

THE SIMON DACK LECTURE

Cardiology: The Past, the Present, and the Future

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THE PAST

The Birth

Although there is abundant evidence that the critical importance of the heart was appreciated during prehistory as well as in ancient times, its function was first defined by William Harvey, a British physician. The inspiration for his seminal discovery, considered by historians as one of the scientific triumphs of the Renaissance, came from the school of great anatomists of the University of Padua, where Harvey studied medicine and from which he graduated four centuries ago, in 1603. In his earth-shaking publication in 1628, *De Motu Cordis*, Harvey stated: "It has been shown by reason and experiment that by the beat of the ventricles blood flows through the lungs and it is pumped to the whole body. There it passes through pores in the flesh into the veins through which it returns from the periphery...finally coming to the vena cava and right auricle...It must then be concluded that the blood in the animal body moves around in a circle continuously, and that the action or function of the heart is to accomplish this by pumping. This is the only reason for the motion and beat of the heart" (1).

Commencing 275 years after Harvey's publication, the 20th century witnessed a series of grand achievements in cardiology that have been critical to the development of the specialty. Ten of the most notable are discussed.

Ten Great Achievements of the 20th Century

Electrocardiography. Although diseases of the heart were recognized well before the 20th century, and whereas great physicians such as William Osler, James Hope, Austin Flint, and Pierre Potain wrote extensively and perceptively about physical examination of the heart and cardiovascular disease, the birth of modern cardiology can be dated to one century ago, when Willem Einthoven (Fig. 1A), a professor of physiology in the small Dutch town of Leiden, first recorded a human electrocardiogram and gave birth to a new specialty. Einthoven devised the first string galvanometer to record the electrical activity of the heart (2). His work was built on the background provided by the German physiologists von Koelliker and Muller (3) and the British physiologist Augustus Waller (4). Einthoven was appropri-

ately rewarded with a Nobel Prize in medicine. Figure 1B shows a reproduction of one of the first human electrocardiograms recorded with a string galvanometer. Einthoven himself described various arrhythmias, including bigeminy, atrial flutter and fibrillation, and "P mitrale," as well as left and right ventricular hypertrophy. Soon others utilized electrocardiography to detect myocardial ischemia and infarction. Indeed, the electrocardiogram became so important that in a few years cardiologists actually became defined as physicians who could interpret electrocardiograms.

Cardiac catheterization. The noted 19th-century French physiologist Claude Bernard catheterized and measured pressures in the various cardiac chambers and great vessels of the animal heart (5). The first catheterization of the living human heart was performed by a young surgeon, Werner Forssman (Fig. 2A), (on himself!) in 1929 in Eberswald, Germany. Forssman's goal was to find a safe way to inject drugs and contrast material into the right atrium for cardiac resuscitation (6). In 1941, Andre Cournand (Fig. 2B) and Dickinson Richards (Fig. 2C) at Columbia University and Bellevue Hospital in New York began the systematic exploration of normal and abnormal hemodynamics (7,8). They recorded intracardiac pressures and cardiac output in normal subjects and in patients with many forms of congenital and acquired heart disease. These investigators established cardiac catheterization as the basis for defining normal and disordered function of the cardiac pump and as a premier diagnostic technique in cardiology. Forssman, Cournand, and Richards were also awarded the Nobel Prize.

Cardiac catheterization opened the way for the study of the mechanical function of the heart in a manner analogous to what electrocardiography had done for its electrical function a half-century earlier. Indeed, by the late 1950s, in what was the dawn of subspecialization, many cardiologists were already beginning to concentrate on one or the other of these two important approaches and, accordingly, were dubbed "electricians" or "plumbers."

Coronary angiography. Cardiac catheterization paved the way for coronary arteriography, which was first performed by Mason Sones (Fig. 3A) at the Cleveland Clinic in 1958 (9). Coronary arteriography, when combined with left ventriculography, led to the diagnosis and then the elucidation of the natural history of coronary artery disease. This technique made possible coronary revascularization, first surgical and then percutaneous.

Cardiovascular surgery. Although there were a number of early scattered attempts to operate on the human heart,

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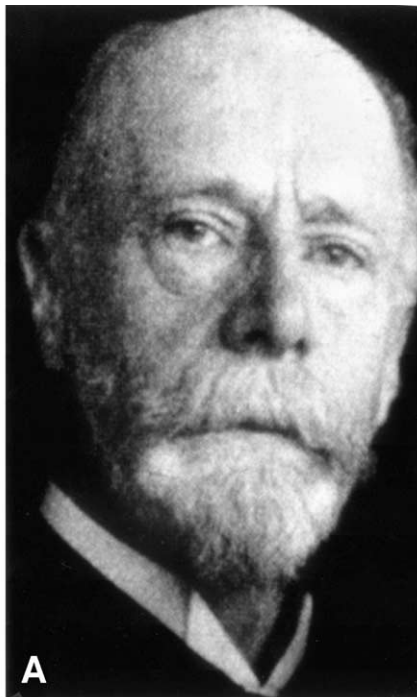


Figure 1. (A) Willem Einthoven. (B) A human electrocardiogram (2).

modern cardiovascular surgery was first applied systematically in 1938, when Robert Gross (Fig. 2D) at Harvard and Boston's Children's Hospital successfully closed a patent ductus arteriosus (10). In 1953, John Gibbon (Fig. 2E) at Thomas Jefferson Hospital in Philadelphia performed the first open-heart operation using cardiopulmonary bypass when he successfully closed an atrial septal defect in an 18-year-old girl (11). The development, successful application, and refinement of open-heart surgery required the close collaboration of surgeons, engineers, cardiologists, anesthesiologists, and experts in blood coagulation. The development of the heart-lung machine also appears to have been among the first of many important successful academic-industrial collaborations in cardiology, as Gibbon's design led to the construction of the heart-lung machine by IBM engineers.

