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REVIEWS

Syndromes of Accelerated Atherosclerosis: Role of Vascular Injury And Smooth Muscle Cell Proliferation

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Vascular injury represents a critical initiating event in the pathogenesis of various vascular diseases, including atherosclerosis. This review discusses 1) the current understanding and a new pathologic classification of vascular injury; 2) the resultant cellular pathophysiologic responses, specifically, lipid accumulation, platelet aggregation, thrombus formation and smooth muscle cell proliferation; 3) the role of vascular injury in the pathogenesis of spontaneous and accelerated atherosclerosis; and 4) emerging therapeutic approaches in preventing these vascular diseases.

The process of type I vascular injury (nondenuding functional injury) followed by lipid accumulation, monocyte and platelet adhesion, smooth muscle cell proliferation and resultant plaque formation represents the prevalent view of the early stages of spontaneous atherogenesis. The syndromes of accelerated atherosclerosis (namely, heart transplant atherosclerosis, coronary vein graft disease and restenosis after percutaneous transluminal coronary angioplasty) appear to share etiologic mechanisms with spontaneous atherosclerosis by means of the "response to injury" hypothesis. However, type II and type III vascular injury (denuding endothelial and intimal injury with or without medial damage) followed by thrombus and its organization by smooth muscle cell proliferation and subsequent fibrosis appear to be responsible for the vascular process. This accelerated and premature occlusive process accounts for significant morbidity and mortality in patients with these conditions.

Better understanding of the nature of vascular injury and its pathophysiologic responses in these clinical situations may aid in developing therapeutic strategies for preventing these vascular diseases.

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Endothelial injury represents a critical initiating event in the pathogenesis of various vascular disease entities including spontaneous atherosclerosis. The prevalent view of spontaneous atherosclerosis is the "response to injury" hypothesis based on early proposals made by Virchow (1) and subsequently modified by Ross (2) more than a century later. The basic tenet is that chronic damage to arterial endothelium by turbulence of blood flow or other undefined injuries, possibly causing functional and nondenuding alterations of the endothelial cell, leads to accumulation of lipid, which is the initial predominant feature in these vascular injury sites. Adhesion of monocytes and platelets, perhaps simultaneously at a later time, also occurs. These cells, together with the endothelium, release various growth factors, leading to the later migration and proliferation of smooth muscle cells. With chronic injury, the typical atherosclerotic plaque could form.

A much accelerated version of this proliferative process appears to be the cause of premature coronary occlusion in patients undergoing heart transplantation, coronary vein graft bypass and percutaneous transluminal coronary angioplasty. This accelerated and premature atherosclerotic process accounts for significant morbidity and mortality in these patients (3–5). In contrast to spontaneous atherosclerosis, a more significant denuding endothelial injury appears to be the critical initiating event, followed by intense platelet involvement and thrombus formation, leading to an initial predominant process of smooth muscle cell proliferation (Table 1).

This review will discuss 1) the current understanding of vascular injury; 2) the resultant cellular interactions, lipid accumulation and smooth muscle cell proliferation as applied to spontaneous and accelerated atherogenesis; 3) the syndromes of accelerated atherosclerosis in transplanted heart atherosclerosis, coronary vein graft disease and reste-

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Table 1. Comparison Between the Processes of Spontaneous and Accelerated Atherosclerosis

	Spontaneous Atherosclerosis	Accelerated Atherosclerosis
Endothelial injury	Type I	Types II and III
Early platelet involvement	–	+
Early monocyte involvement	+*	–
Sources of growth factors	Endothelium/monocyte/ SMC/platelet	Endothelium/platelet/SMC
Pathology		
Initial	Lipid deposition, monocyte and platelet adhesion	Thrombosis, intimal SMC proliferation, fibrosis
Late	Intimal SMC proliferation, fibrosis	Lipid deposition
Complication	Plaque rupture, thrombosis	Plaque rupture, thrombosis
Duration of process	Decades	3 months to 2 years

*If hyperlipidemic. SMC = smooth muscle cells; + = present; – = absent.

nosis after coronary angioplasty; and 4) emerging preventive strategies.

Vascular Injury

Models of Vascular Injury

Various experimental models of vascular injury have been developed to understand the importance of endothelial integrity and to study the cellular proliferative responses after endothelial injury and their roles in the pathogenesis of different vascular diseases. The categories of injury models currently available are the denuding and nondenuding forms of injury. Mechanical denudation of endothelium using different devices (such as balloon and nylon filament) are among the most widely used means of studying endothelial damage and are more applicable for the understanding of the syndromes of accelerated atherosclerosis (6–10). Diet-induced hypercholesterolemia is the most extensively studied form of nondenuding injury; models closely resembling human spontaneous atherosclerosis include hypercholesterolemic swine and nonhuman primates (11–13).

Denudation of Endothelium: Mechanical and Immune Injury

Balloon catheter injury. Baumgartner and Spaet (6) were among the first to introduce the balloon catheter to strip the endothelium from arteries. In subsequent studies (7–10), the process of proliferative responses to balloon injury was well characterized. After complete endothelial denudation and various degrees of medial injury, immediate platelet aggregation and thrombus formation on subendothelium were observed. Several hours later, moderate numbers of leukocytes were also shown to adhere. The platelet aggregates persisted for up to 24 h after injury and subsequently flattened to form a multilayered carpet over the denuded area. At 48 h, some patchy regions of the injured area were reendothelialized by the migrating and dividing endothelial cells, particularly at the edge of the injury tract. At later stages, however, more severe areas of damage were covered by nonthrombogenic neointima composed of smooth muscle cells. Overall, there was a striking correlation between the degree of endothelial denudation and medial injury and the extent of myointimal thickening.

Nylon catheter injury. Because balloon catheter injury can produce severe damage to the vascular subendothelium and media in addition to endothelial denudation, alternative techniques were devised to produce selective endothelial injury with minimal trauma to the intima. With the use of a small flexible nylon filament, endothelial injury of reproducible depth and width could be produced without damage to the internal elastic lamina and the media (14–17). These confined endothelial denudations were accompanied by a moderate degree of platelet and leukocyte adhesion. In contrast to balloon injury, complete regeneration of the endothelium was evident by 48 h. No smooth muscle cell proliferation was observed. These data suggested that the degree or depth of trauma to the vessel wall was responsible for intimal thickening, particularly if endothelial regeneration took place early (16,17). Similar studies (16) also showed that the responses of the vascular cellular elements to a denuding injury were dependent on the way in which the endothelium was removed. In addition, the rate of endothelial regeneration was much more rapid after superficial nylon-induced injury than after balloon injury and appeared to correlate with the lack of smooth muscle cell proliferation (17). Similarly, using an air-dry model for injury in rat carotid artery, Fishman et al. (18) demonstrated maximal myointimal thickening in areas with minimal reendothelialization, indicating inhibition of smooth muscle growth by endothelial cells in regions of minimal injury. Indeed, Cast-

ellot et al. (19) showed that cultured endothelial cells could produce a heparinlike substance that can inhibit smooth muscle cell proliferation and thus may regulate the growth of these cells. In addition, regenerated endothelium appears to contain a higher amount of heparan sulfate glycosaminoglycan, which has also been demonstrated to inhibit smooth muscle cell growth (20).

Endothelial denudation and intimal damage with or without deep medial injury can invariably be found in coronary arteries after balloon angioplasty and in vein grafts after bypass surgery, and they appear to be responsible for the thrombotic and subsequent accelerated atherosclerosis. Indeed, these models of mechanical injury have enhanced our knowledge of the cellular responses after balloon angioplasty and bypass surgery.

Immune injury. Morphologic damage to the endothelium can also be induced by immune injury. Alonso et al. (21) studied coronary atherosclerotic plaque formation in heterotropic cardiac allografts in rabbits. Early lesions were characterized by platelet deposition, necrosis and sloughing of endothelium. In advanced lesions, smooth muscle cells predominated, with abundant elastic and collagenous fibers. Concomitant hypercholesterolemia appeared to have a synergistic effect on the development of the lesions, and the resultant plaques were more fibrofatty in nature. Thrombus formation and organization, presumably secondary to fatty plaque rupture, could occur late in the process. Similar changes have been described (3,22–24) in pig, primate and human allograft recipients. Hardin et al. (25) also found that rabbits given repeated injections of foreign protein and fed a lipid-poor diet developed proliferative fibromuscular intimal thickening without lipid deposition in the coronary arteries. When these rabbits were later fed a cholesterol-rich diet, many of the earlier lesions accumulated lipid preferentially and evolved as atherosclerotic lesions closely resembling those seen in humans. Indeed, such immune mechanisms have been implicated in the pathogenesis of accelerated atherosclerosis in heart transplantation and probably play a role in the progression of spontaneous atherosclerosis.

