

# Heart Failure Society News

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### AHA Highlights

## 1,857 Attended HFSA's Third Annual Scientific Meeting

A record-breaking 1,857 physicians, nurses, and other health care professionals attended the HFSA's Third Annual Scientific Meeting in San Francisco from September 22-25, 1999, to discuss the state of heart failure science and practice.

The meeting provides an important and interactive forum for attendees to learn about the latest trial results, share clinical experiences, discuss treatment approaches, and participate in shaping the future of the quality of care provided to heart failure patients. The event is one means by which the Society fulfills the goals of its mission statement: to promote research, to educate physicians and other heart failure caregivers, to encourage preventive measures, and to enhance the quality and duration of life for patients.

The meeting program offered an ambitious and balanced blend of lectures, Hyde Park Hypotheses, debates, Young Investigator Awards, clinical

practice guidelines, poster presentations, satellite symposia, and practical how-to workshops.

The featured lectures included the State of the Science series, which reported on late-breaking research, and the Landmarks of Heart Failure series, which summarized the results of long-term work and developments. Dr. Norman Shumway, who developed the first definitive heart failure treatment to reduce mortality - transplantation - delivered the Founder's Lecture. The Late-Breaking Clinical Trials session reported the results of four trials: LIDO, IMAC, MERIT, and MOXCON.

The Hyde Park Hypotheses and Debate sessions provided the opportunity to disagree in a stimulating and congenial atmosphere.

Additional opportunities to exchange informa-

*(continued on page 2)*



Arnold Katz, Norwich, Connecticut, discusses data from a late-breaking clinical trial with the presenter.

## Heart Failure Society News

### Editors

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## HFSA President Calls for Campaign to Increase Public Awareness of Heart Failure Issues



HFSA President Arthur Feldman set the tone for the annual meeting in the opening session by noting that "heart failure is a disease of epidemic proportions" that affects 4.6 million Americans. An additional 400,000 new cases are diagnosed annually, he said, and in dollar terms the cost exceeds \$40 billion in the United States alone.

Stressing the need for education to increase public awareness and understanding of the disease, he described the Society's commitment to expand the understanding of heart failure among both the general public and the government agencies. The lack of awareness, he stated, results in misunderstandings by patients and families who receive the diagnosis, as well as disproportionately low funding for research.

Dr. Feldman described the Society's Heart Failure Awareness Initiative, a program to increase public awareness of the nature of and treatments for heart

failure. As part of the program, the Society has asked Congress to declare February 13-19, 2000, to be Heart

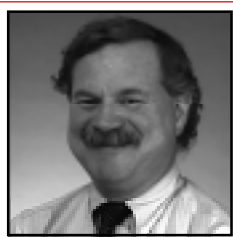
Failure Awareness Week. Senator Arlen Specter (R-Penn.) has placed the resolution before the U.S. Senate. Dr. Feldman sought the active participation of all present to ensure the initiative's success. Specifically, he asked them to write letters to their state's Senators, seeking their support for passage of the Heart Failure Awareness resolution. In addition to national projects in support of the program, he asked the members of the audience to

develop local initiatives to promote Heart Failure Awareness Week. The HFSA will observe the week in collaboration with industry sponsors, the American College of Cardiology, and members of other closely related societies. Corporate sponsors include AstraZeneca, Guidant Corporation, Medtronic Inc., Merck, Sonofi-Synthelabo, and SmithKline Beecham. The Society selected the image of a gold ribbon to symbolize the purpose of the campaign. ■



Arthur M. Feldman, M.D., Ph.D.  
President, HFSA

## HFSA Publishes New Clinical Practice Guidelines



Kirkwood F. Adams

*(Editor's note: Kirkwood F. Adams, Jr., M.D., Chair, Guidelines and Clinical Positions Committee, and Director of the Heart Failure Program, Division of Cardiology, University of North Carolina, Chapel Hill, North Carolina, brings to the committee*

*his unusual combination of hands-on and clinical trial experience. While he has actively engaged in investigative work in heart failure since 1983 and has developed expertise in statistical issues related to clinical trials and the analysis of trial data, he continues to provide direct patient care. In this interview, he discusses the purpose and scope of the HFSA guidelines. He presented the draft guidelines to the attendees at the annual meeting and subsequently incorporated additional changes as a result of the feedback he received.)*

### **Which aspects of heart failure and which treatment areas are within the scope of these guidelines?**

While a comprehensive algorithm is beyond their scope, the guidelines focus on updating and defining pharmacologic therapies for patients with left ventricular systolic dysfunction, the key area of heart failure management. The management strategies included are: beta-adrenergic receptor blockers, digoxin, anticoagulation and antiplatelet drugs, angiotensin II receptor blockers, antiarrhythmic drug and device therapy, aldosterone antagonists, and therapies for myocarditis.

### **What is the purpose of the guidelines?**

Our guidelines have been developed to raise the level of patient care. The HFSA is dedicated to the development of strategies to deal more effectively with the many issues surrounding the syndrome of heart failure. Our committee has the responsibility to review ongoing research and expert opinion and to develop and maintain a dynamic synthesis of this information as a state-of-the-art clinical practice guideline.

