

## Special Article

## SHATTUCK LECTURE — CARDIOVASCULAR MEDICINE AT THE TURN OF THE MILLENNIUM: TRIUMPHS, CONCERNS, AND OPPORTUNITIES

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**A**T the end of every century it is customary to reflect on the events of the past hundred years and to look toward the future, and in this lecture I should like to do this for cardiovascular disease. This is also an especially opportune time to comment on progress in cardiovascular disease, because both the National Heart, Lung, and Blood Institute and the American Heart Association are celebrating their golden anniversaries within the next 18 months. These two organizations have had the most profound influence on the development of research on cardiovascular disease during the 20th century.

A bewildering amount of information and statistics regarding cardiovascular disease is available in the medical literature and the public media. As a result, information about cardiovascular disease has become quite familiar both to health care professionals and to the public. It is timely to bring some perspective to this information, to identify the major trends that have occurred and to discern future directions. To this end, it may be useful to consider knowledge about cardiovascular disease in the 20th century as having developed in four phases. Although these four phases overlap temporally, they are distinct conceptually.

## PHASE 1: THE PANDEMIC OF CARDIOVASCULAR DISEASE EMERGES

As the 20th century began, heart disease was the fourth most common cause of death in the United States, after pneumonia, tuberculosis, and diarrheal disease, but it was already much more common than cancer (Fig. 1).<sup>1</sup> By 1910 heart disease had achieved first place, and except for a brief period after the great influenza epidemic, it has remained the most common cause of death in the United States. During the first half of this century, the percentage of

deaths due to cardiovascular disease increased substantially in all age groups, in both sexes, and in all races. Indeed, by mid-century cardiovascular disease accounted for more than half of all deaths, not only in the United States (Fig. 2) but also in the remainder of the industrialized world. By then the connection between streptococcal infection and rheumatic heart disease was clear, as was the infection of the aorta by *Treponema pallidum* and the subsequent development of luetic heart disease. However, the major causes of death and disability from cardiovascular disease — sudden death and acute myocardial infarction — were still mysterious. Often these appeared unexpectedly like bolts out of the blue, striking persons in their most productive years who had previously been well.

## PHASE 2: THE BATTLE IS JOINED

After World War II the industrialized nations turned their attention to domestic problems, including health, and recognized the enormous toll taken by cardiovascular disease. Therefore, the second phase of cardiovascular medicine in the 20th century began in 1948, when the battle against the pandemic of cardiovascular disease was joined in earnest. It was hoped that the strength of science and engineering developed after World War II could be applied to this battle, and the National Heart Institute (now the National Heart, Lung, and Blood Institute) was created. The enormous advances in mechanical engineering and electronics that had been stimulated by the war seemed to lend themselves particularly well to the study of the cardiovascular system, disorders of which were generally characterized by disturbances in hydraulic (hemodynamic) or electrical (electrophysiologic) function.

The initial research effort of the National Heart Institute was quite modest. The first annual congressional appropriation was only \$500,000 (an amount equal to that for eradication of a parasite that attacked Long Island potatoes).<sup>2</sup> The fledgling institute immediately began a program to stimulate and support both basic and applied research. Among its most far-reaching early actions was the reorganization of the Framingham Heart Study in 1949, thereby creating one of the first major efforts dedicated

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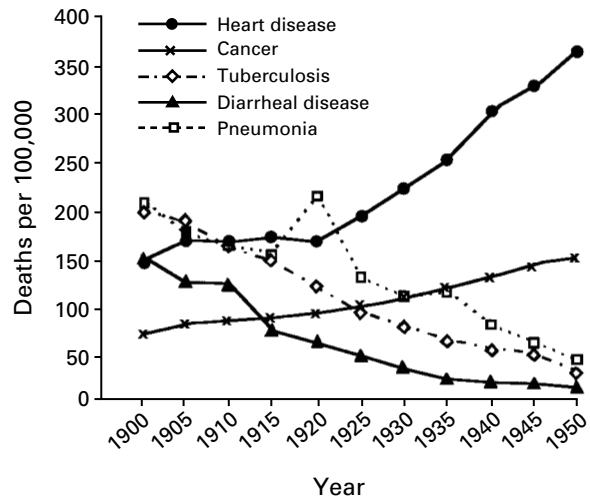
to the study of the epidemiology of chronic disease. This study was to become one of the cornerstones of cardiac epidemiology.<sup>3</sup>

In 1961 the Framingham Heart Study reported on six years of follow-up.<sup>4</sup> The concept of risk factors for coronary heart disease was clearly established, and hypertension and hypercholesterolemia were identified as major contributors to the pandemic of cardiovascular disease. Both the National Heart Institute and the American Heart Association moved swiftly and decisively to develop national campaigns to reduce these risk factors in the U.S. population. The attack on the third important risk factor, cigarette smoking, was reinforced by the Surgeon General's report in 1964. The available information was widely disseminated and supplemented by vigorous campaigns of professional and public education. It is difficult to determine the relative importance of various advances in the impressive improvements in the prevention, diagnosis, and treatment of cardiovascular disease that ensued, but the dominant influences appear to have been the combination of improved care of patients with established cardiovascular disease and the prevention of recurrent coronary events.<sup>5</sup>

