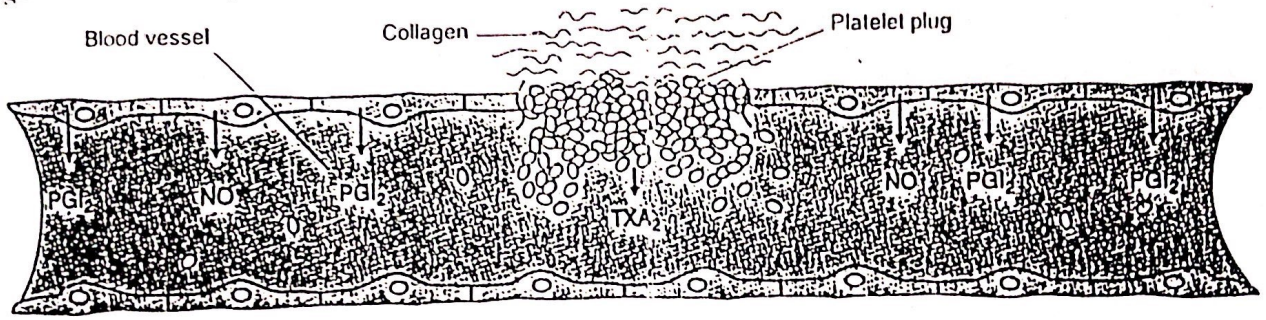
FIGURE 20-21

Platelets produce thromboxane A_2 (TXA_2), whereas normal endothelium adjacent to a platelet plug produces prostaglandin I_2 (PGI_2) from platelet and endothelial-cell arachidonic acid, and this eicosanoid inhibits platelet aggregation. Nitric oxide, NO, also secreted by the endothelial cells, does the same thing as PGI_2. Thus, PGI_2 and NO prevent spread of platelet aggregation from the damaged site.



