Preface

Celebrating 50 Years of Seminars in Thrombosis and Hemostasis—Part I

Emmanuel J. Favaloro, PhD, FFSc (RCPA)[1,2,3,4]

[1] Department of Haematology, Institute of Clinical Pathology and Medical Research (ICPMR), Westmead Hospital, Westmead, New South Wales, Australia
[2] Sydney Centres for Thrombosis and Haemostasis, Westmead, New South Wales, Australia
[3] School of Dentistry and Medical Sciences, Faculty of Science and Health, Charles Sturt University, Wagga Wagga, New South Wales, Australia
[4] School of Medical Sciences, Faculty of Medicine and Health, University of Sydney, Westmead Hospital, Westmead, New South Wales, Australia

Semin Thromb Hemost 2022;48:871–874.

Welcome to another issue of *Seminars in Thrombosis and Hemostasis (STH)*. This is a very special issue, being the first of a series of issues we will publish to celebrate the upcoming 50th anniversary of the journal. As explained more fully in an accompanying editorial,[1] *STH* has been part of the thrombosis and hemostasis landscape for almost 50 years. *STH* was first published in 1974, and so will turn 50 in 2024. As we head toward this landmark date, we believed it is appropriate to celebrate with a series of *STH* issues containing content of a somewhat historical nature. The current issue of *STH*, the last for 2022, marks the first of these issues. We are not yet 50, but we are getting close.

STH was founded by Eberhard F. Mammen (►**Fig. 1**). The journal started small, with only two issues and some 210 printed pages in its first year. The journal has grown over the years, and now publishes eight issues, and some 900 printed pages, per year, having also achieved a landmark of more than 1,000 printed pages in 2020.

This issue contains a range of material related to the broad concepts of thrombosis and hemostasis and with a historical connection. The issue begins with two articles on fibrinogen, the major clotting protein in blood. The first, by Casini and colleagues, is a true historical piece that celebrates a 100-year history of investigation into congenital fibrinogen disorders, but focusing mostly on afibrinogenemia and dysfibrinogenemia.[2] These disorders encompass a broad range of fibrinogen defects characterized by a wide molecular and clinical spectrum. From the first clinical description of afibrinogenemia in 1920, the authors describe the many major achievements that have contributed to a better understanding of these complex disorders. The finding of causative mutations in all three fibrinogen genes has contributed to reveal the molecular mechanisms involved in biosynthesis of the fibrinogen molecule and to clarify the basic processes of fibrin polymerization and fibrinolysis. The compilation of copious cases with detailed genetic, biological, and clinical features has enabled the classification of congenital fibrinogen disorders into several types and subtypes. Such classification is based not only on the clottable and antigenic fibrinogen levels but also on the patient's clinical phenotype, which is usually bleeding, but sometimes thrombosis and sometimes both, as well as the genotype. Fibrinogen supplementation is the cornerstone of bleeding management in fibrinogen disorders. Since the discovery of blood fractionation, the method of production of fibrinogen concentrate has been progressively improved, both in terms of purity and safety. Nevertheless, the availability of such products remains limited to a few countries and the optimal threshold of fibrinogen to target remains to be established.

The second article, by Richard and colleagues,[3] continues the discussion around congenital fibrinogen disorders, but focuses on the mutations that account for these disorders. Fibrinogen is a complex protein and hexamer composed of two copies of three distinct chains: Aα, Bβ, and γ encoded by three genes, *FGA*, *FGB*, and *FGG*, clustered on the long arm of chromosome 4. Congenital fibrinogen disorders are divided into qualitative deficiencies (dysfibrinogenemia, hypodysfibrinogenemia) in which the mutant fibrinogen molecule is present in the circulation and quantitative deficiencies (afibrinogenemia, hypofibrinogenemia) with no mutant molecule present in the bloodstream. Phenotypic manifestations are variable, patients may be asymptomatic, or patients may

Address for correspondence Emmanuel J. Favaloro, PhD, FFSc (RCPA), Department of Haematology, ICPMR, Westmead, NSW, Australia 2145 (e-mail: Emmanuel.Favaloro@health.nsw.gov.au).