Invasive cardiology. Building on the work of two pioneers in radiology, Charles Dotter and Melvin Judkins, Andreas Gruentzig (Fig. 3B), who was trained in cardiology, peripheral vascular disease, and radiology, burst on the world of cardiology in 1977 (5,12,13). By developing percutaneous transluminal coronary angioplasty, in one bold stroke he established a new subspecialty: interventional cardiology.

Gruentzig expanded the use of the cardiac catheter, until then a diagnostic tool, into a powerful therapeutic device. Balloon angioplasty was followed by stenting with bare metal stents, which are now being replaced by drug-eluting stents. In addition to coronary stenosis, almost any abnormal obstruction in the heart and circulation can now be successfully opened, and many abnormal openings can be successfully closed using catheter-based techniques.

The coronary care unit. Before 1961, patients with acute myocardial infarction who were fortunate enough to reach the hospital were treated largely with benign neglect. They were sedated and placed at bed rest, as far removed physically as possible from the noise and excitement of the nurses' station. The early mortality of acute myocardial infarction patients who reached the hospital exceeded 30%. In 1961, Desmond Julian (Fig. 3C), then a registrar in cardiology at the Royal Infirmary in Edinburgh, Scotland, articulated the concept of the coronary care unit (14). This important development rested on four pillars: 1) continuous electrocardiographic monitoring with arrhythmia alarms; 2) cardiopulmonary resuscitation with external ventricular defibrillation; 3) the clustering of myocardial infarction patients in a discrete unit of the hospital where skilled personnel, drugs, and equipment were available; and 4) perhaps most important, a change in policy that permitted, indeed mandated, trained nurses to initiate resuscitation. With institution of coronary care units, the in-hospital mortality of acute myocardial infarction was immediately reduced in half, and in a little more than a year these units had spread across the world like wildfire and soon became a requirement for hospital accreditation.

Cardiovascular drugs. In the 1960s, while working for the British pharmaceutical company Imperial Chemical Industries, James Black (Fig. 4A) developed beta-blockers and was later honored for this and other discoveries with the Nobel Prize (15). These remarkable agents have benefited patients with acute and chronic myocardial ischemia, heart failure, a variety of arrhythmias, and hypertension. The first angiotensin-converting enzyme inhibitor, captopril, was isolated in the 1970s by Cushman (Fig. 4B) and Ondetti (Fig. 4C), working at the Squibb (now Bristol Myers Squibb) laboratories. Angiotensin-converting enzyme inhibitors have become cornerstones in the management of heart failure and hypertension (16). The first HMG-CoA reductase inhibitor (statin) was isolated by Akira Endo (Fig. 4D) of Sankyo Pharmaceuticals in 1976 (17), and was built on the Nobel Prize-winning work on the low density lipoprotein cholesterol pathway by Brown and Goldstein (18). Statins reduce substantially the incidence of coronary events, and prolong life both in subjects with and without hypercholesterolemia. Taken together, beta-blockers, angiotensin-converting enzyme inhibitors, and statins have prolonged and improved the lives of tens, perhaps hundreds, of millions of patients worldwide.

