AHA Special Report

Task Force on Strategic Research Direction
Basic Science Subgroup
Key Science Topics Report

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This report is an outcome of the Basic Science Subgroup’s teleconference discussions and consolidates the topic descriptions written by Subgroup members. The key topics identified by the Basic Science Subgroup are:

I. Complex Systems Analysis
II. Vascular Topics in Cardiovascular Disease (CVD) and Stroke
III. Cardiac Pathology
IV. Obesity
V. Cardiovascular and Neuronal Repair and Remodeling and Cellular Pathology
VI. Bidirectional Translational Research

I. Complex Systems Analysis

Scope
This topic includes systems biology, information theory, computational biology, gene-gene interactions, gene-environment interactions, postgenomic areas such as phenotypic characterization of living systems and proteomics, biomarkers for atherosclerotic CVD and congestive heart failure (CHF), image analysis, genetic factors predisposing individuals to CVD/stroke or decreasing risk, registries of patients/biological samples, application of gene chip technology to stroke, and complex physiological systems.

Introduction
Sequencing of the human genome and other recent developments in science provide new tools that promise to change dramatically—some would say to revolutionize—basic science approaches to many aspects of health, particularly CVD. To use these tools effectively, however, will require the application of the rapidly developing, interrelated fields of systems biology, information theory, and computational biology.

It is possible to imagine a day when knowledge of an individual’s genetic or proteomic makeup, in conjunction with more sophisticated knowledge of gene-environment interactions and other advances such as new imaging techniques, will allow individually based screening protocols, individualized presymptomatic lifestyle and dietary counseling, individualized presymptomatic prophylactic medication use, and individualized therapies. These approaches will serve to lower dramatically the incidence and severity of obesity, hypertension, atherosclerosis, CHF, and stroke, and will provide more effective, individualized therapies to those who still develop these disorders.

Subcategories of Research
Among the ways that these tools will inform our approach to cardiovascular health and disease is the achievement of a much more sophisticated understanding of the actions of single genes. Importantly, a greater contribution will come from the nascent fields of genomics, which will facilitate an understanding of gene-gene interactions and gene-environment interactions, and proteomics, which will facilitate an understanding of how proteins function and of protein-protein and protein-environment interactions. In turn, these fields will enable us to utilize such means as biomarkers, patient phenotype and sample registries, and microarray, or chip, technology to understand more fully the mechanisms that underlie the development of obesity, hypertension, atherosclerosis, CHF, and stroke. New imaging modalities will further add to the array of new techniques that will profoundly increase our knowledge of the basic biological mechanisms responsible for CVD.

Gene-Gene Interactions
The study of gene-gene interactions, for instance, should help elucidate how specific genes interact to affect cardiovascular...
health. For example: How does apolipoprotein E affect cardiovascular risk? What, if any, other genes interact with apolipoprotein E alleles to modify this effect? For instance, is the effect of various genes involved in homocysteine metabolism independent of, or interdependent with, apolipoprotein E in terms of cardiovascular effect? If interdependent, which genes involved in homocysteine metabolism are of clinical importance in modifying the apolipoprotein E effect? Are certain apolipoprotein E alleles affected by such homocysteine metabolism genes and other alleles not? What other genes interact with apolipoprotein E to affect cardiovascular health? Once we understand which genes interact with apolipoprotein E to affect cardiovascular health, what are the biological mechanisms that underlie these interactions? How might we utilize an understanding of these mechanisms in diagnosis, treatment, and prevention of CVD?

**Gene-Environment Interactions**

Similarly, the study of gene-environment interactions should help elucidate how specific genes and specific environmental factors interact to affect cardiovascular health. For instance, what environmental factors affect the influence of the various apolipoprotein E alleles, and by what biological mechanisms do they do so? How might such knowledge be used, in combination with individual genotypic data that will be provided by microarray technology, to allow individuals to achieve a healthier phenotype?

**Biomarkers and Registries**

Biomarker discovery will be a natural derivative of the systems biology/complex systems approach to the study of heart disease. The goal of this research area will be to leverage directly from genomics and proteomics approaches to understanding the underlying mechanisms and fundamental disease pathways contributing to the development of atherosclerosis, CHF, stroke, and obesity. Mining these pathways and the information that underlies them will provide the basis for biomarker discovery.

Biomarkers may be classified as epigenetic tools that allow an objective measure of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention. These markers may be DNA (single nucleotide polymorphism [SNP] or haplotypes), RNA (transcriptional), protein (serum based), or metabolite (serum based) in nature. Markers can be used not only to assess an individual’s response to a therapeutic intervention (monitoring marker) but also as a diagnostic tool, a tool for staging or prognosis of a disease, or a tool to predict the response to a pharmaceutical (pharmacogenomics or pharmacoproteomics) or mechanical (device genomics or proteomics) intervention. If they meet certain stringent functional and temporal criteria, biomarkers can be used as surrogates for clinical end points, thus offering the potential to accelerate the development of therapeutics.

Centralized patient registries consisting of well-annotated patient information, clinical data, and biological specimens will serve as an infrastructure needed for both discovery and validation of biomarkers. Mechanisms must be established for identifying and longitudinally following groups of patients prospectively. This approach is an essential starting point for linking biomarkers to disease outcome. Banking of DNA, tissues, and relevant body fluids should be part of the process, as should systematic collection of research-quality patient records. In addition, bioinformatic and biostatistical methods need to be established for deriving valid inferences about the biological mechanisms of this complex data set.

Biomarker research, in principle, is aimed at shifting medical care to a more preventive strategy and focusing the limited resources of our healthcare system on the individuals who are at greatest risk. In addition, this avenue of research offers the exciting possibility of tailoring an individual’s therapy to his/her genetic background (so-called personalized medicine).

- Who is likely to develop a myocardial infarction, CHF, stroke, or obesity (predisposition markers)?
- Who has asymptomatic CHF or subclinical atherosclerosis (screening markers)?
- Who has clinical CHF, ischemic heart disease, or cerebrovascular disease (diagnostic markers)?
- Who will have a mild versus severe course of their disease or, in the case of obesity, who will have vascular/morbid sequelae (prognostic markers)?
- In whom will a drug be most effective or most toxic (pharmacogenomic markers)?
- Who is likely to suffer short-term deterioration and require the most care/management (prognostic markers)?
- Who is responding favorably to a drug (disease monitoring/surrogate markers)?

**Biocomplexity in Biological Systems and the Need for Integrated Teams of Investigators**

Increasing our understanding of biological complexity is vital for taking molecular medicine to the patient and the community effectively. The advances in reductionist science in the past 20 years have led to remarkable insights into basic mechanisms. Progress in biocomplex behaviors, integrated physiology, and emergent properties, however, has not advanced at nearly the same rate. Hence, the clinical application of many important molecular breakthroughs still awaits further understanding.

