BT 82/5

MEDICAL RESEARCH COUNCIL

Blood Transfusion Research Committee

Report to the Physiological Systems and Disorders Board, November 1981

The Committee was reconstituted in 1978 with the terms of reference, "To advise the Council on research within the field of blood transfusion." The present Chairman was invited to take office following the retirement of Professor P. L. Mollison on 30th June 1979. The membership of the reconstituted Committee is given in Annexe 1. Since its formation, the Committee has met on two occasions, 17th December 1979 and 25th June 198 .

The work of the Committee during the past two years has included the consideration of new projects and the receipt of reports from Working Parties constituted by the former Committee.

MAJOR TOPICS CONSIDERED BY THE COMMITTEE

(1) USE OF RED CELL CONCENTRATES, CRYSTALLOID AND ALBUMIN SOLUTIONS IN HYPOVOLAEMIA

The need for increasing quantities of freshly-frozen plasma for the preparation of coagulation factor concentrates necessitates the removal of plasma from the majority of donations of whole blood. This results in all Transfusion Centres having significant supplies of red cell concentrates for clinical use. It was agreed that the Committee should provide an expert opinion on the use of red cell concentrates in haemorrhagic states, since some clinicians are reluctant to use concentrates in such conditions due to the lowered protein content compared with whole blood.

There is evidence to suggest that moderate degrees of hypovolaemia can be treated using crystalloid solutions; indeed their use may be associated with fewer complications than with the use of albuminoid solutions. If this could be demonstrated then the use of red cell concentrates supplemented with the infusion of crystalloid solutions could be shown to be effective in the treatment of moderate haemorrhage.

To study this problem a Working Party was constituted in December 1979. The membership is given in Annexe 1. The Working Party has met on one occasion and consideration was given to the study of three clinical conditions, viz. acute accidental trauma, burns and major vascular surgery. It was considered that there would be insufficient support for clinical trials on patients suffering from burns. Accordingly, the Working Party has established two working groups to examine the feasibility of mounting clinical trials in the areas of accidential trauma (convened by Professor Ledingham) and vascular surgery (Mr. Ruckley). The working groups have each met on one occasion and are now engaged in the preparation of detailed protocols for trials to study the effects of crystalloid and albumin preparations in the resuscitation of hypovolaemic patients.

80/173

1439

(2) THE CLINICAL SIGNIFICANCE OF A AND B ALLO-ANTIBODIES IN FACTOR VIII AND FACTOR IX CONCENTRATES

The Committee agreed that it would be valuable to ascertain whether the presence of A and B allo-antibodies in coagulation factor concentrates frequently caused clinical complications. The Chairman consulted Directors of Haemophilia Centres and the information obtained suggested that, whilst occasional haemolytic episodes were encountered in Group A haemophiliacs following treatment, it was only a sporadic clinical problem usually associated with high dosage of concentrates administered over a short period.

Nevertheless, it seemed important to study the factors which determined the concentration of A and B allo-antibodies in coagulation factor concentrates. A joint study was undertaken between the Oxford Regional Transfusion Centre and the Plasma Fractionation Centre, Oxford. An automated assay for anti-A and anti-B was devised with adéquate reproducibility. Studies revealed that the anti-A/A polysaccharide complex was cryo-precipitable; thus concentration of the allo-antibody occurred in the concentrate since the initial stage of preparation is cryoprecipitation. It was shown that anti-A (and presumably anti-B also) concentrations in the concentrates can be minimised by avoiding pooling of random donations prior to freezing.

This work has led to two publications, Bowell et al., (1981) and Smith et al., (1981). (See Annexe 2).

(3) THE SIGNIFICANCE OF MONOCLONAL ANTIBODIES FOR USE IN BLOOD TRANSFUSION

The production of antibodies by hybridomas has included preparations of anti-A and anti-B which have had preliminary tests at several Transfusion Centres. It is likely that other antibodies, e.g. anti-Rh(D), anti-IgG and antibodies to complement components, will be prepared in the future.

The Committee agreed that research should be carried out on various aspects of the use of monoclonal antibodies in blood transfusion practice and into the agglutination reaction between red cell antigens and the corresponding antibodies. In order to further these proposals, the Regional Transfusion Directors' Committee has constituted a Working Party. Consideration will be given in the Working Party to all aspects of the use of monoclonal antibodies in blood transfusion and will define research projects which may result in submissions to the M.R.C.

The Blood Transfusion Research Committee will maintain a close interest in this field.

