

Historical Review

SIX CHARACTERS IN SEARCH OF AN AUTHOR: THE HISTORY OF THE NOMENCLATURE OF COAGULATION FACTORS

'Quando i personaggi sono vivi, vivi veramente davanti al loro autore, questo non fa altro che seguirli nelle parole, nei gesti....'. Luigi Pirandello: Sei personaggi in cerca d'autore (Nobel Laureate for Literature, 1934)

Our knowledge of the blood coagulation system has expanded tremendously in the last 60 years. Many of the coagulation factors were identified through the detailed study of individual patients with a clear hereditary bleeding tendency. However, it became apparent by the mid-1950s that a unified nomenclature was desirable because many of the coagulation factors had been named independently by several groups of workers who studied different properties and who initially thought that they had discovered different factors. An international committee was, therefore, established in 1954 with the aim of harmonizing the nomenclature of the various factors. Roman numerals were assigned at various meetings of this committee held between 1955 and 1963. The current nomenclature is not entirely satisfactory, and perhaps the time has now come for a complete revision in the light of recent insights into the complex mechanism of blood coagulation.

INTRODUCTION

This is primarily an account of how the current nomenclature of the blood coagulation factors came into being, but it is also the more personal story of six patients whose names are still associated with several important haemostatic proteins: Christmas (factor IX), Stuart and Prower (factor X), Hageman (factor XII), Fletcher (prekallikrein) and Fitzgerald (high-molecular-weight kininogen). In the modern era of evidence-based medicine, only the results of large randomized and controlled trials and meta-analyses seem to command respect and credibility. It can be difficult in this intellectual climate to appreciate that humble case reports, usually banished to the last pages of modern journals, have often been the source of great advances in the past. In particular, many of the advances in coagulation medicine have come from case reports from physicians who have written about patients encountered in their busy everyday practice, patients in whom they recognized something

special or unusual, and from whom they have learnt important clinical and scientific lessons.

By the middle of the 19th century, a simple theory of blood clotting had evolved which was based upon the work of, among others, Andrew Buchanan (1798–1882), Olaf Hammersten (1841–1912), Alexander Schmidt (1831–1894) and Paul Morawitz (1879–1930). The theory envisaged the involvement of just four factors: thrombokinase (or thromboplastin) derived from damaged tissues or cells, prothrombin, fibrinogen and calcium. Thromboplastin was released into the circulation at the site of tissue damage and reacted with prothrombin in the presence of calcium to form thrombin, which in turn reacted with fibrinogen to form fibrin. By the 1940s, it became clear that other proteins were involved. One of the first relevant observations was made by Armand Quick (1894–1977) who had developed the one-stage prothrombin time. He noted that the prothrombin time of plasma lengthened on storage but was corrected by the addition of fresh plasma derived from a patient being treated with a coumarin anticoagulant (dicoumarin) (Quick, 1943). This observation led Quick to infer that there was a labile factor in plasma that was destroyed on storage, as well as a stable factor, the level of which was reduced by coumarins. In 1947, Paul Owren (1905–1990) published the details of work carried out at the University of Oslo for his doctoral thesis (Owren, 1947). He observed a prolonged prothrombin time in a woman with a lifelong bleeding tendency, which was corrected by adding normal plasma from which all the prothrombin had been removed by adsorption with aluminium hydroxide. He postulated that the patient lacked a factor normally present in plasma and which is necessary for the normal interaction between prothrombin and thromboplastin. He was subsequently able to show that this new factor was relatively labile, unlike prothrombin, and it was not present in normal serum. He initially called it factor V, setting a precedent for Roman numerals to identify coagulation factors. However, he later renamed it proaccelerin on the basis of subsequent work because of the evidence that the factor is a precursor of a substance (accelerin) that accelerates the reaction of prothrombin and thromboplastin. Owren also subsequently assigned the name factor VI to accelerin, which is now known to be the activated form of factor V (Va) rather than an entirely separate entity. Shortly thereafter, it was shown that a small proportion of serum would shorten the prothrombin time of plasma diluted with plasma which had been adsorbed with barium sulphate. This suggested that adsorption had removed not only prothrombin but another

Correspondence: Dr Paul Giangrande, BSc, MD, FRCP (London, Edinburgh and Ireland), FRCPATH FRCPCH, Oxford Haemophilia Centre and Thrombosis Unit, Churchill Hospital, Oxford OX3 7LJ, UK. E-mail: paul.giangrande@ndm.ox.ac.uk

*The author is a Diplomate and Fellow of the Faculty of History of Medicine of the Society of Apothecaries of London.

necessary factor which was replaced by adding serum, which was called 'serum prothrombin conversion accelerator' (SPCA) (De Vries *et al.*, 1949). The same group also described a bleeding disorder in a young girl which they attributed to congenital deficiency of this newly identified coagulation factor (Alexander *et al.*, 1951). In Switzerland, Koller *et al.* (1951) independently identified the same factor, which they termed factor VII.

Although haemophilia was recognized by 1850 as a well-defined clinical entity with a clear pattern of X-linked inheritance, the aetiology remained elusive for many years. While the coagulation time of haemophilic blood, as measured in glass tubes by the Lee and White method, was typically grossly prolonged, the one stage prothrombin time was normal and furthermore the defect could be corrected *in vitro* by the addition of plasma from patients taking coumarin anticoagulants. The possibility that tissue thromboplastin in people with haemophilia was somehow defective was ruled out by showing that haemophilic tissue extract showed normal activity. Similarly, platelet function was also shown to be normal in haemophilia by several groups. The term 'antihemophilic globulin' (AHG) was first used in 1937 to describe a concentrated globulin derived from normal plasma which reduced the coagulation time of haemophilic blood (Patek & Taylor, 1937). With the development of Cohn fractionation, it was subsequently shown that the active factor was present in fractions I and III of normal plasma, but not in similar fractions of haemophilic plasma. Unlike factor V and VII, this 'antihemophilic globulin' (AHG) could not be wedged into the existing classical theory of coagulation as it seemed to play no part in either the thromboplastin-prothrombin reaction or subsequent steps. The development of a new test, the thromboplastin generation test, was an important advance as it enabled a more detailed analysis and localization of clotting defects (Biggs & Douglas, 1953). By using either the absorbed plasma or the serum or the platelet component from the patient and completing the system with the two remaining components from normal blood, it was possible to ascribe the cause to a clotting defect of one or more of these components. As anticipated, the results of the thromboplastin generation test in classical haemophilia were indicative of a defect in the plasma component.

