The ongoing obesity epidemic and its impending cardiovascular consequences represent a serious public health problem with worrisome implications for medical treatment. The urgency of providing new research directions recently led the National Heart, Lung, and Blood Institute (NHLBI) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to convene a Working Group on the Pathophysiology of Obesity-Associated Cardiovascular Disease. Gathered at this meeting were researchers with substantial experience and expertise in either obesity-related sciences, including epidemiology, endocrinology, and metabolism, or cardiovascular sciences, including cardiology, neurobiology, hematology, renal function, and pediatrics. This report is the culmination of the blending of ideas during the 2-day meeting. The resulting research recommendations include the development of new models and synergistic approaches to basic studies of obesity-associated cardiovascular diseases.

Background
The adult US population, whose combined prevalence of overweight and obesity now exceeds 60%,1 is experiencing an unprecedented exposure to obesity-related cardiovascular risk factors and is expected to suffer the adverse clinical consequences in years to come. Also alarming are the ever-rising rates of overweight and obese children and adolescents, which have tripled over the last 30 years.2 Increased rates of co-morbidities such as dyslipidemia, hypertension, type 2 diabetes, and hepatic damage in overweight adolescents indicate that the young are not protected from the metabolic perturbations that accompany excess adipose tissue stores.3-5 We do not know what the consequences might be for the developing cardiovascular system if obesity is present during late stages of growth and maturation.

Overweight or obese individuals experience greatly elevated morbidity and mortality from nearly all of the common cardiovascular diseases (stroke, coronary heart disease, congestive heart failure, cardiomyopathy, and possibly arrhythmia/sudden death).6,7 Because primary treatment and prevention of obesity often fail or are only partially successful, it is anticipated that the future will bring ever-increasing demands to treat the cardiovascular conditions attributable to obesity. Thus, to develop rational therapeutic approaches, we need to understand the basic biology of obesity-related cardiovascular diseases and disorders.

Discussion Highlights
The Working Group’s multi-disciplinary panel of clinical and basic scientists was charged with evaluating the current state of the science on basic mechanisms of obesity-associated cardiovascular disease and identifying research opportunities with a focus on potential therapeutic applications. The group was encouraged to translate problems identified through population and clinical research into clear priorities for mechanistic research.

Mechanistic Studies in Animals and Humans
Adipose Tissue as a Metabolically Active Endocrine Organ
The predominant role of adipose tissue is the storage of lipid energy. Nevertheless, the turnover of adipose tissue triglyceride stores, with the release of free fatty acids (FFA), never ceases. In obesity, basal rates of adipose tissue FFA turnover are increased, and the inhibition of lipolysis by insulin is diminished.8,9 This results in higher FFA flux (ie, release of FFA into the peripheral circulation and increased availability of FFA to various tissues), which is thought to underlie many components of the insulin resistance syndrome, a major contributor to the increased cardiovascular disease risk associated with obesity.10 Related mechanisms needing further clarification include the relative roles and effects of different regional sources of fatty acids (eg, visceral and subcutaneous depots), and whether FFA flux plays a direct role or instead exerts its influence through other risk factors.

Insights into the biology of the secretion of the hormone leptin from adipocytes and its action in the central nervous system are emerging, but more research is necessary to delineate the role of leptin in the regulation of food intake and energy expenditure.11-13 In the central nervous system, the actions of leptin are mediated by specific receptors and second messenger systems that affect the expression of genes involved in the regulation of energy expenditure, appetite, and body weight.11,14,15

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A list of the Working Group members can be found in the Appendix.

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system and organs have been gained from studies identifying leptin gene mutations as etiologic to obesity development in the ob/ob mouse.13 It is still unclear whether the effects of leptin on energy balance (ie, intake and expenditure) are due wholly to its action in central hypothalamic nuclei, or whether other mechanisms are involved. It also is unclear how leptin secretion from adipocytes is controlled under various conditions of energy balance. Much less extensively studied, and even less understood, are the effects of leptin on sympathetic nervous activity and cardiovascular functions such as blood pressure control.12 Likewise, intriguing connections between leptin physiology and sleep physiology are suggested by observations that repeated interruptions in breathing due to sleep apnea may lead to altered plasma leptin levels.15 The effects of this hormone in tissues other than the brain (eg, muscle, pancreatic islets, liver, and adipose tissue) also need further study.