For example, when the blood circulation is arrested, it is not merely a localized major myocardial infarction or stroke or both occurring simultaneously. There is a general insult to every organ, including the heart and the brain, together with complex adaptive responses at the cellular, tissue, organ, and whole-animal levels. The injured organs also have secondary effects on other organs. For example, perfusion of the gastrointestinal tract is impaired, and barriers are reduced, allowing bacterial toxins to enter the bloodstream. Excesses of lactic acid are generated within the liver and in skeletal muscle, altering acid-base conditions throughout the body. Injury not only to organs but also to blood vessels triggers the release of mediators that potentially injure otherwise unaffected tissues and cells. As such, resuscitation after cardiac arrest involves a complex biological system with many emergent properties that cannot be predicted from the study of individual components. Thus, novel strategies that analyze and integrate data at multiple levels, from the genome to the proteome and to the whole host, are needed. This complex
interaction of multiple responses is acknowledged to have important, but as yet poorly understood, actions that are reflected in cardiorespiratory and neurological malfunction and adverse outcomes.

To make significant progress, this complex interplay among the heart, brain, blood elements, vasculature, gastrointestinal tract, muscle, and other organs and tissues calls for a comprehensive complex systems approach by a multidisciplinary team of collaborative investigators who address multiorgan integrated pathophysiology of injury. Important contributions to this work are likely to come from experts in mathematics, biostatistics, computational biology, functional genomics, proteomics, computer science, and bioinformatics. Experts must, therefore, join together to explore complex biological systems in an effort to understand mechanisms and evolve more effective interventions. Central to this goal is the need for support of large teams that can target big questions in cardiovascular (patho)biology—such as resuscitation and reanimation of the globally arrested person—a primary mission of the American Heart Association (AHA).

**Imaging**

The role of imaging in defining normal and disease phenotypes has expanded considerably in the past two decades. Anatomic structures can now be imaged noninvasively with great resolution with the use of techniques such as MRI and ultrafast x-ray computed tomography. In addition and importantly, we are no longer limited by our ability to image only anatomic structures. Functional imaging has become a reality with time-dependent imaging of the active cardiovascular system (with the use of echocardiography and MRI), as has biochemical imaging with the use of positron emission tomography. Newer approaches to defining the biochemical, physiological, and anatomic images of normal and abnormal cardiovascular structures require further refinement. Advances in magnetic resonance angiography will provide fine structural detail of the coronary vascular anatomy as well as its functional effects on coronary blood flow. These advances can be coupled with nuclear magnetic resonance or electron paramagnetic resonance spectroscopy to identify important biomolecular pools in the myocardium that influence function, such as high-energy phosphates (nuclear magnetic resonance spectroscopy) and free radical intermediates that influence oxidative and nitrosative stress (electron paramagnetic resonance spectroscopy). Advanced approaches to imaging metabolic intermediates in functioning myocardium (such as free fatty acids [FFA]) also hold great promise, and involve labeling intermediates of interest or their metabolic precursors with nuclides that provide a positron image. These types of analysis integrate anatomy, physiology, and biochemistry over space and time and, as such, define a complex system, the integration and mathematical modeling of which hold the promise of providing useful insight into the molecular bases of CVDs and potential therapeutic interventions. Addressing this level of complexity will require the interaction of conventional imagers, biochemists, physiologists, signal processors, applied mathematicians, and physicists schooled in complexity in all of its domains.

**Importance**

This research is important because it will help shift health care from a model that emphasizes disease treatment with little understanding of, and thus regard for, individual variation, to an emphasis on prevention and individual variation. This shift will greatly decrease the burden of CVD.

**Suggested Funding Mechanisms**

Funding mechanisms that would further this area of research include:

- **Centers of Excellence in genomics, proteomics, biomarker research, and imaging**
- **Support for program development in computational biology, through Centers of Excellence, fellowships, and/or faculty development awards**
- **Development of Centers of Excellence in biomarker research that integrate systems biology, biotechnology, information technology, and clinical investigation**
- **Centers could encourage training and recruitment of future investigators.**
- **Centers provide integrated core technologies that may not be available to a single investigator attempting to acquire funding on his/her own.**
- ** Consortia involving government, industry, academic, and other nonprofit agencies (National Institutes of Health [NIH], AHA, Howard Hughes Medical Institute, pharmaceutical companies, etc)**
- **Support for investigator-initiated projects in translational research that may not enjoy sufficient funding from government or industry**
- **Investigator-initiated projects could be funded by the NIH or General Clinical Research Centers.**
- **The AHA/NIH could support biomarker and surrogate end-point research.**

**II. Vascular Topics in CVD and Stroke**

**Scope**

This topic includes developmental vascular biology, advanced atherosclerotic lesions, research on the vulnerable plaque and its fundamental biology, and understanding and preventing vascular cognitive impairment and its relationship to Alzheimer’s disease.

**Vascular Developmental Biology**

**Introduction**

In many ways, developmental biology is the basic science of CVD. Genes appearing first during lineage determination or morphogenesis in development are seen again as critical in diseases of the adult. Examples include integrins implicated in thrombosis, angiogenesis factors implicated in myocardial infarction, and growth factors and cytokines implicated in atherosclerosis and in cardiac remodeling in heart failure.

The value of these basic science studies perhaps should have been anticipated. Put another way, to understand diseases of the heart and blood vessels, one probably should begin by understanding the molecules that determine and define these tissues.
The past two decades have been very fruitful in cardiovascular development. We have identified genes that are critical to the formation of endothelium and myocardium. We have begun to identify genes important in morphogenesis of the myocardial chambers.

The obvious challenge is to prioritize these basic studies in ways that are most likely to contribute to discovery of mechanisms of clinical value. Predicting how such basic knowledge will enhance our understanding of clinical disease and its treatment is at best difficult. Major questions now include:

1. How do blood vessels acquire their muscular wall? Without smooth muscle, blood vessels are fragile. Understanding of aneurysm, diabetic retinopathy, fibrous cap rupture, and remodeling of collaterals in the heart may all depend on this simple question.

2. Do endothelial cells and smooth muscle cells have organ-specific lineages? It is likely that this information is central to understanding organ-specific vascular disease. For example, why does atherosclerosis affect only certain vessels?

3. What factors determine vascular branching? Development of a highly ordered branching pattern is essential during embryogenesis. Angiogenesis itself is a process of creating new branches, and specific branch patterns determine everything from vascular resistance to circulatory insufficiency.

4. What is the role of stem cells in forming the heart or vessels in the adult? Only recently has this critical area begun to blossom. Can we build vessels and hearts?

5. How do vessels remodel? The ability of arteries to control wall/lumen ratio must, for simple physical reasons, have arisen early in evolution and must reappear during development as the arterial tree is designed to distribute blood. The mechanism may underlie remodeling in the adult animal, a process that goes awry in atherosclerosis, hypertension, and restenosis.

6. How do organ systems develop system-specific vasculatures? It is very likely that specific vasculatures have very specific sets of genes that control cell function. These sets of genes might be called “molecular phenotypes” and are obvious targets for evaluation by new methods of microarray analysis of transcriptional and protein products. Knowledge of this organ-specific vascular biology may provide critical clues for development of targeted therapeutic agents.

