It is an honor to contribute to this inaugural issue of Circulation: Heart Failure and to provide some personal reflections on the management of heart failure (HF). I will comment on the past and the present and will venture to make some predictions about the future of this important subject.

The Past
In 1950, as a medical student, I first learned about the management of congestive HF from the first edition of Harrison’s Principles of Internal Medicine, which had just been published. Management consisted of strict bed rest, sedation, dietary sodium restriction, digitalis, and administration of morphine and mercurial diuretics; the latter were only modestly effective and were administered by painful intramuscular injection. All of these measures (other than mercurial diuretics) had not changed for about a half century.

I replaced Harrison as the cardiology editor of Harrison’s Principles of Internal Medicine for the sixth edition, which was published in 1970. The management of HF, while still adhering to the principles set forth in the first edition, included 3 new aspects: 1) control of fluid retention with the (then) new orally effective diuretics—thiazides, the powerful new loop diuretics, as well as potassium-retaining diuretics (because of the widespread use of these agents, the adjective “congestive” was gradually eliminated from the name of the condition); 2) recognition and vigorous treatment of the precipitating causes of HF, such as infection, pulmonary embolism, and arrhythmias; and 3) intravenous dopamine, the powerful new β-adrenergic agonist for the management of acute, decompensated HF, including cardiogenic shock.

The Present
If we move forward 35 years and 10 editions of Harrison’s Principles of Internal Medicine, we come to the 16th edition, in which my chapter called attention to the importance of attempting to prevent HF in patients who were at risk for this condition but without overt HF. In these patients, treatment of hypertension and/or lipid disorders, regular exercise, and smoking cessation were recommended, as was angiotensin-converting enzyme inhibition. As in 1970, in symptomatic patients, diuretics, dietary salt restriction, and digitalis were advised. Prolonged bed rest, however, was replaced by early ambulation followed by the encouragement of physical activity. Venesection and heavy sedation were no longer advised. Extremely important new therapies had been introduced since the sixth edition; these included the neurohormonal blockers—β-adrenoreceptor blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and aldosterone receptor blockers. Vasodilators, such as hydralazine and nitrates, were deemed useful in patients whose HF proved refractory to the other therapies. Cardiac resynchronization therapy with biventricular pacing was recommended in patients with symptomatic HF, reduced ejection fraction, and prolonged intraventricular pacing. The use of automatic implanted cardioverter-defibrillators was also advised for patients with systolic HF and a reduced ejection fraction. Intravenous inotropic agents (inhibitors of phosphodiesterase-3 and new sympathomimetics) had been added to the therapeutic armamentarium for short-term treatment. For patients with refractory HF, cardiac transplantation, sometimes preceded by the use of a bridging ventricular-assist device, was recommended.

Both the physiology of the impairment of diastolic function and its clinical expression, that is, HF with normal systolic function, were described, but the section on the treatment of this form of HF was brief—only 8 lines! Reduction of pulmonary or systemic congestion with diuretics and slowing of heart rate with β-blockers to provide more time for ventricular filling were the only treatments recommended.

The major differences between my chapters on the same subject written 35 years apart were not only the specific treatments that were recommended but also the evidence on which they were based. In the sixth edition of Harrison’s Principles of Internal Medicine, recommendations for management were based on personal experience supplemented by the opinions of authorities and review of the literature (Level of Evidence: C). In the 16th edition, they were based largely on the results of multiple randomized clinical trials (Level of Evidence: A).

Evidence for progress in the management of HF comes from improved survival rates in population-based studies carried out over several decades, as well as from observations on the improved outcomes of patients with advanced HF listed for cardiac transplantation who were treated medically.

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58
The Future
Casey Stengel, the great American philosopher, said: “Never make predictions, especially about the future.” Although I will not heed that advice, I will try to play it safe and restrict myself to some of the advances in the treatment of HF that are likely to occur in the next decade or two.

