## Causes of Normal Fluidity of Blood

In healthy conditions, blood does not clot inside vessels because:

1. heparin is present in plasma.
2. clotting factors, e.g. prothrombin & fibrinogen exist in plasma in an inactive from , or removal of some from the circulation by the liver.
3. the blood clotting factors are also reduced to some extent that they are used up during clotting.
4. the liberation from clotting blood of substances that inhibit further clotting (fibrin or fibrinogen degradation products.
5. endothelial lining of vessel is smooth no sticking of platelets to it because both the lining & the platelets have negative charges repelling platelets away from lining.
6. antithrembin III: inhibits the action of thrombin as well as 1Xa, Xa , X1a & X11a.
7. thrombin is bound by a specific receptor on endothelial cells, thrombomodulin. The result of this interaction is conversion of circulating protein C to its active form, Ca , protein Ca in the presence of phospholipid, $Ca^{2+}$ & a co-factor, protein S, inactivates factor V & VII & thus limits the generation of thrombin. Proteins C & S require vitamin K for their synthesis in the liver & protein Ca also enhances fibrinolysis.
8. two other proteins, $\alpha_2$ -macroglobulin &$\alpha_1$ antitrypsin, also contribute to the antithrombin effect of plasma.
9. fibrinolytic system.

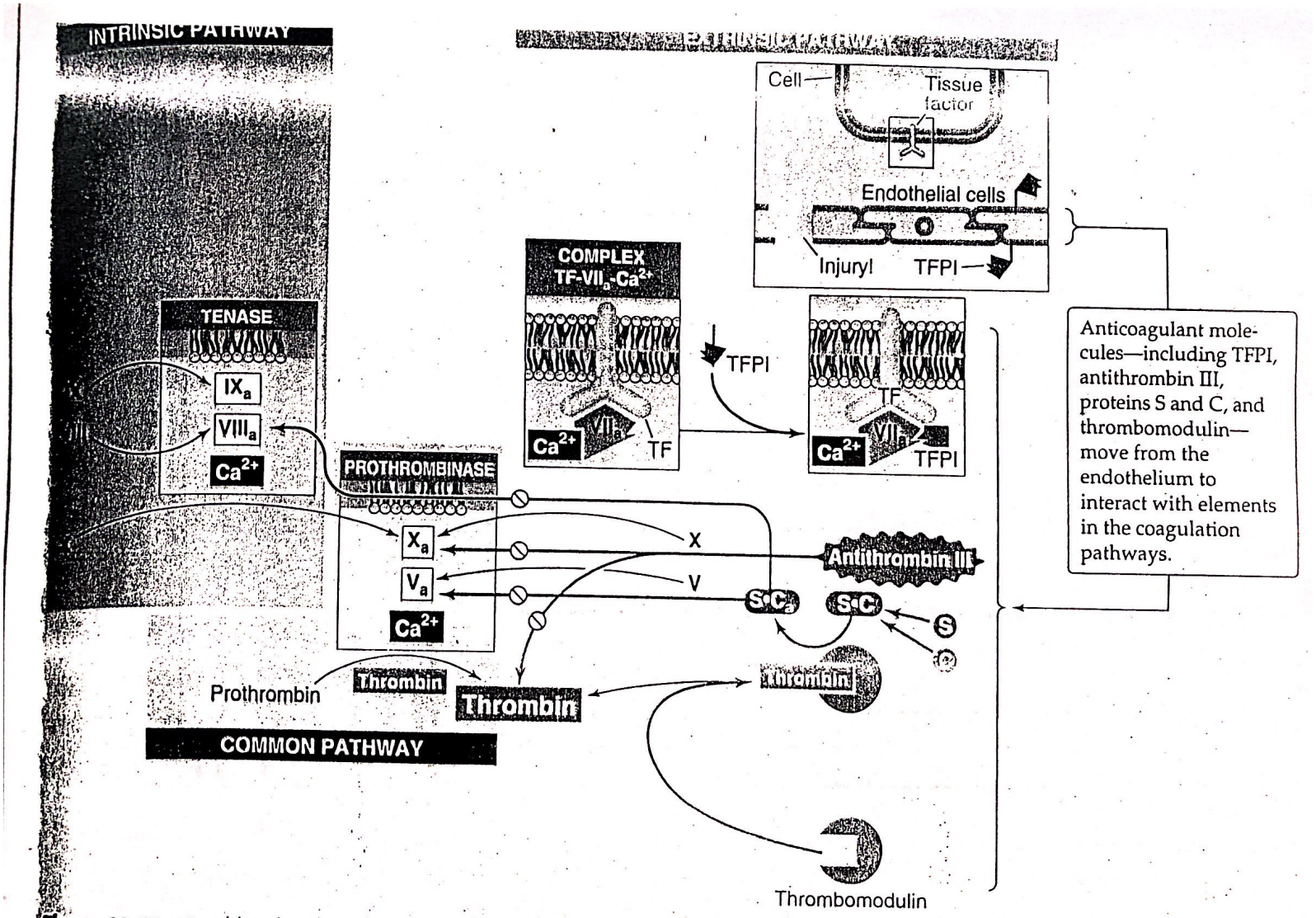



**Figure 18-13** An abbreviated version of the coagulation cascade, showing the anticoagulant factors. The

# Clot retraction

Following the coagulation of blood, the clot gradually shrinks as *serum* is extruded from it. The exact mechanism of this process is not understood but it is believed to be initiated by the action of thrombin on platelets. One idea is that thrombin causes the release of intracellularly stored calcium into the platelet cytoplasm. This