Nondenudation of Endothelium: Hypercholesterolemic and Viral Injury

In the pathogenesis of spontaneous human atherosclerosis, endothelial injury is unlikely to be mechanical. Furthermore, failure to find significant morphologic changes and evidence of denudation has shifted emphasis to a search for more subtle forms of nondenuding injury at the molecular and subcellular levels (2,26,27). Methods that might be applicable include endotoxin, anoxia, administration of carbon monoxide, vasoactive amines, hypercholesterolemia and viral injury. Reidy and Schwartz (28) studied the morphology of aortic endothelium in rabbits after injury by a single dose of endotoxin and during subsequent repair. Within 1 h of the injection, some endothelial cells were curled up and spindle-shaped in appearance. Multiple areas of endothelial desquamation without denudation and platelet adhesion were observed. Regeneration of endothelial cells was apparent at 7 days, and complete reendothelialization was evident at 14 days; no intimal proliferation could be found. Their study (28) demonstrated that endotoxin can produce subtle morphologic endothelial damage. Its relevance to human vascular disease is, however, uncertain.

Hypercholesterolemia (Table 1). This is the most extensively studied nondenuding form of injury. The hypercholesterolemia of nonhuman primates and swine is the model that most resembles human atherosclerosis. Faggiotto et al. (11,29) induced chronic dietary hypercholesterolemia in a large series of monkeys and described the morphologic changes in the arterial wall of the aorta and iliac arteries. They observed that after 12 days of a high cholesterol diet, leukocyte clusters (primarily monocytes) were attached to the endothelial surface and subsequently migrated subendothelially and accumulated lipid. This aggregation of monocytes constituted the first stage of fatty streak formation. Gradual migration and proliferation of smooth muscle cells into the intima with more lipid deposition soon followed. This characteristic myointimal-monocytic lesion is one of the most prominent and consistently found features of atherosclerosis in both humans and experimental animals (13, 30–32).

Despite the vascular response, morphologic endothelial injury has not been described early in cholesterol diet-induced atherosclerosis. Several studies (11,33–35) confirmed the presence of intimal lesions long before any recognizable endothelial denudation. Thus, hypercholesterolemia appears to cause a more subtle form of injury without morphologic alterations. Jackson and Gotto (36) demonstrated that hypercholesterolemia can increase the cholesterol/phospholipid ratio of endothelial cell membrane and, subsequently, membrane viscosity. This change may be important in enhancing monocyte adhesion and the formation of fatty streaks. Indeed, the adherence of monocytes to the arterial endothelium has been shown (37,38) in vitro to increase in the presence of low density lipoproteins (LDL) or very low density lipoproteins (VLDL). In addition, the binding of monocytes to endothelium could be modulated by the secretion of chemotactic factors by the arterial wall because such factors have been found in extracts of aorta from cholesterol-fed but not control swine (39,40). Werns et al. (41) recently demonstrated an abnormal response to vasoactive stimuli in segments of angiographically normal coronary arteries in patients with coronary artery disease. This vasomotor abnormality may indicate the presence of endothelial dysfunction early in atherogenesis.

In addition to endothelial changes, hypercholesterolemia can cause functional alterations in platelets and smooth muscle cells and can accentuate the proliferative responses to endothelial injury. For example, lipoproteins can cause a

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change in platelet composition that can lead to activation (42). Indeed, enhanced platelet adhesion and aggregation have been observed in patients with hypercholesterolemia (42,43).

Virus-induced endothelial injury. In 1973, Benditt and Benditt (44) provided evidence that cells composing some human atheromas are monoclonal in origin. These observations have been confirmed (45,46) and extended to include cells in organizing thrombi, and these studies prompted the search for viral or chemical mutants as the cause of myointimal proliferation. In 1979, Minick et al. (47) demonstrated that an atherosclerotic process resembling that in humans could be induced in normocholesterolemic chickens by infecting them with the Marek's disease herpes virus. Microscopically, arterial changes in infected animals were characterized by occlusive and fatty fibromuscular intimal thickening. Once again, endothelial denudation was not detectable during the early phase of the process. More recent experiments (48) have shed some light on the possible mechanisms of virus-induced endothelial damage; significantly greater cholesterol and triglyceride accumulation was observed in herpes simplex virus-infected human arterial cells than in uninfected cells. This accumulation apparently resulted from a decreased intracellular cholesterol hydrolysis. Furthermore, infected cells have a reduced capacity to produce prostacyclin when stimulated. Prostacyclin has been shown to regulate platelet activity as well as cholesterol metabolism in smooth muscle cells in in vitro experiments (49). Thus, herpes virus can cause functional alternations of endothelial cells at the molecular level and appears to be an adequate stimulus for subsequent cellular proliferative responses that closely resemble the human atherosclerotic process (48).

Functional and Morphologic Classification of Vascular Injury (Fig. 1)

With this background, we propose the classification of vascular injury into three types. In type I there is functional alteration of endothelial cells without significant morphologic changes; in type II there are endothelial denudation and intimal damage, but internal elastic lamina and media are intact; and in type III there is endothelial denudation with damage of both intima and media.

Thus, hypercholesterolemia appears to produce type I vascular injury, leading to monocyte and lipid accumulation and subsequent intimal hyperplasia; in addition, ruptured fatty plaque, which may occur later, may be considered as a type II/III injury that can lead to thrombus formation and organization. In the models of mechanical and immune injury, type II/III injury with intense platelet aggregation appears to be the prerequisite for the subsequent accelerated fibroproliferative responses and plaque formation.

Cellular Response After Vascular Injury (Table 1)

New information over the past few years concerning the role of lipoproteins and the various atheromatous cellular components (specifically, monocytes, lymphocytes, platelets and smooth muscle cells) in spontaneous atherogenesis has allowed us to speculate on the sequence of events after type I endothelial injury that result in formation of an atheromatous lesion. This sequence consists of 1) accumulation of monocytes, foam cell formation and interplay among lipoproteins, lymphocytes and other immune mediators; 2) migration from the media and proliferation of smooth muscle cells in the intima to form a crescentic mass; 3) secretion and synthesis of extracellular matrix and collagen; and 4) at some point, the occurrence of plaque disruption (type II/III vascular injury) with resulting thrombosis, which may play an essential role in the progression of atherosclerosis and the manifestations of acute coronary syndromes.

Monocyte Accumulation, Foam Cell Formation and Role of Lipoproteins and Immune Mechanisms

Monocyte accumulation and foam cell formation. More than 30 years ago, Poole and Florey (50) presented evidence for the possible role of monocytes in the development of atherosclerotic lesions. Twenty years later, Gerrity et al. (13) reported that monocyte accumulation in subendothelial space was responsible for the formation of the fatty streak, an early lesion of atherosclerosis in cholesterol-fed swine. Subsequently, Ross (2) confirmed that monocyte invasion of the intima was the earliest cellular event in the evolution of an atherosclerotic lesion in monkeys and rabbits on an atherogenic diet. Recent studies (31,32,51,52) indicate that fatty streak foam cells in humans are also predominantly macrophages. The molecular mechanism underlying monocyte attachment to the vessel wall is unknown, but it appears to depend on the interaction between a series of glycoproteins (GP) present on the monocyte surface (namely, GP-90, GP-160 and GP-155) and the monocyte binding sites on the endothelial surface (53,54).

Possible mechanisms of increased monocyte adhesion to endothelium in hypercholesterolemia are just beginning to be examined and may involve the regulation of the expression of these receptor sites by various atherogenic stimuli (55). After accumulation in the subendothelial space, monocytes can secrete a large number of products that can participate in the initiation and evolution of the atherosclerotic lesion; thus, products such as interleukins, complement factor fragments and tumor necrosis factors can enhance monocyte adhesiveness and chemotaxis and form an amplification mechanism for recruiting more monocytes into the lesion (56). In addition, monocytes and macrophages can release

