Preface

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

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Welcome to another issue of *Seminars in Thrombosis and Hemostasis* (STH). This is another very special issue, being the third of a series of issues we are publishing 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 50 years. STH was first published in 1974, and so turns 50 in 2024. The current issue of STH, the first for 2024, marks the third of these issues, and celebrates 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 eight 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 online (eFirst) needs to be recognized in this tally (►**Fig. 3**). Thus, a similar number of articles are actually published each year in the print issues.

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

The current issue, like the first two in this series,[2,3] contains a range of materials related to the broad concepts of thrombosis and hemostasis with a historical connection. The issue fittingly begins with a historical account of my own journey in this field.[4] My career in the Thrombosis and Hemostasis field did not start until 1987, but the subsequent 35 years reflected a period of significant change in associated hemostasis/thrombosis disease diagnostics. I began this career in the Westmead Hospital-based "coagulation laboratory," at a time when staff were still performing manual clotting tests, using stop watches, pipettes, test tubes, and a water bath. We also transported these manual clot prerequisites to the hospital outpatient department to run our weekly warfarin clinic, which at that time could easily include 40 or more outpatients per weekly clinic. Semi-automated hemostasis instruments such as the Coag-A-Mate X2 then became available, and over time fully automated

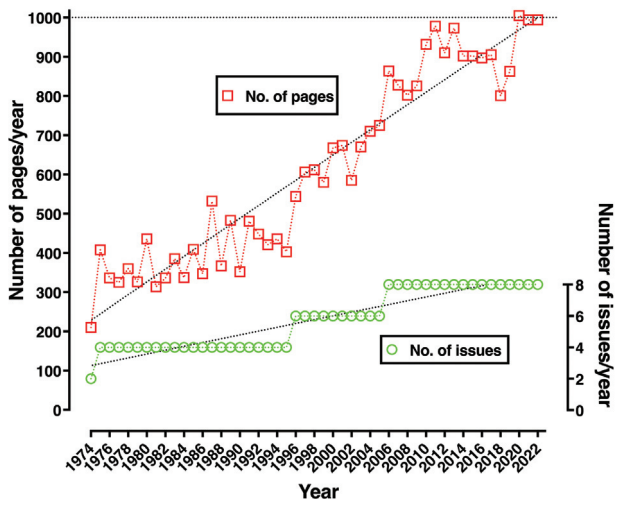

Fig. 2 The historical evolution of STH Part I. The figure shows the number of printed pages and number of issues in each year of publication, from its humble beginnings in 1974 up to the end of 2022.

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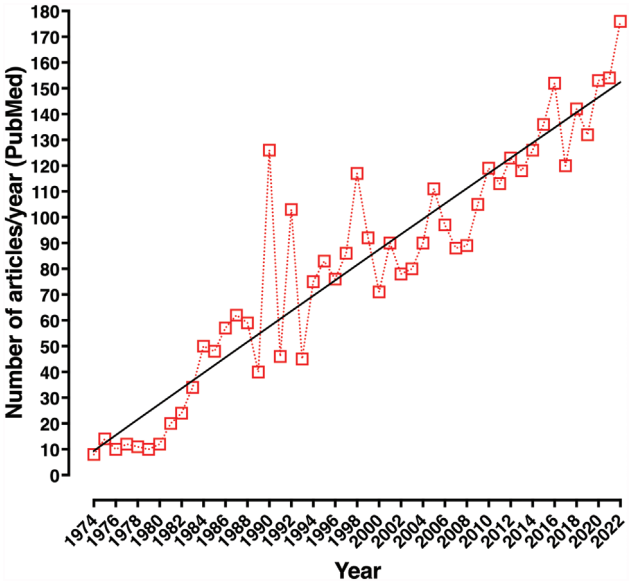

