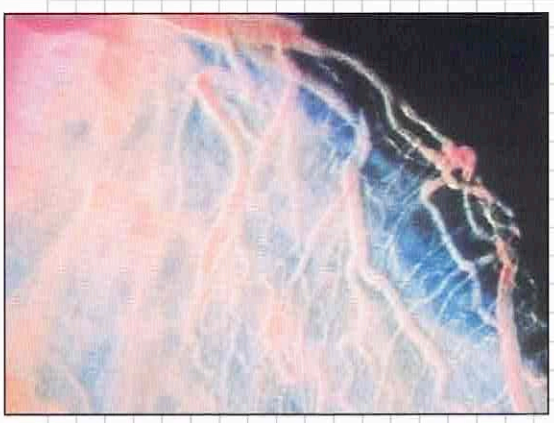
Pathologic Triggers

New Insights Into Cardiovascular Risk



False-color angiogram of coronary artery stenosis

INTRODUCTION

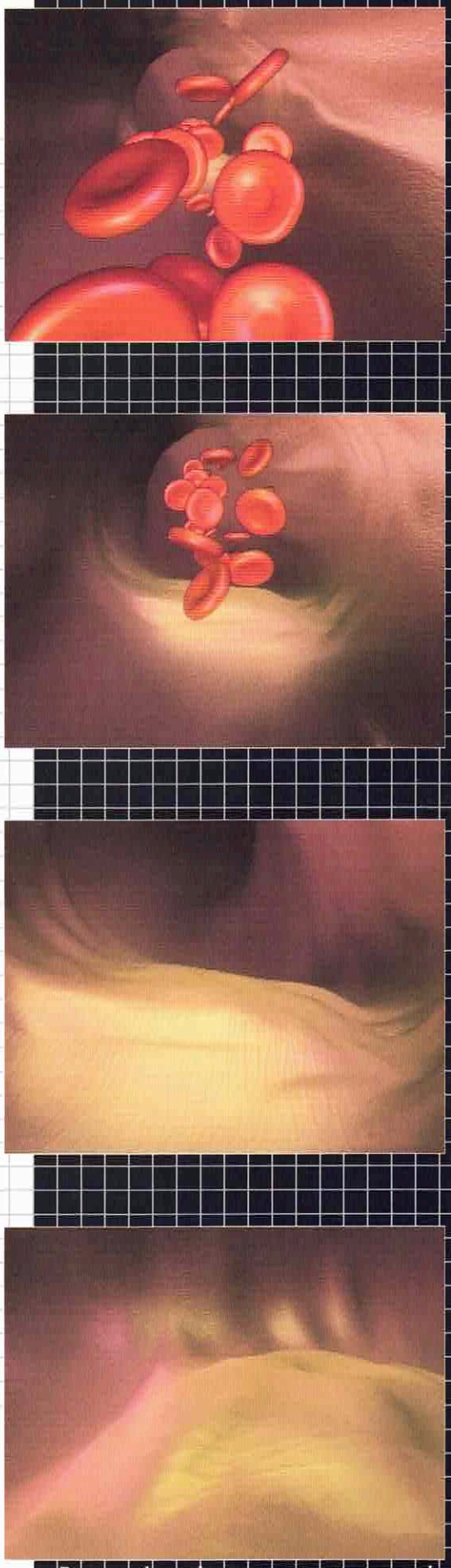
To date, most of our attempts to prevent atherosclerosis have centered on the control of hypertension and hyperlipidemia, as well as lifestyle risk factors. However, recent insights into the pathology of coronary disease have sharpened our focus on the natural history of atheroma and its relentless progression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

ATHEROSCLEROSIS: AN INSIDIOUS PROCESS

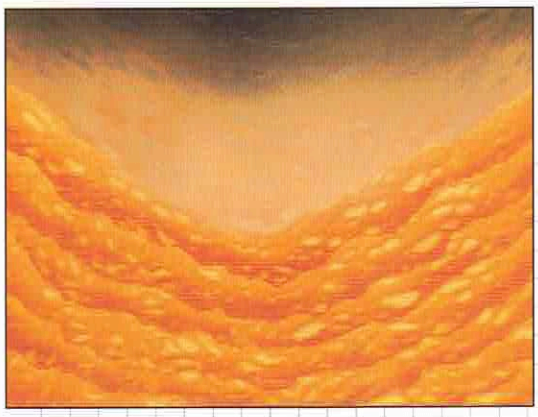
The identification and management of patients with hypertension has not had as large an impact on the incidence of coronary heart disease as might be expected. Many factors contribute to the etiology of this disease, which appears to be a lifelong evolving process starting early in life. Indeed, studies 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]