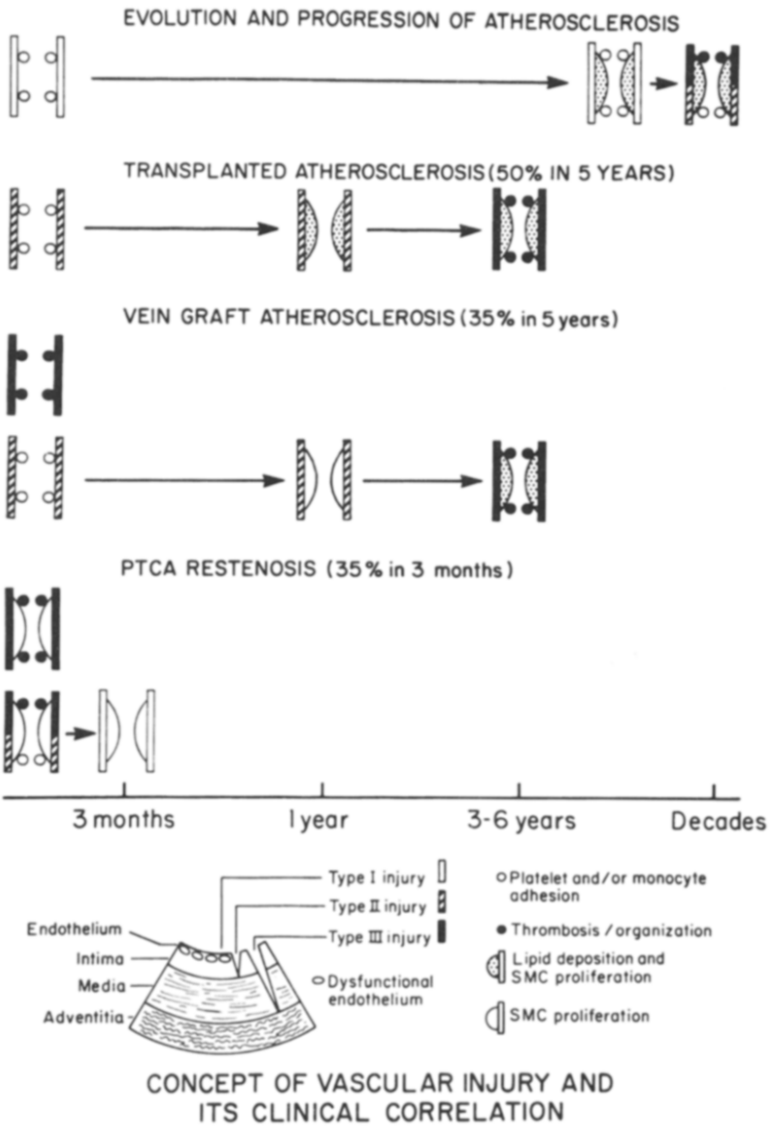

Figure 1. Vascular injury and the syndromes of accelerated atherosclerosis. Note that early type III injury leading to acute thrombotic occlusion after vein graft implantation and coronary angioplasty (PTCA) is also shown in the diagram; however, it is not part of the accelerated atherosclerotic process. PTCA = percutaneous transluminal coronary angioplasty; SMC = smooth muscle cells.

enzymes and oxygen-derived free radicals and may promote further endothelial injury and cytolysis. Released mitogens such as macrophage-derived growth factor may also play a key role on smooth muscle cell migration and subsequent proliferation (56). Finally, lipid uptake in the form of foam cells represents the major mechanism of lipid accumulation in the formation of fatty streak and early atheroma formation (51,55,56).

Role of lipoprotein modifications. Clinical studies (2,55) have shown that increased levels of LDL cholesterol contribute to the pathogenesis of atherosclerosis; however, the precise mechanisms remain unknown. Emerging evidence (57,58) suggests that various lipoprotein modifications (in particular, oxidative modification of LDL) may play a key role in the formation of fatty streaks and early atheromatous lesions. Recent investigations (59–61) have provided evidence that such oxidative modification of LDL may indeed occur in vivo.

In vitro studies (57,58) suggest that oxidatively modified LDL may contribute to the atherogenic process by several mechanisms. First, and perhaps most important, oxidized rather than native LDL is recognized by the non-down-regulating scavenger receptors of macrophages and, thus, could promote foam cell formation. Second, modified LDL may be atherogenic by being chemotactic for monocytes, thereby potentially serving to recruit monocytes into the subendothelial space. Third, oxidized LDL is cytotoxic and may provide a potential mechanism for endothelial injury and cellular necrosis.

Immune mechanisms in atherogenesis. Over the past few years, there has been a surge of new information concerning the potential relevance of immune mechanisms to atherogenesis. Studies (52,62,63) have demonstrated the presence of substantial amounts of T lymphocytes both in early fatty lesions and in advanced fibrous lesions in humans. In addition, the presence of T lymphocytes in the

intima is frequently associated with monocytes and macrophages. Although the precise role of T lymphocytes in atherogenesis is still unknown and highly speculative, this close association with monocytes and macrophages is not surprising in view of the well known regulatory interactions between these two cell types (62). For example, the secretion of monocyte chemotactic factor can enhance the adhesion and migration of circulating monocytes; the release of lymphokines and interleukins from activated T lymphocytes can regulate lipoprotein uptake by the macrophage and thus may influence foam cell formation. In addition, the complex regulatory roles of these cytokines on the expression of growth factor receptors and smooth muscle cell growth raise the possibility that the T lymphocytes may play a pivotal role in atherogenesis (52,62).

Other components of the immune system, such as immunoglobulins and various activated complement factors, have also been identified in human atherosclerotic plaque (62,64,65). Although their mere presence does not necessarily imply a cause and effect relation, it may indicate an ongoing immune response in the atherosclerotic process. Seifert et al. (66) recently demonstrated the deposition of complements C5a-9 complex in the endothelial layer and intima in rabbits as early as 2 weeks after the start of a high fat diet, followed by monocyte accumulation and foam cell formation at the same sites of complement deposition at 6 weeks. Conversely, monocytes and macrophages were not detected in locations devoid of complement activation products. Certain complement peptides have been demonstrated to be chemotactic for monocytes (66). In addition, recent studies (67) of C3-binding proteins in human plaque demonstrated that the smooth muscle cells of the atherosclerotic lesion (but not of normal artery) express a decay-accelerating factor that protects the cells from complement-mediated lysis by inhibiting C3/C5 convertase formation. This shows that the phenotypic changes in smooth muscle cells during atherogenesis may involve the induction of complement regulatory molecules.

These provocative findings are just a few examples in a rapidly growing field regarding the role of immune mechanisms in atherogenesis. The interplay among these cellular components provides numerous potential mechanisms for mediating the inflammatory, reparative and proliferative changes seen in atherosclerotic lesions.

Smooth Muscle Cell Migration and Proliferation

Proliferation of smooth muscle cells is a key prerequisite process leading to vascular occlusion in both spontaneous and accelerated atherosclerosis (Table 1). Animal models of vascular injury designed for the study of the "response to injury" hypothesis have suggested that migration and subsequent proliferation of smooth muscle cells depend on the milieu created by the interactions between blood-borne cells and endothelium after the injury. Elimination of the growth inhibitory effect of intact endothelium and the release of growth factors from activated platelets, monocytes, injured endothelial cells and smooth muscle cells, coupled with thrombosis and thrombus organization, provide the mitogenic stimuli for smooth muscle cell growth.

Migration of Smooth Muscle Cells: Phenotypic Change of Smooth Muscle Cells From "Contractile" to "Synthetic" Mode

Behavior in cell culture. Vascular smooth muscle cells can express different phenotypes (68–70). In young developing arteries, smooth muscle cells have the ability to proliferate and produce large amounts of collagen, elastin and proteoglycans. In the adult artery, their main function is to regulate wall tension, but they may modulate back into a synthetic phenotype and participate in tissue repair or atherogenesis. In forming atherosclerotic lesions, smooth muscle cells appear to regain the phenotypic characteristics of smooth muscle cells in young and developing arteries (69, 70). Our knowledge of the signal or signals that initiate modulation into the synthetic phenotype is still very limited, but much has been learned of the behavior of smooth muscle cells in cell culture systems. Investigators (69,70) have studied the phenotypic changes in smooth muscle cells in primary culture. Their studies demonstrated that when smooth muscle cells from the aortic media of young adult rabbits were dispersed into single cells such that a confluent monolayer was present, they attained the contractile state, characterized by a fusiform shape with abundant bundles of myofilaments in the cytoplasm, and could respond to mechanical and electrical stimuli by slow contraction. If the isolated cells were sparsely seeded, they spontaneously underwent a change of phenotype to the synthetic state, with a loss of the thick myosin-containing filaments and an increase in synthetic matrix. These cells also became broader and flatter and lost their contractility. However, modulation into this synthetic state in vitro was inhibited if smooth muscle cells were grown on a confluent layer of endothelial cells.

Phenotypic changes in vascular injury. Similar phenotypic changes in medial smooth muscle cells from a contractile to a synthetic mode have been demonstrated in various models of vascular injury (68,71–73). After massive endothelial loss from an artery, smooth muscle cells proliferate first in the media and later in the intima. In the balloon catheter-injured rat carotid artery, approximately 30% of the medial smooth muscle cells participated in the immediate proliferative response, reaching a maximum at 48 h. These cells were ultrastructurally similar to the synthetic state cells in culture, with large amounts of rough endoplasmic reticulum, free ribosomes and mitochondria and fewer myofilaments.

These changes could persist for up to 3 weeks after endothelial injury. Smooth muscle cells then began to migrate into the intima at 4 days, and proliferation was maximum in the intima at 7 days (9,10,72,73). The increase in intimal thickening continued into the 8th week after vascular injury and appeared to be mainly due to synthesis and accumulation of extracellular matrix and connective tissue (72). By further analysis of smooth muscle cell types using tritiated thymidine, it was demonstrated (74) that about 50% of the cells that migrated into the intima never divided and accounted for approximately 10% of the intimal cells. Thus, migration alone without proliferation could make up a significant part of the intimal smooth muscle cell accumulation.

