

A. BLOOD PRODUCTS LABORATORY

Report to the Advisory Subcommittee on the Blood Products and Blood Group Reference Laboratory of the Central Committee of the National Blood Transfusion Service - 1976.

Research and Development

Preparative Electrophoresis. A DHSS grant to AERE enabled work to begin in July 1976 on the 12-month programme of investigating the feasibility of using the Philpot electrophoretic separator to plasma fractionation (see Report 1975). Further development of this project, if the results of this programme are successful, is referred to in Appendix A.

Chromatographic Separation of Enzymes and other proteins.

Pseudocholinesterase. A preparation of this enzyme, from Fraction IV, passed tests for safety and potency and is available for clinical trial in specific patients suffering from apnoea caused by certain muscle relaxing drugs in those with genetically determined abnormal pseudocholinesterase or in persons who have been exposed to certain insecticides. One patient has so far been treated. The outcome was successful.

Alkaline phosphatase bone isoenzyme. Following last year's report of the successful administration of this enzyme, plasma from donors with Paget's disease is being collected but the accumulation of a fractionation pool is understandably slow.

Recovery of Albumin. A bench scale model has been devised to separate albumin from Fraction IV and from plasma from time-expired blood and concentrated red cells: haemolysed plasma could also be used.

Separation of C3b inhibitor (KAF). Pilot fractionations were undertaken during the year. Most of the effort has been directed to overcoming difficulties in the assay method. This work is being done in collaboration with [redacted] group at Cambridge.

A fuller description of the chromatographic and electrophoretic work and proposals for its development are given in Appendix A. The application of these new methods will allow separation and purification of plasma components which can be separated by the traditional cold ethanol methods with difficulty or not at all and present a prospect of being able to use methods which will widen the range of clinically useful substances recoverable from plasma with relatively simple equipment. While it is realized that the present time is not financially propitious, the Subcommittee is asked to consider sympathetically and give its support to the proposals in Appendix A because of their potential importance to the future development of plasma fractionation.

Albumin and malaria. The laboratory is collaborating with the MRC Biochemical Parasitology Unit and the Hospital for Tropical Disease in a project for using albumin, from which the fatty acids have been removed, to treat the haemolytic crises in malaria.

Hepatitis B antigen. During 1976 all plasma received at BPL was screened by a micromodification of the reverse passive haemagglutination test. Since January 1976 all plasma has been screened by RIA revealing a higher incidence of positives than had, unexpectedly, been found using RPH. Work is in progress to separate and fractionate the antigen in order to obtain a pure preparation which will be used to prepare antisera in animals for detecting and subtyping antigens, thus reducing or eliminating the use of commercial sera. Authority is requested to purchase in 1977/78 Uvichord II and Uvichord 6 channel recorder, minirac fraction collector and varioperpex pump to be used in connection with this work (see notes on estimates).

Specific Immunoglobulins. Although, perhaps not unexpectedly, regarded by

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Coagulation Factors. There is active collaboration between Elstree and Oxford. During the year improved working procedures for factor VIII assay and statistical evaluation of assay data have been developed and a factor VIII house standard introduced. Both laboratories are collaborating closely with NIBSC in the preparation and standardisation of the first British working reference preparation of factor VIII (concentrate).

The laboratory is collaborating in three clinical investigations:

Trial of factor VIII concentrates in home treatment (BPL Elstree, PF Lab Oxford; Clinical Unit, Haemophilia Centre, Oxford; Dept. of Haematology, St. Thomas's Hospital).

Trial of factor VIII concentrate in prophylaxis (BPL Elstree, Lord Mayor Treloar College, Alton).

Hepatitis in haemophiliacs associated with the transfusion of factor VIII concentrates (BPL Elstree, PF Lab Oxford, Clinical Unit, Haemophilia Centre, Oxford; Haemophilia Centres, Newcastle and Lord Mayor Treloar College).

PRODUCTION

Immunoglobulin and Albumin Preparation Laboratory

Coagulation Factor Preparation Laboratory In 1975 the major task was preparing for the expansion of production of factor VIII concentrate, in particular the designing, installation and testing of equipment for thawing large volumes of frozen plasma and then mixing it, while retaining the temperature within narrowly controlled limits and the investigation of yields obtained with this equipment. The new equipment was taken into routine use early in 1976 and has been tested up to the maximum pool size envisaged (360 litre). Arrangements are nearing completion to issue concentrate in small volumes (250 iu in 15 to 20 ml) of which nearly 1000 have so far been prepared.

The following numbers of 250 iu containers were prepared:-

1974, 4879; 1975, 8770; 1976(Jan - June), 12,268 (incl. 695 vials).

It is expected that the annual target of concentrate equivalent to about 14 million iu factor VIII derived from 1000L fresh plasma fractionated per week, will be reached by autumn 1977.