A further complication arose when it also soon became apparent that haemophilia was not a homogeneous disorder in terms of the clotting defect. Alfredo Pavlovsky (1907–1984) in Buenos Aires reported that '*occasionally (in vitro) the blood of some of the haemophilic patients with a greatly prolonged clotting time...when added to other haemophilic blood possessed a coagulant action nearly as effective as normal blood*' (Pavlovsky, 1947). We now know that this was due to the normal level of factor VIII in the plasma of patients with haemophilia B correcting the defect in patients with the much commoner form, haemophilia A.

Christmas factor (later to be labelled factor IX) was the first coagulation protein to be named after a patient, a precedent established by Biggs (1912–2001, Fig 1) and Macfarlane (1907–1987, Fig 2) in Oxford in 1952. In December of that year, they published the clinical and



Fig 1. Dr Rosemary Biggs (1912–2001). Reproduced from the collection of the Oxford Haemophilia Centre, with permission.



Fig 2. Professor R.G. Macfarlane (1907–1987). Photograph taken on his 60th birthday. Reproduced from the collection of the Oxford Haemophilia Centre, with permission.

laboratory findings of seven patients with what appeared to be classical haemophilia, but in whom the thromboplastin generation test indicated a defect in the serum component. The authors named the disease after their first patient, Stephen Christmas: '*The naming of clinical disorders after patients was introduced by Sir Jonathan Hutchinson [British surgeon 1828–1913] and is now familiar from serological*

research; it has the advantage that no hypothetical implication is attached to such a name' (Biggs *et al.*, 1952). The Christmas edition of the British Medical Journal (BMJ) typically publishes light-hearted and even frivolous papers. The timing of the publication was perfect and the BMJ agreed to accept the paper at very short notice but the response to this important publication was not all entirely positive. As Rosemary Biggs recalled many years later, 'everybody read the article because they thought it was something to do with overeating' (Lee & Rizza, 1998). Some thought it was a student's prank or that the story had been made up. Two letters appeared in the BMJ the following month, from a Dr Kemp of Birmingham and Douglas Collins, Professor of Pathology in Leeds, protesting at the frivolity of using a Christian festival for the name of a disease and suggesting that some sort of an apology would be appropriate. Collins concluded: 'Some parents live to regret the names they have thoughtlessly bestowed upon their innocent children. Would it not be possible ...in your capacity as registrar of its birth, to substitute some less ridiculous name?' Macfarlane, Biggs and Douglas replied that they were too modest to suggest a seven name eponym. The only alternative name they could think of was 'hereditary hypoco-prothrombinaemia'. However, they did promise that if they found the precursor protein, they would resist the urge to call it 'Christmas Eve factor'. The distinguished serologist Alexander Wiener also wrote to the journal to protest at the name and urged the adoption of the alternative name of haemophilia B (Wiener, 1953).

Stephen Christmas (Fig 3) was born on 12 February 1947 and was just 5 years old when his case history was published. Stephen and his older brother, Robin, were born in London to British parents, their names deliberately chosen with an evident sense of humour because of their

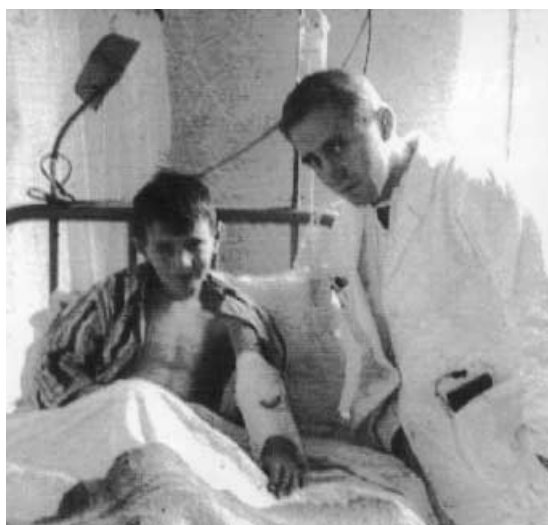


Fig 3. A photograph of Stephen Christmas, taken in 1957 when he was 10 years old, during an admission to Toronto General Hospital to receive a plasma transfusion for a haemarthrosis. The physician on his left is Dr J. Lawrence Naiman. Photograph kindly provided by the patient's brother, Robin Christmas.

