Without question, the past half century has witnessed spectacular advances in cardiovascular medicine and surgery. In the United States, a full two thirds of the 6-year prolongation of life that has occurred has been a direct consequence of these advances\(^1\) that did not spring forth simply from the heads of brilliant, insightful clinicians. Instead, most advances were based on preclinical research that were then translated into improvements in clinical care.\(^2\)

For instance, the microbiologists who connected streptococcal infection to acute rheumatic fever and, subsequently, the discovery of penicillin by a microbiologist, an experimental pathologist, and a biochemist led to the virtual elimination of acute rheumatic fever, which in turn was responsible for the marked reduction of chronic rheumatic valvular heart disease in large portions of the world. Almost all residual cases of the latter can now be corrected by open heart surgery or catheter-based techniques, which were made possible by the efforts of bioengineers, pharmacologists, and physiologists collaborating with surgeons and cardiologists. The striking reduction in mortality of acute myocardial infarction that has occurred since 1960\(^3\) would not have been possible had physicists not previously developed the cathode ray oscilloscope, which enabled the continuous monitoring of the ECG, and if engineers had not developed the capacitors that store the electric charge required for ventricular defibrillation. Without pharmacologists and cell biologists, statins, which are enormously useful in preventing the development and progression of atherosclerosis, would not have been developed. These are just a few examples of the seminal scientific efforts that have provided the underpinnings of modern cardiology.

However, despite the spectacular advances of the past half century, cardiovascular disease is still the most common cause of death and disability in industrialized nations,\(^4\) and its prevalence is rising rapidly in developing nations. Almost one half of all cardiac deaths and disabilities are related to failure to apply well-established, evidence-based, guideline–approved therapies and preventive measures. These failures stem largely from inadequate access to care, poverty, and the disorganization of the medical care system in many countries, and they require political, economic, and societal changes. The remaining cardiovascular events, still a major problem in public health, result in large measure from the deficiencies in our understanding of cardiovascular pathobiology.
One major disorder, heart failure (HF), remains a stubborn problem and is now considered to be the greatest challenge in cardiovascular medicine and surgery. From a clinical perspective, HF has been defined as “a complex syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood. The cardinal manifestations of HF are dyspnea and fatigue, which may limit exercise tolerance and fluid retention, which may lead to pulmonary and/or splanchnic congestion and/or peripheral edema.”

There are now >5 million patients with HF in the United States, and that number is expected to reach 8.5 million by 2030. More than a million hospitalizations for HF occur annually in the United States alone, and >650,000 new cases are diagnosed each year. Approximately one half of persons diagnosed with HF will die within 5 years. The costs are staggering, ≈$40 billion/y, and are expected to double by 2030.

Because basic scientists have contributed so much to the success of prevention and treatment of many cardiovascular disorders, Dr Roberto Bolli, the Editor-in-Chief of Circulation Research, decided to devote this issue of the journal to a Compendium consisting of a series of Reviews about major research advances in HF. In preparing this Compendium, the goal was not to develop a textbook on HF. Instead, it was designed to provide cardiovascular scientists, clinicians, and their trainees with an update on progress in several important aspects of the field, and thereby to stimulate further basic and translational research on this important condition.

Epidemiology of HF

During the past 25 years, landmark randomized trials have demonstrated substantial improvements in the treatment of patients with HF with reduced ejection fraction (HFrEF), also referred to as systolic HF, with clear benefits resulting from agents interfering with the renin–angiotensin–aldosterone system as well as the adrenergic nervous system. However, it often takes several years for the results of clinical trials to be incorporated into clinical practice. It then takes additional time for the results of these changes in practice to make their way into databases, the rear view mirrors on which epidemiologists depend. The tasks of epidemiologists are further complicated by different practice styles and the varying thresholds for hospital admission in different countries, by different providers, and different payers.

Despite these challenges, we learn from Roger’s scholarly review that the steady increase in the age-adjusted hospital admission rate for HF in the United States that characterized the second half of the twentieth century seems, finally, to have stabilized. It is possible that this stabilization is related to a reduction in the incidence of acute myocardial infarction and the effectiveness of preventive measures of atherosclerosis, including reductions in cigarette smoking, severe hypertension, and dyslipidemia. However, hospital readmission rates remain high. Because the prognosis of patients with HF has also shown some improvement, patients live longer after the diagnosis of HF is established and, therefore the prevalence, that is, the number of patients alive with HF is actually rising. Also increasing is the economic burden imposed by the growing number of patients living with this condition, their need for rehospitalization, and sometimes for expensive devices and drugs. Because a large fraction of patients with HF are elderly, they are often burdened by the comorbidities associated with aging, including cancer, diabetes mellitus, and pulmonary and renal failure, as well as neurocognitive decline. HF is more common and occurs at an earlier age in men and in blacks than in women and in whites.

Roger points out that the phenotypic profile of HF seems to be changing. HF with preserved EF (HFpEF), also referred to as diastolic HF, is now as prevalent as HFrEF in community-based studies, whereas the latter remains more common in referral centers. HFpEF occurs more commonly in women and in patients with diabetes mellitus, hypertension, obesity, atrial fibrillation, and the elderly. The reduction in the incidence and severity of ST segment elevation myocardial infarction, a major cause of HFrEF, concomitant with the increases in diabetes mellitus and obesity (diabesity) seems to be responsible for the change in the distribution between the 2 principal HF phenotypes.

HFpEF is not a disease, but it is a syndrome which is not well understood. Diastolic dysfunction is characterized by impairment in the rate of ventricular filling, but the relative importance of slowed relaxation of myocytes, of increased thickness of the ventricular wall, concentric remodeling, and of excessive proliferation of the extracellular matrix (ECM) responsible for this syndrome requires elucidation and undoubtedly varies among patients. Although clinicians classify patients with HF into these 2 categories by an EF threshold (commonly 50%), this is an oversimplification because the majority of patients with advanced HF exhibit abnormalities of both ventricular filling and ejection, and it is often challenging to distinguish the horse from the cart.

There are many opportunities for preclinical scientists to clarify the pathobiology of HFpEF. Although a variety of pharmacological and device therapies effective in the treatment of HFrEF have been described and are reviewed in this Compendium, the management of patients with HFpEF is considerably more challenging. All that is available today are diuretics to reduce sodium and water retention, thereby reducing pulmonary engorgement and resulting dyspnea, and slowing of the heart rate to provide more time for ventricular filling. Efforts are underway to study the potential benefits of mineralocorticoid receptor blockers, as well as nephrilysin inhibitors. It is possible that we will remain in a hit or miss mode with therapies for HFpEF until the pathobiological mechanisms responsible for this syndrome have been identified so that individualized therapies that are tailored to these mechanisms can be developed.

