1 Cardiovascular Disease: Past, Present, and Future

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THE BIRTH

Although the heart was recognized as a vital organ in early human history, its function was not understood but was widely debated over millennia. In 1628, William Harvey, a London physician (Fig. 1.1) who had trained in the great medical school in Padua, Italy, published a monograph, *De Motu Cordis, An Anatomical Treatise on the Motion of the Heart and Blood*,[1] which concluded simply: "The blood in the animal body moves around in a circle continuously, and the function of the heart is to accomplish this by pumping." Harvey based this conclusion on detailed anatomic studies that included the valves in the veins that appeared to permit blood to flow only toward the heart. He conducted experiments in humans and rabbits and then estimated cardiac output. Importantly, Harvey's research was the first major hypothesis-driven research in biology. Although his findings were not uniformly accepted during his lifetime, they are now considered to be one of the scientific triumphs of the high Renaissance, along with the works of Isaac Newton and Galileo Galilei.

Harvey's conclusion was buttressed by two findings. The first was the description of the capillary circulation in 1661 by Marcello Malpighi,[2] who identified this last anatomic link in the circulatory chain. The other, by Richard Lower in 1668, was the role of the pulmonary circulation in changing the color of the blood as it is exposed to the air in the lungs.[3]

Early Stirrings

In 1733, Steven Hales measured arterial and venous pressures in horses and other mammals.[4] "Direct" auscultation (placing the ear on the precordium) to hear the heartbeat was used later in the 18th century. Cardiac examination accelerated after 1823, when René Laennec, a French physician, described the stethoscope.[5] In his 1775 monograph on foxglove (digitalis), William Withering described its effectiveness in the treatment of patients with "dropsy," that is, edema, presumably due to heart failure (HF).[6] William Heberden described angina in 1772[7] and 40 years later the *first* paper in the *first* issue of the *New England Journal of Medicine* by John Warren, a Boston physician, discussed this symptom.[8] However, angina does not appear to have been recognized frequently.[9] In 1879, F.A. Mahomed described hypertension not associated with renal disease, the forerunner of what is now referred to as primary or essential hypertension.[10] Several important arrhythmias were described in the mid-to-late 19th century. These included severe bradycardia by Stokes in 1854 and ventricular fibrillation (VF) by MacWilliams in 1887.[11]

By the end of the 19th century, physiologists and clinicians were aware of electrical depolarization and repolarization of the heart and could recognize some cardiac arrhythmias by cardiac auscultation and palpation of the pulse. They also knew that hypertension could occur both in the presence and absence of advanced renal disease and could be associated with ventricular hypertrophy. They

FIGURE 1.1 William Harvey (1518-1657).

recognized congenital and valvular heart disease, angina pectoris, and HF. However, cardiovascular disease was not considered to be very common; it was treated with bed rest, digitalis, nitrates, and sometimes morphine.

Emergence of a Specialty

The decade from 1895 to 1905, bridging the 19th and 20th centuries, was probably the most important in the history of cardiology because of the discovery of three critically important technologies. In 1895, Wilhelm Roentgen,[12,*] a German physicist, discovered the use of x-ray, the first technique for imaging body parts in intact humans, allowing estimation of the heart's size and shape. The noninvasive measurement of blood pressure (BP) was developed by Riva Rocci, an Italian physician, in 1896[13] and Korotkoff in Russia in 1905.[14] The first recording of the electrocardiogram using a string galvanometer by Willem Einthoven,* a Dutch clinical physiologist, was reported in 1903.[15] When added to the clinical examination, these three new technologies permitted clinical assessment of key elements of the cardiovascular system. It soon became apparent that heart disease was far more common than had been suspected. Physicians who became expert in using and interpreting these new technical wonders were dubbed "heart specialists" or "cardiologists."

Advances came rapidly in this new specialty, and it soon became necessary to develop medical journals to record them. The earliest were the *Zentrallblatt für Herz Krankenheiten* in Germany and the *Archives des Maladies du Coeur* in France, both in 1908. Subsequently, an enormous expansion of cardiac journals occurred. As of 2020, 138 cardiovascular journals are published on a regular basis.

National cardiac societies were created to bring cardiologists and their trainees from each country together to share experiences and describe advances in cardiovascular science and clinical cardiology. The first of these, the British Cardiac Club, was organized in 1922, and in 1937 it morphed into the British Cardiac Society. In addition to organizing annual meetings, these societies also publish national cardiology journals. Beginning in the last third of the 20th century, the societies have developed and promulgated clinical practice guidelines that have improved the accuracy of cardiovascular diagnosis and the quality of care. National cardiac societies have joined with their continental neighbors to form regional societies, such as the European Society of Cardiology. The development of the World Heart Federation reflects the globalization of clinical cardiology and cardiovascular research.

CARDIAC IMAGING (SEE PART III)

The Past

After the development of roentgenography, venous angiography was begun in the 1920s. Selective angiography, in which radiocontrast material is injected through an intracardiac or intravascular catheter, allowed enhanced visualization of specific sites in the heart and great vessels. In 1948, Mason Sones, a cardiologist in Cleveland, described and perfected coronary arteriography, which provided accurate anatomic assessment of the coronary arterial bed.[16]

In 1952, Edler and Herz, a Swedish cardiologist/physicist team, developed echocardiography.[17] This technique assumed growing importance for assessing cardiac structure and function, becoming the "work horse" of cardiac imaging. The devices became smaller, more portable, and even handheld. By the end of the 20th century, three-dimensional echocardiography had become a valuable clinical tool.

The development of computed tomography (CT) by Hounsfield* and Cormack* in 1973[18] and of cardiovascular magnetic resonance imaging (CMR) by Lauterbur* and Mansfield* in the same year[19] have revolutionized cardiac diagnosis. Both technologies provide precise three-dimensional displays of the cardiac chambers and great vessels. CMR is especially useful in assessing regional myocardial perfusion, tissue characteristics, systolic and diastolic function, inflammation, and scar. Although coronary calcium had been detected occasionally by fluoroscopy, the field leaped forward in 1990 when Agatston introduced calcium scoring by CT. Larger and more extensive calcium deposits in the coronary arteries were associated with a higher incidence of subsequent coronary events, thereby enhancing risk assessment (see later).[20]

The Present

Nuclear cardiology, developed in the 1930s, is now used largely to detect the presence and assess the severity of myocardial ischemia. CMR imaging is now used routinely in the diagnosis and assessment of cardiomyopathies and myocarditis and in the assessment of cardiac fibrosis and masses. CT has been shown to be particularly effective in the assessment of aortic stenosis (AS). Dobutamine stress CMR is a sensitive, accurate method of detecting and quantifying myocardial ischemia.[21] Because CMR does not require ionizing radiation, it is used repeatedly to track the progression of disease and the effects of therapeutic interventions. For CMR spectroscopy, the new 7-Tesla magnets provide higher signal-to-noise ratios and more precise quantification of myocardial high-energy phosphates.[22]

Improvements in coronary computed tomographic angiography (CCTA) with intravenous injection of contrast material provide accurate, high-quality, noninvasive visualization of the epicardial coronary arteries. This technique is now widely employed in patients with chest pain of possible cardiac ischemic origin, in whom it has reduced the need for invasive coronary arteriography.[23] Quantitative positron emission tomography has become useful in the assessment of myocardial ischemia and viability and in the evaluation of inflammatory cardiomyopathies and infective endocarditis.

INVASIVE PROCEDURES (SEE CHAPTERS 21, 22, AND 41)

Cardiac Catheterization

The first human catheterization was carried out (on himself!) by Werner Forssmann,* a German surgical resident who was forbidden to repeat the procedure, but who wisely published his experience[24] (Fig. 1.2). In the late 1940s, the technique was applied to a variety of congenital and acquired cardiac disorders by Andre Cournand*,[25] and Dickinson Richards*,[26] in New York. In addition to measuring pressures

* Names followed by an asterisk were awarded a Nobel Prize.

