Crucial advances in our understanding of basic pathogenic mechanisms involved in atherogenesis have been achieved during the past 2 decades. The historical hypothesis of pathogenesis (“lipid accumulation”) has evolved to integrate several causal events contributing to the initiation and evolution of atherosclerosis. Vascular inflammation and apoptosis may play a joint pivotal role in its progression and onset. Hypercholesterolemia and hypertension have synergistic deleterious effects on coronary endothelial function. Impaired fasting glucose, triglycerides and triglyceride-rich lipoprotein remnants, lipoprotein(a), homocysteine, and high-sensitivity C-reactive protein (hsCRP) might contribute to an increased risk of atherosclerosis. The disease also has been related to infiltration of immune cells, which are involved in both systemic and local, innate as well as adaptive, immune responses. Distinct pathways of atherothrombosis seem to develop at different sites of the vascular system (brain, heart, and peripheral circulation). Endothelial dysfunction induced by cardiovascular risk factors is considered to be 1 of the earliest stages in vascular damage and is associated independently with cardiovascular events. There is a synergic action between genetic, ambient, local, and systemic factors, and ultimately the progression of atherosclerosis is responsible for coronary heart disease (CHD) and its complications (such as unstable “in crescendo” angina, myocardial infarction, and sudden death), peripheral arterial disease, and ischemic stroke. The evolution of atherosclerosis, however, is characterized by a long lag time between onset and clinical manifestation, thereby providing an opportunity for implementation of early detection, prevention, and intervention strategies.

Because the development of atherosclerosis commences early in humans, we need to rethink the timing of what is currently considered to be “primary” prevention of atherosclerosis-related diseases. It is likely that we need to start administering effective treatments much earlier than previously assumed. Indeed, much attention would be important when subjects are in a state of wellness before the appearance of clinical signs of atherosclerosis but in the progression of the natural history of the disease. On the other hand, we need to exercise caution because this strategic consideration may raise some serious issues in terms of the safety of long-term treatment available with potent antiatherosclerotic agents and drugs. Moreover, we need to realize that much economic interest is present in the field of drugs effective in primary prevention of atherosclerosis-related diseases. Obviously, lifestyle modifications without the pharmacological treatment would be the optimal strategy.

The Early Onset of Human Atherogenesis

The prodromal stages of human lesions are already set during fetal development, as intimal thickening can be observed in fetal coronary arteries. In children and young adults, fatty streaks become increasingly prevalent and some progress to advanced stages of atherosclerosis. Once initiated, the progression of the atherogenesis is influenced by risk factors that promote vascular inflammation and plaque rupture and may act synergistically.

The prominent role of hypercholesterolemia as a cardiovascular risk factor has been established by the marked reduction of atherosclerosis-related clinical events by cholesterol-lowering interventions. The right timing to initiate primary prevention of atherosclerosis and its clinical sequelae before development of irreversible vascular injury needs to be conceptualized, however. Of critical importance is the observation that maternal hypercholesterolemia is associated with greatly enhanced fatty streak formation in human fetal arteries, suggesting that hypercholesterolemia may also play a pathogenic role in lesion formation even before birth. Fetal lesions occur at the same predilection sites as more advanced lesions in adolescents and adults, but their size is minute, and there is evidence that they may partially regress during the final stages of gestation or early infancy, when cholesterol levels are low. The Fate of Early Lesions in Children (FELIC) study showed that the progression of atherosclerosis was markedly accelerated in offspring of hypercholesterolemic mothers compared with those of normocholesterolemic mothers. Such pathogenic links would be important not
only for expansion of our understanding of the pathogenesis of the disease but also to form the basis for clinical considerations (reviewed elsewhere). The mechanism by which maternal hypercholesterolemia may affect fetal lesion development has been explored in some animal models. Normocholesteremic female rabbits were fed a control chow or hypercholesterolemic diet during pregnancy and were untreated or additionally supplemented with cholestyramine, vitamin E, or both. Lesions doubled in offspring from hypercholesterolemic rabbit mothers, and a linear correlation was observed between maternal cholesterol and lesions at birth. Vitamin E treatment of mothers reduced atherosclerosis at birth by approximately 40%, indicating the involvement of oxidation-sensitive mechanisms in the development of fetal lesions. Indeed, interference with oxidation-sensitive cytoplasmic and/or nuclear signaling pathways may constitute an important framework through which oxidation may promote lesion formation. One of the important mediators of cytotoxicity during conditions of increased oxidative stress is oxidized low-density lipoprotein (oxLDL). Oxidation of low-density lipoprotein (LDL) can already be observed during fetal development and is greatly enhanced by maternal hypercholesterolemia. Evidence that maternal hypercholesterolemia enhances the susceptibility to atherosclerosis later in life was provided in the rabbit model. Consistently, a similar pattern was observed in another model represented by LDL receptor–deficient mice. Lesions in the aortic origin were markedly greater in male offspring of hypercholesterolemic mice than in the control group.

