Cardiovascular disease is the greatest threat to human life and health. The past decade has seen remarkable progress in clinical and basic cardiovascular research, and many areas of opportunity are promising. The pace of current progress in clinical and basic research is such that remarkable improvement in the quality and length of life for those at risk for cardiovascular disease is likely.

Prospects for Cardiovascular Research

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Early 60 million US residents—more than 1 in 5—have heart or vascular disease. Death rates from cardiovascular disease declined 20% from 1987 to 1997, but today 12.2 million US residents have a history of heart attack, chest pain, or both (American Heart Association). Moreover, cardiovascular disease remains the nation’s leading cause of death, claiming nearly 1 million lives each year. More women than men die of heart disease, and 1 million infants are born each year with heart defects. For the year 2000, the estimated cost of cardiovascular disease treatment is $326.6 billion. As the population ages, cardiovascular disease will have an ever greater human and economic impact. Thus, research for improved predictors of cardiovascular disease and improved therapies for prevention and cure must be the goal. In this article, we identify several important advances in clinical and basic research in cardiovascular disease and indicate the direction of probable future advances. Because of space limitations, only a few particularly important and promising areas of opportunity are addressed.

Emerging Risk Factors for Cardiovascular Disease

Delineation of the role of hypercholesterolemia and other risk factors such as hypertension, diabetes mellitus, tobacco use, obesity, and physical inactivity in the predisposition to coronary artery disease has led to interventions that reduce morbidity from cardiovascular disease. However, the known risk factors account for only about half of all cases.

Cardiovascular diseases, including coronary artery disease and hypertension, are clear examples of multifactorial genetic diseases. All aspects of vascular physiology, including lipoprotein levels, coagulation proteins, blood pressure, the immune system, and the biology of the vessel walls, are regulated by multiple genes. As these genes are defined (a task that has been accelerated by the sequencing of the human genome), individuals at risk can be identified and targeted for specific preventive interventions directed at factors contributing to atherosclerosis, such as blood levels of homocysteine and lipoprotein(a). Newly recognized risk factors that influence the development of atherosclerosis include polymorphisms in the genes that encode fibrinogen and platelet glycoprotein IIb/IIIa receptors. Specifically, a positive association exists between polymorphisms in the fibrinogen Bβ 448 and platelet glycoprotein IIa PIa genes and the extent of coronary artery disease.1

Considerable progress has been made in identifying genes that likely play a role in contributing to the development of essential hypertension. In genome-wide linkage analyses of systolic blood pressure, 4 regions of the human genome have been identified that influence systolic blood pressure variation.2 These regions contain a number of candidate genes for physiological regulation of blood pressure. In particular, 2 polymorphisms of the β2-adrenergic receptor gene found on chromosome 5q33-34 (Arg16Gly and Gln27Glu) are positively associated with hypertension in humans.3 Since β2-adrenergic receptors play an important role in the relaxation of arterial smooth muscle, any alteration that diminishes the receptor expression or decreases receptor function might lead to elevations in blood pressure.

It will be some time before all genes and gene polymorphisms involved in the development of cardiovascular diseases are identified. Ultimately, it will be possible to predict disease long before it occurs and to develop therapies that cure and prevent these diseases.

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Injury to the vascular endothelium, inflammation, and oxidative stress play pivotal roles in the development of atherosclerosis. Chronic inflammation appears to be central to initiation and progression of the atherosclerotic process, to instability of the atheromatous plaque, and to development of acute coronary syndromes.

Normal function of the endothelium—the inner lining of cells at the interface of circulating blood and the arterial wall—is a crucial determinant of vascular function. Chronic endothelial injury can be caused by oxidized low-density lipoprotein, tobacco exposure, free radicals resulting from oxidation of homocysteine and other substances, bacterial infection (e.g., chlamydia), and injury caused by interventional therapies such as angioplasty and stenting. Injury causes macrophages to be attracted to the intimal layer of the artery and promotes adherence of inflammatory cells from the circulating blood, predominantly monocyte-derived macrophages, and activated T cells and mast cells. Interactions between mediators from inflammatory cells, platelets, and factors secreted by endothelial and smooth muscle cells enhance recruitment of immune cells and platelets and the proliferation of smooth muscle cells in the neointima. These vascular smooth muscle cells also secrete chemotactic factors that recruit additional blood monocytes (FIGURE). Endothelial dysfunction after such chronic injury is characterized by increased adhesiveness toward platelets and mononuclear leukocytes, increased permeability to plasma lipoproteins, and increased vasoconstriction.

