PROPOSED RESEARCH PROGRAMME

INTRODUCTION

Lord Mayor Treloar College is a unique establishment since there are more than fifty boys suffering from various coagulation defects (namely Haemophilia, Christmas Disease and von Willebrand's Disease) in residence at the College for approximately 264 days each year. These boys usually come to the College at the age of eleven and leave at the age of sixteen to eighteen years of age. They are, therefore, under continual medical supervision for nine months of each year and often for many years.

Day to day treatmentis afforded to these boys by the Treloar Haemophilia Centre, which is under the direction of Dr. P. G. Arblaster, Consultant Physician. This Centre was established three years ago and is now one of the best staffed and equipped Centres in the country. There are adequate laboratory facilities, specialising in coagulation, under the direction of Dr. A. Aronstam, Consultant Haematologist, who is also Associate Director of the Centre. The boys are kept under orthopaedic supervision by Mr. Francis J. Moynihan, Consultant Orthopaedic Surgeon. The staff at the Centre consists of a Medical Officer, who is employed as full time S.H.O. in Haemophilia, and a Medical Officer of consultant status, who is employed for $^{7}/_{11}$ of his time at the Haemophilia Treatment Centre and $^{4}/_{11}$ as Medical Officer to Lord Mayor Treloar College and Florence Treloar School. These Medical Officers have the assistance of a team of Sisters and Nursing Staff specially trained in the treatment of haemophilia by the Research Fellow.

Since 1968 a Research Fellowship in Haemophilia has been established at the College by the National Fund for Research into Crippling Diseases. The present Research Fellow (with secretarial help - also provided by the National Fund for Research into Crippling Diseases) has set up an organisation at the College and meticulous medical records are maintained. It would be unfortunate if such organisation were allowed to lapse for lack of financial support. Lord Mayor Treloar College has a large modern Sick Quarters built in 1968, which provides fourteen beds for in-patient treatment. It is fully equipped with modern surgery, a physiotherapy department and consulting rooms and is staffed by three State Registered Nurses and two Medical Orderlies, all of whom have been fully trained by the Research Fellow in the management and treatment of haemophilia. The College provides an experienced physiotherapist to provide continual physiotherapy treatment when this is required. Hydrotherapy is also available. Arrangements are such that any emergency can now be dealt with at the College.

It will be seen from the foregoing that the College lends itself to a specific type of research into haemophilia and other coagulation disorders, namely to study the relationship between recognised laboratory findings and clinical observations in these somewhat uncommon conditions. It is also the only establishment in the United Kingdom which can provide the opportunity and the facilities for extensive clinical trials of various kinds of treatment. This type of research cannot, at present, be conducted anywhere else.

FUTURE RESEARCH

Clinical and pathological observations made during the last six years at Lord Mayor Treloar College, on boys suffering from haemophilia, strongly suggests that the frequency and duration of spontaneous bleeding is not solely due to a

deficiency of the known coagulation factors. (See Paper 'A'). The most important fundamental discovery concerning the diathesis of haemophilia made over the past few years is probably the recognition of factor VIII related antigen. At present the nature and function of this factor remains to be determined. Investigations on von Willebrand's Disease suggests that this factor may be responsible for the activation of platelets. Most authorities agree that the second line of defence in haemophilia depends on platelet activity. This is supported by the findings in Paper 'B'. It is suggested, therefore, that we should concentrate on this aspect of research in the near future. Furthermore, boys with a deficient platelet activity may develop a more fragile clot, which is more susceptible to action of fibrinolysin. Such cases should, therefore, benefit from the exhibition of antifibrinolytics. (See Paper 'C'). Again, it has been observed when carrying out two-stage factor VIII assays that there is often considerable interference by the presence of a high level of an antithrombin which has been assumed to be anti-Xa. Dr. Rosemary Biggs and her team at Oxford have recently developed a new technique for measuring antithrombin activity and it is therefore proposed that we could concentrate some of our research efforts in studying this aspect of haemophilia and Christmas Disease. With these observations, the following research programme is suggested.

1. Measurement of platelet activity and its relationship to factor VIII related protein and to determine whether the basic levels of factor VIII and its related antigen have any influence on the frequency of bleeding in haemophilia. (It is also possible, of course, that a functionless protein analagous of A+ cases of haemophilia may exist.)

2. To determine whether the post transfusion levels of factor VIII and its related antigen has a bearing on the frequency of bleeding, since we know that the in vivo half life of factor VIII related antigen is approximately double that of factor VIII.

3. Fibrinolysis - With reference to Paper 'C', further work is indicated. It is suggested that a controlled clinical trial, comparing the combined effects of tranexamic acid plus replacement therapy against replacement therapy alone, could be carried out. This must be backed up by antifibrinolytic studies on plasma during treatment and the measurement of the blood levels of tranexamic acid simultaneously. It is understood that this latter assay will be undertaken by the Bichemical Department at Surrey University. It is suggested, therefore, that this clinical trial should be conducted by the division of boys into two groups. One group would receive tranexamic acid 20mgs. per kg., q.d.s., for the first three days whenever they bleed, plus factor VIII replacement therapy. The second group would merely be treated with replacement therapy alone as at present. Following such a trial the frequency of bleeding could be ascertained in both groups together with antithrombin levels, factor VIII levels and factor VIII related protein levels.

