The goals of the Heart Failure Society of America (HFSA) are to improve the diagnosis, treatment, quality of life, and survival of patients with heart failure (HF). One critical initiative was to establish an annual meeting to bring together basic scientists, clinical scientists, clinicians, nurses, and allied health professionals to discuss recent advances in the field in a format that fosters an exchange of ideas among these groups and encourages viewing HF from a translational medicine point of view. This is a report of some of the highlights of that meeting, the 8th Annual Scientific Sessions.

OPENING SESSION—HEART FAILURE 2004: WINDOW INTO THE FUTURE

Marvin Konstam (President of the HFSA from 2002 to 2004; Tufts-New England Medical Center, Boston, Massachusetts) addressed the challenges facing the academic medical center amidst changing times. This is particularly with reference to providing exemplary care for patients with HF in the academic milieu. Historically, academic medical centers have been bound by a “social contract” to provide excellent medical care, advance new knowledge, and train future physicians on behalf of the society. However, this has become economically difficult to sustain, with repeated reductions in government funding. Treating patients with HF poses an additional challenge as the disease entity crosses many traditional academic boundaries including medicine, surgery, and allied health disciplines.

Unfortunately, the incidence of HF has increased by 155% in the last decade, and costs have escalated to $13 billion per year for hospitalization in the U.S. alone, and proportionally in Canada. Paradoxically, HF is a worthwhile program to undertake in academic centers. The therapy for HF is becoming increasingly complex, costly, and difficult to administer. Academic centers can offer this special competency and train future experts in the field while using a system-based approach to disease management. High-quality care also brings high-quality diagnostics and therapeutic procedures. These, in turn, help to finance the operations necessary to maintain this complex program. Thus, focusing on HF allows the academic center to “do well, while doing good.”

Gerald Dorn (University of Cincinnati, Cincinnati, Ohio) addressed “Innovations for Tomorrow” by first looking back at centuries of HF care. Heart failure, or “dropsy,” was first characterized by the Greek physicians as edema and pallor, and Galen initially coined the “humoral theory” of medicine. Neurohormonal activation, including adrenergic receptor activation, of course has since redefined the therapy for HF, but not all patients will benefit. Genetic single nucleotide polymorphisms that influence the activities of, for example, the alpha- and beta-adrenergic receptors, can modify susceptibilities to the disease. For example, the beta1-receptor polymorphism of beta1-Ser49 leads to beta-receptor down-regulation, and patients have a good five-year survival. On the other hand, patients with beta1-Arg389 and alpha2a-Del322–325 have much worse outcomes, paving the way for the exciting potential of a new approach for the treatment and management of patients with HF in the future.

Jay Cohn (University of Minnesota, Minneapolis, Minnesota) addressed the importance of HF prevention: “Why Let the Heart Fail at All?” To deal effectively with the burden of symptomatic HF, we need to identify the risk factors leading to left ventricular (LV) remodeling, and to prevent HF altogether. At the University of Minnesota, Dr.
Cohn has applied a Rasmussen score (including electrocardiogram, echocardiography, and brain natriuretic peptide, in addition to parameters such as pulse pressure, vascular compliance, exercise blood pressure response, and microalbuminuria) to assess risk for LV remodeling; this score appears to be better than the Framingham score in predicting HF. The hope is that earlier intervention can lead to reductions in the slope of progressive remodeling, HF, and deaths. The challenge, of course, is who should pay for the screening, who should do the screening, and ultimately how do we implement the preventive measures?

Bruce McManus (University of British Columbia, Vancouver, British Columbia, Canada) addressed the challenges of knowledge creation to knowledge translation in HF research. The Canadian HF investigators have identified several priority areas of research, including key mechanisms leading to HF, diagnostic and prognostic markers, novel pharmacologic, non-pharmacologic, and cell-based treatment strategies, and new paradigms of health delivery and health policies. As a result, there is a systematic organization of basic science discovery teams, as well as clinical research networks. The national health information database has also been organized to produce a Canadian outcomes map, as a link to organize health delivery priorities. An equal emphasis has been placed on knowledge translation. That is, translating scientific knowledge gained into benefits to patients and society as a whole. The ability to evaluate quality of care and barriers to dissemination of knowledge and changing behaviors and outcomes are also priorities of research at the Canadian Institutes of Health Research. This has formed the impetus to register the outcomes of all clinical trials, to rapidly publish results, and to understand the science of persuasion and interaction with patients. This will ultimately benefit both patients with HF and the medical community at large.

SYMPOSIUM ON CELL-BASED THERAPIES FOR CARDIAC REGENERATION

On Sunday afternoon, a symposium was held for scientists with an interest in cell-based therapies. It drew a large number of individuals interested in learning more about the current research in cell-based therapies for cardiac regeneration.

Amy Wagers (Joslin Diabetes Center, Boston, Massachusetts) opened the session by presenting data that strongly suggest that adult bone marrow cells cannot serve as a significant reservoir for cardiac precursor cells, and that neither these bone marrow cells, nor circulating cells can regenerate myocardium in the post-ischemic heart.