Maternal cholesterol levels increase physiologically during the third trimester, even in normocholesterolemic mothers, and this increase may be much greater in hypercholesterolemic mothers. Placental functions and permeability may change over time, if only as a result of rapid growth. Microarray analysis of aortic segments indicated that several genes were significantly upregulated or downregulated in offspring of hypercholesterolemic mothers. Additional proteomic studies investigating the expression and role of genes affected by fetal programming in offspring exposed to hypercholesterolemic diets after birth are needed. During adolescence and adulthood, atherogenesis is clearly driven by conventional risk factors and becomes a complex process. The relative weight of genetic and environmental factors in fetal programming toward atherosclerosis has been difficult to establish. For example, the Barker hypothesis postulated a correlation between reduced birth weight and hypertension and atherosclerosis-related diseases later in life. This suggests that predisposition to atherosclerosis may be a consequence of inherited genetic traits and has therefore been controversial and difficult to resolve even by large epidemiological studies. However, many nongenetic possible causes of reduced birth weight should be considered. A long-term effect of maternal diet on blood pressure has been suggested, but the large number of genes, postnatal risk factors, and age-dependent factors make it complicated to disentangle genetic from environmental influences on atherosclerosis. Moreover, many pathogenically distinct factors can lead to a reduced birth weight. Therefore, experimental verification of the Barker hypothesis is only in its beginning. The maternal/fetal cholesterol hypothesis differs from the Barker hypothesis in that there is little evidence for a significant role of reduced birth weight in subsequent development of hypercholesterolemia-induced atherosclerosis. In fact, the FELIC study noted an inverse correlation between birth weight and atherosclerosis in children, but only in offspring of normocholesterolemic mothers.

Children and young adults are also vulnerable to the effects of cardiovascular risk factors and show early signs of atherogenesis. Of 12- to 14-year-old children, 65% have lesions containing foam cells and lipid droplets, and an additional 8% show more advanced preatheroma or atheroma stages. Among the cardiovascular risk factors, body mass index, systolic and diastolic blood pressure, and serum levels of total cholesterol, triglycerides, LDL cholesterol, and high-density lipoprotein cholesterol are strongly associated with the extent of lesions in the aorta and coronary arteries. Furthermore, the severity of asymptomatic coronary and aortic atherosclerosis in young people increases in proportion to the number of cardiovascular risk factors.