The reasons for migration without proliferation remain unclear. However, individual smooth muscle cells are believed to possess different degrees of proliferative ability (75); some that migrate lack the ability to divide (76). Whether this heterogeneity in smooth muscle cell proliferative potential plays a role in determining the degree of intimal hyperplasia after vascular injury remains to be established. Control of smooth muscle cell migration has only begun to be explored. In cell culture, a variety of mitogens stimulate smooth muscle cell growth and undirected migration, but only platelet-derived growth factor induces directed migration (77). Other factors generated as part of the injury process, such as platelet factor 4 and interleukins, might also play a role (78–80).

Proliferation of Smooth Muscle Cells

Proliferation of intimal smooth muscle cells has been established as a key event in the evolution of atherosclerosis (2,27,29,31,68,81). One of the principal issues in atherogenesis is the determination of the biochemical signal or signals that underlie smooth muscle cell proliferation. In the normal quiescent state, smooth muscle cells proliferate at a very low rate. Experimental evidence (18–20) suggests that intact endothelium plays the central role in maintaining the low proliferative state of smooth muscle cells under normal vascular conditions. In the case of type II and type III vascular injury, which can be induced experimentally and which clearly occurs in humans at the perianastomotic area of vascular grafts and after coronary angioplasty, platelets, injured endothelial cells and smooth muscle cells can release platelet-derived growth factor and other mitogens necessary for smooth muscle cell growth. In type I injury, as in hypercholesterolemia, adherent monocytes and possibly endothelial and smooth muscle cells may secrete mitogens that can cause smooth muscle cell proliferation.

Inhibitory effect of endothelial cells with intact function. Findings from in vivo experimental models of vascular injury and smooth muscle cell proliferation suggest that intact endothelium is a potent inhibitor of the growth of smooth muscle cells; their proliferation ceases when a mechanically denuded area is reendothelialized. As previously discussed, using an air-dry model for injury in the rat carotid artery, Fishman et al. (18) demonstrated maximal myointimal thickening in areas with minimal reendothelialization. Similarly, after superficial nylon-induced injury, the rate of reendothelialization is much faster than after balloon catheter-induced injury and appears to correlate with the lack of smooth muscle cell proliferation (17,82). The mechanism of apparent smooth muscle cell growth inhibition by endothelial cells is not entirely clear. However, Castellot et al. (19) showed that cultured endothelial cells could produce a heparinlike substance that inhibits smooth muscle cell proliferation in vitro. In addition, regenerated endothelium appears to accumulate more heparan sulfate-containing glycosaminoglycan than does nonendothelializing lumen (20). This type of glycosaminoglycan has been shown (83) in vitro to inhibit smooth muscle cell growth; in actively growing vascular beds of rabbit cornea, the prominent glycosaminoglycan was hyaluronic acid, whereas in the quiescent vascular bed, the major class was heparan sulfate. Changes in the type of glycosaminoglycan in endothelial cells after experimental injury and after atherogenic stimuli (84,85) appear to play a role in determining the degree of smooth muscle cell proliferation. Indeed, the proportion of chondrotin sulfate/dermatin sulfate in human aorta increases significantly with age and cholesterol content, whereas the corresponding amount of heparan sulfate decreases (86).

In contrast to the inhibitory effect of functionally intact endothelial cells, platelet-derived growth factors and other similar mitogens have been found to enhance modulation of smooth muscle cells into the synthetic state (87–89). Sources of these growth factors include platelets, endothelial cells, macrophages and smooth muscle cells. Their interactions play a significant role in promoting smooth muscle cell growth in various vascular diseases.

Stimulatory effect by platelets. Platelets are excellent candidates as the initiators of intimal plaque formation after type II and type III injury. In almost all in vivo experimental models studied (8–10,16,26,72,74), immediate platelet adhesion and degranulation were observed, followed by proliferation of smooth muscle cells within 48 h of denudation. Mitotic activity declines considerably thereafter as platelets disappear. The fact that intimal thickening induced by moderate balloon catheter injury is significantly inhibited in rabbits with severe thrombocytopenia (90) lends additional support to the notion that platelet-derived growth factor may play a role in the induction of the proliferative response after vascular injury. In a model of endothelial injury induced by homocysteinemia, Harker et al. (91) demonstrated desquamation of endothelial cells, followed by platelet adhesion, thrombus formation, smooth muscle cell migration from the media to the intima and subsequent proliferation leading to intimal thickening; antiplatelet therapy with sulfinpyrazone inhibited this process. In humans, it is highly likely that platelets are involved in early lesion formation in catheter-

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induced injury, in perianastomotic lesions of vascular grafts and in other traumatic vascular injury. The role of platelets after type I injury is less certain, as indicated by several experimental models of atherosclerosis in which proliferation of smooth muscle cells and intimal thickening can occur without obvious platelet participation (11,29–33). However, Fuster et al. (92–94) demonstrated that normal pigs on a normal or mildly hypercholestoleremic diet developed extensive proliferative atheromatous lesions, whereas pigs homozygous for von Willebrand disease and thus lacking factor VIII and defective in platelet-vessel wall interaction developed less proliferative lesions. Similarly, thrombocytopenia can reduce atherosclerotic lesions in rabbits (95). Indeed, although platelets may not be important in the initiation of atherosclerosis related to minimal injury (type I), they may play a role in subsequent progression of the disease (2).

Platelet-derived growth factor is a major mitogen for smooth muscle cells. It is a 30 kd basic protein consisting of two disulfide-linked polypeptide chains (A and B) and is one of the primary constituents of the platelet alpha-granule (96). One or both of its chains can also be synthesized by several other cells, including endothelial cells, macrophages and smooth muscle cells. The early response to activation of the platelet-derived growth factor receptor on smooth muscle cells includes a tyrosine-specific autophosphorylation of the receptor in intracellular calcium and active exclusion of protons by means of the sodium-potassium exchanger. The end result is activation of several genes responsive to platelet-derived growth factor and production of their specific proteins (96). These proteins probably play an essential role in such processes as smooth muscle cell proliferation and migration.

Stimulating effect by damaged endothelial cells. Endothelial cells from every source tested, including bovine, monkey and pig aorta, rat heart and human umbilical vein, possess growth-promoting activity for cultured smooth muscle cells and fibroblasts (97). The mitogenic activity is due to the secretion of at least two major mitogens, which are separable by biochemical and immunologic methods (98–100). One of these mitogens is closely related if not identical to platelet-derived growth factor. The mechanism by which growth factor production is regulated in endothelial cells is not known. The amount of growth factor production by cultured endothelial cells can be dramatically increased by increasing the pH or by lethally injuring the endothelial cells with agents such as endotoxin and phobol esters (99). A mathematic model (99) applied to these cell injury experiments suggests that a dying endothelial cell produces as much growth factors in <3 days as does a healthy cell during a 19 day period. These data support the modified version of the "response to injury" hypothesis, in which focal lethal damage to the endothelium can lead to increased local mitogenic activity that can attract and stimulate neighboring smooth muscle cells. In contrast, endothelial cells with intact function may exert an inhibitory effect on neighboring smooth muscle cells.

Stimulating effect by monocytes and macrophages. The relevance of monocytes in atherogenesis, in addition to accumulation of lipid, appears to be related to their ability to stimulate smooth muscle cell growth (56,101). In studies (102) of wound repair in guinea pigs with monocytopenia and subsequently in tissue culture studies, fibroblast proliferation was inhibited when the availability of monocytes was diminished. Conversely, fibroplasia was stimulated by macrophage-conditioned media in vitro (103,104). It was recently reported (105,106) that at least part of the macrophage-derived mitogenic activity is due to production of a growth factor similar if not identical to platelet-derived growth factor.

Self-stimulating effect of smooth muscle cells. Adult arterial smooth muscle cells in primary culture can spontaneously modulate from a contractile to a synthetic phenotype. This transition is followed by rapid growth, which is partly independent of exogenous mitogens and accompanied by endogenous production of a platelet-derived growth factor-like protein (68,73,107–109). The ability to grow in serum-free medium ceases as the cells reach confluence, but it reappears if a wound is produced in the culture. These cells have also been found to express genes for the A chain of the platelet-derived growth factor and to acquire the properties of young developing smooth muscle cells. In accordance with these findings, Walker et al. (108) reported that smooth muscle cells isolated from arterial intima 2 weeks after balloon catheter-induced injury produced 10 times as much platelet-derived growth factorlike substances as smooth muscle cells isolated from the media of uninjured arteries. Libby et al. (110) recently demonstrated that smooth muscle cells isolated from atheroma could secrete mitogenic proteins, some of which resemble platelet-derived growth factor. This capacity to produce endogenous, potentially self-stimulating growth factors may help explain how replication of smooth muscle cells can begin early in atherogenesis, even when the endothelial barrier remains morphologically intact. It can also explain why replication of smooth muscle cells can continue after aggregation of blood cells (platelets and monocytes) has ceased a few weeks after vascular injury.