**Myocardial Infarction**

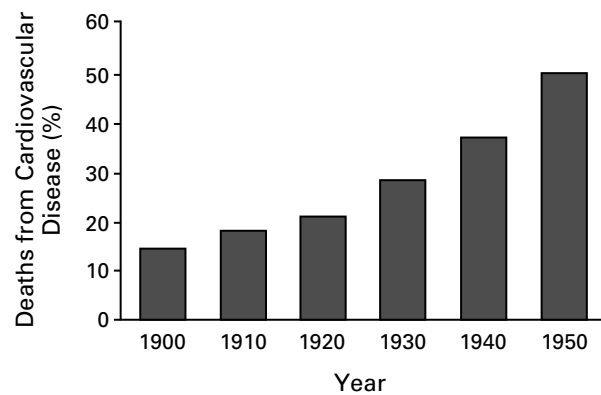
Although acute myocardial infarction was described as a clinical pathologic entity only as recently as 1912,<sup>6</sup> by mid-century this condition was recognized as the single most common cause of death in the United States. The subsequent dramatic reduction in mortality from acute myocardial infarction has played an important role in reducing the overall incidence of cardiovascular disease during the second half of the century (Fig. 3). The introduction and rapid dissemination of coronary care units in the early 1960s immediately reduced the in-hospital mortality due to acute myocardial infarction from approximately 30 percent to 15 percent. This notable success occurred as a consequence of three separate endeavors related to the prevention and prompt treatment of ventricular fibrillation. The first was the achievement of a deeper understanding of cardiac electrophysiology and the ability to relate this to life-threatening ventricular arrhythmias. The second was the development of the external defibrillator.<sup>8</sup> The third was a radical reorganization of clinical care to place patients with acute myocardial infarction at a single site in the hospital, where they were cared for by a specially trained staff. Most important, the coronary care unit nurse was empowered to treat ventricular fibrillation on an emergency basis in the absence of a physician.

The next major development in the care of patients with acute myocardial infarction came in the early 1980s with the introduction of thrombolytic therapy, followed by other reperfusion techniques



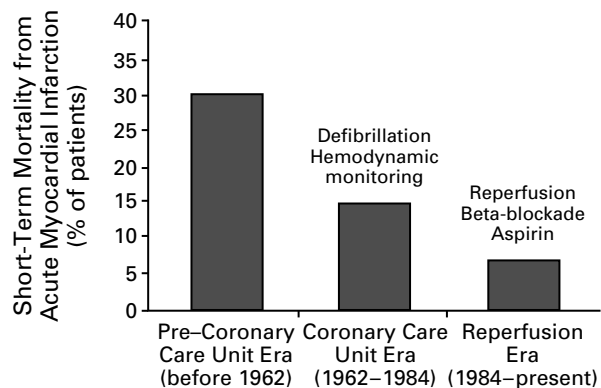
**Figure 1.** Crude Death Rates for Leading Causes of Death in the United States from 1900 to 1950.

Data are from the Centers for Disease Control and Prevention.<sup>1</sup>



**Figure 2.** Percentage of Deaths from Cardiovascular Disease in the United States from 1900 to 1950.

Data are from the Centers for Disease Control and Prevention.<sup>1</sup>



**Figure 3.** Estimated Short-Term Mortality from Acute Myocardial Infarction in the United States in Different Eras.

Modified from Antman and Braunwald,<sup>7</sup> with the permission of the publisher.

that further reduced mortality.<sup>9</sup> A unique four-way relationship developed around the care of the patient with acute myocardial infarction that was to have a profound and positive effect on the care of many cardiac disorders. The four parties were the investigators at academic medical centers and teaching hospitals, the public sector (principally the National Heart, Lung, and Blood Institute), private agencies (principally the American Heart Association), and the corporate sector (the pharmaceutical and medical-device industries).

In the first half of this century, not only was the early mortality from acute myocardial infarction very high, but survivors also remained at substantial risk of reinfarction and death after discharge from the hospital. Beginning in the 1970s, a number of new pharmacologic agents were shown to be of benefit in hospital survivors of acute myocardial infarction.  $\beta$ -Adrenergic-receptor blockers, for example, were found to be effective not only when administered intravenously during the acute phase of myocardial infarction, but also when taken orally after discharge from the hospital to reduce long-term mortality.<sup>10</sup> The next step was the demonstration that patients with left ventricular dysfunction after acute myocardial infarction, with or without heart failure, benefited from treatment with agents that inhibit angiotensin-converting enzyme.<sup>11</sup>

#### Development of Procedures and Devices

In addition to improving care of the patient with acute myocardial infarction, the synergy of basic research and new technology led to an impressive series of advances in procedures and devices for cardiac care. Diagnostic imaging of the heart, great vessels, and coronary arteries, first by invasive techniques such as selective angiography and then increasingly by noninvasive techniques, especially ultrasonography, has greatly facilitated cardiac diagnosis. Notable therapeutic advances include the development of open-heart surgery for the treatment of many forms of congenital and acquired heart disease; catheter-based interventions, such as coronary angioplasty and stenting, for the nonsurgical treatment of coronary artery disease; and cardiac pacemakers and implanted cardiac defibrillators for a variety of life-threatening cardiac arrhythmias. These procedures are now used to treat well over a million patients in the United States each year, and they have improved the quality and, increasingly, the duration of life.

