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Preface

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

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Welcome to another issue of *Seminars in Thrombosis and Hemostasis* (STH). This one is another very special issue, being the fourth of a series of issues we are publishing to celebrate the 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 50 years. STH was first published in 1974, and so turns 50 in 2024. The current issue of STH marks the fourth and final of these special issues and further helps celebrate the 50th year "birthday" for STH.

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 year 2023 saw a return to more normal publication metrics, with 866 printed pages. However, 2024 will likely return us to the >1,000 printed pages mark, given the current count is >500 printed pages at end of issue no. 3. This "excess" of printed pages is in large part due to the celebratory historical connection, as further explained below. The number of articles published per year according to PubMed also seems to be increasing (►**Fig. 3**), although the contribution of manuscripts published as early on line (eFirst) needs to be recognized in this tally. Thus, a similar number of articles are actually published each year in the print issues, but an increasing number of publications are released early online.

The current issue, like the first three in this series,[2–4] contains a range of material related to the broad concepts of thrombosis and hemostasis with a historical connection. The issue begins with an overview of the development of a coagulation disorders unit in Helsinki,[5] Finland, which provides 24/7 services for local and national hospitals and colleagues upon requests, regarding bleeding and thrombosis diagnostics and management, including follow-up. It is likely that this specific unit mirrors those of other similar units set up in other localities. The Nordic unit has a tight connection between the clinic and laboratory, and its maintenance and sharing knowledge and observations have been priorities for the past 20 or more years and will continue to be of major importance into the future. The consultation service is provided by phone during daytime and on-call hours and also in written form sent electronically to the consulting stakeholders. Thrombosis and hemostasis-targeted outpatient clinics are also available for patients referred to the center. Writing local guidance and official guidelines, Nordic, European, and international collaboration, and educational activities including social communication are critical elements for the Nordic Coagulation Disorders Unit. Alertness to acute coagulation abnormalities, such as occurred during coronavirus disease 2019 and vaccine-induced thrombosis and thrombocytopenia, and development of strategies to manage cross-disciplinary problems are topics that call upon broad networking. The Nordic community has an ongoing historical meeting, which has been circulating among coagulation centers for the past 56 years. At the European level, the European Association of Haemophilia and Allied Disorders focuses on bleeding disorders and their management, including safety surveillance. The International Society on Thrombosis and Haemostasis offers excellent basic and clinical benchmarks for any Coagulation Disorders Unit. The authors hope that their description of the development and implementation of their Coagulation Disorders Unit in Helsinki achieves international

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Fig. 1 The founding Editor in Chief of Seminars in Thrombosis and Hemostasis, Prof Eberhard F. Mammen (1930–2008).

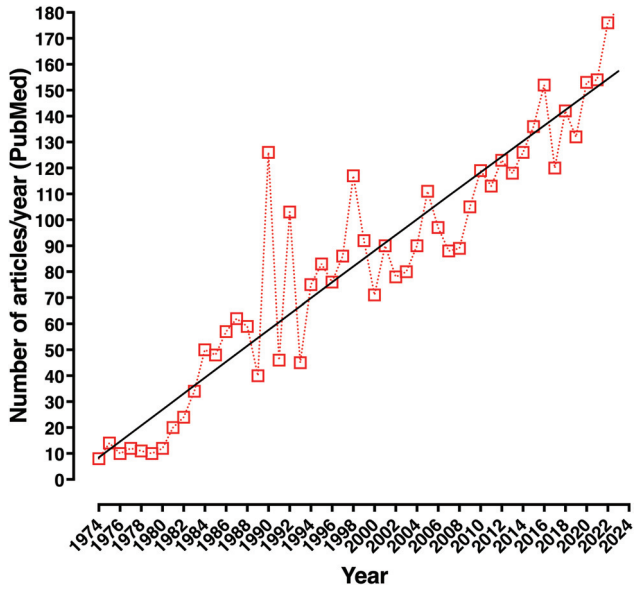

Fig. 3 The historical evolution of Seminars in Thrombosis and Hemostasis Part II. The figure shows the number of articles published in each year of publication according to PubMed, from its humble beginnings in 1974 up to the end of 2023. As Seminars in Thrombosis and Hemostasis is now publishing a larger number of articles early online ("eFirst"), articles will appear as a PubMed listing before the print issue is published.

interest and broadens international collaboration. Finally, they congratulate STH on its great contributions around the globe and for providing a vivid forum to foster the discipline of thrombosis and hemostasis.