### **Why are the guidelines necessary?**

Each physician has two components to consider in developing a treatment plan: objective clinical trial information and subjective observational knowledge of patients. While the individual physician's own experience is certainly important, to rely on it exclusively is not always the best approach. Limited observations may lead to invalid conclusions. There is a huge knowledge base that can be difficult for busy practitioners to digest. Our guidelines, the result of a consensus of many physicians and based on both observational experience and results of clinical trials, will provide sound recommendations based on the most current understanding of the state of the science. This can include such recommendations as how

to dose, how to monitor progress, and how to determine the duration of therapy.

### **Will the guidelines be published as one document or by type of therapy?**

We will release them as one document. We want a single document that will make a strong statement on the best ways to provide the most effective forms of patient care. In the future, we may provide interim updates to be able to comment on late-breaking trial results.

### **How often do you plan to publish guidelines?**

Our goal is to have a yearly update. Other groups are able to update their guidelines only every four to five years. We want to develop a process that allows the HFSA to do this on an annual basis. It is an important role for the Society and distinguishes it from other groups that are not able to perform this service.

### **What strategy did you follow in developing the guidelines?**

The strategy followed by the Agency for Health Care Policy and Research (AHCPR) and other groups issuing guidelines served as our point of departure. The existing guidelines of the American Heart Association, the American College of Cardiology, and the AHCPR were already several years old. We divided up the topics, conducted literature searches in each, reviewed relevant literature and identified key papers. We generated a draft document, which underwent revision by our committee and by the HFSA's Executive Committee. The result of those reviews was presented to the Society's annual meeting in September 1999 and modified based on the feedback we received at the meeting. It was a very dynamic and comprehensive process, in distinction to that of other guidelines.

### **What changes would you make to the process in the future?**

We will seek additional formal review from physicians outside of the Society.

### **Please explain your ranking system for the strength of the evidence.**

It is important to identify the type of evidence when making recommendation. Ours is a fairly standard approach, similar to that used by the AHCPR. It lists, in decreasing order from A to C, the strength of evidence:

- "A" is assigned to the results of well-designed and adequately controlled clinical trials performed in relevant patient populations
- "B" is assigned to cohort studies
- "C" is assigned to expert opinion

### **How do the guidelines address standard therapeutic strategies that stress the role of ACE inhibitors, diuretics, and digoxin?**

These guidelines assume that these fundamental aspects remain essential. They build on this framework by focusing on the evolu-

tion of specific pharmacologic treatments for heart failure that are additive to the benefits obtained from current strategies.

### **To what extent do the guidelines draw upon the paradigm of cardiac remodeling?**

What happens to the heart muscle is a key to optimal treatment, and so the cardiac remodeling process has become the focus of much of the research. The therapeutic implications of cardiac remodeling are evident in the approach taken in the guidelines. However, remodeling is a complex phenomenon, and we are still exploring new neurohormonal factors as contributors as well. Remodeling may occur as a result of both direct effects on myocytes and indirect effects due to cardiac interactions with blood pressure and increased risk of cardiac thrombosis.

We have learned that ACE inhibitors, beta blockers, and spironolactone are all efficacious agents in influencing the remodeling process.

### **What do you consider to be the most significant addition to the pharmacologic management of heart failure that the guidelines offer?**

The single most significant addition involves the use of beta-receptor antagonists, which previously had been contraindicated, in the treatment of patients with LVSD. The trial data indicating the benefits this therapy can offer are very strong and build on current treatment strategies. ■

The full text of the Clinical Practice Guidelines for the Management of Patients with Heart Failure Due to Left Ventricular Systolic Dysfunction was published in the December 1999 issue of the *Journal of Cardiac Failure* and reprinted in the January/February 2000 issue of *Congestive Heart Failure*. They will be posted on the HFSA website at [www.hfsa.org](http://www.hfsa.org).

*(continued from page 1)*

## 1,875 Attend Meeting

tion were provided at the 18 satellite symposia, which covered such topics as the role of angiotensin II and of angiotensin receptor blockade, treatment of acute decompensated CHF, beta-blockers, shared care of patients with heart failure, optimal care strategies, and device-based therapy. The poster sessions, with over 300 posters, presented an impressive array of research and clinical experiences. ■

## Heart Failure Society of America

4th Annual Scientific Meeting  
September 10-13, 2000  
Boca Raton, FL

### ABSTRACT DEADLINE

April 3, 2000 (Monday)  
(Receipt date)

Electronic submission available on  
the HFSA web site [www.hfsa.org](http://www.hfsa.org)

The same abstract may be submitted to the 2000 meetings of the HFSA and the AHA. Accepted abstracts can be presented at both meetings.

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## Young Investigator Award Winner Named

Federica del Monte, MD, PhD, from the Cardiovascular Research Center, Massachusetts General Hospital, in Boston, Massachusetts, was the recipient of the HFSA's Young Investigator Award, which was presented at the Society's annual meeting. Her winning presentation reported on the results of her research on the "Restoration of Contractile Function in Isolated Failing Human Ventricular Cardiac Myocytes by Gene Transfer of SERCA2a." Her crisp and professional presentation on increasing expression of SERCA2a as an important tool to improve the treatment of heart failure included both slides and a video.



