to the released PF_4, forming a complex that acts as an antigen in the plasma.

c. Patients make antibodies to heparin-PF_4 complexes.

d. This complex then binds to the platelet surface via the antibody (The HIT antibody binds to the platelet surface via the Fc portion of the antibody, linking it to the platelet Fc receptor).

e. This binding activates the platelets, which releases more PF_4, and perpetuates the platelet activation cycle.

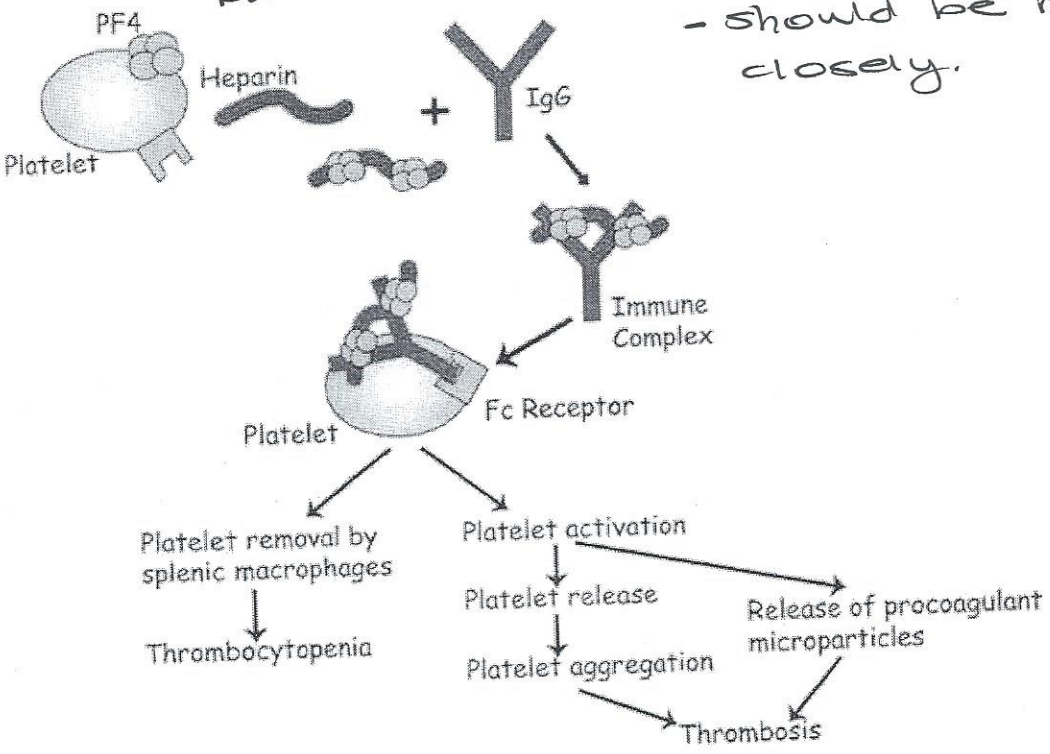
f. In the absence of heparin, HIT antibodies in the plasma cannot bind to the platelet surface.

g. Platelet activation also leads to the production of procoagulant platelet microparticles which are likely to be thrombotic.

h. HIT antibodies also bind to PF_4-heparinoid complexes on endothelial cells, which produces endothelial injury and the release of tissue factor which may overwhelm the anticoagulant effect of heparin given, resulting in thrombosis.

i. PF_4-heparin:antibody:platelet

- Rate of death for HIT is very high.
- should be monitored closely.



- if person does have HIT, heparin must be stopped immediately!
- switch to argatrobam

IV. Inflammation, Heart Disease and Stroke

A. General

1. Learning more and more about association of inflammation and cardiovascular disease/stroke, which are ultimately related to hemostasis
2. Vascular disease important because it may:
   a. weaken the walls of vessels and lead to dilation and rupture
   b. narrow the lumina of vessels and produce ischemia
   c. damage the endothelial lining and provoke intravascular thrombosis
3. Although any artery may be affected, the aorta and coronary and cerebral systems are the prime targets; therefore, myocardial infarctions (heart attacks) and cerebral infarcts (strokes) are the two major consequences of the disease.
4. MI alone accounts for 20-25% of all deaths in the US, almost entirely attributable to atherosclerosis.

