I have selected congestive heart failure as the subject of this lecture because of Professor Denolin’s very important contributions to this field and because it was to this aspect of cardiology that I was originally introduced. I was a third year student at New York University Medical School exactly 50 years ago when my interest in heart failure was first aroused by what seemed to be great opportunities for progress both in clinical care and in research. I was assigned to a heart failure clinic at Bellevue Hospital and had my earliest research experience in the haemodynamic laboratory directed by Professor Ludwig Eichna, one of the first devoted to the study of the pathophysiology of heart failure. In this lecture I shall describe some of the forays that my colleagues and I have taken into this challenging field, and more importantly, to highlight the important progress subsequently made by others in the areas that we studied.

In 1950, our understanding of heart failure and the ability to manage it was little changed from what it had been at the end of the 19th century. Hypertension and rheumatic valvular heart disease were the most common causes of heart failure. The responsible mechanism was considered to be ‘exhaustion’ of the overloaded ventricle, as had been suggested by Osler. The principal goal of therapy was to alleviate symptoms and to reduce excessive accumulation of sodium and water. Treatment was similar for all patients: bed rest, very strict dietary sodium restriction (medical students were told, tongue in cheek: ‘a very low sodium diet may not prolong the patient’s life, but it will certainly make it seem longer’); administration of digitalis to near toxicity was routine, and the only diuretics available were organic mercurials given by (painful) intramuscular injections.

Neurohormonal influences in heart failure

The sympathoadrenal system

A decade later, while working at the National Institutes of Health in Bethesda, my colleagues and I became interested in the role of the sympathoadrenal system in heart failure. This interest developed from the clinical recognition that severe heart failure was associated with what appeared to be increased sympathetic activity — cutaneous vasoconstriction, tachycardia, and suppression of urinary output. We applied the recently developed fluorometric assay for the sympathetic neurotransmitter, norepinephrine in blood, urine and cardiac tissue. In this early, perhaps first, demonstration of a neurohumoral abnormality in heart failure we found that: (1) plasma norepinephrine concentration was elevated in some patients with heart failure but rose to abnormal levels during exercise in all patients[1,2]; (2) 24 h urinary norepinephrine excretion was increased in heart failure, an increase that was a function of the severity of heart failure[3] (Fig. 1); (3) cardiac norepinephrine concentration and total content were markedly lowered both in patients with heart failure[4,5], as well as in models of experimental heart failure[6]; (4) the responses of heart rate and of myocardial contractility to cardiac sympathetic nerve stimulation in experimental heart failure were markedly impaired[7]; and (5) the sudden withdrawal of sympathoadrenal support by large doses of these drugs, especially when administered intra- venously, could intensify heart failure, and on occasion was fatal[8].

Since these early studies much has been learned about the function of the sympathoadrenal system in heart failure. For example, direct microneurography of sympathetic nerves in patients confirmed that efferent sympathetic nerve activity is increased in heart failure[9]. The intensity of this nerve traffic was shown to correlate inversely with the severity of cardiac dysfunction, and directly with the plasma norepinephrine concentration. The latter was shown to be a powerful predictor of...
shortened survival\textsuperscript{[11]}. From a therapeutic perspective it has been demonstrated that when oral beta-blockers are begun at a very low dose and the dose gradually escalated, ventricular function improves, symptoms and the need for hospitalization for heart failure decrease and, most importantly, survival improves\textsuperscript{[11–13]}.

