biotechnology and to a better knowledge of the immune system, immunotherapy would perhaps at last become an effective therapeutic weapon against cancer. The first results were extremely promising and had prompted research in various directions : choice of cells to be activated, choice of cytokines, therapeutic combinations and a better selection of patients.

12. **HISTOCOMPATIBILITY**

Coordinator : Prof. ENGELFRIET

12.1 Report by the Select Committee on the standardisation of reference tissue-typing reagents

Prof. Engelfriet introduced the report and drew attention to the following points :

- European Panel of reference tissue-typing reagents

When the formation of this panel was started the requirements for reference typing reagents were as follows : to establish the presence or absence of a particular HLA antigen, four antisera of the same specificity had to be used. At least 3 of these antisera had to react with the cells of any

individual carrying the corresponding antigen and not more than one of them might react with the cells of any individual negative for the corresponding antigen. It had to be realised that these requirements apply to the recognition of a single HLA antigen. For the determination of an individual full HLA-phenotype, that is for HLA typing, the requirements are much less severe. The Select Committee had therefore decided to include those reagents in the Strasbourg Bank which had been tested by the members and had proven satisfactory reagents for HLA phenotyping.

It was decided to study sera defining HLA-DR2 (DRW15 and DRW16) and DR5 (DRW11 and DRW12) in the 1989 serum exchange.

- Updating of "Essential aspects of tissue typing"

Because several new techniques had been introduced in the field of tissue typing, such as biochemical techniques and DNA techniques, it was considered necessary to update the above booklet to include these new techniques.

- Terms of reference

A request for representation on the Select Committee had been received from Greece and was to be submitted to the European Health Committee. The Select Committee wished to appoint ad hoc advisers to assist them as to specific problems of a highly specialised nature.

- European Course on Histocompatibility testing

The next course would take place in Geneva in October 1989, organised by Prof. Jeannet.

- Conference of Health Ministers, Paris, November 1987

At this Conference it was decided to set up a new Select Committee of Experts to look into organisational aspects of cooperation in organ transplantation.

- European network of HLA-typed bone marrow donors

Efforts were being made to create a European telematic network of non-remunerated HLA-typed bone marrow donors.

- Highly immunised patients

Studies to define acceptable HLA- mismatches for highly immunised patients was an important item and would receive particular attention.

- DNA-RFLP

The results of the studies on DNA-RFLP were very satisfactory. These studies would be enhanced and continued.

- European panel of fully typed cell lines

Such a panel would be set up in the near future.

With regard to the appointment of ad hoc advisers for matters of a highly specialised nature, the Secretariat informed the Committee that this was possible under the terms of a Committee of Ministers instruction to all Committees in the form of ad hoc hearings (having no financial implications).

Conclusions

The SP-HM

- took note of the proposal to update the document "Essential Aspects of Tissue-Typing";

- advised the Select Committee to organise hearings to assist them with specific problems of a highly specialised nature as and when these might arise;

- approved the proposal that a 4th Conference on Histocompatibility should take place in Strasbourg in February/March 1990;

- took note of the Select Committee's intention to continue to initiate the following studies :

  . DNA-RFLP collaborative study ;

  . Serological study of highly sensitised patients;

  . Exchange of sera defining DR2 and DR5, their splits and related antigens.

- requested the Secretariat to examine whether the Co-ordinated Blood Transfusion and Histocompatibility Research Programme on co-ordination of registries of marrow donor volunteers could not be financed from other sources earlier than 1992;

- approved the proposal to hold the 1989 meeting in Switzerland.

12.2 Other developments : Acquired haemolytic anaemia

Dr. Barbolla introduced her report on this subject.

Haemolytic anaemia could occur in transplanted patients as a consequence of a reaction between red cell antigens and antibodies of the recipient and the donor. The specificities of the anti-bodies involved might be against antigens of the ABO-system, but other specifities such as anti-D and anti-C have also been described. In bone marrow transplantation in cases of major ABO incompatibility (recipient O, donor A or B) a haemolytic episode could occur following the infusion of the marrow. It could be minimised by removing red cells from the inoculum. In cases of minor incompatibility (recipients A or B, donor O) the lymphocytes of the donor could produce anti-A or anti-B in the recipient and provoke haemolytic anaemia.