Suggested Funding Mechanisms
The potential for new investigators in this field is enormous. Developmental biology itself is in a period of rapid growth, and many developmental biologists would be excited by any opportunity to take on the vasculature. Such opportunities are rare because the focus of funding in the basic sciences has been on more fundamental issues or on neurodevelopmental biology. At the same time, cardiovascular study sections often see developmental biology as too basic for their support. Funding mechanisms that would further this area of research include:

1. Starter grants. A modest targeting of funds for starter grants in developmental biology would encourage postdoctoral fellows to begin their careers. These might be modeled on the KO8 mechanism of the NIH and require interdisciplinary mentorship.

2. Resource grants. Cell type–specific promoter studies have now advanced to the point that opportunities exist to study the biology of several vessel components systematically. Funds to create resources, eg. Cre-targeted mice, would be widely useful in CVD. Similarly, funds could be provided for development of emu mouse strains and for databases of zebra fish and mouse mutations. Also, the AHA might fund systematic data acquisition that is difficult to fund by NIH mechanisms, such as development of expression data sets for different parts of the heart and blood vessels. Imaging methods are progressing rapidly but are not widely available. This is especially true of MRI resources for small animals and for the human carotid artery (below). Tissue availability is a special problem for any human tissues used, for example, in human microarray or genomic array analysis. Substitute primary resources should be considered, as well as any access to tissues from transplantation centers.

3. Focused grants. Several questions have already been listed above. Arguably, the most relevant may be the common theme of our need to understand how vessels develop into different organ-specific phenotypes. This question, in a larger sense, may even include issues such as how the branch patterns develop and how arteries develop medial layers appropriate to their functional demand.

Organ-Specific Vascular Biology

Introduction
Basic vascular biology has now provided us with the underpinnings needed to understand vascular diseases in specific organs. This critical information includes increasing understanding of how vessels develop and defining differences between the endothelial and smooth muscle cells making up arteries, veins, and capillaries at molecular and functional levels.

Important goals include characterization of physiological responses to acute stimuli and to major risk factors. The availability of comprehensive data on the genes of man and mouse, as well as newly developed technologies such as arrays, congenic animals, and proteomics, should move this effort forward.

Blood vessels have long been known to have many very organ-specific properties. The focus should be on building the basic knowledge of organ-specific vascular biology needed to proceed with more broadly based efforts with a disease focus.

The obvious challenge is to leverage current knowledge of vascular biology with the opportunities offered by new methods to accelerate research. Applications of arrays, congenics, transgenic mice, and proteomics, combined with our now finite knowledge of the entire set of transcribed genes, should greatly accelerate research in this area.
• One approach to building the necessary foundations from basic biology is from vascular development. Today, at a systemic level and in certain specific tissues, we know a great deal about the growth factors and receptors involved in the primary differentiation of endothelium, the role of endothelium in recruiting smooth muscle, and the role of smooth muscle in determining endothelial behavior. Organ-specific developmental biology has received relatively little attention.

• We also know enough about fruitful approaches from some vessels to suggest areas of focus in the adult vasculature. For example, it is very likely that specific vasculatures have very specific sets of genes that control cell function. These sets of genes might be called molecular phenotypes and are obvious targets for analysis by new methods of transcriptional and proteomic analysis. It would be of great value to know the extent of endothelial and smooth muscle phenotypic specificity in different vascular beds, as well as the modulation of these phenotypes in the face of risk factors known to affect vascular disease.

• Another fruitful tool comes from murine genetics. Genetically altered mice have altered functions in areas ranging from the formation of the layers of the vessel wall to inflammation and angiogenesis. These mice can be applied to critical questions in vascular biology by combining the mouse models with advanced physiological methods for determining murine vascular function. Processes of specific interest may include the relative roles of growth and proliferation versus cell death as determinants of vascular responses to several stimuli.

Suggested Funding Mechanisms
See above.

Advanced Atherosclerotic Lesions

Introduction
Advanced atherosclerotic lesions are the substrate for acute coronary syndromes. Acute coronary syndromes are enormously important, with tremendous cost in loss of lives and with enormous economic impact. There have been great advances in the past decade, with better understanding of basic mechanisms and great improvement in treatment, which has been documented with objective studies. This new knowledge may be further accelerated because of the recent development of murine models of advanced plaque with rupture and because of new, noninvasive MRI methods that allow us to image rupture in lesions of the human carotid artery.

Recent advances in the understanding of advanced atherosclerotic lesions include the understanding that maintenance of an intact fibrous cap depends on processes that have previously been seen as bad for plaque progression. These “good” processes include smooth muscle proliferation, resistance of these cells to cell death, and synthesis of connective tissue. Specific foci of current interest include the role of smooth muscle cell apoptosis and metalloproteinases in breakdown of the fibrous cap. These terminal events may depend on acute inflammatory changes in the plaque. Recently, studies in murine and human lesions have identified antibodies and T-cell responses directed toward oxidized LDL, reinforcing the view that lipoprotein oxidation products may be critical to lesion status and suggesting that evolution of the immune mechanisms may play an important role in the pathophysiology of early atherosclerotic lesions. The role of collagen and calcium in stabilization of lesions has received attention recently. Calcification of the arterial wall, modulation by sex hormones, and relationship to osteoporosis are of substantial interest.

Importance
Thrombosis of advanced lesions, often at the site of the rupture of a plaque, represents the major critical complication of active atherosclerotic lesions. The role of endothelium (and deeper tissues, in advanced lesions) in hemostatic regulation is a promising area of research. Better understanding of local and systemic prothrombotic and antithrombotic mechanisms and how these mechanisms change in the setting of advanced atherothrombotic disease are important areas of research, with great clinical implications.

An important distinction for future studies may be between two processes that may involve very different mechanisms:

1. Lesion initiation. Studies in genetically modified mice have given us a huge amount of knowledge of how lesions begin, but we do not know how well these mechanisms explain later events leading to advanced lesions.

2. Risk factor studies. Risk factor studies, largely in humans, usually give us data on clinical outcomes. We typically do not know whether these results represent effects on progression of the lesion itself or changes in systemic factors that predispose to clinical events.

Suggested Funding Mechanisms
See above.

Vascular Cognitive Impairment

Introduction
Cognitive competence is the single most important factor determining self-sufficiency, yet 8% of people over the age of 65 years have enough impairment of their mental function to interfere with daily activities. For each person who is clinically demented, there are two who have some cognitive loss.

Three decades ago, loss of mental capacities with increasing age was almost synonymous with hardening of the arteries, whereas Alzheimer’s disease was thought to be rare. Now the common perception is precisely the opposite. Both viewpoints are demonstrably wrong.

Several factors contribute to the misconception that vascular causes of cognitive impairment are uncommon:

1. Almost all the clinical pathological studies reporting the prevalence of different causes of dementia come from centers interested in Alzheimer’s disease, in which memory impairment is an early and omnipresent symptom. By contrast, there are no established centers interested in vascular cognitive impairment and, hence, there is a strong bias in favor of reporting Alzheimer’s cases in the published series.