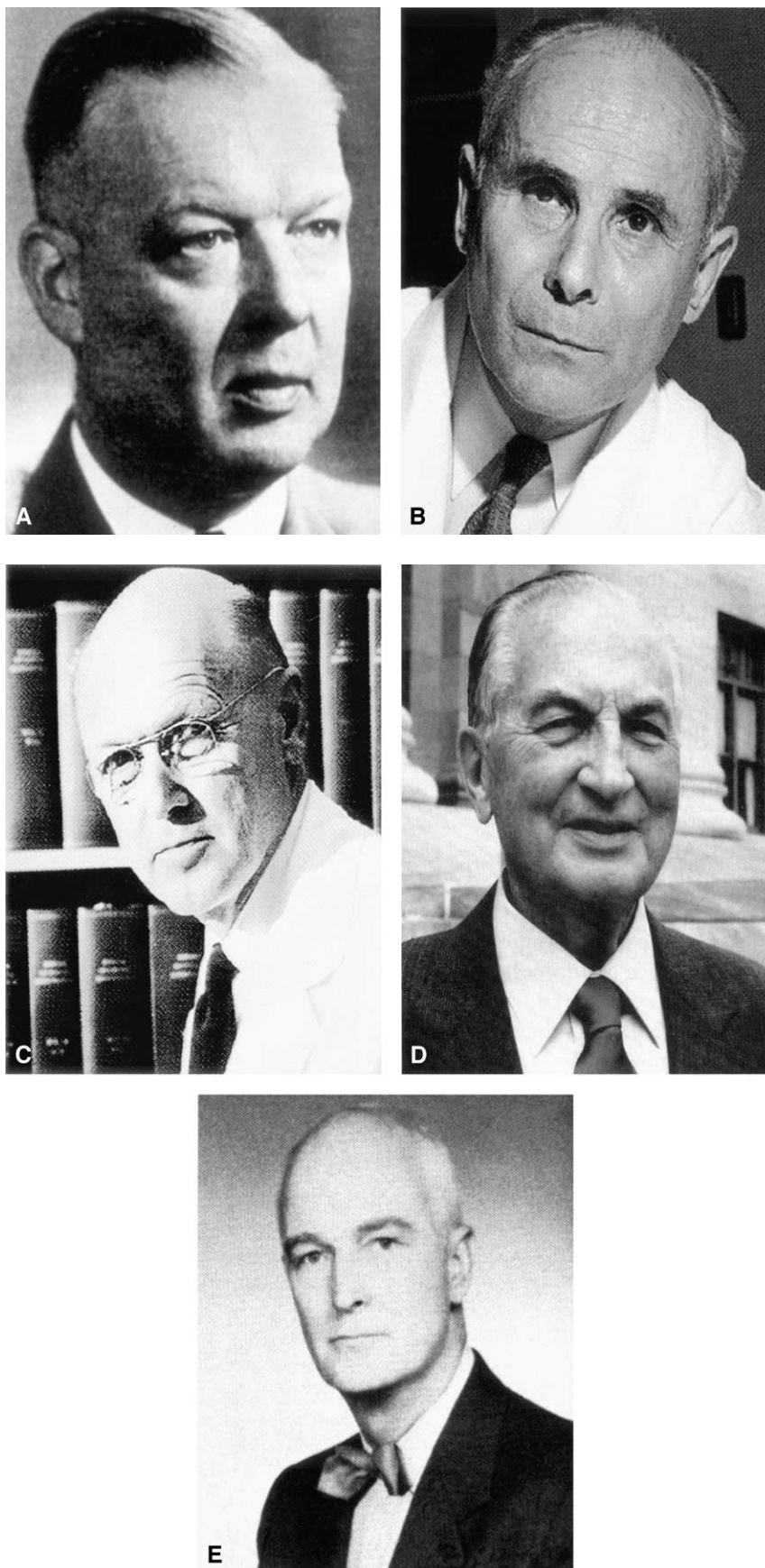


Figure 2. (A) Werner Forssman; (B) Andre F. Cournand; (C) Dickinson W. Richards; (D) Robert E. Gross; (E) John H. Gibbon, Jr.

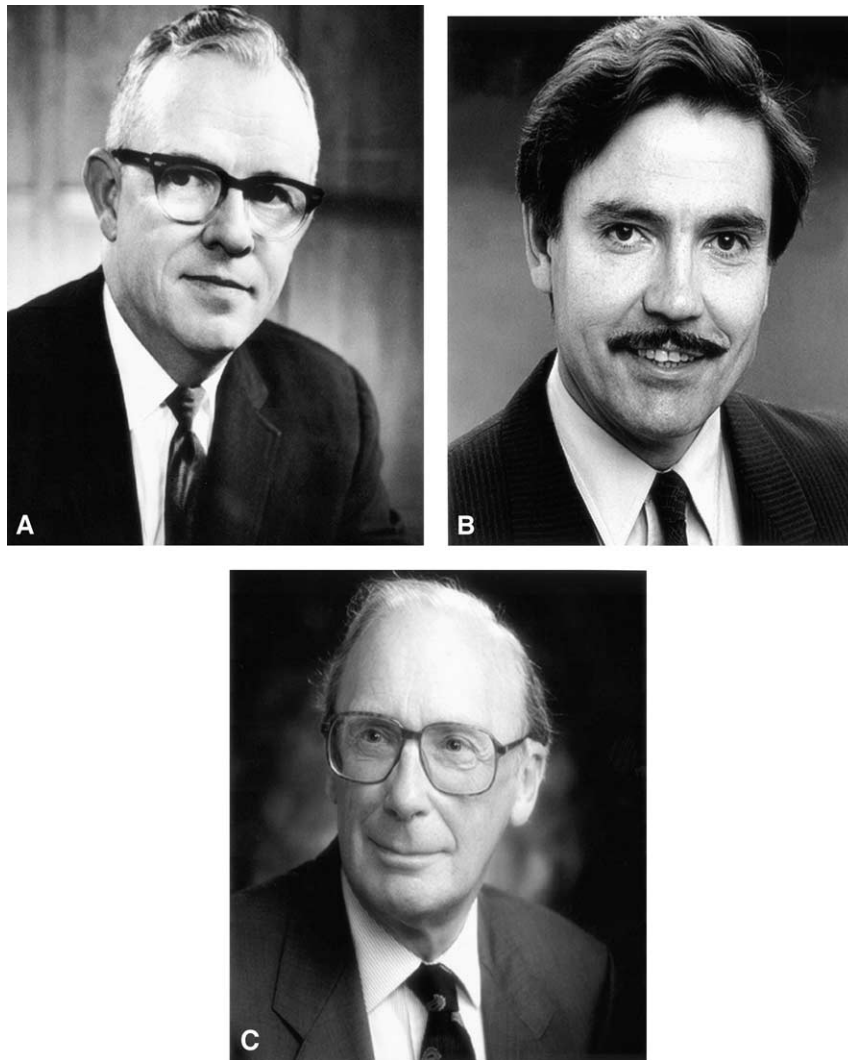


Figure 3. (A) F. Mason Sones, Jr.; (B) Andreas R Gruentzig; (C) Desmond G. Julian.

Preventive cardiology. In 1944, Dr. Paul Dudley White (Fig. 5A), at Harvard and the Massachusetts General Hospital, often referred to as the father of American cardiology, pioneered the concept of cardiovascular prevention (19). Stimulated by White's influential advocacy, in 1948 the National Heart Institute (now the National Heart, Lung, and Blood Institute) established the Framingham Heart Study, the first prospective population-based cohort study that focused on heart disease. The study investigators developed the concept of coronary risk factors, and by 1961 in a now classic paper by Kannel et al. (Fig. 5B) (20), they had identified hypertension, smoking, and electrocardiographic evidence of left ventricular hypertrophy as such risk factors. Based on these (and other subsequently identified) risk factors, the primary and secondary prevention of coronary artery disease has been responsible for almost one-half of the dramatic 70% decline in age-adjusted deaths from coronary artery disease that has occurred since their publication.

