Platelets, endothelium and blood vessel wall

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Summary. Aggregating platelets cause contraction of vascular smooth muscle, because they release serotonin and thromboxane A_2. If the platelets aggregate in a blood vessel with intact intima, the platelet-products cause endothelium-dependent relaxation of the underlying smooth muscle. Hence, the presence of an intact intima considerably reduces the vasospastic response to platelet-aggregation. The major platelet products which trigger endothelium-dependent relaxations are the adenine nucleotides and serotonin. The ability of the endothelium to prevent platelet-induced vasospasm is augmented after chronic intake of cod liver oil, but is reduced after previous intimal injury.
Key words. ADP; ATP; cod liver oil; EDRF; endothelium-dependent relaxations; PAF; regenerated endothelium; serotonin; thromboxane A_2; vasopressin.

Furchgott and Zawadzki[13] first noted that aortic rings of the rabbit, contracted with norepinephrine, relax upon exposure to acetylcholine if they contain endothelial cells; if the endothelium is removed, no relaxation is seen. Similar findings have been obtained in a number of other blood vessels, and with a variety of agents[9, 11, 12, 28, 29] (fig. 1). A number of substances present in the blood under normal or pathological conditions can cause potent endothelium-dependent responses. This implies that such responses may play a role in health and disease. This article briefly discusses this possibility in regard to the interaction between the platelets and the endothelium; it updates earlier similar reviews[7, 21, 24–27].

Contractile responses to aggregating platelets

Rings of canine coronary artery contract if autologous platelets aggregate in their vicinity[4, 5]. The contractions are enhanced markedly if the endothelium is removed mechanically (fig. 2). Similar findings have been obtained in the aorta of the rat[20] (fig. 3) and the coronary artery of the pig[22]. If the rings are first contracted, a definite relaxation to aggregating platelets is observed in rings with endothelium, but only further contraction in denuded rings[4, 5, 16] (fig. 4). In perfused segments of coronary arteries, relaxation to platelets can be obtained only if the platelets are added intraluminally and if the segment still contains endothelial cells. If the platelets aggregate intraluminally after removal of the endothelium, or are added to the bath surrounding the outside of the blood vessel, strong contractions ensue[6] (fig. 5).

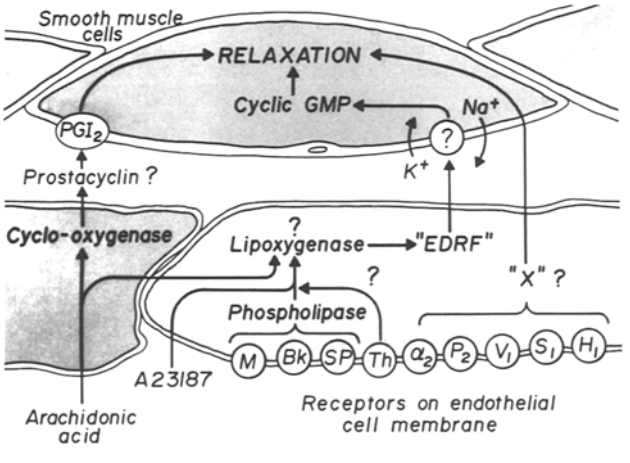

Figure 1. Postulated mechanism of endothelially mediated relaxation of vascular smooth muscle. A host of substances can induce endothelially mediated relaxations (see references in text). More than one endothelium-derived relaxing factor (EDRF) may be produced, or the formation of the same endothelium-derived relaxing factor may result from a number of mechanisms. The action of endothelium-derived relaxing factor(s) on the smooth muscle cell appears to involve stimulation of the membrane Na^+/K^+ pump, and to be mediated by increases in cyclic GMP in the smooth muscle. Th, thrombin receptor; α_2, alpha$_2$-adrenoceptor; P_2, P_2 purinergic receptor; V_1, V_1-vasopressinergic receptor; PGI_2, prostacyclin receptor; S_1, S_1-serotonergic receptor; H_1, H_1-histaminergic receptor; X, unknown intermediate; A 23187, calcium ionophore (from Vanhoutte and Houston[27] by permission of the American Heart Association).

