A Message from the President of the XVth ISTH Congress

Preparations for the XVth ISTH Congress are progressing very well. Numerous abstracts have been submitted and are presently being classified and reviewed by members of the International Advisory Board of the Scientific Program Committee. We expect the review process to be completed by mid-February and will then prepare the final program and timetable of the Congress.

Presenters will be notified regarding their active participation in the scientific program before March 15, 1995, the deadline for reduced registration fees.

Manuscripts of the plenary sessions speakers, symposia chairpersons and colloquia will be received shortly for the State-of-the-Art issue of Thrombosis and Haemostasis. It is our conviction that, as in the past, this issue will be of great help to all of us who wish to keep abreast of the enormous developments in our discipline. All ISTH members attending the 1995 Congress will receive the Abstract and State-of-the-Art books in Jerusalem, free of charge. Only the members and other subscribers of the journal who are unable to attend the Congress will receive these issues by mail. Thus, each ISTH member will receive these issues only once.

The exhibition during the Congress will be quite extensive. At present, 46 companies have acquired space and are making preparations to present their latest products, equipment and drugs.

The Jerusalem hotels as well as the Eilat hotels (site of the Satellite Symposium) are already heavily booked and early reservation is, therefore, highly recommended.

Final decisions regarding the extensive social program and logistic arrangements were made two weeks ago. We are looking forward to these stimulating and exciting events.

From the moment of your arrival at the Ben Gurion Airport, and throughout the Congress, Kenes representatives will assist you with all your needs and wishes. They will be located at the airport, major hotels, Congress venue, and at all social events.

My colleagues and I on the Organizing Committee are very excited by the enormous interest being shown in the Congress and are committed to doing everything possible to make the XVth ISTH Congress a memorable event.

See you all in Jerusalem and Eilat!

Sincerely,
Uri Seligsohn,
President

Announcement of 15th ISTH General Membership Assembly Meeting
As mandated by the ISTH Constitution, the General Membership Assembly of the Society will take place during the week of the XVth Congress (June 11-15, 1995) in Jerusalem at the International Convention Center. All Society members are urged to attend this brief and informative meeting.

ISTH Congress Calendar
The ISTH convenes an international Congress biennially, while the Scientific and Standardization Committee and its scientific subcommittees meet annually. Future meetings will be in these locations:

15th ISTH Congress
U. Seligsohn, President
Amiram Eldor, Vice-President
C. S. Cole, Secretary
June 11-16, 1995
Jerusalem, Israel

16th ISTH Congress
P.M. Mannucci, President
S. Crocker, Vice-President
June 15-21, 1997
Florence, Italy

17th ISTH Congress
V.J. Martin, President
L. Hoyer, Vice-President
August 14-21, 1999
Washington, DC

18th ISTH Congress
D. Meyer, President
G. Tobelem, Vice-President
April 2-8, 2001
Paris, France

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15th ISTH Congress
U. Seligsohn, President
Amiram Eldor, Vice-President
and
41st Annual SSC Meeting
Jerusalem, Israel
June 11-16, 1995

16th ISTH Congress
P.M. Mannucci, President
S. Crocker, Vice-President
and
43rd Annual SSC Meeting
Florence, Italy
June 15-21, 1997

17th ISTH Congress
V.J. Martin, President
L. Hoyer, Vice-President
and
45th Annual SSC Meeting
Washington, DC
August 14-21, 1999

18th ISTH Congress
D. Meyer, President
G. Tobelem, Vice-President
and
47th Annual SSC Meeting
Paris, France
June 30-July 6, 2001
New SSC Chairman/Committee Class of 2000

At the conclusion of the 40th Annual SSC Meeting in Leuven, Belgium, Dr. David Aronson (USA) retired as Chairman of the Scientific and Standardization Committee and Dr. Maria Benedetta Donati (Italy), Secretary/Chairman-elect began her two-year term of Chairmanship.

Dr. Jeanne M. Lusher (USA) was subsequently elected by the current SSC members as the next Secretary/Chairman-elect.

