explaining the occurrence of thrombosis in an individual. The contribution of this knowledge to better management and prevention of venous thrombosis has not yet been defined.

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Inherited coagulation disorders

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Physiology

Injury to a blood vessel initiates a series of events which result in controlled haemostasis. This involves adhesion and aggregation of platelets and activation of the clotting cascade to form a fibrin clot.

Platelets

When the vascular endothelium is disrupted, platelets adhere to exposed collagen. Although platelets have collagen receptors, under conditions of high shear this interaction is mediated via von Willebrand factor (VWF) which binds to the collagen and also to glycoprotein (GP) Ib on the platelet surface. Platelets then form a plug by binding to each other, a process known as aggregation. They are able to do this because when they are activated a fibrinogen receptor on their surface (GP IIb/IIIa) becomes able to bind fibrinogen. This symmetrical molecule can bridge the gap between platelets, holding them together.

Key Points

Platelet adhesion and aggregation, and blood coagulation are all necessary for haemostasis

A careful history and the judicious use of screening tests are necessary to diagnose a bleeding disorder

Haemophilia is an X-linked deficiency of factor VIII or IX in which clinical severity is predicted by factor levels

von Willebrand disease is a common, but complex, bleeding disorder which is underdiagnosed

Platelets contain storage granules and, when activated, they release their contents which recruit and activate more platelets. Inherited defects include:

- inherited thrombocytopenia
- GP Ib deficiency (Bernard-Soulier disease)
- GP IIb/IIIa deficiency (Glanzmann's thrombasthenia)
- a lack of storage granules (storage pool disease).

These are rare diseases and will not be discussed further.

Coagulation

The classic coagulation cascade is represented in diagrammatic form in Fig 1. It is divided into the intrinsic pathway which begins with contact activation, and the extrinsic pathway initiated by the tissue factor/factor VII (TF/VII) complex. Both these pathways result in activation of factor X which then cleaves prothrombin (II) to release thrombin. This simplified version of coagulation is most useful in interpreting coagulation screen results as these pathways are followed in the test tube. However, physiologically, the TF pathway is important, and *in vivo* coagulation is initiated when perturbed endothelial cells express TF on their surface. Indeed, complete deficiency of the contact factors has no effect on haemostasis. The TF/VII complex, in addition to directly activating factor X, also activates factor IX, and *in vivo* coagulation proceeds this way (Fig 2). Factor IXa in conjunction with its cofactor, factor VIII, then activates factor X. Factor VIII deficiency (haemophilia A) and factor IX deficiency (haemophilia B) are the most important coagulation disorders. Patients with factor XI deficiency exhibit a variable bleeding disorder. It seems that thrombin can activate factor XI, which can then activate factor IX in a positive feedback loop which is important for maintaining coagulation.

The diagnosis of a bleeding disorder

The history is important. The bleeding pattern may give a clue as to whether it is