Issue Theme Celebrating 50 Years of Seminars in Thrombosis and Hemostasis—Part I; Guest Editor: Emmanuel J. Favaloro, PhD, FFSc (RCPA)

Thieme Medical Publishers, Inc., 333 Seventh Avenue, 18th Floor, New York, NY 10001, USA

DOI https://doi.org/10.1055/s-0042-1756301.
ISSN 0094-6176.

Fig. 1 Eberhard F. Mammen (1930–2008).

suffer from bleeding or thrombosis. Causative mutations can occur in any of the three fibrinogen genes and can affect one or both alleles. Given the large number of studies reporting on novel causative mutations for congenital fibrinogen disorders since a review published in this journal in 2016 on the same topic,[4] the authors performed an extensive search of the literature and list 120 additional mutations described in both quantitative and qualitative disorders. The visualization of causative single nucleotide variations placed on the coding sequences of *FGA*, *FGB*, and *FGG r*eveals important structure–function insight for several domains of the fibrinogen molecule.

The theme of bleeding disorders continues, with an update to the treatment of hemophilia by Franchini and Mannucci,[5] in an article that partially modernizes another historical article by this authorship team on the history of hemophilia,[6] which *STH* published as part of its 40th anniversary celebrations. The availability of plasma-derived clotting factor concentrates in the 1970s has been followed by the availability of recombinant clotting factor concentrates in the 1990s, both events representing relative milestones in hemophilia care at that time, and enabled not only treatment of episodic bleeding events but also the implementation of prophylactic treatment regimens. The treatment of hemophilia has since reached perhaps even more significant landmarks. First, the traditional clotting factor replacement therapy for hemophilia has been substituted over the past 10 years by novel treatments such as bioengineered factor VIII and IX molecules with extended half-life and also nonfactor treatments including the bispecific antibody emicizumab. These newer therapies are contributing significantly to improving the long-term management of prophylaxis in hemophilia patients. This review also summarizes the current state of gene therapy, which is a promising definitive cure for severe hemophilia A and B.

The last article in this issue of STH with a specific bleeding theme describes the identification of autoimmune acquired von Willebrand factor (VWF) deficiency in Japan.[7] Ichinose and colleagues first discuss VWF, which forms high-molecular-weight multimers and plays an essential role in hemostasis, immobilizing platelets to sites of vascular injury. This leads to activation of platelets, release of granule components, platelet aggregation, and facilitation of secondary hemostasis. Thus, deficiency of VWF leads to bleeding symptoms. Acquired von Willebrand syndrome (AVWS) is rare, but potentially underdiagnosed, and develops from various underlying primary disorders. In turn, AVWS caused by anti-VWF autoantibodies is a rare subcategory of AVWS that can also be referred to as autoimmune VWF deficiency. The authors performed a search of patients with autoimmune coagulation factor deficiencies in a nationwide survey in Japan. Among these, suspected cases of autoimmune VWF deficiency were extremely few, with only 11 case consultations in the last 10 years. Of these, three and five were respectively positive for anti-VWF autoantibodies and VWF inhibitor. They also performed an extensive literature search of other cases from Japan, and in total, 40 cases were finally identified to have autoimmune VWF deficiency, with the mean age of 55.0 years. Most underlying disorders were lympho- or myeloproliferative diseases, followed by autoimmune diseases. The major bleeding sites in patients were subcutaneous and mucosal, the bleeding severity was moderate, and there were no reported hemorrhagic deaths. Bleeding time was prolonged; factor VIII activity, VWF antigen, and VWF activity were decreased; and high-molecular-weight VWF multimers were absent or decreased. These findings are similar to the common abnormal laboratory findings observed among general AVWS cases. Hemostatic therapy often involved VWF concentrates and vasopressin, and antibody eradication therapy often included corticosteroids and achieved remission. Notably, of all cases, 68% had anti-VWF antibodies, and 83% of anti-VWF-antibody-positive patients were also VWF inhibitor positive. However, to accumulate more precise clinical information on autoimmune VWF deficiency, the authors advise that it is necessary to verify and improve the measurement methods for both anti-VWF antibodies and anti-VWF inhibitors. These findings from Japan should be confirmed in other geographic localities.