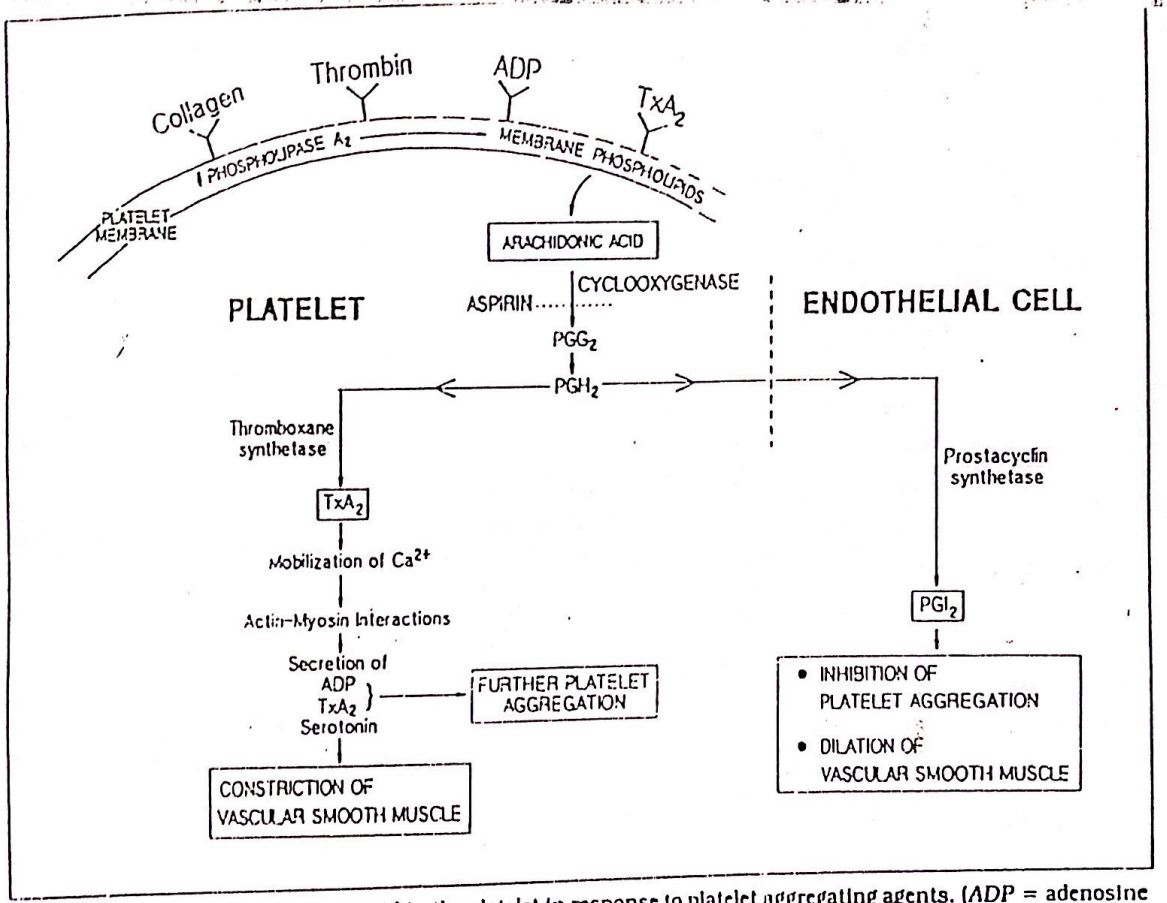


Fig. 24-3. Oxidation of arachidonic acid in the platelet in response to platelet aggregating agents. (*ADP* = adenosine diphosphate; TxA_2 = thromboxane A_2; PGG_2 and PGH_2 = cyclic endoperoxides; PGI_2 = prostacyclin.) Metabolism of arachidonate via the lipoxygenase pathway, leading to the formation of leukotrienes is not shown; its potential role in the platelet aggregation response is not clearly known. To the right of the dashed line is depicted the metabolism of endoperoxides by the endothelial cell.

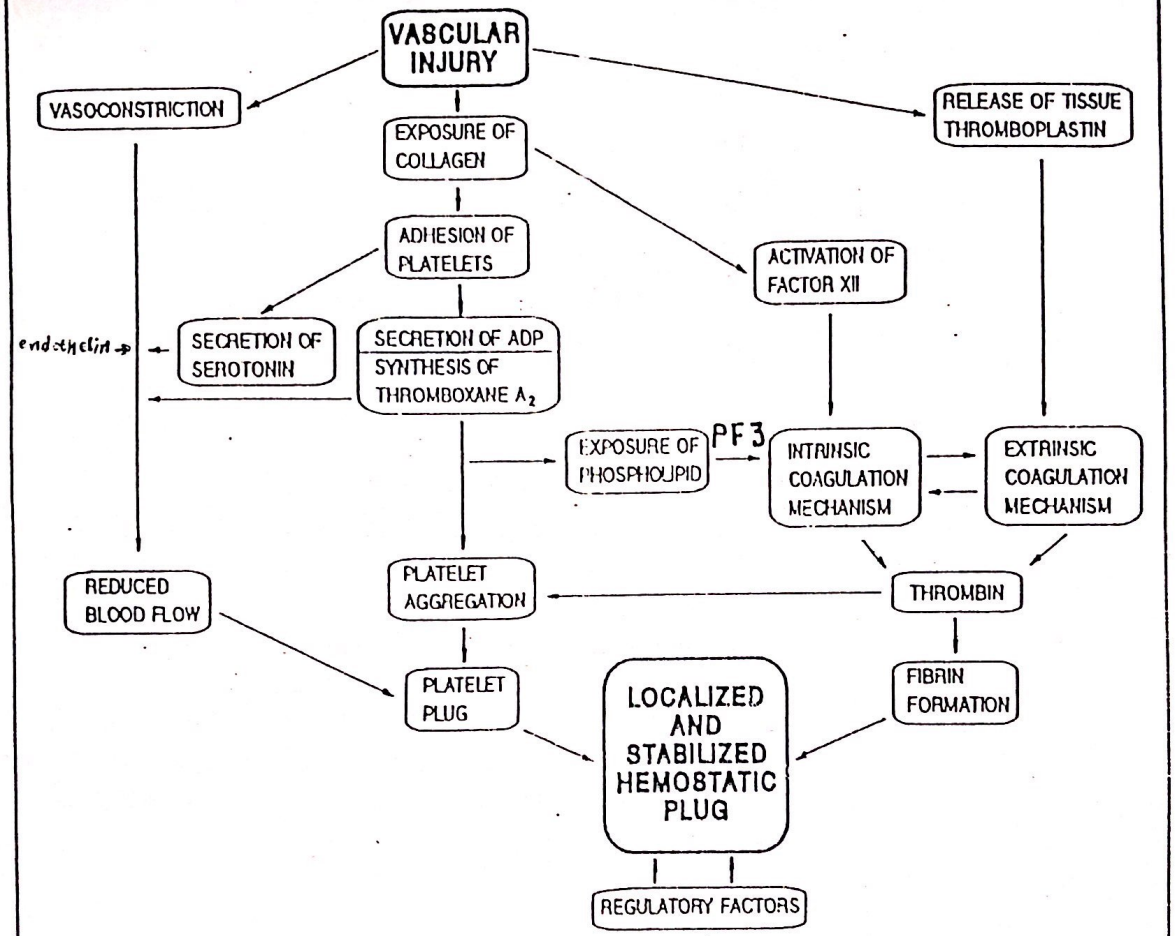


Fig. 25-4. Summary of the integrated hemostatic response to vessel injury. (See text description.)

