

# BLOSSOMS ON THE TREE OF CARDIOLOGY: some predictions for the coming decade

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*Medical history teaches us where  
we came from, where we stand in medicine  
at the present time, and in what  
direction we are marching. It is the compass  
that guides us into the future.*

*Sigerist H: "A History of Medicine"*

*The best of prophets  
of the future is the past.*

*Byron: Journal [January 28, 1821]*

*Past is prologue.*

*Shakespeare: "The Tempest"*

**T**his anniversary issue, which reviews the history of ten key areas of cardiology, documents how new understanding of cardiovascular medicine has narrowed the gap between the basic sciences and clinical practice. In the ancient world, when clinical observations were interpreted largely in a philosophical context, science had virtually no impact on patient care. Studies of pathological anatomy that began in the 16th century, along with Harvey's description of the circulation in 1628, provided some explanations for cardiovascular disease, but these had virtually no clinical benefits for almost 300 years. It was not until the 20th century that invention of the electrocardiogram, developments in hemodynamic physiology, identification of the role of coronary disease in myocardial infarction, characterization of hypertension, discoveries in biochemistry and vascular biology, and other advances began to close the gap between bench and bedside. Practical applications included cardiac surgery, pharmacological agents tailored to correct pathophysiological abnormalities, risk factor modification, and new technologies for diagnosis and treatment. Basic science and clinical medicine moved even closer to one another in the late 1980s, when molecular biology made it possible to identify additional mechanisms of cardiovascular disease. Today, only a few years can elapse before a discovery identifies new ways to help the cardiac patient. The rapid pace at which we are now learning about cardiovascular disease and the increasing relevance of basic science to clinical practice continue historical processes described in this issue. This article projects these trajectories ahead to make a number of concrete predictions regarding cardiovascular medicine in 2016.

**Keywords:** hemodynamics; diagnosis; heart failure; hypertension; ischemic heart disease; atherosclerosis; electrophysiology; autonomic nervous system; surgery; genetics; molecular biology; prediction

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*Dialogues Cardiovasc Med.* 2006;11:157-167

This anniversary issue uses the analogy of a tree to trace the development of modern cardiology. Starting with the roots and trunk, each article describes the emergence of the major branches that support today's rich foliage. In this concluding article, I use these contributions to draw lines from the past to the present and into the future to venture a few predictions as to which of today's blossoms might yield the most luxuriant fruit.

Among the most remarkable features of the history told in this issue is the effectiveness with which cardiology has incorporated data and technologies from other fields of science. Looking back to the clinical observations that lie at the root of Western medicine, the initial effort was to identify specific syndromes. However, ancient medicine was based on a mixture of empiricism and philosophy with virtually no understanding of pathophysiology, so that these efforts had little success. Cardiology did not begin to advance until the 17th century, when increasing use of human dissection, coupled with Harvey's description of the circulation, made it possible to identify the hemodynamic abnormalities associated with anatomical syndromes caused by rheumatic heart disease, then the major cause of cardiac death. However, more than 300 years were to pass before surgical treatment of these structural abnormalities became possible. Bacteriology, which emerged in the late 19th century, made it possible to identify the causes of infective endocarditis, and later of rheumatic fever. Advances in public health, notably improved sanitation, began to eliminate rheumatic heart disease in the early 20th century; these efforts were aided by the discovery of antibiotics, which also made it possible to prevent and

treat infective endocarditis. Epidemiological data regarding the geographic distribution of atherosclerosis and its correlation with diet, smoking, diabetes, and hypertension, along with studies of lipid transport and metabolism, identified treatable risk factors that helped make it possible to reduce ischemic heart disease mortality more than 50% from its mid-20th-century peak. Studies of autonomic physiology led to advances in pharmacology that had a major impact on the treatment of hypertension, while discoveries in cardiac electrophysiology brought new understanding to the pathophysiology of arrhythmias. Newly discovered principles of physics came to be used for cardiac diagnosis at the beginning of the 20th century, when x-rays were used to image the heart and the string galvanometer to record the electrocardiogram. More recent applications of ultrasound, radioisotope decay, magnetic resonance, and other technologies, along with developments in electronics and computer science, have made this technology an essential feature of modern cardiology. Extending this list is not necessary to support my first—and most general—prediction, that cardiology will, over the next ten years, continue to incorporate new discoveries in science and technology to improve the diagnosis and treatment of heart disease. I cannot guess what these areas will be except to suggest that, as in the past, progress will come from unexpected directions.