We switch the discussion from bleeding disorders to thrombotic disorders, starting with a personal look at the past 50 years of thrombotic thrombocytopenic purpura (TTP) from James George.[8] This review begins with his first encounter with TTP 50 years ago when two sisters presented 2 years apart, both pregnant and both of who died. Later, in 1991, a year after he moved to Oklahoma, therapeutic plasma exchange (TPE) was established as an effective treatment of TTP. With the availability of effective treatment, the number of patients presenting with suspected TTP soared, but the diagnosis of TTP remained imprecise. The author worked with the Oklahoma Blood Institute to better understand the management of TTP. Because this institute provided all TPE procedures for most of Oklahoma, the author's team saw all consecutive patients within a defined geographic area who were identified at a uniform time early in the course of their TTP, without selection or referral bias. This became an inception cohort, later to become the Oklahoma TTP Registry. In 2001, they began a very successful collaboration with the University of Bern, Switzerland, to measure ADAMTS13 (a disintegrin and metalloprotease with a thrombospondin type 1 motif, member 13) activity on all of their patients. From these patients, they learned that acquired, autoimmune TTP was a chronic disease with risks for cognitive impairment and depression. Later recognition in 2012 of three sisters with hereditary TTP was reminiscent of the beginning of the author's experience.

Hereditary TTP holds risks for multiple severe morbidities, beginning at birth and especially during pregnancy. The author concludes by looking to the future, and predicts that management of both immune and hereditary TTP will become more effective and more convenient.

The thrombosis theme continues with a review on primary and secondary prevention of venous thromboembolism in carriers of hereditary thrombophilia by Campello and Prandoni.[9] The association between heritability of venous thromboembolism and thrombophilia was first reported clinically in 1956, later followed by the first description of a congenital cause of hypercoagulability—antithrombin deficiency—in 1965. Since then, knowledge of hereditary causes of hypercoagulability that may predispose carriers to venous thromboembolism has improved greatly. Novel genetic defects responsible for severe thrombophilia have been recently identified and we have learned that a wide range of interactions between thrombophilia and other genetic and acquired risk factors are important determinants of the overall individual risk of developing venous thromboembolism. Furthermore, therapeutic strategies in thrombophilic patients have benefited significantly from the introduction of direct oral anticoagulants (DOACs). This review provides an overview of the current knowledge on the mechanisms underlying inherited thrombophilia, with a particular focus on the latest achievements in anticoagulation protocols and prevention strategies for thrombosis in carriers of this prothrombotic condition.

Continuing the theme of treatment or therapy for thrombotic disorders is the review from Carpenè and colleagues, on the journey of heparin from parenteral agent to nasal delivery.[10] Although the worldwide usage of DOACs has continuously increased during the past decade, heparin remains an important weapon in the current arsenal of anticoagulant drugs. Parenteral heparin administration (i.e., either intravenously or subcutaneously) has for decades represented the only possible route for generating a significant anticoagulant effect, although being notoriously associated with some important downsides such as discomfort and risk of low compliance, thus paving the way to search for more amenable means of administration. The authors provide an updated analysis of animal and human studies which have explored the feasibility, suitability, and efficiency of heparin administration through the unconventional nasal route, as a possible alternative to the more traditional parenteral injection. The major hurdles that contribute to impair intranasal absorption and systemic delivery of heparin are represented by its relatively high molecular weight and its negative charge. Therefore, pure drug administration would not be associated with efficient nasal adsorption, or by systemic biological activity (i.e., anticoagulant effect). However, the combination of low-molecular-weight heparins with absorption enhancers such as surfactants, mucoadhesives, cyclodextrins, polyethylenimines, and encapsulation into (nano)carriers seems effective to at least partially improve drug transport through the nasal route and allow systemic delivery in animals. Besides generating anticoagulant effects, intranasal heparin administration can also produce local pleiotropic effects, mostly related to anti-inflammatory properties, such as attenuating airway allergic inflammation or inhibiting the binding of the spike protein of some coronaviruses (including SARS-CoV-2) to their host cell receptors. This preliminary evidence represents a valuable premise for planning future studies in humans aimed at establishing the pharmacokinetics and biological activity of locally and systemically delivered intranasal heparin formulations.