Young Investigator Award Winner Federica del Monte and Session Chair Michael Bristow

ensure quality research in the future. He praised the quality of the numerous submissions and of the research and the presentations of each of the finalists, saying "Each of the five nominees performed outstanding work." ■

The other finalists were:

- **Harold S. Bernstein, M.D., Ph.D.**, Pediatrics and Cardiovascular Research Institute, University of California, San Francisco, California: "Human Cdc5 Controls Mitotic Entry Through Specific DNA-Protein Interactions and is Regulated Through a Mitogen-Activated Pathway"
- **Christopher Depre, M.D., Ph.D.**, Division of Cardiology, University of Houston Medical School, Houston, Texas: "Reprogramming of Dysfunctional Gene Expression by Mechanical Unloading in Failing Human Heart"
- **Bradley J. Martin, Ph.D.**, Division of Cell Biology and Muscle Research, Osiris Therapeutics, Baltimore, Maryland: "Implantation and Myogenic Differentiation of Human Mesenchymal Stem Cells"
- **Guillermo Torre-Amione, M.D.**, Cardiology, Baylor College of Medicine, Houston, Texas: "Regulation of Tumor Necrosis Factor by Volume and Pressure Overload in Human Myocardium: Effect of Chronic Ventricular Unloading and Pressure Overload Elimination"

Dr. del Monte was one of five finalists selected from numerous entries to present their abstracts in a special session at the annual scientific meeting on Friday, September 24. The abstract presentations were judged by a panel on the bases of scientific merit, presentation of abstract, use of appropriate graphics, and effectiveness of discussion. The winner was announced at the opening of the plenary session on Saturday, September 25. Support for this program was provided by an unrestricted grant from AstraZeneca, which had sponsored two previous competitions.

Session chair Michael Bristow explained that the Young Investigator Awards are part of the Society's commitment to encourage research now and to provide forums for young researchers to

## Hyde Park Hypotheses Combined Science, Polemics, and Wit

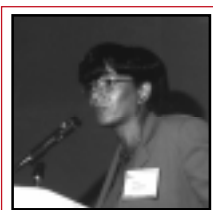
In a lively session that has become an established favorite at the annual meeting, presenters explored new approaches, considered alternative paradigms, and provided a stimulating and humor-filled session, complete with enthusiastic audience participation, moderated by Arnold Katz and Carl Leier.

### Fatigue as a cause and consequence of heart failure

Alan Bank, using the analogy of metal fatigue in failed machines, explored the possibility that plaque fatigue is a cause as well as a result of heart failure. He described a possible progressive causal chain: atherosclerosis, plaque fatigue, rupture, myocardial infarction, and heart failure, culminating in systemic fatigue and eventual failure.

### Abnormalities in myofilaments and not calcium cycling are the main contributors to contractile dysfunction in heart failure

Judith Gwathmey suggested that the principal mechanism underlying contractile dysfunction is initial damage to myofilaments that results in increased calcium concentration as a compensatory mechanism, rather



Judith Gwathmey

than calcium cycling. She said, "Unless you improve your myofilaments, your heart will be in failure."

### Look, I found the cause of heart failure!

Reviewing different factors historically cited as the primary cause of heart failure, and finding them replaced by successive alleged culprits, Steven Houser concluded, after his own 20 years of "humbling" research, that "it is counterproductive" to attempt to focus on a particular factor or condition. "No single genetic or functional defect" is the cause, he argued, saying "the human body is an integrative and adaptive system" and that only a multifactorial approach will be effective.

### Will cardiac slowing prolong life?

If every human has a predetermined number of heartbeats, Herbert Levine asked rhetorically, can we increase life span by slowing down the heart rate? No, he ex-

plained, because of the "hitch" of metabolic rate. However, he argued that we might be able to prolong life if we can reduce heart rate in conjunction with MVC. He concluded by saying that "There are 3 billion heart beats in the average person's life - don't waste any of them!"

### Inotropic therapy in heart failure: flawed assumptions lead to invalid conclusions

Matthew Movsesian argued that inotropic response and mortality are not necessarily congruent and that inotropic therapy should continue to be used, albeit selectively, in the treatment of patients with heart failure.

### Heart failure is a reversible disease

Arthur Feldman reviewed his experiences with patients and data from animal studies to support his hypothesis that, at least in some patients, heart failure is a reversible disease. He proposed that irreversibility of heart failure is caused not by intrinsic myocyte dysfunction but rather by extracellular matrix remodeling and apoptosis. ■

## Debates Provided Vehicles for Discussion, Disagreement, and Sport

Two sessions devoted to public debate of controversial issues provided ample opportunities for participants and attendees to discuss, agree and disagree, and enjoy themselves.

In Session I, moderated by Marc Silver, the pros and cons of two issues – the mechanism of ACE inhibitors and the routine use of anticoagulants in the treatment of patients with heart failure – were debated. Session II, moderated by Prakash Deedwania and Leslie Miller, examined the relative merits of the Batista Procedure and of implantable cardiac defibrillators.

### ACE inhibitors work by reducing the levels of angiotensin II

*Protagonist:* Marvin Konstam  
*Antagonist:* Jay Cohn

"Angiotensin II is a key player," argued Marvin Konstam, in inducing increased protein synthesis leading to myocardial hypertrophy. ACE inhibitors significantly reduce angiotensin II levels, most likely by blocking the generation of angiotensin II in blood vessels, kidneys, and heart tissue. Historically, the clinical efficacy of these agents has been attributed to the direct inhibition of angiotensin II.