4. Antithrombin - To determine whether the antithrombin or anti-Xa has any influence on clinical severity, i.e. the frequency of bleeding in both Christmas Disease and Haemophilia.

5. To determine the relationship of antithrombin-3 complex to the incidence of deep vein thrombosis in patients under treatment with Heparin and undergoing hip replacement surgery. Dr. Biggs and her colleagues have recently developed a test for measuring antithrombin activity and a method of detecting whether or not a Heparin co-factor is present. (Perhaps it should be explained that the Lord Mayor Treloar Hospital is now a recognised Orthopaedic Centre under the Area Health Authority.) Such an investigation would provide data on the distribution of antithrombin-3 in patients free of any coagulation disorder.

COMPLETED PROJECTS

1. A four year study on the incidence of jaundice and the presence of Australia antigen and antibody in boys being frequently transfused with blood products has now been completed in co-operation with the Virus Reference Laboratory, Public Health Laboratory Service, Colindale. Two interim reports concerning this project have already been circulated. It is hoped that a summary of this completed project will shortly be published.

2. Plasma Cortisol Levels and the frequency of bleeding in haemophilia (See Paper 'D').

3. Platelets - The incidence of platelet antibodies in boys subjected to frequent transfusions with blood and blood products has also been completed in co-operation with the MRC Blood Group Reference Laboratory, London. No platelet antibodies were detected in any of fifty boys over a period of one year. It is not considered that this investigation is worthy of publication, nevertheless, it was important to determine these facts and the help afforded by Dr. K.L.G. Goldsmith, Ph.D., M.R.C.P., is acknowledged.

4. See also Papers A, B, C and D. Numerous requests for copies of these papers show them to have been of world wide interest.

CURRENT PROJECTS

1. A prophylactic trial, to determine whether a prophylactic transfusion of factor VIII administered at weekly intervals would reduce the frequency of bleeding in haemophilia, is now almost completed and a report should shortly be available.

2. A research project to determine whether there is a relationship between immune arthritis and Factor VIII antibodies in the joints of haemophiliacs is being conducted in collaboration with the MRC Haemophilia Research Unit, Oxford and the Nuffield Orthopaedic Centre, Oxford. Aspirates from the knee joints of boys at the College are being examined for the presence of factor VIII antibody and their blood for the presence of R. A. factor. In addition, both pre and post transfusion samples of blood are being examined by Dr. E. R. Holborow at Taplow, for the presence of soluble immune complexes, as the presence of (**)

these may have some relationship to the development of kidney disease in haemophilia. In addition, at Taplow, synovial membranes are being examined from boys who have had synovestomies carried out at the Nuffield Orthopaedic Centre, for the presence of intra nuclear antibodies for factor VIII.
(** : MRC Rheumatoid Research Unit, Taplow)

SUMMARY

In proposing this future research it should be mentioned that the Area Health Authority has agreed to provide the Research Fellow with a full time Research Assistant on a permanent basis for as long as a Fellowship exists. It must be fully realised that there is a limit to what the Research Fellow can accomplish with the help of one Research Assistant. It is, however, envisaged that the Centre, which is now fully operational, well staffed and well equipped, will play a full part in assisting to carry out this proposed programme. It is considered that a fully trained and suitable candidate should be available in August 1975 to replace the present Research Fellow. This, of course, will depend on a three year grant being made available, which would secure his future professional advancement to Consultant level.

In addition, the Oxford Haemophilia Centre and the MRC Research Unit at Oxford have in the past assisted in all the research projects carried out at the College and it is assumed that this close collaboration with the proposed research work will continue. It will, therefore, be necessary for this Programme to be agreed, approved and sponsored by Dr. P. G. Arblaster, Consultant Physician and Director of the Treloar Haemophilia Centre and Dr. Rosemary Biggs, Director of the Haemophilia Centre and MRC Research Unit at Oxford.

PUBLISHED WORK REFERENCES

Paper 'A' : A Three-Year Study of Adolescent Boys Suffering from Haemophilia and Allied Disorders
British Journal of Haematology, 1973, 24, p.539-551
Rainsford and Hall

Paper 'B' : Platelet Coagulant Activities and Clinical Severity in Haemophilia
Thrombosis et Diathesis Haemorrhagica, Vo.XXIX
28.VI.1973, p.722-729
Walsh, Rainsford and Biggs

Paper 'C' : Tranexamic Acid in the Control of Spontaneous Bleeding in Severe Haemophilia
Thrombosis et Diathesis Haemorrhagica, Vo.XXX
1.XI.1973, p.272-279
Rainsford, Jouhar and Hall

Paper 'D' Plasma Cortisol Levels and the Frequency of Bleeding
Clinica Chimica Acta 53 (1974) p.351-354
Rainsford, Richardson and Stuart Shaw