associations with the Christmas season. Their father, Eric, was an actor who spent part of the war on tour to entertain troops. Shortly after the end of the war, the family later emigrated to settle in Toronto in Canada, and it was there at the age of 2 years that haemophilia was diagnosed at the Hospital for Sick Children. There was no family history of haemophilia and his bleeding tendency had first been noted when he was 20 months old. The family returned to Britain in 1952 to visit their relatives, and during the trip Stephen was admitted to hospital in London and a sample of his blood was sent to Biggs and Macfarlane in Oxford. Stephen never relinquished his ties with Britain and was the only member of his family not to renounce British citizenship to become a Canadian. Stephen had a passion for photography and studied the subject at the Ryerson Institute of Technology (now Ryerson University) in Toronto. He was employed for some years as a medical photographer at the Hospital for Sick Children in Toronto, although he mainly worked as a cab driver which he found easier because of his disability. Later in life, Stephen became an active worker for the Canadian Haemophilia Society (CHS) and an outspoken critic of the Canadian regulatory authorities. He campaigned tirelessly for the cause of blood safety and helped to secure financial compensation for patients infected with human immunodeficiency virus. His name reappeared in the medical literature again in 1992 when his genotype was studied, which turned out to be a hitherto unreported mutation (cysteine 206 serine) (Taylor *et al.*, 1992). Sadly, he died the following year at the age of 46 years from acquired immunodeficiency syndrome, contracted through treatment with blood products. Ironically, he died just before Christmas on 20 December 1993. In reporting his death, the Toronto Globe and Mail noted that 'Christmas was not only an inspirational symbol for haemophiliacs, but he was also an activist who was critical in bringing the tainted-blood issue to national attention'.

Although the discovery of Christmas factor (factor IX) is usually associated with the names of Biggs and Macfarlane, it must be acknowledged that others described identical conditions some months beforehand. In April 1952, Paul Aggeler (1911–1969) and colleagues in San Francisco described the case of a 16-year-old boy with the classical symptoms of haemophilia but in whom the prolonged coagulation time was not corrected *in vitro* by the addition of antihæmophilic globulin (Cohn fraction I) or plasma adsorbed with barium sulphate (BaSO₄) (Aggeler *et al.*, 1952). The authors of the paper called the new factor 'plasma thromboplastin component' (PTC). Irving Schulman independently reported another similar case in August 1952, involving an 11-month-old boy of Italian extraction (Schulman & Smith, 1952). Among the extensive laboratory investigations carried out, it was noted that the patient's plasma normalized the recalcification time of plasma from a patient known to have haemophilia and that, in reverse, plasma from a patient with haemophilia also normalized the recalcification time of the new patient's plasma. Schulman noted that there was no family history in this case and thus considered that it must be different from the usual hereditary form of haemophilia and proposed the



Fig 4. Miss Audrey Prower (photograph taken in 1956). Photograph kindly provided by Dr Kenneth Denson.

alternative names of 'parahaemophilia' and 'pseudohaemophilia'. However, it is a fact that only the term 'Christmas disease' stood the test of time and still remains in widespread use in the English-speaking world, although the associated term 'Christmas factor' has largely been superseded.

Factor X was discovered by the study of two patients with a congenital bleeding tendency. Miss Audrey Prower (Fig 4) was 22-year-old when she was admitted to University College Hospital in London in 1956 for investigation of a bleeding tendency prior to a dental extraction (Telfer *et al*, 1956; Denson, 1957). She had a significant past medical history, including significant bleeding after two previous dental extractions in 1939 and 1945. She had also bled profusely after tonsillectomy at the age of 8 years, requiring a blood transfusion. Furthermore, her brother had died of postoperative bleeding after tonsillectomy when he was 5 years old. Miss Prower reported that she had heavy periods but said that she did not feel that she bruised easily or bled unduly from cuts or scratches. Both her parents were already dead and there was no definite history in other relatives who were questioned. On this occasion, there was intermittent bleeding for 8 d after the dental extraction which was treated with local application of fibrin foam, thrombin and Stypven. Blood transfusion did not prove necessary.

I am grateful to Dr Kenneth Denson of the Thame Thrombosis and Haemostasis Research Foundation (UK) for sharing his recollections of his work on this interesting patient with me (personal communication, 2002).

'Audrey Prower was a delightful and co-operative young lady who presented with bleeding after dental extraction, and a history of bleeding following tonsillectomy which required blood transfusion, and menorrhagia. She subsequently delivered two male infants following normal

pregnancies in 1959 and 1962. She was given whole blood transfusions post partum after the first because concentrates were not available, and suffered no untoward bleeding. After the second infant she bled seven days post partum and I dashed up to University College Hospital (UCH) in London from Oxford with a newly developed concentrate of factors II, VII, IX and X, kindly provided by Dr Ethel Bidwell. This miraculously stemmed all bleeding and the obstetricians were very impressed. I bled her on numerous occasions. Every new paper necessitated visits to Audrey and she cheerfully donated her rare blood. In the 1954/1960 era, freeze-drying was unheard of, most laboratories had a 4°C fridge but very few boasted a freezer. I managed to persuade the hospital chef to let me keep her plasma samples in the kitchen freezer. They didn't like me using the meat freezer and would only allow me to use the fish freezer, and so all tubes of Prower plasma, some of which were despatched to London, Oxford and the Continent, were deposited among the haddock, cod and plaice, and smelled faintly of fish. Whilst there was an element of serendipity in discovering factor X, Audrey Prower had been seen at two other London teaching hospitals and UCH despatched her to the cottage hospital (St Pancras) for dental extraction without investigating her. Trevor Telfer was a registrar pathologist at UCH who was a visiting pathologist at St. Pancras at the time and we did the work jointly. We both smoked pipes and at times it was difficult to see the water bath for clouds of St. Bruno and Bulwark cut plug tobacco smoke! He left shortly afterwards for a consultant post at Rochester. I got good mileage, with subsequent papers on the assay of VII and X, electrophoretic studies, levels in patients receiving anticoagulant therapy with Dindevan and genetic variants of factor X, and of course moving to the Blood Coagulation Research Unit in Oxford! Audrey lost her unusual surname on marriage and became Audrey Smith. She subsequently changed this to Conway-Smith, which made it even more difficult to finally trace her after I lost touch with her in about 1970 and she had moved house.'

She is still alive and lives in a south-western suburb of London.