Table 10.1 Major blood clotting factors

Factor	Name (synonyms)	Site of formation
I	Fibrinogen	Liver
II[a]	Prothrombin	Liver
III	Tissue thromboplastins	Tissue cells (membrane protein)
IV	Calcium ions	
V[b]	Labile factor	Mainly liver
VII[a]	Stable factor	Liver
VIII[b]	Anti-haemophiliac globulin A (AHG)	Platelets, RES endothelial cells, liver
vWF	von Willebrand's factor	Endothelial cells, platelets
IX[a]	Anti-haemophiliac globulin B (Christmas factor)	Liver
X[a]	Stuart factor	Liver
XI	Plasma thromboplastin antecedant factor (PTA)	Liver
XII	Hageman factor	Liver
XIII	Fibrin stabilizing factor	Liver
TF3	Platelet factor 3	Platelets

Note
[a] vitamin K-dependent [b] pro-cofactors

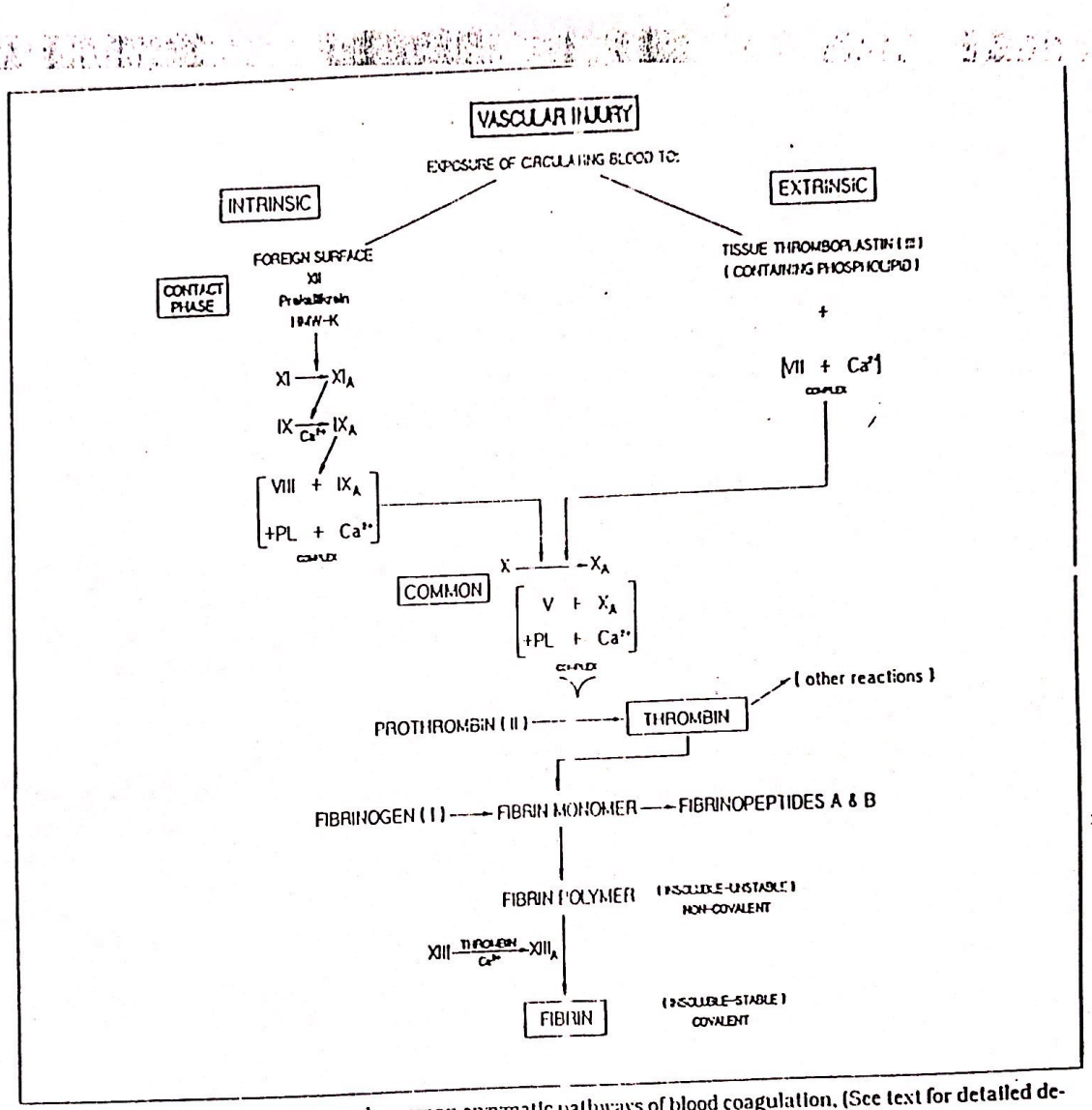


Fig. 24-5. The intrinsic, extrinsic, and common enzymatic pathways of blood coagulation. (See text for detailed description.) (*HMW-K* = high-molecular-weight kininogen; *PL* = phospholipid.)