a platelet or a coagulation problem. The bleeding manifestations of platelet defects often include purpura, petechiae, mucosal bleeding, epistaxis and menorrhagia, whilst coagulation defects often result in haemarthroses and muscle haematomas. It is important to try to ascertain whether the bleeding tendency is new or whether it has been lifelong. Particular attention must be paid to any previous operations or dental extractions. A family history of bleeding and the pattern of inheritance is also important. Examination should be directed to the pattern of bleeding and looking for evidence of any underlying disease. If a bleeding disorder is suspected, the investigations in Table 1 can be performed.
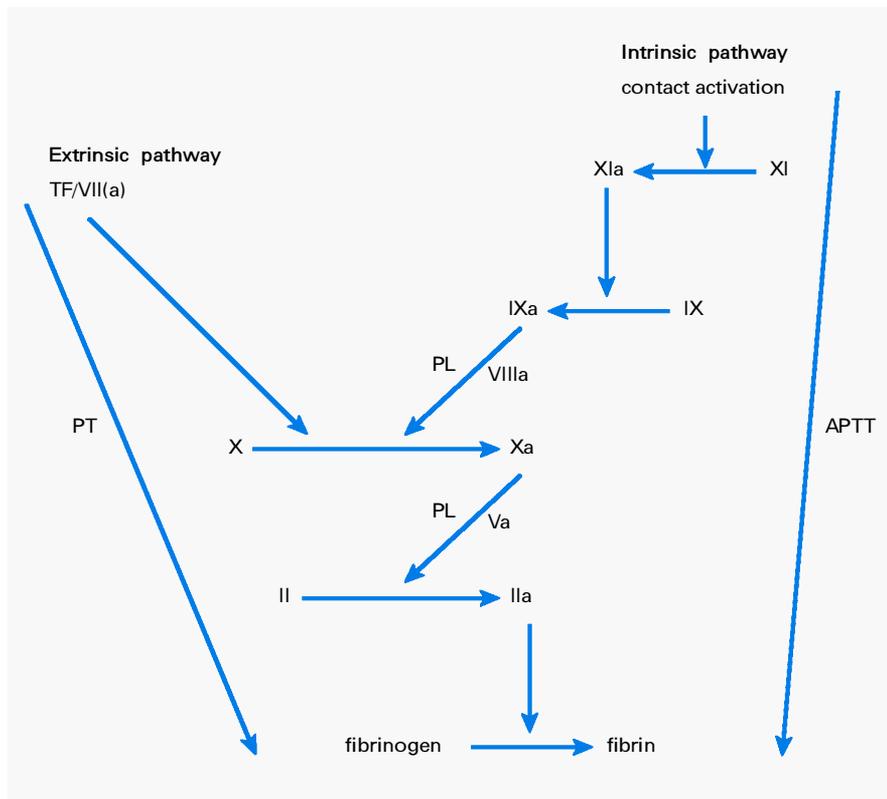

Fig 1. **Coagulation *in vitro*** (PL = phospholipid; PT = prothrombin time; APTT = activated partial thromboplastin time; TF/VII = tissue factor/factor VII).
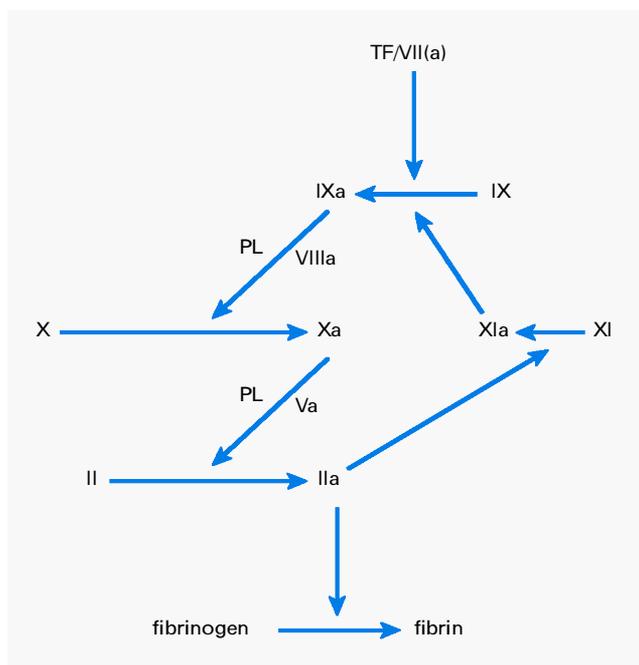

Fig 2.
Coagulation *in vivo*
(PL = phospholipid;
TF/VII = tissue factor/
factor VII).

Coagulation screen

The routine coagulation screen consists of an activated partial thromboplastin time and a prothrombin time. Fig 1 indicates which coagulation factor deficiencies will affect which of these tests. A full blood count will confirm the platelet count. A bleeding time has traditionally been used to assess platelet function, but this is time-consuming, operator dependent and lacks sensitivity. It is therefore being replaced in many haemostasis units by an *in vitro* alternative using the PFA 100 platelet function analyser. Whether this is sufficiently sensitive is not yet clear. If a bleeding disorder is strongly suspected, platelet aggregation and specific tests for von Willebrand disease should be performed.

Haemophilia

- *Haemophilia A*: an X-linked congenital deficiency of factor VIII which affects about one in 5,000 of the male population; 30% of cases arise as new mutations without any previous family history.
- *Haemophilia B*: a clinically indistinguishable disorder due to deficiency of factor IX, affecting one in 25,000 of the male population.