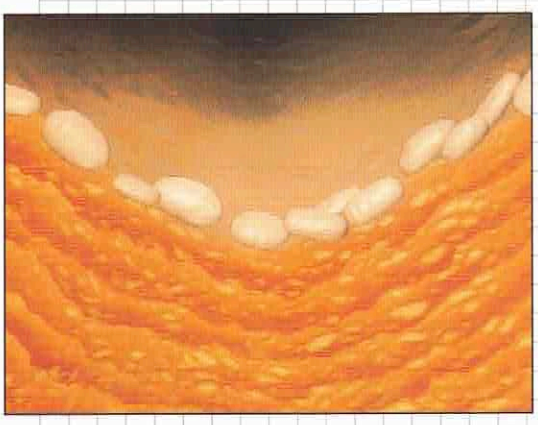
A subsequent increase in endothelial permeability allows the influx of macrophages and LDL particles to form further foam cells.[5,9] This is followed by release from macrophages and endothelial cells of chemotactic growth factors such as PDGF (platelet-derived growth factor). These factors stimulate 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]



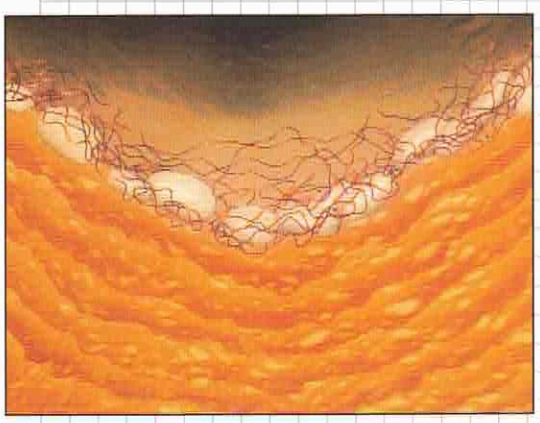
Passage through a coronary artery revealing an established atheromatous plaque



Multilayered appearance of plaque



Platelet aggregation on plaque surface

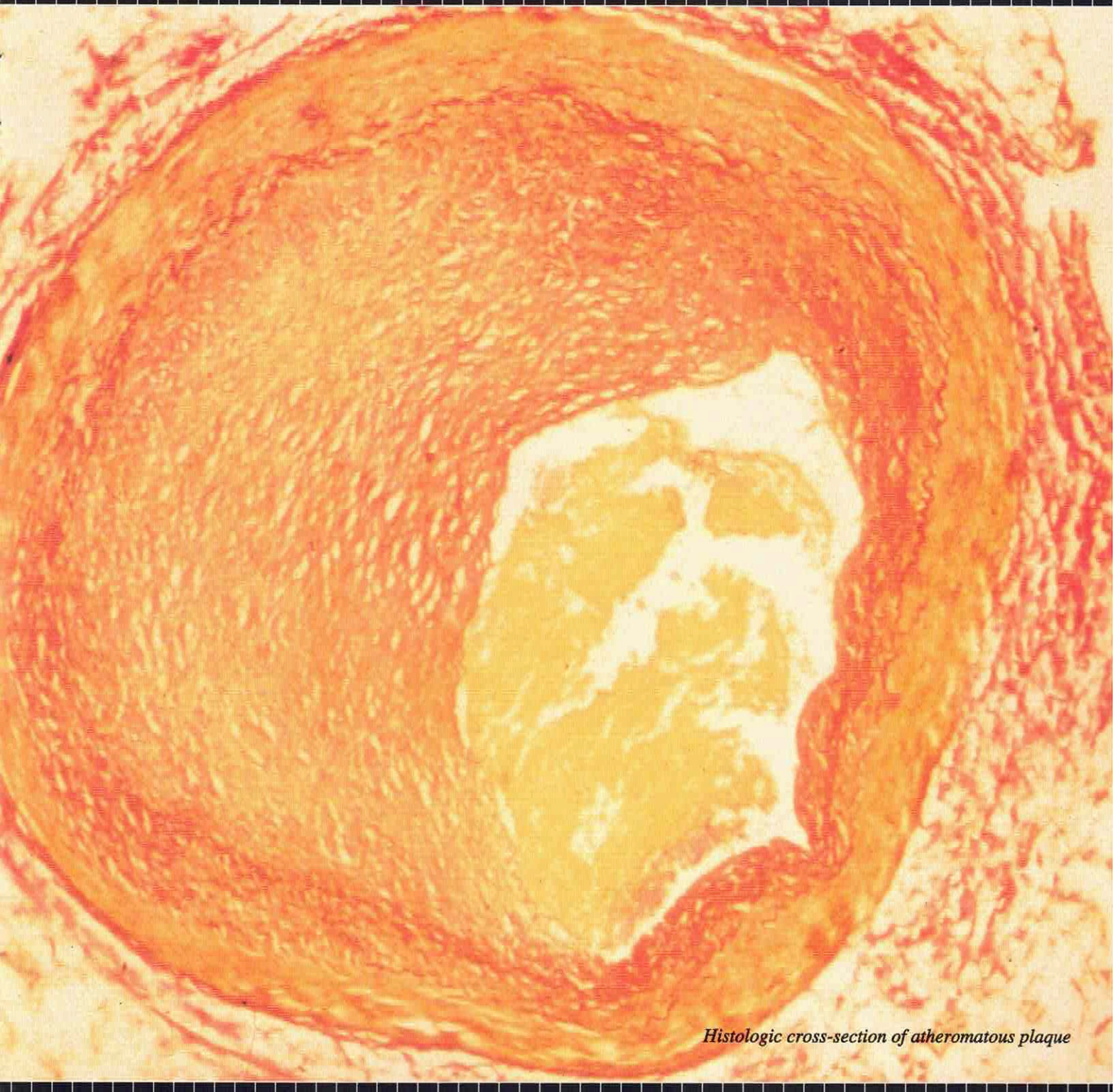


Platelets contribute to thrombus formation and release of growth factors, leading to progression of atherosclerosis

