

## Preface

# A Short History of Thrombosis and Hemostasis: Part I (40th Year Celebratory Issue)

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Welcome to a very special issue of *Seminars in Thrombosis & Hemostasis*, the first of two-planned issue compilations that will evolve around the history of thrombosis and hemostasis research, and specifically aiming to celebrate the 40th anniversary of this journal. *Seminars in Thrombosis & Hemostasis* began its life in 1974, and thus 2014 marks its 40th anniversary in press. The founding editor of *Seminars in Thrombosis & Hemostasis*, Eberhard F. Mammen (–Fig. 1), passed away in 2008, as announced in this journal at that time,<sup>1–3</sup> and as marked at that time with an issue aimed to celebrate his life and contribution to this field.<sup>4</sup>

Some interesting statistics regarding *Seminars in Thrombosis & Hemostasis* can be summarized for the interested readers. The journal began publishing in 1974 with just two issues per year, for a grand total of 210 pages published in that year. This grew to four issues, with a total of 408 pages in the next year. The journal continued publishing four issues per year for the next two decades, with an average 400 pages, plus the occasional supplement, until 1996, where it grew to six issues per year. *Seminars in Thrombosis & Hemostasis* then published an average of just over 600 pages in six issues per year for the next decade until 2006, where it again grew, this time to eight issues per year. The journal has continued to publish eight issues per year, with an average of nearly 900 pages per year from that time. Last year, 2013, we published 973 pages of text. Perhaps, 2014 will be the year that we break the 1,000 page barrier! This data are summarized in –Fig. 2. The other main metric of possible interest to our readership is the journal's Impact Factor, which is shown in –Fig. 3, and which has essentially increased over the years, although an occasional dip has been observed, as may be anticipated from time to time.

In a fitting tribute to the founding editor of *Seminars in Thrombosis & Hemostasis*, we begin this celebratory issue with a contribution by Kubisz et al on the topic of “Sticky platelet syndrome” (SPS),<sup>5</sup> a topic that was close to Eberhard

Mammen's heart, as evidenced by both within the noted contribution as well as by the addition within the Appendix to this issue of a reproduction of an article written by Mammen on this topic in this journal in 1999.<sup>6</sup> SPS is a thrombophilic platelet disorder with familial occurrence and autosomal dominant trait, characterized by increased in vitro platelet aggregation to low concentrations of adenosine diphosphate and/or epinephrine. The clinical manifestations of SPS include arterial thrombosis, pregnancy complications (fetal growth retardation and fetal loss), and venous thromboembolism. Although considered a rare thrombophilic disorder, the authors believe that SPS can relatively often be identified as a cause of unexplained thrombosis, particularly among patients with arterial thrombosis, such as stroke. The history of SPS began in 1983 when Holliday recognized it to be a distinct disorder and SPS was further characterized in the 1980s and 1990s, with Mammen and Rodger Bick providing key findings. Although now recognized for over 30 years, significant issues, namely the syndrome's etiology, inheritance, and epidemiology, remain unclear, in part, because of the lack of investigation and general under-recognition, and in part, because of controversy regarding its very existence.

We continue the exploration into adverse prothrombotic pathophysiology in the next chapter, which explores the diagnostics of acute myocardial infarction (MI) from a historical perspective. In this article, Cervellin and Lippi tell us the tale of “MIs and Men,”<sup>7</sup> which appears to have rather a long history, as atherosclerosis was found to be present in humans several centuries before modern civilization and the subsequent identification of the most common risk factors. It was only at the end of the 19th century and the beginning of the 20th century that physicians acknowledged that MI was essentially caused by coronary thrombosis, as subsequently confirmed at autopsy. With the first description of the electrocardiogram in the 1910s and 1920s, the history of modern MI diagnostics then began. Additional important