In its severe form, haemophilia is characterised by:
- recurrent spontaneous joint bleeds
- intramuscular bleeding
- excessive bruising after trauma.

Severity of the condition depends upon the level of factor in the blood (Table 2). Female carriers of haemophilia may have reduced levels of factor VIII (or IX) which may not be sufficient to ensure good haemostasis after surgery or dental work.

Bleeding in patients with mild haemophilia A may respond to treatment with desmopressin (DDAVP) (see below

Table 1. Investigation of a suspected bleeding tendency.

- Prothrombin time/Activated partial thromboplastin time
- Full blood count
- Bleeding time/Platelet function analyser
- Platelet aggregation
- Factor VIII, VWF activity, VWF antigen

VWF = von Willebrand factor.

Table 2. In haemophilia A and B the factor level accurately predicts the clinical severity.

Level of factor VIII or IX (%)	Clinical state
<2%	Severe haemophilia: frequent spontaneous haemorrhages, and bleeding after any trauma
2–5	Moderate haemophilia: only occasionally spontaneous haemorrhage. Excessive bleeding after any trauma
5–25	Mild haemophilia: excessive bleeding after any operation or accident. Spontaneous haemorrhage very rare
25–50	Very mild haemophilia: bleeding a problem only after surgery or major accident

under von Willebrand disease). Otherwise, treatment is with lyophilised plasma-derived concentrates or recombinant factor VIII (or IX). As many as 15,000 donors contribute to one batch of plasma-derived concentrate, and in the past patients have been exposed to hepatitis C and HIV. Blood donors are now screened for these viruses, and the plasma-derived concentrates are subject to viral inactivation procedures, but concern always remains about new infective agents such as variant Creutzfeldt-Jakob disease. Because of this theoretical risk, UK plasma is no longer used to make plasma products. Recombinant products are the treatment of choice.

In severe haemophiliacs the main goal of treatment is to prevent chronic haemophilic arthropathy due to repeated bleeds. This can be achieved by starting children with severe haemophilia on prophylactic therapy (eg 25 u/kg of factor VIII three times a week) when joint bleeds start, usually around age two.

The most worrying aspect of treatment is the development of significant antibodies to factor VIII or IX which occurs in approximately 5% and 1% of patients, respectively. Immune tolerance with regular factor VIII can be achieved in the majority but is very expensive. When antibodies are present, alternative treatments such as porcine factor VIII, recombinant VIIa, or activated prothrombin complex concentrates are often needed.

von Willebrand disease

VWF is a large glycoprotein produced in endothelium and megakaryocytes. It exists as a series of multimers of molecular weight 800–20,000 kDa. The high molecular weight multimers are the haemostatically most effective form. VWF has two main functions:

1 As a carrier protein for coagulation factor VIII.

2 As an adhesive protein involved in endothelium-platelet interaction (see above).

Inherited defects in VWF may therefore cause bleeding by impairing either platelet adhesion or blood clotting. Up to 1% of the population may have von Willebrand disease as defined by reduced levels of VWF, but only about 125 per million have a clinically significant bleeding disorder. von Willebrand disease is now subclassified into three major categories (Table 3) and type 2 disease is subclassified into four further variants (Table 4).

The most common form of the disease is a partial quantitative deficiency (Type 1) inherited as an autosomal dominant trait. The most common qualitative defect is a loss of the more effective high molecular weight multimers (Type 2A). Type 2B is unusual in that an increased affinity for glycoprotein Ib results in loss of VWF and often platelets leading to reduced activity and thrombocytopenia. Type 2N disease is distinctive; a mutation in the factor VIII binding site gives phenotypic mild haemophilia whilst platelet dependent VWF activity remains

Table 3. Classification of von Willebrand disease.

Subclassification	Type of defect	VWF Protein	% of cases
1	Quantitative Partial deficiency	Normal	75
2	Qualitative Functional deficiency	Abnormal	20
3	Quantitative Complete deficiency	Absent	5

VWF = von Willebrand factor.

Table 4. Secondary classification of type 2 von Willebrand disease.