Cerebrovascular Atherogenesis: Distinct Pathways in Intracranial Versus Extracranial Disease

Brain ischemic infarction accounts for 85% of total strokes, but the pathogenic role of hypercholesterolemia in atherosclerotic cerebrovascular disease is still unclear. Although intracranial arteries eventually develop atherosclerotic lesions, the onset of atherogenesis occurs much later in life, and severity at various ages is consistently less than that in extracranial arteries in most species, including humans. To date, it is unknown whether the difference in prevalence of atherosclerosis is due to anatomic differences between intracranial and extracranial arteries, hemodynamic factors, or other differences in basic atherogenic mechanisms. A previous study demonstrated that intracranial arteries generally contained higher activities of oxygen radical scavenger enzymes, which markedly decreased with increasing age and coincided with a rapid acceleration of atherosclerosis in intracranial arteries of elderly subjects. In contrast, the progression of atherogenesis in extracranial arteries was linear over all ages. Therefore, progression of atherosclerosis in intracranial arteries of older men may in part be due to reduced intracellular defenses against oxygen radical–mediated processes. This is further supported by the observation that endothelial dysfunction is an independent risk factor for stroke in the absence of obstructive atherosclerosis. Interestingly, endothelial dysfunction (and thus early atherogenesis) develops rapidly in rabbit extracranial arteries exposed to oxLDL, but not in intracranial arteries. Furthermore, the activity of antioxidant enzymes, in particular the oxygen radical scavenger manganese–superoxide dismutase, tended to be greater in intracranial than in extracranial arteries of premature human fetuses. Because of the lower pathogenic role of hyperlipidemia in cerebrovascular atherosclerosis, the rationale for primary prevention of stroke with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) is still debated. Modulation of precerebral atherothrombotic...
in the aorta and the carotid artery, preventing plaque rupture and artery-to-artery embolism, and the improvement of endothelial homeostasis by upregulating brain endothelial nitric oxide synthase and the antiinflammatory actions may contribute to neuroprotection and stroke prevention.16,40

Vascular Inflammation in the Development of Atherosclerosis-Related Diseases

Low-grade systemic inflammation is among the major determinants of cardiovascular risk,51 and vascular inflammation is known to play a crucial role in development of virtually every stage of atherosclerosis and its manifestations.15,32,52 Accumulation of LDL in the arterial wall initiates an inflammatory response, and its subsequent oxidation leads to activation of endothelial cells, upregulated expression of adhesion molecules, such as intercellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule–1, and propagation of the inflammatory process. Oxidation or glycoxidation of LDL influences signal transduction pathways involving nitric oxide–mediated regulatory signals.3,53 Both mild and extensive oxLDL also influence the expression of apoptotic factors activated through Fas and tumor necrosis factor receptors,28,54 c-Myc–dependent transcription factors,55,56 and genes regulated by the peroxisome proliferator–activated receptor-γ, eg, genes promoting inflammation or reverse cholesterol transport.57 Apoptotic cell death has been proposed to promote plaque instability, rupture, and thrombus formation; although this may seem a promising starting point for the development of antiatherogenic drugs, it remains to be determined whether modulation of apoptosis can become a clinically important approach to influence plaque progression.

Activated endothelial cells express leukocyte adhesion molecules, which facilitate adhesion of white blood cells rolling along the vascular surface.3 Monocytes that adhere and infiltrate into the evolving plaque differentiate into macrophages, which uptake LDL and transform into foam cells that release cytokines.30,32 Activated macrophages, T lymphocytes, and mast cells are present in atherosclerotic lesions, and CD4+ T cells are involved in autoimmune response to oxLDL and other antigens as well as in thrombogenesis.3 Figure 1 depicts the multiple signaling activation pathways involved in vascular inflammation. As demonstrated by previous studies, serum hsCRP is a marker predicting cardiovascular events in patients with traditional risk factors but does not seem to reflect the severity of the atherosclerotic process but rather a particular type of activity of disease. In fact, hsCRP levels do not differ between stages II, III, and IV of peripheral artery disease, but these levels are higher in such patients in the absence of flow-limiting stenosis. This suggests the need to assess the role of a genetic procoagulation profile in the development of peripheral obstructive arteriopathy and the role of inflammation in the onset of cardiovascular and cerebrovascular events. Such patient populations can be suitable for participation in pilot studies to evaluate the beneficial effects of modulating the inflammatory response and lowering CRP levels, independent of the severity of atherosclerosis.
Recent evidence suggests that low-grade inflammation plays an important role in mediating the effects of cardiovascular risk factors in children and young adults. Overweight in the child and young adult population is an increasing problem in Western society, and its impact on cardiovascular morbidity may be mediated by inflammatory mechanisms. Increased serum levels of hsCRP have been observed in apparently healthy juveniles with obesity, as well as in children with type 1 diabetes, and they independently correlate with intima-media thickness at the common carotid artery in subjects without disturbances in glucose metabolism or hypertension. Nevertheless, it remains to be established whether specific therapeutic options, such as lipid-lowering independent primary prevention with statins, might have antiinflammatory therapeutic actions. Prospective trials are necessary to estimate the effective vascular risk reduction with statins on serum levels of hsCRP in those patients.