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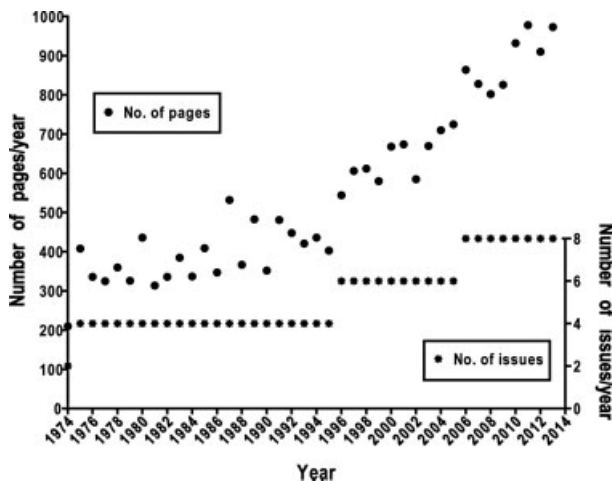
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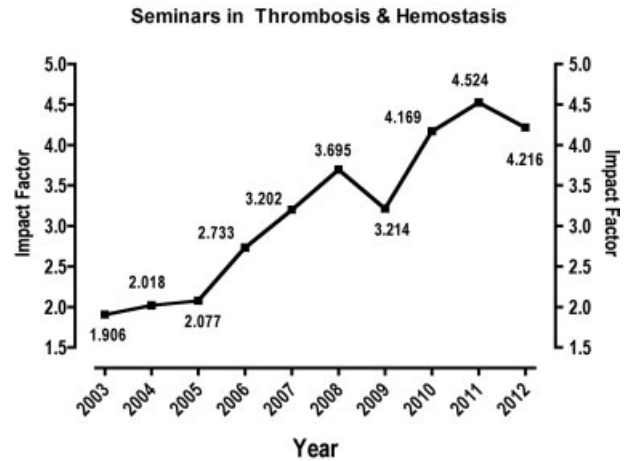
**Fig. 1** Eberhard F. Mammen (1930–2008).

discoveries followed, including radiography, echocardiography, computed tomography, and magnetic resonance imaging of the heart. The development of commercial immunoassays for the measurement of cardiac troponin I and troponin T represented major breakthroughs at the dawn of the third millennium, and these tests now represent the cornerstones for identifying myocardial injury.

The next chapter from Turner et al weaves a more modern tale of linkages that may help to explain enigmatic clinical problems related to thrombotic microangiopathies, including cases of refractory thrombotic thrombocytopenic purpura (TTP), TTP associated with only mild, modest deficiencies of ADAMTS-13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13), the provocation (or exacerbation) of acute episodes in patients with the atypical hemolytic uremic syndrome, and thrombosis in paroxysmal nocturnal hemoglobinuria.<sup>8</sup> The authors report on newly identified molecular linkages between von Wille-



**Fig. 2** *Seminars in Thrombosis & Hemostasis*: number of issues/year and number of printed pages/year, from its birth in 1974 until 2013.



**Fig. 3** *Seminars in Thrombosis & Hemostasis*: Journal Impact Factor from 2003 to 2012.

brand factor (VWF) and the alternative complement pathway (AP) that may be involved in this pathophysiology. Importantly, endothelial cell (EC)-anchored ultra-large (UL) VWF multimeric strings function as an activating surface for the AP. C3 (in active C3b form) binds to the EC-anchored ULVWF strings and promotes the assembly of C3bBb (C3 convertase) and C3bBbC3b (C5 convertase). Moreover, recent findings have also demonstrated that complement factor (F) H performs a dual role: (i) participating in regulation of the AP by binding to EC-anchored ULVWF strings and (ii) functioning as a reductase to decrease the size of soluble VWF multimers. Thus, pathophysiological events that adversely affect FH's ability to moderate VWF activity may explain some of the historically difficult to explain findings. Readers of this journal may note that this contribution is coauthored by Joel Moake, a leading and long-term researcher in the field of hemostasis and thrombosis, and perhaps best known for his pioneering work in the field of TTP, including the initial recognition of the abnormal composition of VWF multimers in the plasma of patients with TTP,<sup>9</sup> which in time helped explain the pathophysiology of the disorder and furthermore the clinical efficacy of plasma therapy.<sup>10</sup>

