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

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

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

Semin Thromb Hemost 2023;49:212–216.

Welcome to another issue of *Seminars in Thrombosis and Hemostasis (STH)*. This is another very special issue, being the second of a series of issues we will publish to celebrate the upcoming 50th anniversary of the journal. As explained more fully in a prior 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 third for 2023, marks the second of these issues, and celebrates the 50th year of publishing for STH. We have not yet reached 50 years of age; this birthday comes in 2024, but we are getting close. As an update to the prior editorial,[1] I can also report that STH online is now "whole." At that time, I reported that the online content of STH was complete but missing the first issue of the journal, as published in early 1974. I am now happy to report that a copy of the first issue has been found and since scanned and posted online (https://www.thieme-connect.com/products/ejournals/issue/10.1055/s-012-55744). Many thanks to one of our senior editors, Ton Lisman, for tracking down a copy of the first issue for us.

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 8 issues, and some 900 printed pages, per year, having also achieved a landmark of just over 1,000 printed pages in 2020 (►**Fig. 2**). The number of printed pages in 2021 and 2022 were just under 1,000, being an identical 994 in each year. The number of articles published per year according to PubMed is also increasing, although the contribution of manuscripts published as early on line (eFirst) needs to be recognized in this tally (►**Fig. 3**). Thus, a similar number of articles are published each year in print.

The current issue, like the first in this series,[2] contains a range of material related to the broad concepts of thrombosis and hemostasis and with a historical connection. The issue begins with a dedication to Prof. Peter Kubisz (1942–2022), from his colleague and friend Guillermo J. Ruiz-Argüelles.[3] Prof. Kubisz sadly passed away late in 2022, and in terms of his connection to STH can perhaps best be remembered for his passion on the topic of sticky platelet syndrome,[4–6] a passion that was shared by the founding Editor in Chief of STH, Prof. Eberhard F. Mammen.[7–9]

Next in this issue is a review from Levy-Mendelovich and colleagues, discussing 50 years of pediatric hemostasis research.[10] These studies have contributed to the expanding knowledge of developmental hemostasis, a dynamic process that begins in the fetal phase and is characterized by physiological variations in platelet counts and function, as well as the concentrations of most coagulation factors and the native coagulation inhibitors in early life, as compared with adulthood. Developmental hemostasis studies since the 1980s to the 1990s established the laboratory reference values for coagulation factors. It was only a decade or two later that thromboelastography or rotational thromboelastometry as well as thrombin generation studies provided special pediatric reference values along with the ability to evaluate clot formation and lysis. In addition, global whole blood-based

Address for correspondence Emmanuel J. Favaloro, PhD, FFSc (RCPA), Department of Haematology, Institute of Clinical Pathology and Medical Research, Westmead Hospital, Westmead, New South Wales, Australia 2145 (e-mail: Emmanuel.Favaloro@health.nsw.gov.au).

Issue Theme Celebrating 50 Years of Seminars in Thrombosis and Hemostasis—Part II; 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-0042-1760334.
ISSN 0094-6176.

Fig. 1 The founding Editor in Chief of STH, Prof. Eberhard F. Mammen (1930–2008).

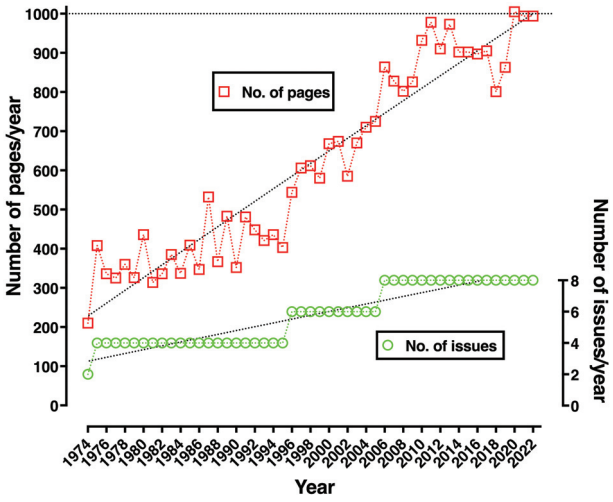

Fig. 2 The historical evolution of STH: part I. The figure shows the number of printed pages and number of issues in each year of publication, from its humble beginnings in 1974 up to the end of 2022.