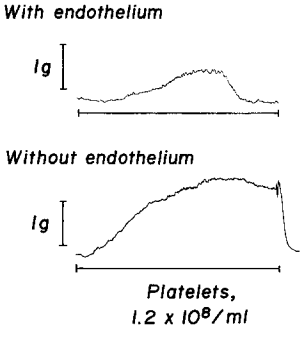

Figure 2. Isometric tension recording in isolated rings of a canine coronary artery with and without endothelium. Platelets added to the organ chamber promptly aggregate and evoke contraction (the time of exposure to platelets shown is approximately 20 min). The contractions produced in rings with intact endothelium are smaller and more transient than those in rings from which the endothelium has been removed, indicating that platelets not only directly stimulate smooth muscle but also initiate an endothelium-mediated inhibition (data from Cohen et al.[4] and Vanhoutte and Houston[27], by permission of the American Heart Association).

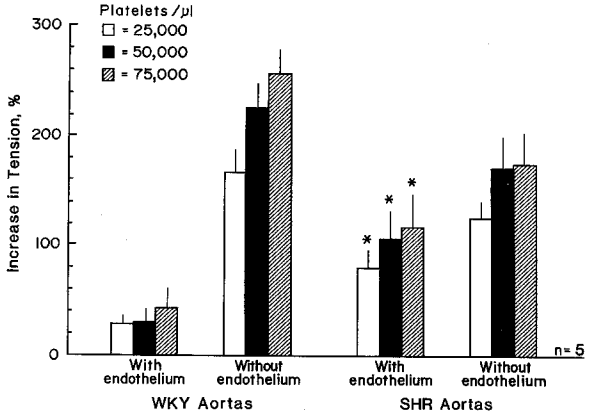

Figure 3. Response to increasing numbers of aggregating platelets in the aorta of normotensive (WKY; left) and spontaneously hypertensive (SHR; right) rats, with and without endothelium (from Luscher et al.[20], by permission of the American Heart Association).

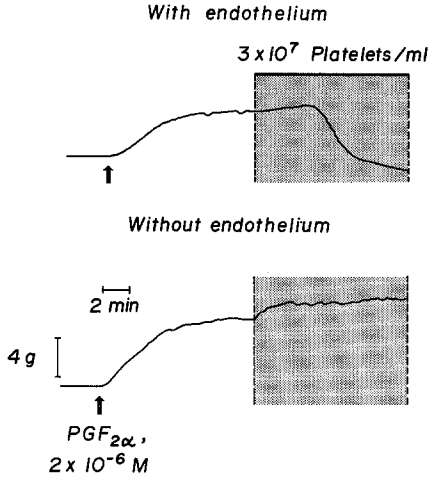

Figure 4. When coronary artery rings are exposed to aggregating platelets, they relax if the endothelium is intact but contract if it is removed. $PGF_{2\alpha}$, prostaglandin $F_{2\alpha}$ (modified from Cohen et al.[4]).

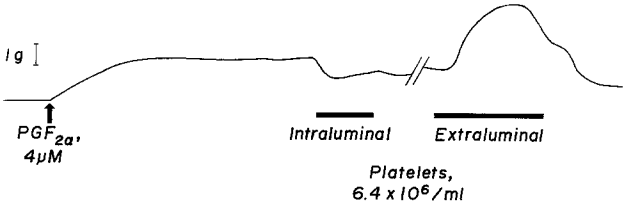

Figure 5. Further evidence of the obligatory role of endothelial cells in the relaxation of a canine coronary artery to platelets is provided by this experiment. A segment of canine coronary artery was perfused with physiological saline solution; hooks in the vessel wall allowed the recording of wall tension. The vessel was constricted with prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$). If only the luminal surface is exposed to aggregating platelets by their addition to the perfusate, a relaxation occurs; if, however, the platelets are added to the organ bath surrounding the outside of the vessel, only further contraction occurs (from Cohen et al.[6], by permission).