The next chapter by Favaloro retains the link to VWF, but turns our attention to deficiencies and defects of this adhesive protein leading to von Willebrand disease (VWD).<sup>11</sup> As outlined therein, this particular piece is dedicated to a past mentor, Jerry Koutts,<sup>12</sup> and in a fitting tribute to his memory has borrowed heavily from an article that he penned for *Seminars in Thrombosis & Hemostasis* a few years ago.<sup>13</sup> We also give tribute here to the founding editor of *Seminars in Thrombosis & Hemostasis*, Eberhard Mammen, by reproducing in the appendix to this issue, an article that he penned on VWD for this journal in 1975,<sup>14</sup> at a time that much was being learnt about this complex bleeding disorder. VWD was originally identified by Erik Adolf von Willebrand, who in early 1924 investigated a large family suffering from a bleeding disorder that seemed to differ from hemophilia. Erik von Willebrand undertook some initial laboratory investigations

to conclude the involvement of a plasma factor, the lack of which prolonged the bleeding time, but failed to impair coagulation times and clot retraction. By the end of the 1960s, VWD was accepted as a combined deficiency of FVIII and another plasma factor responsible for normal platelet adhesion. Just how these two functions related to one another was less clear and the diagnostic tests available at the time were poorly reproducible, cumbersome, and unreliable; thus, VWD was poorly delineated from other coagulation and platelet disorders. The early 1970s saw a revolution in diagnostics when ristocetin was identified to induce platelet aggregation, and this formed the basis of the first consistent and reliable VWF “activity” test, permitting quantification of the platelet adhesive function missing in VWD. Concurrently, immunoprecipitating techniques specific for VWF were defined, and the application of such technologies permitted a clearer understanding of both VWF and VWD heterogeneity. This work helped to resolve some confusion at that time related to the perception that VWF contained both adhesive activity, which promoted platelet functionality, as well as coagulation activity, which is now ascribed to FVIII. Here, readers may note that Jerry Koutts was one of the early pioneers who provided evidence that VWF and FVIII comprised separate molecules.<sup>15–17</sup> The lack of appreciation at that time for the relationship between these linked but separate molecules is further highlighted within the Appendix of this issue in another historical reproduction from Irwin in 1975.<sup>18</sup> Returning to the article by Favaloro, the 1970s onward saw continued exploration of the structure and function of VWF, which contributed greatly to the understanding of platelet physiology, ligand receptor interaction, and pathways of cellular interaction and activation. Recently, additional assays evaluating other functions of VWF, including collagen binding, platelet glycoprotein Ib binding, and FVIII binding, have improved the diagnosis of VWD. In summary, this narrative review explores the history of phenotypic VWD diagnostics, with a focus on laboratory milestones from the past as well as highlighting recent and ongoing innovations, and ongoing challenges and possible solutions.

Next, Franchini and Mannucci review the history of the other common bleeding disorders, hemophilias A and B, as respectively related to defects and/or deficiencies in FVIII and FIX.<sup>19</sup> The inclusion of this chapter in this issue of *Seminars in Thrombosis & Hemostasis* holds great personal pride because I consider the corresponding author of this article, Pier Mannuccio Mannucci, to be one of the fathers of modern hemostasis research. Indeed, we are also proud to include within the Appendix of this issue a reproduction of an article published on hemophilia in this journal in 1992,<sup>20</sup> and in which Mannucci was a collaborator and co-author. The lead author on that particular article was Carol Kasper, another well-known name in hemophilia research, and who otherwise will be remembered for providing the original description for the Bethesda assay,<sup>21</sup> as still used today for assessing factor inhibitors.<sup>22,23</sup> As outlined by Franchini and Mannucci, the history of hemophilia dates back to the second century AD, but a modern description of hemophilia appeared only at

the beginning of the 19th century. The discovery of “anti-hemophilic globulin” in the middle of the 20th century paved the way to the production of cryoprecipitate and then of FVIII and FIX concentrates. Barring the tragic consequences on the hemophilia community of the transmission of blood-borne viruses by non-virus-inactivated factor concentrates during the 1970s and 1980s, first plasma-derived and later recombinant products revolutionized the treatment of hemophilia through the widespread adoption of home treatment and prophylaxis regimens, which improved the quality of life and life expectancy of persons with hemophilia dramatically during the past decade. In summary, this historical article reviews the most important stages of the management of hemophilia from the past century up to present time.