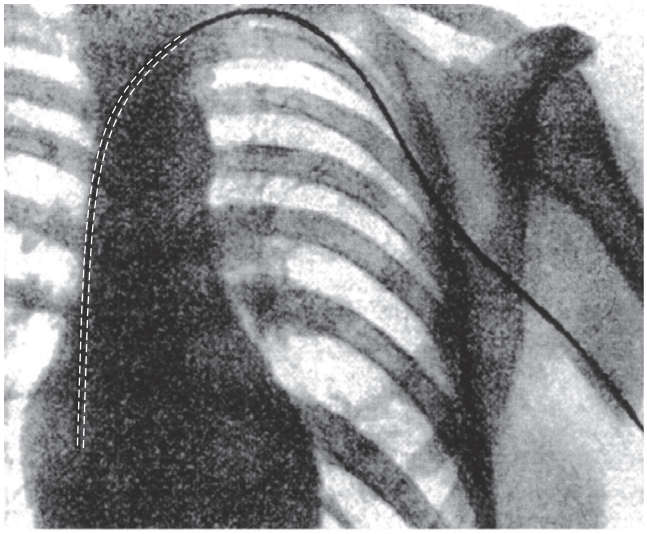

FIGURE 1.2 Cardiac catheter introduced by Werner Forssmann into his own right atrium. Forssmann W. Die Sondierung des rechten Herzens. Klin Wochenschr 1929;8:2085-2087. (Permission from Springer-Verlag, Munich, FRG.)

in the chambers of the right heart and pulmonary arteries, they also determined cardiac output at rest and during exercise. By the third quarter of the century, cardiac catheterization had become extremely important in the diagnosis of congenital and valvular heart disease.

Percutaneous Coronary Intervention

The field of invasive interventions virtually exploded in 1977 when Andreas Grüntzig, a Swiss cardiologist, described a new technique—percutaneous transluminal coronary angioplasty (PTCA), thereby ushering in a new subspecialty, interventional cardiology.[27] PTCA began with the treatment of patients with poorly controlled angina and an obstructive plaque in a proximal coronary artery. It was applied to progressively more complex lesions, and then on an emergent basis to patients with acute myocardial infarction (AMI) (see later).[28] In the late 1980s, coronary arterial stents were introduced to prevent restenosis.[29] Percutaneous coronary interventions (PCIs) expanded rapidly and began to compete with coronary artery bypass grafting (CABG). In properly selected patients it was of equivalent safety and efficacy and greatly preferred by patients who recovered in a day or two, compared with the weeks or months required after surgery.

Cardiovascular Surgery

After a number of early sporadic failures, cardiovascular surgery began in earnest in 1938 when Robert Gross of Boston successfully closed a patent ductus arteriosus.[30] Operative correction of coarctation of the aorta and of a variety of other congenital cardiac malformations soon followed. Mitral valvulotomy for stenosis was begun in 1946. A major step forward was taken by John Gibbon of Philadelphia, who developed a "heart-lung" machine in 1953, which was used for cardiopulmonary bypass[31] and led to the era of open heart surgery. This allowed repair of a large number of congenital and acquired disorders. In 1961, Albert Starr reported mitral valve replacement with a prosthetic ball valve.[32]

Beginning in the 1940s, attempts were made to treat patients with coronary artery disease (CAD) and severe angina by surgery; most were unsuccessful. In 1968, René Favaloro, a cardiac surgeon in Cleveland, Ohio described coronary artery bypass grafting,[33] which proved to be very effective in the management of severe angina pectoris and was shown in randomized clinical trials to prolong survival in patients with severe, multivessel CAD.[34]

Comments

During the last third of the 20th century, cardiology went through a major change. Before about 1970, the diagnosis of many congenital and acquired cardiac lesions were established by cardiac catheterization, often aided by selective angiography. If a mechanical therapeutic intervention was required, it was usually surgical. By the end of the century, as a consequence of the important advances in cardiac imaging, the need for diagnostic cardiac catheterization had declined. Simultaneously, catheter-based therapy advanced rapidly and expanded widely to patients with congenital and valvular heart disease. PCI became the most frequent therapy for improving coronary perfusion in ischemic heart disease and in acute myocardial infarction (AMI) (see later). Surgical therapy was reserved for patients in whom catheter-based therapy was not possible or in whom it had failed.

HYPERTENSION (SEE CHAPTER 26)

The Past

The recognition of hypertension as a critically important clinical entity was made possible by the simple noninvasive measurement of BP (see earlier) leading to the recognition of the high prevalence of the condition. The close relation between renal disease and hypertension goes back to Richard Bright, an English physician, who suggested in 1827 that patients with chronic renal disease were hypertensive.[35] In 1897, Robert Tigerstedt, a Swedish physiologist, injected an extract of rabbit kidney into a normal rabbit. He observed a prolonged elevation of arterial pressure and named the pressure-raising substance "renin."[36] In 1934, Harry Goldblatt, a Cleveland pathologist, demonstrated a rise in arterial pressure in dogs in which renal ischemia had been induced.[37] In 1940, Braun-Menendez, a physiologist in Buenos Aires, Argentina, reported that renin is an enzyme that acts on a globulin (now known as *angiotensinogen*) to produce a polypeptide with pressor properties, which he named *hypertensin* (now known as *angiotensin*), presumably produced by the ischemic kidney that had been described by Goldblatt.[38] In the first quarter of the 20th century, it became clear that in addition to renal disease, coarctation of the aorta, pheochromocytoma, and other endocrinopathies were causes of secondary hypertension. A large majority of patients with hypertension have no discernable cause; these are referred to as primary (essential) hypertension.

The clinical importance of hypertension was recognized and explicitly summarized by Soma Weiss, a Boston physician (who was a predecessor of the present author at Harvard and at the Brigham). In 1930, Weiss wrote:

> Persistently elevated arterial pressure is probably responsible for more disability and death than any other single pathological condition, including cancer and tuberculosis. Persistent hypertension combined with vascular pathology is the etiological factor in the bulk of instances of cerebral accident, myocardial failure and chronic insufficiency of the kidneys.[39]

Weiss was prescient, and today, almost a century after his paper, hypertension remains a major risk factor for stroke, AMI, HF, and renal failure. It plays a central role in cardiology and in internal medicine, neurology, and nephrology as well. However, Weiss' view was accepted very slowly until the 1950s, when systems for grading the severity of hypertension were developed, and followed by the realization of the wide spread and breadth of its serious complications.

Walter Kempner, an internist at Duke University, emphasized the use of an extremely low-salt diet (<200 mg Na^+ daily) based on rice, fruit, and juice.[40] Although this strict regimen reduced elevated BP, the diet was difficult to sustain. The most widely used antihypertensive drug in the mid-20th century was reserpine, an extract of the Indian root—*Rauwolfia serpentina*—which depresses cerebral sympathetic centers. Other early hypotensive agents included veratrum alkaloids, thought to act on the parasympathetic system, and hexamethonium derivatives, which block transmission through autonomic ganglia. The latter, while powerful, were associated with severe side effects. In patients with malignant hypertension who were not responsive to or could not tolerate potent hypotensive drugs, a splanchnic sympathectomy, championed by Reginald Smithwick, a Boston surgeon, could be considered.[41] Although it usually reduced BP, the adverse effects of this difficult operation were substantial.

Two well-designed, well-executed placebo-controlled trials in U.S. Veterans Hospitals, led by Edward D. Freis, a cardiologist in Washington, D.C., provided the first *definitive* evidence of the benefit of antihypertensive therapy. The first, conducted on patients with severe hypertension (diastolic pressures 115 to 129 mm Hg) compared treatment using the combination of hydrochlorothiazide, reserpine, and hydralazine, with placebo.[42] The second trial had a similar design and studied patients with diastolic pressures between 90 and 114 mm Hg. The risks of severe vascular events, especially HF and stroke, were markedly reduced in the treated group in both trials.[43]

The Present

By the end of the 20th century, treatment of essential hypertension had made many advances. They emphasize lifestyle changes, focusing on weight reduction, dietary salt restriction, and smoking. Of the large number of approved antihypertensive drugs, the primary agents include (1) thiazide or thiazide-like diuretics; (2) blockers of the renin-angiotensin system; and (3) calcium channel blockers. Compliance with the regimen is an important first step. Patients whose BP is not controlled with the combination of these drugs are considered to have resistant hypertension[44,45] and may require intensification of their lifestyle changes, the maximally tolerated doses of the primary agents, and/or the addition of a drug from another class, such as a mineralocorticoid receptor blocker, beta blocker, or vasodilator. The drugs for the treatment of hypertension are readily available, usually well tolerated, and inexpensive. One explanation for the inadequate control is that hypertension per se causes few if any symptoms and has been termed "the silent killer," leading to a combination of physician and patient inertia.