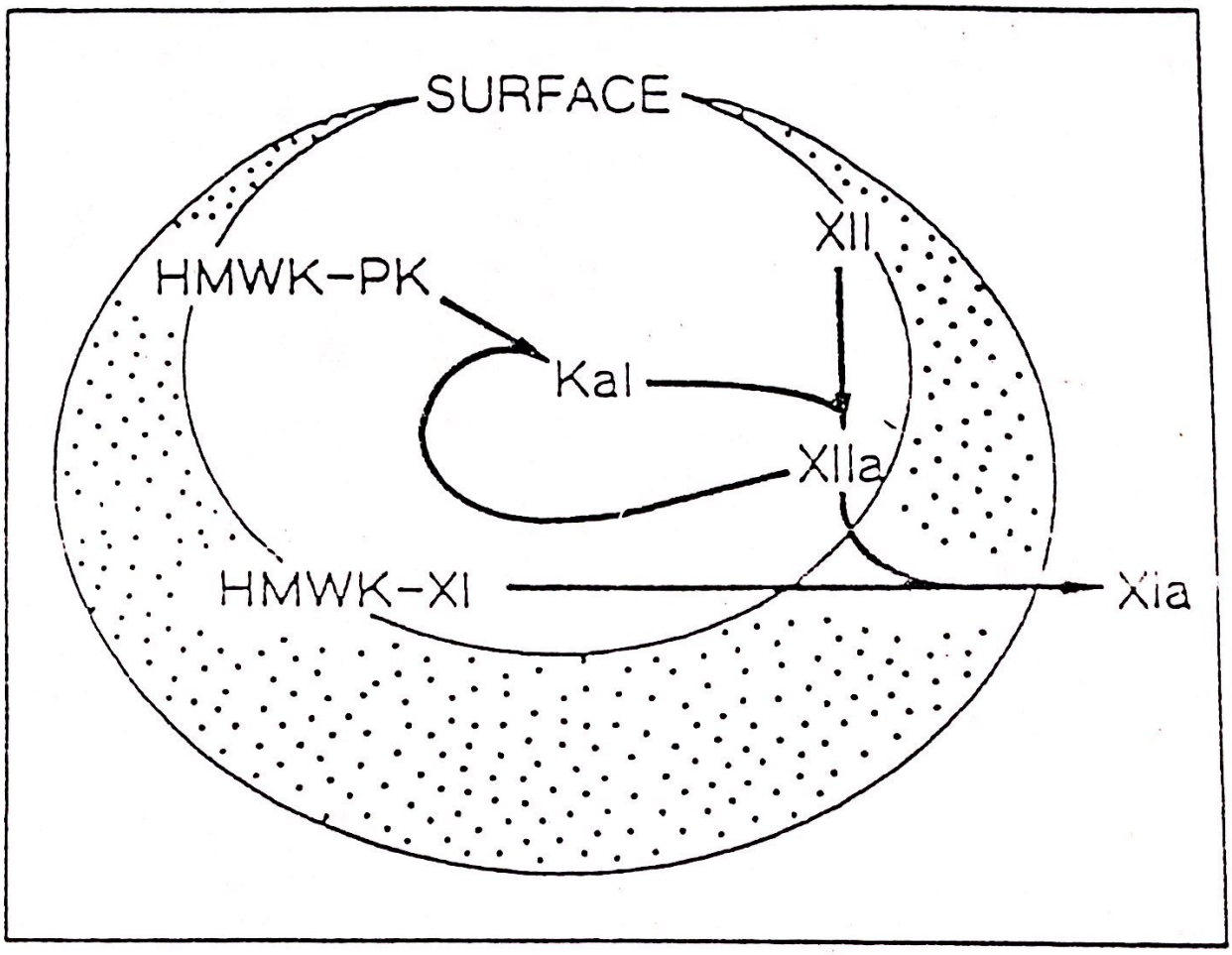


Fig. 24-6. The contact phase of blood coagulation, showing the reactions leading to the activation of factor XI when blood is exposed to a negatively charged foreign surface. (See text for the other explanation.) (*HMWK* = high-molecular-weight kininogen; *PK* = prekallikrein; *Kal* = kallikrein.)

Additional points on the clotting system

1 Both intrinsic and extrinsic pathways are necessary for normal haemostasis.

2 Both pathways are activated when blood leaves the blood-vessels for the tissues.

3 Thrombin is a key factor in both the intrinsic and extrinsic systems, in addition to its action on fibrinogen.

4 The activation of the clotting mechanism along the shorter extrinsic pathway results in the rapid formation of thrombin, which feeds back to activate the intrinsic pathway through factors VII and V. Factor VII can activate factor X to active factor X, and this forms an activation connection between both pathways.