Thus, aggregating platelets release substances that trigger endothelium-dependent relaxations of the smooth muscle of the media of coronary arteries.

If pigs are fed for several weeks with a diet supplemented with cod liver oil, the endothelium-dependent responses of their coronary arteries to aggregating platelets are enhanced markedly[23]. By contrast in the same species, four weeks after endothelial injury of the coronary artery, the regenerated endothelial cells lose the ability to prevent contractions induced by aggregating platelets; the latter do not induce endothelium-dependent relaxations any more in contracted rings[22].

Mediators of the endothelium-dependent response to platelets

Adenine nucleotides. Adenosine di- and triphosphate (ADP and ATP) are contained in the dense granules of platelets and are released during aggregation. Both adenine nucleotides induce endothelium-dependent relaxations in isolated arteries, including the canine coronary artery[8, 10, 16]. The endothelium-dependent relaxation to platelets is almost abolished by apyrase, an enzyme that hydrolyzes ATP and ADP to adenosine monophosphate[16] (fig. 6). If endothelial receptors are saturated with ADP, the platelets cause only contraction, even though acetylcholine is still capable of causing

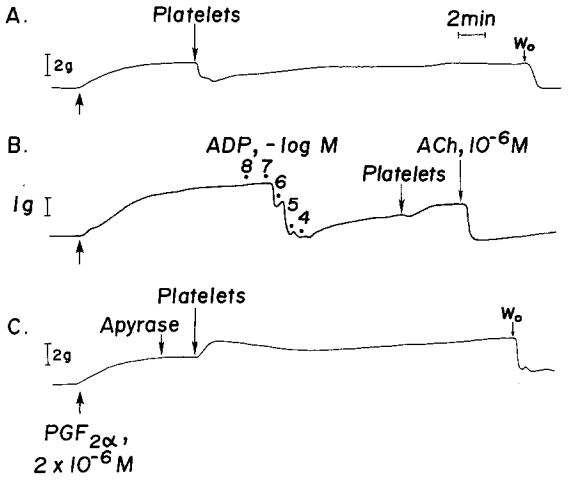

Figure 6. Evidence that adenine nucleotides play a major role in the endothelium-dependent relaxation of canine coronary arteries to aggregating platelets. Rings with intact endothelium contracted with prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) show a typical relaxation to platelets (a); this relaxation is abolished and a contraction seen if apyrase (an enzyme that degrades ATP and ADP) is present in the bath (0.67 units/ml) (c). Canine coronary rings with intact endothelium and contracted with prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) relax to cumulative concentrations of ADP; with the purinergic receptors saturated, aggregating platelets no longer can induce relaxation, although the endothelium-dependent response to acetylcholine (ACh) persists (b). W_{α}, washout (from Vanhoutte and Houston[27], by permission of the American Heart Association).

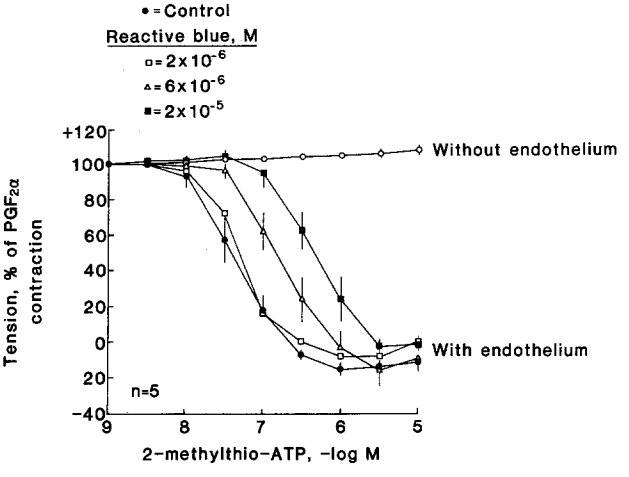

Figure 7. Effects of the P_{2y}-purinergic antagonist, reactive blue on endothelium-dependent relaxations to increasing concentrations of 2-methylthio-adenine triphosphate (ATP) in canine coronary arteries (from Houston et al.[15], by permission).

