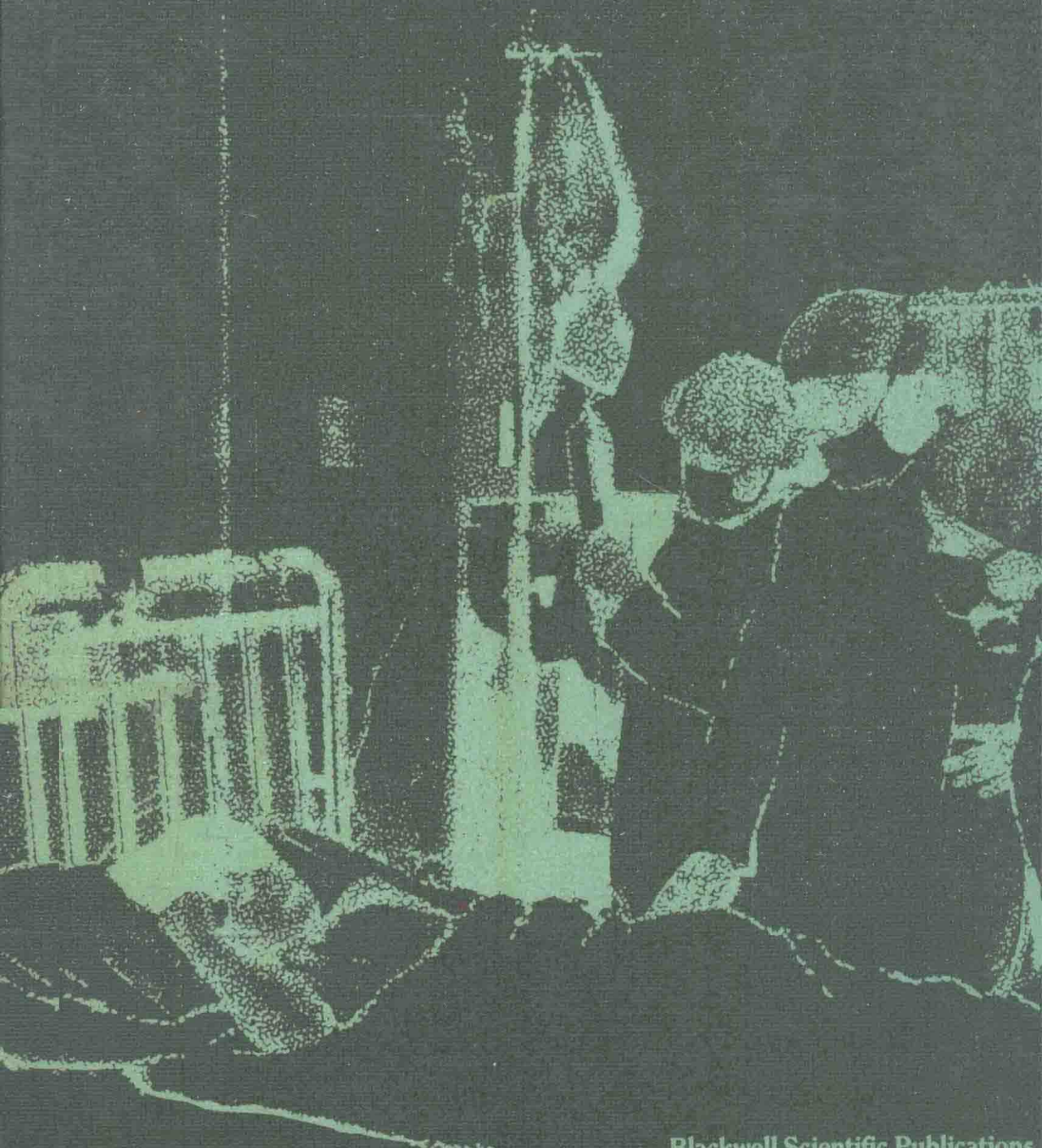
Clinical Paediatric Haematology and Oncology