The entire concept of “leptin resistance,” suggested by observations that circulating leptin levels are elevated in obesity despite the maintenance of large adipose tissue stores, needs further attention.19a These issues requiring exploration include the molecular signaling that results from leptin binding and the ways in which these pathways are altered by leptin resistance. Also not resolved is whether leptin resistance is selective, occurring in some but not all tissues. If this is the case, the physiological implications of selective leptin resistance merit investigation.

Angiotensinogen and angiotensin II derived from adipocytes14 deserve particular attention because the renin–angiotensin–aldosterone system plays a major role in the pathophysiology of hypertension and related sequelae, such as cardiac hypertrophy, diastolic dysfunction, and heart failure.

Many questions remain about the development of the adipose tissue organ and the biology of adipocytes in different anatomic locations. The phylogeny of adipocyte development from stem cell to preadipocyte to mature adipocyte, including the role of apoptosis in maintenance of the adipocyte pool, needs elucidation. This may help distinguish the molecular and cellular basis for adipose tissue hypertrophy and hyperplasia, which are related to regional adipose tissue distribution and function.

**Lipotoxicity in Muscle and Other Non-Adipose Tissues**

The deleterious effects of increased infiltration of FFA into various organs and tissues have been collectively termed “lipotoxicity.”15 The potential importance of this concept was recently highlighted by animal studies that suggested that excess fatty acids help destroy cardiac myocytes by increasing triglyceride content and the rate of apoptosis.16 Lipid accumulation in the pancreas and the liver also conveys serious functional risks.17,18 In the heart, this accumulation can be seen in the myocardium and the conduction system.2,19

Still unclear are the mechanisms for the tissue-specific uptake of FFA and their deposition into stored lipid pools, the molecular and pathophysiological basis for the organ-specific toxicity of lipid accumulation, and the relationship of such lipid deposition to development of various cardiovascular diseases. We also need to understand the ways in which the functional effects of lipotoxicity in the heart and vascular tissues are distinct from those of glucotoxicity, and the mechanisms that underlie the reversal of lipotoxicity by treatment with drugs such as thiazolidinediones. New methods are needed that will allow lipotoxicity to be measured noninvasively and in vivo. In addition, more research is needed on the clinical characteristics of human lipotoxic heart disease (ie, ventricular function, exercise tolerance, propensity for arrhythmias, co-morbidities, and natural history).

**Inflammation and Thrombosis**

It is now well accepted that inflammation is a major component of atherosclerosis. Moreover, adipose tissue is now recognized as a source of inflammatory mediators, with production of cytokines such as tumor necrosis factor (TNF)-α and interleukin-6.20 It appears likely, but is 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) and their relationship to inflammation in obesity also need to be investigated.

Obesity is a prothrombotic state, possibly as a secondary effect of insulin resistance; this is a contributing factor to elevated risk of coronary heart disease and stroke.21 Pulmonary thromboembolic disease also occurs at higher rates in the obese, in part but perhaps not entirely because of venous stasis.22 For example, the increased flux of FFA that occurs in obesity likely promotes thrombosis through alterations in protein C, tissue factor Plasminogen Activator Inhibitor-1, and enhanced platelet aggregation. Enhanced secretion of inflammatory mediators from an expanded adipose tissue compartment may also activate thrombotic mechanisms in obesity.

One such mediator is leptin, which has recently been reported to increase platelet aggregation and arterial thrombosis.23 This aspect of the relationship between obesity and cardiovascular disease is in need of additional study.