The renin-angiotensin system

My next foray into neurohormonal adjustments in heart failure began in the mid 1970s at Harvard and the Brigham. Marc Pfeffer, the late Janice Pfeffer and I sought to determine whether blood pressure reduction would cause regression of left ventricular hypertrophy and restore normal left ventricular function in the spontaneously (genetic) hypertensive rat. We were fortunate to obtain small quantities of a new antihypertensive agent that was being developed by Squibb (now Bristol-Myers Squibb), the angiotensin converting enzyme inhibitor (ACE) captopril, and we found that this drug had a salutary effect; while untreated (hypertensive) rats exhibited progressive left ventricular hypertrophy and impairment of left ventricular performance over one year, further hypertrophy and deterioration of left ventricular performance were arrested in captopril-treated rats (Fig. 2)\textsuperscript{[14]}. This led to our study of the ACE inhibitor in another model of left ventricular dysfunction widely used in our laboratory at the time, the rat with acute myocardial infarction produced by coronary ligation. In this model captopril also arrested progressive left ventricular dilatation (Fig. 3)\textsuperscript{[15]}. We then investigated patients with large anterior wall myocardial infarctions and found that the chronic administration of the ACE inhibitor prevented the elevations of left ventricular end-diastolic volume and pressure that occurred in placebo-treated patients over the course of a year\textsuperscript{[16]}. These observations led us to undertake a trial of the chronic administration of captopril in post-infarction patients with left ventricular dysfunction but without overt heart failure, the SAVE trial, in which we observed a significant reduction in all-cause mortality, as well as in the development of heart failure\textsuperscript{[17]}.

Since SAVE, eight separate trials involving more than 110,000 patients with acute myocardial infarction have shown the beneficial effects of ACE inhibition in patients following acute myocardial infarction, especially those with impaired left ventricular function\textsuperscript{[18,19]}, and it is certainly gratifying that this mode of therapy has become standard for such patients. The principal mechanism of the beneficial effects of ACE inhibition in such patients appears to be interference with the tissue ACE system. The latter has been shown to be upregulated in the surviving myocardium of the rat with myocardial infarction, with increases both in the density of angiotensin II receptors and activity of the ACE enzyme\textsuperscript{[20]}.

In the SAVE trial we observed that captopril also (unexpectedly) reduced the recurrence of acute myocardial infarction and the need for coronary revascularization\textsuperscript{[21]}, i.e. ACE inhibition appeared to slow the progression of atherosclerosis. The HOPE trial has now provided powerful evidence in favour of this contention\textsuperscript{[22]} by demonstrating that the ACE inhibitor ramipril reduced the development of vascular events in patients with coronary artery disease or at high risk for coronary artery disease but without left ventricular
dysfunction. Ultrasound studies of the carotid arteries in the HOPE trial showed that administration of the ACE inhibitor was associated with a significant reduction in the rate of thickening of the carotid media. With Marc Pfeffer and others we are currently studying the effects of the ACE inhibitor trandolapril in the PEACE trial in a population of patients with coronary atherosclerosis who are at substantially lower risk than those enrolled in the HOPE trial[23]. This trial will test the lower limits of risk at which ACE inhibition is effective.

In the past few years, much has been learned about the close interactions between the sympathoadrenal system and the renin-angiotensin-aldosterone systems in heart failure. Four observations in this field stand out: (1) ACE inhibition reduces peripheral sympathetic nerve traffic measured by microneurography in patients with heart failure[24]; (2) Conversely, beta adrenergic blockade reduces the concentrations of circulating renin and angiotensin II in patients with heart failure[25]; (3) The benefits of ACE inhibition in heart failure appear to be dependent on the state of activation of the sympathoadrenal system. Thus, in the V-HeFT II trial, which demonstrated the superiority of the ACE inhibitor enalapril over the vasodilator combination of hydralazine and isosorbide dinitrate, the benefit was confined to patients with an activated sympathoadrenal system, as reflected in an elevated level of circulating norepinephrine[26]; and (4) aldosterone reduces the sympathetic nerve uptake of norepinephrine, and thereby sensitized the heart to the action of the neurotransmitter[27]. When considering the effects of aldosterone we must, of course, note the impressive results of the RALES trial, in which the aldosterone antagonist spironolactone, was shown to reduce mortality in patients with advanced heart failure[28].

**Other neurohumoral mediators**

In addition to norepinephrine and angiotensin II, a number of other mediators play important roles in the progression of heart failure. Norepinephrine, angiotensin II and arginine vasopressin all enhance the production of endothelin by the vascular wall. This peptide stimulates the contraction of vascular smooth muscle causing vasoconstriction, and an elevated concentration of circulating endothelin predicts an adverse prognosis in heart failure[29]. In the rat model of myocardial infarction-induced heart failure, the endothelin receptor blocker bosentan has been shown to improve haemodynamics, and to prolong survival[30]. Early clinical trials with such blockers are encouraging[31].