5 Thrombin stimulates platelets to release ADP and TXA_2 and therefore enhances further aggregation of platelets.

6 Thrombin is essential for platelet morphological changes during haemostasis, which lead to the formation of the primary haemostatic plug.

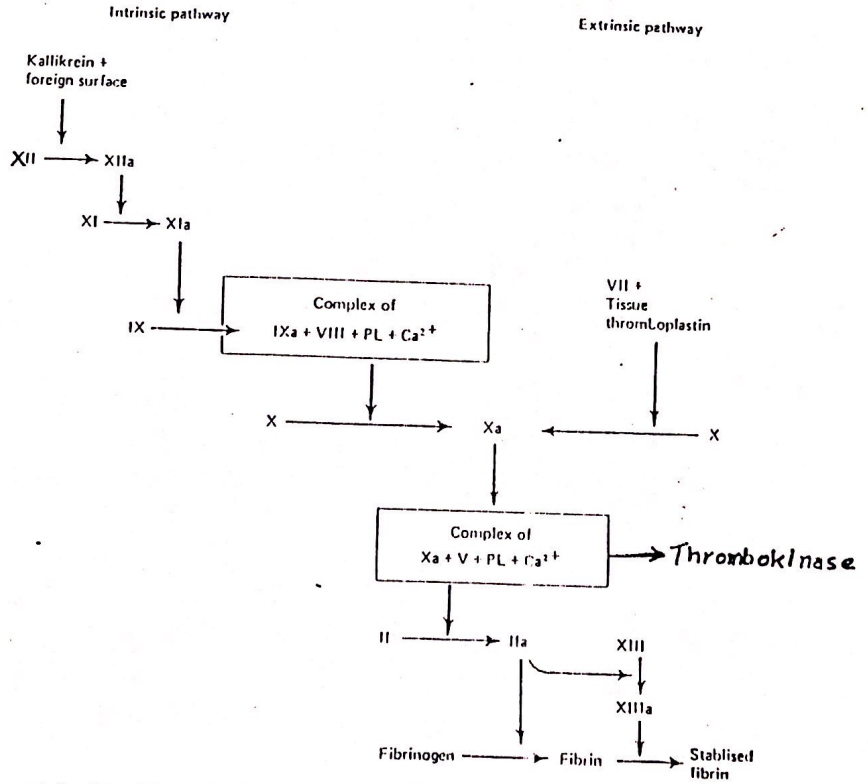
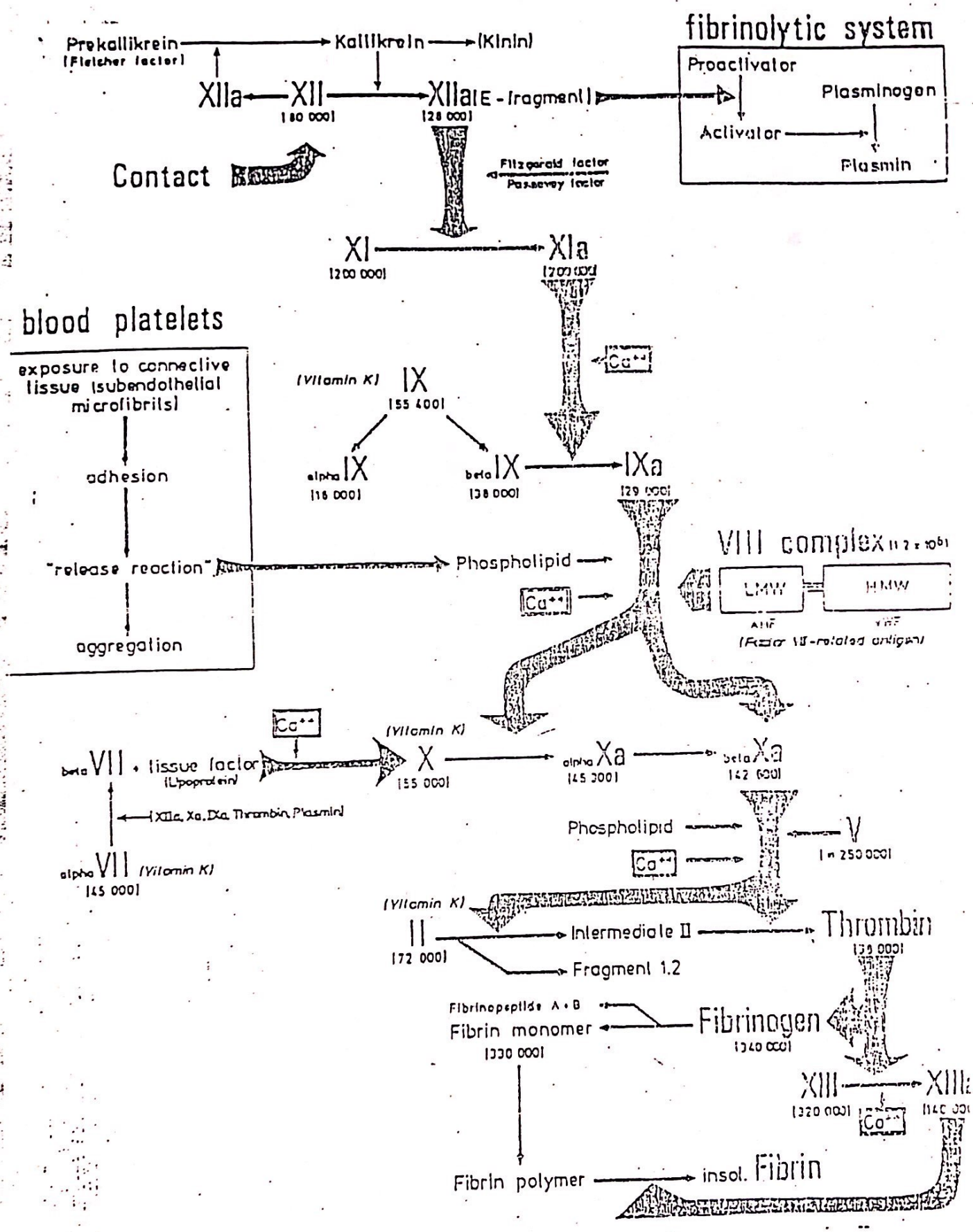


