

inactivate reactions have been omitted. These mechanisms include:

- depletion of local clotting factors
- clearance of activated clotting factors by the liver and mononuclear phagocyte system
- neutralization of activated coagulation factors by forming a complex, e.g. anti-thrombin,  $\alpha_2$  macroglobulin
- proteolytic degradation of active coagulation factors, e.g. protein C
- fibrinolysis; this is of major importance.

The most important enzyme capable of digesting fibrin is **plasmin**. This is produced from plasminogen either by a factor XII-dependent pathway, by therapeutic agents such as streptokinase, or by tissue-derived plasminogen activators. Plasminogen activators (PAs) fall into two classes:

- urokinase-like PA (uPA)
- tissue-type PA (tPA).

They differ in that uPA activates plasminogen in the fluid phase whereas tPA (principally produced by endothelial cells) is active only when attached to fibrin. Conveniently, some plasminogen is bound to fibrin as a thrombus is formed and so is perfectly situated for conversion by the tPA to plasmin, which can then digest the thrombus. Compounds capable of breaking down thrombi have enormous therapeutic potential for restoring blood flow before significant myocardial or cerebral infarction has occurred.

### VIRCHOW POINT 1: ALTERATION IN THE CONSTITUENTS OF THE BLOOD

Blood that clots more readily than usual is termed **hypercoagulable**. This may be caused by a variety of different mechanisms including:

- an increase in blood cells (polycythaemia)
- loss of the plasma fraction of the blood (severe burns)
- increased numbers of platelets (thrombocythaemia)
- increased amount or aggregation of plasma proteins (myeloma, cryoglobulinaemia)
- severe trauma
- disseminated cancer
- late pregnancy
- thrombophilia.

Hypercoagulability can result from an increase in activated coagulation proteins, an increased risk of platelet aggregation or a decrease in anti-thrombotic

proteins; however, the sequence of events leading to this state is complex and varied. Some mechanisms have been elucidated such as deficiencies of protein C or protein S, hereditary lack of anti-thrombin III and factor V Leiden abnormality.



### Dictionary

**Polycythaemia:** an increase in red cells which occurs as a normal compensatory mechanism if the person has chronic hypoxaemia because of chronic cardiorespiratory problems or because they live at high altitude. It can also occur because of uncontrolled erythropoietin production by various tumours (e.g. renal cell carcinoma) or uncontrolled proliferation of the haemopoietic cells. This neoplastic proliferation is called polycythaemia rubra vera and patients often present with thrombosis.

**Thrombophilia:** an inherited or acquired disorder of the haemostatic mechanisms that predispose to thrombus formation.

### VIRCHOW POINT 2: CHANGES IN THE ENDOTHELIUM

#### Normal endothelium

The fact that the vascular tree is lined by endothelium means that the endothelial surface must be resistant to thrombus formation. The endothelium is quite remarkable, for it is capable of initiating both thrombogenic and antithrombogenic stimuli. Normally, these two groups of actions are finely balanced in favour of preventing thrombus formation. Damage to the endothelium, however, will tip the balance towards thrombosis. The endothelium also has another very important role which is to prevent the elements of blood from coming into contact with the subendothelial connective tissue, which is highly thrombogenic. This tissue normally comprises collagen, elastin, fibronectin and glycosaminoglycans. **Collagen** is by far the most important of these constituents and it activates the coagulation pathway as well as being a strong stimulator of platelet aggregation. In vessels affected by atheroma, not only is the endothelium more readily damaged but the subendothelial tissue consists of the components of atheroma which are extremely thrombogenic.