2. Unlike Alzheimer’s disease, in which memory disorders prevail, cognitive impairment on a vascular basis
Impairment tends to affect parts of the brain that have to do with planning, thinking, mood, and personality, features seldom tested either in the clinic or in epidemiological studies.

(3) Current definitions of dementia are obsolete, only including patients whose brains are so devastated that they are extremely dysfunctional. The best chance to prevent cognitive impairment is by intervening in its early stages or before any change occurs.

Evidence is emerging that the risk factors that predispose to stroke also represent risk factors for cognitive impairment, including hypertension, hyperlipidemia, atrial fibrillation, and diabetes. Prospective studies are required to establish whether the control of these risk factors will result in the prevention or mitigation of cognitive impairment.

Approximately one quarter of stroke patients are clinically demented by three months. Half of them will have had some prior cognitive impairment and half not. It remains an open question as to how much of this impairment is due to the convergence of two pathological processes, ie, stroke and latent Alzheimer’s disease, and how much occurs through the triggering of additional processes, such as inflammation.

Most often, vascular cognitive impairment occurs in the context of small vessel disease, which is particularly prevalent among minorities. The biology of the cerebral circulation is virtually unknown, although it has been established for decades that it differs substantially from other vascular beds, particularly because the cerebral vasculature serves as a gateway and gatekeeper of what enters the brain through the special architecture of the cerebral endothelium making up the blood-brain barrier.

Recently, the long-held dogma that the brain was an immunologically inaccessible organ has been overturned, as has the belief that no new neurons arise after birth. Both these recent developments invite intensive research in the understanding of brain damage and repair.

Importance
We are our brains. Any injury to the ability to think, feel, and communicate is a strike at our individuality. With the aging population there will be increasing numbers of individuals at risk of cognitive impairment. Given the great ignorance on this topic, the fact that vascular factors and mechanisms may play an hitherto unrecognized role offers realistic expectations of great dividends in treatment and prevention.

Suggested Funding Mechanisms
Funding mechanisms that would further this area of research include:

- A conference needs to be called to discard the current dogma-derived definitions of dementia and to establish operational definitions to create the bases of a data-driven approach.
- New-initiative competitions for projects need to be developed.
- Comprehensive multidisciplinary centers for vascular cognitive impairment need to be established, broadly along the lines of the highly successful Alzheimer’s centers already in place. These should combine epidemiological, clinical, imaging, genetic, and pathological approaches, and will serve as the training ground for a new generation of investigators.

III. Cardiac Pathology

Scope
This topic includes valves, valvular development, adult valvular heart disease, and cell and molecular biology of the normal and diseased valve; ion channel physiology as it pertains to cardiac arrhythmias; and biology of the failing myocardium.

Valves

Introduction

The Cell and Molecular Biology of Valves and Gaps in Existing Knowledge

Early development. Very early events in valve development are reasonably well understood, in part because of inherent interest in the subject and in part because of the fact that the majority of congenital heart defects are due to abnormal development of the valves and membranous septa. Valves derive from endocardial cardiac cushions. Initially, the cushions appear as thickenings of the extracellular matrix, which resides between the myocardium and endocardium. There is an endothelial-to-mesenchymal cellular transformation, which ultimately results in cellularization of the cushions. The epithelial-to-mesenchymal transformation requires myocardium and occurs in three stages. There is an activation of the endothelial cell, mesenchymal cell formation, and mesenchymal cell invasion into the cushions. The cardiac jelly into which these cells migrate is produced primarily by the myocardium, and this region of the myocardium has been shown to express members of the transforming growth factor (TGF)-β and homeobox gene families. This transformation can be accomplished in vitro, and the requirement for myocardium can be abrogated by treatment with TGF-β3. Activated cells become migratory, and this behavior also requires TGF-β3. The molecular details of this transformation remain unidentified, but several markers of this process have been demonstrated. They are: α-smooth muscle actin, Mox-1 (homeobox transcription factor), GalTase, integrin α6 (both cell surface receptors), tenascin, and fibrillin 2 (secreted extracellular matrix proteins).

Adult valve cell biology. Despite the extensive investigation into the very early morphogenetic events that ultimately result in valve formation, relatively little is known about late events in valve formation and about the cell and molecular biology of the cellular components of the adult valve. Adult cardiac valves consist of several layers of distinct tissues that comprise four cell types: endocardial, cardiac muscle, smooth muscle, and cardiac valvular interstitial cells. The interstitial cells are the most prevalent cell type in the valve, and it is these cells that are of greatest interest. They are found in all layers of the valve and are thought to secrete the matrix of the valve in which they are embedded. Interstitial cells are dynamic and play several important roles in normal and pathological valves.

A number of tools can provide insight into the molecular and cellular phenotypes of these cells that contribute to their interesting biology. The following properties of valvular interstitial cells make them especially interesting to molecular and cell biologists:
contractility in response to angiotensin II, adrenaline, and endothelin;
• prominent microfilaments and intermediate filaments in which actin filament bundles traverse the length of the cell;
• prominent adhesion and gap junctions;
• serum-dependent proliferation;
• mitogenicity to platelet-derived growth factor and basic fibroblast growth factor; and
• expression of α-smooth muscle actin.

Because of these and other properties, interstitial cells have been described as having a phenotype that is intermediate between a smooth muscle cell and a fibroblast. However, interstitial cells are not really either type, and experiments need to be performed that will further characterize these cells and relate them to other myofibroblasts.

Importance
Thousands of people die each year as a result of heart valve dysfunction, including 32,000 children with congenital valve defects, of whom 60% die by the age of 15. Patients who require heart valve replacement are faced with limited options: replacing their valves with mechanical prosthetic devices or xenograft valves, both of which provide imperfect, temporary solutions. However, recent advances in tissue engineering suggest opportunities for engineering living valve tissue that would provide significant advantages compared with existing valve replacement therapies, especially for children. However, there is a great deal that remains unknown about the basic cell and molecular biology of valves. Further research into this area would be very useful in understanding valvular disease and in designing appropriate therapeutic measures.

Ion Channel Physiology/Arrhythmias

Introduction
This subject area deals with the origin of cardiac electrical signals and how such signals go awry in disease states. Disturbances of cardiac electrical signals are known as “arrhythmias” and constitute the single leading cause of sudden death in Western society.

Subcategories of Research
• Molecular basis of excitability: the study of the basic genes and proteins that produce the electrical signal, their structure-function relationships, their regulation by hormones, and their pharmacology
• Cellular electrophysiology: placing various proteins and their regulators into a physiologically relevant context at the level of individual cells or small groups of cells
• Integrative electrophysiology: investigation of the mechanisms of conduction and repolarization in networks of cells or in the intact heart
• Clinical research: involving human subjects with a view to defining propensity to arrhythmias, with the use of a variety of approaches (signal processing, genetics, etc)

Importance
Arrhythmias remain the single leading cause of sudden death. Despite major advances in vascular biology and genetics, clinical impact in the arrhythmia area has been largely limited to devices, such as pacemakers and automatic implantable cardioverter-defibrillators. With deeper biological insight, greater impact may be possible with other approaches, such as drug therapy or gene therapy.