Antibodies produced by residual lymphocytes in the transplanted organ might have other specificities such as anti-C or anti-D, which also induced haemolysis. Most of the patients described with this kind of haemolytic anaemia had been treated with cyclosporine A to prevent graft rejection.

Conclusion

Clinicians should be aware of this problem and because haemolysis due to anti-A or B could be very severe, ABO compatibility should be ascertained whenever possible.

12.3 Immunological diagnosis and treatment of habitual abortions

Prof. Genetet introduced his report on this subject. In the report evidence was presented that in the blood of a high percentage of women with recurrent abortion, non-cytotoxic antibodies and/or plasma factors which specifically block the paternal lymphocytes are detectable. Although the

precise role of these factors were as yet not clear, their presence seemed to exclude defective immunological recognition as the cause of the recurrent abortions. Immunotherapy therefore only seemed warranted in cases in which such antibodies/factors remained undetectable. In such cases injections of paternal or donor leucocytes were successful.

Prof. Speiser recalled that he had asked that an item on habitual abortions be included in the agenda. He then thanked Prof. Genetet for his excellent paper and gave the following information on the handling of this problem in Vienna.

Immunological diagnosis started in the autumn of 1988 and the attempt to treat the cases in November last year. There were now approximately 40 to 50 couples in the programme of diagnosis and treatment of habitual abortion. 2 or 3 cases of infertility of unknown origin were also included in the programme. The experience was so far too small to allow for any conclusions or decisions. The immunisation of the patients had been successful : they developped lymphocytotoxic antibodies against their husband's HLA antigens at the 1st attempt or after reimmunisation with the husband's leucocytes. Some of the women were now pregnant (4-5 months).

He then provided copies of the one page leaflet programme which was given to the couples for information. This information included laboratory diagnosis procedures as ABO, RH, HLA typing, antibody screening against red cell antigens, HLA antigens, etc.

Furthermore this leaflet showed the programme to prevent infection during the immunisation procedures. This included serologic diagnosis for HIV, syphilis, CMV, HBV, Parvovirus. Couples were informed that the success rate was of about 80% and that the patient might acquire infections by intra-dermal injection of white cell concentrates of the husband. In few cases, a second attempt of immunisation had to be carried out after the first injection if there was no trace of lymphocytotoxic antibodies or immuno-phagocytose inhibiting antibodies. As already reported in the literature, an accumulation of HLA-haplotype identity in the couples in question was also appreciated when compared with controls.

Dr Habibi (ISBT) drew attention to the good results which had been obtained with intravenous immunoglobulin. This might be safer than immunisation with leucocytes, but was much more expensive as was pointed out by Prof. Speiser who thought that the success of IV IgG as described Dr. Müller-Eckhardt (Giessen, FRG), could be due to the presence of immunophagocytosis inhibiting antibodies in the IgG preparations in question.

Conclusion

This item should be maintained on the agenda in order to follow further developments.

12.4 File of non-related bone marrow donors

Dr. Reali (Italy) informed the Committee that in Italy a National Bone Marrow Donor Registry had been instituted. This Registry was connected with a European cooperative Foundation, the "Eurodonor", which was coordinated by Prof. Van Rood, in Leiden. The number of Italian Bone Marrow Donors was still low but rapidly increasing. The Tissue Typing Laboratory of Galliera Hospital in Genova had the responsibility of the Italian Registry. Similar registers existed in Belgium, France, Federal Republic of Germany, Ireland and United Kingdom.

## C. RESEARCH PROGRAMME

### 13. CO-ORDINATED RESEARCH IN BLOOD TRANSFUSION

Coordinator : SECRETARIAT

#### 13.1 1988 Programme : "Investigation of the procurement and proper use of human plasma and their relevance for national blood programmes

The report of the 1988 programme entitled "Plasma products and European self-sufficiency : collection, preparation and use" was presented by the study director, Dr Leikola (Finland). He thanked all the members of the study group for their precious collaboration and for meeting the deadlines despite a very tight time schedule. He gave an outline of the study and of the main results. It was emphasised that while some of the data were very accurate and reliable, in some other areas it had been impossible to obtain precise information.