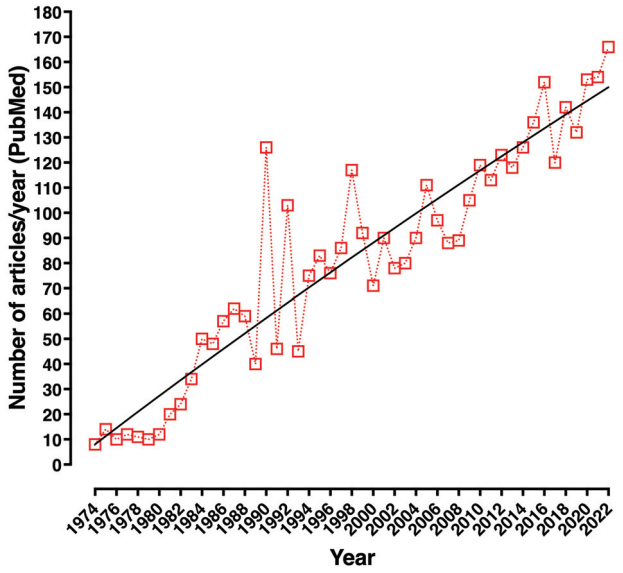

Fig. 3 The historical evolution of STH: part II. The figure shows the number of articles published in each year of publication according to PubMed, from its humble beginnings in 1974 up to the end of 2022. As STH is now publishing a larger number of articles early on line ("eFirst"), articles will appear as a PubMed listing before the print issue is published.

clotting assays provided point-of-care guidance for proper transfusion support to children hospitalized in intensive care units or undergoing surgery. Although uncommon, thrombosis in children and neonates is gaining increasing recognition, typically as a secondary complication in sick children. Bleeding in children, and particularly intracerebral hemorrhage in newborns, still represents a therapeutic challenge. Notably, this review outlines the advancements in understanding developmental hemostasis and its manifestations, with respect to the pathophysiology of thrombosis and bleeding complications in young children. The changes of transfusion policy and approach to thrombophilia testing during the last decade are also mentioned. A brief summary of the data on anticoagulant treatments in pediatric patients is also presented. Finally, the authors point to the 10 most cited articles in the field of pediatric and neonatal hemostasis.

A second "50-year" review follows, and reflects a personal look back at landmark changes during the five decades as a clinical laboratory scientist in U.S. hemostasis laboratories from Robert C. Gosselin.[11] Like the STH anniversary, this year will also mark Mr. Gosselin's fifth decade of working in, or association with, laboratories that perform hemostasis testing. His career started at a large military medical center, but he also worked at several other facilities, including military dispensaries, community hospitals, and a large academic institution. He reflects that the difference between each type of hemostasis laboratory was as expected, with larger facilities having better instrumentation and more prolific test menus. However, whether one worked in a large academic center, or a small rural hospital, regulatory changes affected every clinical laboratory to the same degree. Advances in technology also eventually affected every hemostasis laboratory, but these salient changes were more likely to occur earlier at the larger institutions. As STH celebrates its 50th anniversary, this milestone triggered recollection about those salient events that occurred during his career in hemostasis testing, which of course may mirror those of other diagnostic scientists. Accordingly, Mr. Gosselin describes (his personal impression) the top-ten landmark changes that altered laboratory practice at the facilities where he worked over the past five decades.

Another personal reflection follows from Armando Tripodi.[12] Prof. Tripodi reflects that looking at the history of hemostasis, one can easily conclude that most of the achievements we see today have been done through the ingenuity and dedication of scientists, who devoted their efforts to translate the basic concepts behind their hypotheses from the laboratory to the patient's bedside. He was personally excited by three of these stories. This article therefore aims to review the history on the development of D-Dimer, heparin, and coagulometers, which Prof. Tripodi chose as paradigmatic examples of diagnostic testing, drugs, and measuring devices, respectively. He believes that they should be

considered among the most successful histories of translational medicine.