Many additional growth factors present in platelets and atheroma cells are mitogenic toward vascular myocytes and lead to other contractile and metabolic changes. These include interleukin-1, alpha- and beta-fibroblast growth factors, serotonin and thrombospondin (79,80,111–113). Various neurotransmitters and hormones, such as catecholamines and angiotensin II, are likewise implicated in myocyte growth regulation (114,115).

Secretion and Synthesis of Extracellular Matrix

The formation of fibrous tissue in the arteries contributes significantly to the initiation of the atherosclerotic plaque and most importantly to its progression (2,68,84,85). The formation of fibrous tissue is regulated by fibroblasts and smooth muscle cells when they are stimulated by the growth factors. The elements that make up this fibrous tissue are collagen, proteoglycans, elastin and glycoproteins.

Collagen. Collagen formation is the major contribution to the growth of atherosclerotic plaque, and a recent review (2) has summarized the biochemical events of this collagen deposition. Of the various types of collagen, type I is the primary component of the plaque and is synthesized by arterial smooth muscle cells when they are stimulated by growth factors.

Glycosaminoglycans. Of the glycosaminoglycans (acidic mucopolysaccharides), it appears that dermatan sulfate (formerly called chondroitin sulfate B) is the major one present in the atherosclerotic plaque (84,85). It is also synthesized by the arterial smooth muscle cells under the influence of the growth factors. These glycosaminoglycans appear to be of importance in the binding of lipid into the arterial wall (84, 85).

Elastin. The concentration of elastin in atherosclerotic plaques is low in comparison with that in normal arteries (2). However, it has been suggested that the atherosclerotic arterial wall has abnormal elastin (85), and this fiber may play a role in enhancing lipid uptake; in addition, it contributes significantly to calcification of the atherosclerotic plaque.

Glycoproteins. The glycoproteins are a family of proteins containing bound carbohydrate; they have relatively more protein than the glycosaminoglycans. There is general agreement that atherosclerotic plaque contains an increased concentration of glycoproteins (2) and that, as with other interstitial fibrils, arterial smooth muscle cells play a role in this synthesis when stimulated by growth factors.

The concept of fibrous tissue synthesis assumes that the endothelial injury with the resultant cellular interactions and the release of mitogens lead not only to the migration and proliferation of smooth muscle cells, but also to the synthesis by these cells of the fibrous tissue components. In addition, it appears that the chronic pulsatile distension of the arterial region also favors the synthesis of collagen by smooth muscle cells and, thus, the slow progression of atherosclerotic plaque.

Plaque Disruption and Thrombosis

Platelet aggregation, fissures and thrombosis. The precise role of platelets in the initiation of spontaneous atherosclerosis is currently undefined. However, emerging evidence suggests that platelet aggregation and thrombosis after type II injury appear to play a key role in the progression of the disease. In contrast to the early stage of atheroma formation, type II endothelial injury is common at the later stage (116,117). Davies et al. (117) recently reported that the endothelial surface overlying atherosclerotic plaque in coronary arteries of patients undergoing heart transplantation frequently showed areas of abnormality, varying from focal defects to large areas of frank denudation with platelet deposition. In an autopsy study of coronary arteries in 129 patients with atheromatous disease who died of noncardiac causes, the same investigators (118) demonstrated the presence of fissures in atherosclerotic plaques and, in some cases, overlying thrombus in 16.7% of patients. This degree of frequency of plaque fissure in a static pathologic evaluation suggests that a single plaque may undergo many fissures during evolution into an advanced lesion. Indeed, analysis of the coronary tree in patients who died from ischemic heart disease (119,120) showed that a morphologic appearance consistent with previously healed fissures with various stages of thrombosis and thrombus organization was almost ubiquitous; this finding suggests that most fissures probably reseal with incorporation of thrombus without manifestation of clinical symptoms.

Further evidence supporting thrombosis and thrombus incorporation as part of plaque progression is provided by a recent study by Bini et al. (121), using monoclonal antibody in identifying fibrin, fibrinogen and fibrin(ogen) degradation products. They demonstrated that in advanced and fibrous plaques, fibrin and fibrin-related products were detected in the intima, neointima and deeper medial layer, especially around areas with thrombus incorporation; these fibrin and related products were also found in small quantities in early lesions and in normal arteries.

There are two potentially important metabolic sequelae of thrombus incorporation. First, incorporated thrombus has been demonstrated to enhance lipid uptake in the form of either beta-VLDL or modified LDL by means of their respective receptors on the macrophages (122). Second, thrombin generated during the process of thrombosis has recently been shown to promote smooth muscle cell proliferation, either by acting as a growth factor itself or by enhancing release of mitogens from platelets and endothelial cells (123,124). In contrast, platelet aggregation and thrombosis after type II and type III injury appear to play the major role in the initiation of lesion formation in the syndromes of accelerated atherosclerosis.

Plaque disruption (type II and type III injury) with resultant intraluminal thrombosis also plays a fundamental role in the pathogenesis of the acute coronary syndromes of unstable angina, acute myocardial infarction and sudden cardiac death. It is beyond the scope of this review to discuss these pathogenic mechanisms. However, it is important to bear in mind that it is the degree of the vascular injury

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Table 2. Possible Biologic Mechanisms of Risk Factors in Spontaneous Atherogenesis

Biology	Hyperlipidemia	Hypertension	Smoking	Genetics
Vascular injury (type I)	+	+	+	–
Lipid deposition	++	–	–	++
Monocyte/platelet deposition	+	–	–	–
Fibrointimal proliferation	+	+	–	++
Plaque disruption (type II/III)	+++	++	–	–
Thrombosis	+	–	++	–

+ = mild; ++ = moderate; +++ = severe; – = no effect.

and its corresponding pathophysiologic responses that represent the primary determinant of the severity of the acute coronary occlusion and the clinical outcomes.

Role of risk factors (Table 2). Finally, detailed discussion of the roles of the epidemiologically significant atherogenic risk factors, such as hyperlipidemia, hypertension, smoking and genetic factors, is not possible in this review. However, their potential relation to the underlying pathophysiologic events in the process of spontaneous atherosclerosis deserves special comment. As already discussed, hyperlipidemia, at least in various animal models, induces type I endothelial injury, which enhances lipid deposition into the vessel wall and increases platelet and monocyte adhesion and thrombosis. More important, emerging evidence suggests that hyperlipidemia, by favoring lipid accumulation, may contribute to plaque fissure and rupture (type II/III injury), leading to subsequent thrombus formation. Similarly, hypertension may initiate or perpetuate vascular injury, or both, and may enhance the resultant fibrocellular proliferative responses. In addition, hypertension may play a role in triggering acute plaque rupture caused by the effect of shear stress on the arterial wall. Smoking may also initiate vascular injury by its toxic effects on the endothelium and enhance platelet reactivity and thrombogenic tendency. Genetic factors other than hyperlipidemia may contribute to an exaggerated myointimal proliferative arterial response after endothelial injury.

Pathophysiologic Stages of Atherosclerotic Lesion Formation in Syndromes of Accelerated Atherosclerosis

Stages and Initiating Factors (Tables 1 to 3; Fig. 1)

The process of plaque formation in accelerated atherosclerosis can be divided into four stages: 1) deep intimal injury; 2) interaction of blood-borne cells (platelets, monocytes and lymphocytes) and, most importantly, early thrombosis; 3) smooth muscle cell migration and proliferation; and 4) lipid accumulation leading to plaque rupture and late thrombosis. In contrast to spontaneous atherosclerosis, in accelerated atherosclerosis, type II and type III vascular injury appear to be the critical initiating events that lead to platelet aggregation, thrombosis and thrombus organization. Type II vascular injury occurs in patients after heart transplantation and coronary vein graft bypass, whereas type III vascular injury occurs in patients after coronary angioplasty. In contrast to spontaneous atherosclerosis, platelet aggregation and thrombosis early in the formation of atherosclerotic lesions can be found in all three clinical situations (125–128). Processes of lipoprotein modification and monocyte accumulation probably play an important role in the later stages of the atherosclerotic process in heart transplant and vein graft disease; however, their role in chronic restenosis after coronary angioplasty is unclear because the formation of the obstructive lesion is secondary to excessive smooth muscle cell proliferation.

Table 3. Biologic Factors in the Pathogenesis of the Syndromes of Accelerated Atherosclerosis

	Transplant Atherosclerosis	Vein Graft Atherosclerosis	Coronary Angioplasty Restenosis
Vascular injury	II	II/III	III
Platelet/ thrombosis	+	++	++
Hyperlipidemia	+++	++	+/–
Immunologic	+	–	–

Symbols as in Table 2.