Dr. Högman (Sweden) presented some additional aspects concerning attainement of national self-sufficiency in his country. A comparison between the Nordic countries, having a similar social and economic structure, revealed vast differences with respect to transfusion medicine and use of F. VIII. Whereas Finland and Norway in 1987 used 1.5 and 2.0 IU per inhabitant per year respectively, the corresponding consumption was 3.2 IU in Denmark and 3.7 IU in Sweden. This initiated a description of the two major factors of importance for national self-sufficiency : the usage of F. VIII and the yield of F. VIII from fractionated plasma. The low yield, often substantially below 200 IU/Kg plasma, in the production of high purity F. VIII concentrates seems to be the major present obstacle. The present supply of plasma for fractionation in Sweden is 17 kg per 1000 inhabitants per year. By optimizing usage and yield it should be possible to achieve national self-sufficiency at the present or, possibly at a considerably lower level of plasma supply.

Conclusion

Based on the report a draft recommendation was formulated and approved together with the report. It was decided to publish the report in the same way as the reports of previous coordinated research programmes and to submit the draft recommendation to the CDSP (if possible already at its June 1989 meeting) for approval and transmission to the Committee of Ministers for adoption.

#### 13.2 1990 Programme : choice of subject

The Secretariat recalled that the subject had been proposed by the SP-HM Bureau and confirmed by correspondence. The terms of reference and membership appear in Appendix V. It was decided to include observers as for previous research groups.

## D. ETHICAL, LEGAL AND ORGANISATIONAL ASPECTS OF TRANSFUSION AND TRANSPLANTATION

### 14. AUTOTRANSFUSION

Coordinator : Dr. WALSH

The working party previously established had issued its formal report.

The following comment was made by Prof. Reali : in Italy the Society of Immunohaematology and Blood Transfusion had set up an "itinerant team" which was visiting each Regional delegation, to illustrate and support auto-transfusion and intraoperative salvage of blood. Besides, Prof. Sirchia (Milan) had started a European collaborative Group on blood saving by means of autotransfusion.

Conclusion

It was agreed to keep this item on the agenda.

15. **ETHICAL AND LEGAL ASPECTS ASSOCIATED WITH AIDS**

Coordinator : Prof. ANDRE

The SP-HM examined with interest the questionnaire prepared by Prof. André. It agreed to strictly limit the questions to essential ethical and legal aspects of concern to transfusion centers. General background data would if necessary be collected through the inquiries conducted by Dr. Gunson (UK) and WHO data.

Conclusion

It was agreed that the questionnaire (amended in the light of comments made) would, after approval by the CDSP be sent out to members for reply by the end of 1988 (See Appendix VI).

## E. DEVELOPMENT OF TRAINING CURRICULA

16. **TRAINING IN TRANSFUSION SCIENCES FOR NON-MEDICAL PERSONNEL**

Coordinator : Prof. BARBOLLA

Dr Gunson (UK) reported that in some regional transfusion centers in the United Kingdom a serious shortage of non-medical personnel was developing. In particular this applied to the recruitment of technical staff with appropriate academic qualification for work in the laboratory. Moreover, skilled laboratory workers were being attracted to industry by the greater financial rewards which could be obtained. There was currently a review of grading of laboratory staff and a new grade of medical laboratory assistant had been introduced. These would be persons without previous laboratory experience who would undertake routine well-defined procedures under supervision. They would undergo in-service training.

The British Blood Transfusion Society (BBTS), who had produced general advice on training for laboratory personnel was now actively involved in preparing detailed protocols for in-service training of MLA'S. Also, since there were fewer entrants to scientific training, problems were arising with organised courses of training. The BBTS is also providing advice on this aspect of training.

