

# Heart Failure Society of America

An Official Publication of the Heart Failure Society of America • Volume 5, Number 1 • January 2003

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## Heart Failure Society News

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## 6th Annual Scientific Meeting Opens With Record Attendance

The 6th Annual Scientific Meeting of the Heart Failure Society of America, held September 22 to September 25, 2002, in Boca Raton, Florida, provided the record number of attendees with an exciting blend of sessions designed to present and analyze the latest developments in clinical and basic science research and their applications to improved patient care.

On Monday morning, September 22, the 2002 program committee co-chairs, Barry M. Massie and Michael D. Schneider, formally kicked off this year's annual scientific meeting. The program was carefully designed to attract a diverse group of in-

dividuals interested in heart failure (physicians, research scientists, surgeons, pharmacists, nurses, and other allied health professionals), who make this meeting a "must" on their annual calendars.

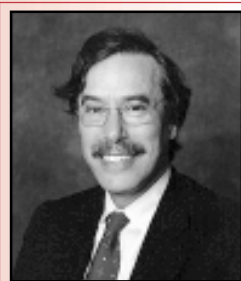


A record-breaking number of attendees with clinical and research interests contributed to the success of the 6th Annual Scientific Meeting.

The scientific content featured a variety of formats for disseminating information and vehicles for fostering research. "We do not intend to have the meeting get much bigger," Dr. Massie said, "and symposia will be limited to not more than four to five simultaneous sessions."

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## Marvin A. Konstam Begins Tenure as New HFSA President



**Marvin A. Konstam**

Delineating the steps involved in improving clinical outcomes – from advancing basic knowledge, to documenting clinical efficacy, to achieving consensus, to implementing improvement in care – provides a roadmap of the vision of the next HFSA President, Marvin A. Konstam, MD, FACC. In assuming his office at the annual scientific meeting, Dr. Konstam told attendees, "I am honored to begin my term as the fourth President of the Heart Failure Society of America, following in the footsteps of Jay Cohn, Art Feldman, and Milton Packer."

Dr. Konstam brings to his new office his extensive background and interest in the clinical and research aspects of heart failure, as well as his substantial relationships with governmental agencies and providers. He is Chief of Cardiology at Tufts-New England Medical Center and Professor of Medicine at Tufts University School of Medicine. He received his doctorate in medicine from Columbia University, and he pursued post-doctoral training in medicine at Massachusetts General Hospital and in cardiology at the Brigham and Women's Hospital, in Boston. His primary areas of research are pathophysiology of ventricular remodeling and heart failure management. He initiated the Tufts-New England Medical Center Heart Failure and Cardiac Transplant Center and is founder and chairman of the Network for Cardiovascular Clinical Trials, a nationwide network of clinical trial sites.

Dr. Konstam's commitment to improving patient care has been manifested in his chairmanship of the national panel that developed the Clinical Practice Guideline in Heart Failure for the

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## President's Message

On at least two occasions since the creation of the HFSA in May 1994, our Executive Council has, albeit briefly, taken up the topic of changing the Society's name. But *Heart Failure Society of America* it is and will stay. We inherited the name of the condition, and it is not about to change. (Could "inotropically challenged" catch on?) We are a Society linked to a clinical condition. This point differentiates us from other subspecialty societies within cardiology, which are linked to procedures rather than conditions. The choice of our name defines our goal: to help patients with heart failure and those at risk for developing heart failure. Having such a straight-forward mission is a luxury. If we follow it, it sets our priorities and guides our agenda. We can inspect our various programs and ask: Are they serving our goal? What more should we be doing?

**Annual Meeting.** When the Society opened shop, the selection of a first initiative was easy: to create an annual meeting, where scientific advancements, ranging from basic science to clinical trials, could be communicated and discussed. At that meeting the HFSA moved from an idea to an institution. That institution had filled a suddenly obvious unmet need: to bring together a wide spectrum of individuals devoted to combating the one common cardiac condition that is increasing in prevalence in the United States – heart failure.

Scientific advancement, as essential as it is, is not sufficient to conquer a disease. Our national meeting, growing year by year, serves the essential step of communicating new knowledge. However, more is needed. Clinical trial results must be integrated into a consensus, and such consensus must be translated into action by clinicians and patients. Delineation of these steps toward improved clinical outcomes – from advancing basic knowledge, to documenting clinical efficacy, to achieving consensus, to implementing improvement in care – provides a roadmap to guide the actions of the HFSA.

**Journal of Cardiac Failure.** In addition to our annual meeting, the Society's journal, the *Journal of Cardiac Failure (JCF)*, provides a forum for peer-reviewed scientific communication. *JCF* is rapidly growing in stature and in importance, and it recently ranked ninth in impact among cardiology journals.

**Practice Guidelines.** In December 1999, we published our first guideline document, providing an update on drug treatment in heart failure based on recent clinical trial developments. We will soon publish a comprehensive clinical practice guideline for evaluation and management of patients with heart failure.

**Heart Failure Awareness.** Most patients with heart failure receive their care from primary care providers. Yet individuals with a special interest in heart failure are more aware of recent advances and deliver higher quality of care according to established standards. Taking the challenge posed by these realities, we have embarked on a number of programs to improve care in the community. Our Heart Failure Awareness program is an annual nationwide effort to educate primary care providers and patients about the condition and its treatment. The educational modules produced by our Nursing Committee provide patients with a wealth of information, which should have an important impact on their understanding of and compliance with treatment recommendations. The HFSA has launched an important collaboration with the Centers for Medicare and Medicaid Services, providing guidance on quality improvement programs and standards, resource expertise from our membership, and educational materials and programs.

**Continued Growth.** In the coming months and years, our plans include expanding on present programs and embarking on new programs. Here are some of the items we are working on.

- **Scientific advancement and communication:** We are about to launch the HFSA Research Fellowship program to help train the next generation of clinician-investigators in heart failure. (Details are available on our website.)

- **Achieving consensus:** HFSA is committed to translating new evidence into guideline recommendations on a timely basis, incorporated into an internet-based resource, and made available for developing measures to improve the quality of care.

- **Delivering care:** We are committed to developing improved methodologies for care through demonstration projects. We are also embarking on efforts to identify and advocate innovative reimbursement models to incentivize quality care.

The HFSA, like any organization, is only as strong as its membership. We need to reach out to all health-care providers, researchers, and others who are interested in heart failure, to offer to them the value of collaborating in the Society's programs of education, development, and advocacy. These new members, particularly those whose training is ongoing or recently completed, will soon become the Society's leaders, whose innovation will strengthen ongoing programs and conceive new ones, all directed toward the goals of advancing our knowledge and improving outcomes in patients with heart failure.

Marvin A. Konstam, M.D., President  
Heart Failure Society of America  
Professor of Medicine  
Tufts University School of Medicine  
Chief of Cardiology  
Tufts-New England Medical Center

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### Marvin A. Konstam Begins Tenure as New HFSA President

Agency for Health Care Policy and Research and in his role as a consultant for the Health Care Finance Administration's quality assurance program in heart failure. He has served as a member of the Cardiovascular and Renal Advisory Committee of the U.S. Food and Drug Administration and has chaired several national symposia on heart failure disease management.

His term as HFSA President runs from September 2002 to September 2004. □

## Plenary Session Addresses Present and Future Heart Failure Treatment Options

Setting the foundation for the two-and-a-half days of the 6<sup>th</sup> Annual Scientific Meeting, the plenary session featured an analysis of the challenges to improve outcomes in the treatment of heart failure, and the future promise and present limitations of heart replacement therapy, cell transplantation, and gene therapy.

### Presidential Address

The ongoing challenges to improving the lives of patients with heart failure and the role of the HFSA in meeting those challenges were the focus of Milton Packer's Presidential Address at the 6<sup>th</sup> Annual Scientific Meeting's plenary session.

**Drug Therapy.** Clinical trial results pose the first challenge: "Over 1000 new treatments for heart failure have been developed in recent years, but only 10 were actually approved and used in a clinical setting." Although several trials provided substantial insights – for example, those evaluating angiotensin receptor blockades, endothelin blockade, cytokine antagonists, and sympathetic outflow – they produced little benefit and even harm in the agents studied.



Milton Packer

**Analytical Methods.** The second challenge is posed by analytical methods used to interpret the results in clinical trials of new agents in heart failure: "We are terribly handicapped by the absence of a reliable way of predicting the success of a new drug before a major commitment is made to its development." The ability to translate good science into clinical reality is likely to become even more challenging. Existing drugs have effects that can be easily measured, but new drugs may have uniquely specific targets.

A sponsor interested in developing such a drug faces the nearly impossible challenge of carrying out a large-scale mortality trial to gain regulatory approval without knowing the appropriate dose or having a reasonable assurance that the drug has an effect that can be measured in patients.

**Devices.** Devices deliver a specific effect in a highly selective manner in ways that can easily be measured and are less likely to have side effects. Devices have been created that bypass conduction defects, reduce the delay in activation of the right and left ventricles, modify the process of cardiac remodeling, and terminate potential rhythm disturbances. However, device development carries many of the same challenges as drug development. Clinical trial design is in its infancy, and questions remain about endpoints, controls, mortality trials, blinding problems, and surgical risk.