The concept of immune-mediated atherogenesis in heart transplant-related atherosclerosis is controversial. Although immunoglobulin and complement deposition have been demonstrated in coronary arteries in heart transplant patients, most evidence for an immunologic basis for transplant atherosclerosis is circumstantial. However, it must be acknowledged that the establishment of a causal relation would be difficult, just as it has been for the relation between spontaneous atherosclerosis and hyperlipidemia and hypertension because of the many factors involved. The relative significance of the biologic factors in the pathogenesis of the syndromes of accelerated atherosclerosis is summarized in Table 3.

Accelerated Atherosclerosis in Heart Transplantation (Fig. 1)

Atherosclerosis in the transplanted heart is a serious and apparently irreversible complication of allogenic heart transplantation. Despite the improvement in supportive care, immunosuppressive methods and the use of antiplatelet drugs, the principal cause of death in those who survive the first postoperative year is premature coronary obstructive

Table 4. Incidence and Nature of Coronary Atherosclerosis in Heart Transplant Recipients*

	% Incidence	
	Patients	Lesions
Time (yr)		
1	20	—
3	45	—
7	50	—
Localization		
Diffuse alone (distal, <2 yr)	—	24 (no collateral vessels)
Discrete with or without diffuse (proximal, >2 yr)	—	76

*Data from references 134, 145 and 146.

disease. The incidence of atherosclerosis defined angiographically in humans has been reported (3,125,129–133) to be between 19% and 36% at 1 year, 45% at 3 years and 50% at 5 to 7 years. This also accounts for approximately 50% of transplant failures within 2 years of surgery (3,125,129–133). Most cases of transplant atherosclerosis are not amenable to coronary artery surgery, angioplasty or atherectomy because of the diffuse and distal arterial involvement. Retransplantation is the only effective therapy, but further uses up the resources of donor heart and has a significantly higher mortality rate than does the initial transplantation.

Types of coronary lesions (Table 4). Gao et al. (134) recently studied the angiographic lesions in 81 transplant patients exhibiting coronary vascular disease and classified the lesions into two main types. The first, which tends to occur after the first postoperative year, is a discrete or tubular stenosis located mostly in primary epicardial coronary vessels and is similar in morphology to that of "ordinary atherosclerosis." The second type, which tends to occur within the first postoperative year, is the most predominant and the one discussed in this section; it is characterized by diffuse concentric narrowing located primarily in distal secondary and tertiary vessels. In the presence of total vessel obliteration, collateral vessels are poor or absent in >90% of cases. Pathologically, the vascular lesion is characterized by marked proliferation of intimal smooth muscle cells, with varying degrees of lipid accumulation and mononuclear cell infiltrates (24,126,135,136). Additionally, most large and severely involved segments have signs of old thrombus, with fibrous replacement and recanalization.

Type II vascular injury. This appears to be the critical initiating event (Table 3) and leads to platelet deposition, mitogen release, subsequent smooth muscle cell proliferation and collagen synthesis. At later stages, presumably as a result of ruptured fatty plaque, thrombus formation and organization have been observed (126,135,136). The causes of type II vascular injury in transplanted hearts are likely to be many, including preimplantation injury, denervation, viral infection, hyperlipidemia and immune injury. Denuding vascular endothelial damage can occur during the procurement of the donor heart with the current methods of cardiac preservation with crystalloid cardioplegia and storage (137). Denervation of the heart at the time of excision can result in depletion of tissue catecholamines and impairment of glucose metabolism, which predispose to endothelial injury (138). A potential viral etiology for atherogenesis is being increasingly recognized (44); cells composing some human atheromas are monoclonal in nature. A recent study (139) found that a significantly higher percent of patients with premature allograft atherosclerosis have cytomegalovirus infection than do those without premature coronary artery disease. This suggests a possible relation between posttransplant cytomegalovirus infection and allograft atherosclerosis.

Hyperlipidemia. This is prevalent in patients after heart transplantation and appears to be a significant predisposing factor for transplant atherosclerosis (132,140). In addition to causing endothelial injury, hyperlipidemia can also increase platelet adhesion and lipid accumulation. Several factors could contribute to elevated plasma lipids, such as the use of corticosteroid and cyclosporin therapy. Moreover, these factors may be superimposed on the primary background of hyperlipidemia, particularly in patients with underlying ischemic heart disease (141,142).

Immune-mediated vascular injury. The concept of ongoing immune-mediated vascular injury as a cause of graft-related atherosclerosis is suggested by the demonstration of both humoral and cellular components associated with vascular damage (52,143,144). The presence of cytotoxic B cell antibody, which may be directed at an HLA-DR antigen on the vascular endothelium, was found to be a predictor of early myocardial infarction and sudden death in cardiac transplant recipients (145). The role of cellular immune mechanisms has been underscored by the findings that activated T lymphocytes and macrophages constitute a major proportion of cells in the atheromatous lesion (144). Although the precise role of these immune mechanisms in the pathogenesis of accelerated atherosclerosis is still speculative, these cells have a potentially significant ability, through their secretory products, to cause vascular injury and to stimulate monocyte and smooth muscle cell accumulation and lipid uptake. For example, the vascular effects of interleukins released by activated T lymphocytes include induction of structural changes in endothelial cells, monocyte and platelet accumulation and stimulation of smooth muscle cell proliferation and secretion of growth factors (52, 79,80,144). Similarly, the effects of interferons, tumor necrosis factors and other cytokines on lipid metabolism and cell proliferation are well documented (52,144). Of interest, however, immunosuppressive agents have not been shown to reduce the incidence or severity of disease in the

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Table 5. Possible Biologic Mechanisms of Risk Factors in the Syndromes of Accelerated Atherosclerosis

	Transplant Atherosclerosis			Vein Graft Disease		Angioplasty Restenosis	
Etiology	PCEI	Immune	Hyperlipidemia	Ex Vivo Injury	Hyperlipidemia	Balloon	Shear Stress
Vascular injury (II/III)	++	++	+	++	+	++	+
Platelet deposition, thrombosis	+	–	+	++	+	++	+
Fibrointimal proliferation	+	–	+	++	+	++	++
Lipid accumulation	–	–	++	–	++	–	–
Plaque disruption	–	–	++	–	++	–	–

PCEI = preimplantation coronary endothelial injury; symbols as in Table 2.

transplanted heart. In fact, with the introduction of cyclosporin and better control of the immune response and fewer acute rejection episodes, there has been no concomitant reduction in the development of accelerated atherosclerosis (146); this suggests a multifactorial nature of the pathogenic process.

Role of antiplatelet agents. Because platelet deposition has been described as an initial event during endothelial necrosis, antiplatelet agents may have therapeutic value. Griepp et al. (147) demonstrated a reduction in the incidence of cardiac graft atherosclerosis and improvement of survival in patients treated with dipyridamole and warfarin. Although this study has several methodologic problems, recent uncontrolled observations (148) on the use of antithrombotic agents suggest a beneficial effect, and therefore, controlled trials are worthwhile.

Summary. Accelerated cardiac graft atherosclerosis appears to share etiologic mechanisms with atherogenesis in the nontransplanted heart by means of the "response to injury" hypothesis. The potential risk factors and their possible roles in the pathogenesis of the atherosclerotic process are summarized in Table 5. Preimplantation coronary endothelial injury has been clearly demonstrated with current methods of cardiac preservation and storage. With the additive detrimental effects of denervation, immune injury and hyperlipidemia, the scene is set for initiation of the events that ultimately lead to the formation of occlusive fibrointimal disease. Our present knowledge of possible predisposing factors should lead us to focus more closely on potential therapeutic interventions including, among others, improving graft harvest and preservation technique and controlling serum lipids.

Coronary Vein Graft Atherosclerosis (Fig. 1)

Coronary vein graft disease contributes to significant morbidity and mortality after coronary artery surgery and is responsible for the recurrence of angina pectoris, myocardial infarction and compromised ventricular function. Approximately 10% of all grafts are occluded after the first or second week, and about 17% and 20% by 6 and 12 months, respectively, after operation. The occlusion rate is then 2% to 4% per year in those grafts still patent at 1 year. At the end of 5 years, about 35% of vein grafts will be occluded (4,127,149–152).

Vein graft disease can be divided into two main stages: an early postoperative stage of thrombotic occlusion related to a type III injury, and a late stage of accelerated atherosclerosis secondary to a chronic type II injury, which begins within the first year and is due to fibrointimal proliferation. In the later years, lipid accumulation and thrombus formation and organization also occur (4,127,149–152).

Type III vascular injury and early graft occlusion (Table 5). Vein grafts are subject to mechanical injury that may occur when the veins are harvested and handled during the operation, resulting in a transient predominantly type III injury, which may lead to acute thrombotic occlusion although in most cases the vessel wall heals quickly (151,153, 154). With the exposure of the vein graft to a relatively high pressure flow and the presence of various biologic risk factors (such as hypercholesterolemia), a type II vascular injury may be induced and hinder the process of reendothelialization that might otherwise occur under normal conditions. This sets the stage for platelet deposition, lipid accumulation, growth factor release and subsequent fibrocellular proliferation. Indeed, vein grafts may show significant injury to the endothelial flow surface with marked platelet and leukocyte aggregation 24 h after implantation despite normal luminal morphology before the operation (154). Similarly, various animal graft models and human autopsy data (4, 153–155) have demonstrated that early vein graft occlusion is thrombotic in origin. In addition to endothelial damage, arterialization of the vein graft results in a significant decrease in vascular synthesis of the platelet antiaggregating prostacyclin; this may play a role in increasing the thrombogenicity of vein grafts (154).