EDITED BY HENRY EKERT



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Preface

This book has been written to provide an overview of the practice of clinical haematology and oncology as it occurs in specialized units within general paediatric teaching hospitals. The text reflects a practical approach to the problems encountered in the wards and outpatient clinics. Whenever possible, attempts have been made to integrate pertinent physiology, pathology, clinical features and management into a short pertinent unit which can be applied to clinical management. The text does not aim to comprehensively cover basic physiology, biochemistry and pathology, nor are there attempts to debate obscure or currently unsolved problems in haematology and oncology. In order to keep the book at a reasonable size, rare haematological and oncological conditions have been omitted. These are already well described in more specialized texts on haematology or oncology.

The authors hope that the book will prove particularly useful to medical students and junior medical officers who work in haematology and oncology units, as well as trainees who intend to specialize in haematology and oncology. For the latter group, the book may act as an introduction prior to consulting more detailed texts. Hopefully, some of the views expressed in this book will stimulate the reader to debate and personal research.

It is hoped that this book will also prove particularly useful for members of medical allied professions who work in or with haematology and oncology units. The comprehensive text books on haematology and oncology are too detailed and theoretical to be of much value to these professions. In this book, we have attempted to provide information which will highlight some of the problems involved in medical management, and to bring the reader up-to-date with current results of treatment and an understanding of the nature of the disease process.

In order to reduce long lists of footnotes and references, statements of fact or theory have not been referenced in the text, but rather a recommended reading list has been provided for each chapter. In this sense, the book serves as an introduction to the subject of haematology and oncology. These lists substantiate the point of view described by the authors, but are clearly not meant as a comprehensive literature review, which, in any case, becomes rapidly dated.

I am indebted to many for the production of this book. My particular thanks are extended to members of staff of my unit and the hospital, who not only contributed to this book but also endured the increased work load and strain entailed in its writing. I am grateful to Mr Peter Jones for encouraging me to undertake the task, and to my wife and family for bearing with me.

Particular thanks are extended to my secretary, Mrs Margaret Cameron, without whose excellent work on the collection and typing of the manuscript, as well as arrangement of diagrams, this book would not have been possible.

Melbourne 1982 Henry Ekert

Contents

Chapter 1
The Physiology of Haemostasis

Definition

Haemostasis is that series of physiological processes which arrest bleeding at the site of injury and initiate repair of the blood vessel. Haemostasis involves three main components: (1) blood vessels, (2) platelets, (3) the coagulation and fibrinolytic enzymes.

There is much detailed knowledge of platelets, coagulation and fibrinolysis. On the other hand, investigations of the role of endothelium, subendothelium and collagen are still preliminary.

INTERACTION OF PLATELETS AND BLOOD VESSELS

Injury to the blood vessel is associated with damage to the endothelium and exposure of subendothelium and, in more severe vessel injury, collagen. Platelets can adhere to the subendothelial matrix and collagen. Adhesion to the subendothelial matrix requires the presence of a functional part of the factor VIII complex, known as the von Willebrand factor. Components of factor VIII are synthesized in endothelial cells and may be released from the cells when there is vessel injury.

Adhesion of platelets is followed by their aggregation (Fig. 1.1). The process of aggregation is mediated by the release of stored materials in the dense granules of the platelets, the principal one being adenosine diphosphate (ADP). The process of storage of ADP in the dense granules and its release require normal platelet metabolism. The release process appears to be mediated by activation of the enzyme phospholipase which produces arachidonic acid from platelet membrane phospholipid. Arachidonic acid is oxidized by cyclo-oxygenase to form prostaglandin intermediates and thromboxane A_2 which greatly promotes platelet aggregation through the release reaction. Thromboxane A_2 is rapidly oxidized to thromboxane B which does not promote platelet aggregation. The process is diagrammatically summarized in Fig. 1.2. Platelet aggregation resulting from thromboxane A_2 synthesis is associated with a decrease of cyclic AMP and an increase of calcium levels in the platelet. These changes are associated with release of the platelet non-metabolic pool of ADP and aggregation of the platelets. For platelet aggregation to occur, there must be receptors for ADP on the platelet membrane. The exact mechanism whereby the reaction of

