Medical Pharmacology

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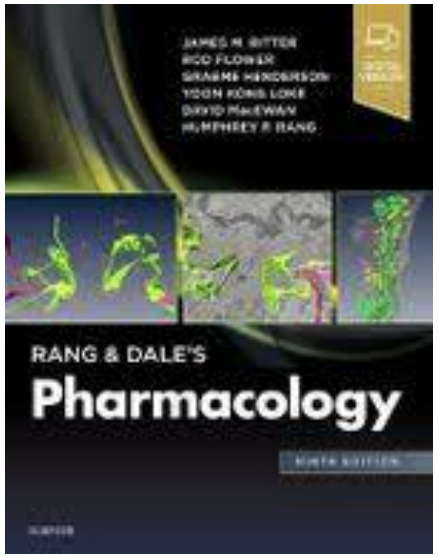
Celebrating 50 YEARS 1970 - 2020

Cardiovascular/Blood

Anticoagulants, antiplatelet drugs & thrombolytics



Rang & Dale's Pharmacology

10th ed 2020

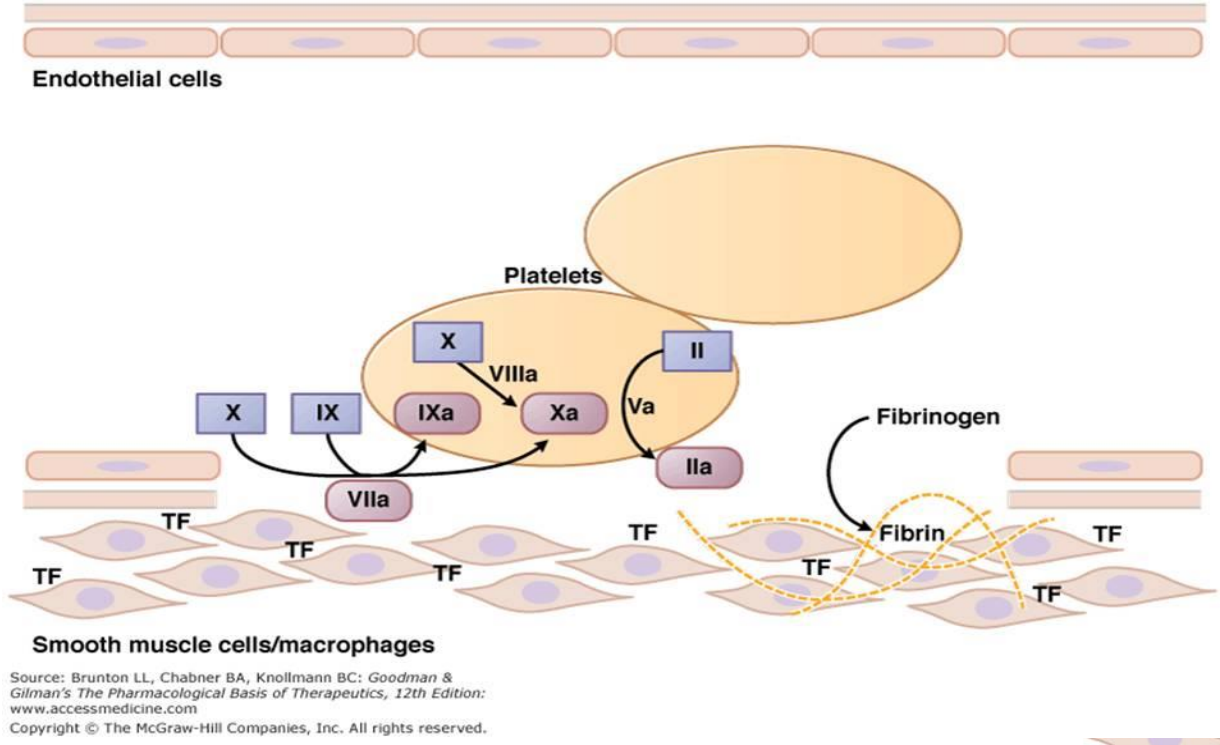
Chap 22 and 25

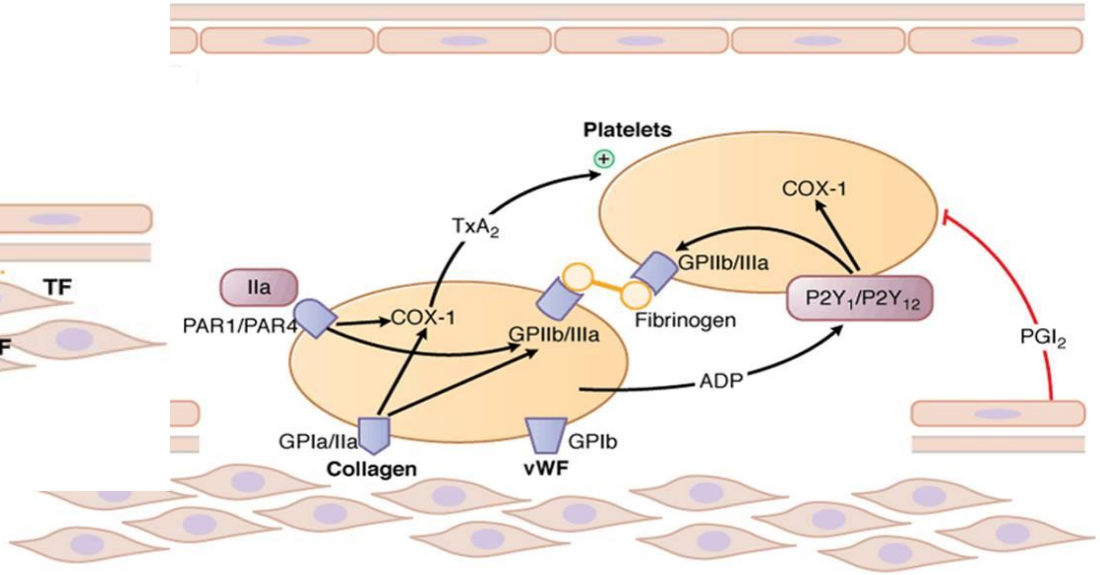
Haemostasis and thrombosis

Haemostasis

- normal response to reduce blood loss from damaged vessels
- key processes
  - platelet adhesion, activation & aggregation
  - blood coagulation (fibrin formation)
- Damaged blood vessel constricts
  - ❑ Vasoconstrictors released include 5-HT and TXA_2 from activated platelets, endothelin…… → to minimise blood loss
- Collagen exposed to blood
  - ❑ Platelets bind collagen → become activated and release mediators (5-HT, TXA_2, ADP)
- Fibrin precipitates (formation of thrombus)
  - ❑ From activation of blood coagulation cascade
  - ❑ Factor IIa (also known as thrombin) also stimulates platelet aggregation

Haemostasis and thrombosis





GP = glycoprotein
COX = cyclooxygenase
TXA_2 = thromboxane A_2
ADP = adenosine diphosphate