Fig. 4.21 The coagulation 'cascade'. 'Intrinsic' means intrinsic to plasma since all the factors can be generated from plasma. The extrinsic pathway requires tissue factors from outside the plasma. Extrinsic coagulation is more rapid and less inhibited than the intrinsic process, fewer steps being involved. PL = platelet phospholipid (Factor III)



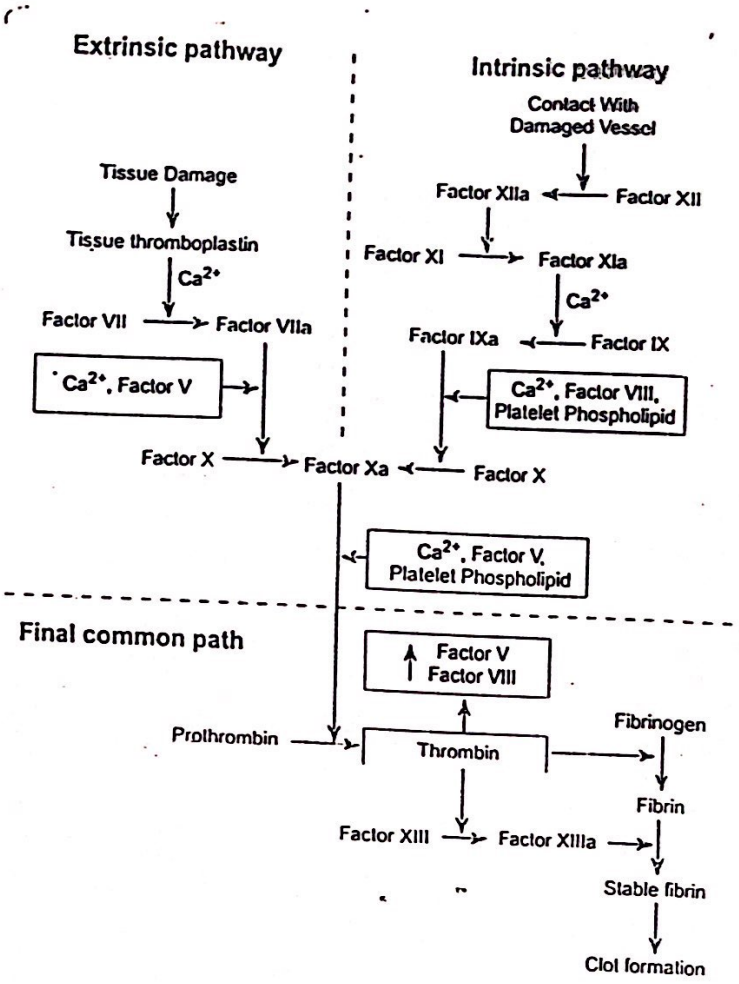


Fig. 13.11 The extrinsic and intrinsic pathways leading to the formation of a blood clot. Note the central roles played by Factor Xa and thrombin in the process of blood coagulation.