Genetics
Genes contribute to many conditions that cause HF, including the cardiomyopathies. Three types of cardiomyopathies (dilated cardiomyopathy, hypertrophic cardiomyopathy, and arrhythmogenic right ventricular dysplasia) are caused by single gene mutations. Dilated cardiomyopathy, a common cause of HF, is familial in 30% to 50% of cases.7 Gene mutations encoding sarcomeric proteins, including cardiac troponin T and β-myosin heavy chain, as well as calcium handling proteins such as phospholamban, have been described in this condition. The latter appear to take a particularly malignant course, with early, progressive HF requiring cardiac transplantation.8 More than 400 separate mutations that encode sarcomeric proteins and are inherited in an autosomal dominant mode have been found in hypertrophic cardiomyopathy; new mutations are found with regularity. There appear to be differences in phenotype depending on the genotype. For example, some mutations of cardiac myosin binding protein C are associated with the relatively late development of HF. Mutations in cardiac troponin T cause relatively mild hypertrophy but are associated with a high risk of sudden cardiac death.9 The third cardiomyopathy, arrhythmogenic right ventricular dysplasia, is usually inherited as an autosomal dominant trait with incomplete penetrance. This pattern results in abnormalities of cell junctions and is a cause of both HF and fatal cardiac arrhythmias. Multiple mutations of genes in 6 loci have been described.10

In another monogenic disorder, Marfan syndrome, severe mitral regurgitation (due to leaflet prolapse and stretching of the valvular annulus) and severe aortic regurgitation (due to dilation of the sinuses of Valsalva) may cause HF.

There is substantial variability of expression of these single-gene disorders, as reflected in the large differences in the time of onset of HF within families. Discoveries of additional genes of familial cardiomyopathies, more detailed genotypic–phenotypic correlations, and the development of animal models of these conditions will undoubtedly enhance presymptomatic detection and early intervention. The elucidation of the molecular mechanisms responsible for these disorders will stimulate the development of more personalized management.

The situation in multigenic disorders is fundamentally similar to that in monogenic disorders, although far more complex. The variable expression of multiple genes interacting with a variety of environmental factors is responsible for the development of common conditions such as hypertension, type 2 diabetes mellitus, some dyslipidemias, and coronary artery disease. Research on identifying multiple genetic markers of increased risk of coronary events is underway. Recently, genome-wide association studies with gene chip–mapping technology have identified single nucleotide polymorphisms at 3 specific chromosomal loci that are associated with coronary artery disease.11 Genome-wide association studies are underway that examine the propensity for the development of cardiac hypertrophy, dysfunction, and HF with similar stressors such as hypertension and myocardial infarction. In a collaborative effort with other groups, we have conducted genetic association studies using polymerase chain reaction–based amplification of genomic DNA in patients with coronary artery disease or at high risk thereof. Polymorphisms in a gene encoding a protein involved in intracellular transport (KIF6SNP)12,13 and of the matrix metalloproteinase gene, ADAMTS14 have been found to be associated with markedly increased risks of coronary events in such patients; treatment with an hydroxymethyl glutaryl coenzyme A reductase inhibitor substantially reduces these risks.12–14

In the next 2 decades, we may expect to see a great expansion of research on variants in multiple genes that alter susceptibility for the development of hypertension and coronary artery disease. Such research will allow more targeted prevention of these conditions that represent the most common causes of HF worldwide.

Pharmacogenetics
The genetic determinants of the responses to drugs have important implications for the clinical course and management of HF. One example is the insertion/deletion polymorphism within the ACE gene. Even though there is no universal agreement on the matter, studies have reported that although the deletion/deletion polymorphism in patients is associated with HF with a poor prognosis, patients with that polymorphism appear to respond favorably to treatment with β-blockers.15 Liggett et al16 have reported that polymorphisms affecting the function of β-adrenergic receptors are important to the response of HF patients to β-blockers. Patients homozygous for the polymorphism that encodes arginine instead of glycine at position 389 in the receptor exhibited improved survival rates when they were treated with the β-blocker bucindolol. Patients with a relatively common polymorphism of the adrenergic α2c receptor (which increases norepinephrine release from postganglionic sympathetic neurons) and of the β1 adrenergic receptor (which enhances the response of the myocyte to norepinephrine) have been shown to be at higher risk of HF but also to respond well to β-blockade.17 Variants in the genes encoding proteins involved in drug metabolism, such as the CYP hepatic enzymes, modify the responses to a number of pharmacological agents used in the treatment of HF. We are now on the threshold of many additional advances in pharmacogenetics, advances that during the next decade or two will enhance both risk stratification of patients with or likely to develop HF and selection of the most appropriate therapy.