80/174

REPORTS OF WORKING PARTIES

(1) WORKING PARTY ON POST-TRANSFUSION HEPATITIS

This Working Party was formed in 1967 but prior to the reconstitution of the Research Committee it had not met for several years. In view of the current interest in non-A, non-B hepatitis it was considered that the Working Party should be reconstituted; the membership of the new Working Party is given in Annexe 1. The Working Party has met on two occasions, 14th February 1980, and 25th June 1981.

Since there are various groups considering aspects of post-transfusion hepatitis, it was agreed that the function of the Working Party was to promote research and assess the nature and size of the problem of post-transfusion hepatitis in the U.K. with particular reference to changes in transfusion practice. The Committee has had wide discussion on the above aspects of post-transfusion hepatitis which can be summarized as follows:

(a) The identification of agents carrying non-A, non-B hepatitis

The Working Party and its parent Committee supported the application of Professor A. J. Zuckerman for financial support for inoculation experiments in chimpanzees.

(b) Prospective study of donors and units of blood associated with possible cases of non-A, non-B hepatitis

Consideration has been given to proposals for a prospective study of 600 patients who would be followed post-transfusion for a period of two years. Donors would be screened by the alanine aminotransferase test (ALT). Points in favour of the study would be the determination of the incidence of non-A, non-B hepatitis and the opportunity to obtain well-documented specimens of serum from known cases of the infection.

It has been agreed that further evaluation of the project should be undertaken before the Working Party could recommend the study to the MRC, particularly with respect to information which may be possibly derived from samples available from the previous study (Post-Transfusion Hepatitis: results of a two year prospective study: J. Hyg., 1974, Annexe 2), and further consideration of the administrative difficulties encountered in this project.

(c) Hepatitis in haemophilia

Observations have been made on the incidence of hepatitis in haemophiliacs by a working group established by the Haemophilia Centre Directors. There have been interesting findings from the study of multiple attacks of hepatitis,

80/175

which confirm the epidemiological evidence for the existence of more than one sero-type of non-A, non-B hepatitis. Also, dependent on the brand of concentrate used, 70-80 per cent. of overt cases of non-A, non-B hepatitis were associated with the first transfusion the patient received. Information is scanty regarding the incidence of symptomless hepatitis and the relative risks following the administration of different brands of coagulation factor concentrates. The Working Party strongly recommended that a prospective study of patients undergoing elective treatment should be undertaken to attempt to provide an answer to these questions and urged Dr. Craske to prepare a submission for consideration by the M.R.C.

(d) Cytomegalovirus (CMV) post-transfusion infection

Papers presented by Drs. Tobin and Gunson on investigations into this problem summarized the present situation, viz. the risk of transmission of CMV depended on the presence of viable leucocytes and could occur therefore after transfusion of whole blood, platelets and leucocytes. The risk probably existed for periods up to ten days' storage at 4°C. Clinical conditions in which CMV transmission could cause complications of importance were exchange transfusion of neonates, transplantation, open-heart surgery in children, acute leukaemia in children and transfusion in early pregnancy.

It was agreed that follow-up studies on the use of CMV-antibody negative blood which has been made available in some Regional Transfusion Centres would be useful before final recommendations are made on the general availability of this product.

(2) WORKING PARTY ON THE USE OF FACTOR IX CONCENTRATES FOR CONDITIONS OTHER THAN CHRISTMAS DISEASE

This Working Party was set up in 1973 and the MRC obtained licences for two clinical trials which began during October 1976.

The report from one of these trials, i.e. controlled trial of factor IX-prothrombin concentrates in patients prior to liver biopsy, has been received by the Committee. The results are disappointing to the extent that the patients studied were mildly affected and thus the question of whether the concentrates presented haemorrhage or caused thrombo-embolism had not been answered.

The second report from this Working Party on the clinical trial on rapid anticoagulant reversal with prothrombin complex concentrates versus whole plasma is awaited.

The Committee hopes to consider the second report at its next meeting, following which the complete report will be submitted to the Systems Board.

80/176

(3) OTHER WORKING PARTIES

(a) Working Party on cryoprecipitates

This Working Party was established in 1967 but has not met for several years. Much of the work originally carried out by this Working Party is now being performed by groups of U.K. Haemophilia Centre Directors. It has been agreed by the Committee that the Working Party should be formally disbanded.

(b) Working Party on the optimal content of anticomplement in antiglobulin reagents

On the advice of Professor Mollison, this Working Party has been disbanded.