### HEMODYNAMICS

Michael Webb-Peploe's article highlights the value of interventional approaches to coronary artery disease, and suggests that molecular interventions like gene therapy will add to their benefit. I am not, however, enthusiastic about the ability of any interventional approach to

prolong survival in patients with *chronic* angina pectoris. Although the procedures used today are effective in controlling symptoms, the few properly designed studies carried out over the last 30 years failed to show much improvement in prognosis. It is unlikely today that any new bioengineering or molecular intervention, alone or in combination, could reduce mortality in patients with stable coronary disease simply because this syndrome is now so benign as to preclude a significant survival benefit from any therapy other than that which can slow or reverse the underlying disease in the arteries. It is not widely appreciated that 40-year-old Metropolitan Life Insurance Company statistics show that a prior myocardial infarction reduced the life expectancy of a "standard" 55-year-old life insurance applicant, which was then about 20 years, by only 4 to 5 years (*Table I*).<sup>1</sup> The small impact of stable ischemic heart disease on prognosis was subsequently confirmed in an analysis of trials completed before 1990, which showed the life expectancy of a 55-year-old medically managed patient with 3-vessel disease, mild angina, and a normal ejection fraction to be more than 17 years; this is only 3 years less than that of a patient with mild angina and single-vessel disease, which, like that of the general population at that time, was more than 20 years (*Table I*).<sup>2</sup> Even when associated with severe angina, 3-vessel disease reduced life expectancy less than 4 years. These small effects of stable coronary disease on survival were documented *before* the widespread use of safe and effective antihypertensive medications, precise blood glucose control in diabetics,  $\beta$ -blockers, angiotensin-converting enzyme (ACE) inhibitors, statins, antithrombotic drugs, thrombolytic therapy, and other treatments now known to im-



prove prognosis in this condition. It is therefore likely that the adverse effect of stable angina on survival is now so minor that no surgical or interventional approach could prolong life significantly. I doubt, however, that anyone will measure this!

Current evidence does support the value of interventional approaches in acute myocardial infarction, so that I will predict, though with some trepidation, that intracoronary ad-

to adapt new knowledge from the physical sciences to produce better images of the heart and vasculature, I am unable to extend the story told by Arthur Hollman into the future. I suspect that by 2016 noninvasive imaging will allow us to hold a 3-dimensional image of the living heart in our hands, examine the patency of the coronary arteries, and analyze cardiac function with considerable precision. However, I am not convinced that these images will be of much benefit for patient care; in

the less. [The physician's] mere presence leaves the patient with more hopefulness and vitality.<sup>3</sup>

## HEART FAILURE

My article in this issue concludes that improved management of heart failure will be made possible by "additional new stems [that] are likely to emerge from unexpected places," and that most of these will be in areas of molecular biology, which is already having a major impact on the diagnosis and classification of the familial cardiomyopathies (Table II, next page).<sup>4</sup> I expect that by 2016 this and other new information will have begun to influence when and how these patients are treated, and I predict that carriers of some of the more dangerous cardiomyopathy gene abnormalities will be found to benefit from treatment with  $\beta$ -blockers, ACE inhibitors, and other therapy *before* they become symptomatic.

I am tempted to predict success in efforts to find selective inhibitors of signaling pathways responsible for maladaptive hypertrophy and activators of pathways that lead to adaptive hypertrophy, but the history in this field is mixed. On the one hand, we have learned that many neurohumoral inhibitors ( $\beta$ -blockers, ACE inhibitors, aldosterone antagonists) can delay, and for a time even reverse, the adverse consequences of cardiac hypertrophy, but it should be remembered that these findings came as a surprise to many experts in this field. The complexity of the interwoven and overlapping cell signal transduction pathways that mediate maladaptive hypertrophy makes it difficult to predict the long-term clinical effects of molecules designed to activate or inhibit specific protein kinases, phosphatases, and other signaling molecules, so that I am reluctant to predict much

### Effect of a history of myocardial infarction (MI) in 55-year-old life insurance applicants prior to 1968. Data from ref 1

Age at death of a "standard" applicant:	74-79 years
Age at death an applicant with history of MI	71-73 years
➔ Reduction in life expectancy:	4-5 years ( $\approx$ 21% of 19-24 years)

### Effect of proven coronary occlusive disease in 55-year-old patients managed medically prior to 1990. Data from ref 2

Age at death, mild angina, single-vessel disease	75.5 years*
Age at death, mild angina, 3-vessel disease	72.5 years
➔ Reduction in life expectancy:	3.0 years ( $\approx$ 15% of 20.5 years)
Age at death, severe angina, 3-vessel disease	71.8 years
➔ Reduction in life expectancy:	3.7 years ( $\approx$ 18% of 20.5 years)

\*Data from this period indicate that survival in this group was similar to that of the general population.

**Table I.** Impact of stable coronary artery disease on survival.

ministration of novel signaling molecules and other chemical mediators at the time of primary angioplasty will be found to improve prognosis in this group of patients. I am less enthusiastic about infusion of bone marrow and other types of stem cells as the risks seem likely to exceed the benefits, in part because these cells produce so many active compounds.

