Until recently, the endothelium was regarded as a relatively inert cell layer. However, over the past 20 years, research has revealed an extraordinary array of endothelial functions, including control over coagulation, fibrinolysis, arterial tone and vascular growth. Importantly, endothelial dysfunction has been implicated as a key event in the pathogenesis of atherosclerosis, coronary vasoconstriction and, probably, myocardial ischemia.

For many decades the endothelium, the cell layer that lines the blood vessels, was viewed simply as a semipermeable barrier between blood and interstitium, facilitating the exchange of water and small molecules. Recently, however, a series of experiments have demonstrated that the endothelium has an enormous range of vital homeostatic functions (1). Instead of serving as an inert barrier, the endothelium is an antithrombogenic vascular lining that also participates in metabolic, synthetic and regulatory pathways (2).

Normal endothelial functions include control over thrombosis and thrombolysis, platelet and leucocyte interactions with the vessel wall and regulation of vascular tone and growth (Fig. 1). Of particular interest to cardiologists, the endothelium secretes both powerful vasorelaxing (e.g., nitric oxide [NO]) and vasoconstricting substances (e.g., endothelin-1 [ET-1]) (3,4).

Given that normal endothelial function plays a central role in vascular homeostasis, it follows that endothelial dysfunction probably contributes to disease states characterized by vaso- spasms, vasoconstriction, excessive thrombosis or abnormal vascular proliferation, alone or in combination, including atherosclerosis and hypertension (Fig. 2).

Indeed in 1986, endothelial dysfunction was found in the coronary arteries of humans with advanced atherosclerosis (5). Subsequent work (6,7) has demonstrated that such endothelial dysfunction predisposes to vasoconstriction at the site of arterial plaque, instead of the more normal dilator response, with potentially adverse clinical consequences. In 1992, endothelial dysfunction was also demonstrated in asymptomatic children and young adults with risk factors for atherosclerosis, such as hypercholesterolemia and cigarette smoking (8). Therefore, abnormal endothelial physiology has been implicated both in early atherogenesis and later in the disease process, in the control of dynamic plaque behavior. The “biologic link” between endothelial damage and atherosclerosis may be related to decreased arterial bioavailability of NO, which may predispose to leucocyte and platelet adherence, vasoconstriction and smooth muscle cell proliferation (9).

Normal Endothelial Function

The endothelium lies between the lumen and the vascular smooth muscle. Although only one cell layer thick, it is able to “sense” changes in hemodynamic forces, or blood-borne signals, by membrane receptor mechanisms and respond to physical and chemical stimuli by synthesis or release of a variety of vasoactive and thromboregulatory molecules and growth factors. Substances released by the endothelium include prostacyclin, NO (the endothelium-derived relaxing factor [EDRF]), endothelins, endothelial cell growth factor(s), interleukins, plasminogen inhibitors and von Willebrand factor (Fig. 1). In addition to these “universal” functions, the endothelium may have organ-specific roles that are differentiated for various parts of the body, such as gas exchange in the lungs, control of myocardial function in the heart or phagocytosis in the liver and spleen.

Studies of endothelial structure and function have been accomplished by a variety of techniques, including ultrastructural studies (10), in vitro experiments for endothelial cell isolation and culture (11,12), physiologic studies in animals (13) and, most recently, clinical studies in humans (5,8). This knowledge has facilitated the development of certain treatment strategies based on administration of endothelial products, such as prostacyclin and NO, or their antagonists.

Thromboresistance. The endothelium has anticoagulant, antiplatelet and fibrinolytic properties. Endothelial cells are
the major site for anticoagulant reactions involving thrombin (14,15). Platelet adhesion to endothelial cells is markedly inhibited by the endothelium-derived arachidonic acid metabolite prostacyclin (16,17). The same stimuli that activate platelets, such as thrombin and adenosine diphosphate (ADP) and adenosine triphosphate (ATP), also act to release prostacyclin from the endothelium, which allows the endothelium to limit the extent of platelet plug formation (18). The interactions between platelets and endothelium regulate platelet function, coagulation cascades and local vascular tone (19).

In addition, endothelial cells may secrete tissue-type plasminogen activator (t-PA) (20), the powerful thrombolytic agent in frequent clinical use for treatment of coronary thrombotic occlusion. t-PA release is stimulated in vivo by norepinephrine, vasopressin or stasis within the vessel lumen. Thrombin may also stimulate t-PA release, providing a further endothelium-mediated safeguard against uncontrolled coagulation.