Gene Therapy
Two decades ago, gene therapy was hailed as the obvious route to the management of many disorders, including HF. There have been many obstacles to the clinical application of this approach, however, and because of several widely publicized deaths, investigators have returned to the laboratory. Hajjar et al18 have outlined 3 challenges to gene therapy:
(1) development of an ideal vector (such as an adeno-associated virus) to provide high levels of transgene expression; (2) an adequate method of delivery of this vector to the myocardium (such as through intracoronary artery injection); and (3) identification of appropriate gene targets, such as cardiac S100A1, a calcium binding protein, and sarcoplasmic reticular Ca\(^{2+}\) ATPase. It has been shown in animal models that genetic enhancement of the latter increases the uptake of Ca\(^{2+}\) by sarcoplasmic reticulum, which enhances both myocardial contractility and the speed of myocardial relaxation. Clinical trials of this approach are commencing. If they demonstrate both safety and improvement in ventricular function, they will lead to a large expansion of clinical research of gene transfer for treatment of HF. However, the jury is still out on this approach.

**Cell-Based Therapies**

Most forms of HF, irrespective of origin, are caused by myocyte loss secondary to necrosis and/or apoptosis complicated by adverse remodeling; many laboratories are investigating cell-based therapies designed to combat these causes. Several cell types are being studied, both in vitro and in animal models. These include embryonic stem cells (which have the potential undesirable effects of being tumorigenic and/or immunogenic); unfractionated bone marrow cells (which contain a variety of stem and progenitor cells); multipotent bone marrow–derived stem cells; mesenchymal stem cells; circulating blood-derived progenitor cells (including endothelial progenitor cells and hemangioblasts); stem cells derived from adipose tissue, testis, and cord blood; and autologous skeletal myoblasts (which have the potential to cause ventricular tachyarrhythmias). The optimal cells for the treatment of various forms of HF require identification.

The mechanism of the apparent beneficial action of stem cells is still unclear. Possibilities include their differentiation into or fusion with cardiac myocytes, enhanced neovascularization that could reduce myocardial ischemia, and paracrine actions that may be antiinflammatory and/or that may stimulate endogenous repair. Optimum methods of cell delivery are being explored; these include the use of balloon catheters for the intracoronary infusion of cells to specific regions of the ventricle; catheter injection into endocardial sites identified by electromechanical mapping; and direct injection into the ventricular wall, either percutaneously or at the time of surgery.

Research into cell-based therapies is being stimulated by the encouraging, albeit modest, early results of several (although certainly not all) trials in which bone marrow cells were infused into the coronary arteries of patients with acute myocardial infarction. Some trials have demonstrated improvement of left ventricular function but they were inadequately sized to demonstrate a change in clinical outcome. Bone marrow–derived progenitor cells have also been administered to patients with HF secondary to old myocardial infarction and HF, but the number of such patients treated thus far has been too limited to draw even tentative conclusions.

Although the intracoronary injection of unselected autologous bone marrow–derived stem cells in patients appears to be safe, many questions remain to be answered. Important among these is how these cells should be treated before their reinjection. There are suggestions that granulocyte colony-stimulating factors and other proangiogenic factors may enhance the mobilization of progenitor cells from the bone marrow without direct injection. More should be learned about the optimum cell types for such therapy, as well as the best preparation and method and timing of delivery. It then will be appropriate to conduct large-scale trials powered to examine the effects on clinical outcomes of patients with acute and chronic HF. Such trials, if positive, could lead to the clinical application of cell-replacement therapy to prevent or treat HF in selected populations.