Echocardiography. One of the most fruitful collaborations in the history of cardiology was between Inge Edler, a Swedish cardiologist, and Helmuth Hertz (Fig. 6), a Swedish physicist. In 1952, they adapted for human use a sonar device for detecting submarines in World War II and recorded echoes from the walls of the heart of one of the coinventors, "Hertz' heart," and thereby launched the field of echocardiography (21). These investigators provided continuous recordings of the movements of the heart walls and of the normal and diseased mitral valve. The visualization of the heart and great vessels by noninvasive imaging, first by echocardiography and subsequently by a variety of nuclear techniques, as well as by advanced radiologic techniques (computed tomography and magnetic resonance imaging) now makes many invasive diagnostic procedures unnecessary. By permitting sequential testing, such imaging allows the optimal timing of interventions and assessment of the response to treatment. Noninvasive imaging represents

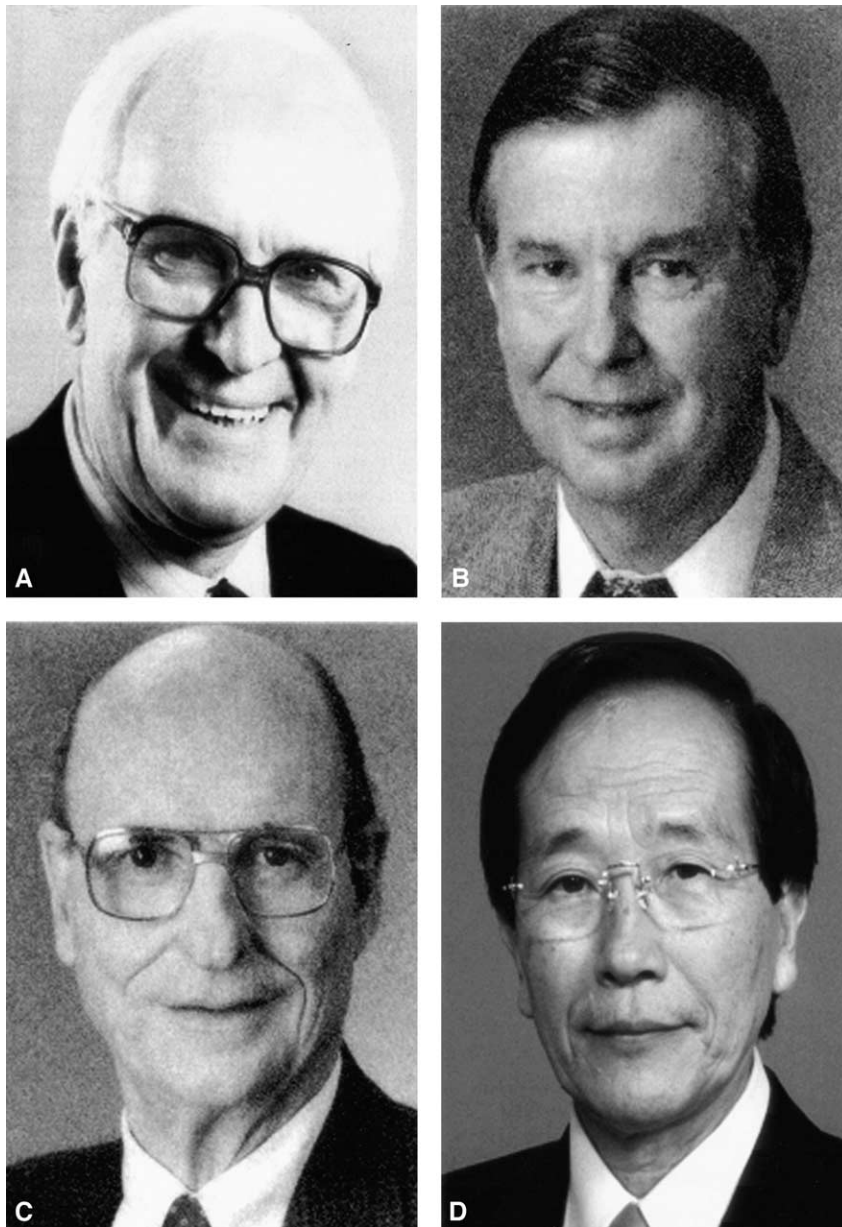


Figure 4. (A) James W. Black; (B) David W. Cushman; (C) Miguel A. Ondetti; (D) Akira Endo.

an enormous advance both in the diagnosis of heart disease and in the care of cardiac patients.

Pacemakers and internal defibrillators. Building on the work of electrophysiologists in the first half of the 20th century, in 1952 Paul Zoll (Fig. 5C), a cardiologist at Harvard and Beth Israel Hospital, developed the first external pacemaker (22) and, in 1959, Elmquist and Senning at the University of Zurich (23,24) reported on the first successful use of an internal pacemaker. In 1970, Michel Mirowski (Fig. 5D), an Israeli cardiologist with training in electrical engineering working at Sinai Hospital in Baltimore, invented the implanted cardioverter-defibrillator (25), and a decade later reported on its successful clinical application (26). A steady drumbeat of successful clinical trials has greatly extended the indications for this important

device, both in the secondary and primary prevention of sudden cardiac death (27).

Key Lessons From the Past

It should be noted that the achievements described here have been selected from many others that also have had major impacts on cardiology. Some of these are included in a recent review by Mehta and Khan (28).