**Regulation of vascular tone.** The central role of the endothelium in controlling vascular tone has only been appreciated since the discovery of the potent vasodilators prostacyclin and NO (16,21). The endothelium controls underlying smooth muscle tone in response to certain pharmacologic and physiologic stimuli (22). This involves a number of lumen membrane receptors and complex intracellular pathways and the synthesis and release of a variety of relaxing and constricting substances, described below. In addition to making their own vasoactive mediators, endothelial cells may transduce signals from, or even inactivate, circulating vasodilators and constrictors, such as thrombin, bradykinin, ADP and ATP (23).

**NO, an EDRF.** The existence of an endothelial relaxing factor was first postulated by Furchgott and Zawadzki (21) in 1980, when they noticed that rabbit aortic rings relaxed in response to acetylcholine only in the presence of an intact endothelium. The biologic effects of EDRF are mediated by NO. NO is synthesized from L-arginine by an enzyme, nitric oxide synthase (NOS) (24). The reaction is stereospecific, and L-arginine is converted to NO and L-citrulline. The generation of NO from L-arginine can also be specifically blocked by arginine analogues, such as N\(^\text{G}\)-monomethyl-L-arginine (L-NMMA), which has recently proved to be a useful tool in clinical research, allowing investigation of the biologic distri-

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**Figure 1.** Some functions of normal endothelium. Factors secreted into the lumen (upward arrows) include prostacyclin and t-PA, which influence coagulation. Cell surface adhesion molecules (such as intercellular adhesion molecule-1 [ICAM-1] and vascular cell adhesion molecule-1 [VCAM-1]) regulate leucocyte adhesion. Factors secreted abluminally (toward the smooth muscle [downward arrows]) may powerfully influence vessel tone and growth. Coronary artery and endocardial endothelium may also influence myocardial contractility (41).

**Figure 2.** Some consequences of endothelial dysfunction. In the presence of certain risk factors, endothelial cells may produce less NO or more oxygen-derived free radicals (such as O\(_2^\cdot\)), or both. These changes may in turn result in certain proischemic or proatherogenic effects, as indicated, including increased transcription of certain redox-sensitive proinflammatory genes (Marui N, Offermann MK, Snerlick R, et al. Vascular cell adhesion molecule-1 (VCAM-1) gene transcription and expression are regulated through an antioxidant-sensitive mechanism in human vascular endothelial cells. J Clin Invest 1993;92: 1886–94). Agents that can lead to increased NO bioavailability in the vessel wall, or decreased O\(_2^\cdot\) production, may be useful in reversing endothelial dysfunction (see text). In addition, decreased endothelial production of the anticoagulant vasodilator prostacyclin or increased production of the vasoconstrictor ET-1 may also be pathogenetically important consequences of endothelial dysfunction.
bution and role of NO. NOS has at least three isoforms, including constitutively expressed and inducible enzymes.

NO maintains low arterial tone at rest, in both the systemic and pulmonary circulations (25–27). In addition, NO release is stimulated by increased flow (leading to increased shear stress on the endothelium) (28) and by bradykinin, thrombin, acetylcholine and a variety of other circulating agents that increase EDRF release through activation of specific endothelial cell membrane receptors (22).

The vasodilator activity of NO is due to interaction with the iron atom of heme in guanylate cyclase, causing its activation and thereby increasing intracellular cyclic guanosine monophosphate levels (29,30). In smooth muscle cells, this results in a reduction of intracellular calcium and thereby relaxation (31). The same pathway is involved in the mechanism of action of exogenous nitrovasodilators, such as sodium nitroprusside and nitroglycerin.

Endothelium-derived hyperpolarizing factor. Stimulation of the normal endothelium by acetylcholine also produces hyperpolarization of the underlying smooth muscle and thereby vasorelaxation. This is not mediated by NO, but by another endothelium-derived factor, which acts by increasing K⁺ conductance. The resulting vasodilation is not inhibited by l-NMMA, the specific antagonist of NO (32,33). In contrast ouabain, a Na⁺/K⁺-ATPase inhibitor, does not affect NO-induced relaxation, but prevents the action of endothelium-derived hyperpolarizing factor. The precise identity and physiologic role of this factor are uncertain.