Another humoral system that is activated in heart failure are the natriuretic vasodilator peptides which are released by the dilated heart. Unfortunately, their vasodilator action is not sufficiently potent to successfully oppose the more powerful vasoconstrictor mediators — norepinephrine, angiotensin II, and endothelin. However, a new class of drugs, the vasopeptidase...
inhibitors, which combine in a single molecule the inhibition both of ACE and of neutral endopeptidase, the enzyme that breaks down natriuretic peptide, appears to be promising in the treatment of hypertension and heart failure[32]. The concentration in the circulation of one of these vasodilator peptides, brain natriuretic peptide, has emerged as a very accurate predictor of survival in heart failure, seemingly superior to the gold standard, the ejection fraction, and it has become available as a rapid bedside test to diagnose, risk stratify and follow the course of patients with heart failure[33]. The haemodynamic benefits resulting from the infusion of nesiritide, a formulation of brain natriuretic peptide, into patients with heart failure have been reported[34].

Inflammatory cytokines

The over-expression of a number of cytokines also appears to play a prominent role in the pathogenesis and progression of heart failure. It has now been well established that patients with heart failure exhibit elevated levels of circulating tumour necrosis factor alpha (TNF-α)[35,36]. Elevated concentrations of TNF-α (and at least one other cytokine, interleukin 1β) in the hearts of patients with severe heart failure have been documented[37]. TNF-α has been over-expressed in the hearts of transgenic mice and this over-expression is associated with systolic dysfunction, myocarditis, myocardial fibrosis, ventricular dilatation, heart failure and shortened survival[38]. The pathophysiological significance of these findings is just unfolding. When TNF-α is infused into rats, left ventricular function becomes depressed but it recovers when the infusion is discontinued[39]. In other experiments, when a TNF-α antagonist, a soluble protein TNF receptor, was injected a prompt restoration of myocardial function occurred despite continued infusion of the TNF-α. The results of early clinical trials with TNF-α receptor blockers in patients with heart failure are encouraging[40]. The increased concentration of TNF-α in the failing human heart appears to be reversible. Histochemical sections of failing human myocardium have shown abundant TNF-α, which disappears in heart failure patients after several weeks of mechanical circulatory support[41].

Evaluation of understanding of neurohormonal and cytokine activation in heart failure

It is interesting to reflect on how the field of neurohormonal and cytokine activation in heart failure has evolved over the years. I should like to do this by using three snapshots in time. Figure 4 shows our working hypothesis when we reported elevated norepinephrine concentrations in the serum and urine of patients with heart failure in the 1960s. At that time, we believed that activation of the sympathoadrenal system was a useful (adaptive) mechanism in heart failure and that the increased adrenergic activity provided support for the failing heart. The rapid deterioration of cardiac function in patients with severe heart failure with large doses of
beta-blockers was consistent with this hypothesis. In retrospect, while not incorrect, our formulation was incomplete and overly simplistic. Figure 5 shows how the picture had changed by 1980. It had become clear that while the response to activation of the sympathoadrenal system is adaptive in acute heart failure, it is largely maladaptive in chronic heart failure because it causes additional myocardial injury. The ‘down-regulation’ of beta-1-adrenergic receptors demonstrated by Bristow et al.[42] appeared to be responsible for the impaired responsiveness of the failing heart to sympathetic nerve stimulation[7]. The (counter-intuitive) idea of blocking this system for therapeutic purposes had already been put forward by the Gothenburg group[43] and was the subject of considerable debate at that time.

Now, another two decades later, the concept of neurohormonal adaptation in heart failure has undergone further transformation and expansion (Fig. 6). The renin-angiotensin-aldosterone system, endothelin, and arginine vasopressin, a product of the hypothalamic-neurohypophyseal system, have joined the sympathoadrenal system in the array of neurohormonal regulators that are activated in heart failure; their activation, like that of the sympathoadrenal system, appears to be protective in acute, severe heart failure in that they are vasoconstrictors and maintain perfusion of the brain and heart in the presence of a severe reduction in cardiac output. However, like the sympathoadrenal system, they exert a maladaptive action in chronic heart failure. Inflammatory cytokines and oxidative stress are potent noxious stimuli in chronic heart failure as well. When these neurohormonal stimuli are active chronically they are responsible for a vicious circle; they increase the load on the left ventricle, cause myocyte hypertrophy, are cardiotoxic, result in cell death and further impairment of cardiac function. A number of neurohormonal and cytokine blockers that interfere with the adverse effects of many of these stimuli on cardiac structure and function are now available. They appear to be able to interrupt or at least slow the progression of the vicious circle.