Michael Schneider (Baylor College of Medicine, Houston, Texas) discussed the loss of the telomeres in the heart in HF, and how Sca-1+ cells may restore the telomerase activity. Stem cells that are Sca-1+ express high levels of telomerase activity, and these cells home to the infarcted myocardium, and can express cardiac differentiation markers such as serum response factor, GATA-4, and myocyte enhancer factor (MEF)-2C. Cardiac Sca-1+ cells represent 25% of the cells in the border zone of an infarct, and another 25% fuse with local surviving cells. The BMP pathway is likely important in the differentiation of cardiac Sca-1+ cells, likely mediated via Smads or the TAK1 cascade.

Annarosa Leri (New York Medical College, Valhalla, New York) discussed the role of c-kit+ cells in the myocardium as cardiac progenitor cells, as documented both in vivo and in vitro. Cardiac niches for these cells are more numerous in the atria and apex in which cardiac primitive cells are surrounded by fibronectin. Cardiac c-kit+ and/or MDR1+ progenitor cells express c-met (hepatocyte growth factor receptor) and insulin-like growth factor-1R. Local injections of insulin-like growth factor-1 and hepatocyte growth factor promote the translocation (and proliferation) of cardiac progenitor cells from their site of storage to the injured area. In the regenerated myocardium after infarction, labeled progenitor cells can be recognized and show c-kit and MDR1 together with markers of cardiac and myocyte commitment (GATA4 and MEF2C). Moreover, they form coronary vessels, capillaries, and resistance arterioles. These cells have a specific integrin phenotype that allows them to translocate through the interstitium by binding to fibronectin.

Stephanie Dimmler (University of Frankfurt, Frankfurt, Germany) updated the audience on the role of endothelial progenitor cells (EPCs) in vascular repair and vasculogenesis. Factors such as granulocyte colony-stimulating factor, vascular endothelial growth factor, angiopoietin-2, statins, peroxisome proliferator-activated receptor agonists, and exercise all mobilize EPCs and are thus vasculoprotective. Interestingly, erythropoietin, which can stimulate production of bone marrow cells and EPCs, increases angiogenesis and is cardioprotective. The signals that can regulate EPC mobilization are now clearer. Granulocyte colony-stimulating factor can activate proteases including elastase, cathepsin, and matrix metalloproteinase-2, and vascular endothelial growth factor activates matrix metalloproteinase-9, cleaves stem cell factor, which then mobilizes c-kit+ cells from the bone marrow. On the other hand, endothelial nitric oxide synthase is also important in the bone marrow to mobilize EPCs, and nitric oxide may be important directly for the maintenance of the stem cell population.

Victor Dzau (Duke University, Durham, North Carolina) reported that transplanted mesenchymal stem cells, which have been transduced with an adenovirus encoding the
pro-survival protein kinase, Akt, are able to persist in the myocardium, reducing infarct size, and restoring function almost to normal. These mesenchymal stem cells express cardiac markers and are able to reduce inflammation and hypertrophy. There is evidence of some cell fusion in the peri-infarct zone, but fusion frequency is very low and cannot explain the efficacy of the therapy. This suggests instead that paracrine effects from the transduced cells may indeed be important. Indeed, conditioned medium of Akt-mesenchymal stem cells confers cytoprotective effects and can protect myocytes from hypoxia-induced damage.

Helmut Drexler (Medical University of Hannover, Hanover, Germany) updated the audience on the mechanistic insights into the Bone Marrow Transfer to Enhance ST-Elevation Infarct Regeneration (BOOST) trial. Although the left ventricular ejection fraction (LVEF) improved significantly in the bone marrow cell transfer group, there was no difference in infarct size by magnetic resonance imaging delayed enhancement or end-diastolic volume. More recent studies with labeled bone marrow cells incorporating $^{15}$F-deoxyglucose and followed with positron emission tomography showed that the majority of cells are in the spleen and liver, with no uptake in the brain, and only 2% to 4% are in the heart. Thus, the mechanism of improvement in LVEF is unclear at present.

Andreas Zeiher (University of Frankfurt, Frankfurt, Germany) conducted the original TOPCARE-AMI study by infusing bone marrow cells in 59 patients after myocardial infarction. Clinical follow-up indicated that the LVEF increased by 6% in the initial four months, and increased by another 5% in the next eight months. The LV mass also decreased over the first four months, suggesting an attenuation of LV hypertrophy with improvement in infarct remodeling. There was also a significant decrease in coronary vascular resistance by Doppler wire measurements. This study is being followed by the ongoing REPAIR-AMI trial conducted in a double-blinded randomized fashion.