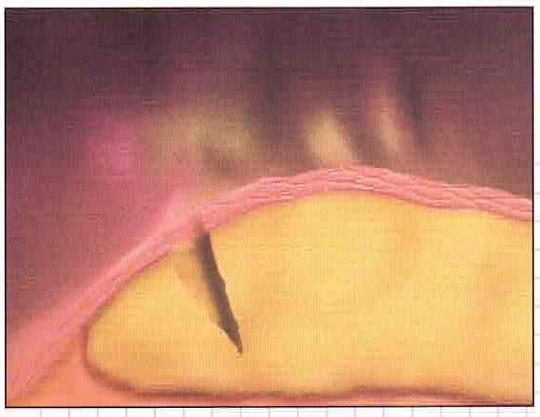
PLATELETS AND ATHEROSCLEROSIS PROGRESSION

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]

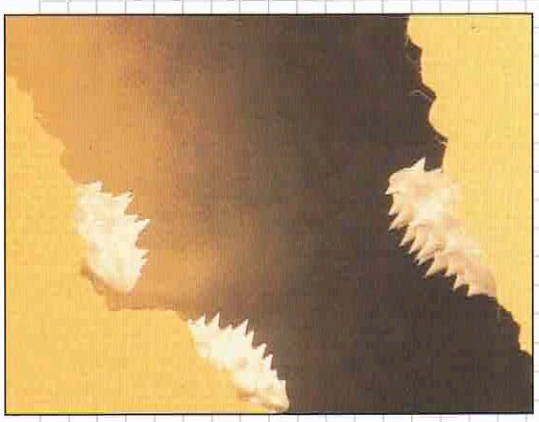
Given the insidious nature of atherosclerosis, it is vital to consider the role of platelets and thrombosis in this process, and the serious events that may be triggered once plaques are already present.[3,11,12]



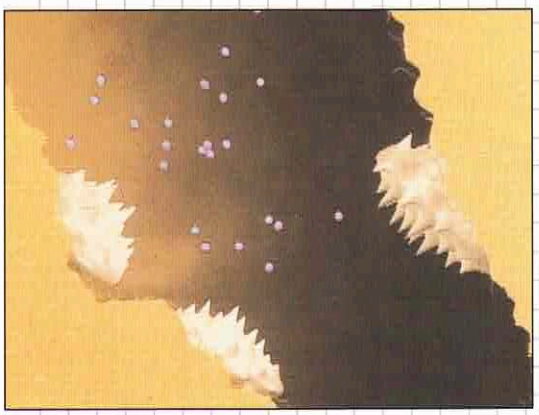
Histologic cross-section of atheromatous plaque



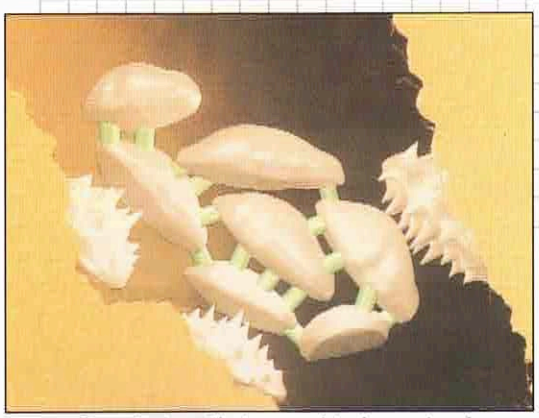
Shear forces lead to a deep tear in the fibrous cap



Platelets adhere to exposed fibrillar collagen



Degranulation promotes platelet aggregation



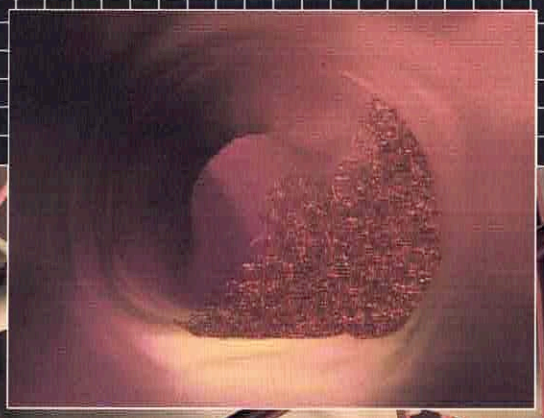
Circulating fibrinogen binds to platelet receptors and forms a bridge between them

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]