The next few submissions largely relate to bleeding disorders and their management. First, Chandran and colleagues discuss aspects of the management of hemophilia A,[6] which has undergone a remarkable revolution, in line with technological advancement, in recent years. Once, the primary concern associated with Factor VIII (FVIII) concentrates was the risk of infections, which is now almost resolved by advanced blood screening and viral inactivation methods. Improving patients' compliance with prophylaxis then became a key focus, as this can lead to improved health outcomes and reduce health care costs in the long term. Recent bioengineering research has been directed toward prolonging the recombinant FVIII (rFVIII) coagulant activity and synthesizing higher FVIII yields. As an outcome, B-domain deleted, polyethylene glycolylated, single-chain, Fc-fused rFVIII, and rFVIIIFc-VWF-XTEN are now available for patients. Moreover, emicizumab, a bispecific antibody, is commercially available, whereas fitusiran and tissue factor pathway inhibitor are in clinical trial stages as alternative strategies for patients with inhibitors. With these advancements, noninfectious complications, such as inhibitor development, allergic reactions, and thrombosis, become emerging concerns requiring careful management. In addition, the recent approval of gene therapy is a major milestone toward a permanent cure for hemophilia A. The vast array of treatment options currently at our disposal empowers patients and providers alike, to tailor therapeutic regimens to the unique needs of each individual. However, despite significant progress in modern treatment options, these highly effective therapies are markedly more expensive than conventional replacement therapy, limiting their access for patients in developing countries.

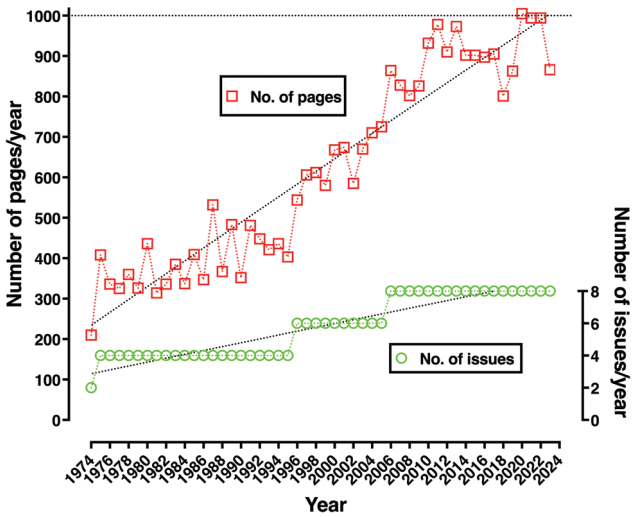

Fig. 2 The historical evolution of Seminars in Thrombosis and Hemostasis Part I. The figure shows the number of printed pages and number of issues in each year of publication, from its humble beginnings in 1974 up to the end of 2023.

Next is another contribution on hemophilia treatment, this one by Rolf Ljung, on prophylactic treatment of hemophilia in children in Sweden,[7] where such treatment was largely initially championed. As our readers well know, hemophilia A/B are caused by plasma deficiency or lack of coagulation factors VIII (FVIII) or factor IX (FIX), respectively. People with hemophilia develop bleeding in the joints and

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muscles at an early age, which, if left untreated, leads to early arthropathy. Preventive treatment can be achieved by regular (prophylactic) administration of FVIII/FIX. In 1958, this was implemented on a small scale in Sweden with FVIII in patients with severe hemophilia A, and in those with hemophilia B in 1972, when FIX containing products became available. However, there were problems with HIV and hepatitis infection from contaminated blood products. In the 1990s, rFVIII and FIX concentrates were introduced. The major remaining problems then were the development of inhibitors and the need for a venous route for the injections in very young children. High-titer inhibitors were treated by immune tolerance induction according to a modified model of the original Bonn high-dose protocol. A central venous line (i.e., Port-A-Cath) has enabled early prophylaxis in many children with poor venous access and has enabled the early start of home treatment with adequate injection frequency. Scoring systems for X-rays, magnetic resonance imaging, and function of joints were developed early in Sweden and have been widely disseminated worldwide, partly with modifications. Extended half-life products with half-life increased 3 to 5 times have been developed, which can provide superior bleed protection when dosed once-weekly and can maintain therapeutic trough levels when administered less frequently. The ultimate prophylaxis therapy in the future may be gene therapy, which has recently emerged in some localities.

