MEDICAL RESEARCH COUNCIL

MRC: IN CONFIDENCE

Systems: 82/S052 June 1982

MRC BLOOD TRANSFUSION RESEARCH COMMITTEE* (BTRC)

Review of activities 1979-82

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1. Papers

Annex 1 - report of the BTRC

Annex 2 - extract from the minutes of the Systems Board meeting in July 1978

2. Background

1939 A research subcommittee of the Emergency Blood Transfusion Committee was appointed under Professor W W C Topley, to co-ordinate investigations on problems associated with blood storage and transfusion. The following year the subcommittee was replaced by the Blood Transfusion Research Committee under the Chairmanship of Dr (later Sir Alan) Drury and, in 1949, was reconstituted to deal with new problems associated with dried blood and its products.

1967 The Committee was reconstituted under Professor P L Mollison, who had taken over the Chairmanship from Dr Drury in 1954, with the following terms of reference: 'to advise the Council on research within the field of blood transfusion'. The Cryoprecipitate Working Party (Chairman: Dr C R C Rizza) and the Post Transfusion Hepatitis Working Party (Chairman: Dr, later Sir William Maycock) were appointed. Two further working parties were appointed: in 1973, on the Use of Factor IX Concentrates for Conditions other than Christmas Disease (Chairman: Dr C R C Rizza) and in 1976, on Optimal Content of Anticomplement in Antiglobulin Reagents (Chairman: Professor P L Mollison).

1978 The Board reviewed the activities of the BTRC for the period 1967-1978 and agreed that there was a continuing need for the Committee which was then reconstituted with its existing terms of reference for a period of three years in the first instance. The full Board minute is given in annex 2.

1979 Following Professor Mollison's retirement, Dr H H Gunson succeeded him as Chairman. The Working Party on the Use of Crystalloids and Colloids in the Management of Hypovolaemia was appointed (Chairman: Dr J D Cash).

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*Membership Dr H H Gunson (Chairman), Dr J D Cash, Dr W J Jenkins, Dr R S Lane, Professor F Stratton, Dr J O'H Tobin, Dr G H Tovey, Professor D J Weatherall, Dr J M Goldman (Secretary), Service Representatives: Brigadier England, Group Captain F R Jones, Surgeon Commander W Whitrow, Observers: Dr D M Walford (DHSS), Dr A E Bell (SHHD)

DBM: Professor D K Peters

S104/20

3. Present position

(i) The Committee is now presenting its first report to the Board since its reconstitution.

(ii) It has disbanded all its working parties and the only remaining subgroup is the Elective Vascular Surgery Subgroup* which hopes to mount a clinical trial to compare the differences between the clinical effects of transfusing crystalloids and albuminoid solutions (annex 1, page 2).

4. Future

Dr Gunson makes a plea for the Committee to be continued to aid collaboration in the field and to allow wide ranging discussions not necessarily restricted to the "narrow field of biomedical research". (annex 1, page 6)

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5. Action required

(i) Consideration of the MRC Blood Transfusion Research Committee's report (annex 1).

(ii) Decision (a) whether the Committee should continue and, if so,

(b) whether the terms of reference and membership are still appropriate.

Membership: Mr C V Ruckley (Chairman), Dr D Brown, Dr J D Cash, Mr D Charlesworth, Mr J Fielding, Dr I D Hill, Mr D P Lieberman, Miss A Mansfield, Dr J McClure, Dr M Pick, Professor C Prys Roberts, Professor G Slaney

MEDICAL RESEARCH COUNCIL

82/5032

Blood Transfusion Research Committee

Report to the Physiological Systems and Disorders Board, June 1982

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. Since its formation, the Committee has met on three occasions, 17th December 1979, 25th June 1981 and 8th March 1982.

The work of the Committee during the past three 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 COLLOID (ALBUMINOID) 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 haemorrhage 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. A review of the previously reported studies has shown that their content had little in common with U.K. clinical practice and, moreover, the regimes proposed could not be readily applied to routine hospital practice. The appropriate use of albuminoid solutions in the management of hypovolaemia remains an unresolved problem.

In an attempt to study the problem and possibly institute clinical trials a Working Party under the chairmanship of Dr J Cash was constituted in December 1979.
At the first meeting of the Working Party it was agreed to establish two sub-groups which would report to the Working Party viz: Acute Trauma Sub-group (Chairman: Professor I McA Ledingham) and the Vascular Surgery Sub-group (Chairman: Mr C V Ruckley).