B. Structure of Artery

1. The normal blood vessel wall is comprised of:
   a. an inner layer of endothelial cells (the intima) in contact with the lumen of the vessel (through which blood flows)
   b. a middle layer of smooth muscle cells and elastic extracellular matrix fibers (tunica media)
   c. an outer layer of connective tissue (tunica adventitia) in contact with the tissues
2. Like other endothelia, normal arterial endothelium is a semipermeable membrane, controlling the transfer of small and large molecules into the arterial wall. It transports relatively slight amounts of proteins through what is called pinocytotic vesicles. In most arterial regions, the intercellular junctions are normally impermeable to such molecules, but intercellular junctions are relatively labile structures that may widen under the influence of hemodynamic factors (such as high blood pressure).
3. Smooth muscle cells in the tunica media synthesize various types of collagen and have receptors for LDL and the enzymes that regulate intracellular cholesterol metabolism.

C. Plaque Process

1. The development of atherosclerotic plaque is a complex process which begins very early in life and continues throughout adulthood.
2. Early coronary atherosclerosis is called fatty streaks and is usually detectable in people by the age of 20.
3. Fatty streaks are composed mostly of lipid (which accumulates within macrophages), other inflammatory cells (such as CD4 T cells), and cells lining the muscular wall of the artery (smooth muscle cells). The lipid is primarily LDL (low-density lipoprotein) cholesterol. [All lipids in plasma circulate in combination with protein.]
4. As more lipid, inflammatory cells, and smooth muscle cells accumulate, fatty streaks may progress to atherosclerotic plaque formation.
5. When macrophages consume the lipid, they are termed foam cells. These foam cells also can contain smooth muscle cells.

IV. Inflammation, Heart Disease, and Stroke

Atherosclerosis Information – 10/8/13
#1 killer in our country!

Structure of Artery and Plaque Formation

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   a. an inner layer of endothelial cells (the intima) in contact with the lumen of the vessel (through which blood flows)
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2. Like other endothelia, normal arterial endothelium is a semipermeable membrane, controlling the transfer of small and large molecules into the arterial wall. It transports relatively slight amounts of proteins through what is called pinocytotic vesicles. In most arterial regions, the intercellular junctions are normally impermeable to such molecules, but intercellular junctions are relatively labile structures that may widen under the influence of hemodynamic factors (such as high blood pressure).
3. Smooth muscle cells in the tunica media synthesize various types of collagen and have receptors for LDL (LDL carries cholesterol and triglycerides from the liver to the tissues of the body) and the enzymes that regulate intracellular cholesterol metabolism.
4. When the intercellular junctions are widened, some of the small dense particles (LDL) are able to get inside the endothelium. Once inside the vessel wall, the LDL molecules particles get stuck and their content becomes more prone to oxidation.
5. The damage caused by the oxidized LDL molecules triggers a cascade of immune responses. First the immune system sends specialized white blood cells (macrophages and T-lymphocytes) to consume the oxidized LDL, forming specialized foam cells. These white blood cells are not able to process the oxidized LDL. They grow and then rupture, depositing a greater amount of oxidized cholesterol into the artery wall. This triggers more white blood cells, continuing the cycle. Eventually, the artery becomes inflamed.
6. The cholesterol plaque causes the muscle cells to enlarge, calcify, and form a hard cover over the affected area. This hard cover is what causes a narrowing of the artery ("hardening of the arteries"), reducing blood flow and increasing blood pressure.
7. This narrowing also can cause disturbances of blood flow (like whirlpools on the edges of fast moving streams). These whirlpools cause friction of blood cells on one another. This shear stress can aid in the activation of platelets, leading to platelet aggregation, therefore exacerbating the thrombus formation noted below even further.
8. When additional factors are present such as high blood pressure, toxins in cigarette smoke, or increased lipids in the blood, the endothelium slowly becomes damaged, and the plaque ruptures.
9. When the plaque ruptures, the contents of the core are exposed to the flowing blood. These contents are thrombogenic (clot-promoting), so together with the subendothelial collagen and tissue factor from the endothelium, platelet adhesion, aggregation, and coagulation will be initiated, thus forming a platelet-fibrin thrombus.
10. This may, within minutes, partly or completely block the vessel, cutting off the supply of blood and oxygen to the affected organ. If the organ supplied by the artery is the heart, this process is called a myocardial infarction, or heart attack.