Prostacyclin. Another major endothelium-derived vasodilator is prostacyclin, which is produced from arachidonic acid through the enzyme cyclooxygenase (16). Prostacyclin also has antithrombotic and antiplatelet activity. Its release may be stimulated by bradykinin and adenine nucleotides. Like NO, it is chemically unstable, with a short half-life (34). However, unlike NO, prostacyclin acts through stimulation of adenylate cyclase and an increase in intracellular levels of cyclic AMP. It is a potent vasodilator and is active in both the pulmonary and systemic circulations.

Endothelins (endothelium-derived contracting factors). Endothelin is an extremely potent vasoconstrictor that was isolated, purified and sequenced in 1988 (4). This 21-amino acid peptide is closely related to the snake venom sarafotoxin and is one of the most potent vasoconstrictors yet identified. There are three isoforms of endothelin, but only one (ET-1) has been shown (35) to be released from human endothelial cells. Like NO, ET-1 is synthesized in the endothelial cells and released in response to a variety of stimuli, such as adrenaline and hypoxia (36). ET-1 has a short half-life (37), suggesting that it, too, is mainly a locally active vasoregulator. Its physiologic role includes maintenance of basal vascular resistance, and it is present in healthy subjects in low concentrations (38). Elevated endothelin levels have been found in systemic and pulmonary hypertension, coronary artery disease and heart failure; in these conditions, a pathologic role has been postulated but not proved (39,40).

In addition, normal endothelium also plays an important role in vascular growth, monocyte adhesion, immunologic regulation, metabolism of circulating amines, lipoprotein metabolism and integration and transduction of blood-borne signals. Endocardial and coronary microvascular endothelium may also regulate myocardial contractility (41).

Clinical Assessment of Endothelial Function

Over the past decade, a large number of studies have assessed arterial endothelial function in health and disease. Most of these have tested the ability of normal endothelium to release the vasorelaxing factor NO in response to pharmacologic or physiologic stimuli, or both. Although this is only one of many endothelial functions, NO release may be particularly important because of its actions on platelets, monocytes and smooth muscle cells (9).

Coronary artery testing. In vivo assessment of coronary endothelial function in humans was first reported in the mid-1980s (5) (Fig. 3). Coronary artery diameter was measured by quantitative angiography before and after intracoronary
infusion of acetylcholine. In normal arteries, acetylcholine stimulated the endothelial release of NO, resulting in vasodilation, whereas in subjects with endothelial dysfunction, vasconstriction was observed (due to a direct smooth muscle constrictor effect of acetylcholine). This response was contrasted with the response to nitroglycerin, an exogenous source of NO and therefore an endothelium-independent vasodilator. Soon after, invasive testing of coronary microvascular endothelium was described (42) by measuring the response of coronary flow to administration of endothelium-dependent and -independent small-vessel dilator substances, using Doppler wires or catheters.

These techniques have given valuable insights into the risk factors for coronary endothelial dysfunction in angiographically smooth arteries (43,44) and into the role of endothelial dysfunction in predisposing to dynamic plaque activation and constriction (5,6,45). More recently, the potential for reversibility of endothelial dysfunction in the coronary arteries has been assessed using this methodology to assess novel therapeutic strategies (e.g., cholesterol-lowering therapy and angiotensin-converting enzyme [ACE] inhibition) (46–48) (see later).

Peripheral artery testing. The major disadvantage of intracoronary testing is its invasive nature, and it is therefore generally unsuitable for use in children or adults who are at high risk of atherosclerosis but who have no clinical symptoms or signs of disease. For this reason, noninvasive or minimally invasive clinical tests of endothelial function have been developed. Noninvasive detection of endothelial dysfunction in the brachial and femoral arteries was first described in 1992 (8) (Fig. 4). In this test, arterial diameter is measured in response to an increase in shear stress, which causes endothelium-dependent dilation, and in response to sublingual nitroglycerin, an endothelium-independent dilator.

The brachial artery dilator response to shear stress has been shown to be reproducible (49), due mainly to endothelial release of NO (50), and to correlate well with invasive testing of coronary endothelial function (51). Endothelial function has also been extensively investigated in the forearm microcirculation by intraarterial infusion of endothelium-dependent and -independent vasodilator substances, followed by measurement of forearm flow using plethysmographic techniques (52,53). Although these peripheral artery techniques provide only “surrogate” measures of coronary endothelial function, they have provided important insights into the risk factors for atherogenesis in childhood and young adult life and are also being used in studies of reversibility of endothelial dysfunction in asymptomatic subjects at high risk of arterial disease (54,55).