The following new members were elected to the SSC Class of 2000 by ISTH Council at its 1994 meeting: Drs. J. Arnout (Belgium), C. Francis (USA), I. Scharrer (Germany), and A. Tripodi (Italy). Their six-year terms began at the conclusion of the 1994 Annual Meeting.

Retiring members of the SSC Class of 1994 are Drs. D. N. Fass (USA), H.R. Lijnen (Belgium), M.W. Mosesson (USA), and H.H. Salem (Australia). These retired members will become members of the SSC Senior Advisory Council and continue their service to the SSC as counsellors and consultants.

As mentioned in the first Newsletter, we would like to offer in each issue a brief article from a Society member on a current scientific topic. Many thanks to Prof. B. Dahlback for kindly submitting our first Current Topic

Resistance to activated Protein C, caused by a Factor V Gene Mutation, as a major pathogenic risk factor of Thrombosis

B Dahlbäck. Department of Clinical Chemistry, Lund University, Malmö General Hospital, S-214 01 Malmö, Sweden.

Venous thromboembolism (yearly incidence of 1/1000) is a serious health problem which causes considerable suffering. Thrombotic events often occur in conjunction with circumstantial risk situations such as surgery, fractures, pregnancy, the use of oral contraceptives, and immobilization. In addition, genetic risk factors are also involved in the pathogenesis because thrombosis is often familial. Until recently, the major genetic defects known to predispose for thrombosis were deficiencies of protein C, protein S, and antithrombin III, which together did not account for more than 5-10% of the cases (reviewed in reference 1). Hereditary activated protein C (APC) resistance, has been identified as a basis for a majority of cases of familial thrombosis in the last years.

Protein C is activated by thrombin bound to thrombomodulin on the surface of intact endothelial cells. APC cleaves and inactivates factors Va and VIIIa. Its anticoagulant activity is potentiated by protein S (reviewed in 1). Recently, we found that APC resistance was present in around 5%, whereas it is around 0.1 to 0.3% in the general population. A clear association between the genetic deficiency and an increased incidence of thromboembolic events has been found in several thrombosis-prone families with protein C deficiency. In contrast, in families with protein C deficient individuals identified during screening of blood donors, the risk of thrombosis does not appear to be particularly high. This suggests protein C deficiency in itself to be a weak risk factor for thrombosis and the incidence of thromboembolism to be high only when protein C deficiency is combined with yet another risk factor. In patients with thromboembolic disease the prevalence of protein S deficiency is similar to that of protein C deficiency, i.e. 2-5%.

Exogenous APC prolongs the activated partial thromboplastin time of normal plasma. A different response was observed when plasma from a middle-aged man with a history of venous thrombosis was analyzed (3). APC failed to prolong the clotting time to any major extent (Fig. 1). This APC resistance was also found in many of his relatives suggesting the APC resistance to be caused by a genetic defect. APC resistance was found to be corrected by intact factor V which suggested the genetic defect to be located in the gene for factor V (4). It is now known that in more than 90% of the cases it is caused by a single nucleotide replacement in the factor V gene, G to A at position 1691 (5-8). This mutation predicts replacement of Arg506 with a Gln. As the peptide bond following Arg506 is an APC cleavage site, mutated factor Va is expected to be resistant to APC, but to express normal factor Va procoagulant activity (5, 9, 10). Slower APC degradation of mutated factor Va leads to stabilization of the prothrombinase complex and higher rate of thrombin generation. Feed-back activation of factors VIII and factor V by thrombin increase the rate of activation of the coagulation cascade.