Genetic Cardiomyopathies Causing HF

In a seminal article titled: “Uncommon myocardial diseases: the non-coronary cardiomyopathies” published in 1957, Brigden, distinguished London cardiologist, noted the familial associations observed in several of these seemingly diverse disorders. My own interest in a form of cardiomyopathy that is associated primarily with ventricular hypertrophy (and now known as hypertrophic cardiomyopathy [HCM]) was sparked a year later, when my surgical colleague A.G. Morrow and I encountered 2 unrelated young men with exertional dyspnea who had severe subaortic obstruction to left ventricular outflow, evidently caused by muscular hypertrophy of unknown pathogenesis. As more patients with this condition presented,
we encountered 3 siblings with subaortic muscular obstruction.15 During the same year, Hollman et al16 reported a family with HCM. We then described the dynamic nature of the obstruction, its provocation or intensification by adrenergic agonists, its natural history, and its treatment with β-blockers and surgical myectomy.17

Three decades after these clinical and pathological observations, the modern study of the genetics of the cardiomyopathies was launched by the discovery by the Seidmans and their associates that a missense mutation in the β-myosin gene was the cause of HCM in some families.18 In this Compendium, Cahill et al19 provide an excellent update on the several primary genetic cardiomyopathies causing HF. As they point out, HCM is recognized to be the most common monogenic cardiomyopathy, present in 1 of every 500 births, and it is associated with HF in about one sixth of cases. Approximately one half of the latter are caused by HFpEF, secondary to the impeded filling of the hypertrophied, stiffened left ventricle. Others are related to late thinning and fibrosis of the ventricular wall, resulting in left ventricular dilatation HFpEF.20 HCM is caused by >1400 mutations in 10 sarcomeric genes, encoding thick and thin myofilaments and the Z discs.18,19 Most of these are missense mutations resulting in the substitution of a single amino acid. The most frequently affected genes encode the β-myosin heavy chain and cardiac myosin-binding protein C. There seems to be a gene–dose effect, in that patients with 2 (or more) mutations are usually affected by a more severe form of the disease.

Among the cardiomyopathies described by Brigden13 were those with thin-walled, dilated left ventricles and HFpEF, the so-called dilated cardiomyopathies (DCM). Some have clear cut, acquired pathogeneses such as chronic alcoholism. Others are idiopathic and, among the latter, about one third are familial. More than 50 gene mutations have been described; those in the gene encoding the sarcomeric protein titin are the most frequent.21

A third important genetic cardiomyopathy is generally referred to as arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D). This condition is characterized by transmural fibrofatty replacement of the myocardium and is usually associated with right ventricular dysfunction and failure, sometimes severe enough to require cardiac transplantation. Ventricular tachycardia, syncope, and sudden cardiac death are frequent complications. Occasionally, there is involvement of both ventricles and, even less commonly, the left ventricle alone is affected. For this reason, in their review, Cahill et al19 refer to this condition as arrhythmogenic cardiomyopathy.

Genetic penetrance is lower in ARVC/D than in HCM or familial DCM.

ARVC/D is considered to be primarily a disease of the desmosome, which is responsible for cell-to-cell adhesion and is required for the effective transmission of force across myocytes during contraction. Many cases are familial. In North America, approximately one half of the patients have a mutation in one of the several desmosomal genes. Such patients tend to have earlier onset of the disease and are more likely to exhibit ventricular tachycardia than those in whom no such mutation is present.22 Multiple mutations, as many as 38 in 1 of the 7 most frequently occurring genes, have been reported. Compound and digenic heterozygosity mutations are not uncommon. In addition to the genes associated with autosomal dominant transmission with reduced penetrance, 2 syndromes associated with recessive transmission have been identified.19

Among the less common inherited cardiomyopathies are those resulting from mitochondrial DNA mutations that cause multisystem diseases, which include cardiomyopathies; the latter may present as HCM or as cardiac conduction disorders; inheritance is, of course, maternal.

Genetic diseases are experiments of nature, which can be extremely informative. For example, the classic experiments of Pauling and Ingram tied a genetic mutation to a single amino acid substitution in the hemoglobin molecule that causes sickle cell anemia. In their Nobel Prize lecture, Brown and Goldstein24 described how their research on the low-density lipoprotein cholesterol receptor was stimulated by observations on patients with familial hypercholesterolemia and how a new class of drugs, the HmGCoA reductase inhibitors, upregulated the expression of low-density lipoprotein receptors and reduced circulating low-density lipoprotein cholesterol concentration. In cardiology, the enhanced risk of serious arrhythmias and sudden death occurring in families, stimulated intense study of the physiological properties of ion channels in the cardiomyocyte cell membrane. A new category of diseases, the ion channelopathies, has been identified; the natural history of each of these is being described, and specific treatments are under development.

These 3 examples demonstrate how genetic diseases can lead to an increase in the understanding of fundamental biology which can, in turn, be used to improve patient care. The genetic cardiomyopathies responsible for the development of HF can play a similar role. For example, mutations in the genes encoding contractile proteins can shed light on the structure, function, and dysfunction of these proteins. An interesting example comes from the provocative study of Robinson et al25 who compared mutations of genes encoding the thin filament regulatory proteins, troponin, and tropomyosin, which occur in both HCM and DCM. These mutations have contrasting effects on the affinities of the cardiac thin filaments for Ca2+, which are increased in HCM and reduced in familial DCM.

These intriguing observations could help to explain how different mutations affecting the same regulatory proteins can cause totally different phenotypic expression. Another example is how inherited cardiomyopathies can increase understanding of the structure and function of the desmosome. The observation that ARVC/D is primarily a desmosomal disease has provided a strong stimulus for the successful identification of the most important genes that encode desmosomal proteins and how their mutations affect desmosomal function.

Elucidation of the biology of genetic causes of HF has led to genetic tests for these disorders that are assuming progressively more important roles in the detection and management of the familial cardiomyopathies. The role of such testing is furthest advanced in HCM.26 In probands with clinical HCM in whom a causative mutation has been identified, the screening of family members, especially those who are asymptomatic, should be performed. In relatives who are genotype negative,
the development of HCM is extremely unlikely. Those who are genotype positive, but without clinical manifestations, that is, phenotype negative, should undergo clinical examination and noninvasive imaging at intervals. Engagement in competitive sports should probably be discouraged in such persons, and genetic counseling is strongly recommended.

In patients with familial DCM, the goal of genetic testing also is to identify mutant genes in both symptomatic and asymptomatic family members of an affected proband. A randomized placebo-controlled trial of prophylactic neurohormonal blockers in genotype positive, phenotype negative subjects would be of great interest to determine whether such therapy can prevent or at least defer the development of HF. Of particular interest are the >300 mutations in the LMNA gene, which encode the proteins that are responsible for defects in the nuclear membrane and that are associated with a variety of arrhythmias that may occur before detectable cardiac dilation and HF. These arrhythmias include atrioventricular block, as well as atrial and ventricular tachyarrhythmias leading to sudden cardiac death. If a mutation in this gene is discovered during family screening, the implantation of a cardioverter-defibrillator might reduce the risk of sudden cardiac death in some asymptomatic subjects.