#### Importance of Platelets and Their Inhibition by Aspirin

Another important development has been the appreciation of the importance of activated aggregating platelets in the development of acute coronary events and the recognition that the platelet cyclooxygenase inhibitor aspirin is effective in lowering mortality from acute myocardial infarction when given alone

or with a thrombolytic agent.<sup>9</sup> Aspirin has also been shown to reduce the incidence of acute myocardial infarction in healthy men almost by half.<sup>12</sup> It is also effective in patients with unstable angina<sup>13</sup> and for the secondary prevention of acute myocardial infarction in patients with a history of infarction.<sup>14</sup> In addition, this widely available and inexpensive drug has been found to be beneficial in the secondary prevention of stroke in patients who have a history of coronary heart disease or cerebrovascular disease<sup>14</sup> or who are having an acute myocardial infarction.<sup>9</sup> These benefits occur regardless of age, sex, and the presence or absence of hypertension or diabetes.

#### Hypertension

In 1971 blood pressure was treated and controlled in only 16 percent of all persons in the United States with a blood pressure of 160/95 mm Hg or higher. In fact, half of these persons were unaware of their condition. Two decades later, the percentage of persons unaware of the presence of hypertension had declined to 16 percent, and the percentage in whom hypertension was controlled had more than tripled, to 55 percent.<sup>15</sup> The beneficial effects of reducing systolic blood pressure on heart failure, stroke, death from coronary artery disease, and nonfatal myocardial infarction, as shown in one major trial, are profound (Fig. 4).<sup>16,17</sup>

#### Hypercholesterolemia

Recognition of the importance of hypercholesterolemia as a risk factor for coronary heart disease during the late 1950s led to a national campaign, spearheaded by the National Heart, Lung, and Blood Institute and the American Heart Association, to encourage Americans to adopt a diet low in saturated fats. In fact, between 1960–1962 and 1988–1994 the percentage of adult Americans with hypercholesterolemia, defined as a serum cholesterol level exceeding 240 mg per deciliter (6.2 mmol per liter), declined from 34 percent to 19 percent.<sup>18</sup> However, proof that a risk factor is of causal importance and not merely statistically associated with disease requires demonstration that its elimination or modification actually reduces the frequency of clinical manifestations. The causal effects of low-density lipoprotein cholesterol in coronary atherosclerosis have been proved.

After a number of suggestive studies that used diet and cholesterol-lowering agents of modest effectiveness, the favorable clinical effects of marked lowering of low-density lipoprotein cholesterol levels have now been demonstrated unequivocally in three large trials that used 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors. Reductions in deaths from coronary artery disease and in the incidence of acute myocardial infarction have been demonstrated in patients with established coronary heart disease and

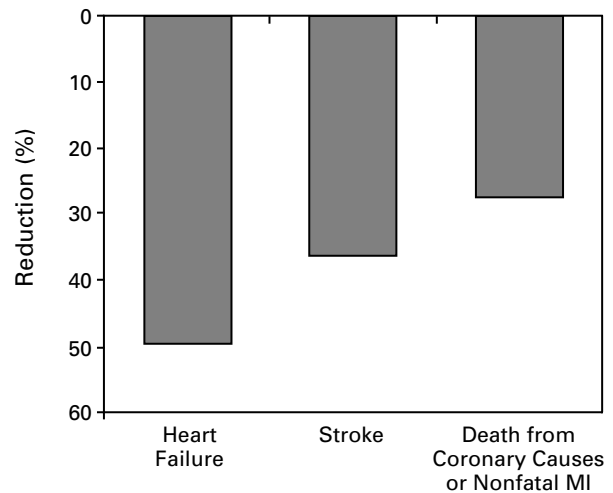
elevated<sup>19</sup> or average<sup>20</sup> cholesterol levels, as well as in men with hypercholesterolemia without overt coronary heart disease.<sup>21</sup>