Donald Orlic (National Institutes of Health, Bethesda, Maryland) has evaluated the effect of cytokines on stem cell mobilization. He has observed that the same stem cell that mobilizes the marrow is also the one that regenerates the myocardium, particularly the lin<sup>-</sup>c-kit<sup>+</sup> cells. The majority of the cells are endothelial cells, with very few myocytes, and apoptosis occurred within 3 to 5 h of implantation. Day 5 after infarction appears to be the maximal for cell repopulation, and studies from a variety of primate models showed that there is some angiogenesis, but very little myogenesis.

**CHEMOTHERAPY-INDUCED HF**

In this important session chaired by Lynne Warner Stevenson (Brigham and Women’s Hospital, Boston, Massachusetts) and Douglas Sawyer (Boston University, Boston, Massachusetts), the increasing problem of HF in patients taking chemotherapeutic agents for cancers was addressed. The first agents discussed were the anthracyclines, including doxorubicin, and in a series of experiments carried out over the last few years in cultured cardiomyocytes and experimental animals, Mona Nemer (Institut de Recherches Cliniques de Montreal, Montreal, Canada) has identified doxorubicin-induced down regulation of GATA4, a transcription factor known to play critical roles in cardiac development and hypertrophy, as a major mechanism underlying doxorubicin-induced cardiotoxicity. She then went on to demonstrate that infusion of the alpha-adrenergic agent, phenylephrine, prevented doxorubicin-induced cardiotoxicity, apparently by preventing the down-regulation of GATA4. The potential implications of these findings for the treatment of patients receiving anthracyclines, as well as of the use of alpha-adrenergic blockers in these patients, were discussed.

Thomas Suter (University Hospital, Bern, Switzerland) then discussed traztusumab (Herceptin), another agent known to induce heart failure. Traztusumab is a monoclonal antibody that blocks activation of a tyrosine kinase receptor called ErbB2, which is a member of the epidermal growth factor (EGF) family and is amplified in about 20% of breast cancers. Herceptin improves survival in these patients but at the expense of HF, which is particularly prevalent when used in combination with doxorubicin (28% of patients develop some degree of HF and in 16% of patients it is New York Heart Association functional class III or IV). In experimental animals, doxorubicin leads to myofiber disarray and this is made worse by traztusumab. In contrast, when an activator of the ErbB2 receptor (neuregulin) is given together with doxorubicin, myofiber disarray is reduced. The mechanism appears to be that the ErbB2 receptor, acting via the ERK-MAPK pathway, leads to the induction of anti-oxidant enzymes that negate the adverse oxidant properties of doxorubicin. The mechanism of the doxorubicin-induced myofiber disarray may be calpain-induced destruction of the sarcomeric protein titin. Of note, although the HF is usually reversible with discontinuation of the drugs, it re-appears with re-challenge and thus limits the amount of drug that can be given. Although not fully studied, it appears that cardiotoxicity with taxol plus herceptin is probably less than with doxorubicin plus herceptin. Finally, combining inhibitors of both ErbB1 (EGF-receptor) and ErbB2 also leads to cardiotoxicity, whereas ErbB1 inhibition alone (an example is Iressa, which has been approved for lung cancer) does not appear to.

Jean-Bernard Durand (M. D. Anderson Cancer Center, Houston, Texas) then outlined concerns about the potential cardiotoxicity of imatinib (Gleevec), a drug that targets the oncogenic tyrosine kinase, Bcr-Abl, deregulation of which is causal in chronic myelogenous leukemia. This drug has revolutionized the treatment of patients with chronic myelogenous leukemia. Although the risk cannot be quantified at this time, it does appear that the agent can be cardiotoxic and lead to HF in some patients. In addition, Dr. Durand showed the large number of chemotherapeutic agents that target tyrosine kinases (other than ErbB2, the EGF-
receptor, and Bcr-Abl) that are now in clinical trials, and suggested that these need to be watched very carefully for cardiotoxicity. This sentiment was echoed by Daniel Lenihan (M. D. Anderson Cancer Center, Houston, Texas), who also addressed the question of whether one could develop guidelines for the treatment of patients with chemo-induced HF. He outlined the striking beneficial effects of angiotensin-converting enzyme inhibition in some forms of chemo-induced HF, including herceptin-induced failure. Finally, all speakers and moderators issued a plea for greater awareness on the part of the oncology community of this problem, both for the treatment of patients receiving known or suspected cardiotoxic agents as well as for the design of future clinical trials with new agents, and suggested that this be a priority of the HFSA.

**MITOCHONDRIA AS SIGNALING PLATFORMS IN MYOCARDIAL DISEASES**

This session examined the role of mitochondria in both metabolism/energy generation and in the balance of cell survival/death. Jeffery Molkentin (University of Cincinnati, Cincinnati, Ohio) described his studies on regulation of the opening of the mitochondrial membrane pore, a process that allows the release of cytochrome c and pushes the cell toward apoptosis. One protein that associates with the components of the pore is cyclophilin D, the function of which in regulating pore opening has not been clear. Molkentin created a mouse with the cyclophilin D gene knocked out and found that the mitochondria of these mice were resistant to pore opening. That this is likely very relevant in vivo is suggested by the finding that the knockout had a 40% reduction in infarct size in an ischemia/reperfusion injury model. This makes cyclophilin D a potential therapeutic target to reduce ischemic (and possibly other forms) of injury. Peipei Ping (UCLA, Los Angeles, California) followed this up with her observations on the protection against pore opening provided by a particular isoform of protein kinase c-epsilon, also a potential therapeutic target.