**Myocardial function in heart failure**

I will now switch gears from extracardiac neurohormonal/cytokine influences on the failing heart to consider **intrinsic** myocardial function in heart failure. Again, I turn the clock back to the 1960s when our work in this area commenced. Although it was recognized at that time that systolic cardiac function was impaired in many patients with heart failure, there was considerable controversy about whether or not this was caused by an intrinsic contractile defect in cardiac muscle, i.e. a defect that was present in the absence of extrinsic influences and abnormal loading conditions. My colleagues and I examined this question in what now seems like a very simple experiment, but one that was then quite challenging technically. Our model was the papillary muscle isolated from the right ventricle of the kitten in which the pulmonary artery had been banded and which gradually developed right ventricular hypertrophy and then right ventricular failure[44]. We observed a progressive impairment of contractility, i.e. a reduction in the
velocity of shortening at any level of tension development, with right ventricular hypertrophy and then overt heart failure (Fig. 7). These results were initially controversial, and I recall having to defend them before rather hostile audiences, but in the last decade or so, the idea that there is an intrinsic contractile defect in the muscle obtained from overloaded muscle in heart failure seems to have been accepted. Indeed, the demonstration of a contractile defect in heart failure has moved progressively from isolated cardiac muscle[44] to myocytes[45], sarcomeres[37], and contractile proteins[46] and have been extended from animal models to the failing human heart. The reports of the recovery of myocyte function when cardiac load is markedly reduced by placing patients with severe heart failure on a left ventricular assist device for several months are intriguing[47]. These findings provide powerful evidence for the concept of reversibility of the intrinsic contractile defect in heart failure and suggest that prolonged unloading of cardiac muscle may serve more than a bridge to cardiac transplantation, but might actually be a ‘bridge to recovery’.

**Mechanisms of heart failure**

In the last 50 years, much effort has been devoted to trying to understand the mechanisms underlying the development of heart failure. Beginning with the vague concept of ‘cardiac exhaustion’ resulting from chronic haemodynamic overload, the proposed mechanisms have become progressively more refined and six principal candidate mechanisms responsible for heart failure have now been identified. All have been shown to be causative in some experimental models and in some patients with heart failure and all lead to vicious circles which perpetuate and intensify heart failure. They appear, however, to be non-exclusive in that multiple mechanisms may be operative in individual patients.

---

**Figure 6** Interplay between cardiac function and neurohumoral and cytokine systems, as postulated in 2000. Myocardial injury of many causes can depress cardiac function, which activates the sympathoadrenal system (ANS) and RAAS and elaborates endothelin, AVP, and cytokines such as TNF-α. In acute heart failure (left) these are adaptive and tend to maintain arterial pressure and cardiac function. In chronic heart failure (right), they cause maladaptive hypertrophic remodelling and apoptosis, which cause further myocardial injury and impairment of cardiac function. Horizontal line on right (†) indicates that chronic maladaptive influences can be inhibited by ACE inhibitors, β-adrenergic blockers (β adren), angiotensin type 1 (AT₁) receptor blockers, aldosterone (aldo) antagonists, and endothelin type A (EtA) blockers. From: Braunwald E, Bristow MR. Congestive heart failure: Fifty years of progress. Circulation 2000; 102: IV-14–IV-23.
In the first, (Fig. 8) genetically determined mutations of sarcomeric proteins, such as those described in familial cardiomyopathies\[46\], neurohumoral-cytokine abnormalities and haemodynamic overload are responsible for the reinduction of the fetal pattern of expression of genes encoding sarcomeric proteins and the calcium-handling machinery of the myocyte\[37\]. This leads to the impairment of myocardial contraction, cardiac dilation, increased wall stress, and augmented myocardial oxygen needs.