**A Perspective on Phase 2**

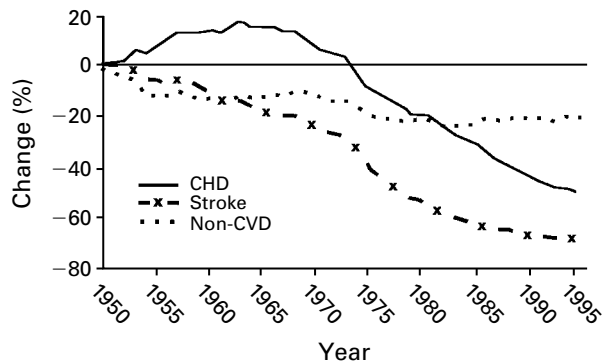
All of the efforts against atherosclerosis reviewed briefly above (and many others) were rewarded by a steady decline in the age-adjusted death rate from coronary heart disease from its peak in 1963 (National Center for Health Statistics: public-use mortality data tapes; and Division of Vital Statistics: unpublished data, 1968–1993) (Fig. 5). The age-adjusted death rate from cerebrovascular disease (often considered together with coronary heart disease because of the similarities in pathogenesis) has also declined impressively, falling by 70 percent. These reductions in mortality have been broad-based and include both men and women, all races, and all age groups. In contrast, the death rates from all noncardiovascular diseases, including cancer, fell only slightly between 1950 and 1975 and have shown little change during the past 20 years. The reduction in cardiovascular mortality in the past three decades has increased the life expectancy in the United States by an average of five years. In fact, 85 percent of the reduction in age-adjusted mortality from all causes between 1963 and 1994 can be ascribed to the decline in deaths from cardiovascular disease and stroke (National Center for Health Statistics: public-use mortality data tapes; and Division of Vital Statistics: unpublished data, 1968–1994). If the mortality rate from coronary heart disease had remained at the 1963 level, 1,076,000 deaths from coronary heart disease would have occurred in 1994 instead of 482,000.<sup>22,23</sup>

Thus, since the battle against cardiovascular disease was joined in mid-century, the news from the cardiovascular front has been almost uniformly favorable. Pacemakers, open-heart surgery, prosthetic heart valves, coronary angioplasty and stents, aspirin, beta-blockers, angiotensin-converting-enzyme inhibitors, 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, and many other drugs, procedures, and devices have all improved clinical outcomes.

Although it is very important for the public to be informed of important medical developments, publicity focused on an almost unbroken series of positive developments has encouraged the perception that the war against cardiovascular disease has been won or is well on the way to being won. As a consequence, as the second half of the 20th century has progressed, the urgency about the pandemic of cardiovascular disease that existed at mid-century has been replaced by growing complacency. The public's fear of heart disease has lessened, and in recent years it has seemed as if a number of other diseases, notably the acquired immunodeficiency syndrome and cancer, have been deemed to be more pressing than cardiovascular disease, to present greater scientific



**Figure 4.** Reduction in Heart Failure, Stroke, and Death from Coronary Causes or Nonfatal Myocardial Infarction (MI) in the Systolic Hypertension in the Elderly Program (SHEP). Modified from SHEP Cooperative Research Group,<sup>16</sup> with the permission of the publisher.



**Figure 5.** Changes in Age-Adjusted Death Rates from Coronary Heart Disease (CHD), Stroke, and Noncardiovascular Disease (Non-CVD) in the United States from 1950 to 1995. Data are from the National Heart, Lung, and Blood Institute.<sup>22</sup>

opportunities, and to be more deserving of public support, including a greater portion of the budget of the National Institutes of Health.

**PHASE 3: THE WAR HAS NOT YET BEEN WON**

As the biologic and technological successes of phase 2 occurred, it gradually became recognized that the war against cardiovascular disease was, in fact, far from over. Although the data on the improvement in cardiovascular health during phase 2 (summarized in Fig. 5) are very impressive, they may

in fact have been interpreted overoptimistically. Indeed, despite the progress in prevention, diagnosis, and treatment, cardiovascular disease still remains by far the leading cause of death in industrialized nations. In the United States, cardiovascular disease is responsible for more years of potential life lost before the age of 75 than any other condition, and it creates an immense economic burden in health care costs and lost productivity. In 1996 the direct costs of cardiovascular disease in the United States, including the costs of hospitals and nursing homes, professional care, and drugs, were estimated at \$259 billion.<sup>23</sup> Therefore, phase 3 of the history of cardiovascular disease is the recognition, beginning in the late 1980s, that the battle is far from over.

It should also be noted that the encouraging reductions in mortality due to coronary heart disease and stroke shown in Figure 5 are based on age-adjusted death rates. Because of the increase in the size of the population and in the proportion of older people, the absolute number of deaths has remained almost constant at nearly 750,000 a year over the past 25 years. Moreover, the outlook is not encouraging. From a demographic viewpoint, the oldest members of the baby-boom generation are only now reaching their early 50s, when the prevalence of coronary heart disease begins its steep rise. Therefore, even if the age-adjusted rate of cardiovascular disease continues its steady decline, the absolute mortality from coronary heart disease will very likely increase as the average age of the population rises and the number of persons over 60 years old grows rapidly. Moreover, the encouraging trends in risk-factor reduction that occurred during the past three decades may not be continuing. For example, an increase in cigarette smoking and obesity and a reduction in physical activity among teenagers occurred between 1960 and 1990.<sup>24</sup> These observations are disquieting, given the known difficulties in changing established behavior patterns later in life.