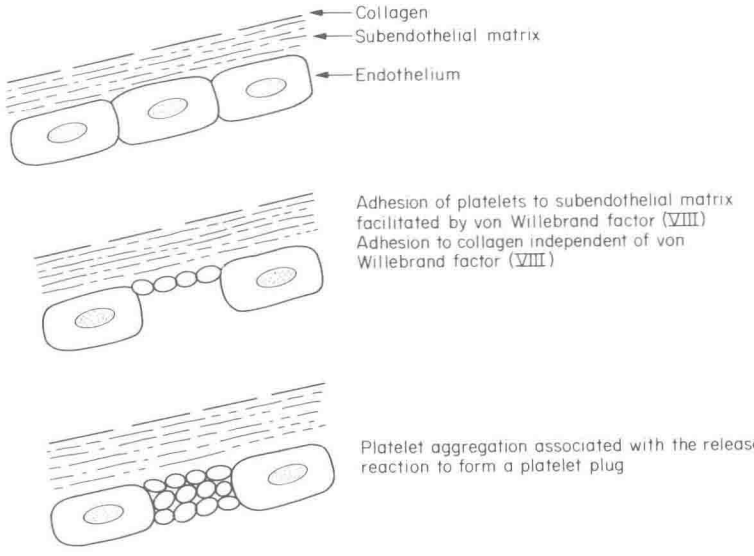

Fig. 1.1 Platelet adhesion and aggregation.

ADP with the platelet membrane receptor causes aggregation of platelets remains speculative. Abnormalities of platelet adhesion and aggregation are generally associated with bruising and mucosal bleeding, and the laboratory findings of a prolonged bleeding time.

Endothelial cells can react with the prostaglandin intermediates synthesized in the platelets to form prostacyclins, and recently it has been shown that prostacyclins can also be produced in the platelets (Fig. 1.2). These substances actively inhibit platelet aggregation. It is possible, but not proven, that a balance between thromboxane A_2 and prostacyclin synthesis may regulate the size and spread of the platelet aggregate that follows vessel injury.

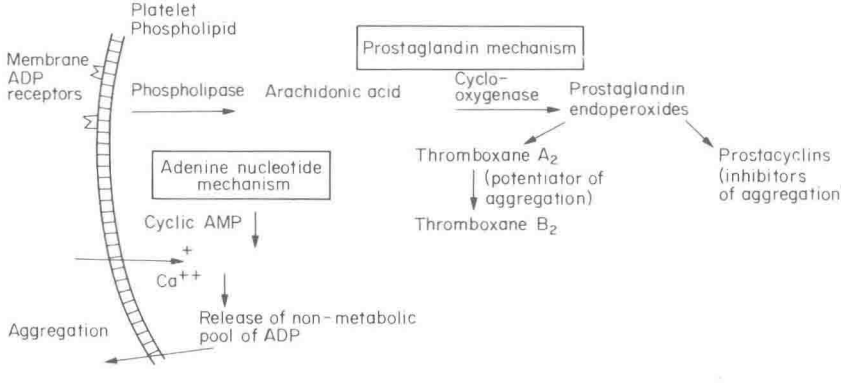

Fig. 1.2 Key processes involved in platelet aggregation.