However, recent research suggests a more complex mechanism. "While there is overwhelming evidence that ACE inhibitors are effective" in reducing mortality and prolonging survival, said Jay Cohn in opposing the affirmative position, he disputed the single-mechanism explanation. He maintained that the fact that angiotensin II levels recover and blood pressure effects decrease during chronic ACE inhibitor therapy suggests the two are "biologically different mechanisms." "The only way we can get into the mechanisms," he concluded, is by applying different combinations of ACE inhibitors and angiotensin II antagonists. "If the combination is better," he said, "then clearly different mechanisms are involved." He said that only

the Val-Heft and CHARM trials will clarify the issue – "stay tuned," he said.

### Anticoagulants should routinely be used in heart failure patients with moderate or severe LV dysfunction

*Protagonist:* Marrick Kukin  
*Antagonist:* Barry Massie



Barry Massie and Marrick Kukin

Routine anticoagulation therapy with warfarin is justified, Marrick Kukin stated, especially given the clinical trial data on its beneficial effects in patients with atrial fibrillation.

Barry Massie disagreed, arguing that "there are no data to support routine administration of anticoagulation" therapy to patients with moderate to severe LV dysfunction. While he conceded that patients with atrial fibrillation should receive anticoagulation therapy routinely, "congestive heart failure patients are not patients with atrial fibrillation alone." Further trials, such as WATCH, are required before this approach should become routine, he concluded, saying "In 4 to 5 years, we will have the answer."

### The Batista Procedure – is it useful?

*Protagonist:* Robert Dowling  
*Antagonist:* James Young

The theoretical, experimental, and clinical data on the Batista Procedure – a partial left

ventriculectomy to resculpt the ventricle to reduce wall stress – were reviewed and discussed in this debate by the respective advocates.

Robert Dowling cited theoretical data showing that the procedure increased left ventricular function, improved systolic function, and decreased diastolic compliance, and accordingly may be an effective therapy for DCM. He stated that experimental data also indicated the procedure restores left ventricular function and improves the ejection fraction and myocyte physiology. Finally, he pointed to clinical data that show that the procedure has a survival rate similar to that of transplantation and improves left ventricular EDD, ejection fraction, and NYHA class. He cautioned that, while attempts should be made to properly identify patients most likely to benefit, the procedure itself should not be discounted. He concluded that the Batista Procedure's 12-month mortality of 35% is acceptable and that the procedure benefits many patients.

Speaking against the procedure, James Young did agree that the procedure might be beneficial for some patients. However, he said, there is no reliable predictor of outcomes, and only 30% of patients have an event-free outcome after 36 months. He noted that, although the concept is interesting, results at the 12-month stage are disappointing: 81% have survived but only 48% have event-free lives, 20% experience sudden death, and 32% have poor outcomes. Accordingly, he concluded, the Batista Procedure is not an acceptable alternative to transplantation.

### Implantable defibrillators should be installed in every high-risk patient with cardiomyopathy and heart failure

*Protagonist:* Keith Lurie

*Antagonist:* Sidney Goldstein

Keith Lurie presented the affirmative case, arguing that "malignant arrhythmias are 98% avoidable" and that mortality from sudden death in patients with stable heart failure and ejection fractions <35% and in patients with ejection fractions <45% with sudden death markers could be reduced to 2% with the use of implantable defibrillators (ICDs). He argued that pharmacotherapy was the appropriate course of treating symptoms and diseases but that ICDs are the best means of preventing sudden death. He concluded that, given the ability to decrease mortality so dramatically, to even enroll patients in trials comparing the performance of ICDs versus drugs was unethical.

Sidney Goldstein disputed the statistics, saying that the NYHA class II-IV patients who are at higher risk of sudden death are "a relatively small group" of approximately 4 million people, and the significant costs of providing ICDs to this population were unacceptably high. ■

### State of the Science lectures

The annual scientific meeting's three State of the Science lectures provided up-to-date information on new research in heart failure.

- Gene regulation of angiogenesis factors by Gregg Semenza, Baltimore, MD
- Genetic discovery in familial cardiovascular disease by Mark Keating, Salt Lake City, Utah
- Pro-inflammatory cytokines as agonists in heart disease by Charles Dinarello, Denver, CO

#### Clarification:

An article in the *Heart Failure Society News* (June 1999) reported the results of the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF). We wish to clarify that the 34% reduction in mortality in heart failure patients was achieved in patients who had received the extended-release metoprolol succinate (TOPROL-XL®), a formulation pharmacokinetically distinct from other metoprolol formulations.

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## Late-Breaking Clinical Trials Presented New Research

Results from four clinical trials, which varied from exciting to disappointing, drew a standing-room-only audience. Attendees had opportunities to comment on the data presented, the trial design, and the conclusions.

### LIDO

Ferenc Follath, Zurich, Switzerland and John Cleland, Cottingham, UK, reported the results of the Levosimendan Infusion versus Dobutamine (LIDO) trial, which compared levosimendan and dobutamine in 200 patients in 41 centers with severe low output function (ejection fraction < 35), including those with severe chronic heart failure and acute heart failure. The primary endpoint was significant hemodynamic improvement after 24 hours. Results indicated that levosimendan was comparable or superior to dobutamine in achieving hemodynamic improvement and reducing mortality. After 6 months, mortality for patients receiving dobutamine was 38% compared with 27% for levosimendan. Levosimendan had better out-of-hospital rates after 1 month. The vasodilatory effects of levosimendan can produce migraines; dobutamine can result in angina.