## DIAGNOSTIC CARDIOLOGY

I am afraid that my crystal ball fails me here. Aside from my first prediction that cardiology will continue

fact, I believe it likely that they will do more harm than good because increased reliance on diagnostic technology is moving physicians from the bedside to the imaging center. As Hollman points out, a precise history and careful physical examination, rather than elegant images, remain the key to diagnosis and therapy for most cardiac patients. Furthermore, when physicians spend more time away from the bedside, they are less able to dispense what A. Conan Doyle called the healing touch... that magnetic thing which defies explanation or analysis, but which is a very evident fact none

## HYPERTROPHIC CARDIOMYOPATHIES

### Myofibrillar protein mutations

$\beta$ -Myosin heavy chain; regulatory myosin light chain; essential myosin light chain; troponin T; troponin I; troponin C;  $\alpha$ -tropomyosin; cardiac actin

### Cytoskeletal protein mutations

Titin; myosin-binding protein C; LIM protein; T-cap

### Mutations in nuclear-encoded metabolic proteins (with intracellular glycogen accumulation)

AMP-activated protein kinase; lysosome-associated membrane protein-2 (Danon's disease); lysosomal acid  $\alpha$ -1,4-glucosidase (Pompe's disease); lysosomal hydrolase  $\alpha$ -galactosidase (Fabry's disease)

### Membrane protein mutations

Calcium release channel (ryanodine receptor)

### Other

Nkx2.5 (homeobox)

## DILATED CARDIOMYOPATHIES

### Myofibrillar protein mutations

$\beta$ -Myosin heavy chain; troponin T; troponin I; troponin C;  $\alpha$ -tropomyosin; cardiac actin

### Cytoskeletal protein mutations

Z-line-related: titin; cypher/ZASP (cypher/Z-band alternatively spliced PDZ-motif protein); telethonin; T cap; desmin

Dystrophin-related:  $\beta$ -sarcoglycan;  $\delta$ -sarcoglycan; dystrophin; dystrobrevin

Desmosome-related (arrhythmogenic right ventricular dysplasia):

plakoglobin; desmoplakin; plakophilin-2; desmoglein; TGF $\beta$ 3; ryanodine receptor

Nuclear: emerin, lamin A/C

Other: metavinculin

### Membrane protein mutations

Phospholamban, SUR2A (KATP channel)

**Table II.** Some molecular causes of familial cardiomyopathies.

Modified from reference 4: Katz AM. Physiology of the Heart. 4th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2006. Copyright © 2006, Lippincott Williams & Wilkins.

success in these efforts by 2016, but I hope that I am wrong. I am even less optimistic about the potential benefits of gene therapy, largely because of problems that emerged when this approach was used to treat other diseases. I am also pessimistic about what I view as a generally overly enthusiastic view of stem cell therapy as it is used today. I am especially troubled by the lack of solid evidence that the infused

cells, even were they do survive and flourish, become functionally integrated with the native cardiac myocytes by forming gap-junction connections.

One syndrome for which I will make a concrete prediction is “diastolic heart failure” (DHF). I share the widely held view that ejection fraction (EF) distinguishes DHF, where EF is usually normal, elevated, or

only minimally depressed, from the more common “systolic heart failure” (SHF), where EF is low. Because EF is simply the ratio between stroke volume and end-diastolic volume, and because stroke volume (like cardiac output) is reduced in virtually every patient with heart failure (the notable exception being high-output failure), simple algebra tells us that the major distinction between SHF and DHF is whether or not end-diastolic volume is increased. As inhibition of progressive dilatation (remodeling) accounts for much of the benefit of therapy that prolongs survival in SHF, drugs that have proven to be effective in SHF should be of much less value in improving prognosis in DHF where, by definition, progressive dilatation does not play an important role. I would be less than honest if I did not admit that this view is supported by data from hypertensive patients, a population that is predisposed to develop DHF, in whom ACE inhibitors and  $\beta$ -blockers—which have a clear survival benefit in SHF—appear to be less effective in improving prognosis, after taking into account their ability to lower blood pressure.<sup>5</sup>

There is also evidence that ACE inhibitors are less effective in delaying the onset of heart failure in hypertensive patients with a left ventricular ejection fraction (LVEF) >35% and no evidence of heart failure,<sup>6</sup> than they are in asymptomatic patients with an LVEF <35%<sup>5-7</sup> (Figure 1). Similarly, an angiotensin receptor blocker given to patients with DHF barely reduced the primary end point of cardiovascular death and hospital admission for heart failure, and had no significant effect on cardiovascular death<sup>8</sup>; furthermore, the beneficial effects of these drugs appear to be less in DHF than in the overall population with heart failure<sup>8,9</sup> (Figure 2).