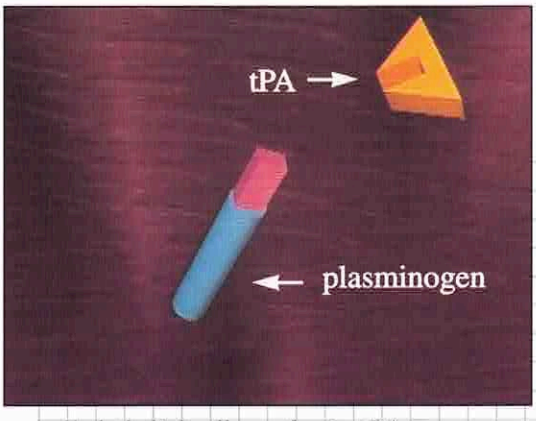
OUTCOME OF PLAQUE INJURY

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]

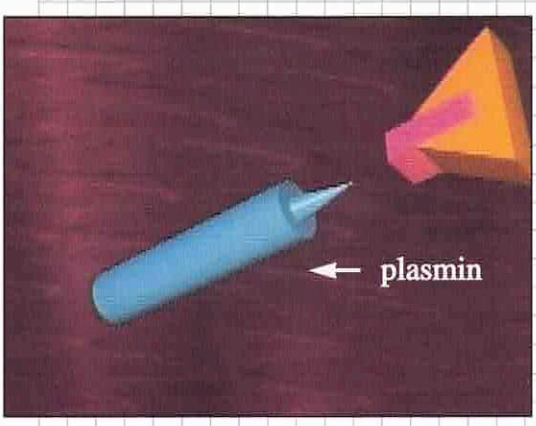


Mural thrombus can give rise to platelet emboli

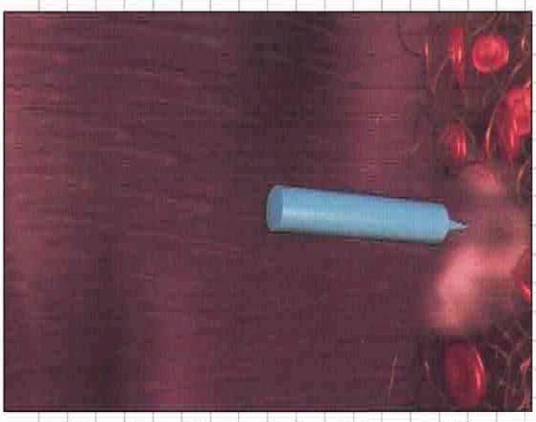
Fibrin reinforces the platelet plug as the clot evolves deep within the plaque



Endothelial cells synthesize tPA



tPA catalyzes the conversion of plasminogen to plasmin

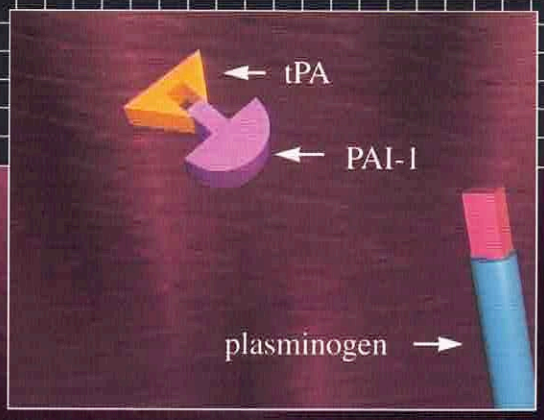


Plasmin mediates the breakdown of fibrin and clot dissolution

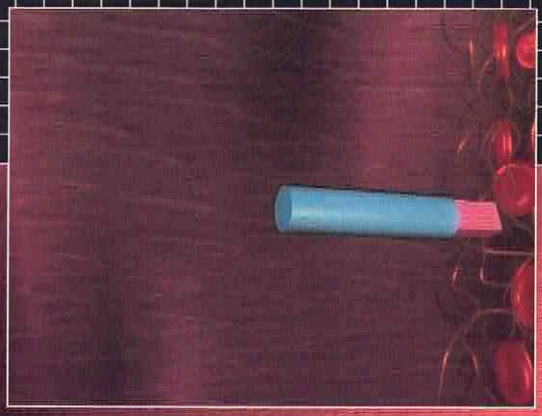
FIBRINOLYSIS

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]