Smoking still accounts for an estimated 200,000 deaths from cardiovascular causes each year.<sup>25</sup> More than 30 percent of U.S. adults are obese (body weight, more than 20 percent above ideal),<sup>25</sup> and this percentage is growing. In addition to being an independent risk factor for coronary heart disease, obesity increases the incidence of other risk factors (high levels of low-density lipoprotein cholesterol, high triglyceride levels, low levels of high-density lipoprotein cholesterol, and increased likelihood of hypertension and diabetes mellitus). An estimated 16 million people in the United States have diabetes; this number is growing, and only about half are even aware that they have the condition. Diabetes is associated with a cluster of risk factors, including hyperglycemia, insulin resistance, hypertriglyceridemia, hypertension, central adiposity, and low levels of high-density lipoprotein cholesterol. As a conse-

quence, more than 80 percent of people with diabetes die of cardiovascular disease.

The death rates from coronary heart disease in the United States do not compare very favorably with those in other industrialized nations. The age-adjusted mortality rates in 18 of 33 such countries are lower than those in the United States. Furthermore, 15 of these other countries have recently had a more rapid decline in deaths from coronary heart disease than the United States.<sup>22</sup>

It has been projected that cardiovascular disease worldwide will climb from the second most common cause of death, with 29 percent of all deaths in 1990, to first place, with more than 36 percent of all deaths in 2020. This is more than twice the percentage of deaths from cancer.<sup>26</sup> The projected rise is related not only to the reduction in infectious diseases and malnutrition as important causes of death in childhood, allowing survival to adulthood and the potential development of heart disease, but also to the alarming increase in smoking and other coronary risk factors, including diabetes mellitus, as populations in developing nations adopt more Westernized lifestyles. Thus, for the first time in human history, cardiovascular disease is likely to become the most common cause of death worldwide; this is hardly a signal of victory in the war against cardiovascular disease. There are four major reasons for this failure to achieve victory.

#### **Inadequate Knowledge**

Although much has been learned about the causes of coronary heart disease, the gaps in knowledge are noteworthy; for example, fully half of all patients with this condition do not have any of the established coronary risk factors (hypertension, hypercholesterolemia, cigarette smoking, diabetes mellitus, marked obesity, and physical inactivity).

#### **Inadequate Use of Established Strategies**

The same facts and statistics that have been accepted as evidence of great progress in the battle against cardiovascular disease in phase 2 can, in fact, be used to support the opposite position. Thus, blood pressure is not yet controlled in 45 percent of patients with hypertension, 19 percent of U.S. adults have hypercholesterolemia,<sup>17,22</sup> and only 40 percent of patients eligible for beta-blockers after acute myocardial infarction receive such therapy.<sup>27</sup> In one recent study, only 45 percent of patients with confirmed myocardial infarction treated at teaching hospitals received aspirin, and of this group, less than one fourth received this drug within a half-hour of arrival, when it is known to be most effective.<sup>28</sup> In other words, a very substantial portion of the U.S. population is not yet receiving the preventive or therapeutic measures that have been proved to be effective against cardiovascular disease.

### Inadequacies of Established Strategies

Even though the therapy available today is effective, it leaves much room for improvement. Indeed, the course of cardiovascular disease remains unchanged in the majority of patients who receive the optimal therapy in the most successful clinical trials. For example, among patients who received active treatment in the Scandinavian Simvastatin Survival Study, which is widely and appropriately hailed as a landmark trial, the incidence of death from coronary causes or myocardial infarction was still two thirds of that observed in patients given placebo.<sup>19</sup> Similar considerations apply to the majority of other advances in phase 2, which must be considered to be only partial victories.

### Emergence of New Epidemics of Cardiovascular Disease

Two new epidemics of cardiovascular disease are emerging: heart failure and atrial fibrillation. Hospital admissions for heart failure have climbed steadily, so that this condition has become the single most frequent cause of hospitalization in persons 65 years of age or older; it is now responsible for more than 875,000 admissions each year in the United States.<sup>23</sup> Despite the development of a number of effective new therapies for heart failure, such as angiotensin-converting-enzyme inhibitors and cardiac transplantation, the prognosis for patients with this condition remains poor, and deaths have more than doubled in just 14 years.<sup>24</sup>

What is the explanation for this increase? The prime candidates for the development of heart failure are patients with hypertension in whom death from stroke has been prevented by antihypertensive therapy and survivors of acute myocardial infarction who have been spared death from arrhythmia. Normally a steady dropout of cardiac cells occurs during life,<sup>29,30</sup> and it may be postulated that heart failure develops once the number of viable myocytes drops below a critical threshold required to maintain cardiac compensation.<sup>31</sup> The programmed death of myocytes appears to be accelerated in the presence of ventricular hypertrophy secondary to hypertension,<sup>32</sup> which also accelerates the development of heart failure in such patients. Similarly, survivors of acute myocardial infarction have a reduced number of viable myocytes, and the ongoing attrition of the remaining cells may make these patients more susceptible to the development of heart failure.

In addition to heart failure, the number of hospital discharges for atrial fibrillation more than doubled from 111,000 in 1984 to 270,000 in 1994.<sup>33,34</sup> This is worrisome, because patients with this arrhythmia are at risk of embolic stroke and heart failure, two conditions associated with early death. With the aging of the baby-boom cohort, the prevalence of age-related arrhythmia will only increase further.