In the 20th century there were dozens of clinical trials, observational studies, and meta-analyses on drugs for the treatment of hypertension. The extent of clinical benefit appears to be related to five features: (1) the level of the baseline BP, (2) the event rate in the control group; (3) the extent of BP lowering by the intervention; (4) the tolerance to side effects; and (5) the duration of the trial. The higher each of these features, the greater is the clinical benefit.

The Future

Recent studies have shown a previously unrecognized primary aldosteronism in many patients with "essential" hypertension.[46] Such patients could be managed with a new nonsteroidal mineralocorticoid receptor antagonist.[47]

There have been multiple efforts to understand the genetic basis of essential hypertension, now recognized as a polygenic condition.[48] In a genome-wide association study (GWAS) in 475,000 persons, Kraja et al. identified 21 single-nucleotide polymorphisms (SNPs) and four novel loci associated with hypertension.[49] These include several candidate genes that may identify specific subgroups, with differing BP regulation and optimal therapies.

In a mendelian randomization study involving more than 600,000 subjects, triglyceride concentration, type 2 diabetes mellitus (T2DM), body mass index, alcohol dependence, insomnia, and smoking were each associated with an increased risk of hypertension, and longer sleep duration, higher high-density cholesterol concentrations, and higher education levels were each associated with a lower risk.[50] Several of these characteristics appear to be causally related, and their modification could prove to be useful in primary and/or primordial (see later) prevention. The combination of a low polygenic risk score for hypertension and adherence to a dietary approach was associated with a low BP in children.[51]

Going forward, more research on the combination of genomic and phenotypic features of hypertension is likely to provide clinically useful, actionable findings. An important goal is to identify the responders and nonresponders before the onset of therapy. In addition, there have been several observational studies suggesting that gut microbiota can influence BP. Their mechanisms are not clear but may involve levels of activation of G protein–coupled receptors.[52] Possible treatment with prebiotics, probiotics, and postbiotics to modify such microbiota may become a fertile field for future research on hypertension.

VALVULAR HEART DISEASE (SEE PART VIII)

The Past

Cardiac involvement in rheumatic fever was described by Wells in 1812.[53] Acute rheumatic fever and its sequel, rheumatic valvular disease, were common in Europe and North America until the mid-20th century and then declined with the introduction of penicillin and some relief of extreme poverty and overcrowding. However, almost simultaneously, a reciprocal increase in degenerative calcific disease of the aortic and mitral valves occurred in the rapidly growing elderly population. Acute rheumatic fever is still observed frequently in developing nations in tropical and subtropical latitudes.

The Present

Mitral Stenosis

In the mid-20th century, surgical treatment of symptomatic severe mitral stenosis (valve area <1.5 cm^2) carried out by closed mitral valvotomy was the most frequently performed cardiac operation.[54] When the valve is calcified, severely fibrotic, with subvalvular fusions, and/or accompanied by more than slight mitral regurgitation (MR), an open valvuloplasty on cardiopulmonary bypass is carried out; occasionally, mitral valve replacement is necessary. In 1983, percutaneous balloon mitral valvuloplasty (PBMV) was described by Inoue et al., a Japanese team.[55] Employing transseptal left heart catheterization[56] and echocardiographic guidance, they introduced a balloon catheter into the mitral orifice; balloon inflation opened the fused commissures. The indications for and results of PBMV are generally similar to those for closed surgical valvotomy. PBMV has gained worldwide popularity because it is relatively safe[57] and shortens the discomfort and duration of hospitalization and recovery. Favorable results have been sustained for upward of 15 years.[58]

Mitral Regurgitation (MR)

Primary MR is caused by an abnormality of the mitral valve leaflets, as in rheumatic heart disease. Secondary MR usually results from ventricular dilation caused by ischemic or nonischemic cardiomyopathy, which prevents coaptation of the normal leaflets. In 2001, Ottavio Alfieri, an Italian cardiac surgeon, treated MR by approximating the free edges of the mitral leaflets with a running suture sometimes referred to as the "Alfieri stitch."[59] In 2003, St. Goar et al. developed an endovascular "edge-to-edge" repair of the mitral valve with a valve clip in a porcine model.[60] Transcatheter mitral valve repair was extended to patients by Feldman et al.[61] Two large randomized clinical trials compared transcatheter edge-to-edge repair with guideline-directed medical therapy (GDMT) in secondary MR with HF. One of these showed superiority of the transcatheter approach,[62] whereas the other showed equivalence.[63] The 2020 American College of Cardiology/American Heart Associate (ACC/AHA) Guidelines provide a recommendation for the edge-to-edge repair in patients with moderate or severe MR with persistent symptoms despite intensive GDMT.[64] Catheter-based replacement of the mitral and tricuspid valves is under active investigation.

Transcatheter Aortic Valve Replacement

In the last third of the 20th century, symptomatic adult patients with severe AS (mean gradient >40 mm Hg) were generally treated by surgical aortic valve replacement (SAVR), and asymptomatic patients were followed closely. In 1992, Andersen et al. described the successful placement of a catheter-based bioprosthetic inflatable prosthetic aortic valve in a closed-chest porcine model.[65] This was followed a decade later by the first human percutaneous implantation of an aortic valve by Cribier et al.[66] In 2006, Webb et al. implanted a bioprosthetic valve using a catheter that was passed retrograde from the femoral artery.[67] The first large transcatheter aortic valve replacement (TAVR) trial was conducted by Leon et al. on patients whose operative risk was too high to undergo SAVR; survival was prolonged when compared with that with GDMT.[68]

Both SAVR and TAVR are effective treatments of adults with severe symptomatic AS. Both early mortality and stroke rates are somewhat lower for TAVR, but vascular complications, paravalvular regurgitation and the need for a permanent pacemaker are higher. Importantly, the length of hospital stay and recovery are much shorter for TAVR and greatly preferred by patients.[69]

TAVR was approved for high-risk patients with severe AS by the U.S. Food and Drug Administration (FDA) in 2011; the indication was extended to low-risk patients in 2019. Although TAVR is generally preferred to SAVR for patients with severe, symptomatic AS, at the time of this writing (2021), TAVR has been carried out for only 6 years and the long-term durability of the bioprosthetic valves used are not yet clear. This remains a concern when selecting TAVR for younger patients, particularly with bicuspid aortic valves.[64] Nonetheless, TAVR has transformed the management of patients with severe AS. In 2019, a total of 72,991 TAVR procedures were performed in the United States compared with 57,626 SAVR procedures.[67] In a national registry, TAVR has been shown to have a hospital mortality of 1.3%; 81% of patients reported a good quality of life after 1 year.[70]

ARRHYTHMIAS (SEE PART VII)

The Past

A "tumultuous" heartbeat was recognized in the 15th century. In 1769, Morgagni, an Italian physician, described patients with very slow heart rates and transient asystole. Although graphic tracings of irregular cardiac movements were made in the late 19th century,[71] it was the development of the string galvanometer electrocardiograph in 1903 that led Einthoven* (see earlier), Sir Thomas Lewis, and other early cardiologists to describe the majority of clinical arrhythmias.

In 1749, Senas recommended use of the bark of the cinchona tree (which contains quinine) for the treatment of palpitations. In 1918, the superiority of quinidine over quinine was recognized and subsequently a variety of other antiarrhythmic agents were developed. The mechanisms of action of these drugs were classified by Vaughan-Williams in 1970,[72] and subsequently updated.[73]

Suspicions arose in the 1970s that many of these drugs had both antiarrhythmic and proarrhythmic properties. These suspicions were proven in 1991 when the Cardiac Arrhythmia Suppression Trial (CAST) showed that several antiarrhythmic agents that markedly reduced premature ventricular contractions in post-MI patients were associated with an *increased* mortality.[74] Since then, the use of antiarrhythmic agents other than beta blockers, amiodarone, and some calcium channel blockers has been curtailed, especially in patients with structural or ischemic heart disease. Multicatheter-based invasive electrophysiologic testing, developed in the early 1970s, includes recording of electrocardiographic responses of a number of intracardiac leads to programmed electrical stimulation[75,76] before and after pharmacologic agents. This technique has proved to be extremely useful for identifying the mechanisms of arrhythmias, distinguishing between automaticity, reentry, and triggered activity and for risk stratification and selecting appropriate therapy.

