THE INTERNATIONAL SOCIETY ON THROMBOSIS AND HAEMOSTASIS

P.M. Mannucci, President
S. Coccheri, Vice-President
C.S. Cole, Secretary

International Headquarters
CB# 7035 • University of North Carolina Medical School • Chapel Hill, NC 27599-7035

Certified Member

The NEWSLETTER of the International Society on Thrombosis and Haemostasis is a privileged communication provided to all ISTH members. It is produced biannually at ISTH Headquarters. Please address questions, comments, or suggestions to Newsletter Editor, ISTH Headquarters. — C.S. Cole

ISTH Council Chairman’s Message

Dear Society Members!

Thanks to the committed effort of all of you, our Society has continued to be active and productive, and it is now the largest and most important scientific organization in the field of thrombosis, hemostasis and vascular biology. Our discipline has thrived on the close interaction between patient care and fundamental research, as shown historically by the discovery of many coagulation factors as a missing factor in patients with rare coagulation disorders. During the past 2 decades, our membership has become much more diverse to the great advantage of the Society. A broad scope of scientific interests ranging from clinical, biochemical, biophysical and molecular biological research, characterizes our membership of over 2,000 individuals from 63 different countries. Members come from universities, research institutes, hospitals and industry. Being multidisciplinary, heterogeneous and international is the hallmark of the ISTH. Our biennial Congresses, Annual SSC Meetings, and publications bring together physicians and scientists from around the world in a forum for the exchange of information and ideas on the biology, pathogenesis, diagnosis, treatment and prophylaxis of thrombotic and hemorrhagic disorders. The large attendance at ISTH Congresses and the prestige of our journal, *Thrombosis and Haemostasis*, attest to the ISTH’s importance in the international scientific community.

The XVIth Congress of the ISTH held in Jerusalem in June 1995 was very successful with more than 3,400 participants from 58 countries. Participants enjoyed an exciting scientific program and a very attractive social program. The ISTH is very much indebted to Dr. Uri Seligsohn, Dr. Amiram Eldor and their colleagues for the outstanding meeting. The XVIth ISTH Congress will be held in Florence, Italy, on June 6–12, 1997, with Prof. P.M. Mannucci as President and Prof. S. Coccheri as Vice President. I hope that all of you will mark these dates in your calendars.

At the conclusion of the 1996 ISTH executive Council Meeting in Barcelona, Spain, where the 42nd Annual SSC Meeting will be held, I will hand the chairmanship of Council to Dr. Yale Nemerson of the USA, our current Secretary/Chairman-elect and Past President of the XVIth Congress. With his strong leadership the ISTH will grow further. I wish him all success. I would like to take this opportunity to thank all the members of ISTH executive Council for their service and initiative in the various Standing Committees. I am also grateful to our Executive Director, Dr. Harold Roberts, and staff of the Headquarters Office for their valuable contribution. It is difficult to oversate the amount of time and effort that they have invested for the smooth administration of this large international Society.

Needless to say, the success of future activities and direction of any organization depend on the suggestions, ideas, and opinions of its membership. As we approach the 21st century, we will need to have the active participation of all our members from many different disciplines.

Your input is always welcome,

*Hidehiko Saito, MD*
Chairman of ISTH Council
February 1996

ISTH and SSC MEETINGS

Second Announcement of the XVIth Congress of the ISTH

Florence, Italy
June 6–12, 1997

The Second Announcement of the XVIth ISTH Congress is now available and Society members are encouraged to mark their calendars for this important event. The Final Announcement with Abstract forms will be mailed to all Society members next summer and **Important Deadline Dates** are as follows: 2 December 1996—Receipt of Abstracts; 28 February 1997—Pre-registration deadline and guaranteed hotel reservation deadline; 30 April 1997—Social Program deadline and Accompanying Persons' Program reservations.