PLATELET COAGULANT ACTIVITIES

It is now well established that platelets contribute procoagulant activities which can accelerate the process of coagulation and possibly localize it to the surface of the platelet aggregate. The platelet surface membrane phospholipids are required for rapid conversion of certain procoagulants (factor X and II) to active enzymes. Platelets may also release particles which act as general procoagulants. These combined activities are known as platelet factor 3 (PF_3). The release reaction is also associated with the appearance of an antiheparin activity known as platelet factor 4 (PF_4), a protein of unknown functional activity and structural similarity to PF_4, known as β-thromboglobulin, antiplasmin activity and antiplasminogen activator activity. In addition, there is good evidence that platelets can release procoagulant activities which have the characteristics of activated factors XI and V. The precise role and sequence in which these platelet procoagulant activities interact to secure haemostasis is unknown at present.

PLASMA COAGULANT ACTIVITIES

A scheme illustrating an acceptable current concept of procoagulant enzyme interactions is shown in Fig. 1.3. It is now considered that factor XII (Hageman factor) plays a more important role in interactions with the fibrinolytic mechanism, the complement system and vasoactive kinins than in coagulation (Fig. 1.4). Factor VIII and V appear to act as rate limiting substances in the conversion of X → Xa and II (prothrombin) to IIa (thrombin) respectively. It is considered that the role of the intrinsic coagulation system is to amplify the coagulation response to vessel injury. The trigger for this amplification may be the generation of trace amounts of thrombin from the extrinsic pathway. Thrombin also acts to activate factor XIII which crosslinks fibrin by transamidation between Σ-amino group of lysine and γ-amide group of glutamine. The coagulation pathway can be summarized as shown in Fig. 1.5.

A combination of two screening tests of the coagulation pathway may give information as to the possible site of the coagulation disorder. The activated partial thromboplastin time (APTT) tests the integrity of the intrinsic and common pathways. The one stage prothrombin time (PT) tests the integrity of the extrinsic and common pathways. Thus, a prolonged APTT and normal PT indicate an intrinsic pathway defect, prolonged PT and normal APTT an extrinsic defect; prolonged PT and PTT on an adequate blood sample are most often due to disseminated intravascular coagulation or congenital defects of the common pathway.

Activated coagulation factors can be inactivated by naturally occurring plasma proteins of which antithrombin III (α_2-ATIII) is the most important. ATIII inhibits the serine protease activity of thrombin and activated coagulation factors Xa, IXa, XIa and possibly XIIa. The rate and amount of