Prevention of early graft occlusion. Clinical studies (149, 156–161) have convincingly demonstrated a significant improvement in graft patency rates at intervals ranging from 10 to 360 days after operation when various antiplatelet regimens using aspirin, aspirin plus dipyridamole, sulfinpyrazone and ticlopidine were instituted perioperatively as com-

pared with placebo. In a randomized placebo-controlled trial, Chesebro et al. (149) reported a significant reduction in early closure from 10% in the control group to 2% in patients treated with aspirin and dipyridamole. Similarly, the recent Veterans Administration Cooperative Study (161) demonstrated that various aspirin-containing therapeutic regimens significantly improved graft patency rates 60 days after operation.

Type II and type III vascular injury and late graft occlusion. The beneficial effect of antiplatelet therapy is less apparent in late graft occlusion because a different pathophysiologic process resulting from repetitive type II vascular injury supervenes. During the first postoperative year, the most notable and consistent histologic change is marked intimal thickening characterized by smooth muscle cell proliferation and an increase in the hyaline matrix (4,150–152). Within 3 weeks after surgery, smooth muscle cells appear in the subendothelial portion of the intima, followed by proliferation and fibrointimal thickening (151). Beyond the first year after operation, there is further connective tissue synthesis from smooth muscle cells and fibroblasts, followed by incorporation of lipid into the lesions. In the presence of various biologic risk factors, such as hyperlipidemia and smoking, this process could be accelerated, leading to vascular occlusion. Thus, graft specimens from patients who had angiographic evidence of occlusive disease 1 to 5 years after operation show typical histologic features of atherosclerosis: a mixture of fibrous plaque with intimal hyperplasia, ulceration, cholesterol clefts, foam cells and, in some areas, calcification with disruption of the medial layer (150,152,157). In addition, because of the predisposition of fatty plaque to rupture (type III injury), occlusive or nonocclusive thrombus formation may also occur during this late stage of graft disease, as documented in surgical specimens and autopsy studies (151,152,157,162); two thirds of vein grafts removed during a second coronary artery bypass operation may show evidence of mural or occlusive thrombus (163). The beneficial effect of platelet inhibition in reducing late graft occlusion is less striking, but can be demonstrated (164).

Prevention of late graft occlusion. No currently available agent prevents the accelerated atherosclerotic process in vein grafts resulting in late occlusion, although control of risk factors, such as cigarette smoking and hyperlipidemia, may be beneficial. The Cholesterol-Lowering Atherosclerosis Study (165) reported that aggressive lowering of LDL cholesterol produced a significant reduction in new atheroma formation in bypass grafts in patients tested with cholestipol and niacin. In a new trial on the prevention of vein graft atherosclerosis, sponsored by the National Institutes of Health, the use of aspirin and lipid-lowering interventions alone or in combination will be tested.

Percutaneous Transluminal Coronary Angioplasty (Fig. 1)

Mechanisms of acute reocclusion or restenosis. Coronary angioplasty has gained wide acceptance as the procedure of choice in many patients with coronary disease since its first clinical application in 1977 (166). Despite improvement in equipment and technique, acute reocclusion after successful angioplasty occurs in approximately 5% of patients, whereas late restenosis (generally within 3 to 6 months) occurs in 25% to 35% of patients (5,167,168). As in vein graft atherosclerosis, experimental observations (169) suggest that the process can be similarly divided into stages of vascular injury, platelet aggregation with thrombus formation and intimal proliferation. In a study of restenosis in pigs, Steele et al. (170) demonstrated that immediately after balloon catheter injury to the carotid arteries, complete endothelial denudation was induced, with marked platelet deposition and mural thrombus formation. Necrosis of medial smooth muscle cells was evident at 24 h. Platelet deposition was markedly reduced at 4 days, coinciding with partial regrowth of endothelium and periluminal cells. Finally, a process of progressive intimal proliferation of smooth muscle cells and reorganization of mural thrombus was evident at 10 to 14 days. This process then led to partial or complete occlusion of the lumen. In experimental studies (171,172) of aortoiliac atherosclerosis induced by mechanical injury in rabbits, angioplasty produced denudation of endothelial cells, platelets and fibrin deposition and disruption and splitting of atheromatous plaque. Restenosis of the lumen occurred within 4 weeks. Pathologic analysis of the restenotic segments showed layers of proliferating smooth muscle cells overlying a cellular, split fibrous plaque.

Type II/III vascular injury (Table 5). Type II/III vascular injury after angioplasty appears to be the critical initiating event in the pathogenesis of both acute occlusion and chronic restenosis. Immediate platelet aggregation and thrombus formation after vascular injury may account for the acute occlusion; mitogens released from platelets, endothelial cells and smooth muscle cells appear to be responsible for the subsequent occlusive fibrointimal hyperplasia. Indeed, autopsy data from 89 patients (reported at the time of this writing [128,173–181]) who died within days to months after successful angioplasty suggest a similar sequence of pathologic changes in the coronary arteries, leading to acute and late restenosis. Type III changes in the vessel wall seen in patients who died several days after angioplasty included focal denudation of the endothelium, intimal necrosis, medial tear, adventitial hemorrhage and thrombosis. In some specimens, proliferating smooth muscle cells were seen migrating from the media into the intima, but with no remarkable hyperplasia (175,179).

Percutaneous coronary angioscopy provides direct visualization of the immediate morphologic changes in coronary

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arteries induced by balloon angioplasty; thus, recent studies (182,183) describe mural thrombi, intimal flaps, dissection and ruptured atheroma as common findings. In contrast to the early morphologic features, specimens obtained weeks to months after successful angioplasty showed marked circumferential fibrointimal thickening and organized thrombus at sites where chronic restenosis occurred (173–181). Similarly, tissues removed from restenotic vessels by atherectomy have been composed mainly of smooth muscle cells and collagen (184).

Effects of shear stress (Table 5). The role of local shear stress in the pathogenesis of fibrointimal thickening after coronary angioplasty deserves special comment. Clinical observations (185) have demonstrated that a less than satisfactory residual stenosis >30% is associated with increased restenosis after angioplasty. The mechanisms by which a significant residual stenosis predisposes to restenosis is not entirely clear, but we postulate that two factors are involved. 1) Using an extracorporeal perfusion chamber technique, we demonstrated (186) that platelet deposition was maximal in areas with high shear rate, such as at the site of a significant residual stenosis. Platelet deposition may then lead to growth factor release and subsequent smooth muscle cell proliferation causing restenosis. 2) Animal studies (187) of atherosclerosis and venous bypass grafts and human cadaver experiments (188) have demonstrated that intimal thickening tends to occur in areas of arteries with sudden changes in degree and direction of wall shear stress (oscillatory shear stress), and further evaluation has revealed that the degree of intimal thickness appears to correlate directly with the oscillatory shear stress. Oscillatory shear stress appears to enhance endothelial cell turnover (187,189), platelet deposition (187) and smooth muscle cell proliferation (190,191). If these concepts are applied to restenosis models after coronary angioplasty, any significant residual stenotic lesion will increase the distal flow separation and the oscillatory shear stress distal to the lesion. These changes will enhance intimal proliferation distal to the residual lesion and narrow the lumen. Thus, a residual stenotic lesion may enhance intimal proliferation and restenosis by the two rheologic mechanisms just described. In addition, severe damage or ulceration may further contribute to the restenosis process by enhancing platelet activation, thrombogenicity and smooth muscle cell proliferation.

Prevention of Restenosis

Technical. Strategies to minimize vascular injury during balloon dilation, such as the use of nonthermal laser angioplasty (for example, the excimer laser) are currently under intense investigation. In addition, newer techniques to achieve optimal lumen size and blood flow could reduce the oscillatory shear stress and thus the intimal proliferation. For example, with the use of a perfusion catheter, inflation times can be prolonged and may optimize initial luminal results. Clinical trials with this technique are currently underway; however, it may increase vascular injury. Thus, an ideal technique would be one that could inflict the minimal degree of vascular injury and yet achieve an optimal rheology after dilation to minimize platelet deposition and smooth muscle cell proliferation.