The induction of pluripotent stem cells derived from fibroblasts through genetic reprogramming represents a major advance for potential cell-based therapy. However, it is too early to estimate the likelihood that this innovative approach will alter the treatment of clinical HF in the next 1 or 2 decades.

**Mechanical Assistance**

For many years, cardiac transplantation was the only proven therapy for endstage HF, but it has been, and for the foreseeable future will be, severely limited by the availability of donor hearts, which actually may be diminishing. Several types of ventricular assist devices (VADs) are now used routinely as bridges to transplantation and are being investigated as destination therapy or as bridges to recovery with ultimate explantation of the VAD. The landmark Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial demonstrated that a totally implantable, pulsatile VAD improved survival rates in patients with endstage HF who were not eligible for cardiac transplantation. However, the device that was used in this trial, the HeartMate Left Ventricular Assist System (Thoratec, Pleasanton, Calif), is large and requires extensive surgical dissection and a large percutaneous lead. Moreover, many complications accompanied use of this VAD, including excess bleeding, thromboembolic events, infection, device failure, right ventricular failure, multisystem organ failure, and immunologic perturbations, resulting in a 2-year survival rate of only 20%.

Efforts to eliminate or reduce the incidence of these complications, as well as to miniaturize the implanted devices, are now underway. The latter include several nonpulsatile axial and centrifugal pumps. These continuous-flow pumps appear to be associated with fewer complications and are undergoing study in pivotal trials. Axial-flow pumps, which can be inserted without cardiopulmonary bypass, appear particularly attractive. In addition, pumps in which the inflow and outflow catheters are placed percutaneously and that can be used for up to 2 weeks in patients with acute, severe HF secondary to cardiogenic shock or fulminant myocarditis are now available. Total artificial hearts are also under active development.

With the anticipated reduction in complications resulting from improved, smaller VADs, the indications for device implantation may be expected to expand rapidly—to first provide destination therapy to patients with advanced HF for
whom a donor heart cannot be obtained and then to patients with chronic, but less severe, HF who at this time are not candidates for transplantation. Another important area of current investigation that might become applicable in certain circumstances will involve weaning patients from assisted circulation with explantation of the device after pharmacologically aided recovery of myocardial function.²⁰

It is not too far-fetched to consider the synergistic application of 2 or even 3 of the experimental therapies discussed here. For example, a patient with severe HF after a massive acute myocardial infarction might first be stabilized with one of the new percutaneously inserted flow pumps mentioned above. This treatment would provide adequate time to obtain and prepare a sufficient number of progenitor cells from the patient’s own bone marrow, These cells would then be treated appropriately, perhaps with gene transfection, and injected into the affected region of the ventricle at the optimal time after infarction. After the interval required for these cells to exert their therapeutic action, attempts would be made to wean the patient from the VAD. If weaning were unsuccessful, permanent support from a miniature implanted continuous flow device could be used as a backup.³¹

Conclusions

The field of HF study is now at a historic juncture. On the one hand, the pandemic of HF is increasing rapidly because of the aging of the population and an ever-increasing number of persons who have survived one or more acute coronary syndromes but who have sustained myocardial damage. On the other hand, progress in the prevention and treatment of HF, which was agonizingly slow in the past, is now accelerating rapidly. Further advances in genetics, cell biology, and molecular pharmacology are certain to enhance understanding of the various causes of and basic mechanisms responsible for HF; this understanding and simultaneous developments in bioengineering could have an enormous beneficial impact on both the incidence and management of HF. Therefore, this is a most propitious time to launch Circulation: Heart Failure. Of my several predictions, the one of which I am most confident is that, in the pages of this new journal, the most exciting advances in HF treatment will be reported, refined, and debated, thereby contributing significantly to progress in this very important field.

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Disclosures

None.

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The Management of Heart Failure: The Past, the Present, and the Future
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