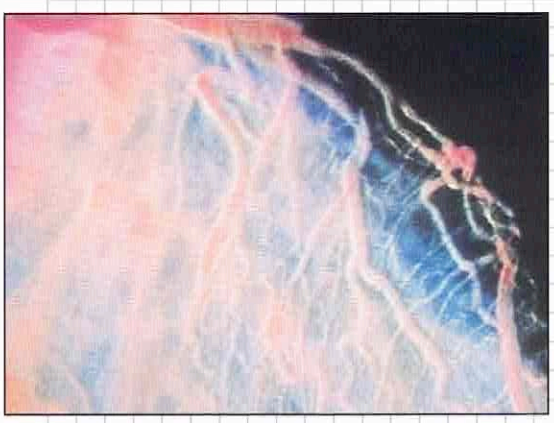
Pathologic Triggers

New Insights Into Cardiovascular Risk



False-color angiogram of coronary artery stenosis

INTRODUCTION

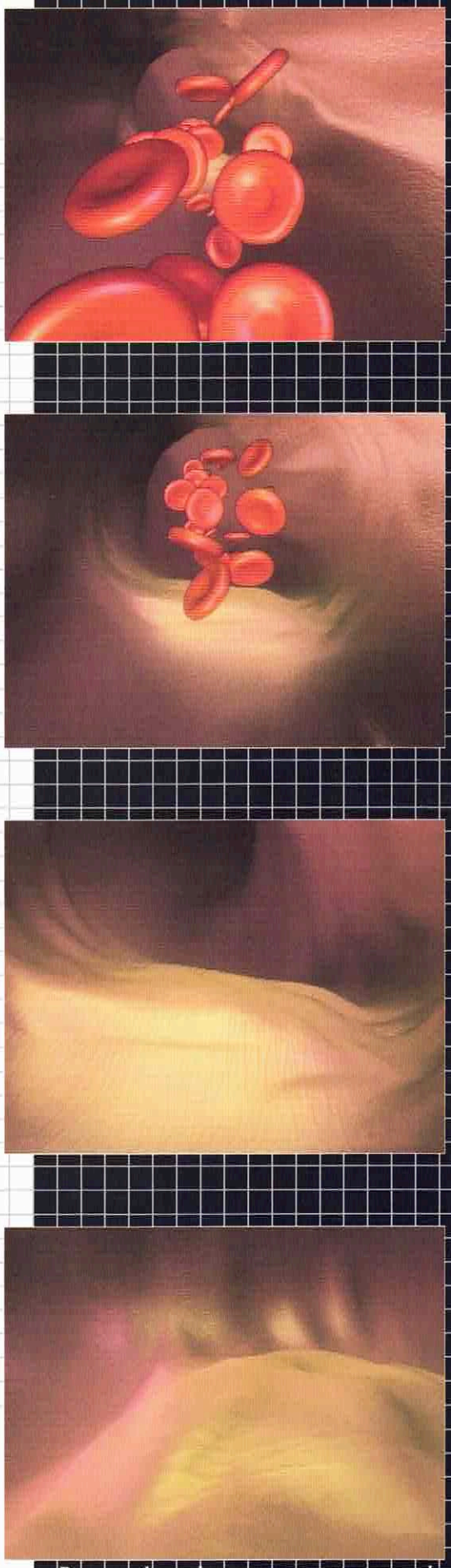
To date, most of our attempts to prevent atherosclerosis have centered on the control of hypertension and hyperlipidemia, as well as lifestyle risk factors. However, recent insights into the pathology of coronary disease have sharpened our focus on the natural history of atheroma and its relentless progression to acute cardiac events.

ATHEROSCLEROSIS: AN INSIDIOUS PROCESS

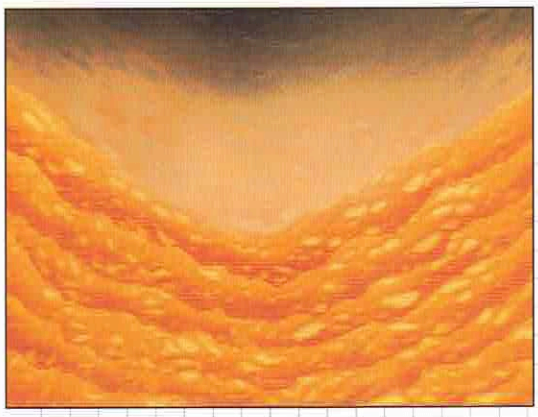
The identification and management of patients with hypertension has not had as large an impact on the incidence of coronary heart disease as might be expected. Many factors contribute to the etiology of this disease, which appears to be a lifelong evolving process starting early in life. Indeed, studies have shown that advanced arterial lesions already exist in young individuals, with an incidence of 10-30% in the successive three year age groups between 15 and 29 years.[1]