A commercial clinical test for ARVC/D is now available, but the complex genetics of this condition, including incomplete and quite variable penetrance, complicates its interpretation. So-called radical mutations (in-frame, frame-shift insertions and deletions) seem to be rare in normal subjects but occur in almost one half of patients who are likely to develop clinical manifestations of this cardiomyopathy. However, missense mutations are observed at similar frequencies in patients and in controls and may be considered to be background noise.

Thus, further study by both basic and translational scientists, of the genetic cardiomyopathies that can be responsible for HF is certain to broaden our understanding of normal and disturbed cardiac contraction, relaxation, and rhythm. It will also continue to improve the care of patients with these disorders.

**MicroRNAs in Cardiac Remodeling and HF**

The discovery, 20 years ago, of short, noncoding RNAs, termed microRNAs (miRs), represents an important, exciting advance in biology. These molecules of 18 to 22 nucleotides are important regulators of gene expression at the posttranscriptional level, are evolutionarily conserved, and are present in virtually all forms of life. More than 2000 miRs have been isolated, and their roles during normal development and in a variety of diseases, including cancers and cardiovascular disorders, are being elucidated. In their thorough review of miRs in this Compendium, Kumarswamy and Thum focus on the role of this class of molecules in cardiac hypertrophy and HF, and they provide several examples of their importance in these conditions.

For example, both miR-1 and miR-133 regulate genes involved in the development of ventricular hypertrophy. In mice with aortic constriction, genetic deletion of miR-133 prevents the development of compensatory left ventricular hypertrophy; instead, the left ventricle develops a dilated cardiomyopathy in response to this stimulus. Overexpression of miR-132 and miR-212 causes HF, and their genetic deletion protects the ventricles from pressure load–induced hypertrophy. MiR-378 attenuates such hypertrophy by suppressing the mitogenic-activated protein kinase pathway. MiR-21 increases fibroblast survival and the development of cardiac fibrosis.

The miR profiles in failing adult hearts resemble those of fetal hearts and may play a role in the virtual disappearances of the α-heavy chain myosin, a rapidly contracting isoform in the normal adult heart in favor of the more slowly contracting β-isoform characteristic of normal fetal hearts. miRs seem to be important in clinical HF as well. Thus, miR-499 has been shown to be upregulated in failing human hearts. As pointed out by Matkovich et al, it is remarkable that the upregulation of just a single miR affects transcription and posttranslational modification sufficiently to cause clinical HF. Also of clinical interest is the finding that miRs may enter the circulation, where they could become useful biomarkers in a variety of conditions, including HF. MiRs may become therapeutic targets as well. For example, antagonists of miRs (antagomirs) are being developed to silence miRs. Antagonists to miR-34 and miR-199 have been reported to reduce cardiac remodeling and improve ventricular function in mice with left ventricular hypertrophy or dilation secondary to myocardial infarction or aortic constriction. Clinical trials with miR inhibitors (in patients with hepatitis C) have begun. The investigation of targeted inhibitors in patients with ventricular hypertrophy is very likely to follow quite soon.

We have entered an important new field that will complicate, but ultimately enrich our understanding of a vast array of physiological and pathophysiologic processes. miRs and, as pointed out by Kumarswamy and Thum, the even more recently discovered longer noncoding RNAs, may play important roles in biology and clinical medicine, including HF.

**Ca²⁺ Cycling in HF**

Many investigators have contributed to our understanding of the critical role played by Ca²⁺ in cardiomyocyte function and dysfunction. Two landmark contributions to this field stand out, and I have been privileged to enjoy a connection, albeit a somewhat remote one, to both. The first is the groundbreaking observation of Ringer in 1883, who discovered, largely by accident, the necessity of this ion in the perfusate for contraction of isolated hearts. In the early 1960s, in a popular experiment on the isolated turtle heart in a course in cardiac physiology which I taught to medical students, we repeated and extended Ringer’s work. Without Ca²⁺ in the perfusate, the heart was relaxed and quiescent. As we increased the [Ca²⁺] progressively, the heart began to beat and the strength of contraction increased, until with higher concentrations, relaxation ceased, and the heart went into contracture. Clearly, there was a sweet spot of [Ca²⁺] in the perfusate.

The second landmark contribution came from the experiments of Alexander and Francoise Fabiato performed in the Department of Medicine at the (then) Peter Bent Brigham Hospital, which I headed at the time they performed these studies in the early 1970s, thereby gaining observer status. The Fabiatos demonstrated that small quantities of Ca²⁺...
enter the myocyte during excitation and cause the release of much larger quantities of this ion from the sarcoplasmatic reticulum (SR), which in turn triggers interaction between the contractile proteins, causing myocyte contraction.60 These observations initiated the modern era of the study of excitation–contraction coupling and of normal and abnormal Ca2+ cycling in cardiomyocytes. It is now known that the Ca2+ released by the SR into the cytoplasm binds to troponin C on the actin filaments, which, in turn, triggers contraction, and that the intracytoplasmic [Ca2+] is a powerful determinant of myocyte force development.

Abnormalities in Ca2+ cycling are central to the changes in contraction and relaxation in HF and are the subject of the comprehensive review in this Compendium authored by Luo and Anderson.41 These abnormalities include changes of Ca2+ influx into the myocyte through the L-type Ca2+ channels during excitation, which in turn leads to alterations of Ca2+ release from the SR through the Ca2+ release channels, also known as the ryanodine receptors (RyR2). In HF, these channels may develop a diastolic leak and, as a consequence, myocyte relaxation may be delayed and incomplete, while the quantity of Ca2+ in the SR available for release during systole and therefore the force of contraction become reduced. Indeed, myocytes obtained from failing human hearts have shown prolonged decay of the Ca2+ transient and reduced peak systolic intracellular [Ca2+], apparently caused by the decreased SR Ca2+ release.42

Although it is agreed that the diastolic leak of the RyR2 is present in both clinical and experimental HF, there has been controversy about the mechanism responsible for this RyR2 dysfunction.43 Luo and Anderson44 review work from their and other laboratories supporting the view that Ca2+ and calmodulin-1–dependent protein kinase II (CaMKII), a multifunctional enzyme consisting of 2 hexameric rings, serves as an important regulator of Ca2+ homeostasis. CaMKII is activated by autophosphorylation resulting, at least in part, from elevations of the neurohormonal hyperactivity that is characteristic of HF.44 Overexpression of CaMKII in turn seems to hyperphosphorylate several key proteins responsible for Ca2+ cycling, including RyR2,45 sarcoplasmic-endoplasmic reticulum ATPase (SERCA2a), L-type Ca2+ channels, and the late Na+ channel. These actions complement one another to cause intracellular Ca2+ overload, apoptosis, HF, and lethal ventricular arrhythmias. Cardiac muscle obtained from patients with HF exhibited increased CaMKII activity. On the other hand, CaMKII inhibition seems to exert a protective effect.44