**HFSA's Role.** The HFSA plays a major role in improving the care of patients with heart failure in significant areas: educating patients and healthcare professionals; serving as an authoritative resource for patients, primary care physicians, and governmental agencies; and advancing scientific research. Dr. Packer invited attendees: "Bring your ideas and energy, and

let us join together in ways that will make a real impact on public health."

### Heart Replacement Therapy

Sir Magdi Yacoub applied the lessons learned from cardiac transplantation to the discussion of mechanical devices, such as the Left Ventricular Assist Devices (LVADs) as a bridge to transplantation and as destination therapy, and to the total artificial heart. Dr. Yacoub evaluated (1) contrasts between biologic and mechanical hearts, (2) challenges in evaluation and deployment of LVADs, and (3) obstacles to and potential for total artificial hearts. Central to any discussion of device capability should be the question, "where and when and at what price?" Dr. Yacoub stressed, "We have to contemplate the costs to individuals, families, and society of a lengthened survival time."

### Cell Therapies for Heart Failure

Cell therapies offer, according to Charles Murry, "the intriguing possibility of actually rebuilding the infarct in a systematic fashion to engineer the vasculature and myocyte compartments independently." The candidate cell types for cardiac repair that he discussed are committed cells, such as cardiomyocytes; skeletal muscle, endothelial cells, or progenitors; and pluripotent cells, such as embryonic or adult stem cells.

"Cardiomyocyte grafts offer the most obvious approach," he said, but further research is needed to identify the best source of cells with optimal chance of survival and differentiation. Dr. Murry concluded, "There is tremendous promise in using both adult and embryonic stem cells, but we need to go slowly. We have seen adverse outcomes in gene therapy trials. We should get the underlying biology straight before we start experimenting."

### Gene Therapies

Anthony Rosenzweig provided an overview of gene therapy, noting that both technology and biology have to come together to produce modest successes and dramatic failures. Originally lionized in the popular press, gene therapy is now a target of criticism. However, Dr. Rosenzweig stated, "cure" is a very stringent test to apply to anything in medicine, and there has been a mismatch between unrealistic expectations and the reality of science." He identified and discussed in detail two broad categories of targets for gene therapy: monogenic and multigenic diseases.

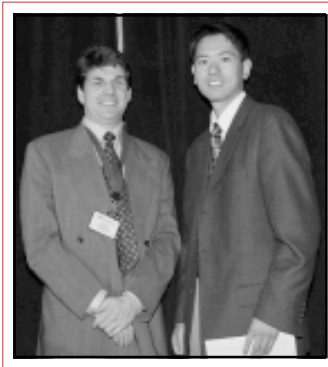
He described the three essential components of gene therapy – the vector, the delivery system, and the biological target – and provided an in-depth overview of these components. Dr. Rosenzweig suggested that gene therapy may be an important adjunct to cell therapies in one of two ways: genetic vectors could transduce the donor cell population to either promote the survival or function of those cells, and genetic vectors could promote trafficking of these cells to the heart. There is cause for "cautious optimism," he said. "We are gaining some insights into how to match clinical goals with technology, and we are enhancing our understanding of pathophysiology to identify vectors that might work." □

## Winners Announced: 2002 HFSA Research Awards

At the 6<sup>th</sup> Annual Scientific Meeting of the HFSA, the winners for the Jay N. Cohn New Investigator Awards (Basic Science; Clinical/Integrative Physiology) and the Nursing Research Award were announced. The finalists, who had been chosen from an outstanding group of abstract submissions, presented the results of their research at the annual meeting. The Jay N. Cohn New Investigator Awards are supported by an educational grant from Novartis Pharmaceuticals. The awards went to:

### Jay N. Cohn New Investigator Award for Clinical/Integrative Physiology

**Tien M. H. Ng:** *Sympathetic Regulation of Monocyte TNF $\alpha$ /IL-10 Balance Is Impaired in Severe Heart Failure.* This study investigated the relationship between sympathetic activation and inflammatory cytokine balance. Dr. Ng is an assistant professor at the University of Nebraska Medical Center, Omaha. He earned his PharmD from Wayne State University, Detroit, and he completed a cardiology fellowship at the University of Utah, Salt Lake City.



Tien M. H. Ng (right) received the Jay N. Cohn New Investigator Award from Steve Zelinkofske of Novartis Pharmaceuticals.

### Jay N. Cohn New Investigator Award for Basic Science

**Tong Zhang:** *Transgenic Overexpression of Cytoplasmic  $\delta$  Isoform of CaMKII Causes Dilated Cardiomyopathy and Heart Failure.* This study investigated the role of Ca<sup>2+</sup>/calmodulin-dependent protein kinase II (CaMKII) in the pathogenesis of dilated cardiomyopathy and heart failure. Dr. Zhang received her MD and PhD from Beijing Medical University. She is currently a research scientist in Dr. Joan Heller Brown's laboratory in the Department of Pharmacology, University of California at San Diego.



Steve Zelinkofske of Novartis Pharmaceuticals presents the Jay N. Cohn New Investigator Award to Tong Zhang (right).

### Nursing Research Award

**Sandra B. Dunbar:** *A Family-Focused Intervention Is Effective in Reducing Dietary Sodium.* This study examined the effectiveness of two family-based interventions on dietary sodium self-management. Dr. Dunbar received her doctorate in nursing science from the University of Alabama in Birmingham and is the Charles Howard Candler Professor at Emory University School of Nursing. She plans to continue her research by strengthening the family partnership intervention, looking at additional outcomes with longer follow-up periods, and increasing the sample size for more sophisticated testing of the family care model.



Susan J. Bennett (left) congratulates Sandra B. Dunbar, winner of the Nursing Research Award.

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### 6th Annual Scientific Meeting Draws Record Attendance

The Society's desire for a balanced format was reflected in the variety of sessions, including an opening plenary session, clinical sessions, basic science sessions with oral presentations of featured abstracts, and a Hyde Park session. Trials, debates, guidelines, and an increased number of how-to workshops rounded out the offerings.

Co-chair Michael Schneider agreed that the annual meeting reflected "a perfect size and perfect mix of interests and backgrounds." Noting the paucity of meetings where physicians and trainees can come together and where basic science and clinical interests are pursued, he said, "This is particularly important because of the rapid pace and range of advances. Devices, and genetic and cell therapies, which were not options a few years ago, are increasingly available."

Former Society presidents Jay N. Cohn and Arthur M. Feldman moderated the plenary session. The session began with founding president Dr. Cohn congratulating outgoing president Milton Packer on his contributions: "The dream of a Society that we organized six or seven years ago has been fulfilled, and the HFSA will continue to strive to fulfill its mission. Being the third president of a nascent organization is no small task. The goal is to ensure that the train stays on track, that you use the brakes and the accelerator appropriately, and that you try to steer in a direction for growth and improvement. Milton Packer has done these tasks extremely well." □

### Future Meetings

<b>2003</b> September 21-24 Las Vegas, NV	<b>2006</b> September 10-13 Seattle, WA
<b>2004</b> September 12-15 Toronto, ON, Canada	<b>2007</b> September 16-19 Washington, DC
<b>2005</b> September 18-21 Boca Raton, FL	<b>2008</b> September 21-24 Boca Raton, FL



Moderated poster sessions provided ample opportunity for attendees to discuss new research.



Five cases were selected to highlight controversial issues in an interactive format at the Case Discussion Session moderated by James B. Young (center).

## February 9-15, 2003: Heart Failure Awareness Week

### Heart Failure 2003: Update for the Primary Care Physician

The HFSA held its 2<sup>nd</sup> Annual HFSA Primary Care Symposium on Saturday, February 1, 2003, at the Hotel Monteleone, New Orleans, LA. The event, co-chaired by Barry H. Greenberg and Mandeep R. Mehra, is part of the HFSA's Heart Failure Awareness initiative.

### Community Events Increase Public Awareness Regarding Heart Failure

If you are planning an event for 2003 Heart Failure Awareness, or if you have held an event, please send an email to [info@hfsa.org](mailto:info@hfsa.org), that includes as much of the following information as possible: type of event, date, location, sponsor, expected number of attendees, and the event contact's name, phone, fax, email, and address. We may contact you after the event for a photo and brief summary to include in a future issue of the *Heart Failure Society News*.

## Update Assesses Old and New Approaches to Pharmacological Therapy

A range of drug classes that have been explored for therapeutic use – including positive inotropic agents, ACE inhibitors, angiotensin receptor blockers, cytokine and immune modulators, and endothelin receptor antagonists – were examined in the session moderated by Peter E. Carson and Sidney Goldstein.

### Positive Inotropic Drugs

Michael R. Bristow defined four categories of positive inotropic intervention: biologic; genetic manipulation in transgenic animals to increase contractility; gene therapy in animals to increase SERCA expression or inhibit phospholamban; and drug treatment, including digoxin, beta agonists, phosphodiesterase inhibitors, and calcium sensitizers.

He provided an overview of lessons learned from the use of positive inotropic agents and discussed negative outcomes associated with the use of neurohormonal cytokine inhibitors in combination with ACE inhibitors and beta-blockers. A new paradigm, he suggested, is one in which drugs positively interact with beta-blockers.