### IMAC

Dennis McNamara, Pittsburgh, PA, presented data from the IMAC (Intervention in Myocarditis and Acute Cardiomyopathy with IV Immunoglobulin) trial on viral and immune triggers initiating the pathogenesis of primary dilated cardiomyopathy. Exploring whether immune modulation could succeed where immune suppression failed, the trial tested the safety and efficacy of high-dose intravenous immunoglobulin therapy at the time of initial presentation. Dr. McNamara said, "While the therapy is safe,

the efficacy was not what we had hoped for." Improvements in ejection fractions after 6 months and 12 months were not significantly better than placebo, nor was peak MVO<sub>2</sub>. Asking rhetorically "What else can we learn?" from trial data, he answered that predictors of improvement include left ventricular ejection fraction and gene expression analysis; fibrosis on biopsy was not an indicator. He concluded that immunoglobulin therapy did not improve ejection fraction, 88% of all patients had event-free survivals, outcomes remain heterogeneous, and the search for better predictors should focus on biologic parameters.

### MERIT-HF

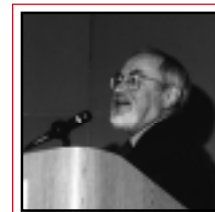


Stephen Gottlieb

Stephen Gottlieb, Baltimore, MD, reported the results of the M E R I T - H F (Metoprolol CR/XL (Controlled Release) Randomized Intervention Trial in Heart Failure), the largest heart failure trial to evaluate the efficacy of a beta blocker. The trial randomized 4000 patients in 14 countries with moderate to severe heart failure to receive once-daily doses of placebo or metoprolol. The addition of the beta-blocker metoprolol to standard treatment in patients with congestive heart failure resulted in a 34% decrease in overall mortality, a 41% decrease in sudden deaths, and a 49% reduction in heart failure deaths; a 32% decrease on the combined endpoint of death and in the number of patients who required cardiac transplantation; and a 35% decrease in hospitalizations due to worsening fail-

ure. According to Dr. Gottlieb, most of the improvements occurred in patients with NYHA class II and III heart failure; improvements in patients with class IV were not as clear. The quality-of-life improvements, which varied with the instrument used, were measured by NYHA, McMaster Overall Treatment, which found "highly significant" improvements, and Minnesota Living with Heart Failure, which found trends toward improvement rather than "significant improvements."

### MOXCON



Jay Cohn

Jay Cohn, Minneapolis, MN, presented the results of the MOXCON (Monoxidine for Congestive Heart Failure) trial. The correlation between plasma norepinephrine levels with mortality, and the effects of inhibiting the sympathetic nervous system to decrease norepinephrine levels, provided the rationale for studying the efficacy of sustained-release monoxidine. The MOXCON trial compared the sustained-release formulation versus placebo in 4540 patients with NYHA classes II-IV in 425 sites in 17 countries. The trial was terminated due to increased rates of mortality, myocardial infarctions, and hospitalizations in March 1999. The preliminary results indicate that monoxidine decreased plasma norepinephrine, increased mortality, increased sudden deaths, and had a higher rate of other adverse events. Dr. Cohn, analyzing the results, suggested several possibilities: there are unidentified issues with sustained-release formulation, the dosage was titrated too quickly, or the study was terminated too quickly. ■

## Landmarks of Heart Failure Series: A Well-Traveled Road Revisited and Future Course Plotted

The journey is long and arduous, the risk of failure is high, the dangers numerous, the outcome uncertain. Yet, each year, many undertake it, some for the first time, some for the tenth or twentieth.



Marc Pfeffer

failure research was clear to everyone in the audience.

Hiking the Appalachian Trail, Dr. Pfeffer related, is a daunting task. The woods are full

of perils from poisonous or predatory animals, toxic plants, virulent diseases, human violence, and unpredictable weather. The threat of hypothermia looms. Hikers lose their way, follow false trails, and retrace their weary steps to start again. The journey is arduous. The precise length of the trail is unknown, although it is approximately 2200 miles. Bryson writes, "What is certain is that it is a long way, and from either end it is not easy. The peaks of the Appalachian Trail are not particularly formidable as mountains go .... but they are big enough and they go on and on .... All together, it takes about five months, and five million steps, to walk the trail from end to end." Nevertheless, hundreds, even thousands, of people take on the challenge each year — and, with the lessons of earlier hikers as guides, they are succeeding in increasing numbers.

### Marc Pfeffer

In his Landmarks of Heart Failure lecture, "Remodeling and its Reversal in Heart Failure," Marc Pfeffer recounted the Appalachian Trail of heart failure research. He began by tracing its origins to the discoveries of biologists such as Ludwig Traube in the last century, to the watershed contributions of Otto Frank and E. H. Starling in the earlier part of the 20th century, and the exploration of the plasticity of the heart by Alfred Chanutin and Edwin Barksdale, as well as Margaret Beznak's work on the weight of the heart and plasticity in the 1950s. He continued his narrative of the progress of the march by relating the work of Maurice Sokolow and Dorothea Perloff, the foundational work in epidemiology by M. E. Framingham, the contribution of Jay Cohn to the essential role of

(continued on page 6)

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clinical trialists, the articulation by W. Grossman of the types of hemodynamic stress, Harvey White's description of how small changes in volume affect outcome, Richmond Jeremy's insights on coronary circulation.