The second (Fig. 9), is calcium overload of myocytes. Haemodynamic overload reduces the activity or expression of the sarcoplasmic reticular ATPase, (SERCA-2a)\[48\] and of the Na-Ca transporter across the myocyte’s plasmalemma\[49\]. Both of these changes raise intra-cytoplasmic calcium concentration, which in turn, interferes with myocyte contraction causing systolic dysfunction and with myocyte relaxation causing diastolic dysfunction.

Myocardial cell death is also considered to be an important mechanism of heart failure (Fig. 10). There are two principal causes of cell death, apoptosis and necrosis. Apoptosis, like the reinduction of fatal sarcomeric proteins, can be caused by excessive neurohumoral or cytokine stimulation and haemodynamic overload, but ageing and ischaemia are important causes as well\[50\]. As a consequence of cell drop-out, the load on the surviving myocytes is increased and this in turn may accelerate the deterioration and death of the surviving cells. Apoptosis may be slowed by blockade of beta-adrenergic receptors and of the renin-angiotensin system. Since myocardial apoptosis contributes to the cardiomyopathy of ageing it is likely to become of progressively greater importance as the population ages and it may well become the dominant cause of heart failure in the future. In contrast to apoptosis, which usually occurs in a spotty manner throughout the ventricles, the ischaemic necrosis of myocardial cell death is generally more diffuse and involves a larger number of cells.

**Figure 7** Force-velocity relations of the three groups of cat papillary muscles. RVH=papillary muscles obtained from kittens with right ventricular hypertrophy without heart failure. CHF=papillary muscles obtained from kittens with RVH and congestive heart failure. Average values ± SEM are given for each point. Velocity corrected to muscle lengths per second $L_O$ (s). Reproduced by permission from: Spann JF Jr, Buccino RA, Sonnenblick EH, Braunwald E. Contractile state of cardiac muscle obtained from cats with experimentally produced ventricular hypertrophy and heart failure. Circ Res 1967; 21: 341–54.

In the first, (Fig. 8) genetically determined mutations of sarcomeric proteins, such as those described in familial cardiomyopathies\[46\], neurohumoral-cytokine abnormalities and haemodynamic overload are responsible for the reinduction of the fetal pattern of expression of genes encoding sarcomeric proteins and the calcium-handling machinery of the myocyte\[37\]. This leads to the impairment of myocardial contraction, cardiac dilation, increased wall stress, and augmented myocardial oxygen needs.

The second (Fig. 9), is calcium overload of myocytes. Haemodynamic overload reduces the activity or expression of the sarcoplasmic reticular ATPase, (SERCA-2a)\[48\] and of the Na-Ca transporter across the myocyte’s plasmalemma\[49\]. Both of these changes raise intra-cytoplasmic calcium concentration, which in turn, interferes with myocyte contraction causing systolic dysfunction and with myocyte relaxation causing diastolic dysfunction.

**Figure 8** Mechanism of heart failure in which several stimuli lead to reinduction of fetal expression of sarcomeric proteins which in turn leads to impaired myocardial contraction; the latter causes ventricular dilatation which enhances wall stress and intensifies haemodynamic overload.
infarction usually causes more localized scarring. The haemodynamic overload placed on surviving heart muscle and the resultant ventricular remodelling is an important cause of heart failure in both forms of cell death.

A fourth mechanism involves abnormalities of the cytoskeleton which can be caused by mutations of genes encoding cytoskeletal proteins and by haemodynamic overload (Fig. 11)[37]. Abnormalities of cytoskeletal proteins interfere with the regulation of the cardiac cytoarchitecture and cause impaired systolic function and ventricular remodelling[51]. A fifth mechanism that is a contributor to many forms of heart failure is proliferation of the extracellular matrix[52]. Increased expression of matrix metalloproteinases enhances production of extracellular matrix protein which causes interstitial fibrosis. Extensive fibrosis interferes with cardiac contraction, and even more so with relaxation and filling. ACE inhibitors and inhibitors of matrix metalloproteinases, can reduce proliferation of the extracellular matrix and the latter may become important therapeutic agent in heart failure[53]. Reduction of turnover of the

---

**Figure 9** Mechanism of heart failure in which hemodynamic overload leads to myocyte calcium overload, which interferes with myocardial contraction and relaxation.

