Nomenclature of Blood Clotting Factors

Acceptance by the International Committee on Nomenclature of Four Factors, Their Characterization and International Number

Physicians often accuse basic scientists, chemists and physicists in particular, of using a strange language which on one outside their own subject can understand, but at least the majority of physicists or chemists can understand what others in their own field are talking about. The field of blood coagulation is one in which medical men and biological scientists have created such chaos that they do not even understand what other workers in the field are talking about, far less the clinician or the medical student.

To improve international communications is a worthy object at any time: to do so in the field of clotting factors has proven a task of major difficulty. To bring together the prima donnas not only from different countries but from the same country, hold them together and persuade them of the importance of a simple understandable classification has been the problem of the Chairman of the International Committee. This activity of course has much wider significance than just the field of blood clotting factors and evidence for this wider significance has been the invitation by the National Advisory Heart Council of the United States to the members of this Committee to organize a series of International Conferences within this field and to invite to these conferences young workers of exceptional promise so that they may listen to the discussion and benefit from the contact with their older colleagues from different countries in the world. The Committee therefore is making a major contribution to international communications in medicine and it is hoped that this type of activity will be seen more frequently as the world grows smaller and nations more fully accept the necessity for living and working together.

The story of this Committee's work began at the first International Congress on Thrombosis and Embolism held in Basel in 1954 when the multiple names for identical substances emphasized that the problem of international communication was a serious one in this field. The International Committee for the Standardization of the Nomenclature of Blood Clotting Factors was established.

Twenty-two members from fifteen different countries were initially appointed. The list included the leading workers in the field and most of the factors recently recognized had been discovered by these gentlemen. The first meeting brought into the open the fact that they had to a considerable extent created the problem and they recognized that they had a moral and scientific responsibility towards unravelling it. It became clear that though they had a paternal pride in the names of their choice, without their cooperation and compromise, no progress could possibly be made. The efforts made by the members of the Committee to yield their own strong positions for the common good have been noteworthy.

One of the first decisions made by the Committee was that whatever system of nomenclature was proposed, names should be avoided which implied an action by any factor. The reason for this had become clear when factors which previously had been given names implying function had later proved not to have that function but a different one. It was agreed that symbols should be used to designate blood coagulation factors until ultimately they were defined and identified in physical and chemical terms. However, certain essential physical and chemical data would have to be presented in support of the identity of any factor before the Committee would give it an international symbol.

With further study and negotiation over a three year period, it became evident that only a numerical system fully met these qualifications and since some factors had already received Roman numerals in addition to their names it seemed logical to consider whether Roman numerals would be suitable as the international symbolic code allowing the author freedom to use whichever synonym he wished. Thus, one would write Factor V (pro-accelerin), or Factor V (labile factor). The Roman numeral would be intelligible in any language, including the oriental. The first four factors are widely known by their names and some identified chemically and Roman numerals are perhaps less necessary. They are, Factor I — fibrinogen; Factor II — prothrombin; Factor III — thromboplastin (tissue); Factor IV — calcium. It seems likely that these names will continue in common usage and in fact very few other names have been used for these factors.

One of the great problems facing the Committee was to decide when sufficient evidence was available to justify any factor or activity being assigned a number. It has been agreed as follows:

1. The minimal requirements for characterization of a clotting factor in whole blood, plasma, or serum, shall be valid data on the reproducible effect on storage, adsorbability, inactivation by heating, effect of pH.

Additional chemical data are considered highly desirable if available.

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2. A clinically identifiable state associated with an abnormality in the clotting mechanism shall be regarded as supporting the evidence for the lack or excess of a factor.

3. Methods of assay of physiological properties shall be listed. An appropriate selection of these methods will be considered as minimal for presentation of a factor before the Criterion Committee. In the case of previously undescribed factors the mechanism used for identification shall be clearly described by the author for study and possible acceptance by the Committee.

The Committee proposes to publish in detail elsewhere the criteria on which they have based their recommendation that four further blood coagulation factors should be recognized and assigned international symbols, namely, Factor V, Factor VII, Factor VIII, and Factor IX. The following is, however, a brief summary.

Factor V

Synonyms: Factor V (Owren)
Proaccelerin (Owren)
Labile Factor (Quick)
Plasma Ac-globulin (Ware and Seegers)
Thrombogene (Nolf)
Proprothrombinase (Owren)
Prothrombokinase (Milstone)
PPCF — Plasmin Prothrombin Conversion Factor (Stefanini)
Component A of Prothrombin (Quick)
Prothrombin Accelerator (Fantl und Nance)
Co-Factor of Thromboplastin (Honorato).