6. Over time, plaque builds within the walls of the arteries, because as foam cells die, their contents are released, which attracts more macrophages and creates an intracellular lipid core near the center to inner surface of each atherosclerotic plaque.
7. In addition, the smooth muscle cells proliferate and migrate from the tunica media to the intima. These cells, because of their receptors, accumulate large amounts of cholesterol. Over time, the wall of the artery becomes thicker and calcifies, hence the term "hardening of the arteries."
8. As the plaque grows, it pushes into the lumen of the blood vessel, thus narrowing the opening of the vessel and reducing the flow of blood to the tissue.
9. This narrowing also can cause disturbances of blood flow (like whirlpools on the edges of fast moving streams). These whirlpools cause friction of blood cells on one another. This shear stress can aid in the activation of platelets, leading to platelet aggregation, therefore exacerbating the thrombus formation noted below even further.
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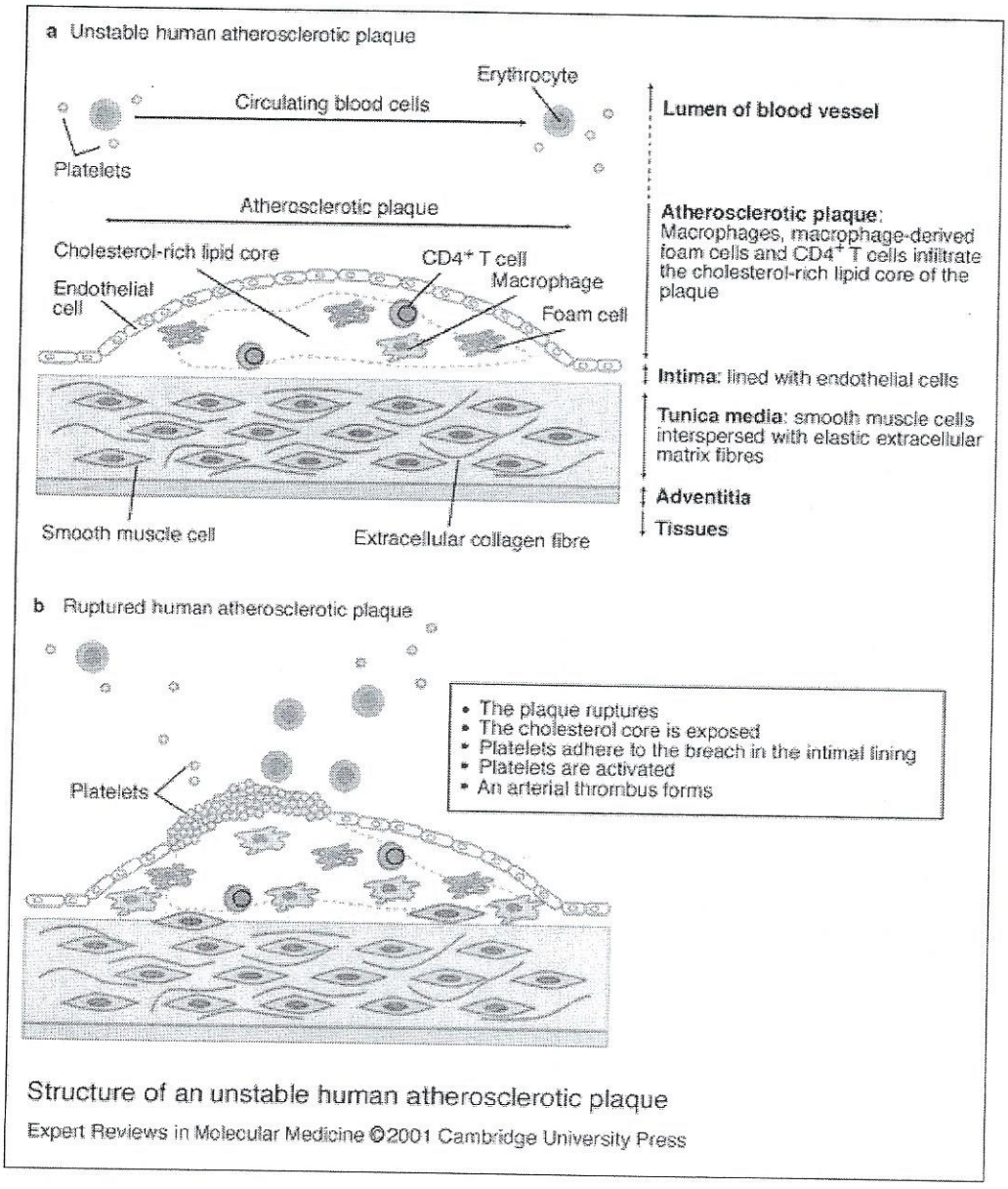