The formation of the potent vasodilator nitric oxide by nitric oxide synthase is one of the most critical functions of endothelial cells. Like prostacyclin, nitric oxide inhibits platelet aggregation, decreases leukocyte adherence to endothelium, and diminishes vascular smooth muscle proliferation. Impairment of nitric oxide formation by endothelium can lead to vasoconstriction, leukocyte adhesion, thrombosis, myointimal hyperplasia, and atherogenesis.
plasia, and enhanced oxidative stress. Thus, nitric oxide plays a crucial role in vascular physiology.6

In addition, disturbed laminar blood flow at branch points and bifurcations of the coronary circulation activates transcription in endothelial cell genes that contain in the promoter regions a “shear stress response element”.7 Such genes include those for the platelet-derived growth factor and the leukocyte intercellular adhesion molecule-1 (ICAM1), both of which contribute to vascular pathology. In contrast, genes that are upregulated by steady laminar shear stress often encode molecules that protect against atherosclerosis, such as nitric oxide synthase and superoxide dismutase. This phenomenon helps explain the predilection of atheromatous lesions for regions of turbulent flow. Furthermore, cyclooxygenase-2, which is upregulated by steady laminar flow, might contribute to inflammatory responses.7

The opportunity to develop novel therapeutic strategies from the improved understanding of the pathological process of atherogenesis is enormous. Particularly attractive targets are nitric oxide donors and antioxidants to decrease endothelial dysfunction; modulators of the inflammatory or immune response; and inhibitors of the adhesion of inflammatory cells to endothelium, such as chemokine and integrin receptor antagonists. For example, the use of hydroxymethyl glutaryl coenzyme A synthetase inhibitors (“statins”) has had a major impact on the course of coronary artery disease. These drugs reduce levels of total cholesterol and low-density lipoprotein cholesterol with the consequent reduction in inflammation and improvement in endothelial function, thereby accounting for the relatively rapid reduction in the incidence of acute coronary events in patients with coronary artery disease after initiation of such therapy.8

Identifying Vulnerable Plaques

Ulceration or fissuring of atherosclerotic plaques is the proximal cause of unstable angina and acute myocardial infarction (AMI).9-12 Degradation of collagen in the fibrous cap by metalloproteinases from inflammatory cells likely leads to plaque fissuring or ulceration and thrombosis.13,14 Transient thrombosis and vasoconstriction cause unstable angina, and more prolonged thrombosis and vasoconstriction result
Atherosclerotic plaques likely to ulcerate have thin fibrous caps, a large number of inflammatory cells, and an adjacent lipid core. Platelet-initiated thrombosis increases local concentrations of thromboxane A2, serotonin, adenosine diphosphate, platelet-activating factor, oxygen-derived free radicals, tissue factor, and endothelin: factors that perpetuate local vasoconstriction, fibroproliferation, and growth of the platelet-derived thrombus. In some instances these inflammatory markers (eg, C-reactive protein) may directly contribute to the inflammatory process. Patients with elevated levels of inflammatory markers often require more intensive medical therapy, interventional therapy (angioplasty and/or stenting), or surgical therapy (coronary artery bypass graft procedures).

Atherosclerotic plaques at risk for ulceration or rupture display temperature heterogeneity. Inflammation in the plaque increases temperature from 0.8°C to 2.0°C above body temperature, and efforts have been made to develop methods capable of detecting temperature heterogeneity to identify the plaques likely to ulcerate or fissure with the hope of preventing the development of unstable angina and MI. Magnetic resonance imaging has also been used to identify thin fibrous caps and lipid cores of atherosclerotic plaques for similar purposes. Future efforts will continue to identify vulnerable atherosclerotic plaques with the aim of preventing unstable angina and MI (and, possibly, cerebrovascular accidents).

**Coronary Revascularization**

Several exciting areas of research portend future advances in the therapy of acute and chronic coronary artery stenoses. In the setting of AMI, the combination of thrombolytic agents and inhibitors of platelet aggregation (such as inhibitors of the platelet glycoprotein IIb/IIIa receptors for fibrinogen) appears promising.

Restenosis continues to be a major limitation of catheter-based vascular interventions such as coronary angioplasty. A promising area for research is the use of intracoronary radiation (with both β and γ emitters) to attenuate such restenosis. In addition, it may be possible to restore to injured endothelium and media the normal inhibitors of thrombosis, inflammation, and restenosis (including prostacyclin and nitric oxide) that are lost with vascular injury, and/or to block the action of promoters of thrombosis and restenosis, using local gene therapy. Clinical trials us-
ing these approaches are expected to begin in the near future.