From a therapeutic perspective, pharmacological agents that increase intracellular [Ca2+] such as ß adrenergic agonists and type 3 phosphodiesterase inhibitors are useful for providing short-term inotropic support and can be lifesaving in acute HF; but their oxygen wasting activity can cause fatal tachyarrhythmias when they are administered during longer periods. Therefore, the goal in the treatment of chronic HF has shifted to reducing neurohormonal activation with ß blockers, angiotensin-converting inhibitors, angiotensin II receptor blockers, and mineralocorticoid receptor blockers. Newer therapeutic approaches currently undergoing development include efforts designed to increase the activity of SERCA2a, which pumps Ca2+ back into the SR, as well as reduction in the activity of phospholamban, an inhibitor of SERCA2a. As pointed out in the review by Pleger et al46 in this Compendium, SERCA2a and phospholamban are important targets of gene transfer. Other agents that may improve myocardial contractility by acting on myocyte Ca2+ cycling include S100A1, a protein that interacts with both SERCA2a and RyR2,47 which also requires gene transfer, as well as small molecules, such as mecamtiv mecarbil, that increase the sensitivity of cardiac myofilaments to Ca2+ and increase stroke volume by increasing the duration, but not the rate, of cardiac contraction and therefore do not require much additional oxygen.48 Also, RyR2 stabilizers49 are being actively investigated.

Cardiac Metabolism in HF

I was recently surprised to learn from my grandchildren that high school students are now introduced into the arcane (for them) subject of the metabolism of the heart. They are taught that each day, the heart pumps upwards of 10 tons of blood and therefore requires more energy than any other organ. To supply this energy, the heart must be fed continuously, and its diet is composed of fatty acids and glucose. The former is the principal fuel. Both are broken down into 2-carbon fragments, which are taken up by the mitochondria of the cardiomyocytes where they enter the Krebs (tricarboxylic acid) cycle in which ATP is generated. When the heart is deprived of oxygen, glucose is broken down to pyruvate, which is converted to lactate in an inefficient production of ATP. They also learn that the metabolism of the heart must be able to adjust virtually instantaneously to sudden changes in its demands for energy, as might occur if a person were suddenly to confront a lion and must sprint away rapidly to stay alive (and, from an evolutionary perspective, to live to help perpetuate the species).

Well, that is about all that was known about cardiac metabolism until relatively recently. However, we now also know that in resting subjects, about two thirds of the ~6 kg ATP that is generated each day is used to fuel cardiac contraction and relaxation, while the remainder provides the energy for cellular housekeeping functions and protein synthesis. During heavy exercise, much larger fractions of the generated ATP are required for cardiac contraction.

Doens et al50 provide an excellent updated review of cardiac metabolism in this Compendium. Cardiac metabolism is more complex in patients with HF than in normal subjects. A major reason for this complexity is that both in patients and in animal models, HF is quite heterogeneous, and varies by species, pathogenesis, and severity. Therefore, not surprisingly, it is not possible to provide a concise, accurate, and specific description of cardiac metabolism in HF. However, the concept that reduced energy stores play a critical role has been around for a long time. In 1939, Herrmann and Decherd51 reported that the creatine content of failing human myocardium was reduced and suggested that HF was attributable to energy starvation. This view is supported by the clinical observation that ß-adrenergic blockers, which reduce the energy requirements of the heart, are very effective in the treatments of chronic HF.52 Conversely, as already noted, administration of positive inotropic agents that increase energy demands is associated
with adverse clinical outcomes in such patients. Also, there is agreement that in virtually all models and forms of HFpEF, mitochondrial morphology as well as the mitochondrial proteome are altered, and that these changes are associated with reduction of both mitochondrial respiration and high-energy phosphate production. Recent work by Ahuja et al.50 has shown in patients with HFpEF and dilated cardiomyopathy that mitochondrial dysfunction is accompanied by damage to its DNA and suggests that the resultant reduction in high-energy phosphate generation is responsible for the left ventricular dysfunction in this condition.

There is increasing evidence that cytosolic [Ca^{2+}] in cardiomyocytes affects their mitochondrial [Ca^{2+}], and that the latter controls several enzymes in the tricarboxylic acid cycle, thereby regulating energy production.54 Lin et al.55 have shown in the Syrian hamster with hereditary cardiomyopathy that abnormal Ca^{2+} cycling may lead to a reduced mitochondrial [Ca^{2+}], which can, in turn, lead to decreased energy production and ventricular dysfunction and thereby play an important role in the pathogenesis of HF.

In 1967, my colleagues and I observed in a feline model of pressure overload HF that the concentration of myocardial creatine phosphate (CP) was reduced, while that of ATP was maintained, and hence the CP/ATP ratio was reduced.56 It was not clear to us whether these changes in high-energy phosphates were the cause or the effect of cardiac dysfunction or simply an epiphenomenon. While our observations were subsequently confirmed, some more recent studies noted modest reductions of [ATP] in HF,57 that was likely more severe than that in our feline model. Measurements of ATP and CP by phosphorus-31 magnetic resonance spectroscopy in human HFpEF have shed some light on these issues. In normal subjects, the CP/ATP ratio is >1.6 and, in HF, the creatine transporter is impaired, leading to reductions in both total creatine and CP, so that the CP/ATP ratio falls <1.6, whereas in patients with severe HF it may even decline to <1.0.58,59 Both mitochondrial and myofibrillar creatine kinase activity may be impaired in HF.

More work is required, both in animal models and in patients with ventricular hypertrophy, with and without HF, to understand the role of these changes in high-energy phosphates in the development of HF. It would be useful to study the sequential changes using both positron emission tomography and cardiac magnetic resonance imaging and spectroscopy technologies. It is likely that not only the total, but also the intracellular distributions of these molecules will prove to be of importance. Various forms of HF, including HFpEF, should be studied.

From a therapeutic perspective, it may be possible to modify the contraction of the failing ventricle by altering its metabolism. Although changing the concentration of circulating fatty acids has not had a consistent effect on the contraction of failing hearts, enhancing glucose uptake and use may exert beneficial effects. Therefore, efforts directed at stimulating glucose use by failing hearts could prove to be useful clinically and should be pursued. As Doons et al.60 point out, activation of adenosine monophosphate kinase, which stimulates myocardial ATP production by increasing fatty acid oxidation and glycolysis,60 may be helpful. Importantly, glucagon-like peptide-1 enhances the production of insulin by the pancreatic β cells and reduces glucagon production by the α-cells. The stimulation of glucagon-like peptide-1 receptors in the heart has been found to enhance contractile function in animal models of HF61 as well as in patients,62 presumably by increasing glucose use. Because glucagon-like peptide-1 agonists are now widely available, are used frequently in the treatment of diabetes mellitus, and are well tolerated (with the exception of a low incidence of acute pancreatitis), their further study in clinical HF should be a high priority.