Addressing the specific issue of remodeling and its reversal in heart failure, Dr. Pfeffer noted that aging results in the decreasing adaptation of hypertrophic hearts, culminating in the remodeling process. "Duration of stress is a factor," he noted, and the condition is treatable.

In spite of the contributions of the many scientists who have participated in the challenge of heart failure research over the decades, Dr. Pfeffer said that "We still don't know the primary genetic defect that causes heart failure, and we still do not know the precise role of hypertension in the process." However, he concluded, we have made the commitment to continue the journey begun decades ago to refine the understanding of the salient mechanisms and processes with the goal of providing optimal care to patients, and we have made our own contributions and marked well the path for those who will come after us.

#### Edward Sonnenblick

Edward Sonnenblick, in his Landmarks of Heart Failure lecture, "Identification of the



Edward Sonnenblick

Physiologic Phenotypes of Myocardial Failure," took a similar approach by providing a historic tour of the mechanisms of systolic dysfunction. He began with the seminal work of Otto Frank and E.H. Starling

on ventricular function curves that culminated in the latter's "Law of the Heart," augmented by S.J. Sarnoff's exploration of other aspects of control of ventricular function, such as heart rate, blood pressure, and inotropic stimulation. He cited Eugene Braunwald's confirmation of the validity of applying Starling's law to the human heart, and B.C. Abbott's and W.F. Mommaerts' advances in analyzing the heart as muscle. He failed to mention that their work, in turn, was complemented by his own description of the biophysical characteristics of contractile elements of isolated cardiac muscle.

Dr. Sonnenblick emphasized the importance of the structural approach rather than the phenotype analysis: "To define heart failure, you have to know the structure, similar to knowing what is under the hood of the car and how the pistons work," he said, before you can fix your car. The articulation of the concepts and interrelationships of muscle force, velocity, and length have provided the foundation on which contemporary research is building. He con-

cluded by placing primacy on the need for research with humans, given the limitations and variables attendant in trans-special investigations.

#### Norman Shumway

Norman Shumway, who played a key role in the development of the first and only



Norman Shumway

definitive treatment of heart failure – transplantation – and who pioneered the study of the diseased hearts removed from transplant patients, delivered his lecture on "Cardiac Transplantation: The First Definitive Treatment of Heart Failure." Dr. Shumway provided a comprehensive historical overview of the development of cardiac transplantation, tracing its origins to the first known transplant attempt in 2500 B.C. He identified the primary challenges to successful cardiac transplantation – the surgical method, the preservation of the donor heart, the performance of the transplant, the homograft rejection, control of rejection, the donor question – and related how he and his colleagues at Stanford University over the past four decades have worked to meet the challenges.

Their efforts included research with canines resulting in the publication of long-term transplant survival results in 1965, the first successful open-heart surgery, and in 1964, the first animal-to-human transplant. In 1968, Ed Stinson treated the first patient in the Stanford clinical program. Endomyocardial biopsies began to be performed in 1972, in large part because of the contributions of Philip Caves and Margaret Billingham. Dr. Borrell's work on the benefits of cyclosporin led to the introduction of this therapy to transplant patients in 1980. Also in 1980 was the first heterotropic transplant. More recent challenges Dr. Shumway described included transplantation in pediatric patients and exploration of xenograft transplantation.

#### Karl Swedberg

Karl Swedberg's lecture, "Activation of the Adrenergic and Renin-Angiotensin System as Critical in the Natural History of Heart Failure," looked at important contributions to the understanding of these processes and to their role in heart failure. Dr. Swedberg was one of the first cardiologists to use beta-blockers in the treatment of atrial fibrillation. In exploring the mechanisms for heart failure, he noted that evidence suggests they include the "classical components of neuroendocrine activation" and that norepinephrine levels, linked to increased angiotensin and aldosterone levels, are important indicators of the prognosis of heart failure.

He pointed out that neuroendocrine activation has long-term consequences, including

structural alterations, functional effects, and phenotype impact. Chronogranin-A (CgA) is a new candidate, he said, and CgA markers are clearly related to functional class; "the higher the level of CgA, the worse the prognosis," he said; "CgA is the best predictor of mortality."

He reviewed treatments, including the use of diuretics, digoxin, and vasodilators in the 1980s, and the more recent trials using beta-blockers and angiotensin receptor blockades, including MERIT and CHARM.

#### Conclusion

In *Walk in the Woods*, author Bryson writes, "The hardest part was coming to terms with the constantly dispiriting discovery that there is always more hill. The thing about being on a hill, as opposed to standing back from it, is that you can almost never see exactly what's to come. Between the curtain of trees at every side, the ever-receding contour of rising slope before you, and your own plodding weariness, you gradually lose track of how far you have come. Each time you haul yourself up to what you think must surely be the crest, you find that there is in fact more hill beyond, sloped at an angle that kept it from view before, and that beyond that slope there is another...."