Daniel Kelly (Washington University, St. Louis, Missouri) then discussed the role of PGC-1-alpha (PPAR-gamma- co-activator-1-alpha) in mitochondrial function. The PGC-1-alpha is a co-activator of gene induction for PPARs (the targets of thiazolidenediones), and plays a critical role in the expression of all myocardial mitochondrial genes necessary for oxidative phosphorylation. Thus PGC-1-alpha must be activated to control mitochondrial maturation. The PGC-1-alpha knockout mice have a relatively subtle phenotype in that heart and skeletal muscle size is only slightly decreased. However, ATP-synthesizing capacity of mitochondria from the KO is reduced, the mice have an abnormal chronotropic response, and LV fractional shortening is decreased. In contrast, chronic activation of PGC-1-alpha leads to a dilated cardiomyopathy.

**“THE TWO FACES OF POSITIVE INOTROPY”**

This session discussed how factors that cause increased cardiac contractility can also cause myocyte death. Physiologic hemodynamic stress (typically exercise) is intermittent and the associated increase in cardiac contractility involves activation of the sympathetic nervous system and increased cellular calcium concentration. In contrast, persistent pathologic hemodynamic stress (e.g., pressure load from hypertension or valvular disease) involves long-term (days to years) elevation in cardiac contractility. Data presented by Steve Houser (Temple University,Philadelphia, Pennsylvania) showed that persistent elevations in Ca\(^{2+}\) influx can lead to Ca\(^{2+}\) overload which eventually activates apoptosis. Rui-Ping Xiao (National Institute on Aging, Bethesda, Maryland) then showed that persistent activation of beta-1-adrenergic receptors, which also leads to persistently high Ca\(^{2+}\) concentrations, activates calcium/calmodulin-dependent kinases (CaM kinases) which can activate mitochondrial death pathways. These studies suggest that pathologies such as hypertension that can induce persistent activation of adrenergic signaling and elevations in myocyte calcium concentration can induce myocyte apoptosis. The subsequent reduction in the number of viable myocytes may be a critical factor that precipitates cardiac decompensation and HF.

**PROTEIN REMODELING IN HF**

Pathologic remodeling in failing hearts involves extensive and highly regulated changes in cellular protein content and function, including targeted protein cleavage and degradation carried out by specific proteases. In this session, four presentations covered different aspects of protease function and their regulation in the process of apoptotic cell death (Richard Kitsis, Albert Einstein College of Medicine, Bronx, New York), gene regulation (Robert Schwartz, Baylor College of Medicine, Houston, Texas), skeletal muscle atrophy (David Glass, Regeneron Pharmaceuticals, Inc., Tarrytown, New York), and myocardial remodeling (Yibin Wang, UCLA, Los Angeles, California). Dr. Kitsis presented new findings that a protein named ARC (apoptosis with caspase recruitment domain) functioned as a potent repressor of myocyte apoptosis by inhibiting both mitochondria-dependent and receptor (tumor necrosis factor and Fas)-mediated apoptotic pathways and may serve as a novel tool to protect myocytes from ischemic injury and death. On the other hand, Dr. Schwartz presented data demonstrating that caspase activity in human failing hearts mediated specific cleavage of serum response factor, a transcription factor regulating expression of a number of critical genes. Thus, caspases contribute significantly to the changes in the gene expression profile of patients with heart
failure. Dr. Glass demonstrated the power of using genomic approaches in signaling studies on skeletal muscle atrophy and hypertrophy by presenting his findings that two novel ubiquitin ligases, MAFbx and MuRF1, are critical components in the process of muscle degeneration. The intricate regulation of these proteins by protective pathways, such as IGF-1/PI3Kinase/Akt, provided both a molecular mechanism in muscle remodeling and a new venue for targeted therapy. Finally, Dr. Wang presented data from both in vitro and in vivo studies to illustrate the important contribution of stress-activated MAP kinases (JNKs and p38-MAPKs) to specific aspects of cardiac remodeling, including the loss of inter-cellular communication through gap junctions and increased fibrosis in extracellular matrix remodeling. In short, the session illustrated the important role of proteases and their regulation in muscle remodeling and dysfunction. It is clear that a better understanding of the underlying regulatory mechanisms of protease expression and activity may lead to new therapeutic targets for HF.