The themes of anticoagulant therapy and bleeding combine in the next installment in this issue by Salter and Crowther, who provide a historical perspective on the reversal of anticoagulants.[11] The authors begin by detailing the landmark shift in the last several decades in the management and prevention of thromboembolic events. From the discovery of parenteral and oral agents requiring frequent monitoring as early as 1914, to the development of DOACs that do not require monitoring or dose adjustment in the late 20th century. Despite the advent of these newer agents, however, bleeding continues to be a key complication, affecting 2 to 4% of DOAC-treated patients per year. Bleeding is associated with substantial morbidity and mortality. Although specific reversal agents for DOACs have lagged the release of these agents, idarucizumab and andexanet alfa are now available as antagonists. However, the efficacy of these reversal agents is uncertain, and complications, including thrombosis, have not been adequately explored. As such, guidelines continue to advise the use of nonspecific pro-hemostatic agents for patients requiring reversal of the anticoagulant effect of these drugs. As the indications for DOACs and the overall prevalence of their use expand, there is an unmet need for further studies to determine the efficacy of specific compared with nonspecific pro-hemostatic reversal agents. In this review, the authors also discuss the evidence behind specific and nonspecific reversal agents for both parenteral and oral anticoagulants.

Vittorio Pengo then provides a narrative review on the interaction between antiphospholipid antibodies (aPL) and the protein C anticoagulant pathway.[12] Thrombotic antiphospholipid syndrome (aPS) is a condition in which thrombosis in venous, arterial, and/or small vessels is ascribed to the presence of aPL. Among the various proposed pathogenic theories to explain thrombotic aPS, those involving the interaction between aPL and the protein C system have gained much consensus. Indeed, robust data show an acquired activated protein C resistance (APC-R) in these patients. The role of aPL in this impairment is clear, but the mechanism of action is uncertain, as the type and to what extent aPLs are involved remains a gray area. Lupus anticoagulant (LA) is often associated with APC-R, but antibodies generating LA comprise those directed against β2-glycoprotein I (aβ2GPI) and phosphatidyl-serine/prothrombin (aPS/PT). Moreover, the induction of APC-R by aPL requires the presence of phospholipids and is suppressed by the presence of an excess of phospholipids. How phospholipids exposed on the cell membranes work in the system in vivo is unknown. Interestingly, acquired APC-R due to aPL might explain

the clinical phenotypes of thrombotic aPS. Indeed, the literature reports cases of both venous and arterial thromboembolism as well as skin necrosis, the latter observed in the severe form of protein C deficiency and in catastrophic aPS.

In the final full-length article in this issue of STH, Iba and colleagues provide an overview of disseminated intravascular coagulation (DIC), from the perspective of past, present, and future.[13] DIC has been understood as a consumptive coagulopathy. However, impaired hemostasis is a component of DIC that occurs in a progressive manner. The critical concept of DIC is systemic activation of coagulation with vascular endothelial damage. DIC is the dynamic coagulation/fibrinolysis disorder that can proceed from compensated to decompensated phases, and is not simply impaired hemostasis, a misunderstanding that continues to evoke confusion among clinicians. DIC is a critical step of disease progression that is important to monitor over time. Impaired microcirculation and subsequent organ failure due to pathologic microthrombi formation are the pathophysiologies in sepsis-associated DIC. Impaired hemostasis due to coagulation factor depletion from hemodilution, shock, and hyperfibrinolysis occurs in trauma-associated DIC. Overt-DIC diagnostic criteria have been used clinically for over 20 years but may not be adequate to detect the compensated phase of DIC, and due to different underlying causes, there is no "one-size-fits-all criteria." Individualized criteria for heterogeneous conditions continue to be proposed to facilitate the diagnosis. The authors believe that future research will provide therapeutics using new diagnostic criteria. Finally, DIC is also classified as either acute or chronic, and acute DIC results from progressive coagulation activation over a short time and requires urgent management. In this review, the authors examine the advances in research for DIC.