APC resistance is highly prevalent in patients with thromboembolic disorders (20-60% in different studies) (11-14). It is at least 10 times more frequent than any of the other known genetic risk factors for thrombosis. In cases with familial thrombosis, APC resistance is present in around 50%. Family studies

Fig. 1 APC resistance in a patient with thrombosis. Addition of APC to an activated partial thromboplastin time (APTT) reaction results in a distinct dose-dependent prolongation of clotting time of control plasma (3). In contrast, plasma from a middle-aged man with recurrent thrombosis did not respond to the anticoagulant activity of APC (○); (modified from 3)

Fig. 2 APC ratios in members from 50 families with APC resistance. Filled circles denote patients with a history of thrombosis. Differences in APC ratios between family members without the factor V gene mutation (n = 143), heterozygotes (n = 142) and homozygotes (n = 16) were highly significant (p <0.001); (modified from 15)
have demonstrated an association between the factor V gene mutation (with APC resistance) and an increased risk of thrombosis (11, 15). Homozygosity leads to more severe APC resistance and to higher thrombosis risk (Figs. 2 and 3). In the general population, 3-7% have the factor V G1691A allele with APC resistance, suggesting the factor V gene mutation to be one of the most common genetic defects. The high prevalence of the factor V gene mutation in the population is striking and suggests that positive genetic selection pressure has been involved in maintaining it in the population. A slight hypercoagulable state may have conferred some advantage during evolution.

APC resistance due to the factor V gene mutation is associated with a life-long increased risk of thrombosis, but unless it is associated with other genetic or circumstantial risk factors, thrombosis may not present until advanced age. In fact, many affected individuals will never suffer from thrombosis. Many people are expected to be homozygous for the factor V gene mutation as its prevalence in the population is high. Consequently, individuals with single gene defects, e.g., protein C or protein S deficiency, may also carry the factor V gene mutation (5, 8, 15, 16). They have a high risk for thrombosis, in particular when exposed to surgery, pregnancy or oral contraceptives.

In years to come, we will learn whether it is worthwhile to screen for APC resistance, e.g., before surgery, during pregnancy and before the use of oral contraceptives. We also need to develop guidelines for how people with inherited APC resistance due to the factor V gene mutation should be managed. In our laboratory, the APC-resistance test is used for screening because it has a high sensitivity for the factor V gene mutation and also picks up cases with APC resistance which do not have the factor V gene mutation. A PCR-based analysis for the factor V gene mutation is performed in all cases which demonstrate low or borderline APC ratios. APC-resistant individuals (heterozygous for the factor V gene mutation) who have no other anticoagulant defect and no personal or family history of thrombosis are given prophylactic anticoagulant therapy only in situations known to provoke thrombosis, like major surgery. They are handled like thrombosis patients with deficiencies of protein C, protein S or antithrombin III if they have a history of thrombosis. Preventive anticoagulant therapy is given at risk situations and long-time therapy is considered if thrombosis is recurrent. Homozygous cases, and heterozygous patients with a second anticoagulant defect, are given preventive therapy at all risk situations. After a thrombotic event, anticoagulant therapy for an extended time period may be warranted.

References


4. Dahlbäck B and Hildebrandt B. Resistance to activated protein C is conferred by anticoagulant cofactor activity found to be a property of factor V. 1994 Proc Natl Acad Sci USA 91: 1396-1400.


BOOK REVIEW:
Life and Achievements of Professor Robert Gwyn Macfarlane FRS
Alistair Robb-Smith
Publication Department
Royal Society of Medicine Services Ltd. London, UK

This book is a thought-provoking biography of a remarkable man, Robert Gwyn Macfarlane. More than the bare facts of Dr. Macfarlane's life or a simple review of his work, this biography also traces how the personal philosophies of this medical scientist influenced scientific progress in the field of haemostasis. Alistair Robb-Smith has succeeded in communicating all this information in an entertaining and lively fashion, interjected with examples of the wit that made Robert Macfarlane so popular. He traces Macfarlane's life from the romantic youth who longed to be born in the clan Macfarlane country to the achievement of a contented retirement in Scotland. Along the way we learn that the medical student with a sense of duty to the patient, who devoted his life to improving the treatment of haemophiliacs, was also "fun-loving" with a passion for ballet and fast cars.