relaxation (fig. 6). Thus, the endothelium-dependent relaxation of isolated canine coronary arteries to autologous aggregating platelets is due mainly to the release of ADP and ATP. A similar conclusion has been reached for human platelets[17]. The endothelial receptor mediating the response to ATP has been subtyped as a P_{2y} purinergic receptor[15] (fig. 7). The endothelium-dependent relaxations evoked by ATP in porcine coronary arteries are enhanced by chronic treatment of the donor animals with cod liver oil[23].

Serotonin. The platelets contain 5-hydroxytryptamine (serotonin) and release it when they aggregate. Concentrations of exogenous serotonin comparable to those released from aggregating platelets cause contractions of isolated coronary arteries of the dog[4, 5, 16, 30]. The contractions of coronary

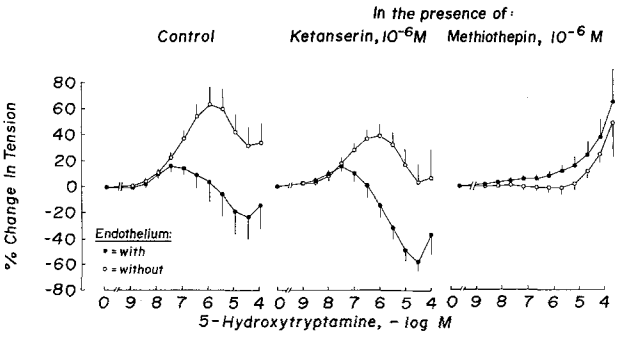

Figure 8. Concentration/effect relationships of canine coronary artery, with and without endothelium, contracted with prostaglandin $F_{2\alpha}$ (2×10^{-6} M), to cumulative addition of serotonin. In rings with endothelium, lower concentrations of serotonin (up to 10^{-7} M) produce a slight contraction; higher concentrations cause relaxation. In rings without endothelium a much stronger contraction is observed. The difference between the curves reflects the inhibitory effect of the endothelium stimulated by serotonin. Ketanserin, a selective S_2-serotonergic antagonist, reduces the contractile effect of serotonin and shifts both curves downward. Methiothepin, an S_1-serotonergic antagonist, abolishes the endothelium-dependent inhibitory effect (from Houston et al. [16], by permission).

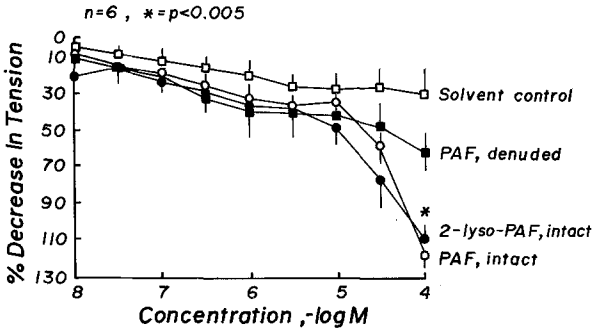

Figure 9. Concentration-effect curves in canine coronary artery, with and without endothelium, contracted with prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$; 2×10^{-6} M) in response to cumulative additions of platelet-activating factor (PAF) and its 2-lyso derivative (2-lyso-PAF) and the ethanol solvent used. Changes in tension are expressed as percent of contraction obtained with $PGF_{2\alpha}$. Relaxation induced by PAF and 2-lyso-PAF occurs in rings with intact endothelium above 10^{-5} M; this effect is endothelium-dependent (* $p < 0.005$ comparing responses of intact and denuded vessels to 10^{-4} M PAF). The lack of a difference between responses to PAF and 2-lyso-PAF suggests that this relaxation is not a specific, receptor-mediated effect of PAF (from Vanhoutte and Houston [27], by permission of the American Heart Association).