A recent report that a stiffer titin isoform is expressed in DHF than in SHF,<sup>10</sup> which is consistent with other evidence that these two types of heart failure are associated with different molecular abnormalities, gains additional significance be-

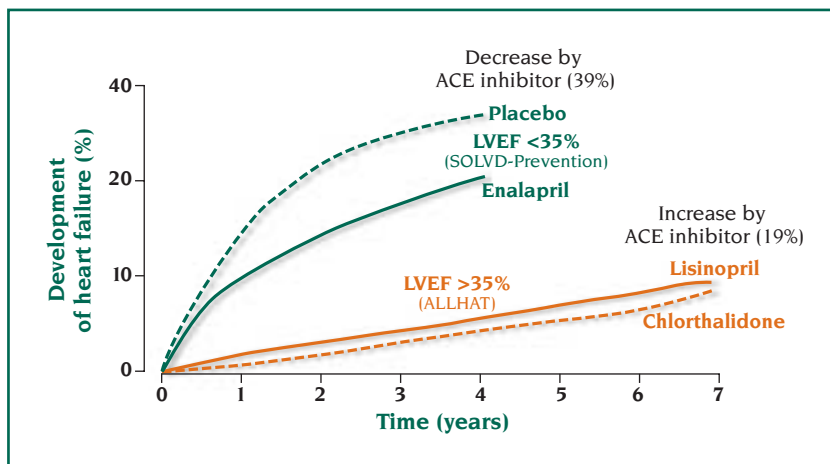
cause titin is not only an important determinant of diastolic stiffness, but along with other cytoskeletal proteins plays an important role in cell signaling.<sup>11</sup> This finding, along with other data suggesting that the cytoskeleton plays an important

role in determining the size, shape, and composition of the heart (see ref 4), leads me to predict that inhibition of maladaptive cytoskeletal signaling will emerge as a major target for new approaches to prevent progressive deterioration of failing hearts.

## HYPERTENSION

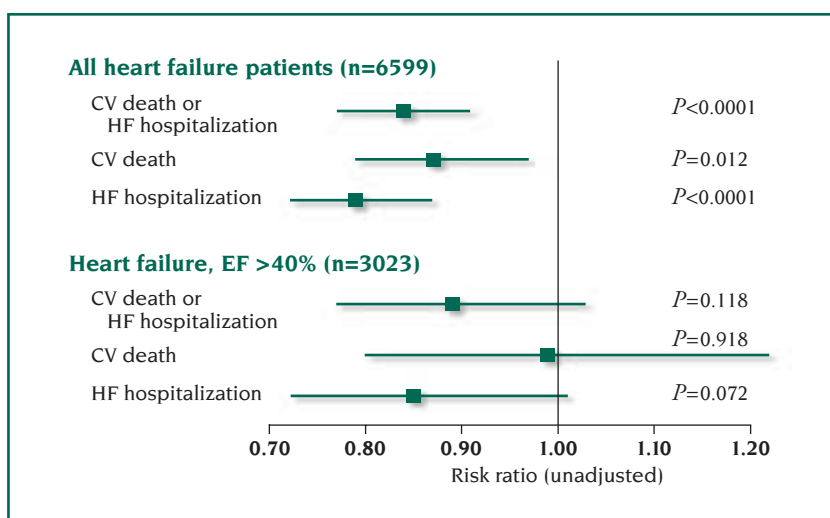
Norman Sharpe's description of the evolution of our understanding of hypertension is remarkably congruent with that of heart failure. In both, clinical pathologists of the 19th century observed morphological abnormalities, in the blood vessels and heart, respectively, that throughout most of the 20th century came to be overshadowed by the hemodynamic abnormalities. Furthermore, the morphological abnormalities in patients with hypertension, like those with heart failure, occur when maladaptive proliferative signaling causes hypertrophy and other changes in the target organ, in this case the arterial wall. Although these morphological changes had not been forgotten, the focus of antihypertensive therapy shifted to dynamic abnormalities like vasoconstriction and fluid retention, so that most of the drugs now used to treat this condition were selected because of their vasodilator properties or ability to rid the body of salt and water.

Recently, however, it has become clear that hypertension, like heart failure, is a complex group of syndromes that are often caused by signaling abnormalities associated with polymorphisms and other molecular abnormalities (Table III, next page).<sup>12</sup> Much remains to be learned about these abnormalities, but I suspect that by 2016 many hypertensive patients will be treated with novel drugs that act on these and other proliferative signaling systems.



**Figure 1.** Effect of ACE inhibition on the development of heart failure in hypertensive patients with LVEF >35% (lower curves), based on data from reference 6, and in asymptomatic patients following myocardial infarction with LVEF <35% (upper curves), based on data from reference 7. Unlike the asymptomatic patients with ischemic heart disease and a low LVEF, who benefited from ACE inhibitors, hypertensive patients without a significant decrease in LVEF who received an ACE inhibitor were no less likely to develop heart failure than those who received a thiazide diuretic. Dashed lines: patients not receiving an ACE inhibitor; solid lines: patients given an ACE inhibitor.