The Acute Trauma Sub-group held two meetings and concluded that a definitive study based primarily on the outcome of crystalloids versus albuminoid solutions in the management of hypovolaemia was not possible. The Working Party accepted these conclusions and agreed that no further consideration of a trial in patients sustaining accidental trauma was justified. The Sub-group was, therefore, disbanded.

The Vascular Sub-Group has also held two meetings and have concluded that a clinical trial could be justified and feasible. The Working Party has expressed doubts that it would be possible to obtain demonstrable significant differences between the use of crystalloids and albuminoid solutions but agreed that the Sub-Group should be given the opportunity of meeting again to finalise a protocol.

The report of the Working Party, summarised above, was received by the MRC Blood Transfusion Research Committee at its meeting on the 8th March 1982. It was agreed that the Working Party itself should be disbanded but the Vascular Sub-Group should continue as a direct Sub-Group of the parent Committee. The Sub-Group will be requested to prepare proposals for a clinical trial for consideration by the Committee at their next meeting.

(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 association 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, requiring no outside funding, 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 adequate reproductibility. Studies revealed that the anti-A/A polysaccharide complex was cryoprecipitable; 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).

(3) THE SIGNIFICANCE OF MONOCLONCAL 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 (R.T.D) has constituted a Working Party, under the chairmanship of Professor F Stratton. 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 MRC.

The Blood Transfusion Research Committee will maintain a close interest in the activities of the R.T.D. Working Party.

REPORTS OF EXISTING 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 Working Party has met on two occasions 14 February 1980 and 25 June 1981.

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 UK 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-documentated 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, and further consideration of the administrative difficulties which may be 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, 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 MRC.

(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 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.

There are several Working Parties, both of the MRC and DHSS, who are considering a wide range of aspects concerning post-transfusion hepatitis*. At the meeting of the Committee on the 8 March 1982 it was agreed that the above Working Party was duplicating work carried out elsewhere. It was decided, therefore, that this Working Party should be disbanded and any unfinished matters would be referred, as appropriate, to other groups such as the proposed working party to be set up by the Regional Blood Transfusion Directors.

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

This Working Party was constituted in 1973 and the MRC obtained licences for two clinical trials which commenced during 1976. The reports from both the trials have been received. The conclusions of each are set out below (2.1, 2.2):-

2.1 Patients before liver biopsy

Conclusions

(1) During the course of this study, and perhaps because of it, interest in the use of prothrombin complex concentrate for patients undergoing liver biopsy declined.

(2) There were no episodes of recognisable thromboembolism in contrast to the experience of Gazzard et al (Gut, 1974, 15, 993) treating fulminating hepatitis. Moreover, autopsy carried out in five out of seven patients who died revealed no evidence of intravascular fibrin deposition.

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*e.g. DHSS Advisory Group on Hepatitis; MRC Committee on the Development of Vaccines and Immunisation Procedures (CDVIP): Working Party on Hepatitis Vaccines (jointly with Health Departments and the Public Health Laboratory Service).

(3) Although in this trial no patient developed recognisable thromboembolism and there was no evidence of post transfusion hepatitis, the number of patients studied was too small to give an assurance of safety.

(4) If coagulation factor replacement is thought to be necessary before biopsy, it may be prudent at present to use plasma, rather than concentrate, because of the hazards which may be associated with the use of concentrate and because of the additional factors (fibrinogen, antithrombin III and factor V) supplied by plasma.

(5) There is no evidence that concentrate is more effective than plasma in preventing bleeding after liver biopsy.

2.2 Rapid reversal of anticoagulant therapy
Conclusions

(1) There was no important difference between the ability of prothrombin concentrate and fresh frozen plasma to reverse the effect of oral anticoagulants whether assessed clinically or by laboratory testing.

(2) Immediate side effects, although few and not serious, were more often observed following the use of plasma than the use of concentrate.

(3) The presumed higher risk of hepatitis following concentrate compared with plasma has been given some support from these studies, although the evidence is not very strong.

(4) Unless there are strong clinical reasons to the contrary we believe that the safest method of rapid reversal of anticoagulant therapy is to give fresh plasma in spite of the occasional observation of mild side effects following its use.