Figure 4. Endothelial dysfunction is also important in the early stages of atherogenesis; for example, significantly impaired endothelium-dependent flow-mediated dilation (EDD) has been found in asymptomatic children and young adults with risk factors for atherosclerosis, such as hypercholesterolemia and cigarette smoking. Adapted, with permission, from Celermajer et al. (8).

Endothelial Dysfunction in Early Atherogenesis

Endothelial injury, either physical trauma or more subtle cellular damage, is now regarded as an important initial event in atherogenesis (56,57). Even in normocholesterolemic animals, physical damage to the endothelium can lead to atherosclerotic lesion formation (58). Hypertension has been shown experimentally to disrupt endothelial integrity (59). Hyperhomocysteinemia, which causes chemical endothelial injury, is associated with premature atherosclerosis and thrombosis (60). The finding that many of these insults, which are associated with clinical progression of vascular disease, are clearly related to endothelial injury has added weight to the “response to injury” hypothesis of Ross and Glomset (61) and its later modifications (56). Other hypotheses have also been proposed to explain the initiating events in atherosclerosis (62).

The consequences of endothelial damage that promote fatty streak and plaque formation include increased adherence of monocytes (63), increased permeability to monocyte/macrophages and lipoproteins, which then accumulate in the vessel wall, increased platelet adherence and increased smooth muscle cell migration and proliferation (64). The latter may be mediated by loss of endothelium-derived heparin-like oligosaccharides, which normally inhibit smooth muscle cells (65), or by allowing platelet adhesion and thereby increased local concentration of platelet derived growth factor, which is also an important smooth muscle mitogen (66). Endothelial dysfunction may also be accompanied by decreased local availability of NO. This may be due to decreased endothelial production of NO or to excess production of superoxide anions, or both, with consequent degradation of NO before it can reach its target tissues. For example, superoxide production is enhanced in the presence of hypercholesterolemia, with consequent decreased bioavailability of NO (67). Because NO is a local vasodilator and also inhibits platelet adherence and aggregation, smooth muscle proliferation and endothelial-cell leucocyte interactions, reduced NO activity may also contribute to the initiation and progression of atherogenesis (9). Indeed, supplementation with oral L-arginine, the physiologic substrate for NO production, has profound antiathero-
genic effects in cholesterol-fed animals (68) and has recently been associated with decreased platelet aggregation (69) and monocye/endothelial cell adhesion (70) in humans.

Endothelial dysfunction has been demonstrated in asymptomatic children and young adults with risk factors for atherosclerosis (8). Hypercholesterolemia is associated with arterial endothelial dysfunction in children as young as 7 years old, with significant correlations between the degree of endothelial impairment and the levels of both low density lipoprotein (LDL) cholesterol and lipoprotein(a) (71). Both active cigarette smoking (72) and even prolonged exposure to environmental tobacco smoke (73) have been shown to be associated with impaired endothelium-dependent dilation, in a dose-dependent manner, in otherwise healthy teenagers and young adults. Aging, too, has been associated with progressive endothelial impairment (74,75), and this age-related dysfunction appears to occur earlier in men than in women (76). Endothelial dysfunction has also been implicated in the pathogenesis of hypertension. Many studies have found impaired endothelial release of NO in hypertensive subjects (77–79), although one large study has failed to confirm this finding (80). Overproduction of ET-1 may also produce hypertension (81). However, it is unclear whether abnormal endothelial production of vasoactive factors can be a primary cause of high blood pressure rather than simply an effect of the hypertensive state.

It has also been shown (44,82) that the traditional vascular risk factors may interact to damage the endothelium in asymptomatic subjects, in the same way as they are known to interact in determining the risk of clinical cardiovascular end points. In the coronary circulation, endothelial dysfunction is not only observed at the sites of obstructive stenoses, but has also been documented in angiographically smooth arteries of subjects with risk factors for atherosclerosis (43,44). Taken together, these data from in vivo human studies indicate the importance of impaired endothelium-dependent NO-mediated dilation in the early stages of the atherosclerotic process.