Thus, it seems that while substantial efforts to elucidate the metabolic changes in the failing heart have been undertaken for several decades, the fundamental question of the role of reduced energy production in various forms and stages of HF has not been answered definitively. The review by Abel et al.63 provides the background to allow investigators to define the direction that both basic and translational scientists might take to advance this field. The payoff from modifying favorably the metabolism of the failing heart could be enormous!

**Myocardial Matrix in HF**

When most physicians, and some basic scientists, think of HF, they think, almost reflexively, of the abnormal contraction and relaxation of cardiomyocytes. But, of course, the heart is much more than a collection of cardiomyocytes and contains many nonmyoctytic components that are essential for its function and, if disturbed, may be responsible for the development or progression of HF. These include the coronary macrocirculation and microcirculation, and the autonomic nerves that innervate both these vessels as well as the cardiomyocytes. Although the existence of the extracellular matrix (ECM), which surrounds these cells, has been known for many decades, it has received little attention until relatively recently. However, we are now beginning to appreciate its important roles in cardiac function and dysfunction. The ECM acts much like an internal scaffold- ing or skeleton of the heart. Normally, it connects and tethers cardiomyocytes, and shapes the ventricles so as to optimize their capacity to eject blood and to fill at a low distending pressure. The normal ECM also plays an important adaptive role in HF, by preventing excessive dilatation when ventricular overload occurs in conditions such as valvular regurgitation or when, for any reason, contractile failure develops.

As pointed out by Spinale and Zile64 in their authoritative Review, the ECM, once thought to be static fibrous tissue, is now recognized to be composed of a variety of structural proteins, enzymes, and cell types. Its principal constituents are 2 fibrillar proteins, collagen types I and III, as well as a variety of proteoglycans, glycoproteins, fibronectin, and elastin. There is constant turnover of these proteins, and normally there is a delicate balance between the degradation of collagen resulting from the activity of the proteolytic matrix metalloproteinases and their tissue inhibitors. In pressure overloaded ventricles, as in hypertension or aortic stenosis, cardiomyocyte hypertrophy is accompanied by an increase in fibrillar collagen between and around myocytes, resulting in both interstitial and perivascular fibrosis.65 This can cause stiffening of the ventricle, and slowed and incomplete relaxation which, in turn, can cause HFpEF.65
Growth factors, such as transforming growth factor-β, are important stimuli of collagen synthesis. At least 4 miRs (miR-21, miR-29, miR-30, and miR-133) also seem to play important roles in ECM synthesis.65 MiR-21 has been shown to be regulated and to be increased in fibroblasts, in which it stimulates interstitial fibrosis.66 When myocardial necrosis occurs, activated interstitial fibroblasts are transformed into myofibroblasts, which enhance fibrogenesis, culminating in a scar, a process that is analogous to wound healing. When the necrosis results from excessive pressure overload hypertrophy, it causes diffuse microscars. In myocardial infarction, on the other hand, a localized scar is formed, in a process that has been referred to as reparative fibrosis.63 When the latter process is inadequate or slow in developing, the infarcted wall of the ventricle thins and infarct expansion occurs. This in turn can cause localized ventricular dilatation and lead to HFpEF, or in extreme cases, to ventricular rupture. An inadequate production of fibrillar collagen may also occur in patients with ventricular volume overload as well as in dilated cardiomyopathy. This can result in an increase in cardiomyocyte length, accelerate ventricular dilatation, and precipitate HFpEF.

Elevated levels of serum markers of collagen turnover, including the carboxyl-terminal telopeptide of collagen type I, the amino-terminal peptides of procollagen types I and III, matrix metalloproteinases 1, 2, and 9 and tissue inhibitor of metalloproteinase 1, have been found in patients with HFrEF who are at high risk of death and HF hospitalization.67 These markers have also been found to be elevated in patients with hypertension with left ventricular hypertrophy and diastolic dysfunction.68

In addition to the use of serum markers of collagen turnover, ECM can also be recognized by cardiac MRI with gadolinium. An increase in the images reflecting the volume of the ECM is a marker of severe HF and a risk factor of adverse outcome.69

The treatment of excessive collagen deposition in the heart (as well as in other organs) is still at a very early stage, and development of such therapies presents major challenges and opportunities to both basic and translational scientists. Under consideration are mitochondrial protective agents such as antioxidants as well as inhibitors of the mitochondrial inner membrane permeability transition pore, such as cyclosporine A.64 Blockers of the renin–angiotensin–aldosterone system are widely used, but their efficacy for the treatment of these conditions has not been established. Also under consideration are blockers of transforming growth factor-β signaling with antisense oligonucleotides or antibodies.65 Antagonists that silence profibrotic miRs are under investigation, and they could become important therapeutic agents as well. Indeed, an antagonist of miR-21 has been shown to inhibit interstitial fibrosis and to improve cardiac function in a mouse model of pressure overload–induced left ventricular hypertrophy.66

Adrenergic Nervous System in HF

In 1962, my colleagues and I, working in the intramural program of the (then) National Heart Institute, hypothesized that the adrenergic component of the autonomic nervous system plays an important role in mediating the response of the circulation to exercise. We first tested this in normal subjects and observed that after treatment with the adrenergic synaptic blocker guanethidine (β-blockers were not yet available), the usual increases in cardiac output and left ventricular work that occurred during muscular exercise were greatly reduced.70 This observation led to a study of the response of the adrenergic nervous system in patients with HF, in whom we observed abnormal elevations of the concentration of the circulating adrenergic neurotransmitter norepinephrine, both in the blood stream71 and in the urine.72 Subsequently others, using microangiography, found that this norepinephrine spillover could be correlated with the intensity of the adrenergic discharge of postganglionic sympathetic nerves.73 In severe HF, the concentration of circulating epinephrine rises as well, suggesting increased sympathetic drive to the adrenal medulla.

At first, this overactivity of the sympato-adrenomedullary system was regarded as an adaptive response that increased the contractility of the failing heart and increased its output, and this concept still remains operative in acute HF. But it then became apparent that chronic overactivity of the adrenergic nervous system was maladaptive and intensified the severity of chronic HF. This led to the seminal observation of Waagstein et al52 that blockade of β-adrenergic receptors was beneficial in patients with chronic HFrEF and this, in turn, led to large-scale clinical trials showing that β-blockers prolong life in such patients. These drugs now constitute one of the pillars of treatment of chronic HFrEF. An important observation by Bristow et al74 was that in HFrEF, the chronic stimulation of β-adrenergic receptors leads to a reduction in their density and their coupling to G proteins.