In 1952, Paul Zoll, a Boston cardiologist, developed closed chest cardiac stimulation for the treatment of complete heart block and asystole.[77] In 1958, William Chardack, an American surgeon, implanted a pacemaker powered by a rechargeable battery.[78] In the same year, William Kouwenhoven, an engineer in Baltimore, described closed-chest cardiac massage.[79] In 1962, Bernard Lown, a Boston cardiologist, described direct current cardioversion of a variety of tachyarrhythmias, including atrial and VF.[80] In 1980, Michel Mirowski, a Baltimore cardiologist, described the implanted cardioverter-defibrillator. This device successfully detects and treats life-threatening arrhythmias, including ventricular tachycardia (VT) and VF.[81]

The Present

Acute supraventricular and nodal tachycardias are usually treated by vagal maneuvers, intravenous calcium channel blockers, or electrical cardioversion. To suppress chronic tachyarrhythmias, radiofrequency catheter ablation or amiodarone is frequently employed. VT is generally managed by cardioversion followed by ablation.[82] Atrial fibrillation can often be abolished early in the course by electrically disconnecting the source of arrhythmia triggers by pulmonary vein isolation sometimes using cryoballoon ablation.[83]

Sudden cardiac death (SCD) is responsible for approximately 15% of all deaths in industrialized countries. It occurs most frequently in patients with arteriosclerotic cardiovascular disease (ASCVD), especially after MI or in patients with HF, and is usually caused by VT or VF. In a minority of patients, pulseless electrical activity and asystole are responsible. SCD may also occur in children and young adults as a consequence of mutations in genes encoding ion channels (channelopathies)[84] or sarcomeric proteins (e.g., hypertrophic cardiomyopathy). Patients at high risk for SCD are managed by implantation of a ventricular defibrillator (see earlier).

DYSLIPIDEMIAS (SEE CHAPTERS 25 AND 27)

The Past

During the 20th century, CAD emerged as the most common cause of *cardiovascular* death and elevation of low-density lipoprotein cholesterol (LDL-C) as the most important cause and progression of CAD. In 1913, Nikolai Anitschkov, a pathologist in St. Petersburg, fed large quantities of cholesterol to rabbits, raising their serum concentrations to about 1000 mg/dL and producing cholesterol-containing deposits in the aorta.[85] In 1938, Carl Müller, a Norwegian physician, described families with a high incidence of both hypercholesterolemia and CAD, thus describing what we now know as heterozygous familial hypercholesterolemia.[86]

In 1954, John Gofman, a biochemist in Berkeley, California fractionated cholesterol and identified the LDL-C responsible for producing atherosclerosis.[87] In 1964, Bloch*,[88] and Lynen*,[89] separately described the multiple steps required for the biosynthesis of cholesterol. This work led to the discovery of 3-hydroxy-3methylglutaryl co-enzyme A reductase (HMGCoA reductase), the enzyme that catalyzes the synthesis of a critically important intermediary. In 1976, Akira Endo, a pharmacologist in Tokyo, Japan, identified an inhibitor of this enzyme that reduces the biosynthesis of cholesterol and lowers the concentration of circulating LDL-C.[90] In the 1970s, Michael Brown* and Joseph Goldstein* in Dallas, Texas discovered, characterized, and cloned the LDL-C receptors on cell membranes.[91] These receptors are key to the cellular uptake of LDL-C and are normally upregulated when the biosynthesis of cholesterol is lowered, thereby reducing atherogenesis.[92] Several large clinical trials showed that the administration of these inhibitors (statins) has reduced the incidence of MI and chronic CAD.[93] These agents have prolonged and improved the lives of millions of patients worldwide and along with the development of the coronary care unit (see later) represent one of the triumphs of cardiology in the 20th century.

In 2003, Marianne Abifadel, a Lebanese postdoctoral fellow working in Paris with Catherine Boileau, discovered two gain-of-function mutations in a gene that encodes proprotein convertase subtilisin/kexin type 9 (PCSK9) in patients with autosomal dominant hypercholesterolemia.[94] PCSK9 shortens the half-life of intracellular LDL-C receptors, thus reducing their recycling to the cell surface, raising circulating LDL-C and the incidence of ASCVD. In the absence or reduced concentration of PCSK9 within the hepatocyte or in the circulation, the degradation of the LDL-C receptor is lowered, raising its concentration at the cell surface, reducing circulating LDL-C and the incidence of ASCVD.[95]

The Present

Administration of monoclonal antibodies to circulating PCSK9 in two large, phase 3 clinical outcome trials, totaling more than 45,000 patients with ASCVD, lowered LDL-C by about 55% and reduced the endpoint of cardiovascular death, MI, or stroke.[96,97] Robert Giugliano, a Boston cardiologist, reported that extremely low levels of circulating LDL-C (<15 mg/dL) appear to be safe and well tolerated.[98] It now appears to be appropriate to reduce LDL-C to below 50 mg/dL on a population-wide basis, especially in patients with or at high risk for ASCVD.

siRNA-inclisiran

The need for monthly or biweekly injections of monoclonal antibodies to PCSK9 has hindered adherence to this approach for long-term therapy. In 1998, Fire,* Mello,* et al. described a small, double-stranded RNA that can interfere with gene expression.[99] This fundamental discovery is leading to a new class of drugs that include inclisiran, a small, synthetic, two-stranded interfering siRNA that inhibits hepatocellular synthesis of PCSK9, thereby reducing circulating PCSK9, upregulating LDL-C receptors on the cell surface, and lowering circulating LDL-C. In contrast to the PCSK9 monoclonal antibodies, inclisiran requires subcutaneous administration only twice yearly to reduce LDL-C by about 50% and maintain this level. This reduction has been observed in studies in healthy volunteers and patients with elevated LDL-C levels at high vascular risk, including patients with heterozygous familial hypercholesterolemia and patients receiving intensive statin therapy.[100,101] Based on the drug's biochemical efficacy, safety, and tolerance, it has been approved for lowering LDL-C. A phase 3 double-blind, placebo-controlled trial of patients with a history of ASCVD (the ORION 4 trial NCT03705234) is currently testing whether the administration of inclisiran is associated with reductions in major cardiac events. The ability to reduce LDL-C by about 50% in patients already receiving maximal LDL-C–lowering therapy and requiring only two injections annually augurs well for LDL-C control in large populations in the future.

The Future

Triglycerides

These lipids have long been known to be coronary risk factors, although not as potent as LDL-C. Genetic activation of the lipoprotein lipase gene (*LPL*) reduces serum triglycerides (TGs) and is associated with a low incidence of CAD and T2DM.[102] Angiopoietin-like 3 (ANGPTL3), a protein that is synthesized by hepatocytes, inhibits expression of *LPL*, thereby *increasing* circulating TGs. Heterozygous loss of function mutations of ANGPTL3 are associated with reductions of both LDL-C and TG,[103] lowering the risk of the development of CAD and T2DM. Three approaches to reducing ANGPTL3 are currently under investigation: (1) a hepatocyte-directed antisense oligonucleotide (vupanorsen) that reduces TG as well as apolipoproteins B and CIII[104]; (2) evinacumab, a monoclonal antibody against ANGPTL3 that reduces TG and has been approved to reduce LDL-C in patients with homozygous familial and other forms of hypercholesterolemia[105]; and (3) very preliminary studies on editing the gene encoding ANGPTL3; if the latter proves to be successful, it could provide a "one-shot long-term therapy."[103] Also, in vivo CRISPR base editing of PCSK9 has been shown to durably lower cholesterol in primates.[103a]

Lipoprotein (a)

Elevations of circulating Lp(a) are associated with four interrelated phenotypic changes, each of which increases cardiovascular risk: (1) accelerated atherogenesis; (2) intensification of vascular inflammation; (3) worsening of calcific AS;[106] and (4) enhancement of a prothrombotic state.[107] Lp(a) can be reduced with antisense oligonucleotides that target the *LPA* gene inhibiting hepatic production of Lp(a) in a dose-dependent manner.[107] Another approach is with siRNA technology. In addition, in the FOURIER-TIMI 59 trial,[96] the monoclonal PCSK9 antibody evolocumab was shown to be moderately effective in reducing elevated Lp(a).[108]

It appears likely that continued reduction of ASCVD by further population-wide suppression of LDL-C will occur, accompanied by reduction of TG and Lp(a). The maximum benefit from these measures will be obtained by starting preventive therapy early in life (see Primordial Prevention, later). The combination of these several "attacks" on the dyslipidemias, if widely carried out, could greatly reduce the incidence of ASCVD and thereby exert an enormous impact on the practice of cardiology.