vascular smooth muscle induced by serotonin also are enhanced in vitro and in vivo by removal of the endothelium [1, 4, 5]. In contracted isolated coronary arteries serotonin causes endothelium-dependent relaxations [3–5] which are not affected by the S_2-serotonergic antagonist ketanserin but are abolished by methiothepin, suggesting the involvement of S_1-serotonergic receptors [16] (fig. 8). The endothelium-dependent relaxation to aggregating platelets persists in the presence of concentrations of methiothepin which prevent those to serotonin [16, 17], illustrating that serotonin is not solely responsible for the response.

In the coronary artery of the pig, studied one month after endothelial injury in vivo, the endothelium-dependent relaxations to serotonin are markedly reduced [22]. Conversely, endothelium-dependent relaxations to serotonin are markedly enhanced by chronic treatment with cod liver oil [23].

Platelet-activating factor. In the canine coronary and femoral arteries, platelet-activating factor causes relaxation only at high concentrations. This relaxation is endothelium-dependent, but it persists in the presence of the selective antagonist of the platelet-effects of platelet-activating factor, CV-3988; the biologically inactive precursor, 2-lyso-platelet-activating factor causes relaxation similar to platelet-activating factor [27] (fig. 9). At the high concentrations required to observe it, a direct membrane effect of these lipids, analogous to that observed with arachidonic and oleic acids [2] is a likely explanation. Unless very high local concentrations of platelet-activating factor are achieved at the sites of platelet aggregation, it is unlikely that this substance contributes to platelet-induced relaxations [25, 27].

Vasopressin. Human platelets contain vasopressin which evokes endothelium-dependent relaxations of coronary and cerebral arteries of the dog [18]. This relaxation is blocked by the V_1-vasopressinergic antagonist, $d(CH_2)_5Tyr(Me)AVP$. However, the antagonist does not affect endothelium-dependent relaxations to platelets [25, 27].

Thromboxane. Thromboxane B_2 can be measured in the fluid from organ chambers where the interaction between aggregating platelets and isolated blood vessels are studied. However, inhibitors of cyclooxygenase do not alter the response of coronary arteries to aggregating platelets [4, 16, 17]. Thus, it seems unlikely that thromboxane A_2 contributes to the endothelium-dependent relaxations induced by the platelets.

Potential role in health and disease

These observations on isolated blood vessels may help to understand coronary vasospasm. One can imagine that if platelets aggregate in an artery with an intact endothelium, the response of the blood vessel to the substances released from the platelets would be dilatation. This would be reinforced if the platelet aggregation were to trigger coagulation of the blood with formation of thrombin. Indeed, thrombin causes endothelium-dependent relaxations, which overcomes the direct constrictor effect that the enzyme has on some vascular smooth muscle [10, 18, 19] (fig. 10). An endothelium-dependent dilatation triggered by the platelet products (and thrombin) would tend to flush away the beginning aggregate before it could occlude the vessel (fig. 11). If on the other hand, the endothelium were absent, damaged or for some reason failed to function properly (e.g. during regeneration after injury [22]), the response of the vessel to platelet products and thrombin would be contraction, as observed in the rings denuded of endothelium in vitro (fig. 11). Such contractions would further reduce the luminal area and in-

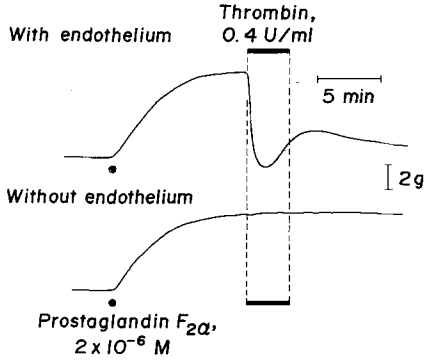

Figure 10. Isometric tension recording of porcine coronary artery with and without endothelium, contracted with prostaglandin $F_{2\alpha}$. Thrombin produces a relaxation which is entirely dependent on the presence of endothelium. A similar endothelium-dependent relaxation is seen in the canine coronary artery (from Shepherd and Vanhoutte [21], by permission).