Conclusion

It was agreed to make these proposals available to the Committee at its next meeting.

x

x x

Supported by Prof. Freiesleben (Denmark) who had directed the study group in 1981 leading to the Recommendation on the training of transfusion specialists, Dr Barbolla suggested to initiate an enquiry to evaluate the follow-up given by countries to that Recommendation.

Conclusion

The SP-HM requested Dr Barbolla to take appropriate action and report back at the next meeting.

## F. INFORMATION

### 17. EUROPEAN AGREEMENTS

Coordinator : SECRETARIAT

#### 17.1 European Agreement N° 26 : revision of the protocol

Dr. Heistø informed the Committee that comments on the most recent draft monographs of Group 6B of the European Pharmacopoeia on plasma and whole blood would be welcome by 15 July 1989. As concerned a draft text on Anti-A and Anti-B Allo-Antibodies titration, Prof. Engelfriet - after discussion with the Amsterdam Serological Laboratory, suggested that Dr Heistø consult Dr. R. Nordhagen (Norway). In view of the importance of the question, the SP-HM was of the opinion that it should be discussed by the Select Committee on Quality Assurance at its 1990 (6-10 March) meeting. Dr. Heistø agreed to inform Group 6B of the importance the SP-HM attributed to this mutual and multi-lateral consultation.

The Secretariat then informed the Committee that it had been proposed by Dr. Heistø that the Protocol to Agreement 26 would only contain a reference to the Monographs of the European Pharmacopoeia if the three countries who had ratified Agreement 26 but not the European Pharmacopoeia Convention could agree to it. The EEC would soon also be consulted on the draft protocol.

#### 17.2 European Agreement N° 39

Conclusion

The SP-HM agreed with the proposal by Prof. Engelfriet to revise the Protocol of the above Agreement and to entrust the Committee on Quality Assurance with this task.

#### 17.3 European Agreement N° 84 : specific provisions of tissue-typing

Nothing to report.

#### 17.4 State of signature and ratification

The Secretariat informed the Committee that Greece had ratified Agreement 39 which had entered into force on 30 December 1988.

### 18. EUROPEAN BANK OF FROZEN BLOOD OF RARE GROUPS (AMSTERDAM)

Coordinator : Prof. ENGELFRIET

#### 18.1 Report for 1988

Prof. Engelfriet said that the number of units sent out by the Bank was again similar as in previous years. This number was not large, but in the cases units were requested, the availability of these units was very important

for the patients. The question was raised what to do with units which were frozen before tests for anti-HIV were performed. For units in the European Bank it had been decided to let the physician responsible for the patient decide whether he wished to accept such a unit or not.

18.2 Computerised list of rare groups at national blood banks

Some additional information has recently been received. As soon as sufficient information was available, it would be incorporated in the list and a new copy of the list would be distributed to the members of the Committee.

19. **EUROPEAN BANK OF REFERENCE SERA FOR TISSUE-TYPING (STRASBOURG)**

Coordinator : SECRETARIAT

19.1 Report for 1988

See item 12.1

20. **TRAINING ACTIVITIES**

Coordinator : SECRETARIAT

20.1 European courses in blood transfusion : 20th Blood transfusion course (Madrid 1990)

Dr Barbolla informed the Committee that thanks to the cooperation of the Bureau the programme had been set up (See Appendix VII). The Course, to be held on 28-30 March 1990, was to include about 200 participants of which two/thirds would be medically qualified. The Spanish authorities were very grateful to the SP-HM and the Council of Europe for organising this course which would greatly contribute to improve the organisational and scientific aspects of transfusion.

20.2 European courses in histocompatibility 7th Course (1989)

See item 12.1

20.3 European conferences/symposia

See item 12.1

## G. PUBLICATIONS

21. **COMPENDIUM OF RECOMMENDATIONS BY THE SP-HM**

Coordinator : Dr. HEISTØ

Further to a discussion on the use and target distribution of the compendium, it was concluded that the text should :

i. serve as a reference book of the work of the Council of Europe in blood transfusion for Health Authorities, administrators and all those responsible for blood transfusion,

ii. consist of a "historical" collection of texts.

iii. serve as a basis for future revision and updating.