The issue concludes with a commentary on high-density lipoprotein cholesterol (HDL-C) and mortality[14] and some correspondence around cancer and thrombosis risk.[15] In the commentary, Lippi and colleagues discuss the latest findings, which indicate that contrary to established dogma, which dictate that high levels of HDL-C are associated with health benefits, that there may instead be a **J**- or **U**-shaped relationship. That is, there seems to be a "sweet-spot" for desirable HDL-C values, and both low and high levels may be less desirable. Finally, Fan identifies the early insights into cancer and thrombosis risk provided by Trousseau's syndrome in 19th century Qing dynasty paintings of breast tumors.[15]

I thank the authors of the in-issue contributions, which marks the first of our historical issues celebrating 50 years of STH, and I look forward to the second issue to publish in 2023.

Conflict of Interest
None declared.

Acknowledgments
I would like to thank all past contributors to *STH*, both those providing material to publish in the journal, but also those who have undertaken reviews for the journal, and all past and present editors of *STH*. *STH* would not be here without these contributors. The views expressed in this manuscript reflect those of the author, and do not necessarily reflect those of NSW Health Pathology.

References

1 Favaloro EJ. Towards 50 years of Seminars in Thrombosis and Hemostasis. Semin Thromb Hemost 2022;48(08):875–879
2 Casini A, de Moerloose P, Neerman-Arbez M. One hundred years of congenital fibrinogen disorders. Semin Thromb Hemost 2022;48 (08):880–888
3 Richard M, Celeny D, Neerman-Arbez M. Mutations accounting for congenital fibrinogen disorders: an update. Semin Thromb Hemost 2022;48(08):889–903
4 Neerman-Arbez M, de Moerloose P, Casini A. Laboratory and genetic investigation of mutations accounting for congenital fibrinogen disorders. Semin Thromb Hemost 2016;42(04): 356–365
5 Franchini M, Mannucci PM. The more recent history of hemophilia treatment. Semin Thromb Hemost 2022;48(08):904–910
6 Franchini M, Mannucci PM. The history of hemophilia. Semin Thromb Hemost 2014;40(05):571–576
7 Ichinose A, Osaki T, Souri M, Favaloro EJ. A review of autoimmune acquired von Willebrand factor deficiency in Japan. Semin Thromb Hemost 2022;48(08):911–925
8 George JN. Thrombotic thrombocytopenic purpura: from 1972 to 2022 and beyond. Semin Thromb Hemost 2022;48(08):926–936
9 Campello E, Prandoni P. Evolving knowledge on primary and secondary prevention of venous thromboembolism in carriers of hereditary thrombophilia: a narrative review. Semin Thromb Hemost 2022;48(08):937–948
10 Carpenè G, Negrini D, Lippi G, Favaloro EJ, Montagnana M. Heparin: the journey from parenteral agent to nasal delivery. Semin Thromb Hemost 2022;48(08):949–954
11 Salter B, Crowther M. A historical perspective on the reversal of anticoagulants. Semin Thromb Hemost 2022;48(08):955–970
12 Pengo V. Interaction between antiphospholipid antibodies and protein C anticoagulant pathway: a narrative review. Semin Thromb Hemost 2022;48(08):971–977
13 Iba T, Marcel Levi M, Thachil J, Levy JH. Disseminated intravascular coagulation: the past, present, and future considerations. Semin Thromb Hemost 2022;48(08):978–987
14 Lippi G, Sanchis-Gomar F, Lavie CJ. Increased HDL-C values and mortality: revolutionizing an historical paradigm? Semin Thromb Hemost 2022;48(08):988–990
15 Fan BE. Trousseau's syndrome in 19th Century Qing Dynasty paintings of breast tumours: early insights into cancer and thrombosis risk. Semin Thromb Hemost 2022;48(08):991–994