Deficiency of this factor results in a hemorrhagic diathesis which is probably inherited and has been described as a parahemophilia or hypoproaccelerinemia. The first case was recognized and described by Owren (1) in a beautiful study carried on under the most adverse conditions due to ware. Several additional cases have since been described. This factor seems necessary for the formation of the prothrombin converting substance in the blood and in tissue extracts. Other interesting properties are fully described in the literature (2, 3, 4).

Factor VII

Synonyms: Factor VII (Koller)
Proconvertin (Owren)

SPCA—Serum Prothrombin Conversion Accelerator
(de Vries, Alexander)
Stabile Factor (Stefanini)
Cofactor V (Owren)
Serozym (Bordet)
Kappa Factor (Sorbye and Dam)
Prothrombinogen? (Quick)
Co-Thromboplastin (Mann and Hurn)
Serum Accelerator (Jacox)
Prothrombin Conversion Factor (Owren)
Prothrombin Converting Factor (Jacox).

Factor VII plays a part in the production of at least three groups of abnormal states as follows: (1) A congenital deficiency may produce hemorrhagic phenomena with purpura and bleeding from the mucous membranes. Many such cases have been described. (2) Acquired deficiency may occur in liver disease, in Vitamin K deficiency, in the immediate neonatal period, and following the administration of prothrombinopenic agents such as the coumarin derivatives used in anticoagulant therapy. (3) Excesses of Factor VII have been found in certain states associated with a high incidence of thromboembolism such as the third trimester of pregnancy. *The level of this substance in the blood is specific.* Deficiency results in a quantitative prolongation of the one stage prothrombin time test. Factor VII accelerates the conversion of prothrombin to thrombin in the presence of tissue thromboplastin, Factor V and Ca. It does not accelerate the interaction of platelet Factor 3 and Factors VIII and IX. It cannot rectify retarded coagulation due to Factor V deficiency. It is not essential for thromboplastin generation in the coagulating of blood. Other interesting properties are fully described in the literature (5, 6, 7, 8, 9).

Factor VIII

Synonyms: Factor VIII (Koller)
Antihemophilic Globulin (Patek and Taylor)
Antihemophilic Globulin A (Cramer)
AHF-Antihemophilic Factor (Brinkhous)
PTF-Plasma Thromboplastic Factor (Ratnoff)
Plasma Thromboplastic Factor A (Aggeler)
TPC-Thromboplastic Plasma Component (Shinowara)
Facteur Antihémophilique A (Soulier)
Thromboplastinogen (Quick)

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Prothrombokinase (Feissly)
Platelet Cofactor I (Johnson)
Plasmokinin (Laki)
Thrombokatalysin (Lenggenhager).

Factor VIII deficiency represents the classical hemophilia A which is well known as the hereditary hemorrhagic disease which occurs almost exclusively in males, but which is female sex-linked. The degree of Factor VIII deficiency varies from patient to patient. Hemorrhage occurs in any tissues following minor injuries and is frequently very serious. Factor VIII enters into the early stages of coagulation with Factor IX and Ca to produce an intermediate product which reacts with platelet Factor 3. The result of this reaction in the presence of Factor V is a very active agent in prothrombin conversion. It is essential in the formation of blood thromboplastin. A deficiency (1) prolongs the clotting time; (2) diminishes the thromboplastin formed; (3) diminishes the prothrombin conversion (10, 11).

Factor IX

Synonyms: Christmas Factor (Biggs and Macfarlane)
Factor IX (Koller)
PTC—Plasma Thromboplastic Component (Aggeler)
Antihemophilic Globulin B (Cramer)
Plasma Thromboplastic Factor B (Aggeler)
Plasma Factor X (Shulman)
Facteur Antihémophilique B (Soulier)

Factor IX deficiency produces hemophilia B or Christmas Disease, named after the now famous patient of Biggs and Macfarlane. This is usually a severe hemorrhagic disorder resembling hemophilia A and inherited in the same way. Studies of this disorder led to the discovery of Factor IX. Factor IX, like Factor VIII, is essential for the formation of intrinsic blood thromboplastin. It probably enters into the reactions leading to the formation of this thromboplastin forming with Ca and Factor VIII an intermediate product which then reacts with platelet Factor 3 and Factor V. It influences primarily the amount of thromboplastin formed and not the rate of its generation (12, 13).

New Factors under Consideration

A number of additional plasma and serum factors have been described by various workers who believe they have established that they play a role in

physiological clotting of blood. These factors are now under study by the Committee and if the evidence indicates that the claims are valid they will be asiggned a Roman numeral.

This ultimate contribution of this Committee to medical understanding and education will depend on the willingness of educators, editors and authors to adopt this system in their day to day efforts to create the medical thinking and literature of the future.

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