The heart failure community knows well the challenges and obstacles of the lengthy Appalachian Trail of research, and all share the sense of arriving at a crest only to discover another and higher crest beyond it. However, as Marc Pfeffer concluded, all also know the depth of their commitment, the benefit of their collegiality on the journey, and the enormous significance of the trail-markers left by pioneering predecessors. Most important, they know the trail does have an end, and they left the annual meeting with a renewed dedication to continue on it until that end is attained. ■

### Landmarks of Heart Failure Series

The Landmarks of Heart Failure series featured the following presentations:

- **Edward Sonnenblick, Bronx, New York**  
Identification of the Physiologic Phenotypes of Myocardial Failure
- **Marc Pfeffer, Boston, Massachusetts**  
The Importance of Remodeling in the Natural History of Heart Failure
- **Norman Shumway, Stanford, California**  
Cardiac Transplantation: The First Definitive Treatment of Heart Failure
- **Karl Swedberg, Goteborg, Sweden**  
Activation of the Adrenergic and Renin-Angiotensin System as Critical in the Natural History of Heart Failure.

## Heart Failure and Ischemic Disease, American Heart Association Scientific Sessions, 1999

The 72nd scientific sessions of the American Heart Association in Atlanta, Georgia, in November 1999 highlighted a number of interesting developments.

### The Role of Gene Therapy in the Treatment of Heart Failure

In less than four years, the question of whether gene therapy can be used to treat heart failure has been transformed into a question of how important these therapies will be as first-line protection against further deterioration. Although few clinical trials so far have evaluated efficacy, several demonstrate feasibility. Gene therapy has promise both for turning on factors that improve heart function and for turning off factors that promote disease progression.

Theory and application are particularly close in the promotion of angiogenesis to improve circulation, according to a status report at the meeting. Clinical trials are already using viral vectors, especially the adenovirus, to introduce recombinant genes into myocytes to produce overexpression of vascular endothelial growth factor (VEGF). Overexpression of VEGF initiates the endogenous events that lead to new capillaries, arterioles, and other vascular structures around the heart, according to Elizabeth G. Nabel, MD, University of Michigan, Ann Arbor.

The approach appears likely to succeed because myocytes, like many other cells, are reasonably characterized as "miniature drug factories," Dr. Nabel explained. By inducing overexpression of genes responsible for producing the proteins that drive desired physiological change, such as new vessels to increase blood supply, pathological forces can be reversed or countered. Whether vessels induced by overexpression of VEGF will carry sufficient blood to improve cardiac function has not been established, but the concept of inducing angiogenesis through injection of recombinant genes is no longer in doubt.

The human trials with VEGF are encouraging to a variety of other potential approaches. One is the effort to use recombinant gene therapy to turn off the beta-adrenergic receptor system by targeting a key enzyme called beta adrenergic receptor kinase (BARK). The down regulation of beta adrenergic receptor responsiveness, a product of increased BARK, is attractive, because this now appears to be an important process driving cardiomyopathy, according to Walter J. Koch, MD, Duke University, Durham, North Carolina.

"The desensitization and down regulation of the myocardial beta adrenergic receptor system in failing hearts appears to be triggered by increased BARK activity and to be maladaptive," Dr. Koch reported. Recombinant gene delivery is a promising approach in the effort to turn off

BARK, because it has been found both feasible and protective against cardiomyopathy in animal models of heart failure.

As positive studies in animal models move to clinical trials, there is a vast array of potential targets for recombinant gene therapy in patients with heart failure or at risk for heart failure after an ischemic event. Although the ability of gene therapy to improve survival has not been proven, the ability to safely introduce recombinant genes to affect physiological change has. It appears likely that the most substantial barrier to clinical application is time.

### BEST Trial Surprise: Beta Blockade Does Not Improve Survival in Class III-IV HF

Long-term treatment with the beta-blocker bucindolol failed to improve the survival of patients with NYHA class III-IV heart failure in a recent large, randomized clinical trial. Given the abundant trial evidence that beta blockade improves survival in mild-to-moderate heart failure, the recent study's surprising results underscore the clinical importance of giving such therapy before the patient's disease has become severe.

The Beta Blocker Evaluation of Survival Trial (BEST), which randomized 2708 patients with class III-IV heart failure to receive bucindolol daily or a placebo, was halted early after a mean of two out of a planned three years because active therapy failed to produce a significant benefit in the primary endpoint of all-cause mortality (Table 1).

**Table 1. Primary and Secondary Endpoints in the BEST Trial**

	Bucindolol N=1,354 (%)	Placebo N=1,354 (%)	P value
All Cause mortality	30.2	33	NS
<b>Death From</b>			
Cardiovascular Causes	24.4	27.9	0.04
Pump Failure	8.6	9.9	NS
Sudden Death	13.1	14.8	NS
MI	0.7	1.0	NS
Noncardiovascular Causes	3.0	3.8	NS
Hospitalization	61	64	NS
HF Hospitalization	35	42	<0.001
Death or Cardiac Transplantation	31.6	35.3	0.042

Patients had been eligible for randomization if they were in NYHA class III-IV heart failure despite treatment with ACE inhibitors and other standard medications and had a LVEF no higher than 35%. About 8% of the randomized patients

were in class IV heart failure; the remainder were in class III, reported Dr. Eric Eichhorn of the University of Texas Southwestern Medical Center, Dallas, in his presentation.