If arrhythmias could be reduced by novel therapies, this would go a long way toward accomplishing the stated goals of reducing morbidity and mortality.

Suggested Funding Mechanisms
The AHA should consider establishing focused multidisciplinary centers in the area of arrhythmia research, similar to the AHA-Bugher Centers or Reynolds Foundation Centers.

IV. Obesity

Scope
This topic includes gene-gene and gene-environment interactions in causing obesity; genetic-molecular mechanisms that confer resistance to development of obesity; molecular mechanisms of obesity-induced target organ injury; and development of new animal models of obesity and type II diabetes mellitus.

Introduction
Few medical problems have generated as much public interest as obesity, the most prevalent nutritional disorder in the United States and in other industrialized countries. Obesity also appears to be a major cause of cardiovascular and renal disease. Cardiovascular morbidity and mortality rise substantially as body mass index (BMI) rises above 25 kg/m², and most health experts consider persons with BMIs above this level to be overweight. By this definition, >55% of adults in the United States are overweight. Similar findings have been reported in many other industrialized countries where surveys have been conducted.

The adult US population is, therefore, experiencing a mass exposure to obesity-related cardiovascular risk factors and will suffer the inevitable consequences in future years. Especially alarming are the rising rates of overweight and obesity in children and adolescents. Increasing rates of non-insulin-dependent (type II) diabetes mellitus in overweight adolescents clearly indicate that children are not protected from the metabolic effects of obesity.

Obesity is now recognized to initiate multiple disorders, including hypertension, diabetes mellitus, dyslipidemia, atherosclerosis, and chronic renal dysfunction, each of which increases the risk for CVD. Many of these disorders are interdependent. For example, abnormal renal function plays a central role in the pathogenesis of obesity-associated hypertension, and the increased blood pressure and metabolic abnormalities associated with obesity are important risk factors for end-stage renal disease (ESRD). The constellation of cardiovascular, endocrine, renal, and metabolic disorders is often referred to as syndrome X, the insulin-resistance syndrome, the deadly quartet, or the metabolic syndrome, but obesity appears to be its root cause.

Overweight or obese individuals experience increased morbidity and mortality from nearly all of the common CVDs, including stroke, coronary heart disease (CHD), CHF, cardiomyopathy, and possibly arrhythmias and sudden death. This is partly attributable to some of the known effects of
obesity, such as type II diabetes mellitus, insulin resistance, hypertension, dyslipidemias, and sleep apnea. The residual effects of obesity on cardiovascular risk, however, suggest a role for less well-characterized mediators. Because efforts toward primary treatment and prevention of obesity have had limited success, there will be increasing demands to treat obesity-related cardiovascular conditions in the future. In order to develop rational therapeutic approaches, it is necessary to understand the basic physiology of obesity-related CVD.

Summary of General Recommendations for Further Research

(1) Underlying mechanisms of altered energy balance regulation in obesity. The molecular basis of obesity is just beginning to be appreciated, and key neurohumoral mechanisms that regulate food intake, adaptive thermogenesis, fat absorption, and energy expenditure and utilization are poorly understood. Increased research emphasis on these areas may guide us to preventing the development of obesity and provide greater insight into the progression of the disease to target organ damage.

(2) Mechanisms of target organ injury in obesity. For example, what are the molecular and cellular mechanisms by which obesity alters renal, cardiac, and vascular gene expression to cause excessive production of extracellular matrix and renal and cardiovascular remodeling? What are the relative importance and interplay (synergy) of physical forces, metabolic factors, and local inflammatory and growth factors in causing these changes? What is the role of lipid infiltration in cardiovascular tissue as a novel pathophysiologic mechanism?

(3) Autonomic dysregulation in obesity. For example, what mechanisms link obesity with excess sympathetic nervous system activation? What patterns of gene expression confer resistance to obesity-induced sympathetic activation and hypertension in some animal models and in some humans?

(4) Cardiovascular consequences of obesity during childhood and adolescence.

(5) The mechanisms that link obesity with increased risk for renal disease.

(6) The mechanisms involved in the pathophysiology of obesity-associated cardiomyopathy.

(7) Adipocyte biology and the role of adipose tissue as a proinflammatory secretory organ. Adipose tissue affects multiple components of the cardiovascular system, such as blood pressure, lipid metabolism, vascular reactivity, myocardial metabolism, clotting and inflammatory pathways, and the cardiac conduction system.

(8) Development and phenotyping of new animal models of obesity. What animal models can be developed to better mimic human obesity and the cardiovascular, renal, and metabolic sequelae that accompany type II diabetes? What patterns of gene expression make some animals resistant to obesity, type II diabetes mellitus, and the development of cardiovascular and renal injury? There is also a need for existing and new animal models to be studied at various stages of the life cycle.

(9) Mechanistic studies of distinct human lean and obese phenotypes.

(10) New methodologies. DNA and protein microarray technology, targeted gene expression, and image analysis developments should be used to speed the search for markers that predict disease, track its development, or influence treatment outcomes.

Specific Recommendations for Further Research

A. Basic Mechanistic Studies

(1) Cardiovascular/hemodynamic regulation in obesity. Many hemodynamic abnormalities have been described in obesity, including increased cardiac output, alterations in vascular reactivity, hypertension, diastolic dysfunction, cardiomyopathy, and a prothrombotic state that may relate to an enhanced sensitivity of the microvasculature to inflammatory mediators. In part, the pathophysiology of hemodynamics in obesity may relate to disorders in the neural/sympathetic regulation of the circulation in the setting of an expanded adipose tissue mass. In addition, altered renal function and excess sodium retention play a major role in obesity-induced cardiovascular changes. However, further study is needed to determine the mechanisms that link obesity and impaired kidney function. The factors that allow risk stratification and those that predict pharmacologic responsiveness, i.e., to angiotensin-converting enzyme inhibitors and aldosterone antagonists, need to be understood.

(2) Role of autonomic dysregulation in obesity. Both the central and peripheral nervous systems appear to be intricately involved in the development of obesity, as well as its cardiovascular consequences. Energy intake and expenditure are dependent on afferent and efferent signals that are complex and integrated, yet poorly understood. Some of the cardiovascular complications of obesity, including hypertension, diastolic dysfunction, CHF, obstructive sleep apnea, and cardiac arrhythmias, involve neural/sympathetic nervous system activation. However, the mechanisms for this autonomic dysregulation are poorly understood. Important questions that remain include: (1) What are the mechanisms that link obesity with increased sympathetic activity? For example, what is the role of increased levels of fatty acids, leptin, and other neurochemical pathway mediators in regulating sympathetic activity as well as energy balance in obesity? (2) Why is there a differential increase in norepinephrine turnover in various organs (eg, kidney versus heart versus skeletal muscle) in humans? (3) Is there an alteration in chemoreceptor sensitivity that leads to obstructive sleep apnea in patients with obesity? (4) Is the neural control of energy intake versus expenditure altered in preobese, obese, and reduced obese subjects to lead to and/or preserve the obese state? Both basic and clinical studies are needed here.