**Early Detection for Primary Prevention**

In regard to the early onset of atherosclerosis, the concept of primary prevention should be revisited and challenged. The major goal of primary prevention is to prevent the first episode of CHD or stroke. There is an increasing interest in further categorizing patients by the level of risk and matching the intensity of intervention to the hazard for cardiovascular events. Extensive evidence indicates that the first acute coronary episode and sudden cardiac death occur in the absence of significant underlying obstructive CHD. Nevertheless, treating nonselected patients over a certain age with a “polypill” strategy is impractical and may lead to side effects. Such a tendency cannot be assumed to be generalized, however. Thus, the scientific quest to identify and potentially treat the vulnerable patient is intense.

Most studies that address primary prevention are based on the landmark Framingham studies. The investigators described the association of traditional risk factors such as hypercholesterolemia, hypertension, sex, family history, diabetes, and smoking with cardiovascular events, although the risk score that originated from the Framingham database may not apply equally to all sex, race, and ethnic groups. Risk factors were classified as modifiable (eg, elevated cholesterol, smoking, or hypertension) or nonmodifiable (eg, sex and family history) risk factors. This strategy should be revisited, however, because ample information challenges this approach. For instance, in the Nurses’ Health Study, subjects with a healthy lifestyle had 84% lower cardiovascular risk by applying simple lifestyle changes such as diet, exercise, smoking cessation, and moderate alcohol consumption, indicating that nonquantified parameters are also associated with successful primary prevention. Moreover, many patients presenting with the first episode of CHD do not have the traditional risk factor profile, and CRP levels correlate minimally with the individual components of the Framingham Coronary Heart Disease Risk Score. This percentage is probably underestimated according to other studies. Thus, application of the traditional primary prevention strategies may not apply to these patients. Some of the most common therapeutic interventions for primary prevention, such as statins, exert a similar beneficial effect at any cholesterol level and have a strong pleiotropic effect on the cardiovascular system beyond lowering cholesterol, for example, on inflammation. One of the most powerful therapies for primary prevention, aspirin, does not have any known effect on the modifiable risk factors and may have a differential effect based on sex. Thus, it may be speculated that the use of technologies more sophisticated than risk factor score should be used. Two main novel concepts should be entertained. The first is that the functional significance or the integrated “risk of the risk factors” should be assessed to identify the vulnerable patient rather than just a static value. Second, when we consider the worldwide epidemic of obesity and early diabetes in adolescents, the identification and intervention should be applied at a very early age, such as in the second or third decades of life. On the other hand, the potential value and effectiveness of pharmacological treatments in later stage in life cannot be overlooked.

The deleterious effects of traditional and novel risk factors on the cardiovascular system are mediated largely through the endothelium, leading to a systemic syndrome of endothelial dysfunction. For example, even mild to moderate obesity was independently associated with abnormal endothelial function and structure in otherwise healthy young children. The obesity-related vascular dysfunction is partially reversible with diet alone or particularly diet combined with exercise training. Age-related gender events may further influence the natural history of CHD (Figure 2).