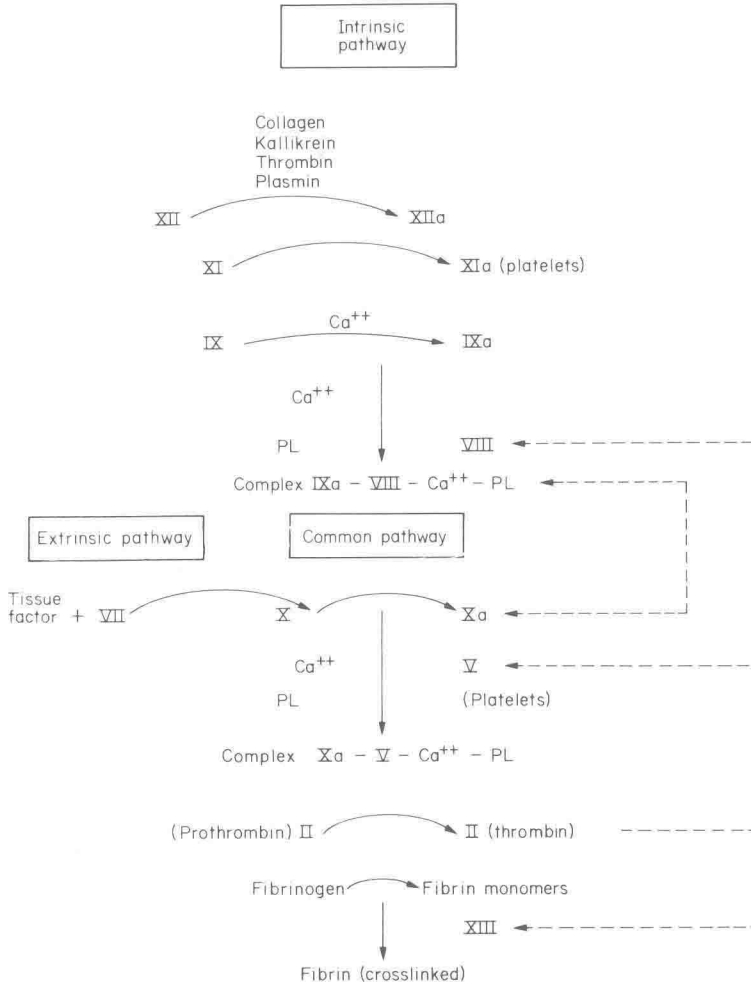

Fig. 1.3 A scheme of the mechanism of blood coagulation. PL: Phospholipid. Broken lines indicate that thrombin or Xa accelerated the reaction.

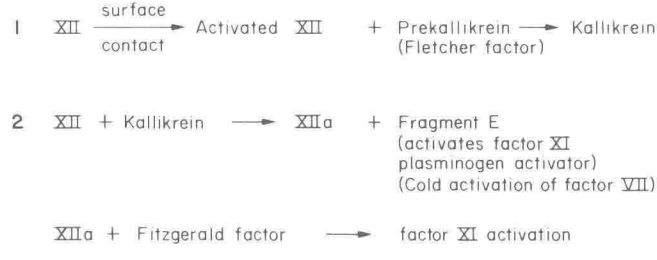

Fig. 1.4 Interaction of factor XII with the fibrinolytic mechanism, the complement system and vasoactive kinins.

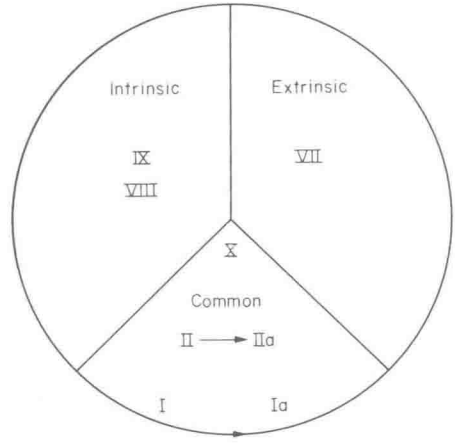

Fig. 1.5 Summary of coagulation pathway.

inactivation of Xa is increased by heparin. Heparin also increases the rate of inactivation of thrombin and XIa, but has little effect on the amount inactivated. Potentiation of ATIII activity by low doses of heparin is considered to be the explanation for the effectiveness of prophylactic low dose heparin in prevention of venous thrombosis.

FIBRINOLYSIS

The fibrinolytic system is based on the activation of a zymogen (plasminogen) to a serine protease plasmin (Fig. 1.6). Plasminogen is present in plasma and is closely associated with fibrinogen. The conversion of plasminogen to plasmin requires the presence of tissue activators which are widely distributed, being

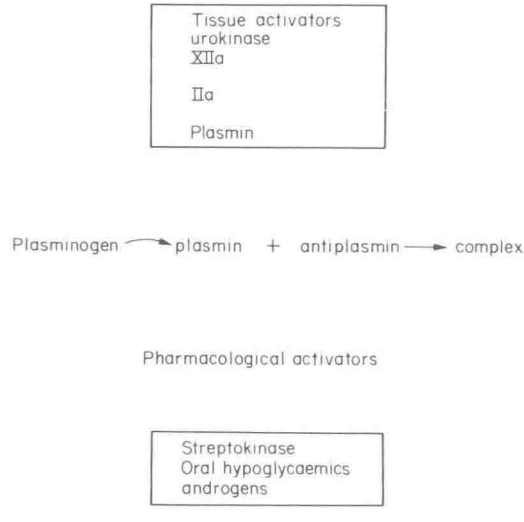

Fig. 1.6 Naturally occurring activators.

present in endothelium and cells of tissues such as lung and uterus. Urokinase which is synthesized in the kidney is an activator recovered from the urine and available in a highly purified form. The mechanism of activation of plasminogen by plasma factors is complicated and has not yet been fully worked out. Plasminogen can be activated by activation of factor XII in the presence of kallikrein, but activators not dependent on factor XII have also been described.