Such an approach would identify maladaptive and altered mechanisms in the human heart, develop a treatment to address the maladaptive mechanism, initiate testing in animal models, and confirm the results in the failing human heart. Abnormal molecular mechanisms that may cause contractile dysfunction in human heart failure include fetal gene induction and a multifactorial decrease in beta receptor signal transduction that decreases phospholamban phosphorylation, the unit of adrenergic stimulation.

A fundamental challenge to drug development has been posed by multiple compensatory signaling pathways that are positively inotropic and produce hypertrophy. Dr. Bristow concluded that beta-blockers in combination with a phosphodiesterase inhibitor can produce “good effects that are additive, and the adverse effects that are subtractive. Combination therapy with a positive inotrope can reduce adrenergic drive. Low-dose phosphodiesterase inhibitors with beta blockade are something we believe is quite rational, and phase III trials are evaluating this strategy.”

### Blockade of the Renin-Angiotensin System

ACE inhibitors and angiotensin receptor blockers (ARBs) were among the current and future options for blockade of the renin-angiotensin system explored by Jean L. Rouleau. ACE inhibitors, which block the conversion of angiotensin I to angiotensin II, offer the beneficial additional effect of reducing the imbalance in favor of endogenous vasoconstrictor substances that are characteristic of heart failure, by blocking bradykinin, thereby enhancing endogenous vasodilators and inhibiting endogenous vasoconstrictors.

After presenting new data from the RESOLVD trial, reviewing the ELITE 2 trial, and discussing briefly the upcoming VALIANT trial, he concluded that ACE inhibitors remain the first-line therapy in patients

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## Session Analyzes Current and Future Role of Natriuretic Peptide Measurements

The keen interest and controversial aspects of identifying which secretory peptide and which assay currently provide the best measurement for heart failure were evident in the session moderated by Margaret M. Redfield and Walter Paulus.

### Evaluation

Stating that the release of natriuretic peptides has important prognostic and diagnostic implications, John C. Burnett, Jr., discussed research evaluating circulating plasma ANP, N-ANP, and BNP levels that identified BNP as the superior biochemical marker for ventricular dysfunction.

After reviewing the literature and reporting significant differences in stability and sensitivity to comorbidity and therapy that make the superiority of either form unclear, he suggested a role for concomitant measurement of ANP as well as BNP. Dr. Burnett concluded that, while BNP is the superior natriuretic peptide as a biomarker for heart failure, we must continue to search for additional cardiac secretory peptides and take advantage of new technology such as proteomic profiling.

### Inclusion Criteria and Endpoints in Clinical Trials?

Inder Anand discussed potential ways to assess the effectiveness of new therapies in treatments of heart failure, including whether surrogate endpoints may supplement mortality endpoints to demonstrate beneficial effects of add-on therapies. He identified the requirements for an ideal surrogate and indicated that an ideal surrogate marker could provide important information about a drug that might result in the ability to measure it in a shorter time and smaller sample size and at less cost to assess its efficacy in every individual.

Citing results from Val-HeFT and his own research studying 600 patients with heart failure, Dr. Anand concluded that the research indicated that BNP changes correlated well with structural changes in the heart, and better correlation is seen between volumes than with left ventricular mass, demonstrating that BNP is an excellent biochemical marker of remodeling. Because BNP changes over time were associated with corresponding changes in subsequent morbidity and mortality independent of treatment, BNP is a "sufficiently robust end point" to demonstrate the beneficial effects of add-on therapies in future heart failure studies.

### Screening and Diagnosis

Reviewing the rationale for the use of natriuretic peptides in the diagnosis and screening of heart failure, Henry J. Dargie cited the growing consensus on the validity of BNP as a sensitive indicator of use in the diagnosis of heart failure. He noted that BNP is particu-

larly helpful to facilitate early diagnosis of patients in the community and those presenting to the emergency department with acute dyspnea.

Dr. Dargie concluded that the use of natriuretic peptides, particularly BNP, has proven diagnostic value, although some questions remain regarding what levels can be considered abnormal and how to develop a strategy of care for patients with high BNP, given the potential for alternative causes. Screening was an important question and uptake of such a strategy was crucially dependent on cost effectiveness being assessed in ongoing studies.

### Patient Management

The rationale for guiding the management of heart failure by using natriuretic peptide measurements, according to Mark Richards, lies in the increasing prevalence of the disease, the complexity of regimens, the current inadequacy of adjusting dosage by using empirical and poor methods, and the approaching need to identify a yardstick to detect diastolic dysfunction in clinical practice. "Heart failure needs some kind of measurement that is objective, reliable, practical, and inexpensive," he said, "and the use of BNP or N-BNP is currently the best candidate to meet this need."

In a pilot study, Dr. Richards studied the use of serial measurements of amino terminal N-BNP and BNP to guide the adjustment or titration of doses in the treatment of heart failure. His hypothesis was that measurement of the peptide may facilitate performance and produce better outcomes than current clinical practice. Results indicated that the group in which treatment was guided by hormone levels showed a significant decline in their hormone levels over time, unlike the clinically managed group. This decline corresponded to a 50% reduction in heart failure events and mortality. To verify the preliminary results of the pilot study, Dr. Richards and his colleagues have launched a larger study of 600 patients with decompensated heart failure. □



Henry J. Dargie explained the concept of regression to the truth in clinical research to a skeptical but enthusiastic audience at the Hyde Park Hypothesis Session.

*Heart Failure Society News* is an official quarterly publication of the Heart Failure Society of America, Court International, Suite 240S, 2550 University Avenue West, St. Paul, MN 55114; (651) 642-1633; www.hfsa.org. It is published by BioScience Communications, 1875 Eye Street NW, Washington, DC 20006.

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## Update Assesses Old and New Approaches to Pharmacological Therapy

who can tolerate them. ARBs may be beneficial in patients who are ACE inhibitor-intolerant, and ARBs in combination with ACE inhibitors reduce hospitalization for heart failure and should be considered in beta-blocker-intolerant patients who can tolerate the combination therapy. Vasopeptidase inhibitors (VPIs) appear to further enhance the efficacy of endogenous vasodilators and probably reduce cardiovascular events by about 10%, compared with ACE inhibitors. VPIs appear to be more renal-protective than ACE inhibitors, are generally as well tolerated as ACE inhibitors, and do not appear to increase angioedema in patients with heart failure, unlike ACE inhibitors.

### Cytokine and Immune Modulation: Still a Target?

In 1990, the observation by Beth Levine and Milton Packer that a number of patients with heart failure had elevated TNF levels stimulated a decade of research. "What we have learned," Douglas L. Mann said, "is that cytokines, expressed at very high levels, have a variety of deleterious effects on the cardiac phenotype – including hypertrophy and degradation of the extracellular matrix via activation of molecules that can promote left ventricular remodeling and dysfunction through a variety of different pathways." This understanding provided the impetus for several clinical trials – RENAISSANCE, RECOVER, and RENEWAL, evaluating etanercept – which were terminated on March 18, 2001, for lack of benefit. The ATTACH trial, evaluating infliximab, was stopped because of worsening outcomes in the treatment arm.

Putting the results in perspective, Dr. Mann reviewed the preclinical rationale for studying TNF antagonism in heart failure. The clinical rationale for TNF antagonism in patients was based on the observation that plasma TNF levels increased in proportion to the clinical severity of heart failure, and TNF levels constituted an independent predictor of mortality in these patients.

He reviewed the ATTACH trial. Based on the findings in this study, the US Food and Drug Administration recommended stopping infliximab therapy in patients who have heart failure. He also reported the results of the RENAISSANCE trial (N=900), which

demonstrated an unfavorable effect on the clinical composite score at 24 weeks of treatment. However, no worsening was observed in the RECOVER trial (N = 900), possibly because of the shorter duration of therapy and the lower doses that were used in that trial. Dr. Mann suggested two possible explanations for the worsening outcomes in the RENAISSANCE trial. "It is possible that the benefits of TNF may outweigh the adverse effects, or that there may be a ceiling to neurohormonal antagonism. Low physiological levels of TNF are there for a reason, and they appear to be cytoprotective." Considering why etanercept works well in the treatment of rheumatoid arthritis and poorly in heart failure, he explained that previous studies have shown that etanercept can work as either an antagonist or an agonist to serum TNF levels in a dose-dependent fashion. The result is that the biological effect of etanercept may vary in different clinical settings. Additionally, he suggested, there may be a ceiling for neurohormonal antagonism. "It is conceivable that the drugs we use have already lowered the level of TNF that can safely be antagonized." Dr. Mann stated that clinical trials were being planned that utilize broader-based anti-inflammatory strategies and that these trials might be more efficacious than the targeted anti-TNF strategies thus far.

### Endothelin Receptor Antagonists

Reviewing the role of endothelin receptor antagonists (ERAs) in the pathophysiology of heart failure, John R. Teerlink described the results of studies of the effects of ERAs in animal models as "compelling." These results include additive beneficial effects on top of ACE inhibitors, improved neurohormonal profile, improved vascular activity, and improved survival. The three main oral agents he discussed were enrasentin, bosentan, and darusentin. Results of two trials were summarized: ENCORE and ENABLE.