At about the same time, Cecil Hougie (1922–present) and colleagues in Chapel Hill (North Carolina, USA) described a similar patient (Hougie *et al*, 1957). In fact, this work was partly based on Hougie's previous work and contacts in Oxford (Robb-Smith, 1993). A year before Hougie arrived in Oxford, Danny Bergsagel joined Macfarlane's laboratory to study for a D Phil on thromboplastin formation. Bergsagel was involved on work on plasma taken from Miss Prower, and he remembered an apparently similar previous case report from North Carolina of what had been described as a case 'congenital hypoproconvertinaemia' or atypical factor VII deficiency (Lewis *et al*, 1953). As Hougie was about to leave for Chapel Hill, Bergsagel suggested that he should try and track down this patient. He succeeded and, sure enough, that patient appeared to have exactly the same defect. Rufus Stuart (Fig 5) was a 36-year-old farmer and lay-Baptist preacher, a member of a large and interrelated



Fig 5. Rufus Stuart (front), with (left to right) Drs Hougie, Barrow and Graham in 1957. Taken from: Owen (2001). By permission of Mayo Foundation for Medical Education and Research.

kindred living in the Blue Ridge mountains of the north-western corner of North Carolina and neighbouring Virginia. His principal problems had been recurrent epistaxis and significant bruising. However, he had also experienced occasional haemarthroses and, in December 1955, he had had a particularly severe haemarthrosis of the right hip which had resulted in anaemia for which he been transfused with one unit of fresh blood. He was partially crippled by these repeated bleeds and had been forced to drop out of school at the eighth grade because of his condition and made his living in the hamlet of Lansing by finding whatever casual manual work he could (Graham, 1988). The family was studied in detail, with information collected on 164 family members. Mr Stuart's parents were consanguineous and were related to each other as aunt and nephew (his father was the son of his mother's oldest sister) and a detailed study of the inheritance pattern clearly indicated an autosomal recessive pattern of this bleeding disorder (Graham *et al.*, 1957). Among his five children, it was noted that one of his sons was troubled with recurrent epistaxis and that 'the buttocks of his daughter often showed persistent bruising after disciplinary spanking.' A brother had died of haemorrhage some years earlier. On a positive note, for many years, Mr Stuart derived a modest but welcome regular income from the sale of his plasma to commercial companies who used it to produce a diagnostic reagent. Later in life, Mr Stuart developed salmonella osteomyelitis of the pelvis in the 1960s, as well as bilateral cataracts. A life-long chain smoker since his youth, he eventually developed a squamous cell carcinoma of the lung for which he underwent wedge resection of the lung but from which he ultimately died on 16 January 1989 at the age of 70 years. One of his physicians, Dr John Graham,

remembered him as a 'noble and unassuming man whom I place near the top of the list of the greatest persons I have ever known' (Graham, 1988).

The results of tests in both of these patients were identical. The one stage prothrombin time was prolonged both with Russell's viper venom (Stypven) and with brain thromboplastin. The abnormal prothrombin time using the snake venom excluded the possibility of factor VII deficiency, and prothrombin deficiency was excluded by using a two-stage assay. Moreover, the serum from these patients was defective in the thromboplastin generation test, but contained normal amounts of Christmas factor (factor IX). The inescapable conclusion was that the bleeding tendency was the consequence of deficiency of yet another coagulation factor, which was named the Stuart–Prower factor. Further tests showed the new serum factor to be relatively stable, adsorbed by inorganic precipitates such as barium sulphate and the level was reduced in the blood of patients on anticoagulant (dicoumarin) therapy.

Deficiencies of Christmas factor and Stuart–Prower factor were undoubtedly associated with a bleeding disorder. The case of John Hageman described in 1955 by Oscar Ratnoff (1916–present) of Case Western Reserve University in Cleveland (USA) proved to be a real conundrum, in that a grossly abnormal clotting time was apparently not associated with any bleeding tendency at all (Ratnoff & Colopy, 1955; Ratnoff, 1980). Mr Hageman was 37-years old when he was admitted to hospital in July 1953 for surgery to correct pyloric obstruction secondary to duodenal ulceration, which he had had since 1943. Routine coagulation tests were performed, although there was absolutely no history of a bleeding disorder and indeed he had undergone tonsillectomy at the age of 6 years and had had dental extraction at the age of 36 years. In the event, partial gastrectomy and gastrojejunostomy were subsequently carried out after the transfusion of 3500 ml of fresh whole blood during and after the procedure. The surgeon was Norman Shumway, who later became a noted cardiothoracic surgeon and a pioneer of cardiac transplantation. Blood loss during surgery was not excessive and postoperative recovery was also uneventful. Further laboratory studies demonstrated that the *in vitro* clotting defect could be corrected by the addition of normal plasma as well as serum adsorbed with barium sulphate. The presumed missing factor, which was also stable when heated to 50°C for 30 min, was called Hageman factor.

The eventual death of John Hageman at the age of 52 years occurred unexpectedly. He worked as brakeman (guard) on the railways and fell from the ladder of the carriage of a moving train on 11 March 1968, fracturing his left hemi-pelvis. He was kept on bed rest in hospital for a week before being allowed to walk on crutches and carry out physiotherapy exercises. Shortly thereafter, on his twelfth day in hospital, 'he was found gasping for breath; he had an ashen colour and was pulseless, and the blood pressure was unobtainable. Despite oxygen and cardiac massage, he died in a matter of minutes' (Ratnoff *et al.*, 1968). Somewhat paradoxically, post-mortem examination revealed that he had died of massive pulmonary embolism, and five emboli were found



Fig 6. Professor Irving Wright (1901–1997). Chairman of the International Committee for the Nomenclature of Blood Clotting Factors, 1954–1962. Original photograph from Owen *et al* (1975). Copyright, Lippincott Williams & Wilkins, Baltimore.

blocking the main right and left branches of the pulmonary artery.