The Committee considered:-

(i) The controlled trial of Factor IX-prothrombin concentrates in patients prior to liver biopsy had disappointing results to the extent that the patients studied were mildly affected and thus the question whether the concentrates would prevent haemorrhage or cause thrombo-embolism was not answered.

(ii) The trial on the use of Factor IX-prothrombin concentrates for the rapid reversal of anticoagulant therapy provided an important negative conclusion that there appeared to be no significant difference between the use of freshly-frozen plasma and Factor IX concentrates for the rapid reversal of anticoagulant therapy. It is clear from the report that difficulties were encountered in standardising the treatment regimens of patients included in the trial and several had to be included which fell outside the criteria laid down.

The Committee considered, at its meeting on the 8 March 1982, that the Working Party had tackled an extremely difficult task in a competent manner. It is unfortunate that the results were not more rewarding and the fault for this could not be ascribed to the activities of the Working Party. It was agreed, however, that the Committee could not recommend to the Board the publication of the results in a major paper but perhaps some of the findings could be published in a brief communication or letter in an appropriate journal.

The full reports of the Working Party are available at HQ to members of the the Systems Board on request.

(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 UK 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 related 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.

Although individual research projects in blood transfusion are undertaken in Regional Blood Transfusion Centres and elsewhere with considerable success, much research requires collaborative effort and it is this aspect in which the MRC Blood Transfusion Research Committee could make a valuable contribution. Discussions in the Committee should be wide-ranging and not necessarily restricted to the narrow field of bio-medical research. Often problems associated with development work lead to the definition of particular research projects. Also the fact that another group is considering a particular field of research should not preclude the Committee considering the same topic, providing that there was particular relevance to blood transfusion and that the consideration was not merely duplicating work elsewhere.

The membership of the Committee might be reviewed since experts with experience outside the speciality of blood transfusion may play an important part in discussions. The Committee might become unmanageably large if all relevant fields were to be represented on it but the formation of ad hoc groups to evaluate specific aspects might be envisaged.

The concensus of opinion of members of the Committee is that it should continue in being since it could play an important part in the consideration of research matters in a field which is expanding rapidly at the present time. It was considered, however, that the meetings should be held more often than once a year and that perhaps it should operate under more closely defined terms of reference.

References

Bowell, P. J., Abdalla, S., Snape, T. J., and Gunson, H. H.
Evaluation of an Auto Analyzer 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.

ANNEX 2
32/5052

Extract from the Minutes of the SYSTEMS BOARD
Meeting held on 4 JULY 1978

91. MRC Blood Transfusion Research Committee: review of activities 1976-78 (MRC 78/472)

The Chairman welcomed Professor Mollison, Chairman of the Committee, to the meeting to introduce this item.

Reviewing the activities of the Committee since its original formation in 1939, Professor Mollison reminded the Board that it had, in effect, acted as a research committee for the National Blood Transfusion Service. It had been the source of a variety of important initiatives, for example in helping to introduce plastic transfusion equipment, and in the use of frozen red cells in clinical practice. Professor Mollison concluded by reporting that the present Committee's view was that it should continue in some form under the aegis of the Council. In reply to a question, Professor Mollison said that the Committee itself was important independently of its working parties; because there were relatively few experts in this specialised field, the Board's interests would not be served so well by disbanding the Committee and retaining relevant working parties reporting directly to the Board. Professor Mollison also considered that if it were accepted that a research committee in the transfusion field was necessary, such a committee would be more successful if sponsored by the Council than by the Transfusion Service.

When Professor Mollison had left, the Board agreed that he should be congratulated on his successful chairmanship of a most valuable committee. The Board further agreed that this was an exceptional case where a standing committee was still required. The Committee should be reconstituted with the existing terms of reference for a period of three years in the first instance, after which it should report to the Board. The Working Parties should also continue for the present, and should normally report to the Committee.

Decisions

(i) The review of the activities of the MRC Blood Transfusion Research Committee was noted with great interest; Professor Mollison and his colleagues were warmly thanked for their valuable service.

(ii) There was a continuing need for the Blood Transfusion Research Committee; the membership should be reconstituted with the existing terms of reference, for a period of three years in the first instance, after which it should report to the Board.

(iii) The office should consult the present chairman of the Committee and the Board Chairman on the chairmanship of the reconstituted committee; the membership should then be agreed in discussion between the office, the new chairman of the Committee and the Board Chairman.