The ENCORE trial evaluated enrasentin (Bosentan), approved for primary pulmonary hypertension. The trial was terminated early because of increased liver enzymes and hypotensive events. A more encouraging finding was obtained by looking at primary end points. Bosentan improved more patients, and some improvement in time to worsening was noted. In the ENABLE trial, results indicated that heart rates and blood pressures were lower, but there was no statistically significant difference in the primary end point. The data are still incomplete,

but possible causes of the failure include the fluid retention by patients receiving bosentan and the association of body weight with worse outcomes. Whether better control of fluid retention could improve outcomes for all patients and whether the absence of fluid retention indicates a group of patients more likely to benefit from ERA therapy are questions under investigation. A dose-ranging trial evaluated darusentin, an ETA receptor antagonist, versus placebo. The primary efficacy criterion was left ventricular remodeling as measured by end-systolic volume using MRI. Results showed a trend to improvement in end-systolic volume but were underpowered.

Dr. Teerlink concluded that dosing titration remains a major issue, and the titration scheme may still be too rapid. Understanding the issues involved in increased edema and hemodilution is extremely important and will hopefully lead to better trial design.

### Aldosterone Receptor Antagonists

Citing the results of the RALES and EPHEsus trials, Bertram Pitt disagreed with the suggestion that a wall has been reached in neurohormonal blockade.

EPHEsus enrolled patients with acute myocardial infarction, evidence of left ventricular dysfunction, and ejection fractions of <40%. Patients were treated with standard therapy and randomized to either eplerenone, a selective aldosterone-blocking agent, or placebo (N = 6400). The primary end points were all-cause mortality and cardiovascular mortality and morbidity. The trial rationale was that blockade affects many neurohormones and, in conjunction with ACE inhibition and beta-blockade, will constitute a successful treatment strategy. One potential mechanism he suggested is prevention of ongoing collagen formation and ongoing remodeling. His research showed that blockade inhibited the marked increase in free radical production in the vascular wall.

A European study examined ACE inhibition in conjunction with aldosterone blockade. The results showed that blocking the aldosterone receptor preserves nitric oxide, and the ACE inhibition increases nitric oxide availability, producing a dramatic improvement in endothelin function when both strategies are used together. Additional information is expected when the EPHEsus data become available in 2003. □

## Interdisciplinary Models for Managing Heart Failure: Putting It All Together

Innovative strategies to improve the management of heart failure were presented at a session moderated by Robin Trupp and Susan Woodley Restaino.

### End-of-Life Care

The changing nature of end-of-life disease and the consequent growing imperative to reform the existing healthcare system to provide better care provided the focus of the featured lecture by Joanne Lynn.



Joanne Lynn

Heart failure has a disease progression that often is unpredictable. This uncertainty requires fundamental reforms in the healthcare system. "The severity of the condition, not the promise to die quickly, dictates the need," she stated. "We have built this whole hospice industry on the presumption that it is only decent to provide excellent care when people promise to leave you before the next federal holiday. Patients with heart failure do not comply."

She advocated a fundamental shift in thinking away from acute intervention to long-term management and eventually to preparation for the end of life. The current model made sense in 1970; a better model would include measures for disease-modification and for palliative care and symptom management. Such planning includes a do-not-resuscitate order, the ability to have morphine in the home, and the discussion of likely complications and how the patient wishes to handle them: "Why isn't this routine?"

**Enhanced Home Care.** "Until we get around to how Medicare pays for things, we are living in a backwards world." Enhanced home care is a key component of advanced care planning. This could be accomplished by mobilizing care providers to come to the home when needed, promising that a skilled person will be at the bedside within one hour, and providing terminal care at home. A promise to provide terminal sedation, avoid suffocation, and offer the backup of a doctor on the phone and drugs in the home will be necessary so that patients will be comfortable remaining at home and not seek emergency room care.

**Good End-of-Life Care.** Dr. Lynn listed the elements of good end-of-life care: ensure

reliability, provide the right treatment without gaps or surprises, eliminate overwhelming symptoms, customize care to the patient's preferences, respect the role of family members, and help patients to live life to their fullest potential. Finally, all health-care givers, including the home, the hospice, and the emergency department, need to know how to treat dyspnea and other symptoms.

**Reforms.** She urged the audience members to seek legislative and regulatory changes in the financing system, particularly to encourage opening the categories of patients and facilitating continuity of care for patients over time. The development of hospice programs to handle heart failure is needed, as well as better measurement of quality and costs with outcomes that make a difference. Patient educational materials should realistically explain the disease and provide an opportunity for patients to discuss their disease and to plan for the end of life. She concluded, "We have a lot yet to learn. We should encourage change regarding how Medicare pays for the care, not simply raise rates, and we should not pay for care that does not measure up to the guidelines."

### Heart Failure Clinics

According to Gregg C. Fonarow, despite our medical therapy advances in clinical trials, we continue to see an explosion of hospitalizations for heart failure. "It is estimated that 66% to 85% of hospitalizations could have been prevented if care had been more optimal. Improving care includes adequate patient education prior to discharge," he said, noting "80% of patients are being discharged without their performance measures." Care failures include failure to prescribe evidence-based medicines, continuation of medications that may exacerbate the disease, failure to adjust medications as the disease progresses, comorbidities, failure of patients to seek care, poor discharge planning, and inadequate follow-up and monitoring. The recent shift from reliance on emergency department care to disease management is important in addressing these failures. Heart failure clinics can involve patients actively in the care process and offer key elements: optimization of the medical regimen, provision of detailed information to family members, daily measuring of weight and sodium, dietary and

activity counseling, fluid restriction, support systems for patients and caregivers, follow-up and monitoring, and direct access on a 24-hour basis to advanced care personnel.

According to the literature, a disease management program can significantly reduce hospital stays, which results in improved functional capacity, increased adherence, reduction in hospitalization, cost savings, enhanced quality of life, and increased use of evidence-based therapy such as ACE inhibitors and beta-blockers. However, Dr. Fonarow reported, 90% of patients with heart failure are not in these programs, and it is important that, prior to discharge, there are procedures to ensure that key evidence-based therapies have been initiated and a plan for care and follow-up has been developed.

### Community Outreach Approaches

Nancy Houston-Miller discussed guidelines for community outreach delivered in patients' homes via phone calls or home visits. She cited studies of six different models of patient education, home visits, follow-up and monitoring. Overall results indicated significant reductions in resource utilization, including admissions, hospital days, and to a lesser extent, total admissions for most of these trials. However, large variations in the trials include treatment approaches, intensity and specificity of the intervention, and the length of time of the intervention. Shortcomings of most of the studies included the fact that many were nonrandomized, 75% were observational, and most were undertaken in academic medical centers; women and minorities were under-represented.

She concluded that, "We need to develop systems that are focused on the entire patient rather than individual disease states" and called for a much broader mandate to integrate across coronary disease, heart failure, risk factors, and environmental concerns. Additional mandates would foster the implementation of consensus guidelines and best practices; the inclusion of standardized education; the identification of which models are most suitable for which populations; determination of the essential components of disease management; and the allocation of resources to support care management systems. □

## Innovative Vehicles Improve Patient Care

The diverse and innovative vehicles to improve the care of patients with heart failure, as well as the obstacles to success, were the focus of a session moderated by Marvin A. Konstam and Edward P. Havranek.

Addressing the factors affecting patient care and the HFSA initiatives to meet the challenges that these factors pose, Dr. Konstam said, "There is a big disconnect between scientific meetings where clinical trials are discussed and the clinical world," where mortality rates are often considerably higher. "Clinical trials simply document efficacy – a whole series of steps need to be taken to get to the point where clinical outcomes are really impacted." The steps involve reaching a consensus on best practice and communicating that consensus to the regulatory process, improving its application by clinicians, and increasing patient compliance with the treatment provided.

### Measuring Quality of Care

Accountability, consumer choice, and quality improvement are three reasons listed by Harlan M. Krumholz to measure quality of care. He noted that efforts to measure care were increasing, citing programs by Leap Frog, Hospital Consortia, JCAHO, ACC, AHA, VAMC, NCQA, and others.

He identified several approaches to quality measurement and noted current systems that use them. These approaches include the structure measures currently used by the Leapfrog Group, the process measures used by the Centers for Medicare & Medicaid Services (CMS) and others, and the outcomes approach typical of many private companies. "We need to remember that measuring quality should include caring, compassion, and the ability to make unusual diagnoses and assess functional outcomes and health status," he stated. Since quality measurement efforts exert an influence on the practice of medicine, it is the responsibility of physicians and nurses to understand and participate in these efforts. "We must recognize those with value, challenge those without value, tailor our practices to provide quality care to all our patients, and continue to try to find value in the art of medicine," he concluded.