ACUTE MYOCARDIAL INFARCTION (SEE CHAPTERS 37 TO 39)

In the 19th century, physiologists noted that ligation of a major coronary artery in the dog led immediately to fatal VF. It was assumed that the same occurred in patients who developed a sudden coronary occlusion. In 1910, Obrastzov and Straschenko, two Ukrainian physicians, reported that coronary occlusion in patients is associated with chest pain and AMI, but that immediate death may not occur.[109] By mid-century, AMI was regarded as the most common single cause of death in industrialized nations; many of these deaths were sudden. The introduction of the coronary care unit in 1961 by Desmond Julian, a British cardiologist,[110] was critical to the prevention of these sudden cardiac deaths and led to a reduction of mortality in AMI from about 30% to 15%. Implementation of these units spread rapidly around the world.

The major remaining risk of AMI was consequent to large infarctions that caused left ventricular failure. To reduce infarct size in patients with AMIs, it was necessary to correct the large imbalance between the oxygen supply and demand of the severely ischemic myocardium.[111] The successful restoration of perfusion of a coronary artery obstructed by a thrombus in a patient with AMI was first reported in 1976 by Yevgeny Chazov, a Soviet cardiologist, who infused a thrombolytic agent, largely streptokinase, directly into the affected coronary artery[112] (Fig. 1.3). In 1986, a large multicenter clinical trial of AMI, the GISSI trial, demonstrated a reduction in mortality with *intravenous* streptokinase.[113] GISSI was closely followed by the ISIS 2 trial led by Peter Sleight, a British cardiologist, that demonstrated that the combination of streptokinase and aspirin was even more beneficial than streptokinase alone.[114]

Ever more effective techniques of myocardial reperfusion began with the development of more potent fibrinolytic agents, such as tissue plasminogen activator,[115,116] followed by the use of percutaneous coronary angioplasty[27,28] and then coronary artery stents (see later).[117] To be effective, reperfusion has to be carried out as quickly as possible after the onset of symptoms. With successful early reperfusion, mortality fell in half again, to about 7%. Mortality was reduced further with treatment using an angiotensin-converting enzyme (ACE) inhibitor as demonstrated by Marc Pfeffer, a Boston cardiologist.[118]

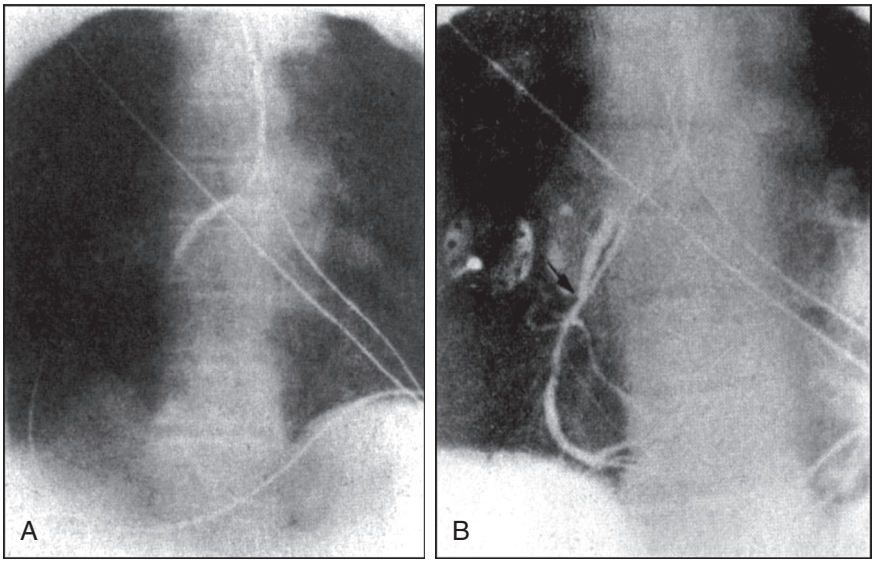

FIGURE 1.3 Acute myocardial infarction. A, Pretreatment total occlusion of right coronary artery (RCA). **B,** Post-treatment with intracoronary fibrinolytic (largely streptokinase). There is persistent nonocclusive narrowing of the RCA, with perfusion of the inferior wall of the left ventricle. (From Chazov EI, Matveeva LS, Mazaev AV, et al. Intracoronary administration of fibrinolysin in acute myocardial infarction. Ter Arkh 1976;48:8-19.)

Coronary Risk Factors

In 1948, U.S. President Truman established the National Heart (now Heart, Lung and Blood) Institute, which has provided substantial

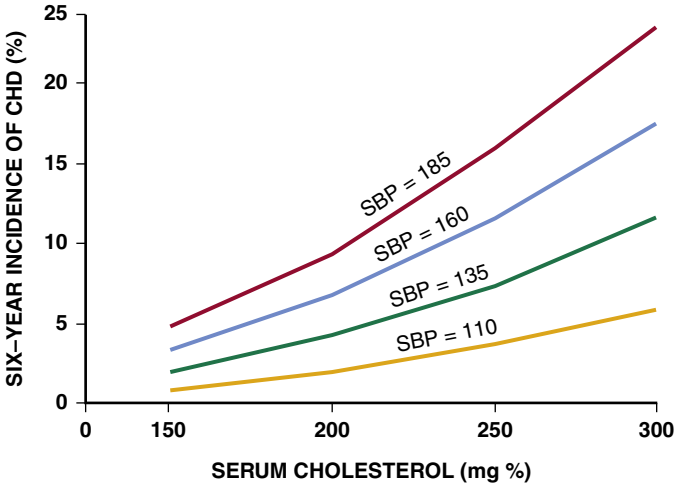

FIGURE 1.4 Synergistic effects of two coronary risk factors. Six-year incidence of coronary heart disease (CHD) according to cholesterol levels and systolic blood pressures (SBP) in men 45 to 62 years. (From Kannel WB, Dawber TR, Kagan A, et al. Factors of risk in the development of coronary heart disease: Six-year follow-up experience. The Framingham Study. Ann Int Med 1961;55:33-50.)

resources for research. One early effort of the institute was the conduct of an epidemiologic study of CAD, carried out in Framingham, near Boston, Massachusetts. The Framingham Heart Study (FHS) was the first large-scale, prospective, multigenerational observational study on a general population in the United States, established primarily to identify the determinants of CAD. In addition to the initial clinical assessments, imaging studies, biomarkers, genomics, and other "omics" technologies were included as they became available to the FHS.[119,120]

In 1961, William Kannel, an epidemiologist with the FHS, reported that the *"risk factors"* for CAD were male sex, hypertension, elevated serum cholesterol, diabetes, and electrocardiographic left ventricular hypertrophy.[121] This led to the development of the FHS risk score, a simplified version of which has been used widely in clinical practice[120] (Fig. 1.4).

HEART FAILURE (SEE PART VI)

The Past

Forty years after Harvey's publication of *De Motu Cordis,* Richard Lower, an Oxford physician-scientist, described HF as a condition "when the heart lacks the strength to preserve a constant circulation of the blood. . . . This can occur when the heart is too laden with fat or suffers from inflammation, so that it is unable to pulsate and contract."[3] In 1831, James Hope described the "backward" theory of HF, with elevation of pressures upstream of the affected ventricle or valve.[122] An opposing theory, the "forward failure" theory, was proposed about a century later by James Mackenzie,[123] who asserted that diminished cardiac output was the principal problem in HF. Irrespective of which theory was accepted, it was agreed that retention of sodium and water causes dyspnea and edema in HF. Before the 20th century, there was no effective treatment of this condition other than digitalis, and the efficacy of this drug is now in question. Mercurial diuretics became available in the 1920s and were widely used but were only moderately effective. By the 1950s, two orally active diuretics, a benzothiadiazine (chlorothiazide) and a mineralocorticoid receptor blocker, were developed and improved the care of patients with HF. More potent diuretics, the "loop" diuretics, were introduced in the 1960s.