Continuing from the discussion of heparin from Prof. Tripodi, comes the fascinating story of anticoagulants as narrated by Hirsh and colleagues, who review the clinical studies with anticoagulants that have changed clinical practice.[13] Anticoagulant therapy is the cornerstone of treatment and prevention of arterial and venous thromboembolism. Taking a historical perspective, starting in the 1960s, and progressing through to 2022, the authors discuss key clinical trials of anticoagulants that have changed clinical practice, and examine obstacles encountered in bringing these anticoagulants to the clinic. The design of some of the early studies that shaped clinical practice was poor by current standards, but their results were influential because nothing better was then available. Both heparin and vitamin K antagonists (VKAs) had been in clinical use for several decades before well-designed trials in the 1980s optimized their dosing and enhanced their safety and efficacy. Low-molecular-weight heparin then replaced unfractionated heparin because it had a more predictable dose–response and a longer half-life, thereby allowing it to be used conveniently in out-of-hospital settings. More recently, direct oral anticoagulants have become the oral anticoagulants of choice for most indications because they have been shown to be at least as safe and effective as VKAs when used in fixed doses without the need for laboratory monitoring. The design of the trials that led to the approval of the direct oral anticoagulants was excellent, but further studies are required to optimize their dosing in selected patients who were underrepresented in these trials.

Another historical review, this time on antiplatelet therapy, as specifically applied to coronary artery disease (CAD), follows from the team of Tscharre and Gremmel.[14] Cardiovascular disease, particularly CAD, remains the leading cause of mortality and morbidity in industrialized countries. Platelet activation and aggregation at the site of endothelial injury plays a key role in the processes ultimately resulting in thrombus formation with vessel occlusion and subsequent end-organ damage. Consequently, antiplatelet therapy has become a mainstay in the pharmacological treatment of CAD. Several drug classes have been developed over the last decades and a broad armamentarium of antiplatelet agents is currently available. This review portrays the evolution of antiplatelet therapy, and provides an overview on previous and current antiplatelet drugs and strategies.

Discussion of platelets continues, with a review by Prof. Anne-Mette Hvas.[15] This review summarizes the time that has passed from the initial registration of the cells that turned out to be platelets up to today's advanced methodologies in platelet investigation. The first reports of "granular masses" appeared in the 1840s, but these "granular masses" remained an unsolved mystery until the 1870s. The breakthrough came in the 1873–1882 period. The cells that later turned out to be platelets were further identified by the German Professor Max Schultze, and later by Osler, who described their disk-like structure. These initial descriptions of platelets were expanded by impressive studies performed by the Italian pathologist Bizzozero who uncovered the anatomy of platelets and described their role, first in experimental thrombosis and later in the clotting process. Nearly 20 years later, in 1906, Wright published the discovery of megakaryocytes as platelet precursors. Shortly thereafter, the clinical proof of concept illustrating the pivotal role of platelets in arresting bleeding was revealed by Duke who introduced the bleeding time test, also in this period. To investigate platelet function more specifically, light transmission aggregometry was introduced in 1962 and remains the gold standard today. This method inspired the development of several devices employing whole blood using different principles for evaluating platelet function. As of today, flow cytometry is the most advanced method and holds promise to provide new insights into platelet activation. Additionally, advances in genetic testing by use of next-generation sequencing will allow further improvement of our ability to diagnose inherited platelet disorders.

Next, Mabrouk and colleagues continue the discussion around platelets, this time as related to platelet-derived extracellular vesicles, and their pathophysiological role.[16] Platelets are very abundant in blood, where they play a major role in hemostasis, inflammation, and immunity. When activated, platelets undergo a conformational change that allows the release of numerous effector molecules as well as the production of extracellular vesicles, which are circulating submicron vesicles (10–1,000 nm in diameter) released into the extracellular space. Extracellular vesicles are formed by the budding of the platelet and they carry some of its contents, including nucleic acids, surface proteins, and organelles. While platelets cannot cross tissue barriers, platelet-derived extracellular vesicles can enter the lymph, bone marrow, and synovial fluid. This allows the transfer of the diverse contents carried by these platelet-derived vesicles to cell recipients and organs inaccessible to platelets where they can perform many functions. This review highlights the importance of these platelet-derived extracellular vesicles under different physiological and pathophysiological conditions.