### CMS Update

Edward P. Havranek traced the history of the creation of peer review organizations (PROs) in the 1970s. In 1992, the approach changed to an overall focus on quality with the creation of the Healthcare Quality Improvement Project. It was hoped that over time the result, based on process measures, would encourage more hospitals to improve performance. Today, Quality Improvement Organizations (QIO) have replaced PROs and seek to protect Medicare beneficiaries, foster education, and collaborate with providers to improve the quality of care. The hospital-based National Heart Failure project initiated in 1999 to assess the performance of QIOs failed to show major improvement nationwide over three years; the results are likely to produce a shift in how CMS approaches performance improvement in the future. Emerging themes include efforts to lower spending on social programs, including Medicare; integrate and promote interest in government and private efforts; and identify a real interest in relying on mar-

ket forces to improve quality. "There is a strong current at CMS to publicly report quality data, starting with nursing homes, to put the data out there and to let consumers decide, but there is also some doubt whether this will come to fruition," he concluded.

### Disease Management

Michael W. Rich traced heart failure disease management (HFDM) to the 1970s, when pre- and post-heart transplant facilities developed multidisciplinary approaches to evaluate and manage patients. HFDM has recently been expanded to include a possible role in managing all patients with heart failure on a population basis.

Dr. Rich identified three factors that contribute to the rationale for expanded use: (1) the shift from considering heart failure as an episodic illness with acute exacerbations to a chronic condition requiring chronic management; (2) recognition of heart failure as having a number of common comorbidities and of behavioral, diet, and psychosocial factors as key elements in outcomes; and (3) the relative failure of new treatments to improve outcomes on a population-wide basis.

After a discussion of the objectives and benefits of HFDM programs, he concluded that these HFDM programs can significantly improve quality of care and reduce hospitalization and costs in selected patients with heart failure. However, their beneficial effects on mortality and quality of life have not yet been convincingly documented. Additional studies are needed to further define the benefits and cost-effectiveness in community and outpatient settings, as well as for patients cared for by primary care providers without heart failure expertise.



Barry M. Massie

### Specialty Care

Barry M. Massie described the limitations of the data on whether specialty care improves outcomes, including the need to rely on surveys instead of randomized clinical trials, difficulty in defining best practices and correlating them to outcomes, challenges to determining who is managing patients, difficulties in defining cost, and problems in interpreting data because of differences in patients referred to specialists vs. patients managed by primary care physicians.

One seminal study he cited of outcomes of care indicated that specialist care reduced one-year mortality and in-hospital mortality, as well as the adjusted risk of myocardial infarction. In outpatient settings, however, only 17% of patients are managed by cardiologists, 43% by internists, and 29% by family practitioners. Results of Dr. Massie's informal survey suggested significant differences in treatment approaches: cardiologists more frequently measured ejection fractions, evaluated for coronary artery disease, and used ACE inhibitors and in higher doses. Results of Edward Philbin's review of 1100 charts in New York state hos-

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## Surgical Advances Offer Expanding Treatment Options

An exciting spectrum of surgical options for the treatment of heart failure – from well-established coronary artery bypass graft (CABG) and reconstruction to devices to recovery – were reviewed at a session moderated by O. Howard Frazier and Leslie W. Miller.

### Bypass Surgery

For Bruce W. Lytle, “The concept of coronary artery bypass for ischemic cardiomyopathy is that symptoms will improve and survival can be prolonged, and the experience of the last 30 years has born out the fundamental validity of this concept.” Dr. Lytle reviewed data from studies of heterogeneous groups of patients with abnormal left ventricular (LV) dysfunction that showed a survival benefit for surgery for some subgroups, including high-risk patients with chronic stable angina as well as unstable angina. Observational studies showed a survival benefit in patients with ejection fractions <36% and in patients with triple-vessel disease with angina; the benefit in the latter group was greater in patients with severe dysfunction and included a lower incidence of sudden death over five years. These results provided the bases for the conclusion that there are anatomic indications for bypass surgery, regardless of the severity of symptoms, for patients with abnormal LV function.

Advances in surgery have been paralleled by advances in diagnostic methods that have allowed the identification of subgroups of patients with abnormal ejection fractions who are highly likely to benefit from surgery. With careful patient selection, functional capacity can be improved as well by surgery.

For patients with ischemic cardiomyopathy and viability of ischemic myocardium, “bypass grafting is a benefit,” and patients who have abnormal LV function, good vessels, and a viable myocardium are surgical candidates. Additional observational studies are needed to confirm the validity of bypass surgery for patients with no or limited ischemic myocardium, patients not easily revascularized, and patients with some degree of myocardial viability in areas that create abnormal geometry.

### LV Reconstruction for End-Stage Heart Failure

Patrick M. McCarthy focused on ventricular changes in patients with ischemic cardiomyopathy who can benefit from LV reconstructive surgery. The complex procedures he discussed increasingly involve bypass surgery, mitral valve repair, LV reconstruction, and “electrical” operations such as biventricular synchronous pacing or bipolar radiofrequency ablation for atrial fibrillation. According to Dr. McCarthy, while LV reconstruction is often performed concomitantly with bypass or mitral valve surgery, the benefit in these patients appears to be related to the reconstruction. He reported the results of a study he conducted of patients undergoing LV reconstruction and with either bypass or mitral valve surgery. Results showed a 100% survival rate at 30 days and 83% survival at three years. Over the past two years, in patients with preoperative left bundle-branch block who undergo the complex surgery, he has also placed epicardial LV pacing wires to facilitate the placement of biventricular pacing in those patients who maintain a wide QRS; no adverse events have been experienced with placement of these wires. In addition to the survival benefit, LV reconstruction reduced late hospitalizations for heart failure and improved ejection fractions. These models suggest beneficial effects in resecting dyskinetic tissue, an equivocal effect in akinetic scarring, and a negative effect in removing contracting myocardium in patients with idiopathic cardiomyopathy.

He concluded that while ischemic cardiomyopathy is a complex disease, surgery can prevent further damage and even reverse pre-existing processes, especially since perioperative risks have been decreased. He stressed that complex problems may need complex solutions, stating, “The days of quick in-and-out surgery to perform bypass are over.”

### LVADs as Destination Therapy

Eric A. Rose discussed trial results showing that the use of left ventricular assist devices (LVADs) for extended periods of out-of-hospital support is possible, device failure may not require reoperation, and the quality of life is reasonable.

He reported the results of the REMATCH trial to evaluate the use of LVADs as destination therapy for patients with end-stage heart failure. Results at one year showed a statistically significant survival rate of 52% in the device group versus 25% in the control group; at two years, the rates were 27% versus 8% ( $P = .001$ ). “Dramatic differences” were seen in quality of life, with significant improvements in pulmonary function and NYHA class. Dr. Rose concluded, “LVADs can provide meaningful survival and quality of life benefits in nontransplantable end-stage patients with heart failure. Intensified efforts to improve devices and patient management are justified to further improve outcomes in terminal patients and to allow the potential extension of these devices to patients with serious but less severe heart failure.”

### Making Bridge to Recovery a Reality

Sir Magdi Yacoub reviewed the use of LVADs as a bridge to transplantation and as destination therapy, and explored their use as a bridge to recovery. In patients using LVADs as bridge, the functional and morphological improvements were noted and explantation of the device became feasible, although the incidence of recovery, predictability, and durability remained unknown.

He evolved a strategy to maximize recovery with combination therapy to induce massive reverse remodeling by LVADs and agents that unload to produce similar results and then to induce physiological hypertrophy. The drugs used in the initial part of combination therapy include digoxin, beta blockers, ACE inhibitors, angiotensin II inhibitors, and aldosterone receptor blockade.

Dr. Yacoub is continuing to evaluate 19 patients, ages 15 to 56 years, with deteriorating end-stage dilated cardiomyopathy, NYHA class IV, who were inotrope dependent. Average duration of treatment was 44 months. There were three perioperative deaths, one due to infection at three months; of the surviving 15 patients, who had a mean duration of LVAD support of 359 days, 79% survived, 67% were explanted, and 3% are ongoing. A mean follow-up of 435 days of the 10 patients who were explanted showed no mortality, and all are asymptomatic with unrestricted activities (Class I); one developed lung cancer. At the last follow-up, the mean ejection fraction was 68%. Dr. Yacoub concluded that the Harefield Recovery Study’s strategy of induction of reverse remodeling followed by physical hypertrophy yielded promising intermediate results that he will continue to follow and the acceptable survival rate may improve with better patient selection.

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## Surgical Advances Offer Expanding Treatment Options

### Cell Transplantation

Richard D. Weisel provided an overview of cell transplantation in patients with myocardial infarction or cardiomyopathy. He reported on the results of research with skeletal myoblasts in humans and with bone marrow versus heart cells in pigs. In his initial animal studies, he used fetal cardiomyocytes grafted into the injured region of the left ventricle. The cells restored function to the damaged region, but the cells were rejected. Subsequently, he employed autotransplantation to stabilize injured regions and prevent heart failure.

**Skeletal Myoblasts.** A study by Professor Philippe Menasche of Paris reported the results of a one- to two-year followup of 10 patients in

whom cells were injected in and around an infarct region at the time of coronary artery bypass grafting to the non-infarcted region. All patients are now NYHA Class I-II, have ejection fractions that have improved from 22% to 37%, and have improved regional perfusion. Arrhythmias occurred in four patients. Dr. Menasche believes that a reduction of the cell dose and the use of amiodarone may decrease the incidence of arrhythmias. A worldwide multicenter phase II trial is enrolling patients.