The atherosclerotic process begins with infiltration of low-density lipoproteins or LDL into the arterial intima to create lipid-rich foam cells which form the basis of the "fatty streak."[2-5] This early lesion contains large amounts of cholesterol, but its development to atherosclerosis is not inevitable. Progression appears to depend critically upon endothelial injury,[2] caused by oxidation of LDL,[2,4-7] by the shearing forces of hypertension,[2,8] and by smoking.[2,3]

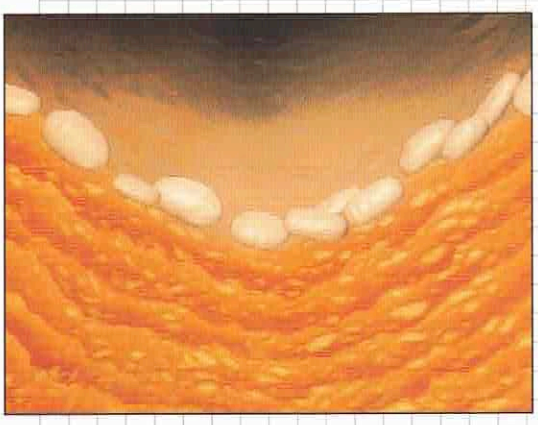
A subsequent increase in endothelial permeability allows the influx of macrophages and LDL particles to form further foam cells.[5,9] This is followed by release from macrophages and endothelial cells of chemotactic growth factors such as PDGF (platelet-derived growth factor). These factors stimulate smooth muscle cells to migrate and proliferate, creating a connective tissue cap over a core of foam cells and extracellular lipid.[3,7] Finally, platelets, fibrin and red blood cells are deposited at the surface to form the mature atheromatous plaque.[3]



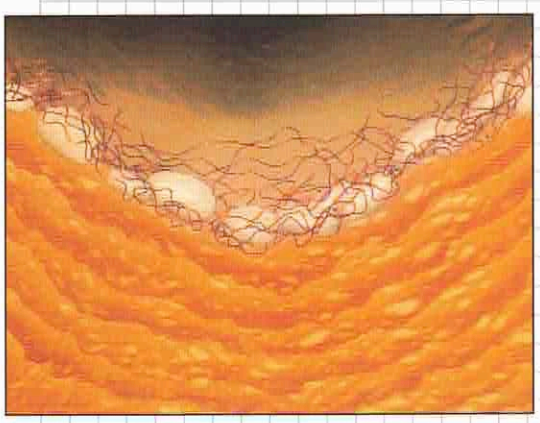
Passage through a coronary artery revealing an established atheromatous plaque