(3) Role of inflammation in obesity. The inflammatory basis of atherosclerosis is now well accepted. Moreover, adipose tissue is now recognized as a source of inflammatory mediators with production of cytokines such as tumor necrosis factor-α, and interleukin-6, among others, as well as C-reactive protein. It appears likely but far from proven that the relationship between
obesity (insulin resistance) and atherosclerosis may depend, at least in part, on the increased production and release of these inflammatory mediators from adipose tissue. Other secretory products of adipose tissue, eg, angiotensin II, among others, and their relationship to the CVD of obesity also need to be investigated. The role of the renin/angiotensin/aldosterone system needs particular attention because of the high prevalence of hypertension in obesity without the expected increase in peripheral vascular resistance seen in settings in which angiotensin II is elevated. Moreover, the pathological effects of angiotensin II on cardiac hypertrophy and ultimately diastolic dysfunction and the cardiomyopathy of obesity need to be examined at the most basic of levels.

(4) Thrombosis in obesity. Evidence suggests that obesity increases the risk for thrombosis. Consequences include a higher incidence of CHD events and stroke. Additionally, obesity is associated with a higher rate of pulmonary thromboembolic disease, in part but not entirely related to venous stasis. The increased flux of FFA, among other mechanisms, may promote thrombosis by alterations in protein C, tissue factor, plasminogen activator inhibitor-1, and/or enhanced platelet aggregation. The role of adipose tissue in the production of inflammatory mediators may also be important here. This aspect of the relationship between obesity and CVD is in need of much additional study.

(5) Obesity, lipid metabolism, and atherosclerosis. The increased incidence of atherosclerosis in obesity is thought to be mediated by multiple risk factors, including hypertension, glucose intolerance, the prothrombotic and proinflammatory states, and dyslipidemia. However, long-term observational studies suggest an independent, or unknown, effect of obesity on atherogenesis. The most common lipid disturbance in obese patients is reduction in HDL cholesterol. The mechanism for this lipoprotein abnormality, in part, relates to the compositional changes in HDL that are linked to the hypertriglyceridemic state (replacement of cholesterol ester by triglycerides). However, reductions in HDL cholesterol are often seen in obese patients without increases in serum triglycerides. Alternative mechanisms include decreases in cholesteryl ester transfer protein, increases in hepatic lipase, and/or reduced activity of the reverse cholesterol transport protein, ABCA1. A more in-depth understanding of the origin of low levels of HDL in obesity is ripe for basic and translational study. When present, hypertriglyceridemia is also accompanied by increases in small, dense LDL, reportedly highly atherogenic. The relative importance of these lipid and lipoprotein disturbances to CHD in obesity needs to be tested prospectively in randomized trials.

(6) Role of obesity in causing ESRD. The two leading causes of ESRD are diabetes mellitus and hypertension, both of which are closely associated with obesity. In experimental animals, excess caloric intake causes renal disease, and caloric restriction protects against glomerular injury. However, the mechanisms that link obesity with renal disease are poorly understood and merit further study. There have been no long-term studies of the effects of food restriction or weight loss on renal function in humans. Although obesity-induced type II diabetes mellitus is recognized as a major cause of renal disease, the mechanisms that cause progressive nephron loss are unclear, and there are few clinical or experimental studies that have examined changes in glomerular structure and function in the early stages of obesity before major disturbances of glucose metabolism occur. Obesity causes microalbuminuria, or even proteinuria, as well as thickening of glomerular basement membranes and increased expression of growth/fibrosis-promoting factors in the kidney, even before there are major histological changes in the glomerulus or evidence of glomerulosclerosis. These early glomerular changes in obesity may be the precursors to development of more severe glomerulosclerosis and eventual loss of nephron function. However, the mediators of these early glomerular structural changes are unknown and warrant additional investigation, especially in light of the parallel epidemics that have occurred in the United States in the prevalence of obesity and ESRD.

(7) Role of adipose tissue as an endocrine organ in obesity. The most recognized role of adipose tissue is to store energy as lipids. Nevertheless, the turnover of adipose tissue triglyceride stores with the release of FFA never ceases. In obesity, basal rates of adipose tissue FFA turnover are increased and the inhibition of lipolysis by insulin is diminished, resulting in increases in FFA flux. This increase in FFA flux is felt to be the basis of many of the components of the insulin resistance syndrome, a major contributor to the increased CVD risk seen in obesity. Mechanisms to explain this pathophysiology, including the regional sources of fatty acids, ie, visceral versus subcutaneous, and direct versus indirect (through other risk factors), need clarification. In addition, the increased availability of FFA to organs may result in lipid accumulation and lipotoxicity. The mechanisms for the tissue-specific uptake of FFA, deposition into stored lipid pools, and the molecular and pathophysiological basis for organ-specific toxicity of lipid accumulation and its relationship to CVD development need elucidation.

The identification of mutations in the leptin gene as pathogenic in obesity development in the ob/ob mouse has resulted in numerous studies to examine the biology of leptin secretion from adipocytes and action in the central nervous system and in other organs. It remains controversial as to whether most, if not all, of the effects of leptin on energy balance (intake and expenditure) are due to the binding and action of leptin in hypothalamic nuclei. The effect of leptin in tissues other than the brain, eg, muscle, pancreatic islets, liver, and adipose tissue, needs further study. Presently, it is also unclear as to what controls leptin secretion from adipocytes and why leptin levels are elevated in obesity. This elevation of circulating leptin in obesity, despite the maintenance of obesity, provides the basis for leptin resistance. The molecular signaling that results from leptin binding and how these pathways are altered by leptin resistance also remain unclear. Also, questions of whether leptin resistance is selective (occurring in some but not all tissues) and the physiological implications of selective leptin resistance merit further study.

Many questions remain about the adipose tissue organ itself. The phylogeny of adipocyte development from
stem cell to preadipocyte to mature adipocyte, including the role of apoptosis in the maintenance of the adipocyte pool, needs attention. This analysis may help distinguish the molecular and cellular basis for adipose tissue hypertrophy versus hyperplasia, which undoubtedly relates to regional adipose tissue distribution and function. Basic mechanisms of adipocyte biology that relate to the hormonal/nutritional control of metabolic activity and release of FFA and to the secretion of hormones, cytokines, and other products may provide important insights into the mechanisms of CVD development in obesity.

(8) Role of race and sex in obesity. Differences in cardiovascular risk among the obese are racially dependent. Obese women clearly have less CHD than obese men, but the relative risk for coronary events may be greater at lower levels of increased BMI for women than men. Although, historically, the reduced rate of CHD was attributed to estrogens, recent trials of hormone replacement therapy in women with or without CHD have not supported this contention. Perhaps adipose tissue distribution and/or the role of androgens need more emphasis. Relevant animal models need to be developed here. Importantly, the number of studies carried out in racial minorities that examine the impact of hormone replacement therapy on the natural history of all forms of CVD is limited. Much needs to be accomplished in this area.