**Flow and Neural-Sympathetic Regulation**

Many hemodynamic abnormalities have been described in obesity, including elevated cardiac output, altered vascular reactivity, hypertension, diastolic dysfunction, and cardiomyopathy.6,7 It is not clear whether these abnormalities stem from direct effects of adipose tissue excess, or whether secondary or indirect mechanisms also play an important role. For example, the hemodynamic pathophysiology in obesity apparently derives in part from maladaptive neural regulation of the circulation in the setting of an expanded adipose tissue mass. Also, the obstructive sleep apnea that frequently occurs in obesity produces abrupt increases in sympathetic activity, with altered vascular responses that include increased blood pressure, all of which persist even through the waking hours. Thus, obstructive sleep apnea may be an important secondary cause of hypertension.24 In addition, altered renal function and excess sodium retention play a major role in obesity-induced cardiovascular changes.25 Further study is needed, however, to determine the mechanisms that link obesity and impaired kidney function. The factors that allow risk stratification and those that predict pharmacological responsive-
ness to drugs such as angiotensin converting enzyme inhibitors and aldosterone antagonists also need to be understood.

Both the central and peripheral nervous systems appear to be intricately involved in the development of obesity and the resulting cardiovascular complications. Energy balance, including energy intake and expenditure, is dependent on complex, integrated afferent and efferent signals that are as yet poorly understood. Sympathetic activation is involved in many of the cardiovascular complications of obesity, including hypertension, diastolic dysfunction, congestive heart failure, obstructive sleep apnea, and cardiac arrhythmias. The mechanisms for this dysregulation are not well understood at present. Clinical and basic research are needed to resolve a number of research issues, including the role of increased levels of fatty acids, leptin and other neurochemical pathways in regulating sympathetic activity as well as energy balance; the differential increase in norepinephrine turnover in various organs (eg, kidney, heart, and skeletal muscle) in humans; the possible alterations in chemoreceptor sensitivity that lead to obstructive sleep apoB in obese patients; and how altered neural control of energy intake and expenditure leads to or preserves the obese state.28,29

Lipid Metabolism/Atherosclerosis

The relative importance of various lipid and lipoprotein disturbances to coronary heart disease in obesity needs to be clarified. The most common lipid disturbance in obese patients is the reduction of plasma HDL cholesterol concentration.6 This abnormality is derived in part from compositional changes in HDL that reflect the hypertriglyceridemic state (ie, replacement of cholesteryl ester by triglycerides); however, reduced HDL cholesterol levels are often seen in obese patients without increases in serum triglycerides. When present, hypertriglyceridemia is also accompanied by increases in small, dense LDLs, which are reportedly more atherogenic. Alternative mechanisms include increases in cholesteryl ester transfer protein, increases in hepatic lipase, or decreases in the activity or levels of ABCA1 (the defective molecule in Tangier Disease that mediates efflux of cholesterol from cells to apolipoprotein apoA-I, giving rise to HDL particles).30,31 A more in-depth understanding of the origin of low levels of HDL in obesity is ripe for basic and translational study.

Increased atherosclerosis in obesity may also be related to increased levels of apoB lipoproteins. Increased secretion of VLDL-apoB has been linked to increased free fatty acid flux, causing decreased intracellular degradation and hence increased secretion.32 A few studies have suggested that insulin resistance at the level of the hepatocyte can also lead to increased apoB secretion. The mechanisms linking free fatty acid flux or insulin resistance (at the level of the hepatocytes) to increased apoB secretion are incompletely understood and deserve further study. Insulin resistance, apparently a primary mechanism of type 2 diabetes, has received little attention as a mechanism of increased atherosclerosis.

Changes related to hyperglycemia or defective insulin signaling may also be involved in the increased atherosclerosis risk associated with obesity, but the nature of this relationship is not obvious. For example, in human diabetes, blood glucose control is not well correlated with atherosclerotic cardiovascular disease, in contrast to the beneficial effects on microvascular disease.33 Also, in murine models, hyperglycemia has not been clearly shown to increase atherosclerosis independent of plasma lipid changes.34 Furthermore, the possibility that obesity-related defects in insulin signaling affect the behavior of cells in the atherosclerosis susceptible regions of arteries warrants investigation. A very small number of studies suggest there may be pro-atherogenic abnormalities of the endothelial cells or macrophages that could be related to defects in insulin signaling.32,35