**DEBATES**

**Should mortality remain the major primary end point for HF trials?** Christopher O’Connor (Duke University, Durham, North Carolina) argued the “pro” point of view, evoking the current acceptance of “life-saving therapy” for cardiovascular patients to include aspirin, angiotensin-converting enzyme inhibitors, beta-blockers and reperfusion therapy. On the other hand, agents such as flolan and vesaninone had attractive mechanisms but did not protect the patients at the bedside, as risk and benefit of unintended targets can only be determined from large trials. Despite the fact that digoxin reduces hospitalizations, its use has declined due to a lack of a mortality benefit. The A-HeFT trial (combined isosorbide dinitrate-hydralazine in African Americans with HF) was recently stopped early mainly for safety. But Dr. Moss agrees that not everyone needs an ICD, particularly end-stage patients, who have multiple comorbidities with shortened life expectancy. Another cohort is the low-risk patients, for example, those who have all of the following features: New York Heart Association functional class ≥II, QRS <0.13 s, age <72 years, in sinus rhythm, serum creatinine <1.4 mmol/l, and LVEF >0.25, for example.

Mark Estes (Tufts-New England Medical Center, Boston, Massachusetts) argued the “con” side by stating that ICD is expensive therapy that is not without risks. The ICD benefit in HF is doubled in secondary prevention compared with primary prevention. The patients who benefit the most are those with ischemic cardiomyopathies with LVEF <30% or 35%. This does not include patients with higher ejection fractions or other forms of HF. Several trials including The Coronary Artery Bypass Graft Patch Trial (CABG-Patch) showed that an ICD does not influence non-arrhythmic deaths, and total mortality may not be different. Finally, one in three patients with an ICD will experience adverse effects such as inappropriate shocks, infection, or DDD or VVI pacing that has adverse hemodynamic effects for the compromised ventricle. Thus, selective use of ICD is essential.

**NANOTECHNOLOGIES IN MEDICINE**

An innovative session chaired by Denis Buxton (NHLBI, Bethesda, Maryland) addressed the question: “The New Nanotechnologies: Where Will They Take Us?” Drs. Buxton, Gregory Lanza (Washington University, St. Louis, Missouri), and Patrick Stayton (University of Washington, Seattle, Washington) outlined applications of these technologies that exist at the micrometer and submicrometer level (i.e., smaller than the size of a red blood cell). Dr. Lanza discussed the application of these technologies to imaging pathologic processes and to drug delivery that can be targeted to individual cells or pathologies. He showed
examples of magnetic resonance imaging of intravascular thrombi utilizing a magnetic resonance imaging agent packaged inside a liquid perfluorocarbon nanoparticle emulsion. The nanoparticles can be targeted specifically to the thrombus via an antibody expressed on the surface of the nanoparticle directed against cross-linked fibrin, allowing even relatively small thrombi to be imaged. He also demonstrated the ability to image angiogenesis in early stages of atherosclerosis. This employed injection of paramagnetic nanoparticles targeted by an antibody to αβ3 integrins, membrane proteins that are highly expressed in areas of neovascularization. He then demonstrated that related technologies could allow targeted drug delivery selectively to areas of disease using "contact-facilitated drug delivery." With this approach, a lipophilic drug is packaged as part of the surface of a liposome that contains a targeted molecule (e.g., an antibody) displayed on the surface of the liposome. The drug is not released until the liposome binds to the target cell. When this occurs, there is exchange of lipid from the liposome with that of the cell membrane, allowing the drug to selectively enter the cell. This targeting allows the delivery of high concentrations of a drug to a desired cell type, thus greatly reducing systemic exposure of the drug, and thereby limiting toxicity. Dr. Stayton then explored approaches to tissue engineering of the heart and demonstrated that cultured cardiomyocytes could be induced to orient themselves in an orderly fashion on parallel microstrips of laminin-coated elastomeric polyurethane films that are biodegradable. This parallel alignment allowed a much more ordered and effective contraction than one could achieve in the absence of this ordering. He went on to discuss approaches that could be used to modify biomaterials to control vascularization around tissue-engineered regeneration materials, and to regulate the foreign body reaction to biomaterials. The use of controlled release of proteins and nucleic acids from hydrogel matrices will permit control of vascularization, an essential component of producing viable tissue repair. Delivery of anti-inflammatory mediators, such as antisense and ribonucleic acid interference therapeutics, that inactivate macrophage signaling targets or inflammatory cytokines, may help to control harmful inflammatory processes. Although still some time away from clinical applications, these studies demonstrated the potential of transplantation of tissue-engineered cardiomyocytes for repairing failing hearts and the need for an integrated strategy to control inflammation and vascularization in addition to providing new myocytes.