Although angioplasty and coronary artery bypass surgery are still of clinical and research interest, the hope has been raised that local and systemic administration of vascular growth factors (or gene therapy to enhance formation of such factors) may provide better means to enhance the development of coronary collateral circulation. Angiogenesis factors include growth factors such as fibroblast growth factors, VEGF (vascular endothelial growth factor), and the angiopoietins, as well as indirectly acting factors such as cytokines, chemokines, tumor necrosis factor (TNF), adenosine, prostaglandins, and integrins. It is hoped that administration of critical factors such as VEGF will initiate “therapeutic” angiogenesis in a manner that will supplement, or even circumvent, invasive coronary revascularization. Clinical trials of such treatments for both peripheral vascular disease and coronary artery disease have shown promise. However, additional factors and receptors will likely be required to orchestrate these complex events, and elucidation of the contributing factors at a cellular and molecular level is a necessary prelude to development of therapeutic angiogenesis that provides optimal benefits for both coronary and peripheral arterial disease.

Congestive Heart Failure

Heart failure is the main complication of many types of heart disease. In the United States alone, 400,000 new cases of congestive heart failure (CHF) are diagnosed each year. Despite significant advances in treatment, the prognosis remains poor and new treatments are urgently needed. Promising targets for heart failure treatment include cardiac myocyte apoptosis (programmed cell death) and its regulation, disordered calcium metabolism within the myocyte, and neurohumoral and cytokine regulation of the heart (eg, catecholamines, angiotensin II, endothelins, and TNF).

As an example, one opportunity is to block sustained sympathetic stimulation in the failing heart. Such sympathetic stimulation, mediated primarily by noradrenergic activation of cardiac β-adrenergic receptors, initially provides inotropic support to the failing heart but ultimately leads to marked desensitization of the heart to further adrenergic stimulation. This phenomenon is characterized by impairment of the cardiac contractile response to β-adrenergic stimulation. The biochemical hallmarks are diminished responsiveness of myocardial adenylate cyclase to β-adrenergic activation, decreased numbers and coupling efficiency of β1-adrenergic receptors, and elevated cardiac levels of β-adrenergic receptor kinase (BARK) or G-protein coupled receptor kinase 2 (GRK2), which mediate desensitization.

The concept that desensitization of β-adrenergic receptors (and possibly other inotropic G-protein coupled receptors) is in fact maladaptive is supported by studies of several genetically altered mouse strains that spontaneously develop heart failure. When these animals were bred with mice that transgenically express a peptide inhibitor of GRK2 in the heart, these hybrid mice had GRK2 levels lowered toward normal, greatly attenuated heart failure, and prolonged survival. Furthermore, in rabbit models in which MI and heart failure are induced by coronary artery ligation, cardiac function is improved by gene therapy in which recombinant adeno virus encoding the peptide inhibitor of GRK2 is injected into the coronary circulation. These data illustrate the potential of small-molecule inhibitors of the βARK enzyme for the treatment of CHF.

Other novel therapeutic targets for stimulation of cardiac contractility have been suggested by studies of transgen- esis- or adeno viral-mediated gene therapy in animal models. For example, modest overexpression in the myocardium of β2-adrenergic receptors increases myocardial contractility without pathological consequences, until overexpression reaches extraordinary (>100-fold) levels while as little as a 5- to 10-fold overexpression of β1-adrenergic recep-tors leads to early cardiomyopathy and heart failure. These and other studies indicate that toxic effects of catecholamines on the heart (eg, myocyte apoptosis) are mediated by β1-adrenergic receptors, whereas β2-adrenergic receptors are protective, implying that gene therapy with β2-adrenergic receptors might provide short-term inotropic support. Further evidence for a beneficial role of the β2-adrenergic receptor in heart failure is provided by findings that a polymorphism in the human β2-adrenergic receptor (T397-I), which compromises β2-adrenergic receptor signaling in the heart, confers a particularly unfavorable prognosis in patients with heart failure.

