Thromboembolism and Haemostasis Programme

J. HIRSH, MD, FRACP, Professor, and E. REGOECZI, MD, Associate Professor, Department of Pathology, McMaster University, Hamilton, Ontario

The Thromboembolism and Haemostasis Programme has major service, educational and research components. The service and clinical research aspects of the programme are contributed to by members of the departments of pathology, medicine, paediatrics, clinical epidemiology and biostatistics, radiology and surgery. The programme is currently centred at St Joseph’s Hospital, with a major component at the Hamilton General Hospital. The major interests at St Joseph’s Hospital are the diagnosis and treatment of haemorrhagic disorders and the diagnosis and treatment of venous thromboembolism. The major interests at the Hamilton General Hospital are the diagnosis and treatment of hyperlipoproteinaemias and the diagnosis and surgical treatment of coronary artery disease and peripheral arterial disease.

ST JOSEPH’S HOSPITAL
The regional laboratory and clinical consultative service for the management of disorders of haemostasis and the management of venous thromboembolism is under the direction of Dr J. Hirsh. This service provides a seven days a week, 24 hours a day coverage for the hospitals in the Hamilton district and surrounding area. The service is provided by a staff of medical technologists who are able to perform complex tests of coagulation, platelet function and fibrinolysis, by the residents in haematology and by three members of the Haematology Group who are on the active staff (Drs J. Hirsh, B. Luke, and G. Pineo). The laboratory also provides a diagnostic service for the Haemophilia Clinic at the Chedoke-McMaster Centre and provides a quality control service for the hospitals in the Hamilton district.

Management of Venous Thromboembolism
Methods of diagnosis, prophylaxis, treatment and laboratory control of treatment of venous thromboembolism are being evaluated. In addition, patients with venous thrombosis or pulmonary embolism are investigated after their episode to determine whether their disorder is associated with and
possibly caused by any abnormalities in fibrinolysis, blood coagulation or platelet function. The treatment and laboratory control of treatment of patients with venous thromboembolism have now been standardised throughout the Hamilton area and it is proposed to extend parts of the development and research aspects of the programme to the Hamilton General Hospital, Henderson Hospital and McMaster University Medical Centre.

Detection of venous thrombosis in high-risk patients. $^{125}$I-fibrinogen scanning, Doppler examination and venography are used to detect venous thrombosis. Because of the possible risk of hepatitis, fibrinogen is prepared locally from four blood donors who are Australia antigen negative and who have been giving blood to the Hamilton Red Cross for over five years without evidence of hepatitis in recipients. This fibrinogen is also labelled and sterilised in the regional laboratory.

To date, $^{125}$I-fibrinogen scanning has been used in over 200 patients at St. Joseph’s Hospital

(a) to scan high risk surgical and medical patients;
(b) to investigate the value of low doses of heparin in the prophylaxis of venous thromboembolism in high risk surgical and medical patients;
(c) to investigate the value of laboratory tests performed before, during and after surgery in predicting either a thrombotic tendency or the presence of early venous thrombosis; and
(d) to evaluate the efficacy of tests used to monitor heparin therapy in preventing extension of venous thrombosis and thromboembolism in patients with established venous thrombosis.

So far, $^{125}$I-fibrinogen scanning has been used only at St. Joseph’s Hospital but it is planned to extend this facility to the Hamilton Civic Hospitals and the McMaster University Medical Centre.

Treatment of established venous thromboembolism. Experience has shown that approximately 30 per cent of patients diagnosed on clinical grounds to have calf vein thrombosis do not have this diagnosis supported when investigated by venography or $^{125}$I-fibrinogen scanning. Therefore, in all except overt cases, an attempt is made to substantiate this clinical diagnosis by ascending venography and/or $^{125}$I-fibrinogen scanning. It has been our policy to monitor the antithrombotic effect of heparin by the partial thromboplastin time. The value of this test in controlling heparin therapy has been investigated and confirmed by Dr. D. Basu (one of the residents in the Thromboembolism Programme) in 250 patients with thrombosis.