22. **DATA ON BLOOD TRANSFUSION ACTIVITIES IN MEMBER STATES AND COMPENDIUM OF NATIONAL LEGISLATIONS**

Coordinator : Prof. GENETET

In the light of the recently adopted Recommendation N° R (88) 4, the EEC draft directive and the goals it set, as well as the report on Plasma Products and European Self-Sufficiency, the SP-HM agreed that collection of legislation, regulations and data might be necessary. It was left to the Bureau to take action as and when necessary in connection with the cooperation with the EEC.

## H. OTHER QUESTIONS

23. **INFORMATION ON THE ACTIVITIES OF OTHER ORGANISATIONS**

Coordinator : Dr. BRITTEN

23.1 League of Red Cross and Red Crescent Societies

Dr. Britten reported on changing roles of Red Cross/Red Crescent activities with the increasing emergence of a new pattern, namely donor recruitment plus blood collection, without responsibility for laboratory processing. Examples are Singapore, Zimbabwe, Botswana and Brazil, with many others considering such a role.

He stressed also certain issues in international aid, (i) long-term vs. short-term and (ii) sufficient vs. insufficient. He emphasised that blood transfusion development efforts must have long-term sustainability in mind, and must be sufficient to correct existing problems.

23.2 World Health Organisation

Dr. Lopez reported on the Global Blood Safety Initiative (GBSI). She stressed widespread existence of the following issues :

- lack of proper documentation and information
- fragmentation of services, lack of government funding
- absence of administrative structures
- inappropriately trained personnel
- lack of leadership
- lack of essential supplies (reagents, recurrent items, collection bags etc.)
- inadequate blood and absence of donor recruitment strategies
- inappropriate use of blood.

A new GBSI data base was available to interested organisations.

GBSI plans included approaches to :

- global programme for training
- global programme for donor recruitment
- guidelines for operational research and other areas eg quality assurance, record keeping, transmissible agents, project development
- supply of cold chain equipment and blood bags.

23.3 ISBT

Dr. Habibi summarised ISBT activities in the past year :

The ISBT membership was now over 1700. However, the distribution of members according to countries showed that 75% of members come from Europe and North America. For this and other reasons the ISBT Council has decided to offer facilities to those with restricted financial conditions to become members, their introduction in the Society being taken in charge by grants from supporting institutions either non profit or commercial.

The first European regional meeting of the ISBT was held in Lugano in early May 1989. This was not a scientific meeting strictly speaking, but was designed to cover the East as well as the West of Europe to improve mutual knowledge about blood transfusion in the 32 European countries, and to pave the way for better bilateral or multilateral working schemes.

These goals had been adequately achieved. The next European regional Congress would probably be held in an Eastern country at a still unestablished date. The proceedings of the Lugano Congress would be published by the end of 1989. The principle of a European blood donor card and a European blood donation day had been prepared.(*)

During its last meeting the ISBT Council reemphasized the adherence of the Society to its code of ethics in accordance with recommendations recently issued by the Council of Europe. Particular reference was made to the necessary dissociation between the collection of blood and blood components and plasma fractionation activities, the former being the role of blood transfusion centres, the latter falling within the scope of the activities of fractionation facilities irrespective of their statutes, non profit or commercial.

Finally the publication Committee of the ISBT has initiated the edition of a new information journal, "Transfusion Today". The Journal appears on a quarterly basis, in three languages (French, English and Spanish) and in 5,000 copies for each issue. The objectives and scope of the Journal had been outlined in the editorial of the first issue dated March 1989. Collaboration and input from European transfusionists was warmly welcome.

23.4 EEC : Draft Directive on the free circulation of blood products

Dr. Sauer (EEC Commission) thanked the coordinated research group for the excellent work carried out and for having managed to perform it in one year (instead of 2 as initially planned) in order to meet the EEC deadlines. He stressed that the directive gave a legally binding dimension to Council of Europe recommendations. He then said that the EEC was speeding up the harmonisation in the pharmaceutical field : the directive on transparency for medicines and the one covering vaccines and radio-pharmaceuticals had recently been adopted.