A change in direction follows, with Woods and colleagues[17] taking us on a journey from the discovery of ADAMTS13 (a disintegrin-like metalloprotease domain with thrombospondin type 1 motifs, member 13) to current understanding of its role in health and disease. ADAMTS13 is a protease of crucial importance in the regulation of the size of von Willebrand factor (VWF) multimers. Very low ADAMTS13 activity levels result in thrombotic thrombocytopenic purpura (TTP), a rare and life-threatening disease. The mechanisms involved can either be acquired (immune-mediated TTP) or congenital (cTTP; Upshaw–Schulman syndrome) caused by the autosomal recessive inheritance of disease-causing variants located along the *ADAMTS13* gene, which is located in chromosome 9q34. Apart from its role in TTP, and as a regulator of microthrombosis, ADAMTS13 has begun to be identified as a prognostic and/or diagnostic marker of other diseases, such as those related to inflammatory processes, liver damage, metastasis of malignancies, sepsis, and different disorders related to angiogenesis.[18–21] Since its first description almost 100 years ago, the

improvement of laboratory tests and the description of novel disease-causing variants along the ADAMTS13 gene have contributed to a better and faster diagnosis of patients under critical conditions. The ability of ADAMTS13 to dissolve platelet aggregates in vitro and its antithrombotic properties make recombinant human ADAMTS13 treatment a potential therapeutic approach targeting not only patients with cTTP but also other medical conditions.

Another prothrombotic condition is the antiphospholipid (antibody) syndrome (APS). As highlighted by Arachchillage and Pericleous,[22] APS is an autoimmune prothrombotic disease characterized by thrombosis and/or pregnancy complications caused by antiphospholipid antibodies (aPL). The history of APS can be traced back to observations made during screening programs for syphilis conducted in the mid-20th century, with identification of subjects with the so-called biological false-positive serological reactions for syphilis. Initial observation linking aPL with recurrent miscarriages was first reported more than 40 years ago. Since then, our understanding of the pathogenesis and management of APS has evolved markedly. Although APS is an autoimmune disease rather than a reflection of immunomodulation, anticoagulation mainly with VKAs is the treatment of choice for thrombotic APS. Direct acting oral anticoagulants (DOACs) are inferior to VKAs, especially in those with triple positive APS and/or arterial thrombosis. Inflammation, complement activation, and thrombosis in the placenta may contribute to pathogenesis of obstetric APS. Heparin, mainly low-molecular-weight heparin, and low-dose aspirin, represent the treatments of choice for women with obstetric complications. Increasingly, immunomodulatory agents such as hydroxychloroquine for thrombotic and obstetric APS are being used, especially in patients who are refractory to present standard treatment.

In the final full-length article in this issue of STH, Morrow and Mutch provide an historical account of plasminogen activator inhibitor 1 (PAI-1).[23] PAI-1 is a SERPIN inhibitor, primarily known for its regulation of fibrinolysis. However, it is now known that this inhibitor functions and contributes to many (patho)physiological processes including inflammation, wound healing, cell adhesion, and tumor progression. This review discusses the past, present, and future roles of PAI-1, with a particular focus on the discovery of this inhibitor in the 1970s and subsequent characterization in health and disease. Throughout the past few decades, diverse functions of this serpin have unraveled and it is now considered an important player in many disease processes. PAI-1 is expressed by numerous cell types, including megakaryocytes and platelets, adipocytes, endothelial cells, hepatocytes, and smooth muscle cells. In the circulation, PAI-1 exists in two pools, within plasma itself and in platelet α-granules. Platelet PAI-1 is secreted following activation with retention of the inhibitor on the activated platelet membrane. Furthermore, these anucleate cells contain PAI-1 mRNA to allow de novo synthesis. Outside of the traditional role of PAI-1 in fibrinolysis, this serpin has also been identified to play important roles in metabolic syndrome, obesity, diabetes, and, most recently, acute respiratory distress syndrome, including COVID-19 disease. This review highlights the complexity of PAI-1 and the requirement to ascertain a better understanding on how this complex serpin functions in (patho)physiological processes.

The issue concludes with some correspondence from Lippi and colleagues on worldwide usage of anticoagulant drugs, and its evolution over the past 10 years.[24] In brief, the administration of anticoagulant drugs is a mainstay in the prevention and management of a kaleidoscope of thrombotic disorders. In relatively recent periods, and more specifically at the beginning of this last century, the armamentarium of such drugs—which basically comprised VKAs and heparin (either unfractionated or low molecular weight)—has been considerably magnified with development, clinical validation, and further commercialization of the so-called DOACs.

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

Conflict of Interest
None declared.

Acknowledgements
The author would like to thank all past contributors to STH, not only those providing material to publish in the journal but also those who have undertaken reviews for the journal, as well as all past and present editors of STH. STH would not have been here without these contributors. The views expressed in this article reflect those of the author, and do not necessarily reflect those of NSW Health Pathology.