Patients with established venous thrombosis are treated with heparin given by continuous intravenous infusion and are then usually discharged from
hospital while on treatment with oral anticoagulants. Heparin is given in a dose to maintain the partial thromboplastin time at 1$\frac{1}{2}$ to twice control levels. A study is currently being planned with the Family Practice Group at St Joseph's Hospital and the Department of Clinical Epidemiology and Biostatistics to evaluate oral anticoagulants in patients with established venous thrombosis after they have been discharged from hospital.

**Investigation of methods of controlling herapin therapy.** The detection of the endpoint of the partial thromboplastin time may be difficult in patients who are treated with heparin. For this reason, attempts have been made to automate the detection of endpoint and to standardise this test throughout Hamilton. After considerable difficulties, success has finally been achieved in developing a reliable method using a soluble Factor XII activator and an instrument which is triggered by optical density change.

**Investigation of patients with idiopathic recurrent deep vein thrombosis.** An outpatient clinic has been established to investigate patients with idiopathic recurrent venous thrombosis. Patients referred for investigation have the following tests performed: euglobulin lysis time and fibrin plate lysis before and after tourniquet stress, antithrombin III level, antiplasmin and antifibrin-kinase levels, and tests of platelet adhesion and aggregation. A significant proportion of patients with idiopathic or recurrent deep vein thrombosis have impaired fibrinolytic activity and these patients are treated with drugs that enhance endogenous fibrinolysis.

**Streptokinase therapy.** Streptokinase therapy is used in the treatment of acute iliofemoral thrombosis, acute major pulmonary embolism and in selected patients with arterial thrombosis or embolism. In addition, the effects of streptokinase and heparin are being compared in patients with $^{125}$I-fibrinogen-detectable venous thrombosis to evaluate the effects of these drugs on the subsequent course of venous thrombosis.

**Haemophilia Programme**

The regional haemophilia programme at the Chedoke-McMaster Centre is under the direction of Dr A. Zipursky and includes a team capable of assessing and dealing with many problems of haemophilia. The initial assessment includes evaluation by physician, paediatrician, specialist in physical medicine, dentist, public health nurse, physiotherapist, social worker, educational consultant and haematologist. Assessment of haemostasis is carried out by the regional coagulation laboratory.

The established programme for these patients includes cryoprecipitate banks which have been established in Hamilton, St Catharines, Niagara Falls, and Simcoe. Cryoprecipitate in these banks is provided by the central
blood transfusion service located in Hamilton and periodic assessment of the Factor VIII content of the cryoprecipitate and the Factor VIII response to infusion are carried out by the regional coagulation laboratory.

A major objective of this programme is to provide facilities for the total care of the patient in his community setting. This necessitates close co-operation between all members of the programme and the community. In this way, the patient can be cared for when and where he needs it and the standard of care of haemophilia can be maintained in the satellite centres. The haemophilia programme has also been of great value for undergraduate and residency education by demonstrating the importance of team work and regional programming in the provision of comprehensive care for patients with chronic disease.

**Multicentre Trial with Drugs that Suppress Platelet Function in Patients with Transient Cerebral Ischaemia**

A large-scale trial, involving twelve centres across Canada, has been organised jointly by McMaster University and the University of Western Ontario. The drugs under evaluation are sulphinpyrazone and aspirin. The experimental design and evaluation is performed by the Clinical Epidemiology and Biostatistics Department at McMaster University and reagents for platelet function tests are provided by the regional coagulation laboratory.

**Hamilton General Hospital**

**Cardiac and Vascular Surgery Programme**

Cardiovascular surgery is performed at the Hamilton General Hospital by a team of four cardio-thoracic and vascular surgeons. The clinical research aspects of this programme are under the direction of Dr G. Evans, and its objectives are to assess the effectiveness of drugs that suppress platelet surface activity on various revascularisation procedures and on the recurrence rate of deep vein thrombosis.