Concerning the draft directive on plasma products he recalled that in October the European Parliament had introduced 8 amendments which took into account the opinion draft by the SP-HM during the Vienna meeting. The Council of Ministers adopted a common position in December 1988 and the second draft was approved by the European Parliament in April. The Council of Ministers would probably adopt the final version (distributed to the Committee) in June. The directive would be implemented on 1.1.1992 for new products and on 1.1.1993 for products already on the market.

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(*) In this connection the SP-HM requested the Secretariat to represent in Madrid the proposals it had made at its 1984 meeting.

The Commission was now entrusted with the drafting of a technical directive which would state the conditions for the implementation of the directive. This technical directive did not need adoption by the Council of Ministers.

Technical cooperation

Mr Sauer proposed that EEC/CE work jointly through governmental and other experts to draft this technical directive. This work should if possible start during the second half of 1989 in order to have a final version of the technical directive by the end of 1990, as it was needed prior to the entry into force of the directive. The working party should essentially draft an addendum (covering plasma products) to the recently adopted Guide of Good Manufacturing Practice (GMP). In order to attain self-sufficiency an effort was to be made to regroup the different manufacturers and study the possibilities of cooperation including the industry with a view to setting a realistic calendar to reach this objective within the EEC member States.

It was also agreed that Recommendation N° (88) 4 on the Responsibilities of Health Authorities in the field of blood transfusion was a good starting point for action in this field.

Conclusion

The SP-HM agreed on these proposals and welcomed cooperation with the EEC which offered a binding framework to most of its recommendations. It also agreed that details of cooperation should be decided upon by its Bureau in cooperation with the Commission. The Bureau should draw expertise from its members as and when necessary and particularly from the members of the 1988 coordinated study on plasma procurement and use.

Prof. André kindly offered hospitality at the Belgian Red Cross Headquarters in Brussels in the Autumn of 1989 to host a joint meeting between the SP-HM Bureau and the EEC Commission to lay down a calendar of cooperation.

The SP-HM submitted to the CDSP (if possible for decision already at its June 1989 meeting) the report of the Coordinated Study Group for publication and the draft Recommendation for approval and transmission to the Committee of Ministers (see Appendix IV).

The SP-HM also requested the CDSP to approve, subject to financial possibilities, the holding of a meeting in the Autumn in Brussels, bringing together the members of the SP-HM Bureau, the Director of the Coordinated Research programme and the EEC Commission.

23.5 Other organisations

A report on the activities of Fiods was presented by Prof. Genetet.

24. **CO-OPERATION WITH BLOOD TRANSFUSION SERVICES OF:**

24.1 European non-member States

The SP-HM took note that several of its members had already contacts (bi-multilateral) with Eastern European countries. Further initiatives had been activated at the Lugano European meeting of the ISBT. It was agreed that the Secretariat would in due course explore possibilities for admitting representatives of Eastern European countries as observers to one of its next meetings or alternatively to a part of such a meeting for a hearing.

24.2 Developing countries

See item 23.1

25. **MISCELLANEOUS**

The Secretariat informed the SP-HM as to the observer status requested by the American Association of Blood Banks (AABB); the Bureau had examined the request with interest, it agreed however that, subject to approval by the members of the SP-HM, the policy adopted in the past should still be followed, namely that the number of observers of the Committee should not be increased so as to exceed 1/3 of the members, with a view to maintaining an appropriate balance between member States and organisations. This argument had already been put forward in the past to refuse similar requests from other non-member States and organisations wishing to join the SP-HM. The Committee agreed with the Bureau decision.

26. **PROGRAMME OF WORK FOR THE 13TH MEETING (1990)**

Coordinator : SECRETARIAT

(See Appendix VIII).

27. **DATE AND PLACE OF THE 13TH MEETING (1990)**

Further to the kind invitation of Spain the SP-HM agreed to hold its 13th meeting in Madrid from 8 - 11 May 1990.

The delegate of Malta informed the Committee that, subject to confirmation, his authorities intended to extend to the SP-HM an invitation to hold its 14th meeting in Malta in 1991.

APPENDIX I / ANNEXE I

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