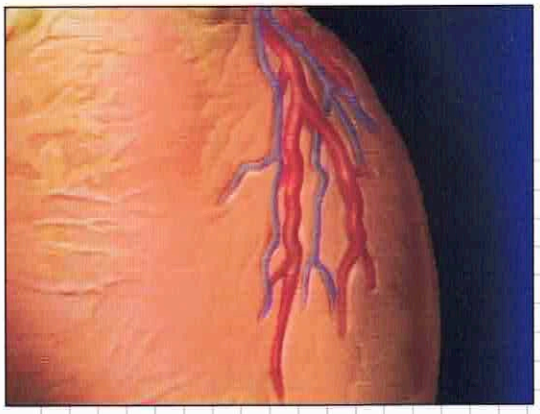


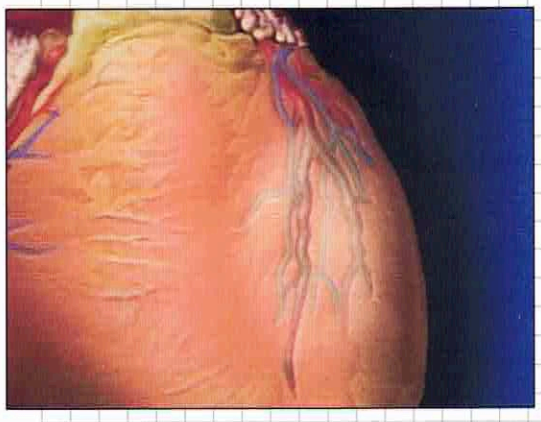
PAI-1 binds to free tPA molecules

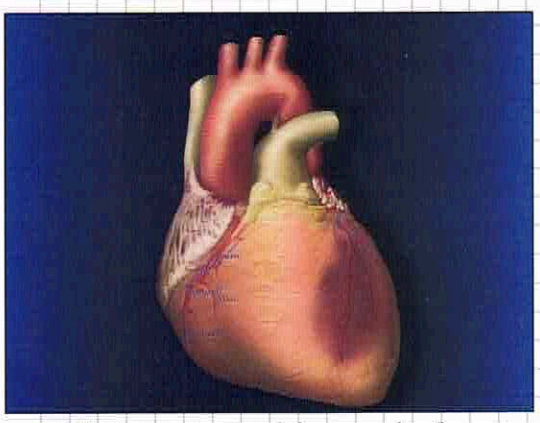


Reduced levels of free tPA prevent the activation of plasminogen and clot dissolution

Incomplete fibrinolysis may lead to severe stenosis





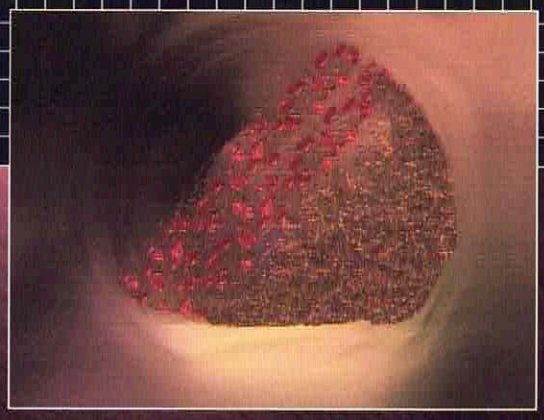


Plaque rupture and the cascade of events leading to thrombosis may account for up to 90% of acute myocardial infarctions

CLOT PROPAGATION

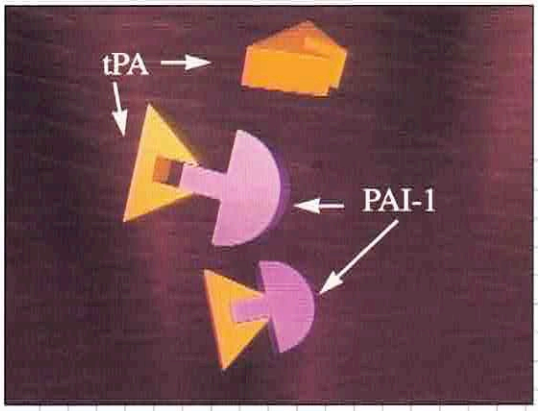
Alternatively, any residual thrombus can act as a powerful stimulant to further platelet aggregation.[8] The growing mass of fibrin, platelets and enmeshed red cells may become solid enough to cause complete vessel obstruction.[3,12,13]

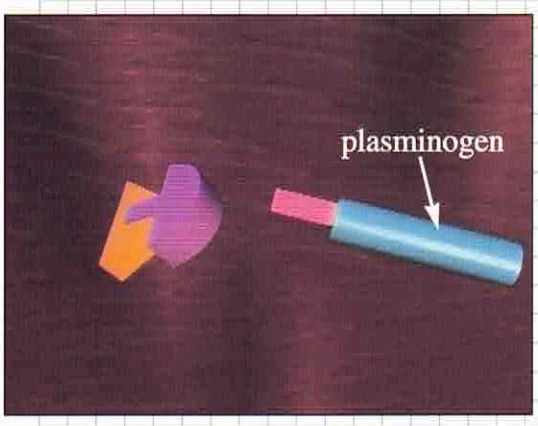
It is significant to note that complete obstruction and myocardial infarction often develops from mild lesions initially causing less than 50% stenosis.[16] Rupture of these plaques and the cascade of events that leads to thrombosis can occur rapidly and is now recognized as a common and major precipitant of unstable angina, myocardial infarction, and sudden cardiac death.[12-14,17] Studies suggest that thrombotic events may account for up to 90% of acute myocardial infarctions.[4,18]

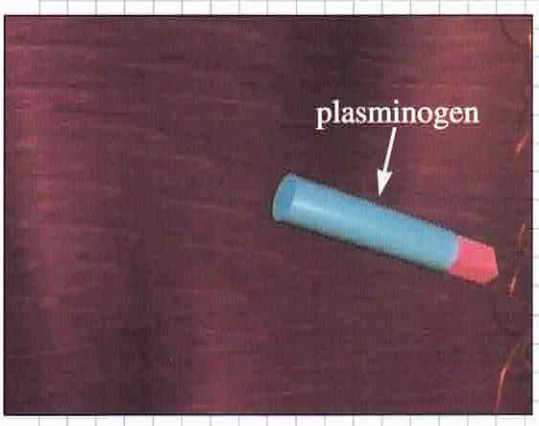


Residual thrombus stimulates further platelet aggregation and propagation of the clot

