Fathers of modern coagulation

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The best contribution we could make for the 50th anniversary of *Thrombosis and Haemostasis*, the former official journal of the International Society on Thrombosis and Haemostasis (ISTH), was to recount the history of some of the people who opened the door to major advances in coagulation research. Many of these people were among the first to contribute articles to the Journal which was initially named *Thrombosis et Diathesis Haemorrhagica*.

The story begins in the early 1950s shortly after the end of the second World War. In the late 1940s through the 1950s, scientists from several nations made major breakthroughs in our understanding of the mechanism of coagulation. This was largely due to the discovery of several new clotting factors. In 1945 the major clotting theory rested on that of Morawitz as shown in Figure 1 (1). Prothrombin was known to be converted to thrombin in a reaction that required both thromboplastin (now know as tissue factor) and platelets. In addition, in 1935, Patek and Taylor described antihaemophilic factor as a component of plasma lacking in patients with classic haemophilia (2), and Kenneth Brinkhous and his colleagues at Iowa showed that this factor was necessary for the rapid conversion of prothrombin to thrombin. Thrombin was also known to convert fibrinogen to fibrin. Also, in 1944, Kenneth Robbins described fibrin stabilizing factor, now known as factor XIII (3). After these observations, things began to change rapidly as new factors were discovered. The trouble was that each new factor was given several names and even some of the older known factors had several names as shown in Table 1. Looking at the different names for the same substance, it is easy to understand how nomenclature could affect ones interpretation of results, and because of this an international committee was formed in 1954 in an effort to establish a common nomenclature for the clotting factors. This committee was first termed "The International Committee on Nomenclature of Blood Clotting Factors". The first meeting of this Committee was held in Basel and subsequent meetings were held in Copenhagen, Boston and Rome.

Figure 2 shows the members of the Committee who attended the Rome meeting in 1958. It was at this meeting that most of the members agreed to use Roman numerals for the clotting factors. The legend of Figure 2 gives the names of those who were present at the meeting. Some members, namely, Gwynne Macfarlane, Rosemary Biggs, Oscar Ratnoff, and Paul Aggeler were apparently absent from the meeting, but their influence was felt. While all of the members of the Committee in Figure 2 are shown with smiles on their faces, the discussions leading to decisions on nomenclature were often heated and forceful (4).

Most of the men shown in Figure 2 are legendary for their contributions to the field of coagulation. H. Jensen (#1), who worked at the US Army Research Labs, studied the proteases in coagulation looking at the balance between proteolytic action (thrombin generation and fibrinolysis) and anti-proteolytic action. Walter Seegers (#2) had isolated prothrombin and had discovered several other vitamin-K-dependent factors in his prothrombin preparation which he called "auto" prothrombins because he viewed them as being derived from prothrombin. His obsession with the autoprothrombin nomenclature probably obscured much of his original discoveries, since it appears that he actually characterized what later came to be known as factor IX, factor X, factor Xa, and activated protein C, among others. He also called Owren's proaccelerin (factor V) "AC (accelerator) globulin". Erik Jorpes (#3), from the Karolinska Institute in Sweden, was interested in all the clotting proteins but was particularly engaged by the actions of heparin. Dr. Jorpes also recruited Birger and Magareta Blombäck who worked on both fibrinogen and factor VIII. Fritz Koller (#4), who discovered factor X with Francois Dukert (5), was one of the first Editors of the Journal. Erwin Deutsch (#5), in addition to his work on anticoagulants, was the main person who started the journal *Thrombosis et Diathesis Haemorrhagica*, the journal that later became *Thrombosis and Haemostasis* which was the official journal of the ISTH for several years. Jean-Paul Soulier (#6) developed the so-called PPSB (Prothrombin-Proconvertin-Stuart factor-antihaemophilic factor B) fraction used for treatment of haemophilia B. Karl Lenggenhager (#7), in addition to work on haemophilia, performed early studies on both platelets and antithrombin. Paul Owren (#8) discovered factor V, which he called proaccelerin, in 1944 during the Nazi occupation of Norway, but his publication was delayed until 1947 (6). Louis B. Jaques (#9)