Increased adrenergic discharges to the systemic vascular bed raise peripheral vascular resistance. This is also an adaptive mechanism in acute HF because it maintains perfusion of the brain and heart in the face of the lowering of arterial pressure that accompanies a sudden reduction in cardiac output. But, just as in the case of cardiac damage from prolonged adrenergic stimulation of the heart in chronic HF, chronic vasoconstriction, which increases ventricular afterload, also is maladaptive; hence, the clinical benefit observed when patients with HF are treated with vasodilators.

In their clearly written Review, Lympertopoulos et al75 provide a contemporary update of this field by describing 9 subtypes of adrenergic receptors, 3 in each of the 3 major classes, α1, α2, and β receptors. They point out that while activation of both β1 and β2 receptors increases myocardial contractility, activation of β1 receptors enhances apoptosis and thereby exerts a maladaptive effect, while the positive inotropic effect resulting from β2 receptor activation seems to protect the heart from apoptosis.

There are many opportunities for future research on the adrenergic nervous system in HF, which requires treatment that is personalized and dependent on its pathogenesis, pathophysiology, and the severity of the condition at any given time. The delicate balance between hyperstimulation and hypostimulation of the abovementioned 9 types of adrenergic receptors in various forms and stages of HF remains to be explored. Additional agonists and antagonists that are specific for each of these receptors remain to be discovered.
Patients with HF may require different profiles of receptor stimulation and antagonism at different stages their disease. Important additional directions of research on adrenergic receptors can come from a greater exploration of their genetic polymorphisms, which are associated with a variety of alterations in inotropic effects, receptor downregulation, and cardiac remodeling.

**Cardiac Toxicity Associated With Cancer Therapies**

Heart disease and cancer are the 2 leading causes of death in industrialized nations. For many years, they seemed to occur together only by chance. In the late 1960s, with the development of cancer chemotherapy, reports about their occurrence in the same patient began to be noted. In 1974, I was asked to consult on a 32-year-old man with Hodgkins lymphoma who was being treated with the combination of adriamycin, then a relatively new antineoplastic anthracycline, as well as irradiation. His disease was improving with marked reduction in the size of his enlarged lymph nodes, but he was rapidly developing HF, with severe shortness of breath on mild activity, as well as orthopnea. Echocardiography revealed a dilated left ventricle and a reduced left ventricular EF of 20%. We treated his HF vigorously with the drugs then available, but to no avail, and he died 3 weeks after the onset of HF. At postmortem examination, there was little evidence of residual Hodgkins disease, but he had an enlarged, dilated left ventricle with degeneration and fragmentation of the cardiomyocytes, which exhibited myofibrillar disarray. Thus, a death from HF was substituted for what would certainly have been a death from Hodgkin disease had he not received this therapy.

Over the years, this story has been repeated innumerable times, as ever more potent antineoplastic agents were discovered. Many important cancer chemotherapeutic agents are now recognized to exert cardiac toxicity. As oncologists have increased the doses in an effort to maximize the possibility of remission and even cure, cardiac complications, especially the development of HF, have become recognized with increasing frequency. However, in some patients, cardiac toxicity does not become manifest until years after drug administration. They may well have asymptomatic borderline left ventricular function during this period, but develop overt HF after an adverse stimulus, such as the onset of hypertension or even a small myocardial infarction, which may tip them over into clinically overt HF.

To prevent cardiotoxicity, patients receiving these drugs are now routinely tested with sensitive cardiac biomarkers of myocardial damage (troponins) and ventricular stress (natriuretic peptides). Elevations of these biomarkers and abnormalities of ventricular performance detected by noninvasive imaging serve as warnings to oncologists to discontinue treatment or to reduce the dose of the antineoplastic agent(s). Ventricular dysfunction and HF may be responsive to angiotensin converting enzyme inhibitors and β-blockers. Indeed, it has recently been shown that prophylactic administration of a combination of these agents begun before starting antineoplastic agents can reduce the risk of development of drug-induced ventricular dysfunction. Statins also seem to offer some protection.

As Ky et al point out in their interesting review, the cardiotoxicity of cancer chemotherapeutic agents is a catch 22: Too little chemotherapy and the cancer progresses too much and HF develops.

Higher doses may control the neoplasm, but HF develops, as in my patient in 1974. The molecular mechanisms responsible for cardiac toxicity are undergoing intensive investigation with the goal of finding replacement drugs that still possess potent antineoplastic activity but that have a greater margin of cardiac safety. Some interesting clues have emerged. Topoisomerase 2 is an important enzyme involved in DNA transcription, which is inhibited by anthracyclines, and this inhibition may be responsible for the toxicity of this important class of agents. Topoisomerase 2 has 2 isomers; because the β-isozyme seems to be responsible for the myocardial toxicity, it is possible that anthracyclines that inhibit only the α isozyme could be myocardial sparing, while retaining their antineoplastic activity.

Kinase inhibitors such as imatinib represent a true advance in the treatment of chronic myelogenous leukemia. Although imatinib itself does not seem to be seriously cardiotoxic, the more recently discovered kinase inhibitors, which have been found to be useful in the treatment of certain solid tumors, can cause cardiomyopathies, perhaps by inhibiting angiogenesis and reducing capillary density in the heart. More work needs to be done to elucidate the mechanism of cardiotoxicity of this important class of drugs.

Trastuzumab is a widely used humanized monoclonal antibody that overexpresses epidermal growth factor and is effective in treating breast cancer. However, it too can cause cardiomyopathy, especially when it is administered in combination with an anthracycline. The fundamental mechanism of trastuzumab-induced cardiac toxicity is currently under study. Inhibition of the neuregulin ErbB2 pathway by trastuzumab seems to be responsible, at least in part, for its antineoplastic effect. However, this pathway is also critical to myocardial function. Alternative agents to trastuzumab are under investigation.

The identification of the fundamental mechanisms of cardiac toxicity of antineoplastic agents might well uncover pathways that may be disturbed in cardiomyopathies unrelated to drug toxicity. This could constitute an important, unexpected dividend of basic research in this field.

**Resynchronization of the Failing Heart**

Electric stimulation of the heart goes back for >2 and a half centuries. An early clinical application was reported in 1952, when Zoll used closed chest external stimulation to treat patients with cardiac arrest associated with total atrioventricular block. Transvenous permanent pacing was developed a decade later. Since then, millions of patients with atroventricular block have been treated successfully with electric pacing. Although this technique has been lifesaving in such patients, it became clear that both dual-chamber pacing (right atrium and right ventricle) and single-chamber pacing (right ventricle) often impaired cardiac function, and this required correction.