Some limitations apply to these studies. To date, large-vessel endothelial function has only been investigated in asymptomatic children and young adults using peripheral arteries (such as the brachial and femoral), which can be studied noninvasively. Invasive coronary studies are confined to symptomatic patients and therefore may suffer from a selection bias. Nevertheless, there appears to be good correlation between coronary and peripheral artery endothelial function in the same subjects (51). Furthermore, no longitudinal studies in humans have yet proved that those young subjects with endothelial dysfunction will go on to develop advanced atherosclerosis; such studies would take decades to complete. Despite this limitation, endothelial dysfunction is spatially and temporally linked to atherosclerosis; endothelial dysfunction occurs first at coronary branch points (83), as do advanced plaques; and endothelial dysfunction also precedes occlusive arterial disease in both the experimental primate model (84) and in human heart transplant recipients (85). These data serve to support an important link between arterial endothelial impairment and later advanced atherosclerotic disease.

Endothelial Dysfunction in Advanced Atherosclerosis

Obstructive coronary stenoses are usually thought to contribute to angina pectoris by providing a fixed limitation to coronary flow during periods of increased myocardial oxygen demand (e.g., during exertion). However, a series of studies over the past 10 years (5,6,45,86) has shown that coronary stenoses are dynamic rather than fixed and that impaired endothelium-dependent dilation at the site of coronary plaques may result in paradoxical vasoconstriction during exercise or mental stress, just when coronary vasodilation is most required.

In 1986, Ludmer et al. (5) first demonstrated this phenomenon in human coronary arteries. Whereas normal arteries dilated in response to intracoronary acetylcholine, which stimulates endothelial NO production, stenotic arteries showed paradoxical vasoconstriction. Subsequent studies demonstrated that coronary endothelial dysfunction (assessed as an abnormal response to acetylcholine) also resulted in impaired flow mediated coronary dilation in response to intracoronary papaverine (45), cardiac pacing (87) and physiologic levels of exercise (6). Abnormal coronary responses to serotonin in the presence of endothelial dysfunction may be particularly important in unstable coronary syndromes in vivo, given the involvement of (serotonin containing) platelets in the pathophysiology of these processes (88).

Similar endothelial dysfunction also occurs in the coronary microcirculation, particularly in response to hypercholesterolemia (89). Because endothelial vasodilator function of the coronary microvessels may be an important determinant of myocardial perfusion during periods of increased demand, microvascular endothelial dysfunction may play a particularly significant role in the pathogenesis of myocardial ischemia (90,91).

Some studies have demonstrated heterogeneous endothelial responses within the same coronary artery or within the same patient (92), and this finding is consistent with in vitro experiments demonstrating nonuniform endothelial cell behavior when exposed to apparently similar conditions of shear stress (93). However, most studies overall have consistently reported the presence of impaired endothelium-dependent dilation in atherosclerotic coronary vessels. Although serial coronary physiologic studies are only infrequently performed, recent intervention trials (46–48) have reported coronary endothelial responses before and after 6 months of placebo treatment; in these studies, the endothelial responses to acetylcholine appeared highly reproducible.

The clinical correlate of impaired endothelial function in the coronary arteries may be episodic myocardial ischemia, either with or without chest pain. It has recently been observed, for example, that cholesterol-lowering therapy may
result in significantly decreased myocardial ischemia (94,95) and improved cardiovascular survival in patients with coronary atherosclerosis (96,97). These benefits have occurred even though angiographic regression trials of cholesterol lowering have demonstrated only very minor (if any) regression of actual coronary plaque size (98,99). The mechanism for clinical improvement in the absence of coronary anatomic changes might relate to beneficial endothelial effects; that is, coronary function rather than structure might improve, resulting in fewer clinical symptoms and events. Alternate hypotheses for this observation include plaque remodeling or stabilization, or both, and a decreased tendency to thrombosis as the mechanisms for clinical benefit.

Coronary endothelial injury may also play an important role in postangioplasty restenosis (100). Balloon angioplasty always results in some degree of endothelial injury, and the response to this injury includes growth factor secretion and consequent myointimal proliferation. Again, the role of endothelium-derived NO may be particularly important, with the recent demonstration in experimental studies (101) that local transfection of endothelial cells with NO synthase after angioplasty may attenuate this proliferative response, with a consequent decrease in the incidence of restenosis.

**Reversibility of Endothelial Dysfunction**

Current research is examining strategies that might improve arterial endothelial function. This is an attractive possibility; if such strategies could be implemented early in the disease process, it might be possible to prevent or retard atherogenesis. Even in advanced disease, modification of coronary artery endothelial dysfunction might decrease the propensity to vasocostriction or thrombosis, or both, and thereby decrease the risk of acute cardiovascular events.