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from Canada was an expert in heparin and helped confirm that heparin, while it had a weak antithrombotic effect alone, worked with another plasma protein to exert its primary effect. Marc Verstraete (#10) was involved in clinical trials in coagulation and headed the group at the University of Leuven. In addition to his work in haemophilia, Dr. Verstraete conducted numerous studies into different anticoagulants and monitoring of anticoagulants. Armand Quick (#11) developed the prothrombin time test and also knew that other, as yet unknown, plasma and serum factors were necessary for coagulation to proceed normally. Benjamin Alexander (#12) was the first to describe SPCA (Serum Prothrombin Conversion Accelerator, factor VII) deficiency. R. B. Hunter (#13) was expert in vitamin K antagonists; his work suggested that factors other than prothrombin were also reduced with vitamin K antagonists and that this reduction might play an important role in the anticoagulant effect. Irving Wright (#14) was the first Secretary General of the Committee and as a clinician was one of the first to use warfarin and heparin as therapy for thrombosis. Kenneth Brinkhous (#15) and his colleagues at the University of Iowa performed much of the early work on factor VIII; with his Chapel Hill colleagues he developed the partial thromboplastin time test in 1953 (7). In addition, Brinkhous and colleagues developed one of the first purified factor VIII fractions, later produced by Baxter Laboratories as "Hemophil". Tage Astrup (#16) from Denmark was an expert in fibrinolysis and performed much of the early work on tissue plasminogen activator. Pietro de Nicola (#17) also studied factor VII and helped to identify it as a separate protein (and activity) from prothrombin.

Although not shown in Figure 2, Alfredo Pavlovsky from Argentina was one of the first to recognize that blood from one phenotypical haemophiliac could correct the clotting time of a similar phenotypic patient; but he did not recognize that he had observed that blood from a patient with classic haemophilia would correct the clotting time of a patient with haemophilia B (8). This

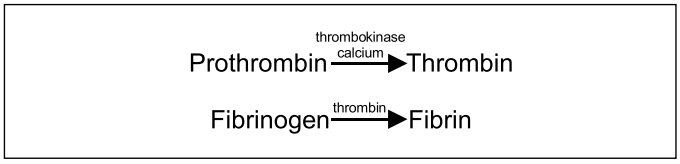

Figure 1: Clotting theory of P. Morawitz.

Table 1: Blood clotting factors and their previously used names.

Factor	Common name(s)
I	Fibrinogen
II	Prothrombin
V	Labile Factor Proaccelerin accelerator (AC-) globulin
VII	Serum Factor Stable Factor Proconvertin Serum Prothrombin Conversion Accelerator (SPCA) Cothromboplastin Autoprothrombin I
VIII	Hemophilia A factor Antihemophilic Globulin (AHG) Antihemophilic Globulin A Antihemophiliac Factor Facteur Antihemophilique A Plasma Thromboplastic Factor Plasma Thromboplastic Factor A Thromboplastic Plasma Component Thromboplastinogen Prothrombokinase Platelet Cofactor Plasmakinin Thrombokatalysin
IX	Hemophilia B Factor Antihemophilic Factor B Christmas Factor Plasma Thromboplastin Component Autoprothrombin II Beta cothromboplastin Pavlovsky Factor
X	Stuart Factor Prower Factor Stuart-Prower Factor Autoprothrombin III
XI	Hemophilia C factor Plasma Thromboplastin Antecedent (PTA)
XII	Hageman Factor Contact Factor
XIII	Fibrin Stabilizing Factor Laki-Lorand Factor Protransglutamidase Robbins Factor

Figure 2: Members of the The International Committee on Nomenclature of Blood Clotting Factors who attended the Rome meeting in 1958. #1: H. Jensen, #2: Walter Seegers, #3: Erik Jorpes, #4: Fritz Koller, #5: Erwin Deutsch, #6: Jean-Paul Soulier, #7: Larl Lenggenhager, #8: Paul Owren, #9: Louis B. Jaques, #10: Marc Verstraete, #11: Armand Quick, #12: Benjamin Alexander, #13: Robert B. Hunter, #14: Irving Wright, #15: Kenneth Brinkhous, #16: Tage Astrup, #17: Pietro de Nicola (photo kindly provided by the ISTH).

remained for Paul Aggeler and his colleagues in California and for Biggs and Macfarlane in England (9, 10). Also, Oscar Ratnoff is not shown in this photo, though he had discovered Hageman factor/factor XII in 1955. Their photographs are shown in Figure 3.