Several signaling elements are involved in mediating inotropic effects downstream of β-adrenergic receptors. The second messenger, cyclic adenosine monophosphate, is generated by cardiac isoforms of the enzyme adenylate cyclase, and transgenic expression of several of these isoforms (type VI, VIII) in the hearts of mice enhance contractility without apparent deleterious consequences. Even further downstream in these pathways is the cellular machinery that directly regulates the contractile process, which is largely orchestrated by cellular CA2+ fluxes. A crucial molecule is the sarcoplasmic reticulum (SR) calcium adenosine triphosphatase pump (SERCA2), which sequesters CA2+ in the SR and leads to cardiac relaxation. However, the resulting increase in sequestered CA2+ enhances release of CA2+ through SR CA2+ release channels, thereby enhancing contractility. In turn, SERCA2 is inhibited by binding to the protein phospholamban, an interaction that is terminated by phosphorylation of phospholamban. Inactivation of the phospholamban gene in mice significantly increases cardiac contractility without pathological consequences. Similarly, adeno viral-mediated overexpression of SERCA2 in rats also enhances cardiac contractility. These findings point to potential targets for treatment of heart failure—either by development of small-molecule regulators of...
the relevant proteins, or by gene therapy approaches. Serum levels of TNF are increased in patients with heart failure. Tumor necrosis factor (and possibly other cytokines) may contribute to the progression of heart failure by exerting direct toxic effects on the heart and circulation. Elevated levels of relevant peripheral and/or intramyocardial TNF recreate many aspects of the heart failure phenotype, including left ventricular dilatation and/or dysfunction, and activation of myocyte apoptosis. Tu-

mor necrosis factor may also produce pulmonary edema and cardiomyopathy in humans, and a soluble p75 TNF receptor-fusion protein that binds to and functionally inactivates TNF can reverse some of the deleterious cardiovascular effects of TNF in vitro and in patients.  

Forecast for Research Advances  
The great cardiovascular scourge of our age, atherosclerotic vascular disease, manifests as disease of the coronary, cerebrovascular, and peripheral vascular circulations. There are several major challenges. The first is to identify susceptible individuals before they actually develop the disease. The prospects for such risk prediction are increased by the success of the Human Genome Project and the beginning elucidation of the genetic alterations that underlie these multifactorial disorders. When all the essential genetic factors that predispose to atherosclerotic disease are known, individuals at risk can be identified at an early age and treated with individually tailored preventive regimens. Intimately tied to this effort is the need to understand the underlying process of atherosclerosis in detailed molecular and cellular terms. Continued advances will provide the underpinning for advances in prevention and treatment of this disease.  

Until atherosclerotic disease is eliminated, revascularization for occlusive disease will be the mainstay of therapy. In this regard, understanding the basic mechanisms of angiogenesis offers promise for therapies, such as treatment with various angiogenic growth factors to promote noninvasive revas-
cularization of affected organs.  

In the shorter term, however, the outcomes of established revascularization strategies must be improved. For example, restenosis complicates 15% to 50% of all coronary and peripheral angioplasties. Current approaches to preventing this phenomenon, many of which involve altering the basic biology of the underlying intimal proliferative process, should obviate the problem in the next decade. Moreover, advances in the bioengineering of blood vessels offer the promise of developing vascular conduits more durable than current venous grafts.  

Similarly, improved procedures for opening acutely occluded coronary arteries will continue to decrease the incidence of morbidity and mortality from acute MI. In this context, enhanced ability to identify atherosclerotic plaques at risk for rupture, and therefore likely to cause MI or stroke, should make it possible to lower the incidence of such vascular catastrophes.  

Development of new therapies for CHF should have high priority. The ag-
ing of the population and increases in the number of patients with chronic ather-
sclerotic disease have caused a virtual epi-
demic of heart failure. Heart failure is now the single most common reason for hospitalization of persons older than 65 years in the US population, involving about 1 million admissions each year.  

The hope is that basic research will elucidate the genes that place individuals at risk and identify the molecular mecha-
nisms that control normal and abnor-
mal cardiac contractility. A variety of novel drug treatments to support the fail-
ning heart should become available by ex-
ploiting insights into cardiac regulatory mechanisms. Complementing these ap-
proaches will be the development of to-
tally implantable artificial hearts and of improved animal and cellular trans-
plants into humans.  

Cardiovascular disease remains the greatest threat to life and health in hu-
mans. Accordingly, the opportunities presented to develop more effective pre-
ventive and therapeutic strategies are commensurately great. The pace of cur-
rent basic and clinical research in cardio-
vascular disease is such that, given appropriate continuing financial support, remarkable improvement in the quality and length of life of individu-
als destined to develop cardiovascular disease can be confidently predicted.  

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