**Figure 10** Mechanism of heart failure in which diverse stimuli cause myocardial apoptosis, which in turn causes haemodynamic overload of surviving myocytes.
extracellular matrix has been suggested as a mechanism responsible for the benefit of spironolactone in heart failure[28,54].

The sixth mechanism, an imbalance between myocardial energy supply and demand, is one in which I have been particularly interested. In an effort to elucidate the mechanism responsible for the contractile dysfunction in our kitten papillary muscle studies discussed earlier[44], we examined the relation between the mechanics of contraction and the concentration of high energy phosphates in the myocardium. The ratio of creatine phosphate to adenosine triphosphate (CrP/ATP) was depressed in hypertrophied, and even more so in failing ventricles[55]. In the late 1960s we developed the pacing-induced heart failure model [56], and found that cardiac CrP/ATP was reduced in that preparation as well. It is now clear that the lower CrP/ATP observed in the hearts of these models of heart failure is associated with depressed total high energy phosphate stores, the ATP/ADP ratio and free energy of ATP[57]. These reductions impair both cardiac contraction and relaxation.

A reduction of high phosphate energy stores represents the key mechanism responsible for heart failure in patients with acute ischemic syndromes, and while it may not represent the fundamental underlying molecular defect in heart failure secondary to haemodynamic overload, it may play an important role in this condition as well[57]. Depression of these energy stores is most profound in the subendocardium of the left ventricle in severe hypertension and aortic stenosis. In patients with mitral regurgitation the cardiac PCr/ATP ratio, measured non-invasively by magnetic resonance spectroscopy, has been shown to vary inversely with ventricular function; thus, as left ventricular end-systolic diameter rises, i.e. as left ventricular function deteriorates, the PCr/ATP ratio declines[58]. In patients with dilated cardiomyopathy the PCr/ATP proved, on multivariate analysis, to be an excellent predictor of survival, even better than the ejection fraction[59].

**Figure 11** Mechanism of heart failure in which abnormalities of cytoskeletal proteins leads to impairment of myocardial contraction.

**Chronic stunning (hibernation) and heart failure**

In 1982, Robert Kloner and I published an editorial on post-ischaemic ventricular dysfunction, which we termed *myocardial stunning*[60]. We proposed that: ‘In patients with severe, diffuse coronary obstruction, the left ventricle may be markedly dilated and severe heart failure cannot be explained by myocardial necrosis. Instead, the heart failure is more readily attributed to chronic, widespread stunning of the myocardium . . . Some patients with ischaemic cardiomyopathy show marked improvement in left ventricular function after coronary revascularization . . . before operation, the ischemic myocardium was chronically stunned, but recovered (after revascularization).’

The term *hibernation*[61,62] has subsequently been used to refer to what we initially termed chronic stunning. However, there is now growing evidence that the persistent myocardial dysfunction that is characteristic of hibernation, may, in fact, be caused by repetitive episodes of stunning[63]. In any event, hibernation, chronic stunning or prolonged ischaemic left ventricular dysfunction, whatever it is called, is now recognized to be a relatively common form of potentially reversible heart failure. A number of clinically useful tests, including positron-emission tomography, thallium scintigraphy and stress echocardiography may be used to detect this condition. When there is metabolism/flow mismatch.
and impaired function, i.e. when myocardium is hypoperfused but viable and with impaired contraction, revascularization improves regional and sometimes global ventricular function. In retrospective analyses, survival has been improved by revascularization in these patients\cite{64}. I am currently participating in the design of a prospective, randomized trial, called the Surgical Treatment for Ischemic Heart failure (STICH) trial comparing intensive medical and surgical revascularization of patients with heart failure and myocardial hibernation. The results could be of importance in the management of ischemic cardiomyopathy.