Fig. 3 The historical evolution of STH Part II. The figure shows the number of articles published in each year of publication according to PubMed, from its humble beginnings in 1974 up to the end of 2022. As STH is now publishing a larger number of articles early online ("eFirst"), articles will appear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

instruments appeared, several of which have since come and gone, including the ACL-300R, the MDA-180, the BCS XP, and several StaR Evolution analyzers. Some instruments remain or have replaced prior instruments, including the PFA-100, PFA-200, the AggRAM (platelet aggregometry), the CS-5100, an AcuStar, a Hydrasys gel system for von Willebrand factor (VWF) multimers, and two ACL-TOP 750s. Our laboratory still has a water bath, but this is primarily now used to defrost frozen samples, and manual clotting tests are only used to teach visiting medical students. Our laboratory migrated across several methodologies in its 45-year history. Laurel gel rockets, used for several assays in the 1980s, were replaced with ELISA assays and most assays eventually placed on automated instruments. Radio-isotopic assays, used in the 1980s, were replaced by alternate safer methods or else abandoned. Test numbers also increased markedly over time. The approximately 31,000 hemostasis assays performed at the Westmead-based laboratory in 1983 had become approximately 200,000 in 2022, a sixfold increase. Some 90,000 prothrombin times and activated partial thromboplastin times (aPTTs) are now performed at Westmead per year. Thrombophilia assays were added to the test repertoires over time, as were tests to measure several anticoagulant drugs, most recently the direct oral anticoagulants (DOACs). I hope my own personal history, reflecting on the changes in hemostasis testing over my career to date in the field, is found to be of interest to the STH readership, and I further hope the readership forgive any inaccuracies that I may have introduced in this reflection of the past.

Another historical account of hemostasis and thrombosis is then presented by Drs. Chen and Pruthi,[5] this time on the contribution of the Mayo Clinic to the field. The Mayo Clinic coagulation group has made significant contributions to clinical and laboratory practice since 1926, including basic and translational research on various hemostatic and thrombotic disorders. The Mayo has also provided a site for education and collaboration, facilitating the sharing and advancement of knowledge in hemostasis through a highly integrated team and practice model. The authors hope that this review, sharing the rich history of the Mayo, inspires medical professionals and trainees to join the efforts to advance general understanding of hemostasis pathophysiology and leads to improved care for patients with hemostasis disorders. I had the pleasure of visiting the Mayo Clinic at Rochester twice in the past, the first time in 2007, and the second in 2012.

Next, Dr. Dorgalaleh[6] provides a historical account of factor XIII (FXIII) deficiency. Despite the early discovery of FXIII in 1944, the diagnosis of FXIII deficiency was not made until 1960, after all the other coagulation factor deficiencies, most likely due to the normality of routine coagulation testing in FXIII deficiency. Although the first case was detected by the clot solubility test, with this test since long used to detect FXIII deficiency, the test is no longer recommended by experts. Over the past 60 years, knowledge about FXIII deficiency has expanded considerably; between 1992, when the first variant was identified, and 2022, 197 mutations have been reported. Almost all missense mutations have a similar effect on FXIII, leading to instability and faster degradation of the mutant FXIII protein. Therapeutic options for FXIII deficiency have evolved from historical use of fresh frozen plasma, old plasma, whole blood, and cryoprecipitate, to plasma-derived and recombinant FXIII concentrates, respectively, available since 1993 and 2012. In summary, this historical review covers various aspects of FXIII-related disorders, including the discovery of FXIII, associated disorders, molecular basis, diagnosis, and treatment of FXIII deficiency.

Next in this issue is a second review from me, on the role of the VWF collagen binding assay (VWF:CB) in the diagnosis and treatment of von Willebrand disease (VWD).[7] The VWF:CB assay was first reported for use in VWD diagnostics in 1986, by Brown and Bosak.[8] Since then, the VWF:CB has continued to be used to help diagnose VWD (*correctly*) and also to help assign the *correct* subtype, as well as to assist in the monitoring of VWD therapy, especially desmopressin (DDAVP). However, the specific value of any VWF:CB is predicated on the use of an optimized assay, being one that selectively binds high-molecular-weight (HMW) forms of VWF, and not all VWF:CB assays are so optimized. There are some good commercial assays available, but there are also some "not-so-good" commercial assays available, and these may continue to give the VWF:CB "a bad reputation" in the hemostasis field. In addition to VWD diagnosis and management, the VWF:CB has found purpose in a variety of other applications, from assessing ADAMTS13 (a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13) activity, to investigation into acquired von Willebrand syndrome (especially as associated to use of mechanical circulatory support or cardiac assist devices), to assessment of VWF activity in disease states where an excess of HMW VWF may accumulate, and thus lead to increased (micro)thrombosis risk (e.g., coronavirus disease 2019 [COVID-19], thrombotic thrombocytopenic purpura).[9]