This issue of *Seminars in Thrombosis & Hemostasis* then turns our attention to other components of hemostasis/thrombosis as well as to other associated pathophysiologies. First among these is the contribution by another well-known contributor to the field of hemostasis, Alan Nurden, who takes us on another historical journey, this time related to platelets and their major membrane glycoprotein (GP) receptors.<sup>24</sup> As he eloquently explores, the search for the components of the platelet surface that mediate platelet adhesion and platelet aggregation began for earnest in the late 1960s when electron microscopy demonstrated the presence of a carbohydrate-rich, negatively charged outer coat that was then called the “glycocalyx.” Progressively, electrophoretic procedures were developed that identified the major membrane GPs that constitute this layer. Studies on inherited disorders of platelets later permitted the designation of the major effectors of platelet function, beginning with the discovery in his laboratory that platelets of patients with Glanzmann thrombasthenia, an inherited disorder of platelet aggregation, lacked two major GPs. Subsequent studies established the role for the GPIIb-IIIa complex (now known as integrin  $\alpha_{IIb}\beta_3$ ) in binding fibrinogen and other adhesive proteins on activated platelets and the formation of the protein bridges that join platelets together in the platelet aggregate. This was quickly followed by the observation that platelets of patients with the Bernard-Soulier syndrome, with macrothrombocytopenia and a distinct disorder of platelet adhesion, lacked the carbohydrate-rich, negatively charged, GPIb. It was then shown that GPIb, through its interaction with VWF, mediated platelet attachment to injured sites in the vessel wall. What follows is his personal reflection on the studies that were performed in those early pioneering days. I am indebted to Alan Nurden, a long-term worker in this field, for this important contribution.

Next, we take a detour to the world of fibrinolysis and beyond, where Hau Kwaan, a Senior Editor of *Seminars in Thrombosis & Hemostasis*, and another long-time worker in this field, takes us on a personal journey into the multifaceted and complex role of the plasminogen-plasmin (P-P) system.<sup>25</sup> In summary, this article reviews the history of the remarkable development of our knowledge on fibrinolysis. Great advances have been made in our understanding of the fibrinolytic system, from the initial discovery of proteolysis of fibrin by plasmin to the current knowledge that the P-P

system is composed of several serine proteases and their inhibitors (serpins), and it is involved in many physiological functions, including embryogenesis, cell migration, and wound healing. The P–P system also plays an important role in the pathogenesis of many diseases, including atherosclerosis, obesity, cancer, and even autoimmune disorders and neuronal degeneration. Knowledge of the role of participants of the P–P system in cancer enables their potential utility as prognostic factors. Therapeutic use of various forms of proteases derived from the P–P system have also been employed as thrombolytic agents, and small molecules designed to inhibit many of the components of the P–P system are now available for evaluation in clinical trials aimed to treat various disorders associated with derangement of this system.