It became apparent by the mid-1950s that a unified nomenclature was desirable because many of the coagulation factors were named independently by several groups of workers who studied different properties and who initially thought that they had discovered different factors. The idea of harmonizing the nomenclature came from Irving Wright (1901–1997), Professor of Internal Medicine with a special interest in cardiology at Cornell University (New York), who made the suggestion during a meeting of the International Conference of Thrombosis and Embolism held in Basel (Switzerland) in 1954 and chaired by Dr Fritz Koller. The International Committee for the Nomenclature of Blood Clotting factors was duly established in that same year under the Chairmanship of Professor Wright (Fig 6) with the primary objective of developing a common scientific terminology in the field, and which was funded with a grant from the National Heart Institute of the United States Public Health Service. As Irving Wright subsequently recalled: 'At that time, the situation was chaotic, with most of the factors being referred to in the literature by multiple, often totally unrelated names: 14 different terms were used for one of them' (Wright, 1962). The Committee was initially composed of 23 members from 15 different countries, all of whom were selected for having 'played significant roles in the discovery or application of knowledge regarding these factors'. The founding members of the International Committee for the Nomenclature of Blood Clotting Factors were as follows (in alphabetical order): Takeshi Abe (Tokyo, Japan), Benjamin Alexander (Boston, USA), Tage Astrup (Washington DC, USA), Ken(neth) Brinkhous (Chapel Hill, USA), Pietro De Nicola (Pavia, Italy), Erwin Deutsch (Vienna, Austria), Paul Fantl (Melbourne, Australia), Robert Hunter (Dundee, UK), L. Jacques (Saskatoon, Canada), Erik Jorpes (Stockholm, Sweden), Fritz Koller (Vice Chairman) (Zurich, Switzerland), K. Lenggenhager (Bern, Switzerland), R. Macfarlane

(Oxford, UK), Willy Merz (Lausanne, Switzerland), Paul Owren (Oslo, Norway), Alfredo Pavlovsky (Buenos Aires, Argentina), Armand Quick (Milwaukee, USA), Oscar Ratnoff (Cleveland, USA), Laszlo Róka (Frankfurt, Germany), Walter Seegers (Detroit, USA), Jean-Pierre Soulier (Paris, France), Marc M. Verstraete (Leuven, Belgium) and Irving S. Wright (Chairman) (New York, USA).

The first meeting of the Committee was a rather informal gathering held in Oxford in 1955, and this was followed by a second meeting in Boston the following year, which was chosen to coincide with a meeting of the International Haematological Conference (IHC). However, it was only after 3 years of deliberation that the designation of factors I to IX was officially approved by the Committee, at a meeting in Rome in 1958 (the same venue as for the IHC meeting that year). For each factor, evidence as to its existence and character had to be presented by a proposer and this required the physical presence of not only the proposer but also of colleagues who had taken part in the research. There had been considerable debate about whether letters or Arabic or Roman numerals should be used. A precedent of using a Roman numeral to identify a coagulation factor had been set by Paul Owren when he described factor V in 1947. In fact, the location of this meeting probably helped to sway the eventual outcome and the Chairman of the Committee himself subsequently recalled that 'finally ideas began to crystallize and appropriately, in Rome in 1958, the system of using Roman numerals was adopted' (Wright, 1963) (Table I). Paul Fantl (Melbourne, Australia) noted that 'through correspondence, I find that the Roman numeral system has made life very easy for

Table I. The Roman numerical system of nomenclature for blood coagulation factors (also showing synonyms in current use as well as former terminologies).

Factor	Current synonyms and/or former terminology
I	Fibrinogen
II	Prothrombin
III	Thromboplastin, tissue extract
IV	Calcium
V	Proaccelerin, labile factor, accelerator globulin (AcG)
VI	First used by Owren to describe what is now recognized as activated V (Va), but which was initially also referred to as accelerin. This numeral is now redundant and no longer used
VII	Proconvertin, serum prothrombin conversion accelerator (SPCA), stable factor, autoprothrombin I
VIII	Antihæmophilic factor (AHF), antihæmophilic globulin (AHG), platelet cofactor I, antihæmophilic factor A
IX	Plasma thromboplastin component (PTC), Christmas factor, antihæmophilic factor B, platelet cofactor II, autoprothrombin II
X	Stuart–Prower factor
XI	Plasma thromboplastin antecedent (PTA)
XII	Hageman factor
XIII	Fibrin stabilizing factor (FSF), Laki–Lorand factor (LLF), fibrinase