calcium then triggers the contraction of contractile proteins within the platelets by a process resembling the contraction of muscle. The contractile process may then cause the extrusion of pseudopodia from the platelets. These stick to the fibrin strands within the clot and, as they contract, the fibrin strands are pulled together, at the same time squeezing out the entrapped fluid as serum.

## Dissolution of the clot

Once the wall of the damaged blood vessel is repaired, the blood clot is removed by lysis. Activated Factor XII stimulates the production of a substance in the plasma known as *kallikrein*. In turn, kallikrein promotes the conversion of inactive *plasminogen* into active *plasmin*, an enzyme that digests fibrin and thus brings about dissolution of the clot.

Various other plasminogen activators are used clinically to promote the dissolution of clots. These include *streptokinase*, a substance produced naturally by certain bacteria, and an endogenous substance called *tissue plasminogen activator* (TPA) which can now be produced commercially by genetic engineering. These substances can be injected either into the general circulation or into a specific blood vessel that contains a clot to promote lysis of the clot.

# FIBRINOLYSIS

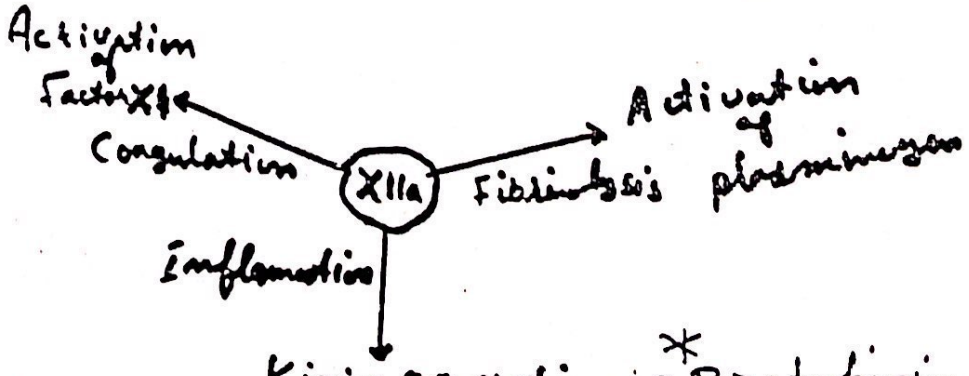
(1) Fibrinolysis (like Coagulation) is a normal haemostatic response to vascular injury.

(2) Plasminogen, a beta globulin pro-enzyme in blood and tissue fluid. It is made by the liver and to a lesser extent by eosinophils and by intravascular endothelium.

(3) Plasminogen is converted to Plasmin by activators either from the vessel wall (intrinsic activation) or from the tissues (extrinsic activation)

(4) Release of Circulating Plasminogen activator from endothelial cells occurs after such stimuli as trauma, exercise or emotional stress.