**Abbreviations:** ACE, angiotensin-converting enzyme; ALLHAT, Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial; LVEF, left ventricular ejection fraction; SOLVD-Prevention, Studies Of Left Ventricular Dysfunction, Prevention arm.



**Figure 2.** Effects of candesartan on the risk of cardiovascular death, heart failure hospitalization, or both, in symptomatic patients with heart failure. Above: Unadjusted risk ratios for all heart failure patients. Below: Unadjusted risk ratios for patients with left ventricular ejection fraction >40%. Based on data in references 8 and 9.

**Abbreviations:** CV, cardiovascular; EF, ejection fraction; HF, heart failure.

### Renin-angiotensin system

Angiotensinogen  
 Angiotensin-converting enzyme  
 Angiotensin II receptor types I and II  
 Renin  
 Renin-binding protein  
 Aldosterone synthetase

### Sodium metabolism

Adducin ( $\alpha$ - and  $\beta$ -subunits)  
 Epithelial sodium channel ( $\alpha$ - and  $\beta$ -subunits)  
 Atrial natriuretic peptide

### Adrenergic and related signaling

G proteins ( $\alpha$ - and  $\beta$ -subunits)  
 Adrenergic receptors ( $\beta_1$ -,  $\beta_2$ - and  $\beta_3$ -receptors)

### Endothelin system

Endothelins 1 and 2  
 Endothelin receptor A  
 Endothelial nitric oxide synthase (NOS3)

### Other

Glucagon receptor  
 Insulin-like growth factor I  
 Apolipoproteins B, CIII, E  
 Lipoprotein lipase  
 Cytokines

**Table III.** Some signaling systems in which genetic abnormalities have been implicated in the pathogenesis of hypertension.

*Modified from reference 12: Marteau JB, Zaiou M, Siest G, Visvikis-Siest S. Genetic determinants of blood pressure regulation. J Hypertens. 2005;23:2127-2143. Copyright © 2005, Lippincott Williams & Wilkins.*

## ISCHEMIC HEART DISEASE

It is difficult to conceive of a paradigm shift as dramatic as that which occurred less than 30 years ago, when, as described by Desmond Julian, acute myocardial infarction was demonstrated not to be a primary abnormality of the heart, as had been stated by several leading

authorities, but instead, as believed by others, to result from coronary artery occlusion. Although there seems no likelihood that we will see another paradigm shift of this magnitude in the foreseeable future, steady progress can be expected in our understanding of both the underlying atherosclerotic disease and the transformation of what is usually a smoldering, often benign, process in the coronary arteries into a rapidly moving conflagration (see below). In patients with pump failure following a large myocardial infarction, I anticipate that technological advances in monitoring and ventricular assist technology, rather than conceptual breakthroughs, will improve management. The mortality after acute myocardial infarction should also continue to improve because better detection of myocardial cell necrosis, by improving the diagnosis of small infarcts, will help identify patients at risk for sudden cardiac death.<sup>13</sup>

The most important unanswered question in ischemic heart disease research today is the identity of the factors that, by destabilizing atherosclerotic lesions in the coronary arteries, cause acute myocardial infarction. During the next decade I anticipate that the outlook for these patients will be improved by better understanding of the mediators of plaque vulnerabilization and rupture, which already include endothelial cell dysfunction and the actions of monocytes and macrophages, platelets, mast cells, proteolytic enzymes, phospholipases, cyclooxygenases, adhesion molecules, cytokines, mediators of apoptosis, and angiogenic and other peptide growth factors. These findings, coupled with well-documented benefits of drugs like ACE inhibitors and statins, along with the likelihood that polymorphisms influence individual susceptibility to plaque rup-

ture, suggest that, as in other areas of cardiology, optimal therapy of ischemic heart disease will soon be individualized. I therefore expect that in 2016 drugs will be available to modify the specific pathophysiological processes that operate in some of these patients. I also predict that novel means will be found to identify patients with vulnerable plaques, and that the use of new imaging modalities to localize unstable lesions will play an important role in preventing and managing acute coronary syndromes.