First, in patients with dual-chamber pacing, optimization of the time interval between atrial and ventricular stimulation improved ventricular performance. Next, attention was directed to the synchronicity of ventricular contraction. It has long been appreciated that patients with HF and intraventricular...
conduction defects, particularly left bundle-branch block, are poorly responsive to the usual therapy for HF and their prognosis is especially poor. Univentricular pacing impairs intraventricular conduction and causes QRS prolongation and dyssynchrony of ventricular contraction. Burkhoff et al reported a negative correlation between QRS duration and ventricular contractile activity in isolated canine hearts in which the ventricular pacing site was varied. This explains the deterioration of ventricular performance observed with abnormal ventricular activation, such as occurs with right ventricular pacing.

A classic article titled “Four chamber pacing in dilated cardiomyopathy,” published by Cazeau et al in 1994, described a single patient with advanced HFrEF, accompanied by first degree atrioventricular block and left bundle-branch block. The pacing reduced the atrioventricular block and, because both ventricles were stimulated simultaneously, the prolonged intraventricular conduction associated with left bundle-branch block was normalized. The patient’s hemodynamics improved immediately as did his clinical state. The authors concluded: “We doubt that this technique will have an impact on long-term survival, but it could be of major importance to improve the patient’s well-being and control heart failure.” In the same year, Bakker et al published an abstract that reported the beneficial hemodynamic and clinical effects of biventricular pacing in 5 patients with severe HF and left bundle-branch block. Thus, this case report and abstract marked the birth of cardiac resynchronization therapy (CRT). By 2005, in a large multicenter trial, Cleland et al showed that CRT improved survival in patients with HFrEF and ventricular dyssynchrony. Cazeau’s prediction was correct in that the technique indeed was important in improving the well-being of such patients, but it did more, it prolonged their lives!

At present, while widely used for the treatment of patients with advanced HFrEF and QRS >150 ms, clinical investigators are seeking to extend the indications. Efforts are underway to determine whether CRT is beneficial in patients with milder degrees of HF and QRS prolongation, as well as in patients with HF without QRS prolongation but in whom mechanical dyssynchrony is demonstrated by echocardiography.

While it is intuitive that a synchronized ventricular contraction should be superior to a dyssynchronized one, whether or not there is also a molecular basis for the observed improvement in ventricular function with CRT remains to be determined. In their review, Kirk and Kass systematically present the evidence for and against specific cellular and molecular changes that occur with ventricular dyssynchrony and how these changes respond to CRT. Biventricular pacing has been shown to cause reverse ventricular remodeling, with reduction in biomarkers, including NT-proBNP and markers of ECM metabolism. CRT improves β-adrenergic function and upregulates presynaptic receptor function. It has also been shown to reverse the apoptosis caused by dyssynchrony and to enhance a variety of mitochondrial enzymes associated with an augmentation of ATP production.

Although CRT is well established in the therapeutic armamentarium, it still offers many opportunities for further research. It is important to determine whether any (or all) of the abovementioned changes contribute to the improvement in cardiac function with CRT. Also, while application of this pacing technique is clinically beneficial in the majority of patients with HFrEF and QRS prolongation, approximately one third of such patients fail to respond. It is important to understand the reason(s) for this failure in order to modify the technique so as to extend benefit to these nonresponders, or at least to avoid long, uncomfortable, and expensive procedures that are not beneficial.

**Left Ventricular Assist Device Support for HF**

In 1964, I was appointed to an NIH committee that was charged with planning the development of a totally implanted artificial heart. This was in the heyday of NASA, which was racing to honor the commitment that had been made by the recently assassinated President Kennedy to place a man on the moon and bring him back to earth safely before the end of the decade. A systems approach, similar to the one used for the moonshot, was planned for the artificial heart, and several senior NASA engineers served on our committee. The goal was to implant the first artificial heart by the second Sunday of February (Heart Sunday, on which the American Heart Association performs its major annual fund-raising drive); the year chosen was 1970.

Of course, this grandiose goal was not achieved, and after several decades of agonizing introspection and advice from external consultants, the institute redirected its focus to a less ambitious but more achievable goal, prolonged left ventricular assistance. Collaborations between the institute, industry, and the academic surgical community have resulted in a series of ever smaller, ever more reliable, and ever more patient-friendly left ventricular assist devices (LVADs). The transition from a large clunky pulsatile pump to a compact continuous flow device was a major achievement. At first, LVAD support was used as a bridge to cardiac transplantation, that is, keeping alive patients with advanced HF who were listed for cardiac transplantation, while awaiting a donor heart. The feasibility of this approach reached widespread public attention when former Vice President Cheney’s circulation was supported by an LVAD for 20 months before he underwent successful cardiac transplantation. Because there are many more patients with advanced HF than donor hearts, an increasing number of the former are now being placed on long-term LVAD support as destination therapy rather than as a bridge to transplantation.

In her fine Review, Birks describes morphological and molecular changes that occur in the hearts of patients on long-term LVADs. These include reverse remodeling of the left ventricle, regression of myocyte hypertrophy, reductions in elevated levels of circulating neurohormones, an increase in the density of β-adrenergic receptors, and an improvement of Ca2+ cycling in the myocytes.

These changes are encouraging and have led to attempts to wean the patients off LVAD and device explantation. Birks et al at Harefield Hospital in England and, more recently, Birks et al in Louisville, KY, have combined prolonged LVAD support together with intensive pharmacological therapy, which is sometimes referred to as the Harefield cocktail. The latter often includes the β1-adrenergic agonist clenbuterol.
Using this approach, approximately two thirds of patients with familial dilated cardiomyopathy on LVAD support have tolerated explantation, and four fifths of the latter have survived for 3 to 4 years. These observations are of intense interest because they indicate that advanced HF is not necessarily irreversible but with appropriate therapy, including LVAD support, can under certain circumstances, go into prolonged remission.

Much more needs to be learned about this reversal of HF. Selecting the time to attempt weaning from LVAD support and the method of weaning are of critical importance. It is clear that although prolonged mechanical support can be lifesaving, it is no panacea. Thus, although it seems sensible to rest an overloaded failing heart, prolonged unloading can exert deleterious effects, including cardiac atrophy as well as more extensive ventricular collagen crosslinking leading to increased myocardial stiffness.39

Myocardial recovery has not been demonstrated with any regularity in patients with chronic ischemic heart disease, the most common cause of HF in industrialized nations. It is possible that earlier intervention in these patients and the aid of cell therapy may be necessary for reversal of HF. Totally implanted LVADs that do not require a transcutaneous wire between the external power source and the implanted pump would greatly accelerate the acceptance of this approach and reduce what are now its enormous financial costs. However, we are still at a very early stage of reversing HF on a regular basis. It will take substantial effort and extensive collaboration of basic scientists, bioengineers, cardiac surgeons, and cardiologists to bring this about.