### PHASE 4: WE CAN PREVAIL

Almost simultaneously with the growing realization that the cardiovascular war is far from over, a number of scientific opportunities are now leading us into the fourth phase of cardiovascular medicine. In considering how modern science may lead to a true victory against cardiovascular disease, it may be useful to review how new knowledge about the normal and disordered circulation has developed. As the specialty of cardiology entered the 20th century, the prime focus was on the individual patient. To study the circulation in health and disease, physicians used their physical senses and recently discovered tools such as electrocardiography, the sphygmomanometer, and roentgenography.

At the beginning of this century, the focus of attention began to shift from the intact subject to the isolated heart or heart-lung preparation. With these preparations, the biochemical milieu and hemodynamic load can be controlled, and the responses to various stimuli can be studied with far greater precision than is possible in the intact organism. This initiated what may be termed the reductionist approach to cardiovascular science, in which ever smaller components of the heart and circulation are studied with ever greater precision.

As this century progressed, the attention of cardiovascular scientists moved progressively to smaller entities: from the isolated heart to isolated cardiac muscle, to individual myocytes, to subcellular organelles such as mitochondria, myocyte membranes, and myofibrils, then to contractile proteins, and ultimately to the genes that encode these proteins. The reductionist approach has also been applied to blood vessels, moving from the arterial wall to its cellular and matrix constituents, and ultimately to the genes that encode the enzymes and growth factors responsible for the development of normal and diseased vessels.

Simultaneously with this reductionist approach, cardiovascular epidemiology has emerged as an ever more powerful science. Coronary risk factors have been identified, principally through population-based methods. For some time, the reductionist and epidemiologic approaches appeared to be competitive, and a lively debate developed about which was likely ultimately to be more useful. Actually, these two approaches complement each other, and they come together in the field of population genetics. It is becoming apparent that both the molecular and the population-based approaches are essential to further progress and that they must, in fact, be applied in tandem.

### New Risk Factors for Coronary Heart Disease

From studies carried out simultaneously in basic-science laboratories and in populations, a number of new candidate risk factors for coronary heart disease

**TABLE 1.** EMERGING CARDIOVASCULAR RISK FACTORS.

Estrogen deficiency
Homocysteine
Plasma fibrinogen
Factor VII
Endogenous tissue plasminogen activator
Plasminogen-activator inhibitor type 1
D-Dimer
Lipoprotein(a)
C-reactive protein
<i>Chlamydia pneumoniae</i>

are now emerging (Table 1). The best known of these is estrogen deficiency, which appears to be responsible for the higher prevalence of coronary heart disease in postmenopausal women. The administration of estrogens to such women establishes a more favorable lipid profile and improves the function of the vascular endothelium, including that of the coronary arteries.<sup>35</sup> The benefits of estrogen replacement in reducing the toll of cardiovascular disease have not yet been demonstrated conclusively in a large-scale trial focusing on clinical end points, but such a study is now under way. Newly developed drugs with the vascular protective effects of estrogen but without its undesired actions on the breast and uterus show promise of being powerful and safe antiatherosclerotic agents.<sup>36</sup>

A second potent emerging atherogenic risk factor is homocysteine.<sup>37</sup> This amino acid has been shown to damage vascular endothelium in vitro. Folate and vitamin B<sub>12</sub> are necessary for the conversion of homocysteine to the nontoxic methionine, and persons with lower levels of folate because of insufficient dietary intake have higher concentrations of circulating homocysteine. Trials are now under way to determine whether supplements of folate and vitamin B<sub>12</sub>, two inexpensive and safe substances, reduce the incidence of coronary events. Elevations of homocysteine may also occur in cigarette smokers and in persons who are homozygous for the gene *MTHFR*. This gene encodes the enzyme methylenetetrahydrofolate reductase, which converts folate from an active to an inactive form.<sup>38</sup>

Five of the other emerging coronary risk factors in Table 1 enhance blood coagulation (fibrinogen, factor VII, plasminogen-activator inhibitor type I, tissue plasminogen activator, and D-dimer). This is not surprising, because thrombosis has long been known to be involved at two critical points in the development of coronary heart disease: first in atherogenesis, and second in the conversion of chronic coronary heart disease to acute coronary syndromes. Three other emerging risk factors are lipoprotein(a),

which appears also to be involved in atherothrombosis,<sup>39</sup> C-reactive protein (a marker of inflammation), which may identify subjects at high risk for the development (or redevelopment) of acute coronary syndromes,<sup>40</sup> and *Chlamydia pneumoniae* infection, which might be involved in both atherogenesis and plaque instability.<sup>41</sup>

An important challenge for phase 4 will be to find ways to reduce these emerging risk factors and then to demonstrate that such reductions actually lower the incidence of coronary events. If such efforts are successful, the positive impact on public health could be immense. Four relatively inexpensive agents may prove to be quite effective in combating emerging risk factors: folate, which reduces homocysteine levels; niacin, which reduces both fibrinogen and lipoprotein(a) levels<sup>39</sup> and raises high-density lipoprotein cholesterol levels; aspirin, which reduces the risk of myocardial infarction in normal subjects with relatively high levels of C-reactive protein<sup>40</sup>; and roxithromycin, which has antichlamydial and anti-inflammatory activity, and which has been reported to reduce risk in patients with unstable angina.<sup>41</sup>

#### Advances in Cardiac Imaging

Substantial progress is being made to allow non-invasive assessment of the site, shape, extent, composition, and risk of rupture of plaques in the coronary arteries. This will facilitate the early identification of patients at high risk for serious coronary events. The application to such patients of newly developing catheter-based techniques for coronary revascularization that incorporate new approaches to prevent restenosis<sup>42,43</sup> should help to reduce the incidence of acute coronary events.