Noninvasive assessment of endothelial function may be achieved by 2 main tests. The primary method, which provides direct information on the functional capacity of the endothelium, involves a measure of the endothelial cell response to direct stimulation and may be regarded as endothelial stress tests. These tests are based on the principle that certain stimuli trigger the release of nitric oxide from the vascular endothelium to mediate vascular relaxation. Alternatively, an indirect test can be used to gain information on the status of the endothelium by the measurements of peripheral markers that are associated with endothelial cell activation and the progression of inflammation and atherosclerosis, such as CRP, ICAM-1, and interleukin (IL)-6. The presence of peripheral endothelial dysfunction is an independent predictor of cardiovascular events beyond the known risk factors. Noninvasive assessment of endothelial function may serve as an independent index of the success of primary prevention intervention.
In slightly more advanced stages, there has been great interest in the possibility of identifying vulnerable plaques that might be the site of future acute coronary events. Plaques are often lipid-rich with an abundance of inflammatory cells and a thin fibrous cap. Several techniques attempting to identify these plaques are in various stages of clinical development (including intravascular ultrasound, magnetic resonance imaging, electron beam computed tomography [CT], helical CT, and novel nuclear medicine and molecular imaging approaches). Although this instrumental approach of identifying the vulnerable plaque seems promising, it may be associated with significant potential limitations. The natural history of a vulnerable plaque is unknown, and clinical trials based on identification and targeted therapeutic intervention are lacking. Moreover, in any given patient, multiple vulnerable plaques are likely to be present, and discerning those prone to be culprit lesions may be difficult. As discussed previously, the endothelium is affected at the earliest stage of the disease. Because there are currently no imaging techniques to visualize endothelial cell injury, however, emerging technologies target endothelial function as a marker for early disease. One of the early structural changes of atherosclerosis is intimal thickening. The carotid arteries are an ideal target to detect these changes because of their size and peripheral location. The development in ultrasound technology created a unique opportunity to monitor the vascular structural changes in progression of systemic atherosclerosis. Carotid intima-media thickness is increased in patients at risk for cardiovascular disease and in those with atherosclerotic disease such as CHD and is often used as a noninvasive surrogate of atherosclerosis (Figure 3). Indeed, data from the Framingham Heart Study showed that carotid intima-media thickness is independently associated with a 10-year CHD risk, supporting its usefulness as a prognostic marker. Thus, the use of carotid ultrasound and other techniques (magnetic resonance imaging, multidetector CT, and molecular imaging) may contribute to the wide identification of patients at risk.

**Some Clinical and Therapeutic Implications in Primary Prevention**

The prominent role of inflammation in mediating cardiovascular morbidity may offer an opportunity for early intervention with drugs with antiinflammatory properties to prevent...
some of the sequelae of exposure even without eliminating all cardiovascular risk factors per se (a summary of completed and ongoing primary prevention trials is provided in the Table).94,95 The recognition of atherosclerosis as an immune-mediated inflammatory disease renewed the interest in the potential role of infectious agents (Helicobacter pylori and Chlamydia pneumoniae) in initiating or modulating atherosclerosis.88,89 Infection with such organisms may lead to a localized infection and a chronic inflammatory reaction. Some clinical trials have shown that antibiotics may reduce adverse cardiac events independent of bacterial seropositivity,90 possibly by reducing endothelial cell activation.91 However, 2 clinical trials comprising >8000 patients showed no benefits of antibiotic treatment.88,92 However, the relationship of infection to early stages of atherogenesis was established in a large study.93 Additional trials might explore the possibility that a similar approach would be more effective as a primary prevention strategy in a selected population of patients with clear evidence of systemic inflammation. Figure 1 also illustrates some of the important drugs that have shown potential antiinflammatory effects. Statins, or 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, have shown potent systemic antioxidant, antiinflammatory, and antiproliferative effects that are beyond their lipid-lowering effects46 and are relevant in the treatment of atherosclerosis-related diseases.18,19 These effects may be mediated by downregulation of proinflammatory pathways. Indeed, although the clinical benefits of statins appears to be primarily explained by the reduction of LDL cholesterol,104 reduction of inflammation may be 1 of the mechanisms for the decrease in cardiovascular events observed with the use of these agents.95
Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers also possess a number of direct antioxidant, anti-inflammatory, and antiproliferative properties and are effective in blunting key components of atherosclerosis.\(^{56}\) The decrease in inflammation may be mediated by downregulation of IL-6, interferon-\(\gamma\), IL-10, and tumor necrosis factor-\(\alpha\) expression, as well as macrophage and activated myofibroblast infiltration.\(^{97,98}\) The Heart Outcomes Prevention Evaluation (HOPE) study clearly demonstrated their efficacy in secondary prevention by reducing the rates of death, myocardial infarction, and stroke in high-risk patients without heart failure.\(^{99}\) Ramipril also attenuated the development and caused regression of left ventricular hypertrophy, independent of blood pressure reduction,\(^{100}\) suggesting potential for primary prevention of cardiovascular events.