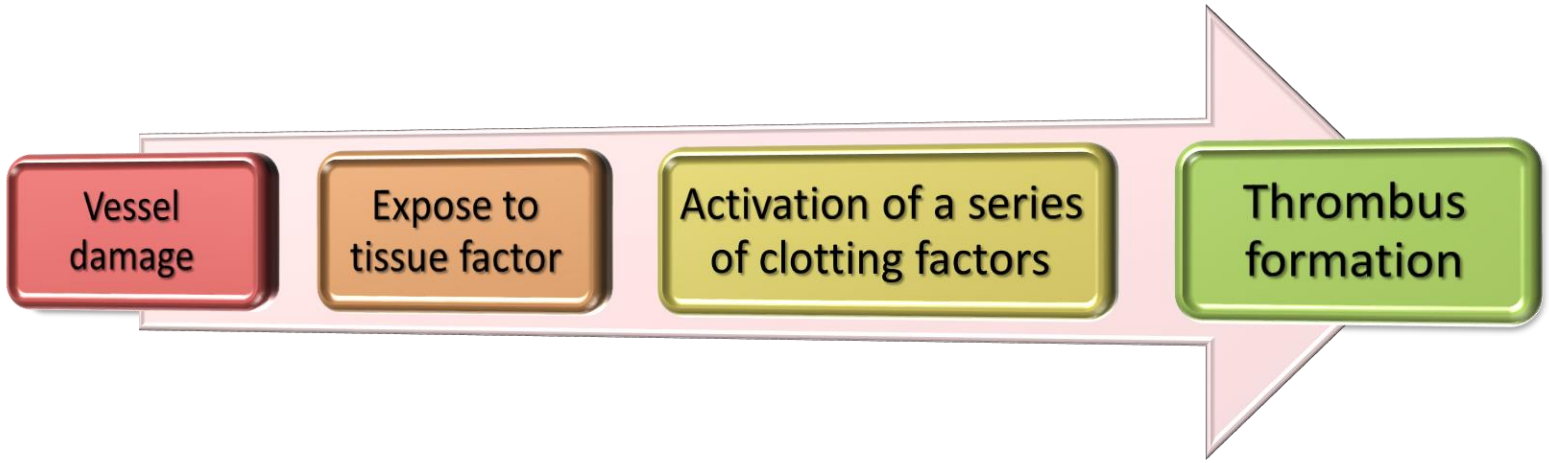
Haemostasis

- **Mechanisms to limit spread of thrombus**
  - **To prevent coagulation of the whole circulation**
  - **Roles of intact endothelium in blood vessels**
    - Release prostacyclin (PGI_2) → inhibits secretion of mediators from platelet and platelet aggregation, vasodilation *via* the release of NO
    - Heparan (heparin-like molecules) on endothelial cell surface with anticoagulation activity
    - Protease inhibitors inactivate clotting factors that escape site of injury, e.g. antithrombin III (ATIII), protein C, protein S produce anticoagulation effect
    - Fibrinolysis (fibrin digestion) by plasmin which is produced from digestion of plasminogen to plasmin by endogenous tissue plasminogen activator (tPA) released from endothelium

Haemostasis and thrombosis

Haemostasis

- **Blood Coagulation**
  - **Blood is normally very fluid but able to coagulate rapidly in seconds**



Haemostasis and thrombosis

Thrombosis

- pathological condition resulting from inappropriate activation of haemostatic mechanisms
  - venous thrombosis - small platelet component / large fibrin component; associated with stasis of blood
  - arterial thrombosis - large platelet component
  - associated with atherosclerosis
- primary cause of ischaemia, infarction, stroke, embolism

Review of thrombus formation processes

- in response to atherosclerotic damage to blood vessel wall, platelets stick to the damaged area
- platelet-platelet aggregation occurs
- excess platelet aggregation may occlude areas of slower arterial blood flow

- in coronary arteries, can lead to unstable angina and MI
- in carotid artery (or other) can lead to transient ischaemic attacks and stroke

- in venous circulation - venous thrombi are easily detached
- thrombi from the lower limb veins can cause embolisation of the pulmonary arteries