The next chapter, by Girolami et al takes us on yet another voyage of discovery, this time discussing the old and the new in prekallikrein deficiency.<sup>26</sup> Prekallikrein is one of the clotting factors involved in the contact phase of blood. Prekallikrein has an important historical role because its deficiency state represents only the second instance of a clotting defect without presenting bleeding manifestations, the first one being FXII deficiency. Prekallikrein deficiency is a rare clotting disorder, and only 11 patients have thus far been investigated by molecular biology techniques. In this article, the authors briefly review some of the history around prekallikrein and its deficiency state, but primarily focus on new findings, in particular presenting recent data on a newly identified family from Argentina suffering from prekallikrein deficiency. Two patients are homozygous whereas other family members are heterozygous. Prekallikrein activity and antigen are 1% of normal in the homozygotes and around 60 to 70% of normal in the heterozygotes. As expected, all patients are asymptomatic of bleeding or thrombosis presentations. However, the two homozygotes showed essential hypertension. The prekallikrein deficiency in this family is due to a new mutation (Arg541Gln) in exon 14, and this defect interestingly segregates together with a known polymorphism, Asn124Ser, in exon 5. The significance of the presence of hypertension in the two homozygotes is primarily discussed in view of the extra coagulation effects of prekallikrein on vasodilation, vessel permeability, and the control of blood pressure. Structure function analysis indicates that the substitution of Arg with Gln probably impedes the transmembrane diffusion of the molecule, which therefore cannot be secreted in the homozygotes. The presence of hypertension in patients with prekallikrein deficiency has been previously reported in some but not all patients with prekallikrein deficiency. Future research activities are likely to concentrate on the effect of prekallikrein and other contact phase factors on the vascular system, rather than on the hemostasis and contact pathway systems.

The final contribution to this issue of *Seminars in Thrombosis & Hemostasis*, by Targher et al, is on hemostatic and fibrinolytic abnormalities in the under-recognized condition called polycystic ovary syndrome (PCOS).<sup>27</sup> Although under-recognized, PCOS is the most common form of anovulatory infertility, affecting up to 10% of women of reproductive age.

This syndrome was first described in 1935 when American gynecologists Stein and Leventhal associated the presence of ovarian cysts with anovulation, obesity, and hirsutism. For many years, the effects of PCOS on coagulation and fibrinolysis have remained largely unexplored. This timely review accordingly summarizes current knowledge on the effects of PCOS on coagulation and fibrinolysis, and the putative mechanisms by which PCOS may contribute to the development of coagulation and fibrinolytic disorders. Till date, there is relatively strong evidence suggesting that PCOS is associated with increased platelet aggregation and decreased plasma fibrinolytic activity. However, whether these hemostatic disorders are linked to the abnormal hormonal system in PCOS remains to be elucidated. Moreover, it should be emphasized that PCOS is a heterogeneous endocrine condition, and that the number of published studies till date is limited, the sample size of these is typically small, and the selection of control subjects not always appropriate. Future well-designed studies on larger cohorts of carefully characterized PCOS patients are needed to provide more comprehensive information on both the condition, and its relationship with hemostasis and prothrombotic tendency.

As always, I thank all the authors of this issue of *Seminars in Thrombosis & Hemostasis* for their original and comprehensive contributions. However, I also especially thank the contributing early pioneers, assuming they will forgive me for calling them so, and namely Pier Mannuccio Mannucci, Joel Moake, Alan Nurden, Hau Kwaan, and Antonio Girolami. For interested readers, Hau Kwaan's original publication in PubMed is dated 1956,<sup>28</sup> and Antonio Girolami's 1959.<sup>29</sup> Pier Mannuccio Mannucci, Joel Moake, and Alan Nurden were introduced to the field a little later, with initial contributions respectively dated 1963,<sup>30</sup> 1970,<sup>31</sup> and 1974.<sup>32</sup> Also outstanding is that these five pioneers have contributed a total of nearly 2,700 publications to the literature according to PubMed.

Nevertheless, as always I would also thank the other contributors, perhaps reflecting the emerging talent in this field, and in particular my sometimes collaborators and frequent contributors to *Seminars in Thrombosis & Hemostasis*, namely Giuseppe Lippi and Massimo Franchini. Finally, as noted in the separate dedication to this issue of *Seminars in Thrombosis & Hemostasis*, I am sure that past pioneers and mentors in the field will have the unending gratitude of the entire thrombosis/hemostasis research community.

I hope that the readership of this journal finds the entire issue of considerable interest, and I look forward to the next installment of the history of thrombosis and hemostasis to be presented in this journal in a few months' time.

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