Structure of an unstable human atherosclerotic plaque

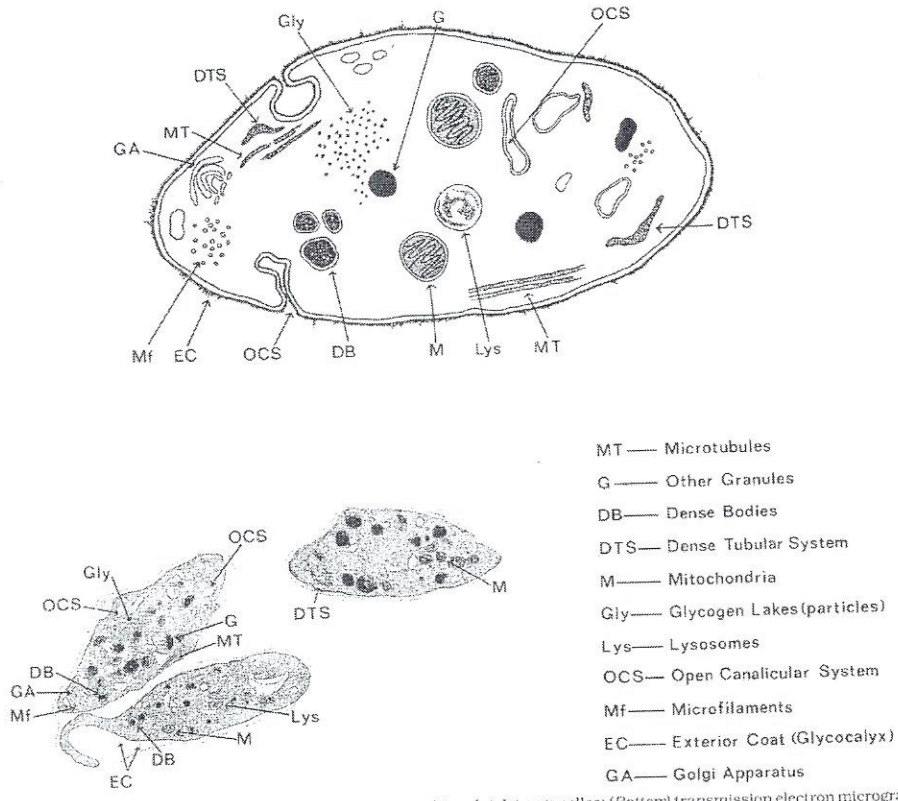


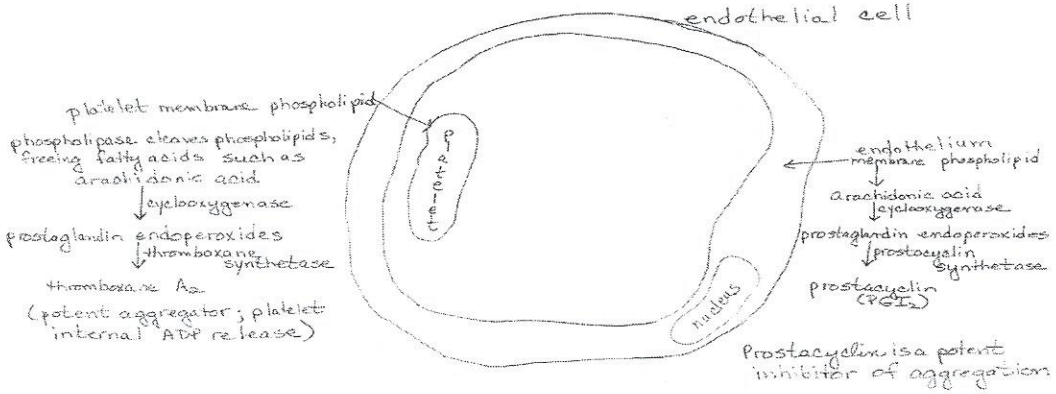
FIGURE 26–4 Discoid platelets: (*Top*) summary diagram of the platelet organelles; (*Bottom*) transmission electron micrograph (TEM) of cross-sectioned platelets illustrating basic ultrastructure.

TABLE 26–8 Platelet Ultrastructural Zones

I. Peripheral zone (stimulus receptor/transmitter region)
  A. Glycocalyx
  B. Platelet membrane
  C. Open canalicular system
  D. Submembraneous region
II. Sol-Gel zone (cytoskeletal/contractile region)
  A. Circumferential microtubules
  B. Microfilaments
III. Organelle zone (Metabolic/organellar region)
  A. Granules
    1. Alpha granules
    2. Dense granules
    3. Lysosomes
    4. Glycogen granules
  B. Mitochondria
  C. Dense tubular system
  D. Peroxisomes

teins serve as receptors and facilitate transmission of stimuli across the platelet membrane. Platelet membrane glycoprotein Ib appears to be a primary receptor for von Willebrand factor (vWF), which serves to mediate the initial adhesion of platelets to subendothelium (see Fig. 26–2).