**Gene Therapy for HF**

Gene transfer (gene therapy when transfer is used for therapeutic purposes) came on the scene in the early 1970s with considerable fanfare. It was expected rapidly to become the definitive treatment of rare monogenic disorders. While early animal studies were encouraging, their application to patients proved to be difficult in the beginning. After the unfortunate death of a subject in a clinical trial, and several other misadventures, clinical research in this field was suspended, and research on gene transfer moved back to the bench. All aspects were intensively investigated, in vitro as well as in animal models. Proof-of-concept studies were performed in rodents, including genetically altered mice, as well as in large animals. Molecular targets were defined; gene dose, vector selection, gene promoters and, above all, safety, were systematically examined. As a consequence, clinical research on gene transfer has been restarted. Many clinical trials have been or are being performed and, for the first time, an important regulatory agency, the European Medical Agency, has approved gene transfer for a defective lipoprotein lipase, a rare monogenic disorder. Thus, we have truly entered a new therapeutic area in medicine.

Except for the relatively rare instances of the monogenic cardiomyopathies,39 HF is not a monogenic disorder, but it is nonetheless a logical target for gene transfer because a number of cellular and molecular targets have been identified. In this Compendium, Pleger et al46 provide a thorough, authoritative review of this important field. In the selection of vectors to transport the gene into the cell, recombinant adenovirus, a single stranded DNA virus, has much to commend it. Recombinant adenoviruses have low immunogenicity and prolonged cardiac expression, although the existence of neutralizing antibodies in patients does represent a limitation. As is the case with cell therapy,56 both intracoronary and catheter-based endocardial injections are the preferred methods of delivery. For optimum safety, gene expression in noncardiac tissues must be minimized. This might be accomplished by infusion via the coronary sinus and with the addition of selective cardiac promoters such as cardiac actin and myosin light chain 2.

The selection of molecular targets is perhaps the most interesting challenge of all. Not surprisingly, the molecular defects in Ca\(^{2+}\) cycling and in β-adrenergic receptor signaling, both important in HF and reviewed in this Compendium,41,75 have risen to the top of the list of possible targets. A reduction of SERCA 2a activity has been demonstrated in failing human heart muscle,39 and myocardial contractility can be improved by transfer of the SERCA 2a gene into cardiomyocytes in various animal models of HFpEF. Clinical studies in patients with HF were begun by Hajjar et al100 after improved contruction was found when the gene encoding SERCA2a was inserted into heterozygous SERCA 2a gene–ablated mice, in rats with hemodynamic overload, in pig and sheep models of left ventricular overload,100 and in isolated cardiomyocytes obtained from patients with HFpEF. This was followed by a phase 1 human trial that demonstrated safety of the procedure. In a dose-ranging phase 2 trial performed in patients with severe HFpEF, the highest dose strongly suggested efficacy,101 and a phase 3 trial is ongoing.

Other molecular targets for gene therapy that are associated with abnormal Ca\(^{2+}\) cycling include the S100A1 protein, which is downregulated in HF,102 and phospholamban. The β-adrenergic receptor kinase carboxy terminal peptide and adenylylcyclase 6 are also candidates for HF gene therapy with the hope that they will improve β-adrenergic responsiveness. Thus, after a halting start, clinical research on gene transfer now seems to be on track. This approach represents an enormous opportunity for basic scientists to uncover new molecular pathways that control cardiac contraction and relaxation in normal animals and to study alterations in these pathways when both experimentally induced ventricular dysfunction and clinical HF occur. It offers equally challenging opportunities to translational scientists to use gene transfer in the reversal and, perhaps someday, in the prevention of clinical HF.

**Cell Therapy for HF**

The 1950s were an exciting period in cardiovascular surgery and in cardiology. Closed heart surgery, such as mitral valvotomy for mitral stenosis, and creation of a systemic-pulmonary anastomosis for tetralogy of Fallot were routinely performed. The development of open heart surgery was eagerly awaited so that intracardiac procedures could be performed under direct vision. By the end of the decade, the major problems associated with cardiopulmonary bypass were pretty much settled, and cardiac surgeons could concentrate on perfecting the procedures themselves. Cardiovascular surgery flourished,
and many lives were saved or prolonged; cardiology would never be the same.

Cell therapy for HF is now at a stage that is reminiscent of the early days of open heart surgery, when the promise of the approach was widely heralded, but before the techniques had been perfected. Many groups all over the world are now focusing on cell therapy, both in experimental animals as well as in patients. Significant new information is published and presented almost weekly. There is great hope that cell therapy will play an important role in the care of patients with HF, and there are glimmers of success, but the techniques are not yet ready for routine use.

In this Compendium, Sanganalmath and Bolli provide an excellent update on this important subject. They systematically review the various cell types that have been or are currently being used, as well as the methods of their delivery. It seems that neither embryonic stem cells nor skeletal myoblasts will become the cells of choice, and there is concern that pluripotent stem cells might prove to be tumorigenic. However, a variety of autologous bone marrow–derived progenitor cells, including specially treated mesenchymal cells have shown promise. Interestingly, transdifferentiation of transplanted cells into myocytes does not seem to be the mechanism of benefit provided by bone marrow–derived cells; a paracrine effect is more likely. Also, the discovery of the existence of cardiac stem cells, the ability to obtain these cells by endo-

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As appropriate for this Compendium, Sanganalmath and Bolli have concentrated on cell therapy in chronic HF, including that resulting from ischemic damage. The major clinical trials that have been completed in this burgeoning field are reviewed. An equivalent effort on cell therapy in patients with acute myocardial infarction is ongoing, but is not included in this Compendium.

The opportunities for both basic and translational scientists to make valuable contributions to this important field are enormous. If I were to guess where this approach will be in another decade or so, it seems likely that off-the-shelf products will be used. The injectate is likely to be a mixture of cells that will differ between patients with recent myocardial infarction and those with chronic HF. I think that they will be infused into the coronary arteries in patients in whom the area of dysfunc
tional myocardium is well perfused, such as patients with dilated nonischemic cardiomyopathy, and will be injected by NOGA-directed transendocardial injection in patients with major blockages in the coronary arterial trees. Although it will be quite often effective, cell therapy is unlikely to emerge as the sole treatment for HF, but is likely to become an important adjunct to other therapeutic approaches, including prolonged mechanical left ventricular assistance and gene therapy.

Conclusions

In concluding this Introduction, it seems to me that when the science underlying HF is looked at from 100,000 feet, as this Compendium attempts to do, there is considerable cause for optimism. Great advances in understanding the pathobiology of HF and their application to further improvements of patient care are within reach. The opportunities for progress in this field have never been more promising.

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None.

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