Fibrin, platelets, and enmeshed cells can cause complete vessel obstruction







Defective thrombolysis, due to increased PAI-1 levels for example, may occur in hypertension and hyperlipidemia. Reduced tPA activity may result in an impaired ability to dissolve clots

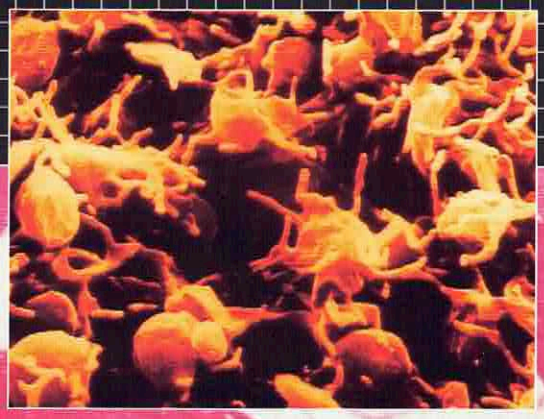
TRIGGERING FACTORS IN THROMBOSIS

As shown previously, the incidence of serious thrombosis arising from atherosclerosis may depend on two key processes: platelet aggregability and the function of the thrombolytic system.

Hypertensive patients are known to have greater platelet adhesiveness and aggregability,[19,20] which could increase clot formation at the site of plaque injury. In addition, thrombolysis is often defective in hypertension and hyperlipidemia,[21] which may result in an impaired ability to dissolve clots in the presence of atherosclerosis.

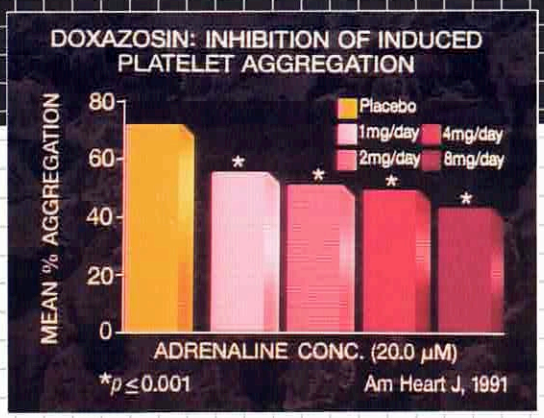
These triggering factors should ideally be borne in mind when devising strategies for managing the overall risk of coronary heart disease in hypertensive patients.

The incidence of atheroma-associated thrombosis may depend chiefly on platelet aggregability and thrombolytic system function

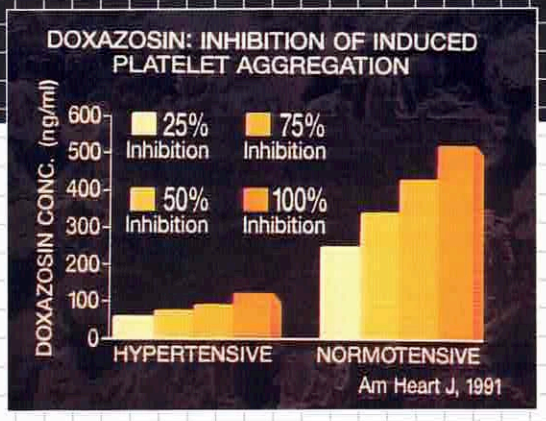


Hypertensive patients have greater platelet adhesiveness and aggregability

Histologic cross-section of plaque with mural thrombus



Ex vivo study: dose-dependent reduction of platelet aggregation with doxazosin



In vitro study: hypertensive subjects require significantly lower doxazosin concentrations to inhibit aggregation than normotensive subjects

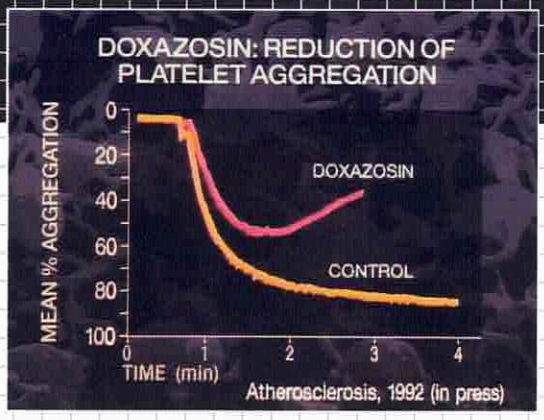
DOXAZOSIN: REDUCTION OF PLATELET AGGREGATION

In the treatment of hypertension, certain agents appear to have a positive effect on the overall cardiovascular risk profile, and therefore warrant consideration as first-line antihypertensives. One such antihypertensive agent is the selective alpha-1 inhibitor, doxazosin, which not only effectively reduces blood pressure and serum cholesterol,[22] but has also been shown to have other important properties.