In order to obtain additional copies of the Second Announcement or to be placed on the Congress mailing list, please contact the Congress Secretariat:

**XVIth ISTH Congress Secretariat**

O.I.C. s.r.l.
Via A. La Marmora, 24
50121 Florence, ITALY
tel: 39 55 500 0631 or FAX 39 55 500 1912
Visit the XVIth Congress on the WorldWideWeb at http://www.cmosinnegri.it/isth97

**Thanks for a terrific job of webmastership to Giovanni Angeli, Head, Unit for Computer-aided Biomedical Research at Consorzio Mario Negri Sud** — CSC

ISTH Congress Calendar

The ISTH convenes an international Congress biennially, while the Scientific and Standardization Committee and its scientific subcommittees meet annually. In Congress years, Society and SSC meetings are held in conjuction. Future Congresses will be in these locations:

<table>
<thead>
<tr>
<th>Year</th>
<th>Congress</th>
<th>President</th>
<th>Location</th>
<th>Date</th>
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<tbody>
<tr>
<td>1995</td>
<td>XVIth ISTH Congress</td>
<td>P.M. Mannucci</td>
<td>Florence, Italy</td>
<td>June 6-12, 1995</td>
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<tr>
<td>1997</td>
<td>XVIth ISTH Congress</td>
<td>S. Coccheri</td>
<td>Florence, Italy</td>
<td>June 6-12, 1997</td>
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<tr>
<td>2001</td>
<td>XIXth ISTH Congress</td>
<td>T. Peake</td>
<td>Birmingham, UK</td>
<td>June 30-July 6, 2001</td>
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<td>2003</td>
<td>XXth ISTH Congress</td>
<td>Gordon Lowe</td>
<td>Florence, Italy</td>
<td>June 6-12, 2003</td>
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Your input is always welcome,

*Hidehiko Saito, MD*
Chairman of ISTH Council
February 1996
**42nd Annual Meeting**

**Scientific and Standardization Committee of the ISTH**

**Barcelona, Spain**

**22-24 June 1996**

The 42nd Annual Meeting of the SSC will take place in Barcelona, Spain, on Saturday through Monday, June 22-24, 1996. This is the second SSC Annual Meeting to be held in conjunction with a Congress of the International Society on Fibrinolysis and Thrombolysis, June 24-28, 1996. Hosts for the SSC Meeting are Prof. M.Li. Rutllant and Dr. J. Feliz and the venue is the new Fira Palace Hotel, adjacent to the Barcelona Congress Center at the foot of Montjuic.

To the extent possible, all SSC attendees will be housed at the Fira Palace or the next closest hotel, the new Hotel Barcelona Plaza on the nearby Pl. Espanya.

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**SCHEDULE AT A GLANCE**

**Saturday, June 22, 1996**

<table>
<thead>
<tr>
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<td>8:00 to 12:00</td>
<td>Special Meetings</td>
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<tr>
<td>12:00 to 1:00</td>
<td>LUNCH</td>
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<td>1:00 to 5:00</td>
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**Sunday, June 23, 1996**

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<tr>
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<tr>
<td>12:00 to 1:00</td>
<td>LUNCH</td>
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<tr>
<td>1:00 to 5:00</td>
<td>Platelet Physiology</td>
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**Monday, June 24, 1996**

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<tr>
<td>8:00 to 12:00</td>
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<td>12:00 to 1:00</td>
<td>LUNCH</td>
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<tr>
<td>1:00 to 5:00</td>
<td>SSC ANNUAL BUSINESS MEETING</td>
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**Current Topic**

**TARGETED MANIPULATION OF THE FIBRINOLYTIC AND COAGULATION SYSTEM VIA GENE INACTIVATION AND ADENOVIRUS-MEDIATED GENE TRANSFER.**

Peter Carmellet, MD, PhD

Center for Transgene Technology and Gene Therapy, University of Leuven, Belgium.

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**Insights via Plasminogen System Knock Out Mice**

The best known role of the coagulation and plasminogen (or fibrinolytic) system relates to their control in hemostasis and thrombosis; however, both proteinase systems have been implicated in several other processes including embryogenesis, reproduction, wound healing, inflammation, atherosclerosis, angiogenesis, restenosis, cancer and brain function. Today, many developed technologies, gene targeting and gene transfer, that allow manipulation of the genetic balance of these proteinase systems in a controllable manner have contributed to a more definitive characterization of their in vivo role in these processes. This review briefly summarized the insights obtained from those studies and discusses the use of adenovirus-mediated transfer of fibrinolytic genes to study and possibly to develop novel strategies for the treatment of restenosis and thrombosis.