Kidney Disease

The two leading causes of end-stage renal disease (ESRD) are diabetes and hypertension, both of which are closely associated with obesity. In experimental animals, caloric excess causes renal disease as well as obesity, whereas caloric restriction protects against glomerular injury.36 The mechanisms that link obesity with renal disease, however, are poorly understood. There have been no long-term studies of the effects of food restriction or weight loss on renal function in humans. The mechanisms that cause progressive nephron loss are unclear, and few clinical or experimental studies 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 kidneys before there are major histological changes in the glomerulus or evidence of glomerulosclerosis.37,38 These early glomerular changes in obesity may not only be the precursors to development of more severe glomerulosclerosis and eventual loss of nephron function, but may also be markers for more generalized vascular disease development. The mediators of these early glomerular structural changes are unknown and warrant additional investigation, especially in light of the ongoing parallel “epidemics” of obesity and ESRD in the United States.

Hyperinsulinemia

The mechanism by which the hyperinsulinemia of obesity contributes to cardiovascular disease is not well understood, and may not be simply explained by an association between insulin resistance and coexisting factors such as dyslipidemia. For example, there are recent data that indicate the metabolic effects of insulin action are biochemically distinct from the mitogenic effects of the hormone.39 Moreover, some models demonstrate that when insulin resistance is present in the metabolic pathways of insulin action, the mitogenic pathways are not only maintained, but in fact show compensatory increases.40 This could promote atherogenic events in the arterial wall. Innovative approaches drawing from both cardiovascular biology and obesity science are needed to understand the molecular mechanisms by which insulin resistance and/or hyperinsulinemia may cause obesity-associated cardiovascular disease.

Gender/Hormones/Race

The risk of developing heart disease increases with increasing weight,41 although the nature of this relationship may vary
considerably with gender and the specific type of heart disease. For example, overweight and obese men and women have similarly elevated risks for congestive heart failure.\textsuperscript{42} There is debate, however, about whether overweight women and men experience similar elevations of coronary heart disease risk.\textsuperscript{41,43} Furthermore, with regard to stroke, several large cohort studies have found that the overall risk increases with increasing weight.\textsuperscript{41,44} However, when gender and racial subgroups are studied separately, this positive association between adiposity and stroke risk is not consistently replicated.\textsuperscript{41,44,45}

These varied findings suggest that complex underlying phenomena may mediate the relationship between excess adipose tissue and elevated cardiovascular disease risk. For example, gender- and race-related differences in adipose tissue distribution should be explored. Furthermore, the biology of obesity-related hypertension may vary among ethnic groups. Also, the differences in hormone metabolism and hormonal effects on cardiovascular biology, including the role of androgens, estrogens, and hormone-replacement therapies, need further study. For example, although the reduced rate of coronary heart disease in women was historically attributed to the lipid-lowering effects of estrogens, recent primary and secondary prevention trials of hormone replacement therapy in women with or without coronary heart disease have not supported this contention.\textsuperscript{46-47}

**Additional Clinical Studies**

Mechanistic studies in humans are needed beyond the basic research mentioned above. Approaches that combine genetic and epidemiological methodologies would also be helpful. As in animal models, the characterization of different human phenotypes of obesity-associated disorders like hypertension, salt sensitivity, increased sympathetic activity, and their genetic factors, may help identify those individuals with higher cardiovascular risks.

Important areas of emphasis not already mentioned and related to the biological basis of development of cardiovascular complications of obesity in humans include genetic markers of body fat distribution, mechanisms of maladaptive responses to nutrient intakes and dietary and activity patterns, genetic prediction of the response to pharmaceuticals (pharmacogenomics), and noninvasive methods of assessing lipid infiltration into tissues and organs. Studies of both high and low extremes in body weight (ie, body mass index [BMI] <18.5 or >40 kg/m\textsuperscript{2}), including distinct lean and thin (ie, low weight but not necessarily low body fat) subjects, may be helpful. In addition, well-designed studies are clearly needed to address the development and pathophysiology of obesity-related cardiovascular disease and associated co-morbidities in children and adolescents.