THE INTERFACE OF ACADEMIA AND INDUSTRY IN HF THERAPEUTIC DEVELOPMENT

In a noontime "How To" session, representatives from the biotechnology and pharmaceutical industry (Seigo Izumo, Novartis Institutes for Biomedical Research, Cambridge, Massachusetts; Ted McCluskey, Scios, Fremont, California; Ralph Kelly, Genzyme Corporation, Framingham, Massachusetts) discussed impediments to the development of novel therapies specifically for the HF patient and potential approaches to breaking down those impediments. Drs. Izumo and McCluskey outlined several problems: 1) the relatively small size of the HF market (in the U.S. it is <10% of the hypertension market and of the statin market); 2) this is compared with the very high cost of bringing a novel therapeutic to market in terms of years (>10) and expense (>}$100 million); 3) in addition, there are extremely strict requirements for efficacy and safety for cardiovascular drugs; this is in contrast to the relatively lenient requirements for novel therapies to treat cancers, despite the fact that the prognosis of many patients with HF is worse than that for many cancers; and 4) finally, the requirement for a novel therapeutic to demonstrate efficacy when added to conventional treatments with previously demonstrated efficacy, which now includes ≥3 agents, is perceived as likely being difficult to achieve. All of these impediments have led many companies to abandon their HF initiatives, despite the steadily rising incidence of HF in the developed world. Approaches to address these difficult problems were suggested to include advocacy by the patients and their families, as well as open forums involving physician/nurse organizations (e.g., HFSA, American College of Cardiology, American Heart Association), industry, and the Food and Drug Administration such as occurred in an earlier session chaired by Uri Elkayam (USC, Los Angeles, California) and Cesare Orlandi (Otsuka Maryland Research Institute, Rockville, Maryland) that focused on drug development for acutely decompensated HF. Finally, Dr. Kelly described novel therapeutic approaches not involving pharmacologic agents, specifically gene therapy utilizing adenvirus-mediated gene transfer. An ongoing trial treating patients with ischemic limbs, in which an adenvirus encoding the transcription factor HIF-1-alpha is injected into the ischemic zone, attempts to induce angiogenesis in the ischemic region. In addition, he discussed potential future applications in HF (targeting the beta-adrenergic system). However, Dr. Kelly repeatedly underlined the critical importance of stringent safety in any future gene therapy trials.

GENETICS AND HF

The interface of genetics and clinical management was addressed in two symposia; the first focused on lessons derived from investigations in familial syndromes. In the familial session, Luisa Mestroni (University of Colorado, Aurora, Colorado) summarized the role of genotype in defining the risk of sudden death for subjects with hypertrophic cardiomyopathy (HCM). Molecular analysis has defined HCM as primarily a disorder of the sarcomere, as mutations of multiple contractile proteins result in the clinical phenotype. The risk of sudden death differs markedly between pedigrees, and much of this clinical heterogeneity reflects differences in the specific mutations. It is expected that the clinical evaluation of arrhythmic risk for
subjects with HCM will soon include genotype assessment, however this form of evaluation remains a research tool which is not yet clinically available. In the key-note address for this session, Jeffrey Towbin (Texas Children’s Hospital, Houston, Texas) reviewed the current understanding based on molecular analysis of the structural basis of dilated cardiomyopathy (DCM) as a disorder of the cytoskeleton. The clinical application of genomics to clinical management for subjects with DCM is still at an early stage of development.

A second session was devoted to clinical applications of population genetics. Variations in genetic background affect the degree of neurohormonal activation and, therefore, influence clinical outcomes. Dennis McNamara (University of Pittsburgh, Pittsburgh, Pennsylvania) presented data from outcome studies at the University of Pittsburgh that the 30% of HF subjects who are homozygous for the ACE D allele have poorer survival. This genetic risk was markedly diminished by therapy with either high-dose angiotensin-converting enzyme inhibitors or beta-blockers. Heart failure is polygenic and polymorphisms of the beta-adrenergic receptors and endothelial nitric oxide synthase also influence clinical outcomes and the effectiveness of pharmacologic therapy. Barry London (University of Pittsburgh, Pittsburgh, Pennsylvania) broadened the discussion to include not only “pharmacogenomics” but also “device-genomics” and presented population data on how variation in Herg, a gene that encodes a potassium channel which is responsible for long QT in some families, can increase the risk of sudden death. Current investigations are focused on developing a genetic profile of arrhythmic risk to determine subjects who receive maximal benefit from prophylatic ICDs. Analysis from the Framingham study presented by Christopher O’Donnell (NHLBI, Framingham, Massachusetts) demonstrates how haplotype analysis allows determination of the key genetic loci determining such clinical phenotypes as LV hypertrophy.

THE ROLE OF EXERCISE IN HF

Andrew Coats (University of Sydney, Sydney, Australia) began the session by reminding the audience of the poor correlation between LVEF and peak oxygen consumption during exercise in HF. Exercise training improves exercise duration, cardiac output, myocardial perfusion and LVEF. Mechanistically, this is associated with improvements in endothelial dysfunction, skeletal metabolism, mitochondrial oxidative capacity, and enhances baroreflex control. Meta-analysis also suggested improvement in survival and decreased hospital admission.

Leslie Leinwand (University of Colorado, Boulder, Colorado) discussed the basic mechanisms of cardiac remodeling in the presence of exercise. Interestingly there appears to be a gender difference in the mouse model, in that female mice are more active, and have greater cardiac hypertrophy, with a unique pattern of gene expression changes. The GSK-3 activation appears to be specific in inhibiting the pathologic hypertrophy seen in banding-induced pressure overload, but not essential for exercise-induced hypertrophy.