What can we learn when we step back and view these spectacular achievements? At least three points are notable. First is that these achievements did not develop *de novo*; they were built on many decades of research, usually by basic scientists and engineers, the unsung heroes of progress in cardiology. Second, in almost every instance, these advances came from interdisciplinary collaborations, such as between a

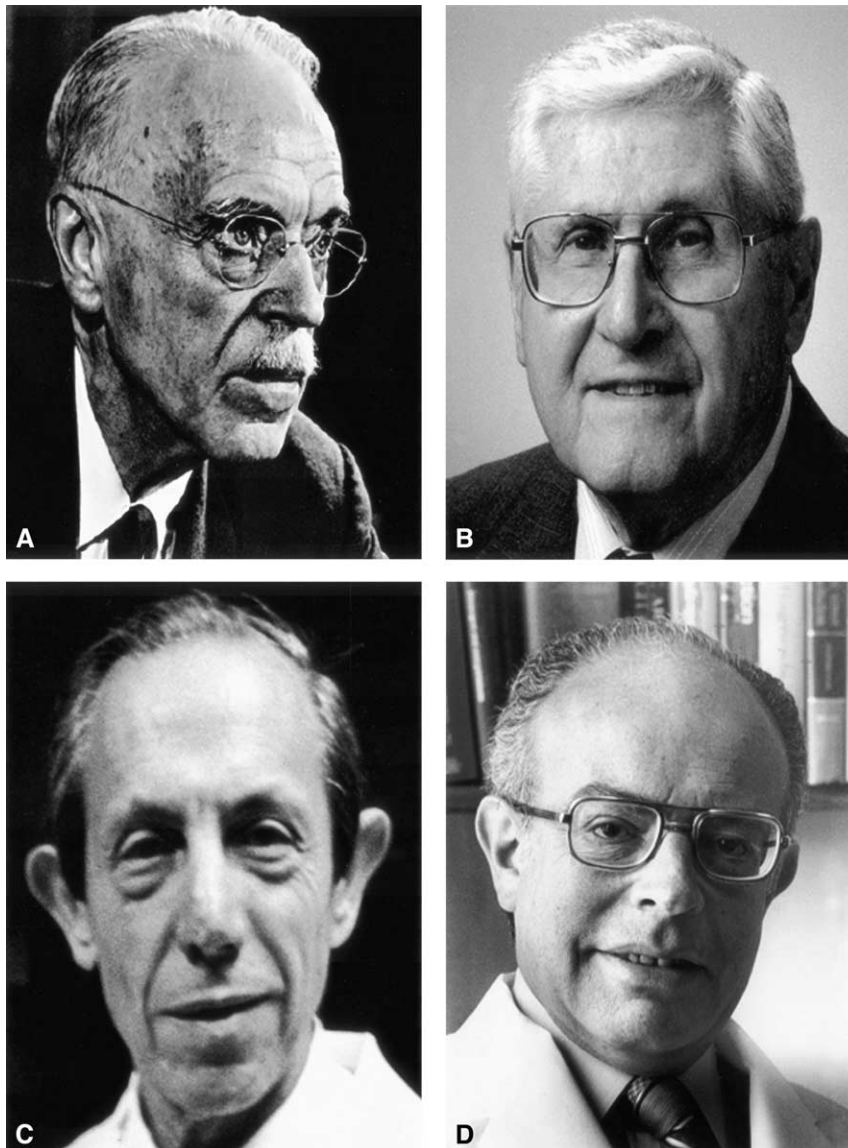


Figure 5. (A) Paul D. White; (B) William B. Kannel; (C) Paul M. Zoll; (D) Michel Mirowski.

cardiologist and physicist in the case of echocardiography, or between epidemiologists and cardiologists in the Framingham Heart Study. Successful collaboration between academia and industry has also been vital to many of these advances. Examples are the first heart-lung machine and cardiac drugs, as well as catheters and electrical devices. Third, these great achievements are international triumphs; investigators in eight countries on three continents are among those mentioned and pictured here. Countless others from dozens of nations have contributed importantly to contemporary cardiology.

THE PRESENT

As a result of the enormous achievements just enumerated, and many others, cardiology is now a vibrant, robust specialty of which we can be justifiably proud, and that is providing enormous benefits to society. However, contemporary cardiology faces several major challenges.

Subspecialization. The growing technical complexities of cardiologic diagnosis and treatment, and the necessity of maintaining very high levels of skill in order to optimize patient care, have led to increasing subspecialization. Contemporary cardiology is composed of multiple subspecialties, many with their own training requirements, professional societies, and journals. In adult medical cardiology alone, there are subspecialists in invasive cardiology, in noninvasive diagnosis, and sub-subspecialists in each of the major imaging modalities. There are electrophysiologists, subspecialists in extracardiac vascular disease, hypertension, lipidology, care of patients with acute coronary syndromes, and heart failure, as well as in prevention and rehabilitation. Others are certain to follow. Pediatric cardiology, cardiovascular surgery, and cardiovascular radiology are now following the lead of adult cardiology and are developing subspecialties of their own.

Undoubtedly, subspecialization has enormous benefits; it



Figure 6. Helmhuth Hertz (left) and Inge Edler (right) with the first echocardiograph.

leads to greater expertise and thereby greatly improves patient care, teaching, and research. However, it also fragments care. Subspecialists might be likened to virtuosi playing different instruments in the orchestra. But one may ask: where is the conductor—the physician who oversees and integrates the care of the cardiac patient? Skilled subspecialists can perform complicated procedures successfully and at relatively low risk, but may not always pay equal attention to the more fundamental question of whether the procedure should be performed in the first place.

