The key topics identified by the Clinical Science Subgroup are:

I. Complex Systems Analysis for Clinical Application of Science Data
II. Translational or Applied Genomics
III. Proteomics
IV. Pharmacogenomics
V. Organogenesis, Tissue Engineering, Vasculogenesis (Including Stem Cell Research)
VI. Addendum: Implementation of Scientifically Proven Treatments

I. Complex Systems Analysis for Clinical Application of Scientific Data

Introduction, Definition, Content

The scope of new biomedical information is rapidly evolving, both in breadth and depth, from multiple research strategies. These sources of data include: (1) major population studies on the epidemiology and results of intervention for disease prevention from clinical trials and epidemiological surveys; (2) new approaches to understanding the pathophysiology of disease, with particular regard to predictors of acute events; and (3) the promise of a major impact on prediction, prevention, and treatment of disease, as well as a much better understanding of the basic biology of cardiovascular disease as a result of genetic insights. Each of these disciplines offers individual analytical challenges in order to understand their meaning and applications, but equally important, the three avenues of study must be integrated to maximize the derived benefits. It will be necessary to construct new methods for complex systems analyses applicable to these biomedical questions. Although this requirement will apply to all phases of large database analysis, it is particularly important for deriving benefits that can be applied to human disease states from molecular genetics.

Completion of the draft sequence of the human genome has provided a broad horizon of opportunity for application of genetically based information to our knowledge of pathophysiology and to the diagnosis, prevention, and treatment of clinical states. Technological advances in high-throughput sequencing and various gene expression methods are anticipated to provide ever-increasing volumes of information, with the potential to generate novel approaches to clinical medicine. It was apparent, even before the completion of the draft sequence of the human genome, that clinical expressions of genetic variations are not isolated deterministic phenomena. Rather, an abundance of information suggests that expression of genetic variations is modulated by other factors. Downstream expression of genetic alterations may be modified by other genes (gene-gene interaction), by nongenetic endogenous physiological influences such as autonomic fluctuations or metabolic states, and by exogenous substances such as drugs and environmental exposures. These relationships are extraordinarily complex and will require complex mathematical analyses, which are new systems for the application of information theory to systemic biology. Such endeavors will lead to understanding of the complex interactions between multiple genes and nongenetic biological factors, as well as to the growth of a relatively new discipline, genetic epidemiology. The latter offers the promise of the ability to predict disease expression in specific subgroups and individuals that might influence application of rational therapy and prevention strategies. These promises will be fulfilled only with the development of a discipline of complex systems analyses specific to the biomedical field. The methods on which this discipline will rest are currently in their infancy.

Subcategories of Research

Gene-Gene Interaction

The expression of a specific genetic variation in a complex biological system is subject to modification by actions of
other genes involved in the same and related physiological functions. These interactions may have quantitative or qualitative influences on expression. Accordingly, the simple identification of a functional polymorphism at a specific gene locus does not itself identify whether or how a genetic variation will be expressed at an integrated physiological level. Complex mathematical analyses are required to define how 2 or more genes will interact in a biological system.

**Gene-Nongene Interaction**

Genetically controlled variations in physiological functions may be modulated by acquired or environmental influences. Genetic influences may range from fully expressed mutations responsible for distinct syndromes to polymorphisms that have no effect under baseline conditions but theoretically may express when stimulated by acquired influences. An example is the distinction between phenotypic congenital long-QT interval syndrome and genotypic variations in the same ion channels, which become expressed phenotypically only when a second influence that alters or “stresses” ion channel behavior is superimposed, such as in drug-induced proarrhythmia. This example highlights the need for combining information from sequencing and expression, to determination of various physiological and pharmacological interactions, and then to studies of distribution of gene variations among general populations. Insights into population genetics offer the possibility of subgrouping large populations into smaller ones with higher event rates, in which preventive strategies are more rational.