Pharmacologic. In experimental models of vascular injury (172,192), platelet inhibition appears to reduce the incidence of acute occlusion. In the clinical setting, three randomized controlled trials (193–195) demonstrated that pretreatment with antiplatelet agents (aspirin, aspirin plus dipyridamole or ticlopidine) significantly reduces the incidence of acute thrombotic occlusion and periprocedural myocardial infarction. Heparin also has been suggested (196) to have a beneficial effect on acute occlusion in an experimental model of carotid angioplasty. The effects of antithrombotic therapy on late restenosis have been disappointing. Clinical trials (195,197) using different platelet-inhibiting regimens have shown no impact on the restenosis rate. Similarly, anticoagulation with heparin or warfarin was of no benefit when compared with results achieved with aspirin (198,199).

The ideal agent for preventing restenosis should have antithrombotic or antiproliferative effects, or both, without incurring the risk of bleeding complications. Recent research was centered on omega-3-fatty acids and low molecular weight heparin, both of which appear to possess some of the characteristics of an ideal agent. Several clinical studies (200–202) have provided evidence suggestive of a beneficial effect of fish oil in reducing the restenosis rate after coronary angioplasty, but further trials are needed to confirm this effect. Results of research on nonanticoagulating, antiproliferative low molecular weight heparin appear to be promising. Potential use of other agents, such as the more powerful antithrombotic drugs and growth factor antagonists, will be discussed next.

Future Directions

Strategies to Prevent Accelerated Atherosclerosis

Coronary artery disease remains the major cause of morbidity and mortality in the United States, despite the decline during the past several years. In patients with left main coronary artery disease, triple vessel disease with compromised ventricular function and anginal symptoms resistant to medical therapy, coronary artery bypass operation is the standard therapy. In recent years, however, coronary angioplasty has been established as a safe and effective alternative to bypass surgery in up to 50% of patients requiring revascularization, and it can reduce the cost of medical care. For patients with end-stage heart disease, cardiac transplantation represents a viable thera-

peutic option. The usefulness of these important interventions is drastically limited by the occurrence of accelerated and premature atherosclerotic coronary disease in patients who have undergone these procedures. The processes of accelerated atherosclerosis appear to share common pathophysiologic mechanisms, namely, endothelial injury with early platelet involvement and subsequent progressive smooth muscle cell proliferation and thrombosis leading to vascular occlusion. Recent advances in the understanding of the nature of vascular injury, platelets and thrombosis, the mechanisms regulating smooth muscle cell growth and the identification of various growth factors and receptors have allowed development of new strategies for preventing these accelerated vascular diseases. These include strategies to limit vascular injury and reduce subsequent thrombotic and proliferating cellular responses.

Limitation of Vascular Injury

Extensive research is currently focused on developing new techniques to limit type II and type III vascular injury and, thus, the subsequent thrombotic and proliferative responses in these clinical situations. For example, improved cardioplegic methods can enhance myocardial graft protection in heart transplantation, improved techniques of vein handling and harvesting can reduce endothelial injury before bypass surgery and the use of new angioplasty devices, such as a nonthermal laser and other mechanical devices, may limit vessel wall injury in patients undergoing coronary angioplasty. The nature of type I injury in the pathogenesis of spontaneous atherosclerosis remains speculative, and until the precise in vivo mechanism of injury can be identified, intervention at this stage currently is limited to the modification of the potential risk factors such as hyperlipidemia and smoking.

Antithrombotic Approach

Use of monoclonal antibodies. Platelet membrane receptors, such as glycoprotein IIb/IIIa and von Willebrand factor, are essential for platelet aggregation and adhesion to the vessel wall. Specific antagonists of these receptor sites may have therapeutic potential. In a baboon vascular graft model, Hanson et al. (203) recently demonstrated that the use of monoclonal antibody against glycoprotein IIb/IIIa complex resulted in a 72% reduction in acute graft closure secondary to thrombosis. Similarly, Bates et al. (204) showed a significant reduction in acute coronary thrombosis after coronary angioplasty in dogs treated with the same monoclonal antibody. Using the extracorporeal perfusion chamber technique, Badimon et al. (205) demonstrated an 81% reduction in platelet deposition on deendothelialized vessel wall and type I collagen in swine treated with monoclonal antibody against von Willebrand factor compared with only a 30% reduction in swine treated with aspirin. This finding suggested that compared with prostanoid blockade by aspirin, blockade of the adhesive von Willebrand factor led to a more powerful inhibition of thrombus formation.

Antithrombin agents. Specific inhibitors of thrombin also appear to have tremendous therapeutic potential. Heras et al. (206) demonstrated that recombinant hirudin significantly decreased platelet and fibrinogen deposition and completely prevented mural thrombus formation when compared with heparin treatment in pigs that underwent carotid balloon angioplasty. In a baboon carotid artery endarterectomy model, Schneider et al. (207) also showed total abolition of acute thrombosis with the use of a synthetic antithrombin agent. Similar findings were reported by Jang et al. (208) with a different synthetic thrombin inhibitor. Thrombin itself may play a role in smooth muscle cell growth, either by acting as a mitogen or by stimulating the release of growth factors from platelets and endothelial cells (123,124).

Potential clinical application of these agents in the syndromes of accelerated atherosclerosis requires further extensive basic and experimental research. The practical problems with hemostasis also need to be overcome.

Antiproliferative Approach

Excessive smooth muscle cell proliferation after vessel wall injury appears to be secondary to the effect of the growth factors released from various interacting cells and the loss of endothelial integrity and naturally occurring growth inhibitory substances. Several pharmacologic approaches to inhibit smooth muscle cell proliferation have been tried with variable success.

Direct growth inhibitory effect on smooth muscle cell: role of heparin. In several experimental models (209,210), exogenously administered heparin has been shown to inhibit smooth muscle cell growth after vascular injury, but the doses required are prohibitively high. The use of short-term intravenous heparin after coronary angioplasty is common and may reduce the incidence of acute thrombotic occlusion, but it appears to have limited effect on chronic restenosis. Longer duration and higher doses of heparin have been proposed, but problems with difficulty of administration and hemostasis make it clinically impractical. The antiproliferative effect of heparin is mediated by a functionally distinct moiety of the heparin molecule and appears to be due to inhibition of thymidine and uridine uptake by smooth muscle cells. This blocks smooth muscle cell proliferation in the G0/G1 growth state and prevents entry into the S phase (211, 212). Recently, Gordon et al. (213) demonstrated that arterial smooth muscle cell proliferation after balloon catheter injury was significantly reduced in rats receiving low molecular weight heparin, which has much less anticoagulating activity. Thus, further development of nonanticoagulating an-

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tiproliferative heparin analogs may have value in these clinical situations.

Decreased platelet-derived growth factor production. In addition to having favorable effects on lipid concentration and platelet aggregability (214,215), fish oil has recently been shown in vitro to inhibit endothelial production of platelet-derived growth factorlike proteins (216). Several clinical trials (200–202) have demonstrated lower rates of restenosis in patients receiving high dose omega-3-fatty acid after coronary angioplasty. Recently, using a cyclosporin-treated heart graft rat model, Saris et al. (217) demonstrated that fish oil supplementation significantly decreased the severity of coronary atherosclerosis in a transplanted allograft. The precise in vivo mechanism and the usefulness in the prevention of human transplanted heart atherosclerosis remain to be determined.

Growth factor antagonist. A platelet-derived growth factor antagonist, such as suramin, which inhibits platelet-derived growth factor binding at the receptor level, has not been extensively studied in experimental models of vascular injury, but it may have therapeutic potential (218).

Other proliferative inhibitors. Recently, Powell et al. (219) demonstrated a significant reduction in intimal hyperplasia in rat carotid artery after balloon catheter injury with the use of the angiotensin-converting enzyme inhibitor cilazapril. The precise antiproliferative mechanism of this agent is unknown, but its effect suggests a possible role of the angiotensin-converting enzyme in modulating the proliferative response after vascular injury. In this regard, angiotensin II has been shown to induce a hypertrophic response in cultured rat smooth muscle cells and the expression of certain growth response genes (115,220,221).

Lipoprotein modification. Finally, considerable progress in the understanding of the role of lipoprotein heterogeneity and its impact on atherogenesis has allowed development of new strategies in delaying and even reversing the process of both spontaneous and accelerated atherosclerosis. For example, the importance of lipoprotein modifications, specifically oxidation, has renewed interest in antioxidants (57,58). In this context, probucol has been demonstrated to slow the progression of atherosclerosis in hyperlipidemic rabbits (59). In addition, realization of the role of reverse cholesterol transport in lipid metabolism has provided new avenues of future research. It has been demonstrated (222) for the first time that high density lipoprotein (HDL) plasma fractions inhibit fatty streak formation in cholesterol-fed rabbits.

Conclusions

We have presented a pathologic classification of vascular injury and the resultant pathophysiologic responses leading to vascular occlusion. The potential roles of these responses in lipid deposition, intimal hyperplasia and thrombosis in the pathologic process of spontaneous and accelerated atherosclerosis have been discussed. We believe that this classification and the resultant pathophysiologic cellular responses may increase our understanding of the pathogenesis of various vascular diseases and aid in formulating therapeutic and preventive strategies.

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