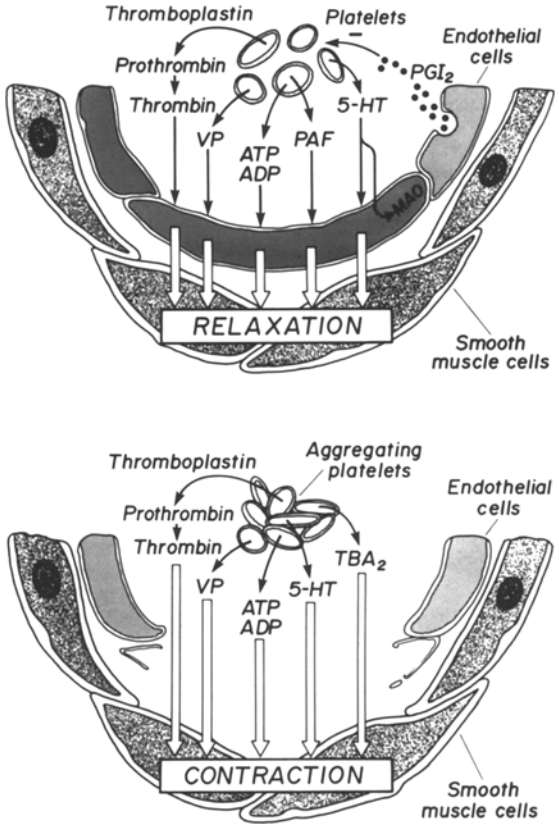

Figure 11. Schematic representation of the role of endothelial cells in the prevention of vasospasm. Aggregating platelets release adenine nucleotides (ATP and ADP), serotonin (5-HT), thromboxane A_2 (TBA_2), platelet-activating factor (PAF), and vasopressin (VP), as well as initiating the coagulation cascade with production of thrombin.
Upper figure: The presence of an intact endothelium prevents platelet aggregation through production of the platelet inhibitor, prostacyclin (PGI_2); prostacyclin is also a vasodilator. Serotonin is taken up by endothelial cells and degraded by monoamine oxidase (MAO). Platelet-activating factor (PAF) (in high concentrations), serotonin, vasopressin, adenine nucleotides, and thrombin can all stimulate the endothelial production of a relaxing factor or factors which have an inhibitory effect on smooth muscle. Relaxation and vasodilatation would tend to flush away any developing aggregate or thrombus. Finally, an intact endothelium and basement membrane probably serve as a diffusion barrier to prevent the above-mentioned substances from reaching the smooth muscle layers of the media.
Lower figure: Platelet aggregation is enhanced by contact with collagen in the exposed vessel wall. Depending on the blood vessel, the thrombin, vasopressin, serotonin, adenine nucleotides, and thromboxane produced all directly activate vascular smooth muscle; these effects would be unopposed if the endothelium is damaged or dysfunctional. Vasospasm may thus result in areas of endothelial abnormality (from Vanhoutte and Houston[27], by permission of the American Heart Association).

crease the obstruction to blood flow[14]. Clinical coronary arterial spasm may be just such a contraction[21, 27].

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Platelets, platelet-derived growth factor and arteriosclerosis

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Summary. Platelets participate in the pathogenesis of arteriosclerosis and in the progression of atherosclerosis by adhering to the damaged arteries and subsequently forming mural thrombi which are either swept away and embolize or are endothelialized and thus become part of the vessel wall. Rheologic considerations predict and blood perfusion experiments using flow chambers with exposed vessel wall components demonstrate that platelet participation increases with the wall shear rate and is thus particularly important in stenosed arteries (acute thrombosis) and the microvasculature (hemostasis). In addition to their involvement in thrombosis, activated platelets release growth factors, most notably a platelet-derived growth factor (PDGF) which may be the principal mediator of smooth muscle cell migration from the media into the intima and of smooth muscle cell proliferation in the intima as well as of vasoconstriction. The recent discovery that PDGF can be produced by additional cells involved in the pathogenesis of arteriosclerosis (endothelial cells, monocytes/macrophages, smooth muscle cells themselves) and that they may play a role in tumorigenesis has tremendously increased the interest in this growth factor and in potential antagonists.
Key words. Thrombosis; blood flow; wall shear rate; platelet adhesion; platelet thrombus growth; fibrin; endothelium; smooth muscle cell migration and proliferation.