**Clinical Syndromes**

Two major categories of clinical syndromes—acute ischemic events and sudden cardiac death—require much higher orders of predictability from risk profiling than are currently available. For both, several avenues of investigation are promising. Although conventional risk factor profiling and clinical descriptors have provided substantial data on population risk, these approaches have lacked the power to predict transition from a steady-state stability to the onset of acute clinical syndromes with practical levels of accuracy. In both syndromes, short- or intermediate-term alterations in the characteristics of atherosclerotic plaques, including inflammatory markers as both pathophysiological events and predictors, as well as familial clustering of clinical expressions, are worthy of further investigation. Identification of genetic factors predisposing to changes in stability and acquired factors for initiating the transition will require powerful mathematical analyses among large populations in order to ultimately achieve the goal of specific risk profiling.

**Bioinformatics and Genetic Epidemiology**

In each of the categories discussed above, an infrastructure of computational power for complex systems analysis is required. The integration of sequence and expression of multiple genes, interacting with one another and with nongenetic influences, is required to generate a rational pathway of information and clinical application of the massive amounts of new data that will be forthcoming. One end point of this endeavor will be the maturation of the science of genetically based clinical epidemiology. The optimistic view is that conventional epidemiological approaches incorporating new genetically based tools will provide a much higher power of individual predictability for life-threatening events. Bioinformatics of the genomic database is a science waiting to be developed, but this strategy will require the generation of a new type of systems analyst to generate applicable models.

**Example**

The cascade from atherogenesis, through the pathophysiology of acute coronary syndromes to the expression of acute coronary events, provides an example of the need for complex systems analysis involving genetic and nongene interactions. A growing body of information suggests that many steps in this cascade are influenced by genetic determinants that may create varying levels of individual risk.

Conventional epidemiological approaches to atherogenesis, which rely on conventional risk factors, are hampered by relatively low absolute event rates among the general population. Subgrouping with multiple risk factors improves predictability, but some data suggest that genetically defined population subgroups might identify even higher profiles of risk. The next level of the cascade, factors influencing the pathophysiological mechanisms of plaque destabilization, platelet activation, and thrombosis, also is receiving increasing contributions from the identification of genetic determinants of functions, such as plaque instability, inflammation processes, and the thrombosis cascade, which trigger acute coronary syndromes. Beyond this, still more information is evolving on the role of mutations and clinically relevant polymorphisms in controlling ion channel function and cellular calcium handling, which may influence the mode of expression of acute coronary syndromes. Viewing the cascade globally, one can envision the ability of complex systems analysis to improve prediction and prevention of events through a combination of highly specific profiles of risk and mechanisms of onset and to determine clinical expressions of this important category of disease.

**Importance**

The interpretation of the outcomes of clinical trials and epidemiological surveys is limited by the low power for individual risk prediction of the effects identified within a large population study. In order to increase individual risk predictive power, better tools for risk discrimination are needed. Many of the concepts cited above can provide those tools if we are able to generate the informational analysis power needed for identification of new methods for risk profiling. Without the ability to carry out complex systems analysis, translational research will only have limited applicability to clinical problems.

**Suggested Funding Mechanisms**

Multiple funding mechanisms are required to achieve the goals outlined above. For the general field of complex systems analysis and bioinformatics, it is necessary to generate a new type of investigator from career development strategies. Current availability of advanced bioinformatics personnel is very limited, though their availability is critical to the complex systems analysis mission. In addition, molec-
ular and applied geneticists need to be brought into the realm of cardiovascular medicine in greater numbers than are currently available.

These needs can be met through support focusing on training programs, in large multidisciplinary centers (and multi-institutional cooperative programs) oriented to population issues in cardiovascular medicine, and individual grants for career initiation of young scientists. Support focused on pairing clinicians with those knowledgeable about bioinformatics, whether they are in biomedicine or in other fields such as computer or space science, would also be important. Critical to this entire mission is the expanded availability of research funding over the long term to offer investigators the security for career commitments.