The subspecialist approach tends to be most effective in young patients with clearly defined diseases, for example, the electrophysiologist diagnosing reentry tachycardia and ablating the abnormal pathway in a young adult. However, older patients often have more complex conditions that involve disturbed structure and function of several components of the cardiovascular system, and they usually have a number of comorbid noncardiac conditions. The elderly, the most rapidly growing segment of the population, require more than expert subspecialists; their care requires a broad multidisciplinary approach. There is a great scarcity of the aforementioned integrators of cardiac care (the “conductors”) and there is insufficient reimbursement for their important contributions to patient care. For example, it is now possible for an experienced surgical team to perform repeat coronary artery bypass grafting on an octogenarian with diabetes, left ventricular and renal dysfunction, and advanced multivessel native coronary artery and graft disease at a risk that is acceptable to the patient and family. Complex presurgical evaluation, including testing for the viability of akinetic myocardium, is conducted routinely in such patients. Although such a patient may have early dementia, careful assessment of cognition is rarely carried out, and the results of formal cognitive testing are rarely considered in the decision whether to proceed with surgery.

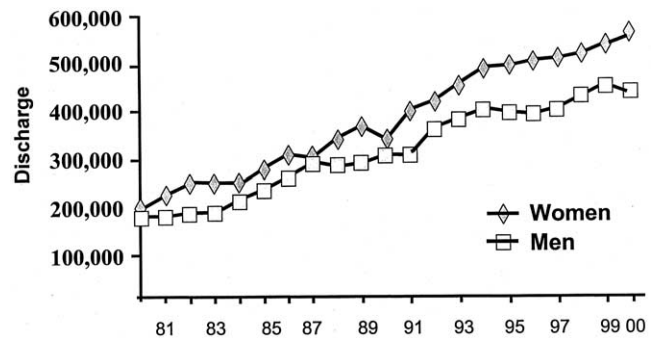


Figure 7. Heart failure hospitalizations. From: Heart Disease and Stroke Statistics: 2003 Update. Dallas, TX: American Heart Association, 2003.

Disease prevention. Despite the dazzling technical advances in cardiology, risk factor reduction and disease prevention in the population are inadequate. Although cardiologists now do quite well in this area, most patients with cardiac disease or risk factors now, and in the foreseeable future, will receive their cardiac and preventive care not from cardiologists, but from primary care internists and family practitioners. The latter usually *know* when aspirin, beta-blockers, angiotensin-converting enzyme inhibitors, and statins are indicated. But a disturbing fraction of patients who require these life-prolonging medications are not prescribed them or fail to take them. Individual cardiologists and cardiovascular organizations such as this College must assume the lead in correcting this unsatisfactory situation.

Costs of cardiac care. After decades of dire predictions, a crisis in the payment for healthcare is now squarely upon us, and the costs of care are spiraling out of control. The fruits of our research, the newest diagnostic devices and therapeutic strategies in cardiology, are prominent contributors to the rapidly escalating costs. Further developments in cardiology that are now in the wings might “break the bank.” The solution to this vexing problem must not be left to legislators or regulators. Instead, cardiac specialists themselves must develop diagnostic and therapeutic strategies that are evidence based, as with the well-developed ACC/AHA guidelines program (29), but they must also be more mindful of limited resources.

Cardiology work force. Ten to 15 years ago armies of well-paid consultants looked into their collective crystal balls and prophesied that primary care physicians serving as

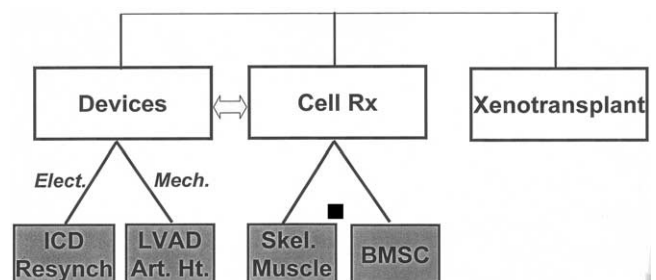


Figure 8. The near-term future of therapy for advanced heart failure. Art. Ht. = artificial heart; BMSC = bone marrow stem cells; ICD = implantable cardioverter-defibrillator; LVAD = left ventricular assist device.

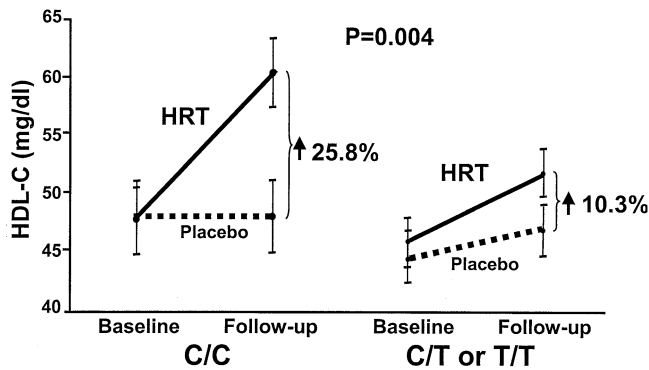


Figure 9. Effect of hormone replacement therapy (HRT) on high-density lipoprotein cholesterol (HDL-C) by genotype. Modified from (41).

gatekeepers in a capitated system would become the model for medical care in the U.S. This approach would reduce costs by keeping patients away from specialists for as long as possible and thereby reduce the need for specialists. Cardiology training programs were downsized at the very time that the needs for cardiologists were expanding. As a consequence, there is now a critical and growing need for well-trained cardiac specialists to apply the new advances in a timely manner. This important issue, too, must now be addressed by organized cardiology.