(5) Activated factor XII also Potentiates the action of Plasminogen activator.




* The central role of F. XII in reactions of Coagulation, Fibrinolysis and inflamation

* Bradykinin: Increases Vascular permeability and is a vasodilator.

See next pages,

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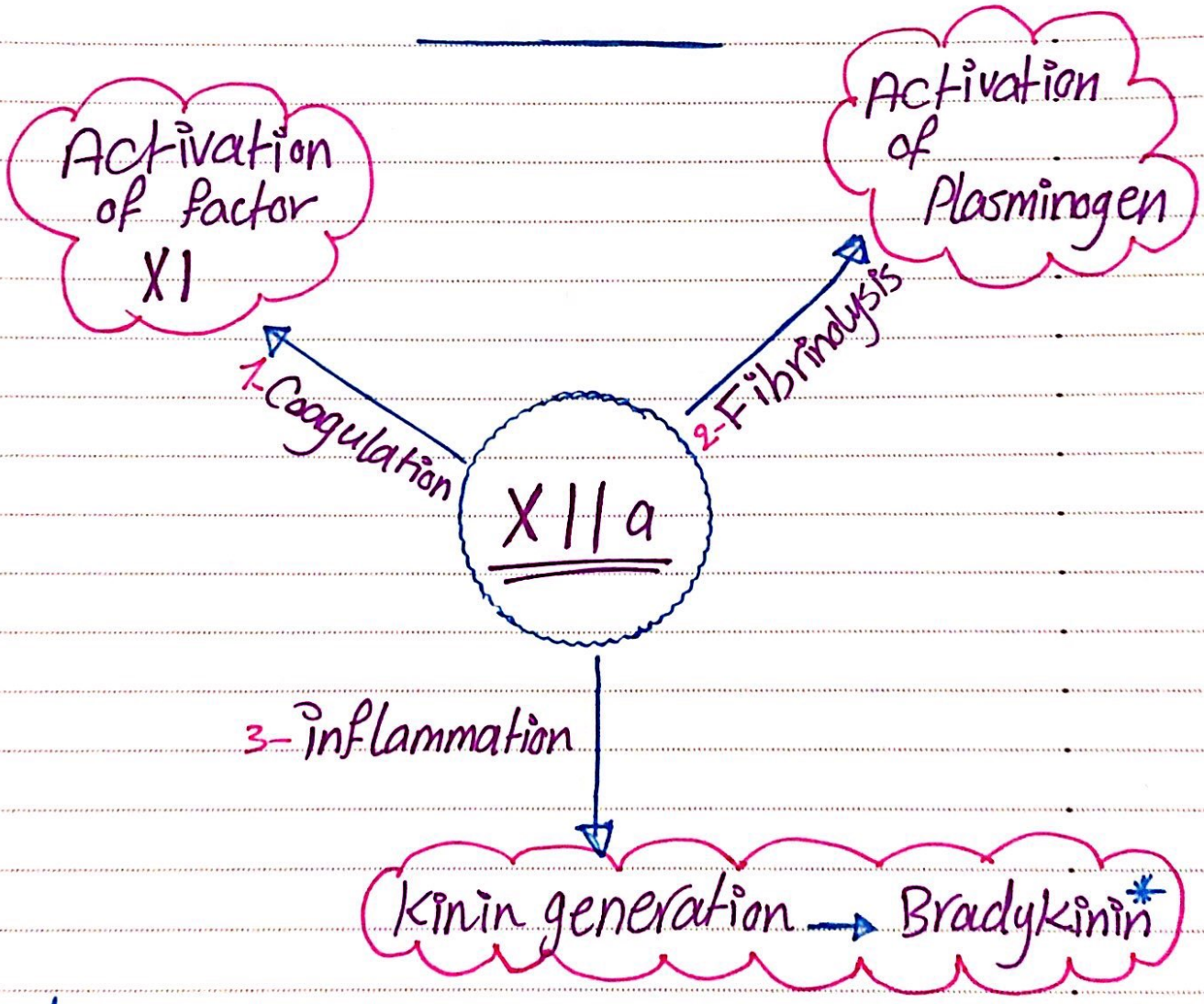


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⟹ The central role of Factor XII in reactions of: 1Coagulation, 2fibrinolysis, and 3inflammation.