Robert McKelvie (McMaster University, Hamilton, Ontario, Canada) discussed the various exercise training protocols. Whether exercise training is done with a cycle ergometer or a treadmill, most patients show an increase in VO_2 of 14% to 25%. An aerobic training protocol is most commonly used, aiming for 50% to 80% of peak performance, 3 to 5 times per week, at 20 to 60 min per session. More recently, the role of resistance training at 40% to 70% of peak strength, incorporating 10 to 15 repetitions up to a maximum of 3 sets, have become more recognized. Interval exercise training also increases endurance and muscle strength.

Ileana Pina (Case Western Reserve, Cleveland, Ohio) presented the rationale for the HF ACTION trial, attempting to determine the role of exercise training on morbidity and mortality. The trial is powered to demonstrate that exercise training can lower death and hospitalization by 20%. The inclusion criteria will include New York Heart Association functional class II to IV HF patients with LVEF <35% on stable medications for 6 weeks. The patients will be randomized to intervention consisting of 36 exercise training sessions, and clinical assessment and cardiopulmonary testing at three months and yearly during follow-up.

CLINICAL TRIALS UPDATE

Oral Enoximone in Inotrope-Dependent Subjects (EMOTE). Arthur Feldman (Thomas Jefferson University, Philadelphia, Pennsylvania) presented this trial to determine if low-dose enoximone can permit weaning of advanced HF patients from intravenous inotropic therapy. The trial enrolled 201 New York Heart Association functional class III or IV inotrope-dependent HF patients with LVEF <25% and LV end-diastolic diameter >54 mm to enoximone 25 or 50 mg po tid (n = 101) or placebo. The primary end point of the trial was being alive and free from intravenous inotropes at 30 days of follow-up, and the secondary end points were measured at later time points up to 26 weeks. The results at 30 days showed that 51% of the patients were alive and free of inotropes at 30 days in the placebo group, and 61% in the enoximone group (p = 0.138). At 60 days, the percent of patients weaned off intravenous inotropes and alive was 30% and 49% in the placebo and enoximone groups, respectively (p = 0.007). At 26 weeks of follow-up, there was a reduction of 32% in terms of death, failure to wean from or re-initiation of intravenous inotropes in the enoximone group compared with placebo (p = 0.04), and the number of days on intravenous inotropes was decreased by 43% in the enoximone group. By intention-to-treat, there were 38 deaths in enoximone group and 31 deaths in the placebo group (hazard ratio = 1.27, p = NS), but in patients who had not
been withdrawn from study medication the enoximone and placebo deaths were 15 and 16, respectively (p = 0.91). Thus, although the primary end point at 30 days was not met, the results for longer treatment periods suggested benefit of enoximone in the ability to wean advanced HF patients from intravenous inotropes.

**Hawthorn Extract Randomized Blinded HF (HERB CHF) study.** Keith Aaronson (University of Michigan, Ann Arbor, Michigan) summarized this trial to evaluate the role of an extract of the leaves and flowers of the hawthorn tree in patients with HF in a double-blind randomized trial. Hawthorn has been shown to have mild inotropic and vasodilatory effects with low toxicity. Patients with New York Heart Association functional class II to III HF were randomized to hawthorn 450 mg po bid (n = 54) versus placebo (n = 57) on standard background therapy. The primary end point was the distance on 6-min walk test at 3 and 6 months of follow-up. The results showed no difference in 6-min walk test between the two groups (from 373 ± 53 m at baseline to 379 ± 52 m at 6 months in the placebo group, vs. 357 ± 52 m at baseline to 371 ± 89 m at 6 months; p = 0.41). The LVEF effects were nominally favorable for the hawthorn group (35% to 33% in placebo arm and 37% to 37% in hawthorn group; p = 0.04). Patient global assessment of quality of life and changes in the Minnesota Living with Heart Failure Questionnaire quality of life score were also indistinguishable between the two groups. Thus, hawthorn did not have a measurable substantial benefit on submaximal exercise capacity, LV function, or quality of life in patients with HF.

**The Warfarin and Antiplatelet Trial in Chronic Heart failure (WATCH).** Barry Massie (UCSF, San Francisco, California) provided an update on the WATCH trial. The WATCH trial was designed to determine the optimal antithrombotic therapy for patients with chronic heart failure who were in sinus rhythm. The WATCH trial randomized patients to three parallel groups: open label warfarin (target international normalized ratio 2.5 to 3.0) or double-blind aspirin 162 mg or clopidogrel 75 mg. The primary end point was the composite of death from all causes and non-fatal myocardial infarction and stroke. Two primary comparisons were planned: warfarin versus aspirin and clopidogrel versus aspirin, with the latter intended to provide indirect information as to whether aspirin has an adverse effect in HF patients who are treated with angiotensin-converting enzyme inhibitors.