Patients who have aorto-iliac and femoro-popliteal arterial bypass surgery, as well as patients with coronary bypass surgery, are randomised and the effects of platelet suppressive drugs on the duration of patency of their bypass procedures are assessed. In addition, the effectiveness of platelet suppressive drugs on the degree of embolisation from prosthetic heart valves and on the incidence of recurrence of venous thrombosis is being assessed. To date, a total of 600 patients have been used in this study. The positive results at this time are: (a) these drugs are effective in the short-term therapy of transient cerebral ischaemic attacks; and (b) they have a significant influence on the incidence of recurrent episodes of deep vein thrombosis.
Lipid Programme

The regional clinical and laboratory service for the investigation of hyperlipoproteinaemia is under the direction of Dr M. A. Mishkel. In addition to routine investigations of lipoprotein electrophoresis, and triglyceride and cholesterol measurements, ultracentrifugal analysis and free fatty acids determination are performed on selected cases. The clinical research component of this programme includes: (a) large-scale epidemiological studies to define the incidence of hyperlipoproteinaemia in population groups (this is being carried out in collaboration with Dr D. L. Sackett of the Department of Clinical Epidemiology and Biostatistics); and (b) the mechanism of action of hypolipidaemic agents.

Education

The undergraduate is taught basic principles of blood flow in vessels and response of blood and vessels to injury in Phase II. The physiology, pathology, and principles of diagnosis and management of haemorrhagic disorders and the pathogenesis and principles of management of thrombosis are taught in Phase III, and practical aspects of diagnosis and management of haemorrhagic disorders and thrombosis in Phase IV.

At present, most of the resident training in haemostasis and thrombosis is carried out at St Joseph's Hospital. Training encompasses laboratory and clinical aspects of haemostasis, heparin control, streptokinase therapy, the use of diagnostic procedures such as $^{125}$I-fibrinogen scanning and Dopplerogram. A senior post is available for a resident who has already received considerable training in haematology to obtain training in greater depth.

Members of the programme have regular work meetings once a fortnight. The agenda is circulated in advance and includes presentations of work in progress, basic research techniques presented either by experts in the programme or invited speakers, and symposia on general controversial subjects, e.g. the pill and thrombosis.

These meetings have become a very important component of the programme and have served to integrate a heterogeneous group of research workers from many different specialities. Members are encouraged to present details of research grant applications and experimental papers before publication and to present research projects while they are still in the planning stage.

Research Programme

Recruitment of members for the Faculty of Medicine at McMaster University has been designed to promote a strong research component in the fields of
vascular disease, haemostasis, and thromboembolism. There are now 25 faculty members at McMaster whose major research activity is in this area. They are scattered over two faculties (medicine and chemical engineering) and six departments, and they represent a variety of disciplines including haematology, biostatistics, biochemistry, cell biology, engineering, nuclear medicine, radiology, clinical chemistry, experimental surgery and tissue pathology. They possess research equipment worth more than 750,000 dollars and the aggregate of their operating budgets is well in excess of 250,000 dollars per annum. (Both these figures are only modest estimates.)

Partly because of the diversity of the approaches and disciplines involved, and partly to ensure optimal use of available resources, some form of organisation appeared necessary. This need has recently been recognised by several senior research workers who therefore agreed to assume responsibility for establishing a suitable framework for research activities in these fields.

Prerequisites for creating research groups at McMaster are provided by the programme concept of the Committee on Scientific Development (CSD). Therefore, our aim has been to establish a Vascular Disease, Haemostasis and Thromboembolism Programme within the terms of reference that have been established by the CSD.

The purpose of the programme is to provide a structure for research in the general area of the cardiovascular system, haemostasis and thrombosis. It is open (on a voluntary basis) to all faculty members and their associates who have research interests (full or partial) in these fields, provided that they accept and actively support the programme in its final form. The three major categories of research activities, i.e. basic, developmental and applied research, receive equal rating. (For example, investigation into general protein labelling methods would qualify as basic, elaboration of a technique to yield labelled fibrinogen for use in humans would qualify as developmental, and the clinical use of labelled fibrinogen for detecting thrombi would qualify as applied research.)

The specific aims of the programme are:

(a) to improve the quality of research and to maintain it at the highest possible standard;
(b) to provide continuing education for programme participants and their associates in basic research techniques relevant to their work;
(c) to provide facilities for the education of graduate students and faculty;
(d) to assist members in their needs regarding funds, space and personnel;
(e) to co-ordinate use of equipment in various locations, provide facilities in highly specialised techniques, exchange information, etc.
During its present stage of organisation, the acting programme co-ordinator is Dr E. Regoezzi. The proposed future structure, which is still subject to approval by the CSD and the Faculty Council, is summarised in Table 1.