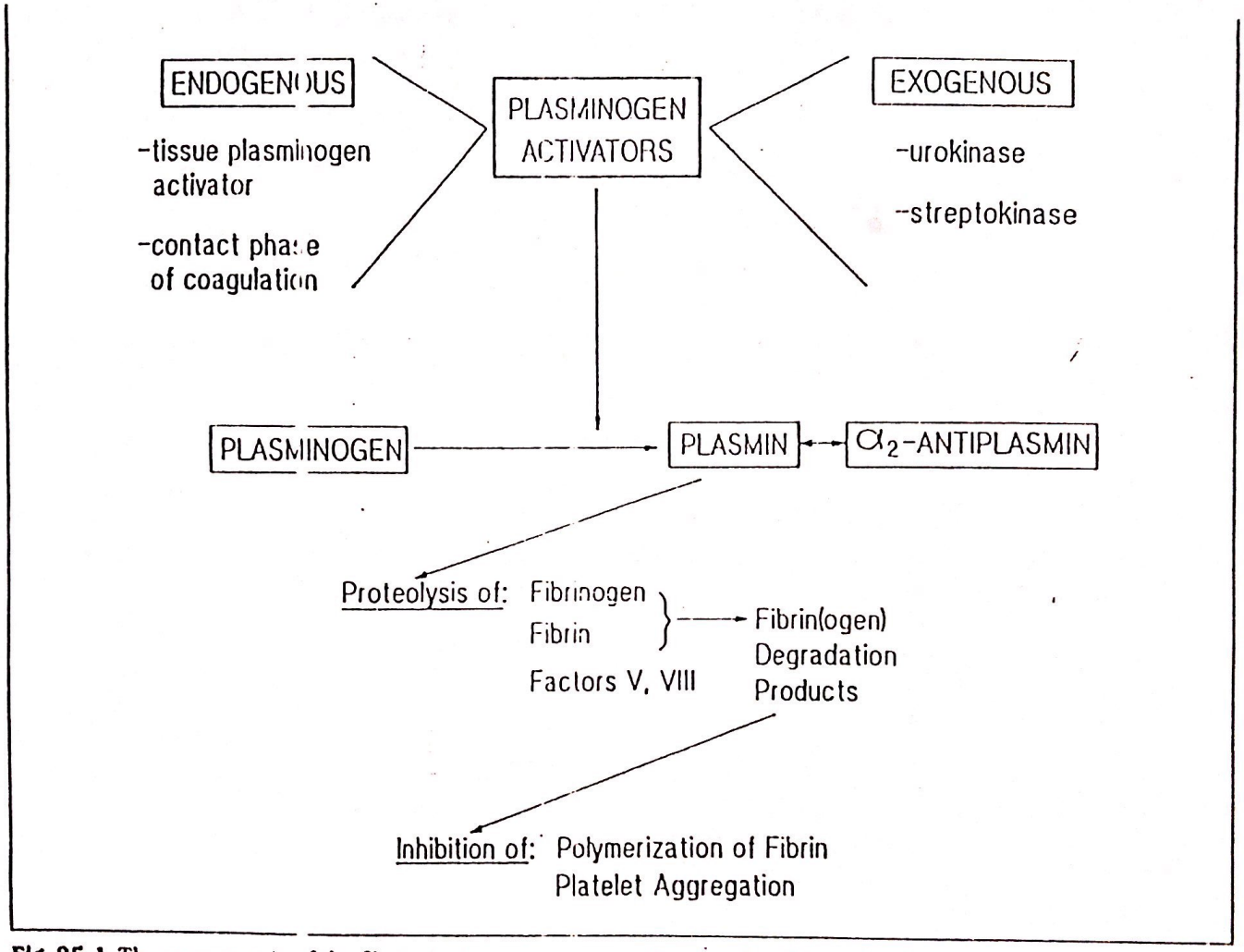


**Fig. 25-1.** The components of the fibrinolytic enzyme system. (See text for elaboration.)

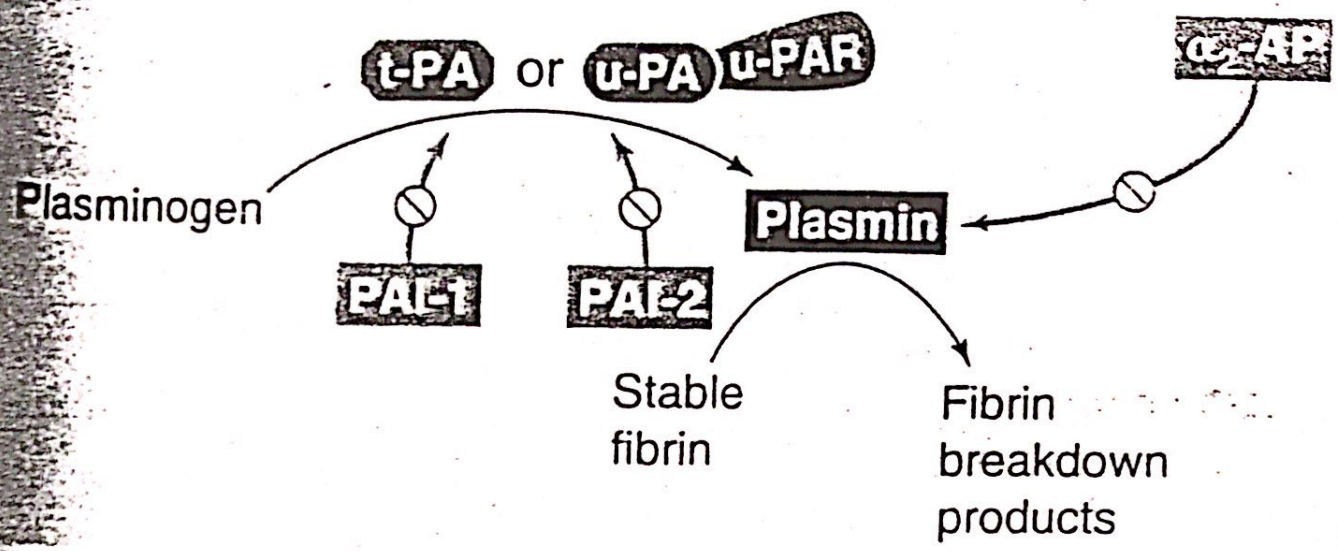


**Figure 18-14** The fibrinolytic cascade.

## CLASSIFICATION OF HAEMOSTATIC DEFECTS

Although the action of platelets, the clotting mechanism and the integrity of th vascular wall are all closely related in the prevention of bleeding, it is convenier to consider that abnormalities in haemostasis arise from defects in one of thes three processes. The commonest cause of bleeding is undoubtedly a deficienc of platelets; the second commonest cause is an abnormality in the clotting mechanism. The remaining patients do not have any demonstrable lesion of the platelets or clotting mechanism and appear to be bleeding as a result of vascular abnormalities.

## Thrombocytopenic purpura

When the platelet count is low, clot retraction is deficient and there is poor constriction or ruptured vessels.Is characterized by easy bruisability and multiple subcutaneous hemorrhages.

## Thrombasthenic purpura .

Purpura may also occur when the platelet count is normal, and in some of these cases, the circulating platelets are abnormal