CHAIRMAN'S COMMENTS ON THE WORK OF THE COMMITTEE

Developments in the field of blood transfusion are progressing rapidly. There is considerable interest in the metabolism of red cells, platelets and leucocytes so that a better understanding will lead to longer survival of these components in vitro. Research into plasma fractionation technology, particularly with respect to the factors involved in the stability of factor VIII will have important implications in blood transfusion, e.g. it will be necessary to study the effect of heparin on the membranes of cellular components of blood in relation to storage in vitro. Blood transfusion also has important associations with other fields of medicine, e.g. immunology, particularly with respect to transplantation, microbiology and virology, the study of diseases related to various deficiency states and disease associations with markers found in either the cellular or fluid components of blood, and certain aspects of obstetric practice in relation to allo-immunization. The rapidly developing work on genetic engineering and in vitro production of immunoglobulins will undoubtedly have a major impact on blood transfusion during the next decade.

Individual research projects in blood transfusion are undertaken in many Transfusion Centres and often the results are of substantial value. However, other projects require collaborative effort and it is in this area that the Blood Transfusion Research Committee can make valuable contributions. Experience over the past two years has suggested that the work of the Committee can be improved. To be more effective the Committee should meet more frequently and this can be arranged in the future. Also, the discussions of the Committee should be wide-ranging and not restricted to the narrow field of bio-medical research. Problems associated with development work often lead to the definition of particular research projects, and the presence of other groups considering a particular field of research should not necessarily preclude the Committee from consideration of the same topic if it can be shown to have particular relevance to Blood Transfusion.

80/177

Experts with experience outside the speciality of blood transfusion per se play an important role in such discussions, and as commented in the 1978 report to the Systems Board, such persons are more likely to respond if the Committee is sponsored by the Medical Research Council than to one constituted within the National Blood Transfusion Service. It is not possible to embrace all the specialists within the main Committee and the ability to form sub-groups to discuss certain problems would be a valuable asset, since not all projects warrant the establishment of a formal Working Party. In this way it is hoped that the Committee could fulfil its terms of reference in a satisfactory manner.

H. H. GUNSO

November 19

80/178

ANNEXE 1

Membership of Blood Transfusion Research Committee

Dr. H. H. Gunson	(Chairman)
Dr. J. Goldman	(Secretary)
Dr. A. E. Bell	(S.H.H.D. Observer)
Dr. J. D. Cash	
Dr. W. J. Jenkins	(Retired 31st March 1981)
Dr. R. S. Lane	(From 1st April 1981)
Professor F. Stratton	
Dr. J. O'H. Tobin	
Dr. G. H. Tovey	(Retired 30th Sept. 1981)
Dr. D. M. Walford	(D.H.S.S. Observer)
Professor D. W. Weatherall	

Service Representatives:

Brigadier England.
Group Captain F. R. Jones
Surgeon Commander W. Whitrow

Membership of the Working Party on Crystalloids and Colloids

Dr. J. D. Cash	(Chairman)
Mr. I. Anderson	
Mr. D. Charlesworth	
Professor H. A. F. Dudley	
Mr. I. D. Hill	
Mr. J. Hindle	
Dr. A. T. Lambie	
Professor I. McA. Ledingham	
Miss A. Mansfield	
Dr. A. L. Muir	
Lt. Col. E. S. Parry	
Professor C. Prys-Roberts	
Mr. C. V. Ruckley	
Professor H. B. Stoner	
Dr. D. M. Walford	(D.H.S.S.)

Membership of the Working Party on Post-Transfusion Hepatitis

Dr. H. H. Gunson	(Chairman)
Dr. J. Craske	(Secretary)
Dr. D. B. L. McClelland	
Dr. Sheila Polakoff	
Professor Dame Sheila Sherlock	
Dr. J. O'H. Tobin	
Dr. D. M. Walford	(D.H.S.S.)
Professor A. J. Zuckerman	

80/179

ANNEXE 2

References

Bowell, P. J., Abdalla, S., Snape, T. J., and Gunson, H. H.
Evaluation of an AutoAnalyzer method for quantitating anti-A and anti-B haemagglutinins in factor VIII preparations.
J. Clin. Path. (1980): 33: 958-962.

Smith, J. K., Bowell, P. J., Bidwell, E., and Gunson, H. H.
Anti-A haemagglutinins in factor VIII concentrates.
J. Clin. Path. (1980): 33: 954-957.

Post-Transfusion Hepatitis: results of a two-year prospective study.
Report to the Working Party of the Blood Transfusion Research Committee.
J. Hyg. (1974): 73: 173-188.

80/180