Subtype	Functional defect
2A	Reduced platelet function due to loss of high molecular weight multimers
2B	Increased binding to glycoprotein Ib
2M	Reduced platelet function despite normal multimer distribution
2N	Reduced binding to factor VIII

normal. The rare autosomal recessive Type 3 disease is a severe disorder.

Management of von Willebrand disease

At present, two main options are available for the management of patients with von Willebrand disease: DDAVP and blood products containing VWF. In addition, tranexamic acid, an anti-fibrinolytic agent, can be used alone in the management of epistaxis and menorrhagia and it is used in combination with DDAVP- or VWF-containing concentrates to cover dental extractions and surgery.

DDAVP causes VWF to be released from endothelial stores. The mechanism for the rise in factor VIII was thought to be due to its consequent stabilisation in plasma. However, the use of DDAVP in type 2N disease indicates that it must also release factor VIII from a storage pool. It is often effective in type 1 disease where increasing levels 2-5 fold is sufficient for haemostasis. It is of no use in type 3 disease. In types 2A and 2M, increasing the levels of the abnormal VWF has a variable effect. DDAVP therapy is controversial in type 2B disease as the release of the abnormal VWF may induce platelet agglutination and thrombocytopenia. If DDAVP cannot be used or is ineffective, a plasma-derived concentrate must be used.

Further reading

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Evidence-based management of deep vein thrombosis and pulmonary embolus

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Diagnosis of deep vein thrombosis[1,2]

Deep vein thrombosis (DVT) most commonly arises in the leg. The diagnosis is designated distal when thrombus is confined to the calf, and proximal when the thrombus extends into the popliteal, femoral or iliac veins. Recent studies indicate that DVT is present in fewer than one in four ambulant outpatients presenting with symptoms or signs suggestive of this diagnosis. Pulmonary embolus (PE) is present in at least 50% of patients presenting with DVT, indicating that PE and DVT are clinical manifestations of a single pathological process, venous thromboembolism (VTE). However, at presentation only one in five patients with VTE has symptoms due to PE.

The clinical assessment of symptoms and signs can do no more than raise a suspicion of the diagnosis. Objective diagnostic methods must be used to confirm or exclude DVT and/or PE. There is increasing interest in the negative predictive value of D-dimer tests, which can be used to limit the use of radiology. D-dimer is a fibrin degradation product indicative of *in vivo* thrombin activity. Rapid enzyme-linked immunosorbent assays (ELISA) and automated latex agglutination methods are both quick and sensitive. D-dimer tests should be used in conjunction with pre-test clinical probability scoring because the negative predictive value depends not only on the sensitivity and specificity of the test but also on the prevalence of VTE. Thus, a patient with a negative D-dimer result but a moderate pre-test clinical probability score (see Table 1) still has about a one in 50 risk of VTE, whereas a patient with a high pre-test clinical probability score has a one in five risk of VTE even with a negative D-dimer result[3].

Initial therapy: anticoagulation

Anticoagulation is standard therapy for patients with VTE who are clinically stable (other treatment options are shown in Table 2), except patients in whom anticoagulation is contraindicated. Insertion of a vena caval filter may be more appropriate. Some patients are haemodynamically unstable and may benefit from initial thrombolytic therapy before starting anticoagulation.

Unfractionated heparin

Unfractionated heparin (UFH) should be given either as a continuous intravenous infusion or by twice daily subcutaneous injection at a dose sufficient to prolong the activated partial thromboplastin time ratio to 1.5–2.5 times normal (level Ia). (The levels of evidence are according to the US Agency for Health Care Policy and Research, summarised in the British Committee for Standards in Haematology (BCSH) guidelines on oral anticoagulation[4]). Weight-based dosing schedules have been developed for both intravenous and subcutaneous therapy. Treatment with heparin should continue for at least five days (level Ib) and until the international normalised ratio (INR) is therapeutic. For patients with large thromboses heparin may be administered for a longer period (up to 10 days).

UFH should be reserved for the small number of patients who require emergency invasive procedures when it is useful to be able to 'turn on and off' the anticoagulant effect at will. This is not possible with once daily administration of low molecular weight heparins (LMWHs). Furthermore, the anticoagulant effect of UFH can be