**Heart vs. Bone Marrow Cells.** Dr. Weisel compared bone marrow and heart cell transplantation in a pig infarct model and found that both cell types engrafted in the infarct region. Clinical trials will be necessary to identify the optimal dose and cell type, the optimal mode of delivery, and the mechanism of benefit of cell transplantation. He added that cell transplantation may provide cardiac regeneration in patients with cardiomyopathy as well. □

## Late-Breaking Science Session Reports Cell and Gene Therapy Data

Michael D. Schneider and Gerald W. Dorn II moderated the late-breaking science session, which featured timely research on a range of issues in cell and gene therapy.

Stephen Liggett reported the results of a study evaluating the potential effects of two polymorphisms alone or in combination and whether either or both could be associated with increased risk of heart failure. The results indicated significant differences between black and white patients in the allele frequencies of both polymorphisms. There was a high incidence of  $\alpha_2$ Del 322 in black patients – 10 times as common in blacks as in whites. No significant differences in the frequency of the  $\beta_1$ Arg389 polymorphism between black patients with heart failure vs black controls were noted; blacks had a slightly lower frequency of this variant than whites, and this variant alone was not judged to constitute a risk factor for heart failure. However, the risk increased significantly in blacks homozygous for the two polymorphisms. These patients might benefit from genotyping to identify higher risk; additional study is required to determine if they would benefit from pharmacological therapy to target the altered genetic response and if prophylactic therapy might benefit asymptomatic patients.

Another promising area of investigation is sarcoglycan deficiencies, associated with cardiomyocyte degeneration and the induction of vasospasm. Elizabeth McNally discussed the results of her research focusing on the inhibition of vasospasm as a therapeutic target to address sarcoglycan deficiencies and possibly limit the progression of heart failure. She evaluated the efficacy of verapamil, which inhibited vasospasm and eliminated stenoses.

Glenn I. Fishman discussed his research to identify novel signaling pathways regulating conduction system formation, as well as gene mutations or sequence variants that may result in conduction defects or arrhythmias. His work involved the optical mapping of the developing conduction system in embryonic transgenic mice and the identification of the timing of changes in the activation pattern. He determined that neuroregulins promote working myocytes to assume a conduction system–like phenotype, suggesting that these ligands play a key role in conduction system formation and func-

tion. These data have been published in *The Proceedings of the National Academy of Sciences of the United States of America*.

Chunhui Xu described the steps necessary before clinical applications of cell transplantation using human embryonic stem cells (hESCs) can be developed: the growth of undifferentiated cells must be simplified, appropriate differentiation must be established, and cell populations must be characterized. She facilitated cell proliferation and investigated the ability of the hESCs to differentiate into cardiomyocytes. hECS-derived cardiomyocytes expressed cardiac transcription factors and surface and structural proteins; demonstrated appropriate responses to pharmacological agents; and enriched cells expressed appropriate markers. Remaining challenges include refinement of methods to optimize delivery and further research to establish the safety and efficacy of transplantation.

Cecilia Hertig reported the results of her investigation of the role of the neuregulin receptor tyrosine kinase erbB4 in cardiac maturation and function by monitoring the *in vivo* consequences of erbB4 loss of function in ventricular muscle cells. Conditional erbB4 knockout mice developed a severe dilated cardiomyopathy and the early onset of conduction defects; this cardiac dysfunction may account for the subsequent heart failure and death in adult mice. The longer survival of the erbB4 CKO mice revealed that the conduction system was abnormally formed; this malformation, together with the mislocalization of Cx40-containing gap junctions, may contribute to conduction defects. “Our findings suggest that erbB4 is required for normal postnatal cardiac remodeling and for the differentiation of trabecular cardiomyocytes to form the peripheral conduction system,” she said.

Peter Mundel discussed his research exploring the role of myopodin in cardiac development and pathogenesis. To investigate distribution during myocyte differentiation and determine any involvement in myocyte proliferation, he studied reduced myopodin expression in myopodon heterozygous mice. Myopodin-null mice were embryonically lethal and died of development with cardiogenesis; older mice with myopodon deficiency present with dilated cardiomyopathy. These results demonstrated the essential role of myopodon function in the nucleus during development and in structure. □

## Late-Breaking Clinical Trials Session Analyzes Range of Data

Barry M. Massie and Henry Krum moderated the session on late-breaking clinical trials, which reported the results of studies on the efficacy and safety of inflammatory cytokine antagonism, immune modulation therapy, defibrillator implantation, and statins in the treatment of heart failure.

Douglas L. Mann reviewed the disappointing results of the RENAISSANCE/RECOVER and RENEWAL trials, which evaluated the effects of antagonism of tumor necrosis factor- $\alpha$  (TNF $\alpha$ ) with etanercept on morbidity and mortality. He concluded that etanercept failed to demonstrate any clinical benefit and did not reduce the combined risk of mortality or hospitalization for heart failure. Although the combined studies did not conclusively demonstrate harm, he said, the risk ratio for worsening of heart failure was increased in RENAISSANCE, the trial that used the highest dose and longest duration of etanercept therapy.

Milton Packer reported on an alternative way of looking at the TNF antagonism hypothesis provided by the ATTACH pilot study, which evaluated infliximab, a monoclonal TNF antibody. TNF antagonism with infliximab did not produce clinical improvement, and the use of high doses was associated with a higher frequency of worsening heart failure that persisted

despite cessation of therapy. Accordingly, Dr. Packer concluded that TNF $\alpha$  antagonists should be avoided in patients with heart failure.

Targeting of immune activation processes as a treatment approach in heart failure was evaluated by Guillermo Torre-Amione, who reported the results of investigations into the efficacy and safety of immune modulation therapy (IMT) in patients with advanced heart failure. Analysis of primary endpoints showed no significant differences. However, the combined endpoint of event-free survival was 40% in the placebo group versus 70% in the treatment group ( $P = .005$ ). Analysis of secondary endpoints demonstrated significant benefits in reducing all-cause mortality and the clinical composite score. Dr. Torre-Amione concluded that the clinical effects were consistent with the theoretical targeting of immune activation in heart failure and stated that the results formed the basis for the large phase III trial, ACCLAIM.

Arthur J. Moss discussed the results of the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II), which evaluated the effect of prophylactic implantable cardiac defibrillator (ICD) therapy on survival in patients with prior myocardial infarction and left ventricular dysfunction and was terminated prematurely in November 2001 by the Data Safety and Monitoring Board because of favorable results. The use of ICDs re-

sulted in a 31% reduction in mortality vs. conventional therapy ( $P = .016$ ). The rate of sudden deaths was 65% in the conventional group versus 35% in the ICD group. The results were consistent across all 20 subgroups. Dr. Moss concluded that prophylactic ICD therapy as an adjunct to established medical therapy can promote increased survival in patients with coronary heart disease and left ventricular dysfunction.

Stefan D. Anker presented a retrospective analysis of two independent investigations on the use of statins in patients with heart failure: the ELITE-2 trial and a study conducted at five European centers. Results from ELITE 2 showed a 30% reduction in mortality independent of cholesterol levels and BMI at baseline, whereas the European study showed a 39% risk reduction in mortality in patients on statin therapy from baseline. This reduction was independent of gender, NYHA class, peak oxygen consumption, BMI, ejection fraction, or age. When adjusted for higher lipid levels, the risk reduction was 24%. According to Dr. Anker, these retrospective studies show that treatment with statins was independently related to lower mortality in patients with heart failure, especially in those with an ischemic etiology. In patients with a nonischemic etiology, the benefit appears to be restricted to those with more advanced heart failure. □

## Genomics and Genetics (Part I)

Recent developments in the identification of genetic mutations that can give rise to cardiomyopathies and hypertension in humans, as well as in the understanding of the genetics of wound repair and regeneration in animal models, were highlights of the basic science session moderated by Michel Komajda and Elizabeth McNally.

### Molecular Basis of Hereditary Cardiomyopathies

In her featured bench-to-bedside presentation, Christine E. Seidman provided an overview of the complexities of the genetic bases of heart failure, focusing on those related to dilated cardiomyopathy (DCM). She noted that epidemiological studies demonstrate that 20% to 30% of patients with DCM have a family member who also has that diagnosis. She cited research showing that electrophysiologic abnormalities precede manifestations of DCM and explored how we can relate this genetic insight to disease progression in these individuals. Transgenic mouse models with the Lamina A/C mutation evidence relative preservation of the atrial and ventricular myocytes, but these mutations allow for rapid deterioration of the AV node conduction system. Will restoration of electrophysiology mitigate against development of left ventricular dysfunction? According to Dr. Seidman, understanding the inherited gene mutation provides the opportunity to address these problems. A second kind of mechanism is seen in sarcomere mutations, which are in the contractile apparatus and

can give rise to either hypertrophic cardiomyopathy or DCM. While the data from mouse models are too preliminary to discuss, she said that there is considerable evidence that these sarcomere gene mutations give rise to abnormality of calcium cycling. Studies in humans are exploring whether other mechanisms are involved in the development of DCM.