**Conclusions**

It is interesting to compare heart failure as we now observe it, with the condition that I first encountered in 1950 as a student (Table 1). Every aspect of heart failure, its most common causes, the mechanisms responsible, all aspects of management and the attitude to this condition have undergone marked changes during my professional life. However, despite enormous progress, heart failure remains a very serious medical problem. The American Heart Association has estimated that 4.6 million Americans are affected, with 550,000 new cases annually. Almost one million patients in whom heart failure is the primary diagnosis are discharged from U.S. hospitals each year, making heart failure the most common reason for hospitalization in the Medicare (≥65 years) population. There are an estimated three million outpatient visits each year, and the annual total costs of this condition has reached $21 billion. The 5-year mortality is about 50% and from 1979 to 1998 heart failure deaths increased by 135%\cite{65}. With the ageing of the population, all of these numbers may be expected to rise. We are now witnessing a marked increase in the prevalence of heart failure in the face of great advances in the management of all forms of heart disease. Perhaps the explanation for this paradox lies in the fact that modern treatments of cardiovascular disease reduce acute deaths but allow patients to survive with a damaged heart which ultimately fails. An example is the reduction of acute deaths due to arrhythmias and acute pump failure in patients with acute myocardial infarction. Such patients are not cured of their underlying condition by the new therapies but instead they become candidates for the subsequent development of heart failure. Similarly, while contemporary approaches to the prevention of coronary atherosclerosis are reasonably effective, they are far from perfect, and often merely defer cardiac events. As life span is prolonged, there is a growing older population, which may be more vulnerable to the development of heart failure because of the loss of myocytes caused by apoptosis.

I see six major opportunities for dealing with heart failure: (1) Since arteriosclerotic coronary artery disease is the most common cause of heart failure, more vigorous prevention of atherosclerosis is likely to be the most

---

**Table 1 Changes in focus on heart failure**

<table>
<thead>
<tr>
<th></th>
<th>1950</th>
<th>2000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most common aetiologies</td>
<td>Hypertension</td>
<td>Ischaemic HD</td>
</tr>
<tr>
<td></td>
<td>Valvular HD</td>
<td>Cardiomyopathies</td>
</tr>
<tr>
<td>Mechanisms</td>
<td>‘Exhaustion’ of overloaded ventricle</td>
<td>Molecular mechanisms</td>
</tr>
<tr>
<td>Goals of Rx</td>
<td>Reduce symptoms by: fluid accumulation</td>
<td>Abnormal gene expression</td>
</tr>
<tr>
<td></td>
<td>contractility</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ûvent, rate in AF</td>
<td></td>
</tr>
<tr>
<td>Management</td>
<td>Similar therapy for all</td>
<td>Individualized therapy</td>
</tr>
<tr>
<td></td>
<td>Digitalis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bed rest</td>
<td></td>
</tr>
<tr>
<td>established</td>
<td>Na+ restriction</td>
<td>ACE inhibitors, β-blockers, loop diuretics, moderate exercise, spironolactone, digitals, anticoagulants</td>
</tr>
<tr>
<td></td>
<td>Mercurial diuretics</td>
<td>LVAD, ICD, transplantation</td>
</tr>
<tr>
<td>encouraging experimental therapies</td>
<td>L.V. catecholamines for acute pump failure</td>
<td>AT1 receptor blockers, endothelin blocker, TNF α-blockers, vasopeptidase inhibitors</td>
</tr>
<tr>
<td>Attitude</td>
<td>Hopelessness</td>
<td>Guarded optimism</td>
</tr>
</tbody>
</table>

HD=heart disease; AF=atrial fibrillation; HF=heart failure; AT=angiotensin; LVAD=left ventricular assist device; ICD=internal cardioverter defibrillator.
effective approach to the prevention of heart failure; (2) Established therapies for heart failure must be applied more broadly; e.g. more than one-third of patients with heart failure do not receive ACE inhibitors and more than two-thirds do not receive beta-blockers; (3) Substantial benefit can probably be derived from the development of new blockers of neurohormonal mediators and cytokines as well as of oxidative stress; (4) There should be additional investigation of prolonged mechanical support of the failing heart, which as noted above, can sometimes reverse heart failure and make the patient more responsive to conventional therapy; (5) Permanent cardiac replacement with an artificial heart and a xenotransplant for irreversible heart failure require much more work, but neither of these solutions seem as far fetched as they did even a decade ago; (6) Finally, novel therapies such as myocyte and gene replacement, while still on the distant horizon, may ultimately prove to be extremely effective.

It has been enormously exciting for me to have had the opportunity to observe at close range the many advances in the understanding and management of heart failure which have occurred during the past half century, and to have participated in a few of them. I have been fortunate to have had inspiring mentors, talented collaborators, and extraordinary trainees.

References