Short- and Long-Term Benefits
Population studies, interacting with deeper studies into clinical syndromes and applied genetics, will accelerate improvement in mortality rates, morbidity, and quality of life in cardiovascular disorders and, in doing so, will contribute to the American Heart Association (AHA) 2010 goal of reducing coronary heart disease and stroke by 25%.

II. Translational or Applied Genomics
This topic includes the following categories:

- Bioinformatics
- Gene transfer
- Human genetic aspects of disease
- Stem cell
- Bench to bedside

Introduction
Translational genomics, or “applied genomics,” refers to the investigation of the human genome and the application of knowledge of the human genome to the understanding and treatment of human disease. This field of research provides the opportunity to develop new approaches to the diagnosis and treatment of cardiovascular disease and stroke.

Examples of research in this field include the development of diagnostic tests to identify genetic diseases and tests to determine genetic predisposition to disease. Such testing includes blood tests focused on identification of single gene abnormalities and microarray (or “chip”) technology to screen for a large number of genetic traits that might affect risk for cardiovascular disease. Translational genomics also encompasses the study of gene transfer and gene therapy, which have great potential in the prevention and treatment of atherosclerosis, in stimulating angiogenesis, and in the treatment of cardiomyopathies. Translational genomics will also encompass research in cardiovascular stem cells, which holds promise in treatment of heart failure, angiogenesis, stroke, diabetes, and arrhythmias.

The AHA has created an Interdisciplinary Working Group on Functional Genomics and Translational Biology in 2002. The purpose of this working group is to foster communication across the scientific councils, to disseminate scientific knowledge through writing groups and presentations at Scientific Sessions, and to make recommendations on research funding and advocacy.

Importance
Translational genomics has enormous potential to advance prevention, diagnosis and treatment of cardiovascular disease and stroke. Diseases that are likely to be affected heavily include atherosclerosis, diabetes, heart failure, arrhythmias, and some forms of congenital heart disease.

Suggested Funding Mechanisms
Several funding mechanisms, in addition to investigator-initiated applications, might move this field forward. One such mechanism is a paired grant awarded to a cardiologist clinical investigator and a molecular biologist. This would be aimed at fostering translational research from bench to clinical trials. A second proposed mechanism is small training grants to support young investigators embarking on careers in translational genomics. Such training grants could be aimed at both clinical trainees and bench scientists but optimally would support programs in which interdisciplinary training and research are fostered. Additional thought in this area is needed, and input from the AHA Interdisciplinary Working Group on Functional Genomics and Translational Biology should be encouraged.

III. Proteomics
This topic includes the following categories:

- Bioinformatics
- Gene transfer
- Human genetic aspects of disease
- Stem cell
- Bench to bedside

Introduction
Proteomics refers to studies of the ensemble of proteins expressed in a given organ, age, and state. By analogy to genomics, the distinguishing emphasis of which is the sequence, organization, and expression of the genome in its entirety, proteomics characteristically encompasses high-throughput, genetically unbiased studies of specifically which proteins differ (between health and disease, between samples with and without an experimental intervention, between populations, etc). Differences in protein modification also are especially germane (phosphorylation, ubiquitination, acetylation, cleavage). The enabling technologies for proteomics thus include rapid, sensitive methodologies to resolve quantitative differences of proteins in complex mixtures, as well as methods necessary to disclose or verify the identity of the proteins (2D gel electrophoresis, nanoscale chromatography, mass spectrometry, isotope coded affinity tags). In addition, advances in bioinformatics facilitate the acquisition and systematic analysis of these large and complex data sets.

Importance
Proteomics is indispensable for a complete understanding of cell and organ function and dysfunction as they relate to cardiovascular health and disease. Proteomic studies are an extension of the information that we gain from comparisons of the “transcriptome” (what genes are expressed, at the
mRNA level), providing key information that is not present in the analysis of RNA alone. As applied to clinical research, the fruits of proteomic research are expected to include: (1) novel markers of disease susceptibility, resistance, severity, and regression; (2) a revolution in diagnostic technologies; and (3) novel pathophysiological mechanisms and, hence, novel targets for drug development.