A number of additional drugs that interfere with vascular wall injury may play a role in slowing the progression of atherosclerosis. For example, aspirin has an important role in primary prevention of cardiovascular events.\(^{101}\) In addition to decreasing platelet activation, aspirin decreases the expression of inflammatory mediators such as inducible nitric oxide synthase, CRP, tumor necrosis factor, IL-6, and ICAM-1 and inhibits vascular smooth muscle cell proliferation.\(^{101}\) Hormone replacement therapy decreases the soluble forms of ICAM-1, vascular cell adhesion molecule-1, and E-selectin,\(^{102}\) although the Women’s Health Initiative cast a serious doubt on its efficacy in primary prevention of cardiovascular events.\(^{103}\) Agonists of the peroxisome proliferator-activated receptor-\(\gamma\), a ligand-activated transcription factor belonging to the nuclear hormone receptor superfamily, decrease levels of IL-4, IL-5, and IL-13\(^{104}\) and downregulate the expression of proinflammatory genes induced during macrophage differentiation and activation.\(^{105,106}\) Antioxidants inhibit atherosclerosis in animal models, but human trials have yielded conflicting results\(^{111,107–110}\) and are yet to disclose significant benefits of these drugs for prevention of cardiovascular diseases.\(^{111,112}\) The majority of these trials measured clinical outcomes in adult subjects with preexisting and often advanced lesions, in whom multiple risk factors were present and who were treated for a limited time period, often with relatively low doses of antioxidants. Moreover, the duration of follow-up (1 to 4 years) may have been too short to assess the definitive clinical outcome of such a chronic disease. It is therefore doubtful that they provide useful indications regarding the efficacy of early administration of antioxidants during the human life span, in which the prevention of pathogenic effects on oxidation-sensitive regulatory pathways may be more important than the reduction of other atherogenic or thrombogenic effects of oxLDL.

If it can be established that fetal pathogenic events linked to maternal risk factor exposure contribute significantly to atherosclerosis-related morbidity and mortality, then early recognition of the risk would be desirable. Maternal hypercholesterolemia should therefore be added to the list of risk factors justifying such steps.\(^{20,24,25,113–116}\) This may introduce a therapeutic dilemma because statins are contraindicated in pregnancy but may motivate more aggressive alternative approaches to treat maternal hypercholesterolemia. Interestingly, cholestyramine exerted protective effects in rabbits,\(^{105,106}\) and often advanced lesions, in whom multiple risk factors were present and who were treated for a limited time period, often with relatively low doses of antioxidants. Moreover, the duration of follow-up (1 to 4 years) may have been too short to assess the definitive clinical outcome of such a chronic disease. It is therefore doubtful that they provide useful indications regarding the efficacy of early administration of antioxidants during the human life span, in which the prevention of pathogenic effects on oxidation-sensitive regulatory pathways may be more important than the reduction of other atherogenic or thrombogenic effects of oxLDL.

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subject of an earlier review and will not be discussed in the present study.

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