Pressure for supplies of factor VIII increases constantly and annual targets for U.K. of 35 and 40 million iu (cryoprecipitate and concentrate combined) are now mentioned.

The capacity of the Elstree laboratory is about 1000L weekly or 14.0 million iu per year. However by rearranging the preparation of factor IX concentrate so that certain stages will be carried out at Elstree and then sending the material to Oxford for the final stages of preparation, assay and safety testing, it should be possible to double the volume of plasma used at Oxford to prepare AHG concentrate, and thus increase the output from 5000 x 250 iu to 10,000 x 250 iu containers per year without encroaching on the time or space devoted to research and development. AHA (Teaching), Oxford is providing an extra blood collecting team at RTC Oxford to "tap" new population at Milton Keynes. It is expected that this reorganization will be completed in 1977/78. Financial provision is included in the revised 1976/77 and forecast 1977/78 estimates. (See Appendix B for summary of fractions prepared).

Small pool 10-donor Dried Plasma. Some clinicians prefer to use dried plasma because it is a more "complete" fluid than PPF, which contains little protein apart from albumin or electrolyte other than Na and Cl and some Ca. The risk of transmitting hepatitis B is minimal, since all pools are tested by RIA. The Ministry of Defence continues to use dried plasma for certain purposes because of the relatively large number of donations needed per container of PPF. H.M. Ships at sea likewise continue to be stocked with dried plasma. (See Summary of Products, Appendix B).

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laboratory assistants is acute and, unless overcome, will prevent attainment of the factor VIII concentrate target and increased preparation of albumin fractions.

General.

Medicines Act 1968. Application has been made on behalf of both BPL Elstree and PF Laboratory, Oxford for manufacturing licenses. Application for product licenses for factor VIII and factor IX concentrate has been made on behalf of PF Laboratory; at present this laboratory prepares no other products. Application has been made on behalf of BPL for a product license for factor VIII and is about to be made for a license for PPF but there remains a long list of fractions for each of which the lengthy and repetitive procedure of preparing applications will have to be followed. This activity tends to be put aside because of more urgent demands upon the time of a staff which has not been increased to deal with this work.

PF Laboratory has been inspected. BPL will be visited in October. The outcome of both visits will presumably be reported to Med 4B and HS2B, the divisions of DHSS responsible for these two laboratories as central laboratories of National Blood Transfusion Service.

It is not unlikely that the accommodation of both laboratories will be criticized and, in certain respects, found inadequate. Both were designed before the Medicines Act was passed and therefore several years before those responsible for applying this Act had formulated the criteria to be met.

The design of BPL was virtually fixed by 1965 and later altered in the interests of economy. The general concept of the laboratory is therefore nearly 12 years old. The design age of PF Laboratory, Oxford is only slightly less; the original design was ruthlessly altered in the interests of economy and a return to something resembling the original design has gradually been achieved by adding to the laboratory as first built, but the resulting building is obviously less satisfactory than one built to the original plan would have been.

Future. To design, build and occupy a laboratory building takes several years; in my experience it has never been less than 5 years and in the case of BPL nearly 7 years. Because of this long gestation period it is my opinion that DHSS should begin to consider very soon what changes will be necessary in arrangements for providing plasma fractions in England and Wales in, say, 10 years time, by when both Blood Products Laboratory and Plasma Fractionation Laboratory will be out of date in most respects and possibly have been condemned by Medicines Act Inspectorate or others.

The following factors should be taken into account -

- (i) the number of fractionation laboratories needed
- (ii) site - preferably in a University town with a medical school, near a regional transfusion centre and a hospital (preferably teaching); and also near public transport and, in the case of BPL, closer to sources of staff than Elstree and neighbourhood.
- (iii) room for expansion
- (iv) adequate services
- (v) elasticity of design
- (vi) compliance with the highest standards expected by Medicines Act
- (vii) adequate provision for research and development

One aspect of the NHS which affects plasma fractionation is the liberal attitude towards provision of drugs and other agents for treatment. Yet such lavishness was not in the minds of those who planned NHS: "No one concerned with its planning and development from 1946 onward can have imagined that we had the resources, material or professional, to give everyone any conceivable service which might relieve their condition" (Godber, G.E. Lancet, 1976, ii, 622). In the instance of plasma fractions or other transfusion media, limits have not yet been suggested and, assuming the "policy" adopted hitherto does not change, much greater account than before must be taken of it when new fractionation laboratories are designed. These laboratories and the regional transfusion centres, in close cooperation with which they work and on which they depend for plasma, are all part of a functional whole. However the nature of the activities of the fractionation laboratories does not fit easily into the present system of financing and this fact, like the open-ended obligation to provide blood and its derivatives, should also be given due weight.

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27/7/76