## ATHEROSCLEROSIS

I believe that, at least for the next 10 years, this will remain a “mature” field; by this I mean that while important progress will be made, there will be no shifts in direction as dramatic as those of the past 30 years when, as described by Anton Becker, atherosclerosis was recognized to be an inflammatory response to endothelial injury. As is true of other topics in this anniversary issue, many of the seminal observations in this field were stimulated by thoughtful examinations of human autopsy material. I vividly recall the pulmonary artery of a young woman with primary pulmonary hypertension whom I cared for in the 1960s; the pathologist pointed out that the endothelial surface of the main pulmonary artery exhibited atherosclerotic lesions as severe as those seen in the aortas of much older patients who had died of a myocardial infarction, and suggested that the atherosclerotic process must be the way that large arteries respond to various types of injury. It is not surprising, therefore, that most of the deleterious effects of the traditional “risk factors” have been found to reflect their ability to damage the vessel wall. Of course, no one 40 years ago could have predicted the impact of the many advances in



signal transduction discussed in Becker's article. I hope that I am not overly optimistic in predicting that, by 2016, better understanding of what converts a stable, and so benign, atherosclerotic lesion to a dangerous unstable lesion will have improved both prevention and treatment of acute myocardial infarction and related syndromes.

## ELECTROPHYSIOLOGY

The article by Michael Rosen and Michiel Janse ends with a description of the electronic pacemakers and cardioverter-defibrillators that have revolutionized the management of clinical arrhythmias. Over the next decade, there is little doubt that the proven benefits of these and other devices will be enhanced by miniaturization and other improvements in electronics. It also seems likely that clinical use of antiarrhythmic drugs, which, a generation ago, were the mainstay of arrhythmia management, will continue to decline. Aside from molecules that interact specifically with membrane proteins, such as  $\beta$ -receptor blockers, there seems little future for drugs with what were once called "membrane-stabilizing" actions. Amiodarone, which represents the major exception to this generalization, will probably continue to be prescribed for patients at risk for dangerous arrhythmias who do not have a long life expectancy, but I believe that this drug is too toxic for use in the growing population with serious arrhythmias who can be expected to live for 5 or more years.

A promising branch of the arrhythmia tree that I predict will have a growing impact on prevention and management has emerged from rapid advances in the molecular biology of cardiac ion channels and related proteins. Identification of

ion channel abnormalities that cause, or increase susceptibility to serious arrhythmias (*Table IV*)<sup>4</sup> represents a promising area whose impact on patient care over the next decade will be largely to improve diagnosis. Evidence that polymorphisms in these and other proteins can modify the clinical manifestations of a given ion channel gene

mutation<sup>14</sup> increases the complexity of this field. For these reasons, I predict that by 2016, patients suspected of being at high risk for sudden cardiac death will be screened for many of the potentially arrhythmogenic mutations and polymorphisms listed in *Table IV*; an updated list can be found on a database maintained by investigators of the Molecular Cardiology Laboratories of the IRCCS Fondazione Salvatore Maugeri, Pavia, Italy.<sup>15</sup> All this leads me to predict that the "gold stan-

dard" for identifying patients at high risk of a dangerous arrhythmia will not be the ECG, 24-hour ("Holter") monitor, indirect tests such as heart rate variability, late potentials, and T wave alternans, or even formal electrophysiological testing; instead, a blood sample from a patient judged to be at risk of sudden cardiac death will be examined for gene

Structure	Gene	Mutated protein	Clinical syndrome
$I_{Ks}$ channel	KCNQ1	KvLQT1	LQT1 syndrome
	KCNE1	MinK	LQT5 syndrome
	KCNQ1	KvLQT1	Familial atrial fibrillation
$I_{Kr}$ channel	KCNH2	HERG	LQT2 syndrome
	KCNE2	MirP1	LQT6 syndrome
	KCNH2	HERG	Short QT syndrome
$I_{Na}$ channel	SCN5A	hH1 (Nav 1.5)	LQT3 syndrome
	SCN5A	hH1 (Nav 1.5)	Brugada syndrome
	SCN5A	hH1 (Nav 1.5)	Lenègre's syndrome
$I_{K1}$ channel	KCNJ2	Kir2.1	Andersen-Tawil Syndrome
Ankyrin	ANK2	Ankyrin	LQT4 syndrome
Ryanodine receptor	RyR2	Ryanodine receptor	CPVT 1
Calsequestrin	CASQ	Calsequestrin	CPVT 2

**Table IV.** Some molecular causes of sudden cardiac death.

**Abbreviations:** CPVT, catecholaminergic polymorphic ventricular tachycardia; LQT, long QT. **Modified from reference 4:** Katz AM. Physiology of the Heart. 4th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2006. Copyright © 2006, Lippincott Williams & Wilkins.

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mutations and polymorphisms that predispose to a lethal arrhythmia. It is already clear that the nature of the molecular abnormality determines individual risk; for example, arrhythmic events are more frequent in patients with HERG channel mutations when the abnormality is in the pore region,<sup>16</sup> and the prognosis of right ventricular dysplasia/cardiomyopathy is worse in patients who have a mutation in plakophilin-2.<sup>17</sup> For this reason, it is safe to predict that identification

of specific gene abnormalities will play an increasing role in determining which patient needs a pacemaker, a cardioverter-defibrillator, or a drug such as a  $\beta$ -adrenergic blocker. This information should help provide a rational basis for alerting carriers of some genes to the hazards of strenuous activity and the need to avoid drugs that interact with cardiac ion channels, such as anti-depressants that prolong the QT interval.

