INTRODUCTION

Lord Mayor Treloar College is an unique establishment since there are more than fifty boys suffering from various coagulation defects (namely Haemophilia, Christmas Diseases 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 treatments afforded to these boys by the Treloar Haemophilia Centre, which is under the direction of Dr. P.C. 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, 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.

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.

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 a 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 present Research Fellow (Dr Rainsford) in the management and treatment of haemophilia. The College has 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.

The present Research Fellow accomplished a great deal during his stay at the College and was responsible in part for the research on which the foundation of the Alton Centre was based. It is anticipated that Dr Rainsford will stay in the locality of the School and continue to work part time at the Centre for the next two to three years and be paid by the Regional Health Authority. During this extension of his work Dr Rainsford will support the Centre, complete his present research projects and give assistance to the new Research Fellow.

The present arrangements at the College are particularly suitable for a specific type of research into haemophilia and other coagulation disorders, namely the study of the relationship between laboratory findings and close day to day clinical observations. It is the only establishment in the United Kingdom which can provide the opportunity and the facilities for extensive clinical trials of various kinds of treatment which cannot, at present, be conducted anywhere else.

A work of explanation is required about the proposed association of the new Research Fellow and Project with the Oxford Haemophilia Centre. There has been close liason between the Oxford Haemophilia Centre and the care of haemophilic boys at the Treloar College for the last ten years and more. In the last year this type of association has been given recognition by the DHSS by a plan to organise Haemophilia

Treatment and Research on a supra regional basis. It is proposed that certain supra regional centres, of which the Oxford Centre is one, shall be responsible for administrative duties such as ensuring an adequate supply of Factor VIII, providing a reference laboratory and teaching facilities, providing holiday support, determing the number of haemophiliac patients in their area of care and organising research on a regional basis. Alton is included in the region provionally assigned to Oxford. In this new organisational frame work it is hoped that exchange of NHS staff may be arranged between the Oxford Centre and that at Alton and it is proposed that the research facilities of the Oxford Centre should be available to the Research Fellow at the Treloar College. It is our opinion that the basic NHS organisation at the Treloar College is now such that a young Research Fellow could work for and obtain a research degree by working both at the College and at Oxford. The present application is for financial support of such a fellow.

THE RESEARCH PROJECT

The Research Project is entitled "The Promotion of Haemostasis in Patients Suffering from Congenital Deficiency of Blood Clotting Factor VIII or IX". The research will form the basis of a research degree to be submitted by the fellow to a United Kingdom University.

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 (British Journal of Haematology 24 539 1973). 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

as 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 at Treloar College and are already published (Thrombosis et Diathesis Haemorrhagica 29 722 1973). 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 fibrinolysis. Such cases should, therefore, benefit from the exhibition of antifibrinolytics. (Thrombosis et Diathesis Haemorrhagica 30 272 1973). 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 antithrombin which has been assumed also to have anti-Xa activity. 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.

The existence of commercial concentrates of human Factor VIII has lead to the much more liberal use of fractions prepared from large donor pools in the treatment of haemophilia. The consequences for the patients of this increased treatment are improved protection from crippling deformity and much extended horizons of possible activities. But the danger of contracting the blood born viruses causing hepatitis is also increased. The residence of these boys in one place provides an ideal opportunity to study this complication of treatment.

The Project will have two main aspects:-

1. Laboratory

2. Clinical planning and observation.

LABORATORY OBSERVATIONS

In the laboratory observations will be made on the levels of various important plasma constituents in relationship to the clinical state of the boys at the Trelour College and to observe the effect of treatment on these constituents.

(a) The levels of antithrombin and anti Xa will be measured in plasma samples from a selected group of boys before and after they are treated with factor VIII or Factor IX

(b) The measurements of platelet activity by a modification of the method reported by Walsh, Rainsford and Biggs (1977 Thrombosis et Diathesis Haemorrhagica 28 722) will be carried out on boys who are or are not bleeding and before and after treatment.

(c) The stability of clots formed will be observed in the plasma of boys who are receiving antifibrinolysic therapy (tranexamic acid) in comparison with those formed in the plasma of boys who are not treated with tranexamic acid.

(d) Liver function tests such as SGOT SGPT alkaline phosphatase 5-Nucleotidase will be carried out at regular intervals on blood samples which are collected at the time of infusions given to the boys. These samples will also be tested for Hb Ag and Ab. An attempt will be made to trace the source of infection in every instance of hepatitis however mild clinically. Some of the tests proposed may give abnormal results in response to conditions other than viral hepatitis and such associations will be recorded.

(e) Observations will be made on blood samples from boys having antibodies to Factor VIII in an attempt to determine the natural history of such antibodies in the patients.

CLINICAL STUDIES

(a) Depending on the results of the current trial of prophylactic therapy being completed by Dr Rainsford there may well be the need to hold a new prophylactic trial

with increased and more frequent dosage of Factor VIII.

(b) The careful studies of the records already carried out by Rainsford and Hall (1973 British Journal of Haematology 24 339) will form the basis for comparison in all clinical studies. These records will be continued to ensure comparability with previous observations and to provide the background against which to measure the effects of treatment.

(c) Some work on the role of tranexamic acid in haemostasis has been completed (Thrombosis et Diathesis Haemorrhagica 30 272 1973). It is suggested that this work should be extended by 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 Biochemical 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 20 mgs. per kg., o.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. This trial will need to be arranged so that it does not interfere with any future trial of prophylactic therapy.

(d) In association with the laboratory study of hepatitis clinical observations will be made of the condition of the boys with particular attention to the possibility of hepatitis. The work on hepatitis will be co-ordinated with that of Dr Craske of the Microbiology Laboratory at Bournemouth and with observations at Oxford.

THE RESEARCH FELLOW

Should the application for research support be granted Dr Peter John Kirk has expressed interest in undertaking the research project. Dr Kirk's curriculum vitae is appended. We consider Dr Kirk to be quite unusually well qualified to profit by the research opportunity and to make best use of the exceptional facilities at the College and at the Oxford Centre.

It will be seen from Dr Kirk's curriculum vitae that he has an excellent background for this research project. He has final qualifications in Laboratory Technology and is a qualified Medical Practitioner. Dr Kirk qualified in Medicine at the University of Aberdeen in 1972 and is now taking his M.R.C.P. examinations. During his work as Senior House Officer at the Alton Haemophilia Centre Dr Kirk has shown great initiative, competence and responsibility and is already engaged in many of the research projects at present in progress. These include the study of antithrombin levels in patients and the study of hepatitis.

It is proposed that if Dr Kirk is appointed he should register as a student for the degree of Doctor of Medicine (M.D.) at the University of Aberdeen. We have every confidence that he would obtain the degree in three years. Moreover we are sure that three years of research would be particularly beneficial to the future career of Dr Kirk who wishes to qualify as a Consultant Clinical Haematologist.