The plasminogen system is composed of the inactive proenzymic plasminogen (Pgl) which can be converted to plasmin by tissue-type plasminogen activator (t-PA) or urokinase-type plasminogen activator (u-PA). This system is controlled at the level of plasminogen activators by plasminogen activator inhibitors (PAI), of which PAI-1 is believed to be physiologically the most important (1), and at the level of plasmin by alpha2-antiplasmin (1). Due to its fibrin-specificity, t-PA is primarily involved in clot dissolution, whereas u-PA binds a cellular receptor, the urokinase receptor (u-PAR), and has been implicated in pericellular proteolysis during cell migration and tissue remodeling. Binding of u-PA to u-PAR can localize u-PA on the cell surface, thereby accelerating the conversion of plasminogen to plasmin (2). Despite circumstantial evidence, it is yet unclear whether or in what conditions binding of u-PA to its receptor is (absolutely) required for plasminogen activation and cellular migration in vivo.

Initiation of the plasma coagulation system upon exposure of blood to nonvascular cells is triggered by tissue factor (TF), which is expressed by a variety of cells surrounding the vascular as a hemostatic envelope and functions as a cofactor for activation of factor VII (3). This complex is able to directly activate factor X via the extrinsic pathway, or indirectly by activation of factor IX via the intrinsic pathway, which results in the generation of thrombin and conversion of fibrinogen to fibrin (3). In contrast, within intact vessels, thrombin functions as an anticoagulant because it activates the protein C anticoagulant system when bound to its cellular receptor, thrombomodulin (TM). A revised hypothesis of coagulation has been suggested in which factor VIIa/TF is responsible for the initiation of coagulation, but owing to tissue factor inhibitor-mediated feedback inhibition, amplification of the procoagulant response through the actions of factor VII, IX, and X is required for sustained hemostasis.

**Embryonic development, reproduction, health and survival**

Deficiencies of t-PA and/or u-PA (4), u-PAR (5,6), PAI-1 (7,8) or Pgl (10) do not compromise embryonic development, a surprising observation considering their specific expression during early development and embryogenesis. Only a transient
Thrombosis, thrombolysis and hemostasis

Deficient fibrinolytic activity, e.g., resulting from increased plasma PAI-1 levels or reduced plasma t-PA or plasminogen levels, might participate in the development of thrombotic events. Mice with u-PA deficiency displayed excessive fibrin deposition but only in inflamed tissues (4), whereas in t-PA-, u-PAR- or PAI-1-deficient mice, no spontaneous fibrin deposits were observed (4-8). However, mice with a single deficiency of Pcl (9,10) or a combined deficiency of t-PA+u-PA (4), but not of t-PA+u-PA (13), revealed extensive fibrin deposits in several organs. Mice deficient in t-PA and u-PA were significantly more susceptible to inflammation-induced venous thrombosis (4). The increased thrombotic susceptibility of t-PA-deficient mice and the severe spontaneous thrombotic phenotype of Pcl-deficient and combined t-PA+u-PA-deficient mice could be explained by their significantly reduced rate of spontaneous lysis of 125I-fibrin labeled pulmonary plasma clots (4,9). Intravenous injection of adenosine 5'-(triphosphate) 1'-chloroethyl-3'-aminobenzoyl phosphorothioate (NS-398) in t-PA-deficient mice increased plasma rt-PA levels 100- to 1000-fold above normal and restored their impaired thrombolytic potential in a dose-related way, demonstrating the efficiency of thrombolytic t-PA gene therapy (14). On the contrary, PAI-1 deficient adenoviruses expressing a recombinant PM-1-resistant human t-PA (rt-PA) gene in t-PA-deficient mice could be explained by their significantly reduced rate of spontaneous lysis of 125I-fibrin labeled pulmonary plasma clots (4,9). Intravenous injection of adenosine 5'-chloroethyl-3-aminobenzoyl phosphorothioate (NS-398) in t-PA-deficient mice increased plasma rt-PA levels 100 - to 1000-fold above normal and restored their impaired thrombolytic potential in a dose-related way, demonstrating the efficiency of thrombolytic t-PA gene therapy (14). On the contrary, PAI-1 deficient mice were virtually protected against development of inflammation-induced thrombosis, consistent with their increased thrombolytic ability (8). However, adenosine-mediated transfer of recombinant human PAI-1 in PAI-1-deficient mice reduced their increased thrombolytic potential (unpublished observations). The increased susceptibility of u-PA deficient mice to thrombosis associated with inflammation or injury might be due to their impaired macrophage function, as revealed by their reduced ability to degrade 125I-labeled fibrin (4).