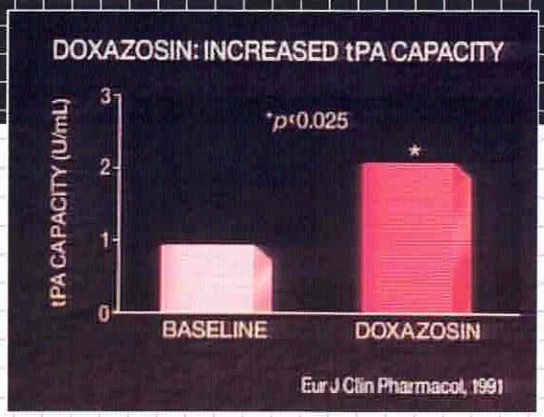
Hernandez and coworkers investigated the effects of doxazosin on platelet aggregation in ex vivo and in vitro studies, using platelet-rich samples prepared from hypertensive and normotensive subjects.

Results from the ex vivo study, in which plasma was obtained from hypertensive patients who had received a placebo or therapeutic concentrations of doxazosin, showed a dose-dependent reduction of platelet aggregation in the presence of inducers such as adrenaline.[23]

In addition, the in vitro study showed that the concentrations of doxazosin required to inhibit collagen-induced aggregation from 25% to 100% inhibition were significantly lower in hypertensive than in normotensive subjects, suggesting that platelets in hypertensive patients are more responsive to the effects of doxazosin therapy.[24] This is particularly important since hypertension increases platelet reactivity.[19,20]



Platelet aggregation in doxazosin-treated animals is significantly decreased compared to controls, and exhibits a dissociation response



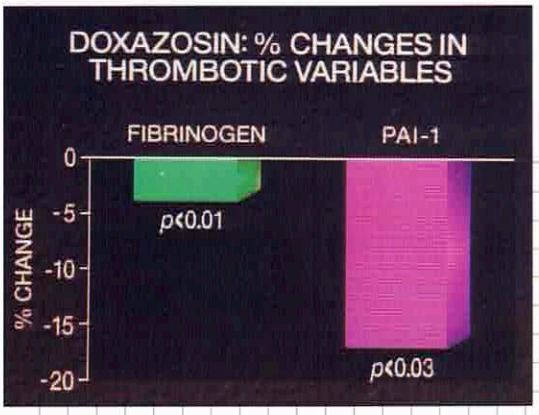
Increased tPA capacity with doxazosin

DOXAZOSIN: INCREASE IN PLATELET DISSOCIATION

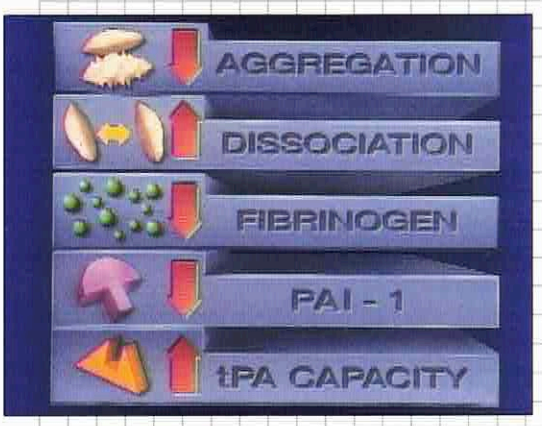
Not only does doxazosin decrease overall platelet aggregability, but it also contributes to platelet dissociation, as demonstrated in animal studies conducted by Weiner and Nicolosi. These studies confirmed that, in animals treated with doxazosin, the platelet aggregation response was significantly decreased compared to untreated controls.[25] Importantly, the platelet aggregates in doxazosin-treated animals subsequently displayed a dissociation response, leading to rapid reversal of aggregation.[25] This result was in marked contrast to the untreated controls. Further research is needed to elucidate this interesting antithrombotic property.

DOXAZOSIN: INCREASE IN tPA CAPACITY

Another potentially significant property of doxazosin is its positive impact on thrombolytic function. This was demonstrated in a recent primary intervention study conducted by Jansson and coworkers in Sweden.[26] Eighty-four patients with mild-to-moderate hypertension and elevated serum cholesterol were randomized to receive either doxazosin or the beta-blocker, atenolol, for six months. In each group, the activity of fibrinolytic variables was measured. These included the activity of tPA before and after a 10-minute venous occlusion test, and the tPA capacity, which is the difference between the two tPA activity values. Doxazosin produced a significant increase of 137% in the tPA capacity compared to baseline values, indicating an increase in fibrinolytic capability. In the atenolol group, no significant change was observed.[26]



Decreased fibrinogen and PAI-1 levels with doxazosin



Antithrombotic properties of doxazosin

DOXAZOSIN: REDUCTION OF PLASMA FIBRINOGEN AND PAI-1

Further antithrombotic properties of doxazosin have been demonstrated in sixty-nine hypertensive nonsmokers in a study conducted by Westheim. Blood samples were drawn before medication and after 16 weeks of doxazosin treatment. Levels of plasma fibrinogen and PAI-1 were determined at both points. In addition to its efficacy in lowering diastolic and systolic blood pressure, doxazosin produced a significant decrease of almost 5% in the level of plasma fibrinogen, an important independent coronary risk factor, and a significant reduction of almost 17% in the baseline level of PAI-1,[27] a major inhibitor of fibrinolysis.