The VWF:CB turns 38 in 2024, and this review is a celebration of the utility of the VWF:CB over this near 40-year history.

A review on the history of extracorporeal membrane oxygenation (ECMO) and the development of ECMO anticoagulation by the group of Bartlett et al follows.[10] Bartlett is considered to be the "Father of ECMO," since he led the initial use of ECMO for humans in the early 1970s. Since its inception, there have been numerous challenges with extracorporeal circulation, such as coagulation and platelet activation, followed by consumption of coagulation factors and platelets, and biocompatibility of tubing, pump, and oxygenator. Unfractionated heparin has historically been the de facto anticoagulant until recently. Also, coagulation monitoring was mainly based on bedside activated clotting time and aPTT. In the past 50 years, the technology of ECMO has advanced tremendously and thus survival rates have improved significantly. Indications for ECMO have also expanded. Among these are clinical conditions such as post-cardiopulmonary bypass, sepsis, ECMO cardiopulmonary resuscitation, and even severe COVID-19. Not surprisingly, the number of ECMO cases has increased according to The Extracorporeal Life Support Organization Registry and prolonged ECMO support has become more prevalent. It is not uncommon, for example, for patients with severe COVID-19 to be on ECMO support for more than 1 year until recovery or lung transplant. With that being said, complications of bleeding, thrombosis, clot formation in the circuit, and intravascular hemolysis still remain and continue to be major challenges. In summary, in this review, several clinical ECMO experts, including Bartlett, describe the history and advances of ECMO.

Nest, Barcellona and colleagues provide a historical account of oral contraceptives (OCs) and the risk of thrombosis.[11] The development of OCs began in 1921 and continued in subsequent years until the first regulatory approval from the Food and Drug Administration was granted in 1960. However, it took several additional years to realize that OCs presented an important but not frequent risk of venous thrombosis. Several reports ignored this dangerous effect, and only in 1967 did the Medical Research Council clearly state this as an important risk. Later, research led to the formulation of second-generation OCs containing progestins, which nevertheless presented an increased thrombotic risk. In early 1980s, OCs containing third-generation progestins were introduced into the market. Only in 1995 it became clear that these new compounds induced a higher thrombotic risk than that related to the second-generation progestins. It appeared clear that the modulating action of progestins was against the procoagulant activity of estrogens. Lastly, at the end of the 2000s, OCs containing natural estrogens and a fourth-generation progestin (dienogest) became available. The prothrombotic effect of those natural products was not different from that of preparations containing second-generation progestins. Moreover, research over the years has produced much data on risk factors associated with OCs use such as age, obesity, cigarette smoking, and thrombophilia. These findings allowed better assessing the individual thrombotic risk (both arterial and thrombotic) of each woman before offering an OC. Furthermore, research has shown that in high-risk people the use of single progestin is not dangerous as far as thrombosis is concerned. The authors conclude that the OCs' road has been long and difficult, but has led to a great and otherwise unthinkable scientific and social enrichment since the 1960s.