Under normal circumstances, plasmin forms a complex with its inhibitor antiplasmin (α_2-macroglobulin and α_1-antiplasmin) so that there is no free fibrinolytic activity. α_2-macroglobulin has some weak antithrombin and anti-Xa activity, while antithrombin III has weak antiplasmin activity. Inhibitors of plasminogen activators are present in platelets and may be of importance in inhibiting plasmin activity within a haemostatic plug.

The mechanisms whereby plasmin causes dissolution of a thrombus are not fully understood. There are three favoured theories which are not mutually exclusive:

1 Diffusion of activators from damaged endothelium may set up a localized fibrinolytic process.

2 Diffusion of plasmin bound to antiplasmin may occur from plasma to thrombus because of the greater affinity of plasmin for fibrin than antiplasmin.

3 Perfusion of the thrombus by circulating plasminogen may result in the activation of the plasminogen by tissue activators in the thrombus.

Plasmin digestion of fibrinogen and fibrin takes place as an orderly sequence. First, large molecular weight breakdown products appear with immunological characteristics similar to the protein of origin. The initial high molecular weight degradation product of fibrinogen or fibrin is called X and is due, principally, to digestion of the α chain of fibrinogen. Its further degradation by plasmin in the case of fibrinogen liberates a smaller molecular weight product with a distinct antigenic site called D, which is a disulphide linked portion of β and γ chains, and the remainder of the degraded now asymmetric molecule is called Y and retains the antigenic properties of the parent molecule. Further digestion of Y leads to two distinct end products of digestion, another molecule of D and a smaller molecular weight product E consisting of disulphide linked *N*-terminal portions of α, β and γ chains. In the case of crosslinked fibrin plasmin digestion proceeds to produce the product X, E and dimers of D (D–D). The scheme of fibrinogen lysis is outlined in Fig. 1.7.

Fibrinogen/fibrin degradation products can act as anticoagulants by absorbing thrombin; interfering with fibrin polymerization and probably with the process of platelet aggregation.

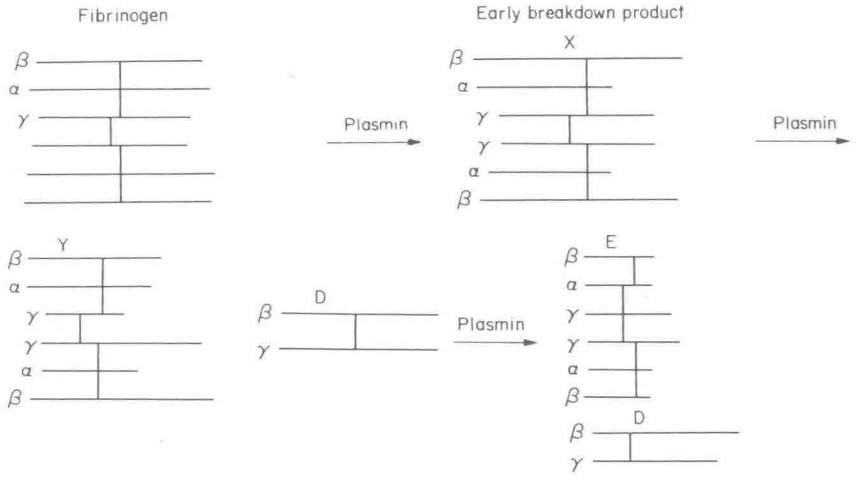

Fig. 1.7 Schematic representation of degradation of fibrinogen by plasmin. Fibrinogen is composed by α, β and γ chains held together by interchain disulphide bonds. Cleavage of predominantly the α chain results in the formation of the large MW (X) breakdown product. Further digestion results in cleavage of β + α polypeptides which are linked by interchain disulphide bond(s) and constitute fragment D. The asymmetric remaining molecule is fragment Y which is further degraded to D and a residual portion linked by *N*-terminal disulphide bonds, fragment E.