Platelet membrane GP IIb/IIIa functions as a receptor for substances such as fibrinogen (a necessary precursor for fibrin strand formation, which will eventually reinforce the platelet plug), fibronectin (an adhesive protein), and vWF (binding may help expose the site for binding to fibrinogen), thereby mediating platelet aggregation. Although the primary receptor for vWF seems to be GP Ib, vWF is more likely to bind to GP IIb/IIIa under high shear stress (rapid flow within a small blood vessel with the accompanying increased chances of cellular shearing) because the vWF molecules distort to form extended filaments,[4] thus strengthening the chances for platelet attachment,[5] or to enhance platelet-to-platelet interaction.[6] Calcium


endothelial cell
platelet membrane phospholipid
phospholipase cleaves phospholipids, freeing fatty acids such as arachidonic acid
cyclooxygenase
prostaglandin endoperoxides
thromboxane synthetase
thromboxane A2
(potent aggregator; platelet internal ADP release)
platelet
endothelium membrane phospholipid
arachidonic acid
cyclooxygenase
prostaglandin endoperoxides
prostacyclin synthetase
prostacyclin (PGI_2)
nucleus
Prostacyclin is a potent inhibitor of aggregation

Stages of atherosclerotic plaque development

Robert J. Stevens, Karen M.J. Douglas, Athanasios N. Saratzis and George D. Kitas

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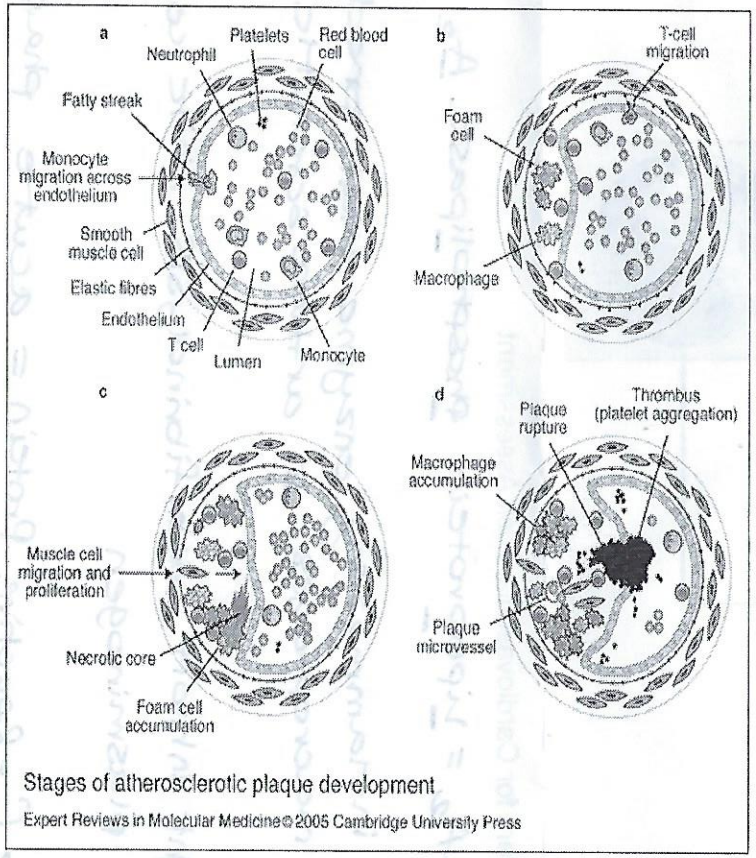

Figure 1. Stages of atherosclerotic plaque development. (a) The fatty streak is the earliest identifiable morphological change. This may be pre-dated by endothelial dysfunction, which can be detected using methods assessing vascular function (rather than morphology), and may persist or deteriorate as the atherosclerotic process advances. (b) The fatty streak is followed by the formation of an established plaque (often termed an intermediate lesion), characterised by the accumulation of increasing numbers of macrophage foam cells and a local chronic inflammatory infiltrate. (c) The complicated plaque is characterised by smooth muscle cell migration and the formation of a fibrous cap, the formation of a necrotic lipid core and an ever-increasing inflammatory infiltrate. (d) Plaque rupture may occur after the fibrous cap has been weakened by the production of degradative enzymes and reactive oxygen species by the inflammatory cellular infiltrate. This exposes highly prothrombotic material, which leads to the formation of thrombus that may result in the clinically recognised acute coronary syndromes.

PAI – 1

⊣

TPA (plasminogen)

plasmin ← plg