THE FUTURE

The near term (2003 to 2020). In the near term, until approximately 2020, it is likely that there will be continuing subspecialization in the pursuit of technical virtuosity and clinical excellence. This situation will at first both aggravate the escalation of costs and intensify the workforce shortage. At the same time, preventive measures based on patient characteristics, such as phenotypes, will expand. New phenotypic risk markers, of which the C-reactive protein may be considered to be a prototype (30), will be helpful in this regard. The prevalence of heart failure will grow. There will be increasing application of pharmacogenomics.

Heart failure is the last great battleground in cardiology.

Figure 7 shows the ominous increase in the number of annual discharges of heart failure patients from U.S. hospitals. In the near-term future the management of heart failure is likely to advance along three paths (Fig. 8). The first will come from a great expansion and broadening of the indications for electrical device therapy such as cardiac resynchronization (31) and implanted cardiac cardioversion and defibrillation (27). Mechanical assistance for long-term management is improving steadily (32). Innovative efforts are underway to coax the failing heart to recover following the removal of a left ventricular assist device in so-called “bridge to recovery” therapy (33). Cell therapy represents a very promising approach. Two modes are now under active investigation: the injection of cultured autologous myoblasts (34) and the use of autologous bone marrow-derived stem cells (35). For patients with acute severe heart failure, mechanical ventricular assistance is likely to be employed as bridging therapy while cell therapy regenerates the heart. Cardiac xenotransplantation (36) might become a reality, and this could change drastically the entire landscape of the management of severe heart failure.

Pharmacogenomics represents the “low-hanging fruit” of the genetics/genomics revolution. The goal of this emerging field is to identify patients likely to exhibit adverse effects and those most likely to respond well to specific drugs. One example of how pharmacogenomics could influence cardiology practice is in the use of warfarin. The hepatic microsomal enzyme CYP2C9 is required for the metabolism of this anticoagulant. There are three variants of the gene that encodes this enzyme (37): the so-called wild type occurs in approximately 70% of the population and the other two variants combined occur in the remainder. The latter cause a defect in warfarin metabolism that is associated with markedly reduced requirements of maintenance doses (38), a longer period until stable dosing is achieved, and a more than doubling of the rate of serious bleeding, even after stable dosing has been achieved at these lower doses (39). Screening for these variants could improve

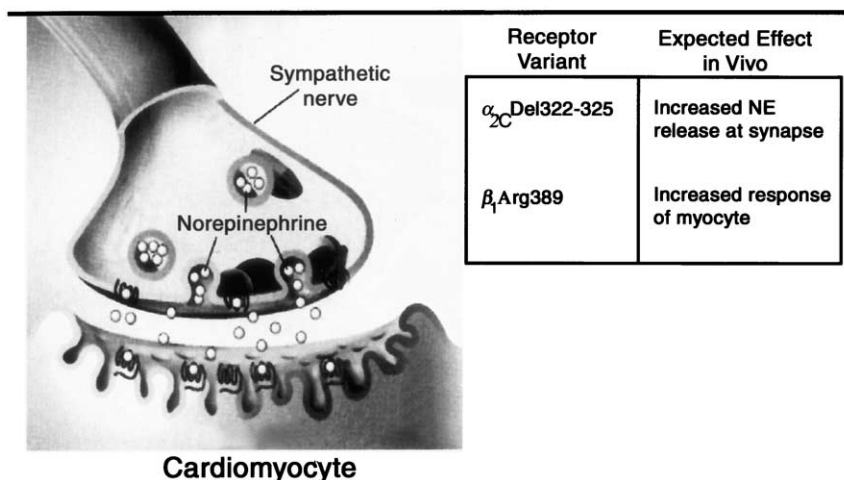


Figure 10. Adrenergic receptor variants in heart failure. Modified from (47). NE = norepinephrine.

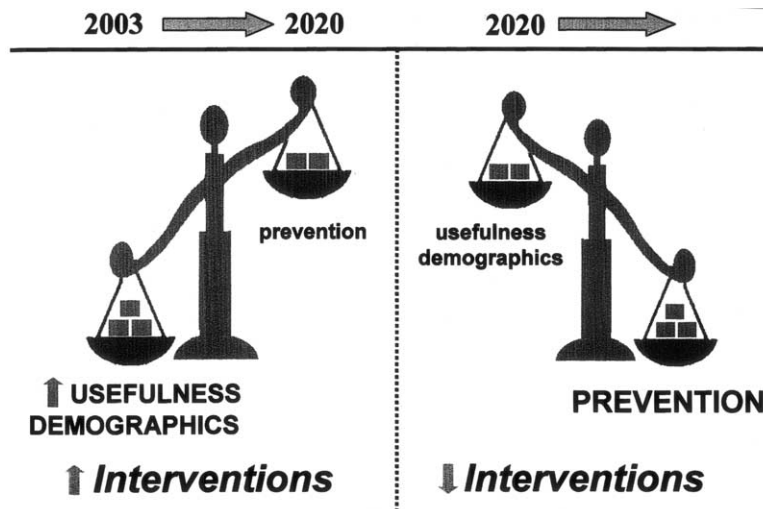


Figure 11. Prediction of the relative impact of interventions and prevention.

dosing and surveillance and greatly improve identification of patients who do not tolerate warfarin and who would therefore become prime candidates for the new, expensive oral anticoagulants that will soon be available. Conversely, and equally importantly, such screening could also identify the many patients who are likely to tolerate the inexpensive warfarin. Once commercialized, this genetic test, conducted only once, could improve the care of the hundreds of thousands of patients who require chronic anticoagulation, and significantly reduce the cost of their care.