Multilayered appearance of plaque



Platelet aggregation on plaque surface

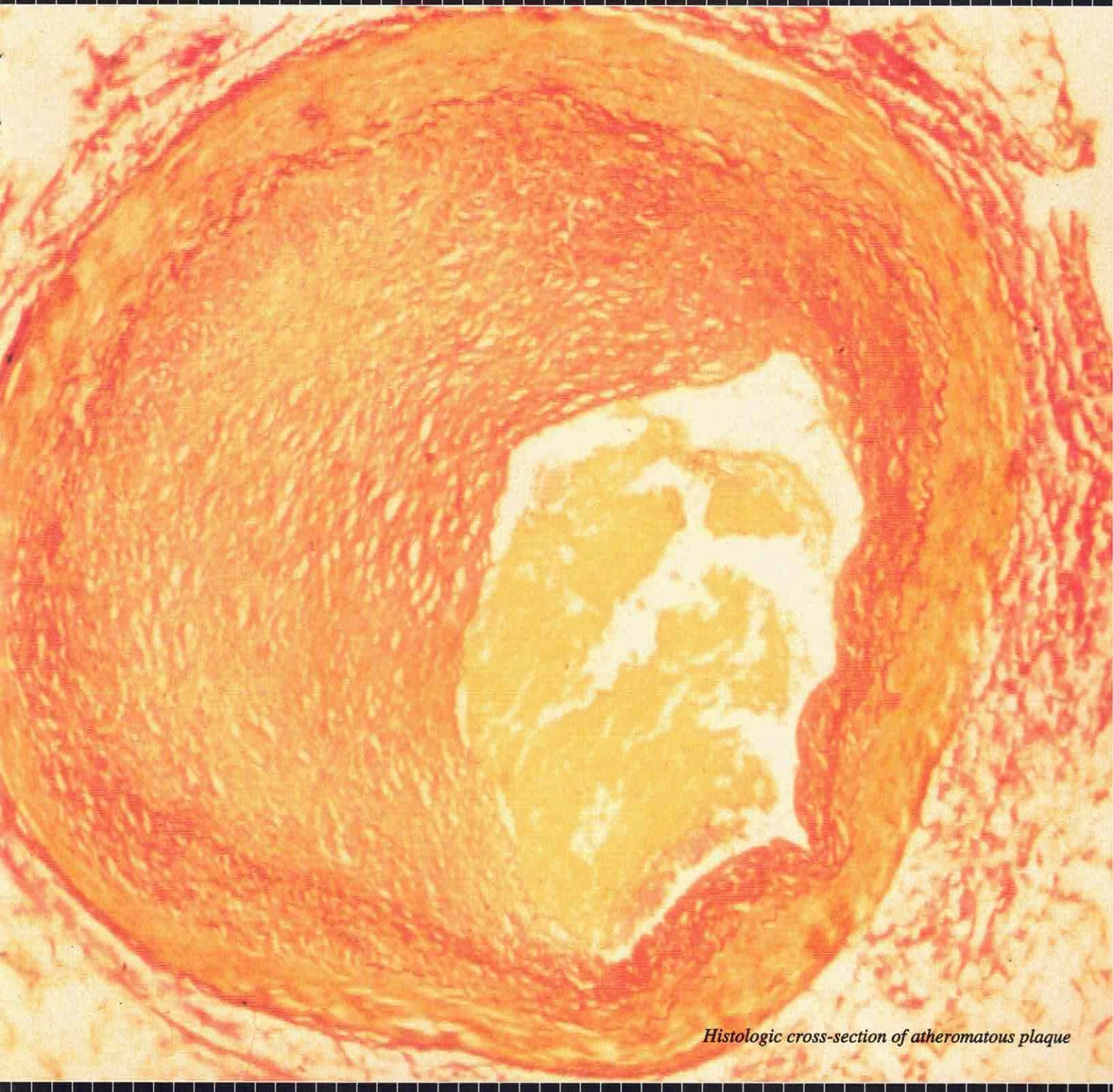


Platelets contribute to thrombus formation and release of growth factors, leading to progression of atherosclerosis

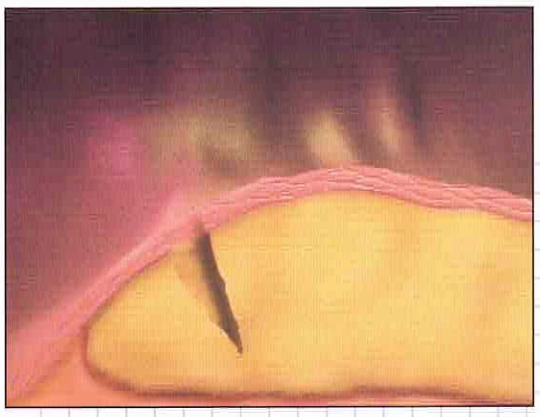
PLATELETS AND ATHEROSCLEROSIS PROGRESSION

Several features of mature plaques, such as their multilayered pattern, suggest that platelet aggregation and thrombus formation are key elements in the progression of atherosclerosis.[4,10] Platelets are also known to provide a rich source of growth factors, which can stimulate plaque development.[2-4]

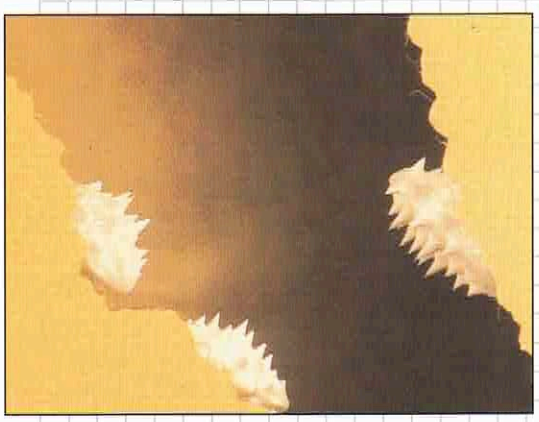
Given the insidious nature of atherosclerosis, it is vital to consider the role of platelets and thrombosis in this process, and the serious events that may be triggered once plaques are already present.[3,11,12]