#### Molecular Approaches to Vascular Disease

A deeper appreciation of the molecular bases of vascular disease has identified a wide variety of new therapeutic opportunities.<sup>44</sup> These are shown in Table 2. The first two items appear to be particularly promising. Prevention of the rupture of atherosclerotic plaques is obviously a critical step in the prevention of acute myocardial infarction. The metalloproteinases are enzymes secreted by macrophages that are centrally involved in plaque rupture,<sup>45</sup> and their inhibition could stabilize plaques and thereby prevent acute coronary events. The prevention of thrombosis in disrupted plaques is another important objective. Although aspirin is a valuable antiplatelet agent, and heparin and warfarin are effective anticoagulants, it is almost certain that they can be greatly improved. Platelet glycoprotein IIb/IIIa-receptor blockers, tissue-factor inhibitors, and antithrombins are all potentially more potent than the available drugs, and they may also prove to be more effective in reducing the incidence of coronary events. Intravenously administered glycopro-

tein IIb/IIIa-receptor blockers reduce the incidence of acute coronary events in patients undergoing percutaneous catheter-based revascularization.<sup>46</sup> Trials of the use of orally effective platelet glycoprotein inhibitors to limit the development of new coronary events are now in progress.

**Transgenic Techniques**

The insertion or deletion of individual genes into animals, usually mice, is rapidly advancing the understanding of atherosclerosis and hypertension. Transgenic mice with hypertension caused by multiple copies of the gene for angiotensin have been created,<sup>47</sup> as have mice with atherosclerosis secondary to deletion of the gene for apoprotein A-I or apoprotein E.<sup>48</sup> This approach is also being applied to the study of heart failure by creating transgenic mice that overexpress  $\beta_2$ -adrenergic receptors.<sup>49</sup> The existence of such genetically altered animals should aid the development of newer therapies for these conditions.

**Advances in Molecular Genetics**

A number of monogenic disorders have now been shown to cause hypertension (Table 3), and new ones are being reported with regularity.<sup>50</sup> Although the discovery of these conditions is eroding the concept of essential hypertension, it appears that in the majority of cases hypertension results from the interaction between multiple genes and environmental influences such as sodium intake and body weight. When the Human Genome Project is completed early in the 21st century, it should become possible to genotype people at all risk-factor loci and thereby divide patients with hypertension into subgroups and tailor specific preventive and therapeutic approaches to these subgroups. For example, certain classes of antihypertensive drugs, such as those that block the renin-angiotensin system, may be most useful in particular genotypes, whereas the limitation of sodium intake and the use of diuretics might be particularly effective in others. Indeed, the recent discovery of polymorphisms for the gene encoding adducin, a protein found in the renal tubule that regulates sodium transport, identified a relatively common form of salt-sensitive hypertension.<sup>51</sup>

In the past few years, mutations responsible for several monogenic cardiovascular disorders have been identified (Table 4). In many forms of these conditions, genotype analysis can confirm the diagnosis, establish a presymptomatic diagnosis, predict the severity of the condition, determine the risk status of the patients' relatives, and establish the basis for genetic counseling and treatment.

An example of the successful interplay between population-based observations and laboratory science is the familiar story of the low-density lipoprotein receptor. The association between familial hy-

**TABLE 2. MOLECULAR THERAPIES FOR VASCULAR DISEASES.\***

PATHOLOGIC EVENT	THERAPEUTIC TARGET
Plaque rupture	Metalloproteinase inhibitors, leukocyte-adhesion blockers
Thrombosis	Glycoprotein IIb/IIIa-receptor blockers, tissue-factor inhibitors, antithrombins
Endothelial dysfunction	Nitric oxide donors, antioxidants
Endothelial injury	VEGF, FGF†
Dysregulated cell growth	Cell-cycle inhibitors
Dysregulated apoptosis	Integrin antagonists
Matrix modification	Metalloproteinase inhibitors, plasmin antagonists

\*Data are from Gibbons and Dzau,<sup>44</sup> with modifications.  
 †VEGF denotes vascular endothelial growth factor, and FGF fibroblast growth factor.