Suggested Funding Mechanisms
Potential funding mechanisms could include establishment of an AHA study section expert in these technologies, and also the establishment of AHA centers of excellence for these technologies. Such centers would provide training or even sabbatical support for cardiovascular investigators seeking to cross-train. The success of the AHA–Bugher Foundation Centers for Molecular Biology in the Cardiovascular System should be considered a possible model. Alternatively, one might take the point of view that proteomics is just a technology (albeit exciting), the application of which to cardiovascular science (atherosclerosis, thrombosis, ischemia and infarction, heart failure, cardiac development, and congenital disease) is merely one component of functional genomics more broadly defined.

IV. Pharmacogenomics
This topic includes the following categories:

- Bioinformatics
- Gene transfer
- Human genetic aspects of disease
- Stem cell
- Bench to bedside

Introduction
Pharmacogenomics is a critical area for AHA-supported research. Pharmacogenomics generally refers to the utilization of individuals’ genetic information to explain variability in responses to drugs or individuality with regard to drug dose response for patients with known genetic polymorphisms. For example, an individual’s resistance to warfarin’s anticoagulant action can be caused by an alteration in the vitamin K epoxide reductase enzyme expression. Another example is the hemolytic anemia that can develop in African-American males given primaquine for malaria, which may occur in as many as 10% of black men. This reaction is related to a deficiency of erythrocytic glucose-6-phosphate dehydrogenase. Although these examples focus on idiosyncratic reactions to drugs that create problems, it is likely that determination of genetic polymorphisms or other genomic characteristics will determine, in one fashion or another, a patient’s risk of developing atherosclerotic cardiovascular disease or having progression with adverse outcome.

Furthermore, it is possible that one might be able to identify more specifically patients who would respond to unique pharmacotherapeutic agents. For example, at the present time, we are challenged by having to prescribe many drugs for the treatment of heart failure. It is not uncommon for patients with systolic left ventricular dysfunction and congestive heart failure to be on a half-dozen therapeutic agents, including an angiotensin-converting enzyme (ACE) inhibitor, β-blocker, aldosterone antagonist, digoxin, a diuretic, and electrolyte supplementation. We know, however, that only a few select patients actually respond to ACE inhibitor or β-blocker therapy.

With regard to ACE inhibitor treatment, wide variability in the response to treatment exists, and ~5% to 10% of patients are intolerant of this class of drug. Cough and hypotension are seemingly much more common in Asians treated with ACE inhibitors, whereas angioedema is more common in African Americans. Perhaps there are genetic polymorphisms that potentially modulate the patient’s response to treatment to alter the natural course of the disease or set the stage for adverse drug reactions. Such polymorphisms can effect protein structure, including degratory hepatic enzymes and their receptor structure, thus changing the pharmacodynamics and kinetic actions of the drug in a heart failure patient. An additional example might be the amount of vascular bradykinin and/or nitric oxide activity evident in response to the ACE inhibitor. Perhaps pharmacogenomic studies will ultimately provide insight into these specific polymorphisms and allow more rational therapy of these patients. Indeed, we have known for quite some time that the deletion allele (D) of the ACE-controlling gene is associated with high tissue ACE levels. Those who are homozygous for the D-allele display enhanced vasoconstrictor response to angiotensin I. Insertion (I) rather than the deletion allele of the ACE gene is associated with lower ACE activity in body tissue but may be associated with improved responses to physical training.

Importance
Advances in the area of pharmacogenomics could allow us to identify more specifically patients who would respond to unique pharmacotherapeutic agents. Pharmacogenomics might allow identification of the patient likely to benefit from a specific drug. Perhaps pharmacogenomic studies will ultimately provide insight into specific polymorphisms and allow more rational therapy of patients who exhibit them.

Suggested Funding Mechanisms
Perhaps large population studies will allow us to understand these polymorphisms and give greater insight into the importance of pharmacogenomics in patients with cardiovascular disease. This may be an area that the AHA Pharmaceutical Roundtable would be particularly interested in supporting.