Next, Moser and colleagues turn our attention to von Willebrand disease (VWD) and its management.[8] VWD is a very heterogenous disease, resulting in different phenotypes and different degrees of bleeding severity. Established therapies (i.e., desmopressin, antifibrinolytic agents, hormone therapy for heavy menstrual bleeding, and von Willebrand factor [VWF] concentrates) may work in some subtypes, but not in all patients. In recent years, progress has been made in improving the diagnosis of VWD subtypes, allowing for more specific therapy. The impact of VWD on women's daily lives has also come to the fore in recent years, with hormone therapy, tranexamic acid, or recombinant VWF as treatment options. New treatment approaches, including the replacement of lacking FVIII function, may work to prevent bleeding in those subgroups affected by severe FVIII deficiency. Reducing the clearance of VWF is an alternative treatment pathway; for example, Rondaptivon pegol is an VWFA1 domain binding aptamer, which not only improves plasma VWF/FVIII levels, but also corrected platelet counts in thrombocytopenic type 2B VWD patients. These approaches are currently in clinical development, which is an additional focus of this review. In addition, half-life extension methods are also important for the improvement of patients' quality of life. Targeting specific mutations may further lead to personalized treatments in the future. Finally, a few randomized controlled trials (RCTs), although relatively small, have been published in recent years, aiming to achieve a higher level of evidence in future guidelines.

Next is a short historical review from Franchini and coworkers[9] on tranexamic acid, a hemostatic agent used as adjunct therapy in a wide range of bleeding conditions or disorders, including both VWD and hemophilia A. Tranexamic acid is an important antifibrinolytic agent, which inhibits plasminogen activation and fibrinolysis. Several RCTs have investigated the role of tranexamic acid in preventing or decreasing blood loss across different surgical interventions or medical conditions characterized by excessive bleeding, consistently documenting its effectiveness and safety. Although the first clinical use of tranexamic acid dates back to more than 60 years ago, tranexamic acid remains the focus of intense research. This narrative review summarizes the more recent results and indications on the clinical use of tranexamic acid.

We then switch attention from bleeding to thrombosis, with a series of manuscripts discussing the other side of the hemostasis coin. First, Martens and colleagues take us on a journey through the history of diagnostics for venous thromboembolism (VTE).[10] An accurate and prompt diagnosis of deep vein thrombosis (DVT) and/or pulmonary embolism is important to prevent serious complications and mortality. Because the clinical presentation of VTE is often nonspecific, objective testing by means of radiological imaging is required to confirm the diagnosis. Historically, a diagnosis of VTE involved invasive imaging techniques, such as contrast venography or conventional pulmonary angiography. Technological developments toward more accurate and less invasive diagnostics have driven the implementation of a variety of newer technologies over the past decades, as well as the derivation and validation of clinical decision rules (CDRs) that can be used to rule out VTE in combination with D-dimer blood tests. In this narrative review, the authors provide a historical overview of the most notable developments in the imaging techniques and CDRs for VTE diagnosis.

Then, Anetta Undas takes us through the rich history of fibrin clot research, also focusing on the clinical relevance of this work.[11] Fibrin is the major component of most thrombi and was first described on a single-lens microscopy by Malpighi in 1666 and named by de Fourcroy. Fibrin has been extensively studied by biochemists, biophysicists, and more recently by clinicians, who recognize the importance of fibrin in clot formation. Elucidation of key reactions leading to fibrin clot formation in the 1950's and 1960's grew clinical interest in the clinical relevance of altered fibrin characteristics. The implementation of scanning electron microscopy to image fibrin clots in 1947 and clot permeation studies in the 1970's enabled evaluation of average fibrin plasma clot pore size characterization in cohorts of patients. Unfavorably altered fibrin clot structure was demonstrated by Blombäck's group in coronary artery disease in 1992 and in diabetes in 1996. Fifteen years ago, similar plasma fibrin clot alterations were reported in patients following VTE. Multiple myeloma was the first malignant disease to be found to lead to abnormal fibrin clot phenotype in the 1970's. Apart from anticoagulant agents, aspirin was first shown to increase fibrin clot permeability in cardiovascular patients in 1998. The current review presents key data on the rich history of fibrin research, in particular those that first documented abnormal fibrin clot properties in a variety of human disease states, as well as factors affecting fibrin phenotype.