It was a particularly distressing encounter with a young haemophiliac that prompted Macfarlane to pursue the subject of blood clotting. His single-minded concentration upon understanding haemophilia led within his lifetime to the discovery of blood clotting factors and the biochemical action of Russell's viper venom on blood. The clarity of his ideas, unhindered by dogged following of traditional hypotheses, led to the rejection, in his youth, of the then accepted model for blood coagulation and, later in his life, to the proposal of the coagulation cascade as a possible mechanism for blood clotting. The reader also learns of his mechanical inventiveness which resulted in the design of essential experimental apparatus.

The tremendous advances made in his laboratory were the product of a small and energetic team for Macfarlane refused to expand the laboratory to the extent that it became impersonal. The long and productive working relationships and friendships he held with so many colleagues are evidence of Macfarlane's ability to guide and enthuse. Throughout the narrative of Prof. Macfarlane's career, Mr. Robb-Smith leads the reader through the questions Macfarlane posed and how he approached and answered them; the problems he faced and how he overcame them. Each page recounts small events that give the reader a sense of Macfarlane the man, as well as Macfarlane the medical scientist. The result is a delightful book, full of the humor and warmth that characterized Macfarlane himself.

Jean-Maurice Lavergne
Dominique Meyer
July 1994

COAGINFO

We have all been in the position where we had a coagulation question or problem that we didn't know the answer to. At times we need other opinions to help develop new ideas or approaches. If you are like me, then you speak to the people that you are most closely involved with. These are usually people who approach problems in a similar fashion. It is clear that both laboratory and treatment issues are approached in different ways in different parts of the world. They may even be approached differently in different parts of a country.

It is obvious that we would all benefit from a forum, available at any time, that we could access from our desk, that would address these problems. It recently became obvious to me that such an environment exists. The Internet is an international computer network that was originally developed by the defense advanced research project agency (DARPA) that links academic and non-academic establishments. It is possible to use the Internet for electronic mail (email).

I have worked with the people at computer services at Tufts University to develop coaginfo. Here is how it works. To join coaginfo you simply email me at my address "SLIMENTA@OPAL.TUFTS.EDU" and ask me to put you on the distribution list for coaginfo. After I put you on the distribution list you will receive a copy of any message that is sent to coaginfo. If you want to respond, or you have a question, you send it to "COAGINFO@OPAL.TUFTS.EDU." After you send it, your message will automatically be distributed to everyone on the list.

What would be reasonable for coaginfo? I don't know. I am purposely leaving this vague. I am not sure of specific areas. Some areas are clinical coagulation, clinical laboratory coagulation and basic research questions. For now I do not want to limit coaginfo to any one of these areas. If coaginfo is popular enough then it will make sense to develop subgroups for specific topics.

My hope is that coaginfo can be an international forum for all of us to discuss issues which we find interesting or problematic. If you are interested you will need to gain access to the Internet, which can usually be achieved through your computer services people. If you do not have access through your institution there are for profit companies that will give you access for a fee. If you have questions please feel free to contact me.

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Questions Frequently Asked ISTH Headquarters

I wish to sponsor a colleague for appointment to ISTH Council. How is this done?
The 15-member Council of the ISTH is elected by the membership-at-large of the Society. Society members are annually invited to submit nominations for the next five-member Council Class. From these nominations, Council members preselect a ballot of twice the number to be elected. This ballot is submitted to the voting members of the Society for final election.

Will there be any financial support for young scientists or scientists from developing countries to attend the XIXth Congress this summer in Jerusalem?
Yes, Council has approved funds from the "Reach the World" initiative and from general funds to support the attendance of deserving young researchers and researchers from Third World and economically developing countries. Individuals with financial need should make themselves known to the Congress President who has discretion to disburse the funds.

You may contact Prof. U. Seligsohn, XIXth Congress President, at

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FAX: 972 3 660 325 or 972 3 517 5674

The next issue of ISTH Newsletter will appear in the late Summer of 1995. Contributions of news and information are welcome before 15 July 1995 and should be addressed to: ISTH Headquarters.