V. Organogenesis, Tissue Engineering, Vasculogenesis (Including Stem Cell Research)
Introduction
Organogenesis is the initial developmental process that forms the cardiovascular system. Undifferentiated stem cells arising from at least 3 distinct sites—endo- and mesocardium, neural crest, and perihepatic body—coalesce to form the complex heart and circulation. Understanding this process will undoubtedly provide opportunities for prevention and treatment of heart and blood vessel disease.

The heart is the first functioning organ. Each adult once had the heart of an embryo. At the earliest stages of formation, the heart is a mere muscle-wrapped tube without
valves, septa, or recognizable conduction tissue, yet this primitive heart provides circulatory support to the embryo during rapid growth and differentiation. Congenital and much of adult-onset cardiovascular disease likely begins during this developmental process. The complex interaction of genetics determines cell differentiation and migration, whereas epigenetic factors like blood pressure, blood flow, and micronutrients are critical to cardiac morphology.

Today, we know that folate supplementation dramatically reduces the risk of certain complex congenital cardiovascular malformations. Other examples of simple prevention for structural and functional heart diseases likely exist.

**Importance**

Studies of cardiovascular organogenesis provide unique therapy for a broad range of cardiovascular diseases. For example, tissue engineering holds the promise of replacement valves grown from individuals’ own cells, thereby removing the complications of rejection, calcification, and chronic anticoagulation. Techniques to control blood vessel growth can expand the vascular bed de novo or provide grafts for surgical implantation. Cardiac myocytes grown in vitro and seeded into a failing heart would be a preferable source of contractile elements compared with whole heart transplantation. Pacemaker cells placed in the atrial wall might become the preferred form of pacemaker therapy, rather than relying on complex and often unreliable electronic devices.

**Suggested Funding Mechanisms**

Organogenesis is a key area of investigation in the post-genomic era and requires multiple experimental models, a new kind of cardiovascular scientist and new techniques for investigation. The understanding of cardiovascular organogenesis comes from integrated studies of fish, amphibians, birds, and mammals. No longer can investigators be wedded to one model system. We also need a new category of investigators. These biophysical developmental biologists must have the computational tools of an engineer combined with the biological expertise of a developmental geneticist. We urge traditional developmental biology programs to establish research consortia with colleagues in electrical, mechanical, and bioengineering to create the environment for training this new class of investigator. Funding will come from government consortia of the National Institutes of Health and the National Science Foundation, nongovernmental organizations like the AHA, and from industry. However, without easily marketable products, industry is less likely to commit the vast resources needed.

**VI. Addendum: Support for Implementation of Scientifically Proven Treatments**

The AHA should strongly support continued research on the implementation of scientifically proven treatments. Research is needed in healthcare systems that deliver evidence-based quality care, especially in medically underserved segments of the population, and result in optimal outcomes. Such research will be essential for the AHA to achieve its 2010 strategic impact goal.

The greatest limitation of most of the large clinical trials is the distinction between the effect expressed in relative risk reductions and the impact on individual patients expressed by calculations such as absolute risk reduction or numbers needed to treat. The discrepancy in magnitude between these two figures in most of the large clinical trials can be reduced by population subgrouping to identify those individual candidates or subgroups of candidates who will accrue the greatest benefits from the interventions. When the individual impact figures become impressive, utilization will improve. Identifying those subgroups is the subject of much of the material in this section, but additional subgroup analyses based on more conventional population studies and subgroups studies will be useful.
Task Force on Strategic Research Direction: Clinical Science Subgroup Key Science Topics Report
Robert Bonow, Edward B. Clark, Gregory D. Curfman, Alan Guttmacher, Martha N. Hill, D. Craig Miller, Aubrey R. Morrison, Robert J. Myerburg, Michael D. Schneider, Myron L. Weisfeldt, James T. Willerson and James B. Young

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