Some members of two classes of neurohormonal blockers, beta-adrenergic blockers first described by James Black,*,[124] a British pharmacologist, as well as ACE inhibitors,[118,125] diminished the symptoms of HF, and prolonged life in patients with HF. Cardiac transplantation, introduced in 1967,[126] extended life in the small number of patients for whom a donor heart could be identified.

During the 19th and most of the 20th centuries, cardiovascular physiologists and cardiologists assumed that HF was caused by the inability of the left ventricle to eject blood during systole, and because the left ventricle dilated, its ejection fraction declined, causing HF with reduced ejection fraction (HFrEF). Other patients with HF were described in which systolic function is largely preserved, but in which ventricular filling (diastolic function) is impaired[119] because of slowed ventricular relaxation[127] and reduced ventricular compliance. This led to HF with preserved ejection fraction (HFpEF), which by the end of the century was responsible for almost half of the patients with HF.

The Present

Three types of devices introduced in the latter half of the 20th century have had beneficial effects in the treatment of HF: (1) cardiac resynchronization therapy,[128] in which multisite pacing of the ventricles enhances ventricular performance; (2) implanted cardioverter-defibrillators[81] which reduce the incidence of sudden death in patients with HF; and (3) left ventricular assist devices (LVADs, see later).[129] In the 21st century *three new* disease-modifying therapies were shown to reduce cardiovascular mortality in patients with HFrEF. The first are the mineralocorticoid receptor antagonists; spironolactone was shown by Pitt, Zannad, and colleagues to be life prolonging in patients with HFrEF (the RALES trial was published in 1999).[130] The second is sacubitril/valsartan, a first in class angiotensin neprilysin inhibitor (ARNi), which was superior to enalapril, a widely used ACE inhibitor.[131] The third are the sodium-glucose transporter 2 inhibitors (SGLT2is) that cause glucosuria and had been employed as second-tier antidiabetic agents until they were shown to reduce cardiovascular mortality and prevent HF hospitalization in patients with T2DM.[132] At the time of this writing (May 2021), three drugs in this class, dapagliflozin, empagliflozin, and sotagliflozin, have also been shown to be effective in nondiabetic patients with HFrEF.[133,134,134a] SGLT2i has been shown to be renoprotective in patients with diabetic and nondiabetic chronic kidney disease.[135]

Each of these three drug classes are relatively well tolerated, and representatives of each group can be administered together and with a beta blocker. Two trials, one with spironolactone led by Marc Pfeffer and Bertram Pitt,[136,137] and the other with sacubitril/valsartan led by Scott Solomon, a co-editor of this book,[138] have shown encouraging benefit. Innovative trials of nonpharmacologic approaches using the creation of left-to-right atrial shunting are under evaluation. Preliminary studies of an antisense oligonucleotide have reported favorable results in HF as well.[139]

ASSISTED CIRCULATION (SEE CHAPTER 58)

The Past

In 1968, the use of an intra-aortic balloon pump (IABP), was reported by Kantrowitz, a cardiac surgeon in New York.[140] This device was used in patients with cardiogenic shock, secondary to AMI or after cardiotomy. Although IABP exerted a modest favorable effect on hemodynamics, it did not improve clinical outcome with regularity and it became clear that more powerful devices were required for the treatment of severe HF. During the 1980s and 1990s, a variety of pneumatic LVADs underwent extensive animal testing and clinical trials.[129] They were used in patients in cardiogenic shock, and as a bridge to cardiac transplantation, but it was not clear whether they were superior to GDMT.

The REMATCH trial published in 2001 was the first controlled randomized trial that compared long-term LVAD support with optimal GDMT in patients with advanced (Class IV) HF who were ineligible for cardiac transplantation. This trial, led by Eric Rose, a New York cardiac surgeon, showed that 1 year after randomization, survival in the LVAD group was twice that in the medical arm.[141] This landmark trial served as a potent stimulus to the field and led the FDA to approve the LVAD employed in the trial for destination therapy, that is, for the patient's lifetime. The device, while reflecting the state of the art at the turn of the century, was bulky and noisy, with the large pulsatile pumping chamber placed in the abdomen. Although its use prolonged survival, it was associated with many adverse events,

including local and systemic infections, stroke, excessive bleeding, thrombosis, and device failure.

The Present

Many refinements were made in LVADs in the last two decades. An important step was the development of an intrathoracic continuous axial flow pump, the HeartMate II,[142] which was associated with better outcomes than the pneumatic device used in REMATCH. A further development was the Heart Mate 3, a magnetically levitated centrifugal flow pump, which was even smaller, and in a trial led by Mandeep Mehra, a Boston cardiologist, it was shown to be safer as well, with elimination of pump thrombosis and lower stroke rate.[143]

Early in the 21st century, several reports appeared of a small fraction of patients on chronic LVAD support who exhibited recovery of sufficient cardiac function to allow explantation of the device.[144] Teams in London,[145] Berlin,[146] and Louisville, Kentucky[147] described the phenotypes of patients in whom recovery was possible. These patients are younger than the patients usually receiving an LVAD, have a shorter duration of HF, and are more likely to have a dilated rather than ischemic cardiomyopathy.

The Future

Although the currently available LVADs reflect striking advances when compared with their predecessors, they are still reminiscent of the Model T Ford of a century ago. With the demand for these pumps increasing steadily and the ongoing rapid strides in bioengineering and material science, it is likely that the next generation of LVADs will be smaller, easier to implant, and less likely to thrombose, with transcutaneous transmission of power without the need of a drive line, and perhaps less expensive than current versions.

Looking forward, it has been suggested that mechanical assisted circulation might also be provided by an implanted extra-aortic counterpulsation system for patients with moderately severe, chronic HF. In a preliminary feasibility trial, Abraham et al. wrapped an inflatable cuff around the ascending aorta and connected it to an external battery–powered pneumatic driver triggered by an epicardial lead.[148] This device, designed for chronic ambulatory use, would not be in contact with blood and therefore would not require anticoagulation. Possibly, it might be activated intermittently when needed. A second possible form of partial ventricular support described by Meyns et al. was implanted via a mini-thoracotomy and positioned in a subclavicular subcutaneous pocket, like a pacemaker. In a feasibility trial it showed substantial hemodynamic benefit and appeared to slow the progressive deterioration of advanced HF.[149] Although neither of these two devices is ready for clinical application, they do point to possible future directions. It is likely that further technologic advances will provide sufficient mechanical support of the circulation at an earlier stage of chronic HF and thereby reduce the need for pharmacologic inotropic support and/or the need for an LVAD of the current variety.

GENOMICS AND GENETICS (SEE CHAPTER 7)

The Present

The first decade of the 21st century was ushered in by one of the most important scientific accomplishments in the history of biology—the initial draft of the Human Genome Project (HGP), which provided an analysis of approximately 90% of the human genome.[150,151] The HGP was developed by a team at the National Institutes of Health, led by Francis Collins, and simultaneously by Celera Genomics, a private company led by Craig Venter. Each group provided maps that defined the positions of individual genes and their DNA sequences. The "finished" sequence, more than 99% complete, was published by the HGP in 2004.[152] This was soon followed by the genomes of the mouse, rat, dog, chimpanzee, and multiple bacteria and viruses and the partial genome from extinct Neanderthals.[153]

An ever-increasing number of studies have correlated specific cardiovascular disorders with single gene mutations. These include a number of dyslipidemias, a variety of arrhythmias, several cardiomyopathies, hypercoagulable and hypocoagulable states, and Marfan syndrome, among others. In many of these monogenic disorders, the diagnosis can now be established by genetic testing carried out in commercial laboratories; others require analyses in research laboratories. Screening of close relatives of patients with monogenic disorders is increasing, and many asymptomatic carriers are now being identified and counseled.

GWAS[154] have enabled discovery and mapping of DNA variants and have identified phenotypes that are controlled by multiple genes. The implications of GWAS for clinical medicine, including cardiology, are profound. For example, GWAS have been applied to CAD, T2DM, essential hypertension, and atrial fibrillation. These GWAS have identified multiple risk variants that appear to enhance the likelihood of these conditions, and they have facilitated the development of polygenic risk scores. Fortunately, the cost of GWAS is declining rapidly, and at the time of this writing the combination of GWAS and whole exome sequencing can be obtained for $230.