B. Development of New Models of Obesity

(1) Animal models of obesity. The animal models currently used to examine the impact of obesity on CVD have been limited. An important question to answer is whether large animals rather than rodents are needed to address adequately questions relevant to human obesity-related CVD. If rodent models are used, studies are needed to determine which of these models closely mimic what is found in larger animals or in humans. Monogenic, transgenic, and knock-out and knock-in rodents, in addition to diet-induced obese rodents, should be further studied, especially their cardiovascular phenotypes. An important question yet to be answered is whether weight reduction in obese animals increases life span, and, if so, whether or not the extended longevity is related to reductions in CVD development. Additionally, the impact of leanness, or long-term hypocaloric feeding, on the cardiovascular system may provide insights into mechanisms by which obesity increases the risk of disease. Finally, it will be important to determine if genetic engineering can be used to test hypotheses and establish molecular mechanisms responsible for obesity-induced CVD.

(2) Human studies. In parallel with detailed studies in animals, there is a need to investigate the pathogenesis, natural history, and therapeutics of obesity-related CVD in humans. Leptin resistance in humans is poorly characterized and needs a multi-system analysis. What are genetic markers for body fat distribution, response to nutrient choices and their metabolism, development of cardiovascular complications, and response to pharmaceuticals? How important is lipid infiltration in tissues in humans, and how can this be better assessed? What are the mechanisms for autonomic dysregulation seen in obese humans? Studies of the extremes in body weight, ie, BMI <18.5 and >40 kg/m², may be helpful in understanding genetic/environmental interaction in the regulation of body weight. Emphasis is clearly needed in the development and pathophysiology of obesity-related CVD comorbidities in children and adolescents. Clinical trials need to address the impact of sustained weight reduction on CVD and other disease-related morbidity and mortality in patients with obesity and without diabetes mellitus. Additional studies that examine the impact of therapeutic modification of CVD risk factors on hard outcomes, eg, stroke, myocardial infarction, and related deaths, are also important to consider.

C. New Technology and Research Resource Development for Obesity Studies

(1) Imaging methods. The sophisticated technology development of the past several decades should be made more accessible to obesity investigators, including those studying mechanisms of the cardiovascular complications of obesity. Ultrasound, computed tomography, and MRI availability will enhance the definition of body and organ composition and phenotype. The increased application of mass spectrometric analysis to the study of stable isotope turnover may identify pathophysiological mechanisms for tissue-specific fuel utilization and organ function. MRI spectroscopy will permit in vivo real-time assessments of molecular pathways of tissues that relate to substrate partitioning and organ biochemistry. Areas of new technology development may also facilitate the study of the cardiovascular complications of obesity. Included here are further developments in positron-emission tomography (PET) scanning and their application to the vasculature, skeletal muscle, myocardium, central nervous system, and adipose organ. A method for high-throughput macromolecular identification of tissues and cells would be useful, as would better methods to assess macronutrient intake, particularly for the various types of proteins, carbohydrates, and fatty acids in the diet, eg, saturated versus unsaturated, including monounsaturated, versus polyunsaturated versus very long-chain unsaturated fats (n-3 fatty acids).

(2) Physiological genomics and proteomics. DNA sequence information and gene identification for animals and humans will permit an understanding of the genomic basis for CVDs related to obesity and their therapeutic targeting. DNA and protein microarray comparisons between tissues from exaggerated body compositional phenotypes and/or animals and humans with or without obesity-related cardiovascular complications are also ripe for application. As new data emerge to better determine genes/proteins that define the risk for the cardiovascular complications of obesity, using microarray technology, the impact of over-expression and/or elimination of these genes and their impact on phenotypes should be tested in vivo. This would allow the relevance to the cardiovascular complications of obesity in humans to be examined. Gene expression and protein markers may be directly linked to the underlying biology that leads to obesity and its...
myocytes do not divide to a functionally significant degree in adults. Thus, loss of myocardium through aging and disease has been thought to be irreversible. More research needs to be done on this issue, however, especially in view of more recent work suggesting that primordial cardiomyocytes are located in the myocardium and, with the appropriate signals, can be induced to proliferate. A second way that the heart could beneficially respond to an insult is for the remaining cells to enlarge. It is well established that ventricular myocyte remodeling occurs after injury of the myocardium or with oxidative stress, resulting in ventricular hypertrophy. As discussed in another section above, however, once compensatory hypertrophy has occurred, unknown signals can trigger decompensation, leading to heart failure. Much research has focused on the signaling pathways that evoke decompensation, and interesting leads are being followed.

In addition to these lines of investigation, it seems very clear that two additional avenues should be vigorously pursued. The first category deals with cardiac myocyte cell death and division. Investigation into the prevention of apoptosis and the “coercion” of myocytes to reenter the cell cycle should be supported. This latter venue needs to be pursued with caution because uncontrolled cardiac myocyte proliferation could be worse than the original disease. The second category has to do with stem cells as potential therapeutics for CVD. Many attempts have been made to introduce cells of noncardiac origin into an injured heart. There has been some initial promise with cells of skeletal muscle cells, but to date there has been no evidence of real functional coupling. More recently, however, three groups have reported that bone marrow–derived stem cells are capable of differentiating into cells resembling cells of the cardiovascular system and that these cell implants result in improvement in contractile function. These results need to be replicated, and improvements can undoubtedly be made in the technical approaches.

**Neuronal Repair and Remodeling**

There are important fundamental neuronal topics, beyond the more general vascular topics, that are likely to be high yield in the future. These might include mechanisms of excitotoxicity, glutamate, hypothermia, Ca, free radicals, cell membrane integrity, heat shock proteins, apoptosis, preconditioning, hibernation, signaling, and nitric oxide.

**Cellular Pathology: Mechanisms of Ischemia, Reperfusion, and Adaptation**

Advancing the mission of the AHA depends on deepening our understanding of the basic science surrounding cellular processes that occur during conditions of ischemia, reperfusion, and adaptation. Because these conditions are central to clinical conditions like myocardial infarction, stroke, and cardiac arrest, the knowledge gained in one area often has broad implications across disciplines and medical specialties. New emerging fundamental scientific concepts that have particular importance for the treatment of myocardial infarction, stroke, and cardiac arrest would be particularly important to target for special emphasis because small investments now would be expected to produce large yields in the future. Such topics include:

**Suggested Funding Mechanisms**

The NIH has also recognized obesity as a major health problem in the United States and is devoting considerable resources to understanding the pathophysiology of obesity-related disorders, including cardiovascular and renal diseases. Therefore, the AHA should seek to partner with the NIH and other organizations to fill gaps where funding is likely to yield the greatest dividends. One gap that has traditionally been filled by AHA is funding of beginning investigators. The field of obesity research, like most areas of cardiovascular research, suffers from a lack of attention by many bright young investigators who are attracted to other fields. Moreover, important for advancing research on obesity-associated CVD are ways to encourage beginning investigators who use a multidisciplinary approach, bridging fields such as genomics, molecular biology, cardiovascular physiology, endocrinology and metabolism, and clinical physiology.