Although the WATCH trial was originally designed to enroll 4,500 patients, the trial was terminated prematurely because of slow recruitment. Nonetheless, with 1,587 patients with New York Heart Association functional class II to IV congestive HF and LVEF ≤35% and followed for a mean of 1.9 years (3,068 patient-years of follow-up), it is the largest trial of antithrombotic therapy in a HF population.

No significant differences between the three treatment groups were observed in the primary composite end point or in all-cause mortality. However, significant differences emerged for secondary end points. The incidence of stroke was lower in warfarin-treated patients than either aspirin or clopidogrel (0.7% vs. 2.1% and 2.5%, respectively); the stroke rate was significantly lower when warfarin was compared with the combined antiplatelet therapy groups (p < 0.001). The number of patients hospitalized for worsening HF and the number of hospitalizations were 27% and 31% lower with warfarin versus aspirin (p < 0.01 and p < 0.001, respectively). Similar, but not statistically significant trends toward fewer HF admissions were seen with clopidogrel versus aspirin. Dr. Massie speculated that the poorer HF outcomes with aspirin may represent an adverse effect of prostaglandin inhibition. However, he concluded that in the absence of significant differences in the primary end point, these observations should be viewed primarily as hypothesis-generating.

**The Bone Marrow Transfer to Enhance STEMI Regeneration (BOOST) trial.** Kai C. Wollert (University of Hanover, Hanover, Germany) updated the audience on the objective of the study, that is to evaluate the effects of intracoronary autologous bone marrow cell infusions on LV remodeling and ventricular function. Patients with acute ST-segment elevation myocardial infarction who had successful percutaneous coronary intervention with stent implantation and regional LV hypokinesis, underwent magnetic resonance imaging to evaluate LVEF, and were randomized to receive unselected nucleated bone marrow cells aspirated from the iliac bone or conventional treatment according to current practice guidelines. On day 5 after percutaneous coronary intervention, the patients randomized to intervention received four to five infusions of nucleated bone marrow cells during transient balloon occlusion into the infarct-related coronary artery. The primary end point was LVEF change at six months as determined by magnetic resonance imaging and evaluated by two blinded observers. The control group had an LVEF of 51.3% at baseline, and 52.0% at six months' follow-up, representing a 0.7% change. The cell transplantation group had a baseline LVEF of 50.0% and 56.7% at six months, or a 6.7% LVEF change (p = 0.0026). Regional wall motion in the infarct border zone also significantly improved in the bone marrow cell group. Cell transfer did not significantly impact on LV end-diastolic volumes. No enhanced in-stent restenosis or ventricular arrhythmias were observed. However, as noted by Dr. Drexler in the stem cell session, mechanisms of the improvement in LVEF are unknown at the present time.

**The Beta-Blocker Evaluation of Survival Trial—Single Nucleotide Polymorphism (BEST-SNP) substudy.** Stephen Liggett (University of Cincinnati, Cincinnati, Ohio) reminded the audience that the objective of this substudy was to determine if the position 389 variant of the beta-adrenergic receptor modified the response to beta-blockers in HF from the original Beta Blocker Evaluation of Survival Trial (BEST) cohort. Previous basic studies have demonstrated that of the position 389 variant of BAR, the adenyl
cyclase activity of Arg389 is much greater than Gly389, suggesting hyperactivity of BAR in patients with this polymorphism, which may be associated with a worse prognosis. On the other hand, response to the beta-blocker, propranolol, was much more marked in hearts harboring the Arg389 allele. The BEST trial evaluated bucindolol in patients with moderate to severe HF, followed for five years. The primary end point was not met in terms of a significant difference in outcomes between the treated or placebo groups. In this follow-up substudy of 1,040 patients designed to determine whether there were differences in response to beta-blocker between the polymorphisms, 525 patients were in the placebo arm, and 515 patients were in the bucindolol group; Gly389 carriers were 289 in placebo, and 258 in the bucindolol group. The Arg389 patients who were treated with bucindolol had significantly improved survival compared with those on placebo, with a hazard ratio of 0.62 (p < 0.01). On the other hand, the Gly389 patients did not benefit from beta-blocker therapy. Thus polymorphic variation at position 389 of the beta-adrenergic receptor may significantly influence pharmacologic response. This represents one of the first systematic examinations of pharmacogenetic influences of beta-blocker therapy in HF.

Acknowledgements
We are particularly grateful to Denis Buxton, Dennis McNamara, Steve Houser, Yibin Wang, and all of the presenters of the Opening Plenary and Clinical Trials session for contributing their thoughts and feedback on this Highlights article. We are also most appreciative of the efforts of Ms. Cheryl Yano, Executive Officer of the HFSA, for the superb organization of the meeting and facilitation of this Highlight publication. We thank all of the attendees for contributing to an excellent scientific meeting that helped to define the frontiers of HF research.

Reprint requests and correspondence: Dr. Thomas Force, Tufts-New England Medical Center, Molecular Cardiology Research Institute, 750 Washington Street, Box 8486, Boston, Massachusetts 02111. E-mail: TForce@tufts-nemc.org.