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Chapter 2
Investigations of Patients with Suspected Congenital Bleeding Disorders

HISTORY TAKING

Family history

A detailed family history of a bleeding tendency may give an excellent clue to the type of investigations which may most readily establish the diagnosis of the bleeding disorder. Haemophilia and Christmas disease are the most common sex-linked disorders of haemostasis and a family history which shows that males were predominantly affected or that there were unexplained deaths of male infants, suggests sex-linked inheritance. Sometimes with sex-linked inheritance, the family history of bleeding may skip generations when unaffected males were born. In the case of the above type of family history, investigations should be directed at the diagnosis of haemophilia or Christmas disease.

Von Willebrand's syndrome is the second most common disorder of haemostasis. It is usually inherited as an autosomal dominant disorder. Both sexes can be affected and frequently there is a history of bleeding in successive generations. The remainder of the congenital disorders of haemostasis are usually inherited in an autosomal recessive manner. The inheritance pattern of congenital bleeding disorders is summarized in Tables 2.1 and 2.2.

Table 2.1 Inheritance and presenting symptoms in the most common bleeding disorders.

Disease	Inheritance	Most common presenting symptoms
Haemophilia	Sex-linked	Bleeding post-circumcision, mouth trauma, haemarthroses
Christmas disease	Sex-linked	As above
Von Willebrand's syndrome	Autosomal dominant	Epistaxis and excessive bruising, unexpected postoperative haemorrhage
Congenital disorders of platelet function	Autosomal recessive occasionally dominant	As above

Table 2.2 Inheritance and presenting symptoms of rare bleeding disorders.

Disease	Inheritance	Most common presenting symptoms
Factor XI deficiency	Autosomal recessive	None or post-traumatic bleeding, spontaneous bruising, particularly in females
Factor VII deficiency	Autosomal recessive intermediate penetrance	Haemorrhage in newborn period (gastro-intestinal, cord, cerebral), gum bleeding, haemarthroses
Factor XIII	Autosomal recessive	Haemorrhage in newborn period characteristically from umbilical cord. Muscle haematomas
Factor V deficiency	Autosomal recessive ? dominant	Haemarthroses, mouth bleeding, epistaxis
Combined V and VIII deficiency	Autosomal recessive	Bruising, haematuria, bleeding after dental extraction
Factor X deficiency	Autosomal recessive	Easy bruising, epistaxis
Factor II deficiency	Autosomal recessive	Easy bruising, post-traumatic bleeding, epistaxis
Factor I deficiency hypo- and dysfibrinogenaemias	Autosomal recessive	None, post-traumatic bleeding, tendency to recurrent thromboses

GROUPING OF PATIENTS FOR INVESTIGATION

1 History of clinically significant bleeding with family history suggestive of a sex-linked disorder. The activated partial thromboplastin time is prolonged and the prothrombin time is normal. Haemophilia is the most likely diagnosis and can be confirmed by a factor VIII assay. If the factor VIII level is normal, then a factor IX assay may be performed to diagnose Christmas disease.

2 History of clinically significant bleeding with family history suggestive of autosomal dominant inheritance. Von Willebrand's syndrome is the most likely diagnosis. The investigations required to establish it are outlined below (Table 2.3).

3 History of clinically significant bleeding tendency but no family history of bleeding. Although haemophilia is the most likely diagnosis, there are other significant possibilities and in order to diminish the number of venepunctures that may be required to establish the diagnosis, sufficient blood should be sent for screening investigations and specific coagulation factor assays and a bleeding time (BT) should be performed.