Not all of the fathers of modern coagulation initially agreed with the Roman numeral nomenclature. Outstanding holdouts against the nomenclature were Walter Seegers and Oscar Ratnoff, though they continued to make major contributions to our knowledge of coagulation.

The initial International Committee on Nomenclature of Clotting Factors was changed in 1959 to the International Committee on Clotting Factors and later, in 1964 the name of the Committee was again changed to The International Committee on Hemostasis and Thrombosis. Committee activities were enlarged to deal not only with nomenclature but also with standards for assays and purification methods and other practical matters. Beginning in 1959, Committee activities were usually accompanied by a scientific session but international congresses as we know them today were not yet started. In addition, membership in the Committee was "elective" and since there were an increasing number of people in the scientific community who became interested in coagulation, the Committee was increasingly viewed as "elitist". As a result, in 1969 the ISTH was formed, largely due to the influence of Dr. Sol Sherry. For a while the Committee remained separate from the Society, although they met together. In 1979, largely due to the influences of Victor Marder, Sol Sherry, Ken Brinkhous and Harold R. Roberts, the ISTH and the International Committee on Thrombosis and Haemostasis were completely amalgamated. The Committee became known as the Scientific and Standardization Committee (SSC) which is now the "working arm" of the ISTH that deals with standards and methods and other practical matters of coagulation. The SSC works closely with regulatory bodies in North America, Europe, Asia, Australia and South America. The ISTH is now the foremost international forum for investigators interested in thrombosis and haemostasis. It was formed in large measure from the efforts of those shown in Figures 2 and 3.

In 1964, Oscar Ratnoff and Earl Davie, at the same time as R. Gwyn Macfarlane, proposed an organizational scheme for the coagulation factors. All modern views of coagulation mechanism derive from these schemes, made possible in part by the order brought to the chaos of coagulation factors by "The International Committee on Nomenclature of Blood Clotting Factors". Thus the work of these outstanding pioneers created the framework for the subsequent explosion of knowledge about coagulation. This framework provided the basis for the development of therapies for haemophilia: first purified factors VIII and IX, then highly purified factors, followed by recombinant proteins, leading to the ongoing studies with gene therapy that hold the promise of a cure. This framework also provided the basis for targeting anti-thrombotic drugs with ongoing studies directed to anti-thrombotic agents with minimal risk of bleeding. Finally, the work of these leaders demonstrates how international cooperation and pooling of knowledge, even in the face of strong personalities and occasional disagreements, can advance our knowledge and understanding of science.

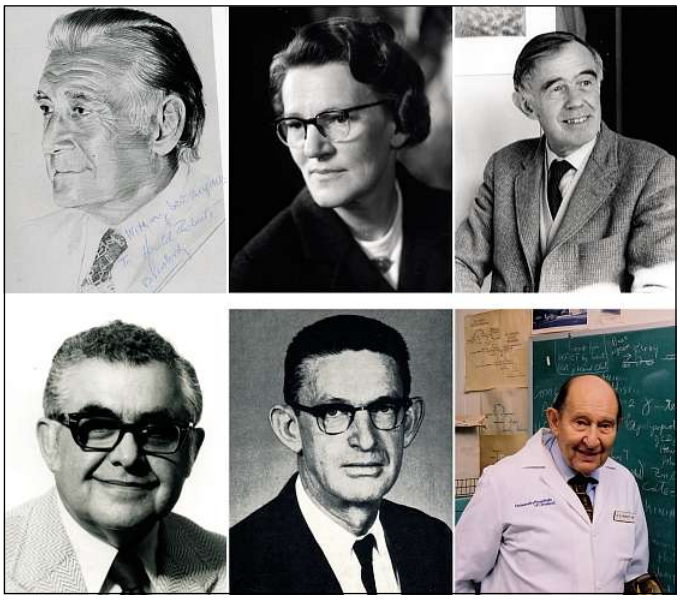

Figure 3: Alfredo Pavlovsky, Rosemary Biggs, Robert Macfarlane, Kenneth Robbins, Paul Aggeler and Oscar Ratnoff (from top left to bottom right; photos kindly provided by the ISTH).

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