The role of calcium in hemostasis

As Fig. 13.11 shows, calcium ions are required for each step in the clotting process except for the first two reactions of the intrinsic pathway. Adequate levels of calcium ions are therefore necessary for normal clotting. In reality, plasma calcium levels never fall low enough to impair the clotting processes since death would have resulted from other causes (most notably tetany of the respiratory muscles) long before. It is, however, possible to prevent the coagulation of blood removed from the body and stored *in vitro* by reducing the calcium ion concentration of the plasma. This may be achieved by the addition of substances such as EDTA (ethylenediaminetetraacetic acid) or citrate, which bind calcium.

BLOOD COAGULATION

The coagulation reaction may be initiated in two different ways. The first is by exposure of the plasma to a foreign surface, that is a surface bearing a negative electrical charge, which in some way causes alteration and activation of factors XI and XII. The product of this reaction is activated factor XI - usually designated as XIa which then acts on factor IX to give IXa. Factor IXa then combines with factor VIII and with phospholipid from platelets to activate factor X. Factor X similarly complexes with factor V, calcium and phospholipid to form thrombokinase (sometimes called thromboplastin). Thrombokinase activates factor II (prothrombin) to form thrombin. It will be noted that apart from the 'foreign surface' all the components of this reaction chain are contained in the blood, hence the name intrinsic coagulation system. In the second coagulation reaction, the extrinsic system, the surface activated reactions of the intrinsic system are bypassed; phospholipid and protein from injured tissue (also sometimes called thromboplastin) combine with calcium to activate factor X; from this point onwards the reactions are as in the intrinsic system. In both systems the function of the phospholipid seems to be physical rather than chemical, the lipid-protein micelles forming a suitable surface on which the reactions may take place.

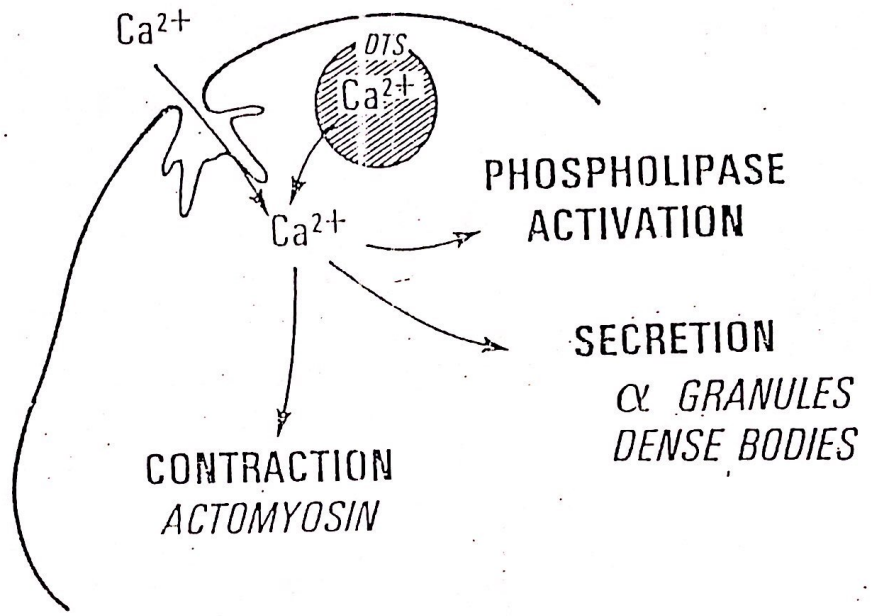


Figure 3.32. The flow of calcium into the cytoplasm of the platelet after stimulation and responses that this inititates. DTS, dense tubular system.

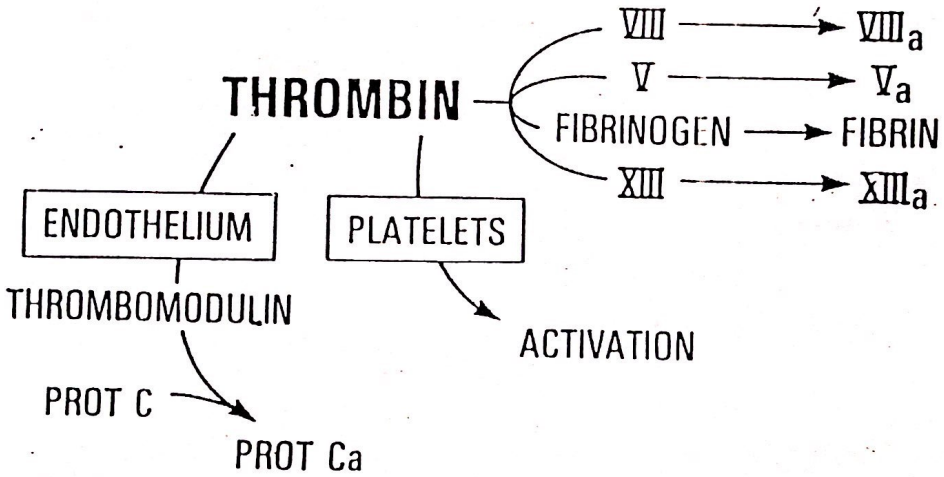


Figure 3.27. The multiple actions of thrombin in blood coagulation. *Prot C*, protein C; *Prot Ca*, activated protein C.