Dr. Seidman concluded, "Increasingly, we are identifying a wide myriad of different types of gene mutations that can give rise to the dilated phenotype, and we are increasingly able to cluster them in terms of both their phenotypes and their mechanisms by which they may give rise to those phenotypes." Some of the successes and failures of new therapies for DCM that are not recognized to be genetic "may be attributable to the lumping of all of these pathways into a single pharmacological strategy for success. . . . There may be common pathways, but dissecting the mechanisms of infection, hypertrophy, and ischemia through these genetic mechanisms may allow us to target our therapeutics in a more appropriate fashion."

### Titin Cardiomyopathy

Ludwig Thierfelder reviewed recent literature on DCM disease genes, par-

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## Contributing Comorbidities in Heart Failure Patients: Importance and Management

The potential roles of sleep apnea, chronic kidney disease (CKD), diabetes, anemia, and depression in the progression of heart failure and the possible effects of treatment on heart failure outcomes were the focus of the session moderated by Robert Moskowitz and Michael Fowler.

### Sleep Apnea

T. Douglas Bradley discussed two types of apnea – obstructive and central – that occur with similar incidence in 50% to 60% of patients with heart failure. Three major events occur in obstructive apnea that could lead to the progression of cardiac failure. The upper airway collapses and the patient generates pressure that increases cardiac demand. The patient develops asphyxia, reducing the amount of oxygen delivery at the same time as the demand increases. In a patient with ischemic heart disease, this process could trigger additional ischemia and arrhythmias. Patients with central sleep apnea develop hypoxia and arousal from sleep that activates the central nervous system and causes surges in blood pressure and heart rate. The failing left ventricle has reduced cardiac output and increased left ventricular filling pressures, leading to pulmonary edema and hyperventilation and driving carbon dioxide below the threshold required to stimulate breathing. The resulting apnea and hypoxia lead to sleep disruption and may well produce some of the fatigue symptomatic of heart failure.

Dr. Bradley discussed three small studies of nighttime oxygen: two in which patients received room air vs. oxygen and his own study in which patients received continuous positive airway pressure (CPAP). Although there was a decrease in sleep apnea in the first two studies, the patients receiving CPAP also showed improved left ventricular ejection fraction over three months, as well as decreased plasma norepinephrine and urinary catecholamine levels, with a reduction in overnight sympathetic activity.

Dr. Bradley concluded that CPAP is associated with improvements in transplant-free survival and that these improvements were associated with early improvements in ejection fraction and reductions in sympathetic activity. A multicenter mortality trial (CANPAP) now underway will randomize patients to optimal medical therapy or optimal medical therapy in conjunction with CPAP.

### Chronic Kidney Disease

Glen Chertow described potential mechanisms by which chronic kidney disease (CKD), loosely defined as GFR <60 ml/min/1.73 m<sup>2</sup>, might constitute an important contributory cause to heart failure.

Noting the lack of epidemiological evidence, he reviewed data from SOLVD Prevention and Treatment trials, as well as several smaller studies. In the original SOLVD trial, results suggested significant associations between low creatine clearance (GFR <60) and mortality. A multivariate analysis showed a relative risk of 40% to 60% when using a typical model; this risk was independent of any subgroup effects. Even very small increases in serum creatinine 0.3 mg/dl were significantly associated with increased mortality, length of stay, and costs of hospitalization of elderly with heart failure.

Mineral metabolism disorders in patients not on dialysis, and dyslipids and hyperhomocysteinemia could directly complicate heart failure.

Increased phosphorus levels increase relative risk and death in hemodialysis patients and risk of cardiovascular complications. Patients with high calcification are at increased risk of developing atherosclerosis. Dialysis-specific causes of heart failure include uremic cardiomyopathy, hyperparathyroidism, high-output heart failure, dialysis-related amyloidosis, and levocarnitine deficiency.

“We need to define ‘cardiorenal syndrome’ and research key issues together,” he said, and recommended the following management strategies: think GFR, not creatinine; emphasize sodium restriction; make loop diuretics the cornerstone of therapy; think glomerular remodeling, e.g., ACE inhibitors are renal protective; consider increased use of spironolactone; and explore peritoneal or hemodialysis or ultrafiltration strategies in refractory patients.

### Anemia

Maria N. Ansari considered whether anemia, defined by the World Health Organization as <13 g/dl in males and <12 g/dl in females, plays a contributing or causal role in heart failure because there is a significant prevalence of anemia in this population. She discussed the results of several studies, all of which showed a significant association between anemia and increased risk of heart failure.

According to Dr. Ansari, chronic severe anemia has a causative role in heart failure, but it is “less clear” whether mild to moderate anemia does. “It appears to make symptoms worse and increase hospitalizations and death; and the severity of anemia progresses with severity of heart failure,” she said. Anemia correction appears to have beneficial effects on symptoms and function in heart failure symptoms. “We don’t know the appropriate Hb/Hct target, and we really don’t understand why anemia is present in heart failure,” she said.

### Diabetes

Noting that from 25% to 30% of patients with heart failure have Type II diabetes, Daniel L. Dries explored direct and indirect mechanisms that may underlie the adverse impact of diabetes on heart failure. According to Dr. Dries, the limited retrospective data suggest an interaction between the etiology of heart failure and Type II diabetes with respect to prognosis. “We need to test this metabolic hypothesis in prospective trials and develop targeted therapies,” he concluded.

### Depression

Exploring the potential impact of depression on patients with heart failure, Christopher O’Connor, director of the Duke Heart Failure Program, noted its prevalence in cardiovascular disease. Potential mechanisms of increased risk of morbidity and mortality in depressed patients include increased risks of arrhythmias, heightened platelet aggregation, alterations in lipid metabolism and inflammatory markers, and reductions in coronary blood flow and endothelial function, as well as decreased patient compliance with treatment regimens. Dr. O’Connor discussed his research and concluded that depression is an important risk factor for increased mortality and morbidity in patients with heart failure and that it is underrecognized and undertreated in these patients. Treatment strategies and mechanistic studies now under way will enhance the understanding of the relationship and future directions for treatment. □

## Results of Cell Transplantation Research Offer Promise of Tissue Repair

The results of preclinical and clinical research evaluating the safety and efficacy of transplanted cells from adult and embryonic sources to repair damaged myocardium were reported at the first session on cell and gene therapy moderated by Leslie J. Reinlib and Karen K. Hirschi.

### Human Endothelial Progenitor Cells

Investigation of endothelial progenitor cells (EPCs) has produced promising indications of their ability to transdifferentiate into cardiomyocytes. Andreas Zeiher discussed the results of work showing that human EPCs demonstrate the following essential capabilities: expression of cardiac proteins, calcium oscillations, gap junction coupling, and cell-to-cell communication.

He reported the results of the Transplantation of Progenitor Cells and Regeneration Enhancement in Myocardial Infarction (TOPCARE-AMI) trial, which evaluated EPCs vs bone marrow cells infused via balloon catheter directly into infarcted coronary arteries of 20 patients with acute myocardial infarction who were initially successfully reperfused and then randomized. Results showed a "significant improvement" in ejection fractions in both groups. Cell transplantation is safe and feasible, he stated, but promising initial results need further study in a randomized control trial that will start soon.

### Human Embryonic Stem Cells

Lior Gepstein reported on his research on human embryonic stem cells as a source of human cardiomyocyte tissue. Cell therapy and tissue engineering are emerging as novel therapeutic paradigms for myocardial repair and future treatment of heart failure. Key stages for this therapeutic approach are to develop sources of cells for transplantation, to assess the *in vitro* properties of the candidate cells, to develop delivery methods of the cells to the heart, and to evaluate the *in vivo* effects of cell transplantation. These strategies have been hampered, however, by the lack of a source for human cardiac tissue. Human embryonic stem cells may provide a solution for the cell sourcing problem since these cells, generated for the first time in 1998 from human blastocysts, can be propagated in large quantities outside the body and

coaxed to differentiate into different cell lineages, including cardiomyocytes.

Dr. Gepstein identified areas for future development: "We need to increase cardiomyocyte yield by defining strategies for directing cardiomyocyte differentiation; this can be achieved by using growth factors, transcription factors. We need to design cell selection protocols to obtain 100% pure cardiomyocytes. We need to upscale the procedure in order to generate large quantities of cardiomyocytes and to assess their *in vivo* effects following transplantation. In addition, antirejection strategies should be developed, and we need to consider safety aspects, particularly the development of malignant transformation of the cells and the triggering of arrhythmias."

### Marrow-Derived Stem Cells

Donald Orlic reviewed the results of his investigation of the potential of bone marrow-derived stem cells (BMSCs) to differentiate into cardiac myocytes and vascular smooth muscle cells and endothelium in myocardium that has been damaged by ischemia. In a second series of experiments, he evaluated the efficacy of BMSCs mobilized by several injections of stem cell factor and granulocyte colony-stimulating factor. The results demonstrated that the cytokine-mobilized BMSCs traffic to the infarcted myocardium and differentiate into cardiac myocytes and vascular structures, offering the potential for repair following induction of acute ischemic myocardial damage.

### Adult Liver Stem Cells

Transdifferentiation of adult tissue-derived stem cells holds promise for tissue repair. Yet, functionality, clonality, and lack of fusion have not been always demonstrated. Nadia Malouf reported the results of her research using a cloned liver stem cell line from an adult male rat, called WB F344 cells, to test whether these cells respond to inductive signals from the microenvironment of a normal heart and differentiate into cardiac cells.