Coronary endothelial function can be improved in hypercholesterolemic subjects by lipid lowering (46,47), either short term, for example, by LDL apheresis (102), or in the longer term, with either diet and resin therapy (103) or HMG CoA reductase inhibitors such as lovastatin. In these latter studies, coronary vasoconstriction observed at baseline was significantly attenuated after cholesterol-lowering treatment for 6 months. Improved dilation has been particularly observed in patients treated with a combination of cholesterol-lowering and antioxidant therapy (46), highlighting the importance of oxidative stress in the pathogenesis of endothelial dysfunction. Oral administration of high dose vitamin C has also been shown (55) to improve brachial artery endothelial function in patients with established coronary disease, although it is not known whether this effect is sustained with prolonged therapy.

Improvement in endothelial function has also been obtained by therapeutic manipulation of the L-arginine–NO pathway. Short-term parenteral administration of L-arginine has been associated with improved coronary and peripheral microvascular function (89,104), and a recent study (54) has demonstrated improved endothelium-dependent dilation in young hypercholesterolemic subjects given oral L-arginine for 4 weeks (Fig. 5). However, animal data suggest that the beneficial effects of L-arginine on endothelial function and atherosclerosis may not be sustained over the long term (105), although the experimental data on this point are not consistent (106).

ACE inhibition with quinapril has also been shown (48) to improve coronary endothelial function in patients with atherosclerosis. This effect may contribute to the potential anti-ischemic effect of this class of drugs and may be mediated in part by suppression of vascular wall superoxide production and consequently by enhanced bioavailability of NO (107). Such findings suggest important links between the renin–angiotensin and the L-arginine–NO systems in the vessel wall. Some animal data have indicated that calcium channel blocking agents, as well as angiotensin blockade, might improve endothelial dysfunction in experimental models of hypertension (108), and short-term calcium channel antagonism has recently been associated with improved coronary vasomotion in hypertensive humans (109); however, long-term human studies with calcium channel blockers have not yet been reported.

Estrogen therapy has also been shown (100–112) to have a beneficial effect on endothelial function in postmenopausal women. This effect may mediate some of the apparent cardioprotective benefit of estrogen replacement in older women. Recent data (113,114) indicate that the addition of progestosterone to estrogen, in combined hormone replacement therapy, may also be associated with beneficial effects on endothelial function.

Early data suggest that the same therapeutic strategies that improve arterial endothelial function may also be associated with a decrease in myocardial ischemia and with ischemic events rates. For example, cholesterol-lowering therapy not only improves coronary endothelial physiology in hypercholesterolemic subjects, but may also significantly reduce the number and duration of transient myocardial ischemic episodes.
(94, 95). Furthermore, ACE inhibition may improve coronary endothelial physiology and may also reduce the incidence of clinical cardiovascular events (115). Although there may be other non–endothelium-related benefits of these therapeutic manipulations, it is possible that at least some of the observed benefit of such interventions may relate to reversibility of endothelial dysfunction.

**Future Directions**

**Diagnosis.** A simple noninvasive test for endothelial dysfunction would potentially have immediate clinical applicability. Such a test might identify presymptomatic subjects at high risk of atherosclerotic complications and therefore allow specific “targeting” of primary preventive strategies. Although endothelial function testing is available in the research setting, no technique yet exists that is simple, safe, reproducible and easily performed as a screening method.

**Treatment.** Current research has raised the exciting possibility that endothelial dysfunction might be reversible with certain interventional strategies (46–48, 54, 55). In the case of naturally occurring substances, such as L-arginine and vitamin C, future studies in humans will be directed toward defining the sustainability of any beneficial arterial effects with prolonged therapy. Certain pharmacologic agents have been identified that result in improved endothelial function over at least a 6-month period (46–48). It is now important to investigate whether such improvements in arterial physiology will be correlated with evidence of clinical benefit.

Potentially, the most exciting future direction relates to improvement of arterial endothelial function in children and young adults, early in the atherogenic process. Intuitively, it is at this early stage that arterial wall damage is most likely to be easily reversible (116). If strategies to protect the endothelium early in life can be defined and applied successfully, this may have important public health benefits into the next millennium.

**References**

Endothelial Dysfunction