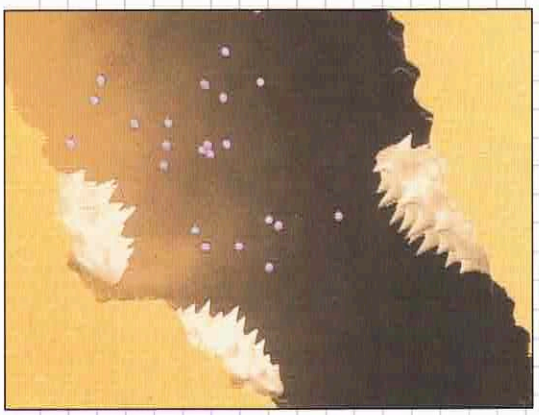
Histologic cross-section of atheromatous plaque



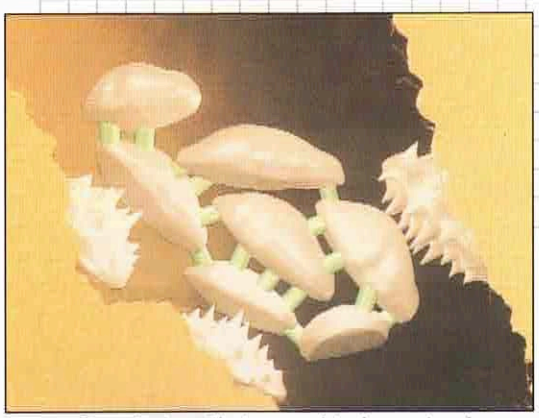
Shear forces lead to a deep tear in the fibrous cap



Platelets adhere to exposed fibrillar collagen



Degranulation promotes platelet aggregation



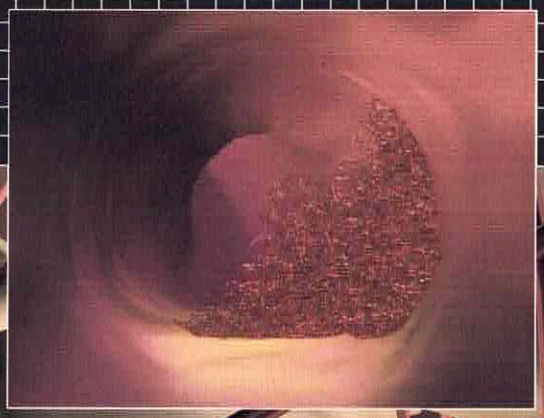
Circulating fibrinogen binds to platelet receptors and forms a bridge between them

PLAQUE INJURY AND THROMBOSIS

Shear forces, caused by hypertension for example,[2] can lead to a deep tear in the fibrous cap of established plaques.[13,14] The resulting exposure of fibrillar collagen, present in deeper layers of the vessel wall, acts as a powerful stimulus for platelets to adhere and to become activated.[13,14] These then degranulate and secrete substances that promote further platelet aggregation.[4,13] In addition, circulating fibrinogen is bound to activated receptors on platelet membranes, and forms a bridge between neighboring platelets.[13,14] Simultaneously, the coagulation pathways are activated, leading to the formation of fibrin, which reinforces the platelet plug as the clot evolves deep within the plaque.[4,13,14]

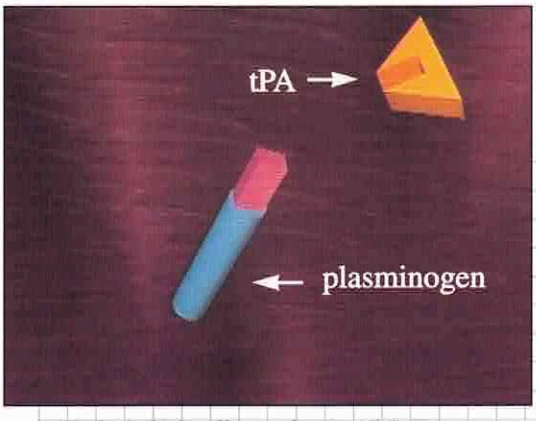
OUTCOME OF PLAQUE INJURY

There are several possible outcomes to plaque injury. The majority of fissures appear to reseal,[2,3] but sometimes the formation of a mural thrombus, which projects into the lumen, can cause obstruction or give rise to platelet emboli.[3]