References

1 Favaloro EJ. Toward 50 years of seminars in thrombosis and hemostasis. Semin Thromb Hemost 2022;48(08):875–879
2 Favaloro EJ. Celebrating 50 years of seminars in thrombosis and hemostasis - Part I. Semin Thromb Hemost 2022;48(08):871–874
3 Ruiz-Argüelles GJ. Dedication: Professor Peter Kubisz (1942–2022) - Un hommage à trois étincelles. Semin Thromb Hemost 2023;49 (03):209–211
4 Kubisz P, Stasko J, Holly P. Sticky platelet syndrome. Semin Thromb Hemost 2013;39(06):674–683
5 Kubisz P, Ruiz-Argüelles GJ, Stasko J, Holly P, Ruiz-Delgado GJ. Sticky platelet syndrome: history and future perspectives. Semin Thromb Hemost 2014;40(05):526–534
6 Kubisz P, Holly P, Stasko J. Sticky platelet syndrome: 35 years of growing evidence. Semin Thromb Hemost 2019;45(01): 61–68
7 Mammen EF, Barnhart MI, Selik NR, Gilroy J, Klepach GL. "Sticky platelet syndrome": a congenital platelet abnormality predisposing to thrombosis? Folia Haematol Int Mag Klin Morphol Blutforsch 1988;115(03):361–365
8 Mammen EF. Sticky platelet syndrome. Semin Thromb Hemost 1999;25(04):361–365
9 Frenkel EP, Mammen EF. Sticky platelet syndrome and thrombocythemia. Hematol Oncol Clin North Am 2003;17(01):63–83
10 Levy-Mendelovich S, Cohen O, Klang E, Kenet G. 50 years of pediatric hemostasis: knowledge, diagnosis and treatment. Semin Thromb Hemost 2023;49(03):217–224
11 Gosselin RC. From ink pens to computers: a personal look back at landmark changes during 5 decades as a clinical laboratory

scientist in US hemostasis laboratories. Semin Thromb Hemost 2023;49(03):225–233
12 Tripodi A. Hemostasis from bench to bedside. The history of three successful stories of translational medicine. Semin Thromb Hemost 2023;49(03):234–241
13 Hirsh J, Eikelboom JW, Bhagirath V, Chan NC. Clinical studies with anticoagulants that have changed clinical practice. Semin Thromb Hemost 2023;49(03):242–254
14 Tscharre M, Gremmel T. Antiplatelet therapy in coronary artery disease: now and then. Semin Thromb Hemost 2023;49(03): 255–271
15 Hvas A-M. Crucial stepping stones in platelet history. Semin Thromb Hemost 2023;49(03):272–278
16 Mabrouk M, Guessous F, Naya A, Merhi Y, Zaid Y. The pathophysiological role of platelet derived extracellular vesicles. Semin Thromb Hemost 2023;49(03):279–283
17 Woods AI, Paiva J, Dos Santos C, Alberto MF, Sánchez-Luceros A. From the discovery of ADAMTS13 to current understanding of its role in health and disease. Semin Thromb Hemost 2023;49(03): 284–294
18 Favaloro EJ, Henry BM, Lippi G. Increased VWF and decreased ADAMTS13 in COVID-19: creating a milieu for (micro)thrombosis? Semin Thromb Hemost 2021;47(04):400–418
19 Favaloro EJ, Pasalic L, Henry B, Lippi G. Laboratory testing for ADAMTS13: utility for TTP diagnosis/exclusion and beyond. Am J Hematol 2021;96(08):1049–1055
20 Favaloro EJ, Henry BM, Lippi G. VWF and ADAMTS13 in COVID-19 and beyond: a question of balance. EMJ Hematol. 2021;9(01): 55–68
21 Reardon B, Pasalic L, Favaloro EJ. The intriguing relationships of von Willebrand factor, ADAMTS13 and cardiac disease. J Cardiovasc Dev Dis 2021;8(09):115
22 Arachchillage DJ, Pericleous C. Evolution of antiphospholipid syndrome. Semin Thromb Hemost 2023;49(03):295–304
23 Morrow GB, Mutch NJ. Past, present and future perspectives of plasminogen activator inhibitor 1 (PAI 1). Semin Thromb Hemost 2023;49(03):305–314
24 Lippi G, Mattiuzzi C, Favaloro EJ. 10-year evolution in worldwide usage of anticoagulant drugs. Semin Thromb Hemost 2023;49 (03):315–317