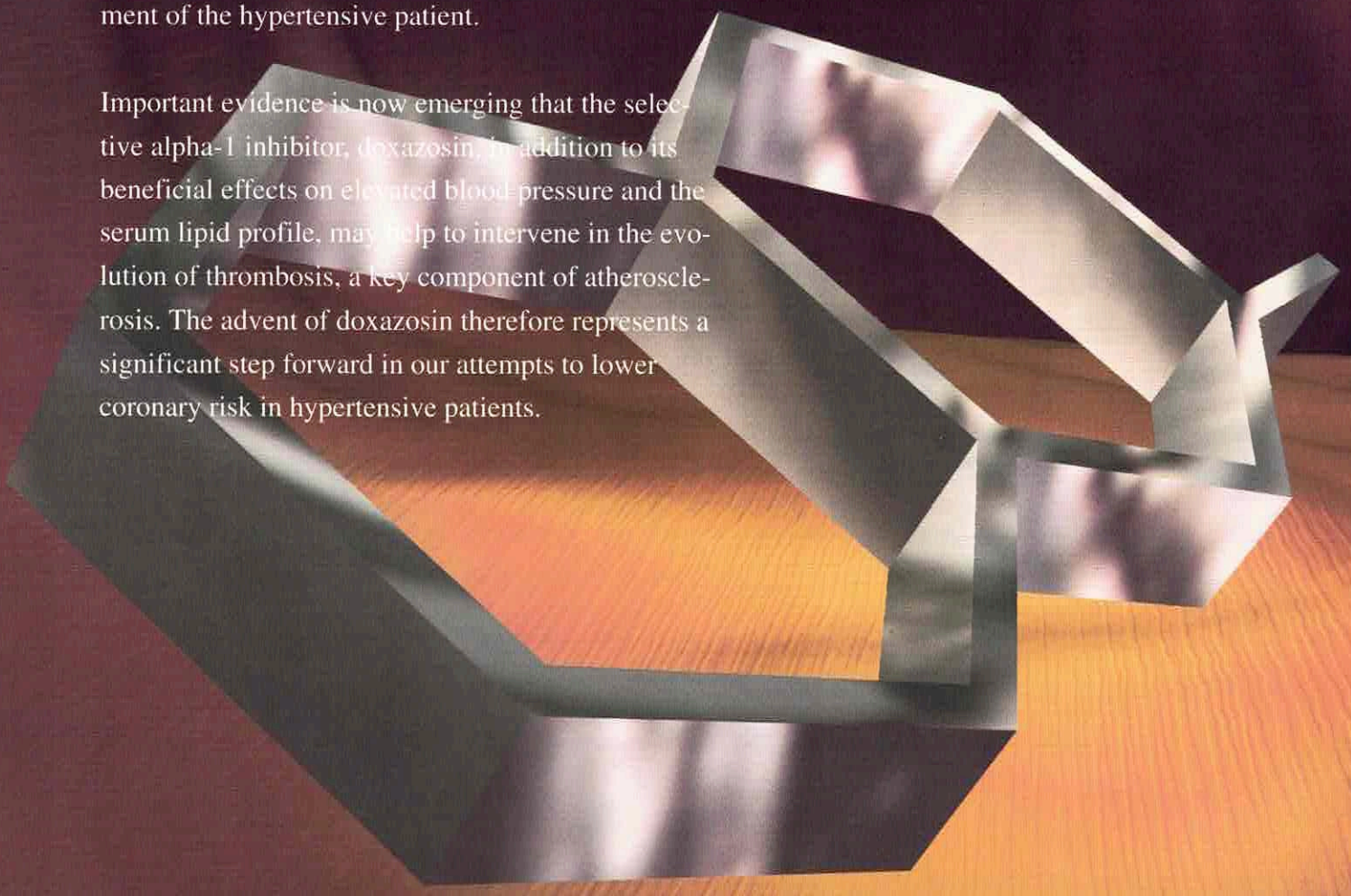
DOXAZOSIN: ANTITHROMBOTIC PROPERTIES

These recent studies suggest that doxazosin may have a range of significant antithrombotic effects in many patients, in addition to its proven beneficial effects on hypertension and hyperlipidemia. Following doxazosin treatment, a reduction in platelet aggregation and a tendency toward dissociation, together with a reduction in fibrinogen levels, might prevent excessive degrees of thrombosis at the site of vascular injury. In addition, reduced levels of PAI-1, and increased tPA capacity with doxazosin might stimulate fibrinolysis and early clot dissolution at these sites, and prevent the evolution of an acute coronary event.

CONCLUSION

With each decade, new insight is gained into how drug therapy can reduce the risk of coronary heart disease and stroke, the primary goal in the management of the hypertensive patient.

Important evidence is now emerging that the selective alpha-1 inhibitor, doxazosin, in addition to its beneficial effects on elevated blood pressure and the serum lipid profile, may help to intervene in the evolution of thrombosis, a key component of atherosclerosis. The advent of doxazosin therefore represents a significant step forward in our attempts to lower coronary risk in hypertensive patients.



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