Next Theodore Warkentin takes us through an interesting journey, albeit often representing a catastrophic outcome,

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through a historical account of limb ischemic necrosis secondary to microvascular thrombosis.[12] Ischemic limb injury can be broadly classified into arterial (absent pulses) and venous/microvascular (detectable pulses); the latter can be divided into two overlapping disorders—venous limb gangrene (VLG) and symmetrical peripheral gangrene (SPG). Both VLG and SPG feature predominant acral (distal) extremity ischemic necrosis, although in some instances, concomitant nonacral ischemia/skin necrosis occurs. Historically, for coagulopathic disorders with prominent nonacral ischemic necrosis, clinician–scientists implicated depletion of natural anticoagulants, especially involving the protein C system. This historical review traces the recognition of natural anticoagulant depletion as a key feature of nonacral ischemic syndromes, such as classic warfarin-induced skin necrosis, neonatal purpura fulminans, and meningococcemia-associated purpura fulminans. However, only after several decades was it recognized that natural anticoagulant depletion is also a key feature of predominantly acral ischemic microthrombosis syndromes—VLG and SPG—even when accompanying nonacral thrombosis is not present. These acquired acral limb ischemic syndromes typically involve the triad of (1) disseminated intravascular coagulation, (2) natural anticoagulant depletion, and (3) a localizing explanation for microthrombosis occurring in one or more limbs, either DVT (helping to explain VLG) or circulatory shock (helping to explain SPG). In most cases of VLG or SPG there are one or more events that exacerbate natural anticoagulant depletion, such as warfarin therapy (e.g., warfarin-associated VLG complicating heparin-induced thrombosis or cancer hypercoagulability) or acute ischemic hepatitis ("shock liver") as a proximate factor predisposing to severe depletion of hepatically synthesized natural anticoagulants (protein C, antithrombin) in the setting of circulatory shock.

The last full-length paper in this issue is by a large authorship team, Rashedi et al,[13] on historical aspects of fibrinolytic agents used in thromboembolic diseases. Fibrinolytic agents catalyze the conversion of the inactive proenzyme plasminogen into the active protease plasmin, degrading fibrin within the thrombus and recanalizing occluded vessels. The history of these medications dates to the discovery of the first fibrinolytic compound, streptokinase, from bacterial cultures in 1933. Over time, researchers identified two other plasminogen activators in human samples, namely urokinase and tissue plasminogen activator (tPA). Subsequently, tPA was cloned using recombinant DNA methods to produce alteplase. Several additional derivatives of tPA, such as tenecteplase and reteplase, were developed to extend the plasma half-life of tPA. Over the past decades, fibrinolytic medications have been widely used to manage patients with venous and arterial thromboembolic events. Currently, alteplase is approved by the U.S. Food and Drug Administration (FDA) for use in patients with pulmonary embolism with hemodynamic compromise, ST-segment elevation myocardial infarction (STEMI), acute ischemic stroke, and central venous access device occlusion. Reteplase and tenecteplase have also received FDA approval for treating patients with STEMI. This review provides an overview of the historical background related to fibrinolytic agents and briefly summarizes their approved indications across various thromboembolic diseases.

The last issue-specific related contribution is a Letter (Correspondence) from Bingwen Eugene Fan, who provides us with historical insights into cancer-associated thrombosis from leukemia ("Leucocythemia") from the 19th Century.[14] Dr Fan takes us through a personal and clinical journey of John Menteith, a young 28-year-old Scottish male slater, who was Dr John Hughes Bennett's (1812–1875) index case of leucocythemia, and who on February 27, 1845, was admitted to the Royal Infirmary of Edinburgh under the care of Dr Robert Christison (1797–1882). Menteith suffered from a chronic, progressively enlarging left hypochondrial tumor and generalized lymphadenopathy and died from his condition a few days later. An autopsy identified massive hepatosplenomegaly, extensive lymphadenopathy, and blood clots within the blood vessels. Thus, began the recognition of cancer-associated thrombosis from leukemia.

However, this Correspondence is not the last story being told in this issue of STH. As this issue is being published in 2024, and since we are republishing a manuscript from the STH archive with each issue of STH in 2024, along with an accompanying Commentary, this issue concludes with these elements. For the current issue, we are including a republished manuscript originally published in 2005[15,16] and noted to be the second most highly downloaded paper from STH in recent history (from 2014)[17] as well as the 6th most highly cited STH paper of all time.[18] These markers of popularity and relevance are a true marker of this paper's enduring popular appeal. To conclude this issue of STH, we have an accompanying Commentary from one of our senior editors, Julie B. Larsen.[19]

As always, I thank the authors of the in-issue contributions, for which marks the fourth and final of our historical issues celebrating 50 years of STH. Like the prior three Celebratory Historical issues,[2–4] this issue is rich with interesting historical aspects of thrombosis and hemostasis. I am personally very proud to present this issue to the readership, and I look forward to starting another 50 years of STH publishing in 2025, albeit most of these future publications will likely be published in STH when I am no longer at the helm!

Conflict of Interest
None declared.

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