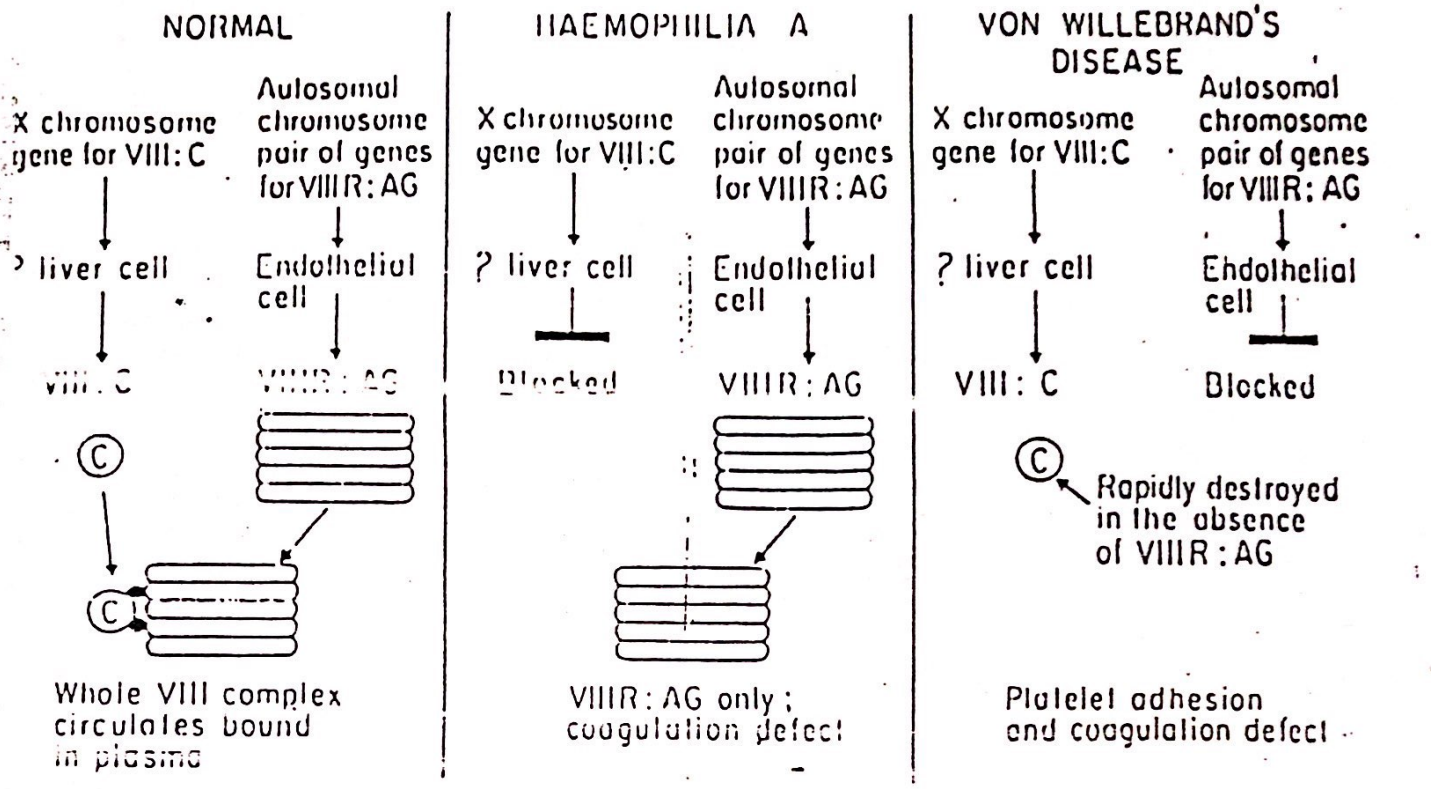


Fig. 13.2 The synthesis of factor VIII in normal individuals, in haemophilia A and in von Willebrand's disease.

## Clinical features

Severely affected infants may suffer from profuse post-circumcision haemorrhage. Prolonged bleeding occurs after dental extraction. Operative and post-traumatic haemorrhage are life-threatening both in severely and mildly affected patients.

Table 13.2 Main clinical and laboratory findings in haemophilia A, factor IX deficiency (haemophilia B, Christmas disease) and von Willebrand's disease.

| | Haemophilia A | Factor IX deficiency | Von Willebrand's disease |
|---|---|---|---|
| Inheritance | Sex-linked | | Dominant |
| Platelet count | Normal | Normal | Normal |
| Bleeding time | Normal | Normal | Prolonged |
| Factor VIII:C | Low | Normal | Low |
| Factor VIII:AG | Normal | Normal | Low |
| aggregation | Normal | Normal | Impaired |

## Hereditary Disorders of other Coagulation Factors:

1- All these disorders are rare.
2- In most inheritance is autosomal.
3- There is usually a good correlation between the patient's symptoms and the severity of the coagulation deficiency.
4- F. XII deficiency is not associated with abnormal bleeding
5- F. XI deficiency produces mild symptoms. (Haemophilia C)
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