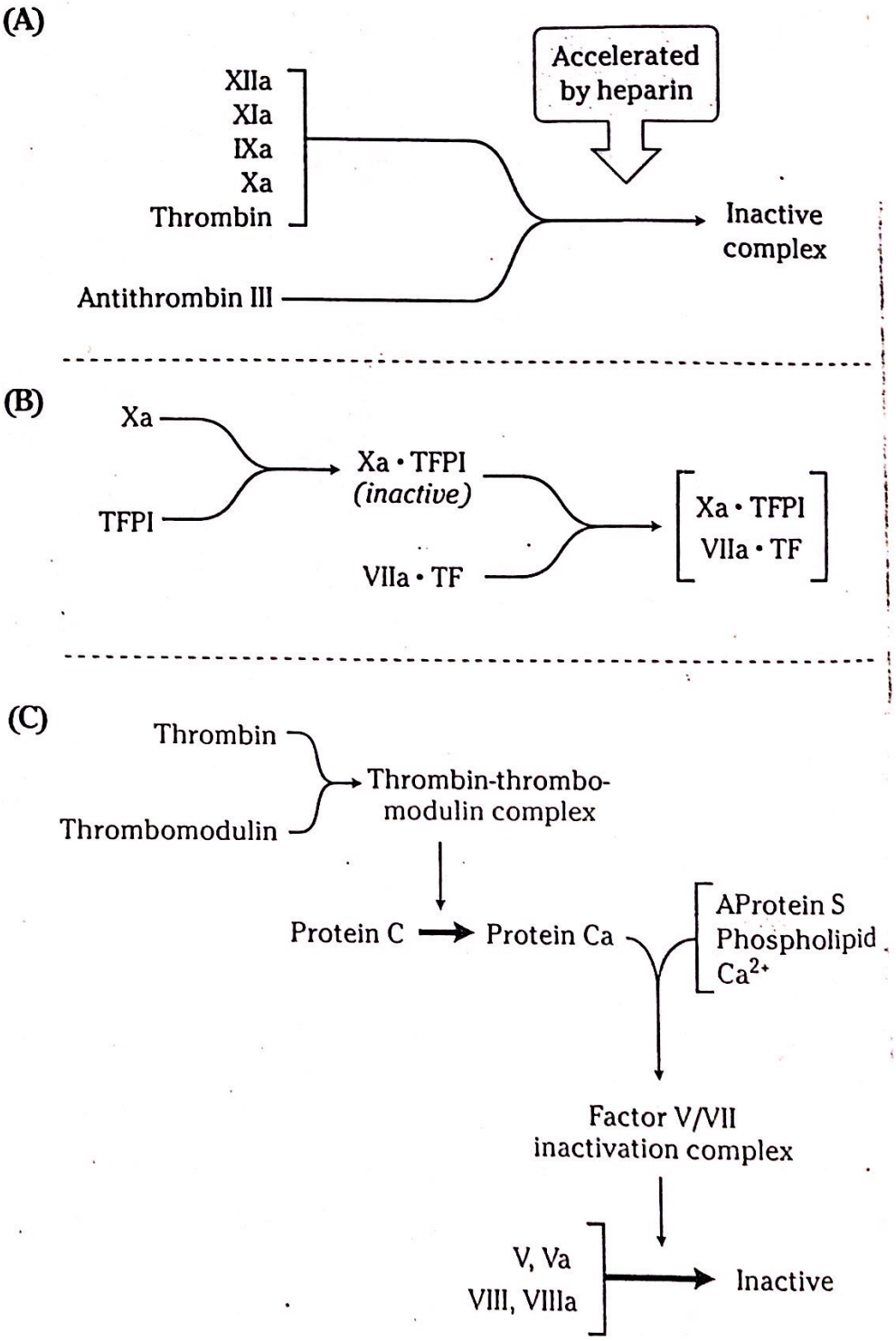


Figure 10.5 The natural anticoagulant mechanisms. The three mechanisms inhibit the clotting cascade by degrading or inactivating activated factors. **A,B.** The antithrombin III system and the TFPI system both inactivate factor Xa, the first member of the common final pathway. **C.** The powerful proteins C and S system, while largely restricted to factors V and VIII, can degrade both the active forms and the proenzymes.