**TABLE 3. MONOGENIC DISORDERS RESPONSIBLE FOR HYPERTENSION.\***

Glucocorticoid-remediable aldosteronism
II $\beta$ -Hydroxylase deficiency
17 $\alpha$ -Hydroxylase deficiency
II $\beta$ -Hydroxylase steroid dehydrogenase deficiency (syndrome of apparent mineralocorticoid excess)
Mutations in $\beta$ or $\alpha$ subunits of epithelial sodium channel (Liddle's syndrome)
Mutations in Na <sup>+</sup> -Cl <sup>-</sup> cotransporter (Gitelman's syndrome)
Mutations in $\alpha$ or $\beta$ subunits of epithelial sodium channel (pseudoaldosteronism)
Angiotensin variants
Adult polycystic kidney disease

\*Data are from Lifton,<sup>50</sup> with modifications.

**TABLE 4. MONOGENIC DISORDERS RESPONSIBLE FOR HEART DISEASE.**

Familial hypercholesterolemia
Osteogenesis imperfecta
Hypertrophic cardiomyopathy
Prolonged-QT syndrome
Atrial fibrillation
Marfan's syndrome
Holt-Oram syndrome
Dilated cardiomyopathy

percholesterolemia and premature coronary heart disease was first noted in individual families and subsequently was established in populations. Brown and Goldstein then characterized the low-density lipoprotein receptor and showed how a number of genetic abnormalities are associated with reductions or abnormalities in the expression of this receptor, which in turn is responsible for an elevation of low-density lipoprotein cholesterol.<sup>52</sup> However, reduction or abnormality of the low-density lipoprotein receptor mediated by mutation of a single gene appears to be responsible for only a minority of cases of hypercholesterolemia. Instead, like many other chronic conditions, such as most forms of hypertension, diabetes, and asthma, most cases of hypercholesterolemia result from the interaction between multiple genes and environmental influences. The importance of genetic factors is underscored by the marked racial differences in the prevalence of coronary risk factors, such as the incidence of diabetes mellitus in Pima Indians and South Pacific Islanders, as well as in the differing contributions that these risk factors make to the prevalence of coronary heart disease.

Genomic analysis should make it possible to predict in childhood, indeed in utero, not only the genetic predisposition, but even the particular type of pathophysiologic disruption, that may occur, and thus should help in planning a rational preventive strategy specific to each person. This approach should not only allow identification of those in whom initial or recurrent coronary heart disease is likely to develop, who are now targets of primary and secondary prevention, but also permit going much further back into the process by helping to identify and target those in whom coronary risk factors are likely to develop. For example, some people may be at risk for coronary heart disease because of a mutation in the *MTHFR* gene and might benefit from early supplementation with folate and vitamin B<sub>12</sub>. Such supplementation might not be necessary in all persons. Others may possess one or more genes encoding proteins that increase salt reabsorption in the distal renal tubule, thus predisposing them to hypertension. A totally different preventive approach would be appropriate for this group. A third approach would be indicated in persons who have genetic abnormalities that lead to a procoagulant state, yet a fourth in persons at high risk for rupture of a vulnerable plaque, and so on. In other words, in preventive cardiology it is unlikely that one size will fit all. Instead, it is much more likely that genetic analysis will allow targeted prevention. In patients who already have clinical cardiovascular disease, the identification of the responsible genes will allow elucidation of the mechanisms of the disease, and this in turn should lead to therapies tailored to these mechanisms.

### Gene Transfer

An important advance in molecular genetics is the development of gene-transfer techniques for the enhancement of normal cellular function or the inhibition of abnormal function. Efforts are under way to introduce genes directly into the cells of the vascular wall to prevent atherosclerosis or restenosis. The long-range goals of gene transfer include transforming cardiac mesenchymal cells into cardiac myocytes, thereby enhancing the contractile ability of hearts that have suffered large infarctions, and increasing the expression of angiogenic growth factors in order to stimulate the growth of new vessels into ischemic tissue, including the myocardium.<sup>53</sup>

### CONCLUSIONS

The 20th century has been something of a roller-coaster ride for cardiovascular disease. During the first half of the century, a pandemic of cardiovascular disease developed and raged across the industrialized world. By mid-century the battle against the pandemic was joined and cardiovascular research began in earnest. An enormous amount was learned about the mechanisms, diagnosis, treatment, and prevention of cardiovascular disease, and the tide began to turn against these conditions. However, despite some major successes, as an increasing fraction of the world's population is reaching the age at which coronary heart disease is prevalent, it is likely that for the first time in human history cardiovascular disease will become the most common cause of death worldwide.

Developments in the 20th century have laid the foundation for future progress, and both the challenges and the opportunities for the earliest decades of the 21st century are now becoming apparent. There appear to be two major challenges. First, the important information about the prevention and treatment of cardiovascular disease that is already available must be applied more broadly. Second, the revolution in biology and the results of the Human Genome Project must be used to characterize the genetic contribution to the complex disorders that lead to cardiovascular disease. Research in genetic epidemiology incorporating both fundamental biology and population science is likely to be very rewarding. With a renewed commitment to the reduction of cardiovascular disease, there are good reasons to be optimistic that the battle against cardiovascular disease could be won well before the 137th Shattuck Lecture is delivered 30 years from now in 2027.

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