workers who do not read English or any other western language' (De Nicola, 1961). Perhaps not surprisingly, Dr Taki Abe (Tokyo, Japan) concurred: 'I agree with Dr Fantl's idea, particularly for India, China and the South-east Asian countries. We prefer numbers, at the present moment at least. Therefore, I want to continue this system for some time'. Dr John Graham of Chapel Hill wrote some years later that the adoption of a system of impersonal numbers also served another purpose: 'the political subtlety of the Latin numerals lay in the fact that replacing the names bypassed the ego investment of each of the discoverers as well as foiling all claims for priority' (Graham, 1988). Factor X (previously commonly referred to as Stuart–Prower factor) was so designated at a meeting of the committee in Montreux in 1959. What was originally described as a third type of haemophilia or haemophilia C was reported in 1953 and attributed to deficiency of a plasma thromboplastin antecedent (PTA) which was present in both serum as well as BaSO₄-treated plasma (Rosenthal *et al*, 1953; Rosenthal, 1954). The typical clinical scenario, described in a joint paper from the Jewish Hospital in Cincinnati and the Beth Israel Hospital in New York, was bleeding after surgery or trauma (rather than spontaneous) but in contrast to classical haemophilia, haemarthrosis was rare and both males and females were affected. The *in vitro* abnormality in the clotting tests was corrected by addition of plasma from patients with classical haemophilia. The Committee voted at a meeting in Wiesbaden (Germany) in September 1961 that PTA (plasma thromboplastin antecedent) and Hageman factor should be assigned the Roman numerals XI and XII, respectively, based on the historical sequence of discovery. A congenital bleeding disorder associated with poor wound healing and excessive scarring was described in 1961 and correctly ascribed to deficiency of a fibrin stabilizing factor (Duckert *et al*, 1961). The status of this new factor was considered at a meeting of the Committee in Gleneagles (Scotland) in July 1963, and it was designated factor XIII. However, a transcript of the meeting reveals that the issue was more controversial than with other factors and the vote was certainly not unanimous. Dr Birger Blombäck (Karolinska Institute, Stockholm, Sweden) opposed 'using (the term) XIII until it is shown that the fibrin stabilizing factor is not a fibrinogen derivative or closely related to fibrinogen'. Dr Roger Hardisty (London, UK) stated that he felt 'it would be a retrograde step to give this factor a number rather than a name, because there is in fact so much agreement already about the physiological function and, therefore, potentially about the name'. By 1964, what Wright had termed 'a symbolic tower of Babel' (Wright, 1963) had been demolished and the pieces of the jigsaw were beginning to fit into place. The following year saw the publication of a seminal article by Macfarlane in which he set out for the very first time the concept of blood coagulation as a cascade of eight enzymatic reactions which culminate in the formation of fibrin, and which involve activation of factors, as well as biochemical amplification and negative feedback to control the process (Macfarlane, 1964). In this paper, he also used for the first time the suffix 'a' as a subscript to denote activated clotting factors, but credited Dr Peter Esnouf, a



Fig 7. The Fletcher family. Photograph kindly provided by Professor H. Saito.

biochemist at the Radcliffe Infirmary in Oxford, for this 'convenient device to denote activation of a factor'.

The closed and initially rather informal meetings of the International Nomenclature Committee slowly evolved to become more open and formal international conferences, where scientists could present new data to the Committee members who still retained exclusive voting rights. Eventually, the Committee became the International Committee on Thrombosis and Haemostasis (ICTH) in 1964, and this body in turn promoted the formation of the current International Society on Thrombosis and Haemostasis (ISTH). The ICTH decided to commemorate Robert P. Grant, a distinguished cardiologist. As Director of the National Heart Institute he had given valuable support to the International Committee when it was working with on the nomenclature of blood clotting factors. The first recipient of the Robert P. Grant medal in 1975 was Professor Macfarlane of Oxford 'in recognition of his achievements in the field of blood coagulation'.

Although no more clotting factors were designated with Roman numerals after factor XIII in 1963, other important proteins involved in the coagulation pathway were soon discovered. In the winter of 1963, the mountain cabin of a family named Fletcher (Fig 7) in eastern Kentucky was destroyed by fire. Several members of the family were admitted to hospital because of exposure to severe cold and frostbite. During this period of hospitalization, an 11-year-old girl member of the family was deemed to require adenoidectomy. Routine coagulation tests were carried out but the results were markedly abnormal and she was referred to the University of Kentucky for investigation (Hathaway *et al*, 1965). Three other siblings were also found to have similar results, although there was no personal or family history suggestive of a bleeding disorder. A fraction of normal plasma was prepared which appeared to contain a hitherto unknown coagulation factor that corrected the *in vitro* clotting defect of the children, to which the name of Fletcher factor was applied.



Fig 8. Allen Fitzgerald. Photograph kindly provided by Professor H. Saito.

In August 1973, a 71-year-old man was admitted to the Henry Ford Hospital in Detroit (MI, USA) with gunshot wounds. The activated partial thromboplastin time (APTT) was greatly prolonged at 300 s, compared with a control value of 29 s, but the prothrombin time was normal. Professor Hidehiko Saito takes up the story (personal communication, 2002).

'Mr Allen Fitzgerald (Fig 8) was an old man with no known history of bleeding or abnormality of infection or inflammation. Dr Robert Waldmann brought a small icebox containing a plasma sample from the patient to the University Hospital of Cleveland, where I was then working in Oscar Ratnoff's laboratory. We confirmed the routine coagulation studies of Henry Ford Hospital, and excluded the presence of a circulating anticoagulant. We thought initially that this patient may have Fletcher factor deficiency but within one hour the activities of all known clotting factors in the intrinsic pathway including Fletcher factor were found to be normal, leading us to hypothesize that his plasma was missing a new clotting factor. As Dr Ratnoff and I were interested not only in surface-mediated fibrinolysis but also in kinin generation, we examined other surface activated reactions which turned out to be defective. Dr Waldmann and I also performed a preliminary study on the in vivo inflammatory reaction using skin-window technique, together with Dr Rebuck, a pathologist at Henry Ford Hospital. I went to Chicago to get blood from Mr Fitzgerald a couple of times. He was a quiet man, as I recall.'

The authors concluded that *'the deficient factor operates after activation of Hageman factor but precedes the activation of PTA'*. Skin-window studies elicited unusually florid

inflammatory reactions in response to applied toxins such as diphtheria toxoid. The authors of this report accordingly named the missing factor as Fitzgerald factor (Waldman *et al*, 1975). Almost at the same time, similar patients with abnormal coagulation tests but no apparent bleeding tendency were identified and described variously as having 'Williams trait', 'Fleaujeac trait' and 'Reid trait.' At first the nature of these factors was uncertain, but further studies showed that Fletcher factor was actually identical to plasma prekallikrein and that Fitzgerald factor was the same as high-molecular-weight kininogen.