Next, Tufano and Brenner provide an update on the prevention of venous thromboembolism (VTE) in medical patients with thrombocytopenia or with platelet dysfunction, and considering the last 10 years.[12] Current guideline recommendations for primary prophylaxis of VTE are based on randomized clinical trials that usually exclude subjects at a potentially high risk of bleeding complications. For this reason, no specific guideline is available for thromboprophylaxis in hospitalized patients with thrombocytopenia and/or platelet dysfunction. However, except in patients with absolute contraindications to anticoagulant drugs, antithrombotic prophylaxis should be always considered, for example, in hospitalized cancer patients with thrombocytopenia, especially in those with multiple VTE risk factors. Low platelet number, platelet dysfunction, and clotting abnormalities are also very common in patients with liver cirrhosis, but these patients have a high incidence of portal venous thrombosis, implying that cirrhotic coagulopathy does not fully protect against thrombosis. These patients may benefit from antithrombotic prophylaxis during hospitalization. Patients hospitalized for COVID-19 need prophylaxis, but frequently experience thrombocytopenia or coagulopathy. In patients with antiphospholipid antibodies, a high thrombotic risk is usually present, even in the presence of thrombocytopenia; VTE prophylaxis in high-risk conditions is thus suggested in these patients. At variance with severe thrombocytopenia ($<50 \times 10^9$/L), mild/moderate thrombocytopenia ($\geq 50 \times 10^9$/L) should not interfere with VTE prevention decisions. In patients with severe thrombocytopenia, pharmacological prophylaxis should be considered on an individual basis. Aspirin is not as effective as heparins in lowering the risk of VTE. Studies in patients with ischemic stroke demonstrated that thromboprophylaxis with heparins is safe in these patients also during antiplatelet treatment. The use of DOACs in the prophylaxis of VTE in internal medicine patients has been recently evaluated, but no specific recommendation exists for patients with thrombocytopenia. The need for VTE prophylaxis in patients on chronic treatment with antiplatelet agents should be evaluated after assessing the individual risk of bleeding complications. Finally, the selection of patients who require postdischarge pharmacological prophylaxis remains debated. New molecules currently under development (such as the inhibitors of factor XI) may contribute to improve the risk/benefit ratio of VTE primary prevention in this setting of patients.

The last full-length review follows, by the authorship team of Volod, Colon, and Arabía, reflecting on the search for the holy grail of artificial hearts.[13] The total artificial heart (TAH) has a long and rich history, being the product of decades of innovation, hard work, and dedication. This review examines the history of the TAH, a device that has revolutionized the treatment of end-stage biventricular heart failure. The manuscript also reviews the development of the device from early

concepts to the current state-of-the-art device, the SynCardia TAH, which has been implanted in over 2,000 patients worldwide. The article also discusses the challenges and successes experienced by researchers, clinicians, and patients throughout the development of TAH devices. The authors also discuss the hemostatic alterations in patients implanted with TAH and anticoagulation strategies to decrease associated thromboembolic risks. The article concludes with a look at other novel TAH devices and the future of TAH as an increasingly viable treatment for end-stage heart failure.

Following this is a commentary from Jecko Thachil on Russell viper venom (RVV), representing a historical journey from the bedside to the bench and back to the bedside.[14] Named after Dr. Patrick Russell, the venom represented a clinical challenge for managing patients who experienced snake bite. The venom entered a new chapter when it started to be used to investigate hemostasis in research laboratories, culminating in current use in a variety of laboratory assays—most notable, the dilute RVV time,[15–17] as used to investigate lupus anticoagulant, but also within the activated protein C resistance landscape.[18] Also notable is that RVV has had an interesting comeback to clinical medicine this year. A group from China engineered Staidson protein-0601 (STSP-0601), a factor X activator from RVV and showed that it has the potential to be used as a hemostatic treatment of patients with hemophilia and inhibitors.[19]

The issue then includes some correspondence. First, Goh and colleagues review the condition known as hematohidrosis in 15th Century Renaissance Art and also provide a review of modern literature.[20] Additionally, these historical series of STH get a strong endorsement from Michael Safani,[21] in a fitting final correspondence to this celebratory issue. Finally, as this issue is published in 2024, the issue concludes with a republished paper from the STH vault, on the structure and function of fibrinogen,[22] as well as an accompanying Commentary.[23] The historical paper was the first paper ever published in STH.[24]

As always, I thank the authors of the in-issue contributions, for which marks the third of our historical issues celebrating 50 years of STH, and I look forward to the fourth and final issue in this compilation to publish in late 2024.

Conflict of Interest
None declared.

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