The results from her studies suggest that WB F344 stem cells respond to clues from the microenvironment and acquire cardiac phenotypes in a niche-dependent manner in the heart *in vivo*, and they acquire a myocardial

phenotype and function in culture. The cross-species transdifferentiation of a cloned, liver-derived stem cell line met the criteria of function, clonality, and lack of fusion.

### Grafting Efficacy and Safety

Doris A. Taylor, in discussing her work with cell transplantation using autologous skeletal myoblasts in animals and humans, identified three key questions: Does this form of cell transplantation work, is it safe, and what is the best type of cell?

Dr. Taylor discussed her group's use of three animal models to determine whether cell transplantation affects contractility vs remodeling: mouse, rabbit, and pig models. Ongoing trials in Europe and the United States are evaluating the safety of autologous skeletal myoblasts in humans delivered during CABG or LVAD placement. One recurring problem has been electrical instability, which has affected continuation of trial or outcome.

"Before we can decide which is the best cell type, we have to better understand the role of the disease state, the time after injury, and the dosing, and none of these has been answered," she said. As the questions are answered, "We will have the tools in place to do definitive preclinical work to design clinical trials to provide needed data for the development of future treatment." □ \_\_\_\_\_

### Abstract Deadline:

April 14, 2003



Heart Failure Society  
of America

SEPTEMBER 21-24, 2003  
Mandalay Bay Resort & Casino  
Las Vegas, Nevada

7TH ANNUAL SCIENTIFIC MEETING [www.hfsa.org](http://www.hfsa.org)

Instructions to submit an abstract for the scientific meeting are available at [www.hfsa.org](http://www.hfsa.org)

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## Genomics and Genetics – Part One

ticularly in the 2q31 chromosome, where mutations in *TTN*, a gene encoding the giant muscle protein titin, are associated with disease in humans, fish, and mice. He studied mutations of the human titin gene implicated in the etiology of DCM in two large families. The mechanisms by which titin mutations in humans clinically affect cardiac but not skeletal muscle are unclear. While further research is needed, he concluded that studies of these mutations in humans, zebra fish, and mice “favor a critical role for titin in sarcomeric development and integrity.”

### Insights Into Cardiac Regeneration

Investigating the process of regeneration in animal models, Ellen Heber-Katz discussed the varied responses to wound healing in different species and her research using the MRL mouse model, in which she identified multiple genetic loci that control this wound-healing trait. In published results (*PNAS* 98;2001), Heber-Katz and colleagues showed that, in fact, massive cryoinjuries to the right ventricle healed with the replacement of myocardium with little scarring and function returned to normal. Current studies involve the role of angiogenesis and specific proteinases in the breakdown of the ECM as a key event determining whether wounds heal by regeneration or scarring. In this cryoinjury model and in this mouse, an increased

level of apoptosis correlated with more rapid and extensive regeneration, and “It is possible that apoptosis is an important step in regeneration.”

### Hypertension: A Multigene Disorder

“Blood pressure as a phenotype is a complex trait determined by the interaction of multiple genetic, environmental, and demographic factors,” stated Ali Gharavi, who reported the results of human studies conducted in Richard P. Lifton’s laboratory. Although blood pressure distribution in the general population follows a normal curve, a number of people have a greater genetic component, and the number of monogenic forms of high blood pressure have been identified and studied via molecular mechanism of blood pressure homeostasis. He explored the pathophysiology of hypertension in several mendelian forms of the disease and identified several factors, including increased aldosterone, increased salt reabsorption, increased intravascular volume, increased blood return to the heart, increased cardiac output, and increased blood pressure. Each of the findings that characterize the mendelian forms converges on a pathway of salt reabsorption in the nephron, each of these genes when mutated produces a dramatic phenotype, and each has polymorphisms that have been identified in the general population and may contribute to blood pressure variations. “We have evolved selecting for avid salt retention, and it may be that genes that were once adaptive may now contribute to the disease,” he concluded. □

## Genomics and Genetics (Part II)

Three presentations and two original communications offered new insights into advances in the development of appropriate mathematical approaches to the analysis of large data sets that accrue from gene expression analysis at the session moderated by J. David Port and Seigo Izumo.

### Bioinformatics

Michael B. Eisen described his work in comparative genomics, with particular attention to regulation of the 250 genes relevant to cardiovascular disease. He is optimistic that the future will bring a genomic database that will feature an index of all protein products, including posttranslational modifications, leading to a census of all biological molecules present in a cell. The potential impact of this accomplishment on clinical studies is enormous: “In the near future we will have access to an individual patient’s genome sequence and be able to do an immediate molecular characterization of any readily attainable tissue sample.... The ultimate goal of genetics and genomics has to be the ability to understand these unique characteristics of the individual and relate them to the phenotype.... We need to go beyond associated studies to develop an advanced understanding of the cellular and molecular systems that allows us to understand the consequences of any specific sequence variation on the phenotype.”

One change already occurring is to shift away from the gene centrism of current genome databases that

focus on protein-coding sequences to explore noncoding portions. “We hope this is a first step toward being able to look at the human genome and recognize where all of the functional noncoding sequences are and then understand how the particular constellations of sequences are specifying a particular pattern of expression in their target genes and what that pattern might mean,” he said.

### Expression Profiling

Martina Schinke discussed the role of the CardioGenomics Program for Genomic Applications (PGA), a National Heart, Lung and Blood Institute (NHLBI)-sponsored initiative, in the integration of the results of transcriptional studies to identify genes for therapeutic interventions. Among the questions CardioGenomics is addressing are the determination of how many genes are differentially expressed in these models; which genes showed an altered expression, and, if both models show changes, whether a common pathway is identifiable; and whether gene expression can be correlated directly with increased heart weight and body weight in each model. All data are available within 60 days of generation at the cardiogenomics website at [www.cardiogenomics.org](http://www.cardiogenomics.org). She concluded that transcriptional changes yield important insights into the pathology of pressure-overload-induced cardiac hypertrophy, but that changes in gene expression alone will not provide a complete picture of the disease process. Methods to integrate this knowledge with changes observed

on other regulatory levels, such as posttranscriptional and posttranslational modifications, must be refined. “By combining the different approaches, we may be able to identify genes for therapeutic interventions in the future.”

### Genomic Approaches To Cardiovascular Disease

William L. Stanford offered the perspective of a geneticist in biomedical engineering to develop directed approaches following microarray analysis to integrate different strategies into functional genomics. He explained two philosophies in mutagenesis—whole animal mutagenesis and embryonic stem cell (ESC) mutagenesis—and reviewed his research using ESCs *in vitro* and *in vivo* to model development. Dr. Stanford defined his strategy as producing a mutation that knocks out a specific domain mutation *in vivo* and studying the function of that domain in the context of not only the protein but also the animal. These genes have been posted on Centre for Modeling Human Disease website at [www.cmhd.ca](http://www.cmhd.ca).

In addition to the three presentations were original communications on age-associated gene expression profiles in a mouse model of hypertrophic cardiomyopathy by Laura P. Edgerley and on the effects of implantation of an ICD on ACE dose-dependent genetic risk in heart failure by Maninder S. Bedi. □

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## Innovative Vehicles Improve Patient Care

pitals showed that care by cardiologists tended to involve more procedures at higher cost, produce longer lengths of stay, and reduce in-hospital mortality; the only statistically significant decrease was in heart failure readmission rates.

The paucity of data and the difficulties in distinguishing among providers in the hospital and post-discharge providers supplied the impetus for a new study designed to minimize the differences and provide a strong methodological ground. A cohort study in an HMO environment randomized patients with new-onset heart failure to management by cardiologists or by primary care physicians. Results showed that the best predictor of two-year mortality or cardiovascular admission was low ejection fraction; the only other significant variable was cardiology care, which reduced the combined endpoint by 38%. Although the results require corroboration, analysis of the database at his Veterans Affairs hospital showed that mortality rates were lowered by nearly 50% in outpatients with heart failure who received specialty care.

Dr. Massie concluded that outcomes can be improved by specialty care, but costs may be higher. Specialists should be involved with

significant heart failure disease, but models that use specialty-directed care or train non-MDs may be more practical and effective, and better integration between specialty and primary care is necessary. Involvement of a nurse practitioner may be one way to enlarge the population of patients who get specialty care.

### The Managed Care Environment

Among the challenges Steven Lampert cited to developing a disease management program were enrollment, staff productivity, guideline development, and finances. He discussed the experiences at his own institution. As a result of the combined efforts of nurses, case managers, and internists, he now has 650 patients, 340 of whom are new this year.

Deciding when to implement “cutting-edge” therapies for which no guidelines exist, developing guidelines that incorporate new information, justifying new and expensive therapies and measuring incremental benefits, selecting a methodology, defining the patient population, and assessing the impact of a program are issues that must be addressed when designing and analyzing models. The financial model will be affected by changes in enrollment, in the payor mix, or in management. Risk sharing, straight Medicare or straight fee for service, and payment for providing a comprehensive program are also factors for consideration. □

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