The Postdoctoral Fellowship Grant, Scientist Development Grant, and Established Investigator Award are all excellent mechanisms for encouraging young investigators to begin research in the area of obesity-associated CVD. It may be useful to issue a special call for proposals in obesity-associated CVD using these three mechanisms for funding. It may also be helpful to work with the NIH to encourage funding that will make new technologies and new animal models, as well as funds for clinical trials, available to obesity researchers. In addition, it may also be possible to partner with the NIH and the American Diabetes Association to sponsor jointly funded Center(s) of Excellence that would house the (expensive) technologies and (rare) biological/clinical samples that would be needed to yield rapid advances in the field of obesity-associated CVD.

**V. Cardiovascular and Neuronal Repair and Remodeling and Cellular Pathology**

**Scope**

This topic includes stem cell research, repair of damaged myocardium, organogenesis, and the biopathology of ischemia and reperfusion and its adaptive mechanisms.

**Cardiovascular Repair and Remodeling**

For many patients, a severe myocardial infarction means death or the need for a transplant. Heart failure represents the single largest healthcare cost in the United States. It is clear that if it were possible to supply healthy myocardial cells or blood vessels to patients before end-stage heart failure has developed, many lives and many dollars would be saved. One solution would be to stimulate the remaining myocardial cells to divide. Although this approach is not without some controversy, it has generally been accepted that cardiac myocytes do not divide to a functionally significant degree in...
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(1) Understanding cellular death. Despite much research, we still do not understand when an injured cell transitions beyond the point of no return with regard to cell survival. The rationale of many current therapies, whether involving the brain or the heart, is to protect injured cells from death. Therefore, protecting vulnerable or injured cells on the verge of death is a promising goal of resuscitation therapy. Recent data suggest that cells exposed to ischemia and reperfusion could be saved long after the interval that we currently regard as beyond the threshold of reversible cell death. Processes such as apoptosis, cellular signaling, cellular ion channel regulation, membrane integrity, and inflammatory cascades all appear to offer extremely important fundamental targets for clinical advances.

(2) Controlled reperfusion. Much data suggest some adverse cellular events persist and are accelerated by reperfusion after ischemia. If true, our current emphasis on immediate reperfusion of the heart after myocardial infarction, the brain after stroke, and the entire body after cardiac arrest may be significantly improved if better and more effective reperfusion strategies that do not promote the deleterious effects of reperfusion, especially those related to the toxic effects of oxidative stress, can be developed. Cellular insights into reperfusion injury and preventing reperfusion injury are likely to have nearly immediate clinical impact across a broad range of diseases.

(3) Adaptation physiology. Natural defenses against ischemia are poorly understood and are increasingly being recognized as important areas for future clinical therapies. For example, during hibernation the heart rate decreases to as little as 5% of normal, a level that would be lethal during active states. Remarkably, no damage occurs during this prolonged “ischemic” state, nor does the cardiac rhythm deteriorate into ventricular fibrillation. After arousal and restoration of normal blood flow, the reperfused organs and tissue show no evidence of ischemic injury. Potent hibernation-signaling molecules, membrane receptors, and intracellular cascades have recently been described, but there is very little molecular mechanistic insight into these natural protective mechanisms. The possibility exists that therapeutically induced hibernation or hypometabolic states may be an ideal option to obviate both ischemic and reperfusion injuries. The development of a transient therapeutic hibernation or stasis state wherein injury to human organs would be prevented during ischemia may have a profound clinical impact after major injuries and critical reductions in vital organ perfusion. The fundamental science of hibernation, hyperthermia, preconditioning, natural adaptation, and hypometabolic states deserves special emphasis in the battle against myocardial infarction, stroke, and cardiac arrest.

Importance
Advancing the mission of the AHA depends on deepening our understanding of the basic science surrounding cellular processes that occur during conditions of repair, organogenesis, ischemia, reperfusion, and adaptation. Because these conditions are central to clinical conditions like myocardial infarction, stroke, and cardiac arrest, the knowledge gained in one area often has broad implications across disciplines and medical specialties. New emerging fundamental scientific concepts that have particular importance for the treatment of myocardial infarction, stroke, and cardiac arrest would be particularly important to target for special emphasis because small investments now would be expected to have large yields in the future.

Suggested Funding Mechanisms
See above.

VI. Bidirectional Translational Research
Scope
This topic includes application of proven techniques; flow of information between basic and clinical research; translating laboratory findings to the bedside; and networking among laboratory, clinical, and social scientists.

Introduction
Clinically inspired laboratory research has been long recognized as a fruitful investigative effort. Less recognized is the importance of applying basic observations to the clinical arena. Optimal investigative success requires that the flow of information between basic and clinical research communities be bidirectional.

In the era of the genome, we now recognize anew that studying the phenotype is as important as knowing the genotype. For this reason, the need for clinician scientists has grown even more acute.

A further difficulty in translating laboratory findings to the bedside and beyond relates to the stepwise, discontinuous nature of the path from discovery to application. Typically an investigator will make a discovery that is of interest to a pharmaceutical company. The pharmaceutical company will organize a preclinical team to test the drug in animals. Later another team will do the safety testing in humans, and yet another team will try to find clinicians who actually evaluate the drug. There is little communication across this spectrum and long delays between steps. All participants need to be aware simultaneously of each others’ needs and the resources required to accelerate the process.

In applying what is already known, research has to go beyond biological investigations and needs to involve the social sciences, as well. This point is best illustrated by the following examples showing that the results of sound clinical investigation are not readily applied to clinical care.

Remarkably, only 30% of hypertensive patients are adequately controlled, only about 20% of patients with atrial fibrillation who should be anticoagulated are receiving warfarin, and fewer than 40% of the individuals placed on statin agents for hyperlipidemia remain on medications long enough to benefit from them.

The fact that these phenomena have been observed in different countries and in different healthcare systems suggests that the problem goes beyond accessibility and economics. Almost certainly different risk perceptions and attitudes to their management play a role.

Importance
The rapid pace of genomic and proteomic developments calls for matching efforts to apply and evaluate these discoveries in
order to shorten the time between discovery and application. The translational investigator will need to have access to and understand these exciting measures of disease complexity as they apply to the clinical arena.

Because only \( \sim 20\% \) of individuals with major vascular risk factors have them controlled, an increase to even 30\% would have a major impact in fulfilling the AHA’s goal of reducing heart disease and stroke by 25\% by the year 2010.

**Suggested Funding Mechanisms**

The recruitment, nurturing, and support of clinician scientists needs to be emphasized. A closely linked network needs to be developed among laboratory, clinical, and social scientists working in the area of heart disease and stroke. A recently established Canadian Stroke Network is an example of an attempt to do so.

High priority needs to be given to projects that address the huge gap that exists between what is known in basic cardiovascular biology and what is being applied to the clinical arena. The need to expand our knowledge of the molecular basis of disease remains important. The need to understand how to apply what we learn is urgent.

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