**Technology and Research Resources**

**New Animal Models**

Suitable animal models for examining the impact of obesity on cardiovascular disease are limited at present. An important issue is whether large animals (eg, non-human primates, swine) are needed rather than rodents. If rodent models are used, preliminary studies are needed to determine which, if any, of these models substantiate what is found in larger animals or in humans. In some circumstances, novel use can be made of currently available genetic and experimental models to examine the cardiovascular and respiratory pathophysiology of obesity. In addition to diet-induced and genetically-based animal models of obesity, distinct lean and thin models need consideration. Furthermore, studies evaluating the impact of leanness or long-term hypocaloric feeding on the cardiovascular system may be useful. Still unanswered is whether weight reduction in obese animals improves survival, and if so, whether or not the extended longevity produces reductions in cardiovascular disease development; leanness may not always confer health. Also needed are models of immature and growing animals to be studied at various stages of the life cycle. The earlier onset of obesity and the presence of risk factors for cardiovascular disease during late childhood and adolescence demand better studies of gestational and early life experiences that impact obese youths.

**Technology Acquisition and Development**

The sophisticated technology developed during the last several decades needs to be made more accessible to investigators studying the mechanisms of cardiovascular complications of obesity. For example, ultrasound, CT, and MRI techniques can enhance the definition of body and organ composition and phenotype. Also, mass spectrometric analysis of stable isotope turnover may be useful in identifying mechanisms for tissue-specific fuel use. More realistically, MRI spectroscopy will permit in vivo real time assessments of molecular pathways that relate to substrate partitioning and organ biochemistry. DNA sequence information and new and existing gene identification in animals and humans will increasingly permit an understanding of the genomic basis for the cardiovascular diseases related to obesity and their therapeutic targeting. DNA and protein microarray comparisons between tissues from exaggerated body compositional phenotypes of animals and humans are also set for study. Methods 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. Computing and statistical efforts are key but often insufficiently developed components of successful investigation with these methodologies.

**Shared Resources**

Shared resources would be effective as incentives to explore new research areas and would also save duplicated effort and expense. Examples include repositories for highly inbred or congenic, transgenic, or knockout animals; immortalized cells or cell lines; tissue banks; and DNA/protein databases. Expensive and sophisticated instrumentation for phenotyping (eg, whole room calorimeters for the assessment of animal and human energy balance) could be shared within geographic regions. Website development of shared data sets, including microarray expression data, could also save effort and expense. Finally, coordinated approaches among funding agencies, regulatory agencies, and industry should be encour-
Anderson to enhance access to novel products (e.g., leptin) for animal and human testing.

Summary of Research Recommendations

Areas that were identified as particularly high priorities for further research in humans and animals are:

Adipose tissue as a pro-inflammatory endocrine organ affecting multiple functional and anatomic components of the cardiovascular system at every level of biological organization.

Lipid infiltration as a novel pathophysiological mechanism in causing target organ injury, including cardiomyopathy.

The mechanisms of central nervous system adaptation and autonomic activation, and their impact on cardiovascular, respiratory, and sleep regulation in obesity.

Pathophysiological mechanisms by which obesity increases the risk for hypertension and renal disease.

Cardiovascular and related adaptations to obesity during childhood and adolescence, and the role of gestational and early life experiences that impact obese youth.

The mechanisms by which the hyperinsulinemia and other endocrine dysregulation syndromes of obesity contribute to cardiovascular disease.

Areas that were identified as particularly high priorities for technology development and research resources are:

Improved animal models and novel use of existing genetic and experimental models to examine the cardiovascular and respiratory pathophysiology of obesity.

Accessibility to sophisticated technology such as ultrasound, CT, MRI, and DNA and protein microarray.

Shared resources such as animal repositories, tissue banks, cell lines, and website development of shared databases.

Novel multidisciplinary approaches that draw on combined expertise in both obesity biology and the cardiovascular sciences have the potential to enhance the back-and-forth translation of clinical and epidemiological observations to basic research. The knowledge gained from such mechanistic studies is needed for diagnosing, preventing, and treating the cardiovascular consequences of obesity.

Appendix

The authors thank the members of the Working Group, who all contributed to the concepts explored in this paper. The following is a roster of participants:

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