These factors are designated by Roman numerals in the order they were discovered, not in the order they participate in the clotting process. Most of these clotting factors are plasma proteins synthesized by the liver. One consequence of liver disease is that clotting time is prolonged due to a reduced production of clotting factors. Normally, they are always present in the plasma in an inactive form, such as fibrinogen and prothrombin. In contrast to fibrinogen, which is converted into insoluble fibrin strands, prothrombin and the other precursors act as proteolytic (proteinsplitting) enzymes when converted to their active form. These enzymes activate other specific factors in the clotting sequence. Once the first factor in the sequence is activated, it activates the next factor, and so on, in a series of sequential reactions known as the **clotting cascade**; this continues until thrombin catalyzes the final conversion of fibrinogen into fibrin. Several of these steps require the presence of plasma calcium and *platelet factor 3 (PF3)*, a phospholipid secreted by the aggregated platelet plug. Thus, platelets also contribute to clot formation.

INTRINSIC AND EXTRINSIC PATHWAYS

The clotting cascade may be triggered by the *intrinsic pathway* or the *extrinsic pathway*:

• The **intrinsic pathway** precipitates clotting within damaged vessels as well as clotting of blood samples in test tubes. All elements necessary to bring about clotting by means of the intrinsic pathway are present in the blood. This pathway, which involves seven separate steps (shown in blue in Figure 10-14), is set off when **factor XII (Hageman factor)** is activated by coming into contact with either exposed collagen in an injured vessel or a foreign surface, such as a glass test tube. Remember that exposed collagen also initiates platelet aggregation. In this way, the formation of a platelet plug and the clotting reaction leading to clot formation are simultaneously set in motion when a vessel is damaged. Furthermore, these complementary haemostatic mechanisms reinforce each other. The aggregated platelets secrete PF3, which is essential for the clotting cascade that, in turn, enhances further platelet aggregation (❯ Figure 10-15; also see Figure 10-13). • The **extrinsic pathway** takes a shortcut and requires only four steps (shown in grey in Figure 10-14). This pathway, which requires contact with tissue factors external to the blood, initiates clotting of blood that has escaped into the tissues. When a tissue is traumatized, it releases a protein complex known as **tissue thromboplastin**. Tissue thromboplastin directly activates factor X, thereby bypassing all preceding steps of the intrinsic pathway. From this point on, the two pathways are identical. whereas the extrinsic mechanism clots blood that escaped into the tissue before the vessel was sealed off. Typically, clots are fully formed in three to six minutes.