The adverse effects of hormone replacement therapy in postmenopausal women has received enormous medical and public attention since the publication of the results of the Women's Health Initiative (40). Vague recommendations are made to physicians, and by them to tens of millions of women. It is unsatisfactory to expect primary care physicians to analyze and interpret the totality of evidence on this complex issue and in the final analysis, ask every woman to decide this matter for herself. The ability to raise high-density lipoprotein cholesterol (HDL-C) concentration has been a major impetus for hormone replacement therapy. However, HDL-C is not elevated uniformly by hormone replacement therapy and the differences in responses appear to be strongly influenced by the genetic background of the woman. There are two variants of the gene that encodes the estrogen receptor alpha, termed C and T. Fifteen percent of women have the CC genotype, and with hormone replacement therapy this subgroup showed a robust 26% increase in HDL-C (Fig. 9) (41). Epidemiologic considerations suggest that such an elevation could reduce the development of coronary events by half. On the other hand, little change in HDL-C was seen in the 85% of women with the other two genotypes (TT or CT). Therefore, the subgroup of postmenopausal women with the CC genotype are logical candidates for consideration of hormone replacement therapy.

Another genetic variant, the prothrombin 20210G-A variant, has been shown to be associated with elevated concentrations of circulating prothrombin and an increased risk of venous thrombosis (42). In hypertensive women with this

variant who receive hormone replacement therapy, the risk of myocardial infarction was increased 11-fold (43)! Pharmacogenomics should lead to more rational use of these agents and deal with what is now a vexing public health problem.

The long-term future (2020 and beyond). Prediction beyond 2020 is more problematic. However, it is very likely that advances in genetics and genomics will allow the subclassification of disease, which will lead to gene-informed therapy, that is, "smart" therapy. Also, genetic identification of the future development of risk factors will lead to gene-informed personalized prevention: "smart" prevention. Several examples illustrate these possible strategies. Alpha-adducin is a cytoskeletal protein involved in cell signaling. A variant of the alpha-adducin gene is present in about one-third of hypertensives, and leads to excessive sodium re-absorption by distal renal tubule cells. There is now considerable discussion about the role of diuretics in the treatment of hypertension (44,45). Psaty et al. (46) reported that in two-thirds of hypertensives with the most common, so-called wild-type, genotype of the alpha-adducin gene, diuretic treatment did *not* reduce the risk of myocardial infarction or stroke. In the other third with the variant genotype, diuretic treatment was associated with a reduction of myocardial infarction or stroke by half. If this work is confirmed, it could lead to the screening of hypertensives for this variant in selecting antihypertensive therapy, an example of gene-informed therapy. It might prove useful even to screen normotensive subjects for this variant and to treat them prophylactically with a salt-restricted diet or even a diuretic, leading to gene-informed prevention.

Two synergistic variants for adrenergic receptors have been described (47). A variant of the α_{2c} -adrenergic receptor increases norepinephrine release from sympathetic nerve endings, whereas a variant of the β_1 -receptor increases the response of myocytes to norepinephrine (Fig. 10). In African-American subjects with both of these gene variants, the risk of development of hypertension was increased more than 10-fold, making these patients prime candidates for very early therapy with an α_2 -adrenergic agonist and β_1 -blocker. Perhaps even

prophylactic therapy in subjects with this combination of gene variants but without heart failure might be considered.

Some early examples of how genetics will enhance risk stratification for atherosclerosis are also available. The presence of specific variants of the genes for connexin 37 (resulting in changes in endothelial gap junctions) in men and in the genes for plasminogen activator inhibitor-1 (altered inhibition of fibrinolysis) and stromelysin-1 (associated with altered matrix metabolism) in women are associated with increased risk of myocardial infarction (48). Variants of an ATP-binding cassette transporter gene (ABCC-6) are associated with a more than four-fold increase in premature coronary artery disease (49). On the other hand, several gene variants (p22^{phx}, associated with vascular smooth muscle production of reactive O₂ species [48] and the toll-like receptor 4, associated with a diminished immune response [50]) are associated with reduced risk of atherosclerosis. These early observations point the way to gene informed prevention.

Intervention versus prevention. Figure 11 represents a prediction of the future use and impact of interventional and preventive cardiology. In the short-term future, until approximately 2020, many more useful interventions of all types (drug-eluting stents, more effective electrical and mechanical devices, cell therapy, perhaps xenotransplants) will become available. This will be accompanied by a great expansion of the population that can benefit from these interventions: a large increase in the elderly, in persons at high risk, including diabetics and the obese, and in those who have had a previous intervention. Simultaneously, there will be a greater focus on prevention, using progressively greater refinements of markers of inflammation and of plaque instability. However, the balance of these two influences will favor intervention and the number of procedures will continue to expand. Beyond 2020, interventions are certain to continue to become more useful, and they will continue to become simpler, more effective, and less expensive. However, the application of genetics and genomics to cardiovascular disease will tip the balance and the need for intervention will decline, at first gradually, then rapidly.

CONCLUSIONS

The principal role of the cardiologist will change from recognizing and managing established disease, as is the case today, to interpreting and applying genetic information in prevention and treatment in 2020 and beyond. The grand goal, of course, is to eliminate cardiovascular disease as a major threat to long, productive life. It is hoped this will be well underway by 2028, the 400th anniversary of William Harvey's discovery of the circulation and the 125th anniversary of Willem Einthoven's development of the string galvanometer.

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