

## Anniversary Issue Contribution

# Thrombosis and haemostasis, where clinical and basic science meet

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The journal *Thrombosis et Diathesis Haemorrhagica* was founded fifty years ago, at a time when coagulation laboratories were being set up in many university departments around the world. The reason for the latter was two-fold; on the one hand, new congenital clotting disorders were continuously being discovered, and their differential diagnosis required laboratory investigation; on the other hand, the notion that oral anticoagulants could be beneficial following a myocardial infarction had just been introduced by Irving Wright (1, 2) among others; laboratories were needed to monitor this new form of therapy. In addition, open heart surgery was at its beginning, and expertise was needed to monitor heparin anticoagulation and its reversal by protamine.

Many of the clotting factors, starting with factor V and upwards, were discovered by clinician-scientists, from careful study of the plasma of patients with a congenital clotting disorder; when the plasma of two such patients was mixed, and the clotting process was not corrected, the patients were defined as having the same clotting factor deficiency; if the defect was corrected by mixing, it was assumed that the patients had different defects, so that they could substitute for each other; in this way new clotting factors were identified. Clotting factors were further defined by whether the correcting activity was present or absent in normal serum or in barium sulfate treated plasma, etc.

It should be emphasized here that most clotting factors were discovered in this way by careful patient studies in the 1950s, and that it took another 20 years before they were adequately purified

and characterized biochemically. This early scientific development remains perhaps one of the most dramatic examples of how detailed patient studies can contribute to forwarding basic knowledge. On the other hand these clinical discoveries often occurred simultaneously in different parts of the world, and each clinician-scientist introduced a new name for his/her newly discovered clotting factor (either the patient's name or the presumed physiological role, e.g. "plasma thromboplastin antecedent"). As a result, a "Tower of Babel" situation emerged, different coagulation schools using their own personal nomenclature to define a specific entity (3).

It is in this setting of explosive increase in knowledge and confusion that Professors Erwin Deutsch, Rudolf Jürgens and Fritz Koller had the brilliant insight to approach Professor Paul Matis and Schattauer Publishers and to convince them to start an international journal specifically oriented towards thrombosis and haemostasis, the international character being emphasized by choosing the Latin title "*Thrombosis et Diathesis Haemorrhagica*". At about the same time, an International Committee for the Nomenclature of Blood Coagulation Factors was set up, and fortunately agreement was gradually reached on a Roman Numeral Nomenclature that we still use today and that allowed to diminish the confusion. Detailed accounts of this committee's deliberations were published in the early issues of *Thrombosis et Diathesis Haemorrhagica*. The International Committee for the Nomenclature of Blood Coagulation Factors eventually evolved into the International Society on Thrombosis and Haemostasis that quite naturally selected *Thrombosis et Diathesis Haemorrhagica* to become the official journal of the Society, while changing its name into *Thrombosis and Haemostasis*.

It was during the exciting period in the late 1950s that Marc Verstraete wished to study the effects of varying the loading doses of different vitamin K antagonists on the various clotting factors that had then been defined. For this purpose, he entered a lecture room for preclinical medical students and asked for some students to volunteer in this experiment (at that time there was no detailed informed consent or ethics committee supervision). This is how I came to know the laboratory for blood coagulation at the University of Leuven. The enthusiasm of those working there was contagious, and so I joined the lab the next vacation as a summer

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student and I have remained linked to it ever since. An older medical student started trying to explain to me the clotting process, but after an hour or so I was completely lost and he decided to put me with his fellow student, the late Professor Antoon Amery, who was studying an apparently simpler enzymatic system, fibrinolysis. This led to my first co-authorship on an international paper, in 1962, in *Thrombosis et Diathesis Haemorrhagica* (4).

Fibrinolysis is another example of an early encounter between clinical and basic science. It had gradually become apparent that the clotting system not only was needed for preventing bleeding, but that fibrin also was involved in vessel occlusion. The concept of fibrinolysis to open up occluded vessels seemed attractive. Already in the early 1960s, Verstraete et al. used the knowledge on fibrinolysis gathered at that stage to provide "proof of principle" that an occlusive arterial thrombus could indeed be lysed enzymatically (5). Marc Verstraete in Leuven together with Jürgen van de Loo in Münster then organized the first multinational, multicenter studies to demonstrate the usefulness of thrombolytic therapy in myocardial infarction (6–7). These efforts by "clotters" were viewed with scepticism, if not with derision, by academic cardiologists, some of whom claimed, until late into the 1970s, that coronary thrombosis is the consequence, not the cause, of myocardial infarction. It is only when coronarographic evidence was obtained that cardiologists suddenly were convinced (8).

Not only in coagulation and fibrinolysis, but also in platelet physiology, has the clinic sometimes driven basic research; Glanzmann's thrombasthenia for the first time illustrated the importance of the platelet glycoprotein IIb/IIIa complex (9); the study of von Willebrand disease has driven the knowledge on the interaction between von Willebrand factor and platelet glycoprotein Ib. On the other hand, physiological or pharmacological observations, such as the inhibition of platelet aggregation by aspirin (10), were also very rapidly applied to patients with vascular disease (11), even before thromboxane A<sub>2</sub> was actually discovered (12); this therefore is another striking example of the early fruitful interaction between basic and clinical science in the

areas of thrombosis and haemostasis. More recent examples abound; the existence of patients with thrombosis and resistance to the anticoagulant effects of activated protein C (13) led to the identification of the factor V Leiden mutation (14); the study of deficient von Willebrand factor cleaving protease in patients with thrombotic thrombocytopenic purpura (15) led to the discovery of congenital or acquired ADAMTS 13 deficiency (16). Undoubtedly the clinic will continue to inspire the researchers. In the other direction, advances in basic science will continue to inspire clinicians to refine their diagnosis and improve their treatments.

At this stage of medical history, expressions such as "translational research", "from bedside to bench and back" have very much become buzz words. As illustrated in this brief paper, scientists involved in thrombosis and haemostasis have a long tradition in translational research. But the isolated clinician-scientist may well be a dying species, his/her role being taken over by multidisciplinary teams. This does not mean that there is no future for clinicians. As example, with the current knowledge of the human genome, new genetic defects are being discovered in protein structure (e.g. congenital defects of glycosylation) or in signal transduction mechanisms, that can lead to a complex phenotype, including a bleeding problem (17–18). Progress in this area will depend on a close interaction between astute clinicians and molecular biologists. Similarly, the increasing use of anticancer or other drugs blocking various signal transduction pathways is likely to affect normal platelet production and behavior, but also vascular function, potentially resulting in new bleeding or thrombotic manifestations. Also in this regard, careful clinical observations will remain essential to identify and perhaps help prevent such complications.

It therefore is obvious that journals devoted to thrombosis and haemostasis should continue to aim at being major means of communication between and an important source of inspiration for both basic and clinical scientists. It was a privilege for me to assist this Journal in these functions by being its Editor-in-Chief between 1993 and 1999, a period during which *Thrombosis and Haemostasis* still was the official journal of the International Society on Thrombosis and Haemostasis.

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