These gene targeting and gene transfer studies confirm the importance of the plasminogen system in maintaining vascular patency and indicate that both plasminogen activators significantly cooperate in this process. It is interesting that u-PA appears to play a more significant role than previously anticipated in the prevention of fibrin deposition in pericellular proteolysis following injury. Furthermore, a surprising finding, however, is that u-PA can exert significant pericellular proteolysis in the absence of t-PA (as revealed by the difference in the thrombotic and health/survival phenotypes between combined t-PA+u-PA-deficient and t-PA+u-PA-deficient mice), suggesting that sufficient pericellular plasmin proteolysis can occur even in the absence of u-PAR and suggests, therefore, that binding of u-PA is not required for these processes. That the phenotype of the Pcl-deficient and combined t-PA+u-PA-deficient mice also suggests that t-PA and u-PA are the only important physiological plasminogen activators in vivo. A hemorrhagic tendency has been observed in patients with deficient coagulation or increased fibrinolysis. Deficiency of factor VIII results in severe bleeding (15). Contrary to patients with low or absent plasma PAI-1 levels, PAI-1 deficient mice did not, however, reveal spontaneous or delayed rebleeding even after trauma (8). Lower plasma PAI-1 levels and the occurrence of alternative PAIs in murine plasma (unpublished data) might explain the less pronounced hyperfibrinolytic phenotype and the species-specific difference in plasmin proteolysis control.

Neointima formation

Several components of the coagulation and plasminogen system have been implicated in the process of restenosis after vascular injury. A recent study (16) has shown that neointima formation was similar after arterial injury in wild type t-PA- and u-PA-deficient arteries, accelerated in PAI-1-deficient arteries but markedly reduced in u-PA-, Pcl- and combined t-PA+u-PA-deficient arteries, most likely as a result of impaired migration of smooth muscle cells. A surprising observation, however, was that deficiency of u-PA, but not of u-PAR, reduced neointima formation in vivo. Since u-PA is expressed by smooth muscle cells and endothelial cells, binding of u-PA to its cellular receptor appears not to be required for migration of these cells. The involvement of plasmin proteolysis in neointima formation was further supported by intravenous injection in PAI-1-deficient mice of a replication defective adenovirus that expresses human PAI-1, which resulted in more than 1000-fold increased plasma PAI-1 levels and in a similar degree of inhibition of neointima formation as observed in u-PA-deficient mice (16). Our studies therefore suggest that strategies aimed at reducing u-PA-mediated plasmin proteolysis may be beneficial for reduction or prevention of restenosis; however, antifibrinolytic strategies should be targeted at inhibiting plasmin proteolysis and not at preventing the interaction of u-PA with its receptor.

Tissue remodeling and wound healing

Impaired fibrinolysis resulting from reduced u-PA or increased PAI-1 activity has been implicated in the deposition of fibrin and of extracellular matrix components in the kidney and the lung during inflammation. Electron microscopy demonstrated that combined t-PA+u-PA-deficient mice developed fibrin deposits not only in the intravascular lumens but also in extravascular compartiments such as in the alveoli of the lung, the mesangium in the kidney, and in the subendothelial space of Disse in the liver (unpublished observations), similar to those observed in glomerulonephritis and acute respiratory distress syndrome. In addition, Pcl- and combined t-PA+u-PA-deficient mice, and to a lesser extent u-PA- or t-PA-deficient mice, suffered severe experimental glomerulonephritis after challenge with anti-glomerular membrane antibodies (unpublished data). Furthermore, bleomycin-induced lung injury resulted in significant deposition of fibrin and collagen-rich matrix in PAI-1 overexpressing mice, whereas PAI-1 deficient mice are protected against such fibrotic reaction (Ginsberg et al., personal communication). Pcl-deficient mice also suffered gastric ulcerations in association with infection by the etiologic pathogen Helicobacter (9,10). Thus, the plasminogen system appears to play an important role in tissue remodeling, inflammation, and wound healing.

Other biological processes

Percellular plasmin proteolysis has been claimed to play a role in tumor invasion and metastasis. PAI-1 overexpressing mice displayed a significant reduction of pulmonary metastases, possibly due to reduced lodging of tumor cells in the pulmonary tissues (17). The plasminogen system has also been implicated in brain function. Overexpression of murine u-PA in the brain was associated with impaired learning of tasks and reduced food intake (18), whereas deficiency of t-PA resulted in the abolishment of the late phase of long-term potentiation in the hippocampus (unpublished observations) and protection against neuro-excytotoxic induced seizures (19).