The abnormalities detected in these two families were not associated with a bleeding tendency despite the marked abnormalities in the coagulation tests. Hageman factor, Fletcher factor and Fitzgerald factor were all classified as 'contact factors'. However, a study of these interesting patients has also shed light on the phenomenon of contact activation and the important link between the pathways of inflammation and coagulation (Schmaier, 1997). Factor XII can be activated by contact with negatively charged surfaces and converts prekallikrein to kallikrein, which in turn acts on high-molecular-weight kininogen to liberate bradykinin. Bradykinin is a potent modulator of vascular biology, including vasodilation, release of tissue plasminogen activator and liberation of prostacyclin.

There is no doubt that standardization of the nomenclature of coagulation factors has facilitated research and clinical developments in the field. The work of the International Nomenclature Committee provides an outstanding early example of international collaboration to resolve a scientific problem. This sort of co-operation is now commonplace, but was certainly not typical in this post-war period. However, the nomenclature we have inherited does not fit easily with the evolution in our understanding of the clotting process (Walsh, 2001). The sequence of numbers in current terminology is simply based on the historical order in which the coagulation factors were discovered and certainly takes no account of the natural sequence of the putative involvement of coagulation factors. Just like the classification of fine wines of Bordeaux, which was devised in 1855 but which remains in widespread use to this day, we have inherited a nomenclature for coagulation factors which was established half a century ago but which is now recognized to be somewhat outdated if not inaccurate or, at least in some cases, positively misleading. Factors I and II are now more usually referred to by their synonyms of fibrinogen and prothrombin, respectively, and factors IV and VI are redundant. Somewhat ironically, the international nomenclature Committee was itself *'fully aware of the dangers of solidification of concept and the desirability for change if new evidence warrants it'* (Wright, 1962). There is still no consensus as to the identity of factor III, and the Committee even considered deleting it in 1963. In closing the Gleneagles meeting in July that year, Macfarlane swayed opinion to retain it by commenting that *'we cannot just drop III and delete it just like that; it is there. This is not really premature, it is post maturity. We cannot do anything in retrospect. I think – and this is not collusion – that Dr Biggs' suggestion, that factor III should be reserved for a specific factor which really will fulfil the original idea*

of thromboplastin, is a very good compromise, because it involves us in doing absolutely nothing at the moment!' (Irsigler, 1963)

In coagulation medicine, we have allowed the former names of some coagulation factors to be replaced by an impersonal list of Roman numerals. By contrast, the names of many patients who have contributed to advances in transfusion medicine remain in widespread use around the world to this day, including the names of red cell antigens such as Duffy, Kell and Kidd. Perhaps if changes are to be introduced into our system of nomenclature of coagulation factors, some consideration could be given to restoring some of the more evocative and personal names from the past.

Oxford Haemophilia Centre PAUL L. F. GIANGRANDE*
and Thrombosis Unit,
Churchill Hospital, Oxford, UK

ACKNOWLEDGMENTS

I am particularly grateful to Robin Christmas of Toronto (Canada) for sharing his memories of his late brother, Stephen. Dr Kenneth Denson of the Thame Thrombosis and Haemostasis Research Foundation (UK) provided invaluable material and anecdotes about Audrey Prower and the early work on factor X. Professor Hidehiko Saito of the Nagoya National Hospital (Japan) kindly provided the photograph of Allen Fitzgerald as well as background information about his work on this case.