Formation of an arterial thrombus

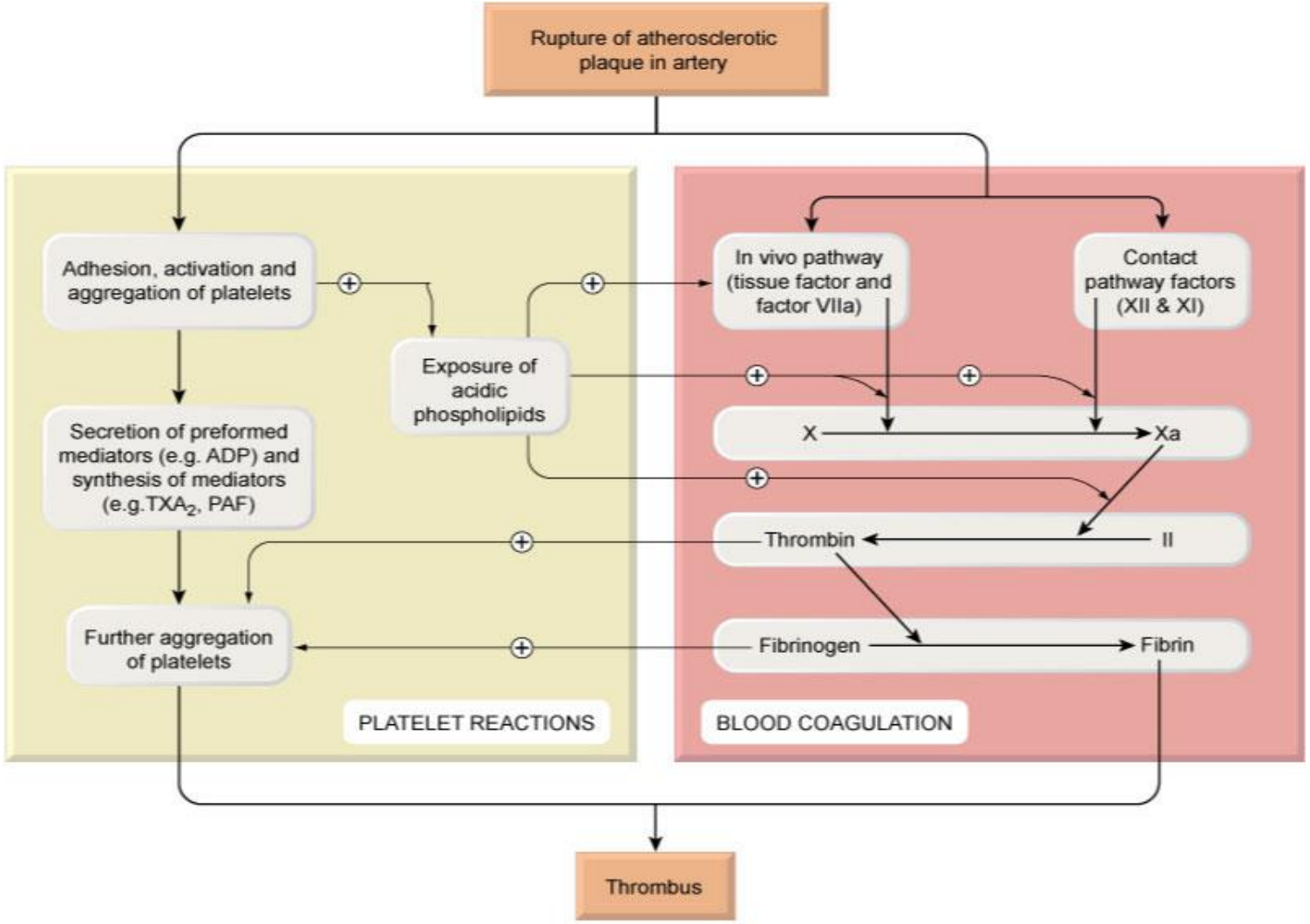


Fig. 24-1. **The main events in the formation of an arterial thrombus.** Exposure of acidic phospholipids during platelet activation provides a surface on which factors IXa and VIIa interact with factor X; factor Xa then interacts with factor II, as illustrated in more detail in Figure 24.4. Activation of factor XII also initiates the fibrinolytic pathway, which is shown in Figure 24.10. (A similar series of events occurs when there is vascular damage, leading to haemostasis.) PAF, platelet-activating factor; TXA_2, thromboxane A_2.

Damaged endothelium (atherosclerosis)