I am willing to offer better than 50-50 odds that by 2016 a few molecular causes of arrhythmia will become amenable to specific treatment. Gene therapy, while of potential benefit, has proven to be both difficult and dangerous, but the value of simpler approaches is suggested by evidence that the HERG mutations responsible for the type 2 long-QT syndrome often impair trafficking of this potassium channel protein to the plasma membrane.<sup>18</sup> A practical value of this knowledge is suggested by the ability of a drug that interacts with an abnormal HERG protein to promote channel transport to the cell surface, which can “rescue” a model of the clinical abnormality.<sup>19</sup>

Another, quite different, group of patients at risk for a lethal arrhythmia, is found in the large and rapidly growing population with heart failure. In addition to reentry caused by fibrosis and increased heart size, electrical abnormalities associated with the molecular changes that accompany cardiac myocyte hypertrophy play a major role in causing sudden death in these patients. Most important is the depolarizing current that accompanies calcium efflux from the cytosol via the sodium/calcium exchanger, which is increased by the reversion to the fetal phenotype seen in cardiac myocytes from failing hearts.<sup>20</sup> Al-

though there is some rationale for trying to inhibit the sodium/calcium exchanger, thereby reducing the depolarizing currents that cause afterdepolarizations and triggered activity, I believe that success in this effort would represent a Pyrrhic victory, because the resulting calcium overload would accelerate myocardial cell death and so worsen prognosis in these patients. A potentially more promising approach would be to reverse the loss of sarcoplasmic reticulum that accompanies the reversion to the fetal phenotype; in fact, efforts are already under way to test this approach in patients with end-stage heart failure.<sup>21</sup> I am afraid, however, that costs and risks will preclude this approach for this large population. For this reason, I predict that for the next decade implantable cardioverter-defibrillators will remain central to preventing arrhythmic deaths in these patients.

### AUTONOMIC BIOLOGY

Gary Francis and Wilson Tang set the stage for developments in this field when they describe how, at the beginning of the 20th century, the autonomic nervous system was believed to consist of two opposing arms: sympathetic and parasympathetic. The simplicity of this early view is reminiscent of the atomic structure I was taught in the early 1940s (protons, electrons, neutrons, and for a bit of “spice” the newly discovered positron), but which has now been replaced by an increasing number of subatomic particles, forces, and other arcania. Similarly, a growing list of specialized autonomic nerves, receptors, and receptor subclasses, neurotransmitters, and other components has added a cacophony of new mediators, whose names are both logical and weird, to known autonomic signaling systems. We have become aware that

peptides like endothelin, vasopressin, neuropeptide Y, adrenomedullin, leptin, ghrelin, cytokines, and growth factors; the arginine derivative agmatine; prostaglandins, which are synthesized from fatty acids; the steroid hormone aldosterone; and even nitric oxide, a free radical gas, have important effects on the heart and vascular system. We are also beginning to learn how interwoven networks of intracellular signal transduction systems can alter the clinical manifestations of cardiovascular disease when extracellular messengers modify both the reactivity and structure of the heart and blood vessels.

I cannot predict which of the known, not to mention “yet-to-be discovered” signaling systems will turn out to be important for cardiovascular disease, but I suspect that *all* will be found to have important actions in some individual patients. Clinical studies of drugs that modify these systems have already provided a number of important surprises, such as the improved prognosis in patients with heart failure who receive  $\beta$ -adrenergic and aldosterone blockers. Unfortunately, other surprises have been less pleasant, notably the excess mortality when patients with chronic heart failure are treated with inotropic drugs that increase cellular levels of cyclic AMP. It is too risky to try to speculate how modification of any of these systems will affect individuals with cardiovascular disease, but I feel safe in predicting that there will be additional surprises when therapies that modify these and other signaling systems are tested in humans.

### CARDIAC SURGERY

There are several reasons why the remarkable success of cardiac surgery described by Robert Litwak is not likely to be repeated during the



next decade. In the first place, the number of patients eligible for surgical repair of cardiac abnormalities is decreasing. The changing nature of heart disease, notably the rapid decline in rheumatic valvular disease, coupled with increasingly early repair of congenital malformations, has virtually eliminated the reservoir of cardiac abnormalities that are amenable to surgical correction in the adult population. Furthermore, a growing number of these patients can be treated using new percutaneous approaches. Finally, new knowledge of cell signaling, by adding to available therapeutic options, will reduce the need for surgical treatment, as is already apparent in the ability of statins and ACE inhibitors to slow progression of coronary artery disease and other complications of atherosclerosis.