REFERENCES

As stated in the preface to this small book, Treatment of Venous Thrombosis and Pulmonary Embolism is distributed to general practitioners and specialists within relevant branches of medicine in Norway and Sweden, and also to a number of foreign scientific journals and specialists. The booklets are also distributed to the WHO information officers.

In terms of time lines, the booklet is a product of an expert meeting in April 1994 arranged by the Norwegian Medicines Control Authority in cooperation with the Swedish Medical Products Agency.

The booklet is well-organized with an initial yellow page section summarizing the recommendations of the consensus report. In the section under the heading "Prophylaxis and Management of Deep Venous Thrombosis and Pulmonary Embolism" are the following specific topics: Epidemiology, Pathogenesis, Investigation of Predisposition for Thrombosis, Thrombosis Prophylaxis, Deep Vein Thrombosis, Therapy for Acute DVT, Drug Administration and Monitoring in DVT, Pulmonary Embolism (PE), Diagnosis of PE, Management of PE, Post-thrombotic Syndrome, Thromboembolism During Pregnancy and Delivery, Prophylaxis During Pregnancy and Puerperium, the Use of Oral Contraceptives and Post-menopausal Estrogen Therapy, and Definition of the International Normalized Ratio. The remainder of the booklet is made up of specific reviews.

The booklet provides a worthwhile reference text which clearly outlines the consensus as to the standard of care that should be provided in prophylaxis and managing patients with venous thromboembolism in Norway and Sweden. On reviewing the text, a number of issues are noted that may differ in terms of standard of care in other countries:

- The consensus recommendation that the benefit of prophylaxis is uncertain after a stroke: this statement would certainly be seen as controversial by many.
- Of the various pharmacological techniques for prophylaxis, low molecular weight heparin is recommended as the standard prophylaxis. Indeed, in North America, although this is not the current standard of practice, in time, given the abundance of data, this is also likely to be so. An important unresolved issue with regard to the use of low molecular weight heparin is the potential for differences among specific low molecular weight heparins. Presently, however, data is unavailable to guide the clinician in this regard.
- The recommendation that lifelong anticoagulation be given to patients with venous thromboembolism and proven thrombophilia: the correctness of this recommendation will be resolved by future studies.
- The recommendation that the intensity of oral anticoagulation be higher if the clinical symptoms are serious and there are no signs of increased risk of hemorrhage in patients undergoing treatment of venous thromboembolism is controversial. Many would disagree that the INR should be in the range of 2.5 to 3.5 in such patient. Indeed, the evidence suggests that increasing the INR above 3 unacceptably increases the bleeding risk. Thus, this recommendation should be supported by adequate data before it is used widely.
- The recommendation that plasma fibrinogen be measured daily in patients receiving thrombolysis is controversial. Furthermore, the statement, that, in the therapy for acute deep vein thrombosis, thrombolysis should be considered for patients under 60 years of age if the thrombosis is recent and there is no known risk of hemorrhage is highly controversial. The need for clinical trials supporting such an approach is pressing.
- The routine use of a vena cava filter in patients with deep vein thrombosis and simultaneous pulmonary embolism is controversial, as is the comment that subcutaneous heparin is probably a better alternative than continuous IV heparin for treatment of DVT.
- The recommendation that the initial dose of oral anticoagulant therapy, e.g., warfarin, should be 10-15 mg is higher than current North American practice.
- The consensus group felt that iliofemoral thrombosis are more common during the last trimester of pregnancy. Recent data do not support this view and suggest that deep vein thrombosis can occur at any time during pregnancy without a predisposition for a particular trimester.
- The consensus report recommends ultrasonography as the primary diagnostic method for suspected deep vein thrombosis during pregnancy. The report does not identify, however, the possibility of missing isolated iliac thrombosis. The report does, however, suggest that plicatherapy be used if there is still uncertainty.

In summary, although there are differences between Nordic and North American practice, this booklet is a useful guide to the treatment of venous thrombosis and pulmonary embolism, particularly for those practicing in Nordic countries.

Russell D. Hull, MBBS, MSc, FRCP(C), FACP, FCCP
Profession of Medicine, General Internal Medicine
Director Clinical Trials Unit
The University of Calgary School of Medicine

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N-0050 Oslo, NORWAY
Box 26
N-751 03 Uppsala, SWEDEN

ERRATUM: Deadline for receipt of ISTH Council nominations is 15 March 1996. Return forms to Headquarters by this date, not June 1st as indicated at the bottom of the nomination form.