Direct-to-consumer (DTC) genetic testing began in 2006, and in 2017 the FDA issued its first approval of a genetic health screen. DTC is now a widely advertised, successful business. However, there is little control of the interpretation of the results and counseling of the "customers." The electronic medical record, with its description of phenotype, including clinical features, imaging, biomarkers, and responses to interventions is used increasingly to interact with genetic information, enhancing accurate diagnosis and risk of disease, that is, precision medicine.

The Future

In 2012, Emmanuelle Charpentier* a French geneticist, and Jennifer Doudna,* an American biochemist, demonstrated that CRISPR/Cas (clustered regularly interspaced short palindromic repeats with CRISPR-associated protein) can edit DNA with great precision.[155] This technique permits the identification of the specific variants that contribute to disease and will be enormously helpful in molecular diagnosis of many disorders, including those involving the cardiovascular system.[156] Initial reports of CRISPR-Cas9 editing of patients with sickle cell disease and beta-thalassemia are encouraging.[157] Gene editing in cancer, HIV, and lysosomal storage disease is ongoing.[156]

Precision Medicine

During the first two decades of the 21st century, emphasis on human variability, both inherited and acquired, increased rapidly. In many patients, important genetic differences and phenotypic features will be identified by the other so-called "omics" technologies; they need to be considered in establishing a diagnosis and developing a personalized management plan, hence the term *Personalized Medicine*.[158,159] The goal of assessing these characteristics with great precision has led to a closely related term, *Precision Medicine,*[160] which has been defined by Leopold and Loscalzo as "an integrative approach to cardiovascular disease prevention and treatment that considers an individual's genetics, lifestyle, and exposure to determinants of their cardiovascular health and disease phenotype."[161]

PRIMORDIAL PREVENTION (SEE CHAPTER 25)

The Present

The goal of *primordial* prevention is to promote health.[162] Primordial prevention is sometimes confused with primary prevention; primary prevention *reduces or eliminates established risk,* whereas primordial prevention is designed to *avoid future development of risk*. In 2010, the AHA developed a 7-item tool to promote cardiovascular health; it emphasizes a diet low in salt and cholesterol, regular physical activity, avoidance of smoking, and maintaining optimal levels of BP, body mass index, fasting blood glucose, and cholesterol.[163] Lifetime cardiovascular risk was shown to be proportional to the number of risk factors and their severity.[164,165]

Elevated BP in childhood tracks into adolescence and then adulthood and can be responsible for the development of at least two important risk factors for subsequent ASCVD: left ventricular hypertrophy and an increase in the carotid intima–medial thickness, the latter a predictor of arterial plaques.[166] Primordial prevention in children is important in preventing trends to an elevated BP, obesity, and excessive dietary salt intake while encouraging physical activity. It has become apparent that environmental influences in childhood play an important role in the subsequent trajectory of cardiovascular disease.

The Future

If GWAS is carried out in infants and neonates, it might be possible to commence primordial prevention early in life. There is increasing interest in primordial prevention even during the prenatal period. Maternal diabetes, obesity, and hypertension can be transmitted to the offspring, involving, at least in part, epigenetic mechanisms. The function of placental mitochondria may be impaired in maternal diabetes, and it has been proposed that metformin stimulates placental mitochondrial biogenesis, thereby providing protection to offspring.[167]

INFLAMMATION (SEE CHAPTER 24)

The Past

In 1858, the great German pathologist Rudolph Virchow recognized the importance of inflammation in the development and softening of arteriosclerotic plaques.[168] Sixty years later, Russell Ross, a Seattle pathologist, in a classic paper, focused on the various cell types and their DNA in atherosclerotic plaques concluded: "Atherosclerosis is clearly an inflammatory disease and does not result simply from the accumulation of lipids."[169]

Substantial research—both experimental and clinical—has provided strong, albeit circumstantial, support for the inflammatory hypothesis for atherogenesis.[170] Ridker, a Boston cardiologist, demonstrated that high-sensitivity C-reactive protein (hsCRP), an inflammatory biomarker, is as potent a predictor of cardiovascular risk as LDL-C.[171] Despite the logic and attractiveness of the inflammation hypothesis, until recently there had been no proof of its clinical relevance.

The Present

Canakinumab

In 2017, this relevance was demonstrated by the publication of the CANTOS trial, a 10,000-patient placebo-controlled trial on patients with prior MI and residual inflammation. Ridker, Libby, and colleagues used canakinumab, a humanized monoclonal antibody that blocks the interleukin (IL)-1β innate immunity pathway.[172] CANTOS validated the inflammatory hypothesis by demonstrating a statistically significant, albeit modest, reduction in lipid independent cardiovascular events.

Colchicine

Colchicine is a well-known anti-inflammatory agent that is effective in halting acute gouty arthritis, familial Mediterranean fever, and acute pericarditis. It appears to act by inhibiting tubulin polymerization and reduces activation of IL-1β. Tardif, a Canadian investigator, demonstrated that colchicine reduced major cardiovascular adverse events in post-MI patients in the COLCOT trial,[173] and Nidorf, an Australian investigator, observed a similar benefit in patients with chronic CAD in the LODOCO-2 trial.[174]

The Future

Further preclinical and clinical research on a variety of anti-inflammatory agents is being actively pursued. Attention is now directed to a proximal step in the inflammatory pathway. The activation of the NLRP3 inflammasome stimulates the formation of IL-1β and IL-18, two highly inflammatory cytokines,[175,176] which in turn activate IL-6, which enhances the production of CRP by the liver. Looking ahead, we can anticipate continued progress in the development of anti-inflammatory agents for the prevention and/or slowed progression of atherosclerosis. Just as a variety of drugs have been found to be useful in the treatment of hypertension, dyslipidemias, and HF, it is likely that a number of anti-inflammatory agents will be available as well. Their relative efficacy in patients with various manifestations and stages of atherosclerosis, their safety, tolerance, and cost will be important in selecting the right drug, at the right dose, at the right time, and for the right patient.

CLONAL HEMATOPOIESIS (SEE CHAPTER 24)

In 2014, Jaiswal et al. reported on whole exome sequencing of DNA obtained from leukocytes in the peripheral blood. They detected somatic mutations leading to expansion of hematopoietic stem cells associated with an increase in cardiovascular disease.[177] These cells acquire a progressive increase in such mutations, especially in the elderly. In an important follow-up paper[178] they referred to this condition as *c*lonal *h*ematopoiesis of *i*ndependent *p*otential, abbreviated as CHIP.

CHIP is associated with accelerated atherosclerosis, an increased risk of coronary artery calcification, MI, calcific AS, intravascular thrombosis, and T2DM (Fig. 1.5). The most commonly mutated CHIP-driver genes frequently occur in patients with severe AS and are associated with increased proinflammatory leukocytes, and an excessive mortality after successful TAVR.[179] CHIP is associated with an almost doubling in the incidence of cardiovascular disease and a 40% increase in all-cause mortality.[180]

For almost two thirds of a century, there has been broad agreement about the identity and importance of the classic risk factors for ASCVD, including elevated LDL-C, hypertension, T2DM, and smoking. During this extended period there has been some fine tuning of these factors. About 20 years ago a new risk factor—inflammation—was added (see earlier). More recently, CHIP has emerged as yet another potent risk factor independent of the classic (canonical) coronary risk factors. It is exciting to contemplate the implications of this discovery, as well as the challenges and opportunities it presents. First, the fundamental mechanisms through which the somatic mutations operate must be understood. In addition, the recognition and diagnosis of CHIP should be facilitated and therapies identified. Although no specific treatment has been described, Libby et al. have recommended aggressive control of classic risk factors.[180] It has been suggested that canakinumab, the monoclonal antibody that has been shown to block IL-1β in the CANTOS trial (see earlier) was associated with a marked reduction in the risk of major cardiovascular events in patients with CHIP.[181] This intriguing observation requires confirmation.

ARTIFICIAL INTELLIGENCE (SEE CHAPTER 11)

The Present

This is a broad field in which machines are programmed to perform a variety of complex tasks; machine learning is an important subfield. Artificial intelligence (AI) is playing a rapidly expanding role in biomedical research and in many branches of clinical medicine, especially those in which the information base is enormous, often referred to as "big data." Cardiology, with its numerous waveforms, images, genomic analyses, biomarkers, devices and their output, and detailed clinical data contained in voluminous electronic medical records, is becoming a major area to which AI can make enormous contributions.