REFERENCES

- Aggeler, P.M., White, S.G., Glendening, M.B., Page, E.W., Leake, T.B. & Bates, G. (1952) Plasma thromboplastin component (PTC): a new disease resembling hemophilia. *Proceedings of the Society for Experimental Biology and Medicine*, **79**, 692–694.
- Alexander, B., Goldstein, R., Landwehr, G. & Cook, C.D. (1951) Congenital SPCA deficiency: a hitherto unrecognized coagulation defect with hemorrhage rectified by serum and serum fractions. *Journal of Clinical Investigation*, **30**, 596–608.
- Biggs, R. & Douglas, A.S. (1953) The thromboplastin generation test. *Journal of Clinical Pathology*, **6**, 23–29.
- Biggs, R., Douglas, A.S., Macfarlane, R.G., Dacie, J.V., Pitney, W.R., Mersky, C. & O'Brien, J.R. (1952) Christmas disease: a condition previously mistaken for haemophilia. *British Medical Journal*, **ii**, 1378–1382.
- De Nicola, P. (1961) Report of the sub-committee on new clotting factors. In: *Progress in Coagulation. Transactions of the conference held under the auspices of the International Committee on Blood Clotting Factors, Wiesbaden, Germany, 3–6 September 1961* (ed. by I.S. Wright, F. Koller & E. Beck), p. 363. Friedrich-Karl Schattauer-Verlag, Stuttgart.
- De Vries, A., Alexander, B. & Goldstein, R. (1949) A factor in serum which accelerates the conversion of prothrombin to thrombin. I. Its determination and some physiologic and biochemical properties. *Blood*, **4**, 247–258.
- Denson, K.W. (1957) Electrophoretic studies of the Prower factor: a blood coagulation factor which differs from factor VII. *British Journal of Haematology*, **4**, 313–325.
- Duckert, F., Jung, E. & Shmerling, D.H. (1961) A hitherto undescribed congenital haemorrhagic diathesis probably due to fibrin stabilizing factor deficiency. *Thrombosis et Diathesis Haemorrhagica*, **5**, 170–186.
- Graham, J.B. (1988) 'Stuart factor' (coagulation factor X). A North Carolina saga. *North Carolina Medical Journal*, **49**, 328–331.
- Graham, J.B., Barrow, E.M. & Hougie, C. (1957) Stuart clotting defect. II. Genetic aspects of a 'new' hemorrhagic defect. *Journal of Clinical Investigation*, **36**, 497–503.
- Hathaway, W.E., Belhasen, L.P. & Hathaway, H.S. (1965) Evidence for a new plasma thromboplastin factor. I. Case report, coagulation studies and physicochemical properties. *Blood*, **26**, 521–532.
- Hougie, C., Barrow, E.M. & Graham, J.B. (1957) Stuart clotting defect. I. Segregation of an hereditary hemorrhagic state from the heterogeneous group heretofore called 'stable factor' (SPCA, proconvertin, factor VII). *Journal of Clinical Investigation*, **36**, 485–496.
- Irsigler, K. (1963) Human brain tissue thromboplastin. The International Committee on Blood Clotting Factors: the past, present and future. In: *Fibrinogen and Fibrin. Turnover of Clotting Factors. Transactions of the conference held under the auspices of the International Committee on Blood Clotting Factors, Gleneagles, Scotland, July 1963* (ed. by R.B. Hunter, F. Koller & E. Beck), p. 441. F. K. Schattauer-Verlag, Stuttgart.
- Koller, F., Loeliger, A. & Duckert, F. (1951) Experiments on a new clotting factor (factor VII). *Acta Haematologica*, **6**, 1–18.
- Lee, C.A. & Rizza, C.R. (1998) Witnessing medical history: an interview with Rosemary Biggs. *Haemophilia*, **4**, 769–777.
- Lewis, J.H., Fresh, J.W. & Ferguson, J.H. (1953) Congenital hypoproconvertinemia. *Proceedings of the Society for Experimental Biology and Medicine*, **84**, 651–654.
- Macfarlane, R.G. (1964) An enzyme cascade in the blood clotting mechanism, and its function as a biochemical amplifier. *Nature*, **202**, 498–499.
- Owen, Jr, C.A. (2001) *A History of Blood Coagulation* (ed. by W.L. Nichols & E.J.W. Bowie), Mayo Foundation for Medical Education & Research, Rochester.
- Owen, Jr, C.A., Bowie, E.J.W. & Thompson, Jr, J.H. (1975) *The Diagnosis of Bleeding Disorders*, 2nd edn. Little Brown, Boston.
- Owren, P.A. (1947) Parahaemophilia: a haemorrhagic diathesis due to absence of a previously unknown clotting factor. *Lancet*, **i**, 446–448.
- Patek, A.J. & Taylor, F.H.L. (1937) Hemophilia. II. Some properties of a substance obtained from normal human plasma effective in accelerating the coagulation of hemophilic blood. *Journal of Clinical Investigation*, **16**, 113–124.
- Pavlovsky, A. (1947) Contribution to the pathogenesis of hemophilia. *Blood*, **2**, 185–191.
- Quick, A. (1943) On the constitution of prothrombin. *American Journal of Physiology*, **142**, 212–220.
- Ratnoff, O.D. (1980) A quarter century with Mr. Hageman. *Thrombosis and Haemostasis*, **43**, 95–98.
- Ratnoff, O.D. & Colopy, J.E. (1955) A familial hemorrhagic trait associated with a deficiency of a clot-promoting fraction of plasma. *Journal of Clinical Investigation*, **34**, 602–613.
- Ratnoff, O.D., Busse, R.J. & Sheon, R.P. (1968) The demise of John Hageman. *New England Journal of Medicine*, **279**, 760–761.
- Robb-Smith, A.S. (1993) *Life and Achievements of Professor Robert Gwyn Macfarlane FRS*, pages 43–44. Royal Society of Medicine Services, London.
- Rosenthal, L. (1954) Plasma thromboplastin antecedent (PTA) deficiency in man: clinical, coagulation, hereditary and therapeutic aspects. *Journal of Clinical Investigation*, **33**, 961.
- Rosenthal, R.L., Dreskin, O.H. & Rosenthal, N. (1953) New hemophilia-like disease caused by deficiency of a third plasma

- thromboplastin factor. *Proceedings of the Society for Experimental Biology and Medicine*, **82**, 171–174.
- Schmaier, A.H. (1997) Contact activation: a revision. *Thrombosis and Haemostasis*, **78**, 101–107.
- Schulman, I. & Smith, C.H. (1952) Hemorrhagic disease in an infant due to deficiency of a previously undescribed clotting factor. *Blood*, **7**, 794–807.
- Taylor, S.A.M., Duffin, J., Cameron, C., Teitel, J., Garvey, B. & Lillcrap, D.P. (1992) Characterization of the original Christmas disease mutation (cysteine 206serine): from clinical recognition to molecular pathogenesis. *Thrombosis and Haemostasis*, **67**, 63–65.
- Telfer, T.P., Denson, K.W. & Wright, D.R. (1956) A 'new' coagulation defect. *British Journal of Haematology*, **2**, 308–316.
- Waldman, R., Abraham, J.P., Rebeck, J.W., Caldwell, J., Saito, H. & Ratnoff, O.D. (1975) Fitzgerald factor: a hitherto unrecognised coagulation factor. *Lancet*, **i**, 949–951.
- Walsh, P.N. (2001) Roles of platelets and factor XI in the initiation of blood coagulation by thrombin. *Thrombosis and Haemostasis*, **86**, 75–82.
- Wiener, A.S. (1953) Christmas disease. *British Medical Journal*, **i**, 559–560.
- Wright, I.S. (1962) The nomenclature of blood clotting factors. *Thrombosis et Diathesis Haemorrhagica*, **7**, 381–388.
- Wright, I.S. (1963) The International Committee on Blood Clotting Factors: the past, present and future. In: *Fibrinogen and Fibrin. Turnover of Clotting Factors*. Transactions of the conference held under the auspices of the International Committee on Blood Clotting Factors, Gleneagles, Scotland, July 1963 (ed. by R.B. Hunter, F. Koller & E. Beck), p. 1. F. K. Schattauer-Verlag, Stuttgart.

Keywords: history, coagulation factors, nomenclature, haemophilia.