The platelet is the key participant in thrombosis and hemostasis, particularly at high shear conditions. Furthermore, it has received a lot of attention from investigators whose primary interest was not related to platelet function in health and disease. These investigators probably chose the platelet as their research tool because it is an easily accessible human cell fragment which has numerous features in common with more complex nucleated cells, such as smooth muscle cells and neurons.

This contribution does not look at the platelet as a model for pathophysiological research but rather tries to elucidate its role in the pathogenesis of thrombosis and arteriosclerosis. These growing fields of research have benefitted a great deal from the work of biochemists and pharmacologists who used the platelet as a research tool. In addition, the study of platelet interactions with vessel wall components in flow systems, the molecular characterization of congential defects of platelet function, the successful culture of vascular endothelial and smooth muscle cells, as well as connective tissue research have contributed to the substantial progress made during the past decade in our understanding of the role of platelets in arterial thrombosis and arteriosclerosis. This progress is summarized below and was highlighted by the identification, isolation and cloning of the platelet receptors and adhesive proteins involved in platelet adhesion and aggregation and last but not least by the discovery, isolation and cloning of platelet-derived growth factor (PDGF) and other growth factors which may be involved in the pathogenesis of arteriosclerosis.

Arteriosclerosis, atherosclerosis and platelets

The term *arteriosclerosis* encompasses all forms of arterial disease which lead to a thickening of the intima and thus to a narrowing of the lumen of an artery [10].

Atherosclerosis, the most common form of arteriosclerosis, is usually associated with hypercholesterolemia. The main feature of a fully developed atherosclerotic lesion is the atheroma which consists of a nucleus containing cholesterolester, cellular debris and fat laden foam cells surrounded by a fibrous cap made of connective tissue and a few smooth muscle cells [28]. The fatty streak consists of an accumulation of subendothelial foam cells and is believed to be the precursor of an atheromatous lesion. Most foam cells of fatty streaks are derived from monocytes which migrated from the blood through the endothelial lining into the subendothelial space where they accumulate cholesterolester by the scavenger pathway [26, 32]. It is very unlikely that platelets play a role in this initial process. However, once large numbers of subendothelial foam cells have accumulated, occasional disruptions of the endothelial lining occur and accumulation of platelets is observed at such sites [26]. These observations in non-human primates and rabbits are corroborated by the fact that human atherosclerotic lesions contain substantial amounts of platelet-specific material [24]. Thus platelets contribute to the progression of atherosclerotic lesions by forming mural thrombi. Such thrombi release factors, most notably PDGF (see below) which stimulate smooth muscle cell migration and proliferation. Thrombi may not only be swept away by the blood stream, but also be endothelialized and thus become part of the vessel wall.

Other forms of arteriosclerosis such as those observed in *homocystinuria* or induced by *iatrogenic arterial damage* (angioplasty, bypass surgery) are primarily proliferative in nature. Homocystinuric patients develop severe fibromuscular intimal thickening of arteries at an early age and often die of severe arteriosclerosis with thromboembolic complications before age 20 [7, 19]. Harker et al. [19] were able to induce homocystinuria-like vascular lesions by infusion of homocystein into baboons. They observed desquamation of endothelial cells followed by platelet adhesion, thrombus formation, smooth muscle cell migration from the media into the intima, smooth muscle cell proliferation and connective tissue synthesis leading to intimal thickening. Antiplatelet therapy