**Table 1. Proposed organisation of the Vascular Disease, Haemostasis and Thromboembolism Programme**

| Programme Executive | Programme Director |
|---------------------|--------------------|
|                     |                    |
| **Membership**      |                    |
| Full Members        |                    |
| Associate Members   |                    |
| **Consultants**     |                    |
| Bioengineering      |                    |
| Biostatistics       |                    |
| Cell Biology        |                    |
| Clinical Haemostasis and Thromboembolism | | (J. Hirsh) |
| Experimental Haemostasis |             | (S. Niewiarowski) |
| Experimental Surgery |             | (G. Evans) |
| Experimental Thromboembolism | | (J. F. Cade) |
| Haemophilia         |                    |
| Histology           |                    |
| Lipid Metabolism    |                    |
| Lipoproteins        |                    |
| Pharmacology and Enzymology | | (R. Haslam) |
| Radiobiology        |                    |
| Red Cell Metabolism |                    |
| Vascular and Endothelium |            | (G. J. Schwartz) |

A most important aspect of the programme is the regular work meetings which have served to integrate members from many different departments, have encouraged team projects, and have helped to eliminate duplication of effort. Although team work is encouraged, it is agreed that the freedom of individual research must be preserved within the programme. This has already bridged a large gap that would otherwise exist between individuals interested in applied and basic research, and the continuous contact provided has encouraged a mutual respect between two groups of research workers which is often not achieved in a more conventional setting.

Some of the problems currently under investigation by members of the group are listed below:

1. Origin of arterial lipid, focal lipid uptake and accumulation of cholesterol in the aorta and metabolism of the arterial wall (Drs C. J. Schwartz, F. P. Bell, I. Craig and J. B. Somer).

2. The role of the platelet emboli from sclerotic abdominal aorta in the development of hypertension and nephrosclerosis (Dr S. Moore).

3. Dynamics and patterns of flow in biological systems, such as normal and
diseased arteries, lung and artificial kidney (Drs I. A. Feuerstein and J. Reimers).

4. Interaction of polymerising fibrin with platelets, fibroblasts, red cells and white cells (Drs S. Niewiarowski, E. Regoecki and J. F. Mustard).

5. The effect of platelet function suppressive drugs in patients on the duration of patency of arterial prosthetic devices, and on the incidence of thromboembolism from prosthetic heart valves (Dr G. Evans).

6. Diagnosis and management of clinical disorders of lipid metabolism and relationship between hyperlipoproteinaemias (types II-V) and platelet function and the platelet membrane (Dr M. A. Mishkel).

7. Development of methods for isolating platelets from plasma, interaction of platelets with viruses, and immune complexes and the influence of drugs on these interactions (Drs J. F. Mustard, A. G. G. Turpie, M. Packham, R. K. Rathbone, E. Regoecki and S. Moore).

8. Turnover of platelet membrane phospholipids (Drs J. Lloyd and J. F. Mustard).

9. Isolation and identification of platelet antiplasmins (Drs H. Joist and J. F. Mustard).

10. Development of a method to measure fibrinogen turnover by means of neutron activation analysis (Drs E. Regoecki and H. Brunnader).

11. Studies of blood coagulation in newborn infants and studies of the purification of Factor VIII (Drs B. Luke, A. Zipursky and J. Hirsh).

12. Epidemiology of arterial diseases and evaluation of various drugs used for the management of thrombotic and embolic diseases (Drs D. L. Sackett, M. Gent and G. Hill).

13. Studies of red cell metabolism, in particular the relationship between plasma inorganic phosphate and 2,3-DPG (Dr M. C. Brain).

14. Investigation of the physiological consequences of major pulmonary embolism, the mechanism of pulmonary hypertension in major pulmonary embolism, the mechanism of spontaneous resolution of major pulmonary embolism, and a comparison of the effect of heparin and streptokinase (in various concentrations) on the resolution of major pulmonary embolism (Drs J. F. Cade, J. Hirsh, E. Regoecki, D. M. Hynes and N. L. Jones).

15. Investigation of the time of action of drugs that suppress platelet function on various in vitro and in vivo models (Drs J. F. Cade and J. Hirsh).

16. The relationship between platelet function and platelet energy metabolism (J. C. G. Doery and Dr J. Hirsh).