Attia et al. at the Mayo Clinic have shown in subjects in sinus rhythm that their AI program could identify those who had previously experienced atrial fibrillation and are at risk of recurrence.[182] Similarly, they developed a program that identifies asymptomatic subjects with an abnormally low ejection fraction and subjects with normal left ventricular function at risk of future development of dysfunction.[183] Thus, with the aid of AI, a simple 12-lead ECG could become a much more powerful screening tool; it can also aid in estimating prognosis, including predicting future cardiovascular mortality in patients with

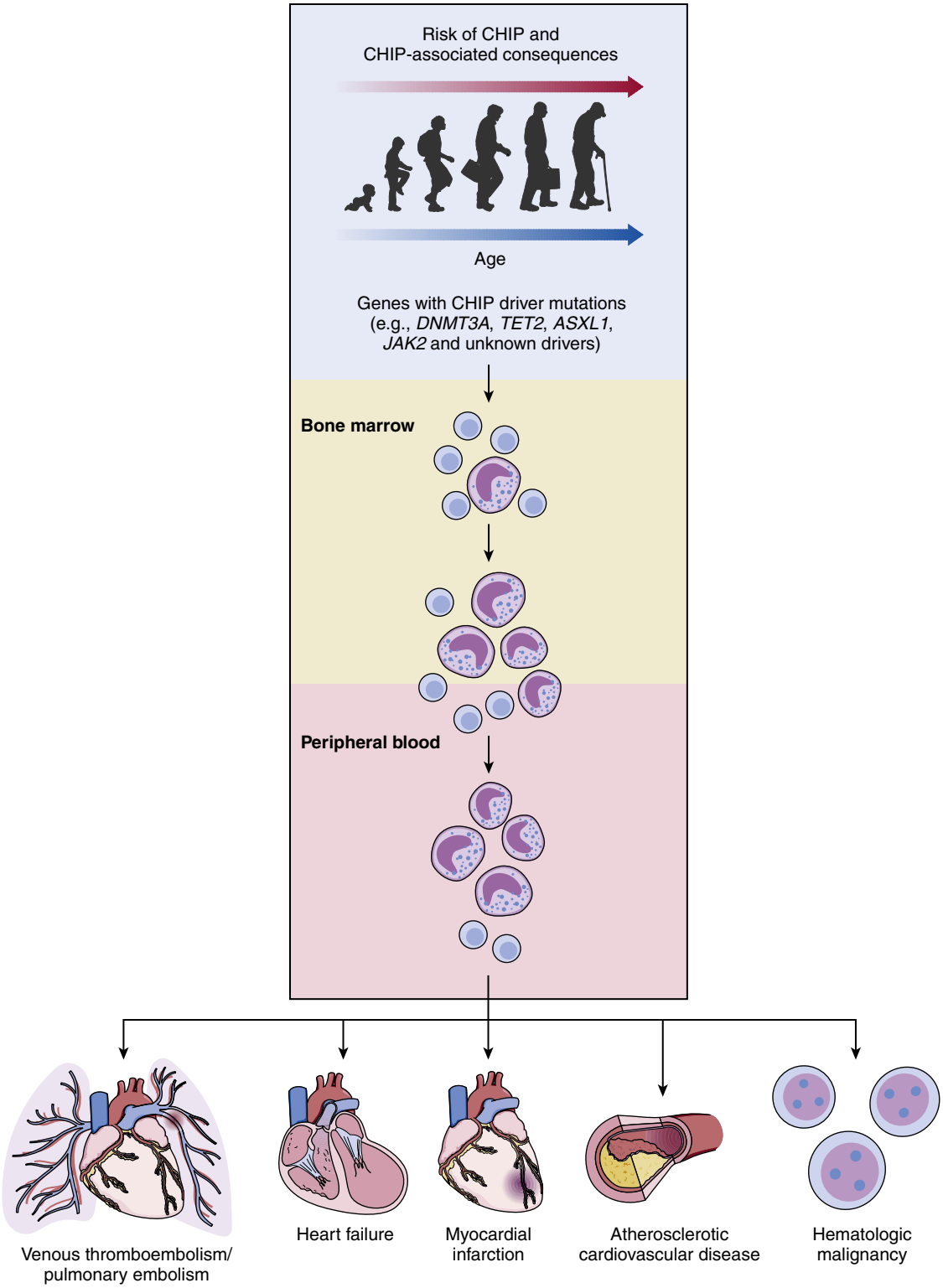

FIGURE 1.5 The progression of clonal hematopoiesis of indeterminate potential (CHIP). In ASCVD CHIP-driven expansion of myeloid cells enhances inflammation and cytokine production in the plaque. CHIP may also worsen response to pressure-induced cardiac remodeling and promotes thrombosis. (From Khetarpal SA, Qamar A, Bick AG, et al. Clonal hematopoiesis of indeterminate potential reshapes age-related CVD. J Am Coll Cardiol 2019;74[4]:578-586.)

HF.[184] AI has also been reported to use the ECG to detect hypertrophic cardiomyopathy, estimate the response to cardiac resynchronization therapy,[185] and identify patients at high risk of adverse events when undergoing TAVR.

AI appears to be useful in assessment of the rate of ventricular relaxation and in screening for diastolic dysfunction. Segar et al. have used AI to identify distinct phenotypic subgroups of patients with HFpEF. They identified three separate phenogroups with distinct clinical characteristics and outcomes.[186] Such an approach could be used to select and/or stratify patients enrolled in clinical trials of HFpEF. Given the heterogeneity of this condition, it may help in the identification of subgroups who respond to different therapies. Similar phenotyping has been reported in patients with dilated cardiomyopathy.[159] In its analysis of cardiac imaging AI can analyze both the structure and function of individual cardiac chambers and of specific regions of these chambers.[187]

The Future

The several examples of AI mentioned earlier represent pilot studies on selected patients. To determine their generalizability and to adapt this technology for routine patient care, the findings will require additional validation in specific and carefully phenotyped patient subsets. The ultimate goal of AI in clinical cardiology is to accelerate the practice of precision medicine (see earlier) and thereby to improve health care. AI could become of particular value in populations with limited access to specialists. However, concern has been raised that AI could place yet another technologic barrier between caregivers and their patients. Hopefully, it will have the opposite effect; by accomplishing complex tasks rapidly and accurately it could increase the efficiency of busy caregivers who would be freed up to provide more time for direct patient contact. Despite the initial expense of developing the necessary programs, AI could lower costs by reducing the need for expensive nonessential diagnostic procedures and shortening or avoiding hospitalizations.

CONCLUSIONS

As we approach the 400th anniversary of the publication of *De Motu Cordis*,[1] it may be of interest to consider the author of this founding document of cardiovascular science and its subsequent impact on clinical cardiology. William Harvey was a highly respected physician, the doctor to two kings of England, an admired lecturer, and, of course, an extraordinarily gifted investigator. Today he would be classified as an academic "triple threat." A majority of the investigators cited in this review were (or are) also triple threats. Eighteen have been rewarded with a Nobel Prize. Thus, cardiology is a science-based clinical specialty with a distinguished history.

Cardiovascular diseases were considered to be quite rare until the beginning of the 20th century, when over a relatively short period they became recognized as the most common causes of death in industrialized nations. Diagnosis and management of these conditions have improved immensely since 1950. It has been a unique privilege for this author to have had a ringside seat during this period and witness the enormous progress in this field. However, despite this progress, the incidence of cardiovascular morbidity and mortality remain disturbingly high.[188]

We have now reached a critical point in the history of cardiology. Going forward, it would seem wise to move in three directions: The first is to continue to apply further advances in the basic sciences to improving cardiovascular care; this has served our specialty well for almost 400 years and will continue to do so. The second, which is socioeconomic and political, is to ensure that the entire population benefits from the many advances that have been achieved.[188] This is certainly not the case today. Cardiovascular care is lagging in developing countries and in pockets of poverty and in minorities in industrialized nations. However, even when treatment and prevention are affordable they are often not employed. For example, hypertension remains a critically important risk factor for cardiac and cerebrovascular disease. Effective, well-tolerated and inexpensive antihypertensive drugs have been available for years. Yet BP is well controlled in only half of the hypertensive population in the United States. The third, and perhaps the most important direction, is to place greater emphasis, intellectual energy, and resources on prevention of cardiovascular disease and to begin this as early in life as possible.

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