Active therapy consisted of bucindolol at 3 mg bid, titrated over six to eight weeks to a maximum dosage of 50 mg bid for patients weighing less than 75 kg or 100 mg bid for those weighing 75 kg or more. Bucindolol was chosen for the trial because it is well tolerated, blocks both beta 1 and beta 2 receptors, does not upregulate beta receptors, reduces plasma levels of norepinephrine, has no sympathomimetic activity, and is a mild vasodilator.

Treatment with bucindolol was associated with significantly reduced plasma norepinephrine levels (Table 2) and significantly increased LV function (Table 3) at both three and 12 months. Although these benefits did not correlate with improved all-cause mortality, patients who received bucindolol did show a significant decrease in cardiovascular mortality, which was a secondary endpoint (Table 1).

**Table 2. Changes in Plasma Norepinephrine Levels from Baseline in BEST**

	Bucindolol (pg/ml)	Placebo (pg/ml)	P value
3 Months	-70	+24	0.0001
12 Months	-18	+56	0.0001

In an analysis of patient subgroups, race was found to have a significant influence on outcome. Bucindolol was not associated with a significant decrease in all-cause mortality in African-American patients, who made up 23% of the study population. However, a significant effect was observed for the remaining patients, which included Caucasians and "other" races (70% and 7% of the population, respectively). Also, a trend toward improved survival was observed for patients initially with class III heart failure but not those with more severe disease.

"The patient population had a heterogeneous response to therapy," said Dr. Eichhorn. "The results of the BEST study highlight the need to examine gender, racial, and ethnic differences in cardiovascular disease," he concluded.

**Table 3. Changes in LVEF from Baseline in BEST**

	Bucindolol (pg/ml)	Placebo (pg/ml)	P value
3 Months	+5.5	+2.1	0.0001
12 Months	+7.3	+3.3	0.0001

(continued on page 8)

(continued from page 7)

**ELITE-II: A-II Blockers Are No Better than ACE Inhibitors at Lowering Heart Failure Mortality**

Angiotensin II (A-II) receptor blocker therapy was only about as effective as conventional ACE inhibition at reducing 2-year mortality in patients with symptomatic heart failure in a large, double-blind, randomized trial. The findings dash hopes inspired by a previous, much smaller—and thus far less conclusive—trial that found A-II blockers to be superior in a similar patient population.

The larger, more authoritative trial randomized 3152 elderly patients with NYHA class II-IV heart failure and LV ejection fractions no higher than 40% to receive either captopril at 50 mg tid or the A-II blocker losartan at 50 mg/day. Heart failure was ischemic in 80% of patients. After 2 years, the primary endpoint of all-cause mortality was 15.9% for those who took captopril and 17.7% for those who received losartan ( $P=0.16$ ), reported Dr. Bertram Pitt of the University of Michigan, Ann Arbor, for the investigators of the international Losartan Heart Failure Survival Study, also called ELITE-II. Most secondary endpoints also were observed at similar rates with the two agents (Table 1).

“We conclude that ACE inhibitors clearly remain the therapy of choice for patients who have heart

**Table 1. Primary and Secondary Endpoints Over Two Years in ELITE-II**

	Captopril N=1,574	Placebo N=1,578	P value
<b>Primary Endpoint (%)</b>			
All Cause Mortality	15.9	17.7	0.16
<b>Secondary Endpoint (%)</b>			
Sudden Death/ Resuscitated Cardiac Arrest	7.3	9.0	0.08
All-Cause Mortality/ Hospitalization	44.9	47.7	0.21
Withdrawal Due to Adverse Effects	14.5	9.4	<0.001

failure and systolic dysfunction. If an ACE inhibitor is contraindicated, then one could consider use of an angiotensin receptor antagonist, such as losartan,” said Dr. Pitt.

In the first ELITE study, published in 1997, treatment with losartan was associated with 46% and 64% reductions in all-cause mortality and the sudden death rate, respectively, over four years as compared to treatment with captopril. These “unexpected and exciting” findings were based on a randomized population of just 722 patients, observed Dr. Pitt, and so were considered only “hypothesis-

generating.” A second and much larger ELITE trial was launched to more conclusively compare the two agents.

Although no differences were seen in other prospective endpoints, the rates of treatment withdrawal due to adverse effects were 14.5% with captopril and 9.4% with losartan ( $P<0.001$ ), suggesting that A-II blockade was better tolerated. However, the ELITE-II investigators concluded that ACE inhibitors should be preferred in systolic heart failure because of their voluminous safety and efficacy record. Numerous clinical trials have shown ACE inhibitors to lower heart failure mortality and also to benefit patients with asymptomatic LV dysfunction, not only by preventing heart failure progression but also possibly by reducing the risks of sudden death and infarction. “There are more data coming,” said Dr. Pitt, “but at the moment every member of the ELITE-II steering committee feels very strongly that ACE inhibitors remain the therapy of choice.” ■

**Suggested Reading**

Pitt B, Segal R, Martinez FA, Meurers G, Cowley AJ, Thomas I, Deedwania PC, Ney DE, Snavely DB, Chang PL. Randomised trial of losartan versus captopril in patients over 65 with heart failure. *Lancet* 1997;349:747-752.