↓

Platelet aggregation (white)

↓

Formation of thrombus

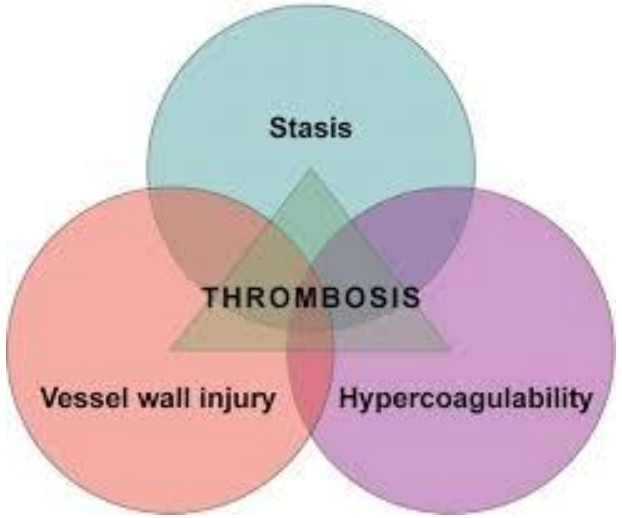
↓

Local occlusive ischaemia

↓

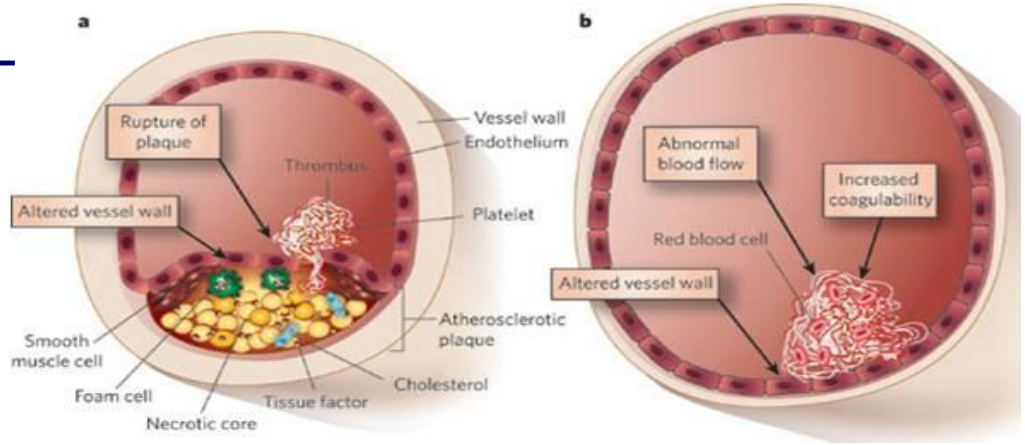
Angina, myocardial infarction (MI)

Inappropriate Thrombus Formation



Virchow's Triad

- injury to blood vessel wall
  - atherosclerosis, aneurysm, blood vessel disorders
- changes to blood flow
  - atrial fibrillation
  - long-haul plane flight / post surgery / DVT
- changes to coagulability
  - during pregnancy
  - some drugs (eg. oral contraceptives)
  - conditions of excess blood cell formation



http://www.nature.com/nature/journal/v451/n7181/fig_tab/nature06797_F1.html