### GENETICS AND MOLECULAR BIOLOGY

The concluding section of Sir David Weatherall's article, headed "The Future," highlights the importance of genetics and molecular biology for the future of cardiology. These descriptions of the role of genetic factors in the pathophysiology and clinical manifestations of disease, and the influence of genetic polymorphisms on the response of individual patients to specific therapy, are similar to predictions made in the present article. I have no doubt that the impact of genetics and molecular biology on patient care during the coming decade will be enormous.

I expect that growing recognition of individual responses to disease and drugs will dampen the current enthusiasm for "evidence-based medicine," where the results of large randomized clinical trials dominate clinical decision-making. These trials, while invaluable in telling us

how a given approach can be expected to operate in a population, are limited in their ability to tell us what will happen to an individual patient. I therefore expect the focus in patient care to shift back to the more traditional "physiologically-based medicine" that views each patient as a unique entity. This change in emphasis would represent a paradigm shift of the magnitude described by Thomas Kuhn,<sup>22</sup> as it would no longer be feasible to generate optimal diagnostic and therapeutic plans by viewing patients simply as members of a large database. Instead, optimal decision-making would require integration of a careful history, detailed physical examination, and thoughtful *and selective* use of laboratory data from each patient. I have italicized "selective" because, as noted by Weatherall, vast quantities of new genomic and proteomic data are being added to the large existing body of anatomical, biochemical, and physiological data as we move into the new era of individualized "postgenomic medicine." Reliance on therapy directed to the needs of individual patients will also make it difficult to develop "blockbuster" drugs that are appropriate to deal with the diverse pathophysiology in large populations of patients.

### CONCLUSIONS

The changes in cardiology predicted in this article can be expected to have a major impact on aspects of medicine other than diagnosis and treatment. Most important are medical economics and medical education, which are especially vulnerable to stresses that would occur if only a few of my predictions were correct. In fact, both are already experiencing severe stress because of the enormous progress, documented in this anniversary issue, that has occurred during the past decades.

The cost of health care can be both increased and decreased by the advances I have anticipated in this article. An optimist might predict that these advances will lead to savings as it is now clear that careful outpatient management of heart failure reduces expenditures, largely by keeping these patients out of hospital. The optimist would also point out that genetic screening to determine an individual's susceptibility to sudden death would be less expensive, and probably more accurate, than electrophysiological testing. The pessimist, on the other hand, might say that expenditures would be increased because physicians tend to overuse new tests, procedures, and treatments, of which there will be many. I cannot predict the future costs of health care delivery because these economics differ markedly in various countries, and because expenditures are heavily influenced by politics, which follow rules that are incomprehensible to most physicians, including myself.

The flood of new information that is now sweeping over cardiology poses a daunting challenge for medical education. Much as inflating a balloon separates the points on its surface, expansion of both basic and clinical knowledge is drawing preclinical and bedside teaching away from one other. This is a major reason why it has become increasingly difficult to identify teachers competent in both basic science and clinical medicine, which leads to the common complaint that medical students are taught basic science by professors who know little about the clinical problems relevant to their laboratory research, and clinical medicine by professors who know little about the basic sciences that can explain what is wrong with their patients. In the United States, this has led to a sea change in med-

ical education since the 1970s, when basic science professors were often physicians, and most full-time clinical teachers had at least some meaningful training in a research laboratory. Today, in contrast, most basic science teachers are molecular biologists with no clinical training, and few clinical teachers have had any research experience. Exposure of students to the scientific foundations of modern medicine is also being reduced by curricular changes that, at least in the United States, are increasing the time spent in courses and electives that highlight social aspects of medicine, at the cost of decreasing the time allocated to teaching the basic sciences.

Sadly, these considerations lead me to a final prediction; that economics and a shortage of appropriately educated physicians will deny many patients access to new knowledge. This prediction does not, however, describe a new situation; in 1964, my father wrote:

As far as application of new knowledge is concerned, no serious gap appears to exist between the laboratory and clinical research... [instead] there appear to be difficulties in bringing new information to the attention of the physician in daily practice. The gap thus appears to be between the medical center and the community hospital rather than between the laboratory and the physician in the medical center...<sup>23</sup>

Looking back over the 50 years since I graduated from medical school, I believe that deficiencies in both undergraduate and postgraduate medical education have widened the distance between what is known about disease and what is prescribed for our patients. As we move toward 2016, current trends indicate that an increasing number of physicians will have had neither an adequate opportunity to learn the scientific foundations of modern

medicine nor enough time away from revenue-generating activities to remain up to date in this rapidly changing profession. I am therefore afraid that ten years from now an increasing number of patients will not have access to the full benefits of the physiologically based approach to cardiovascular medicine that will be made possible by the advances described in this article.

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