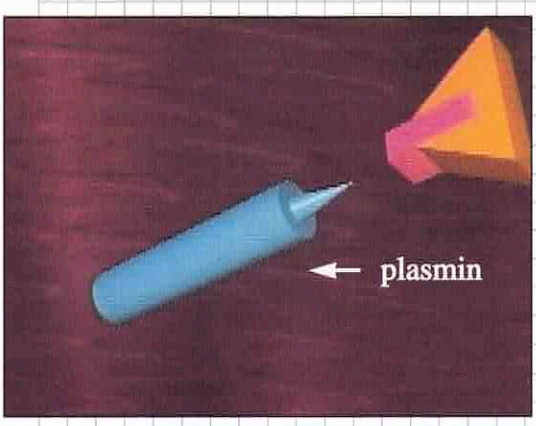


Mural thrombus can give rise to platelet emboli

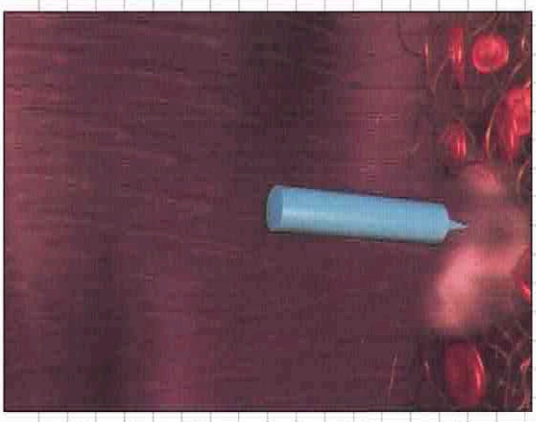
Fibrin reinforces the platelet plug as the clot evolves deep within the plaque



Endothelial cells synthesize tPA



tPA catalyzes the conversion of plasminogen to plasmin

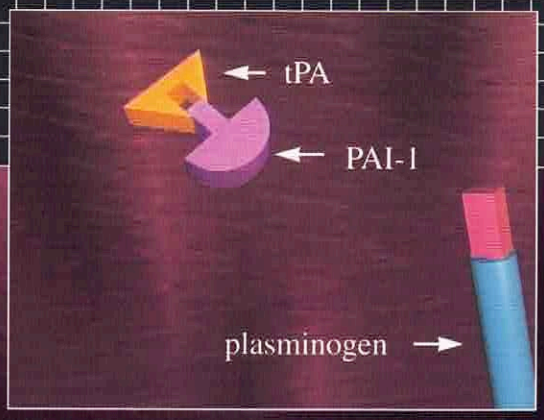


Plasmin mediates the breakdown of fibrin and clot dissolution

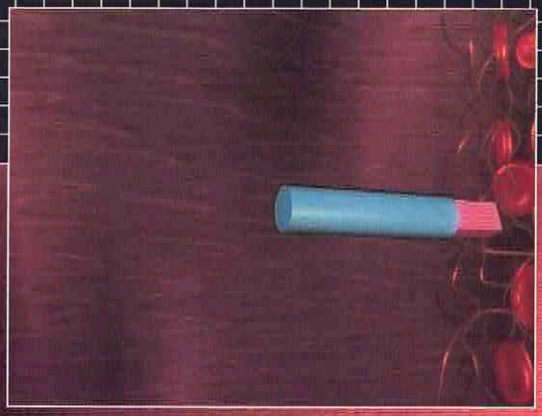
FIBRINOLYSIS

However, mural thrombi can be completely or partially resolved by the activity of the fibrinolytic system.[11] Endothelial cells have been shown to synthesize a factor known as tissue plasminogen activator, or tPA, which is the major activator of clot lysis.[15] This protease molecule catalyzes the conversion of the inactive precursor plasminogen to plasmin. Plasmin, in turn, mediates the breakdown of fibrin by the cleavage of peptide bonds, leading to dissolution of the clot.[11,15] As a natural control mechanism, inhibiting factors, such as plasminogen activator inhibitor or PAI-1, bind to free tPA molecules in the plasma, reducing their activity, and thereby keeping the whole process in check.[11,15]

If fibrinolysis is incomplete, thrombus may become incorporated into the plaque, and may cause severe stenosis.[3,13]



PAI-1 binds to free tPA molecules



Reduced levels of free tPA prevent the activation of plasminogen and clot dissolution

Incomplete fibrinolysis may lead to severe stenosis