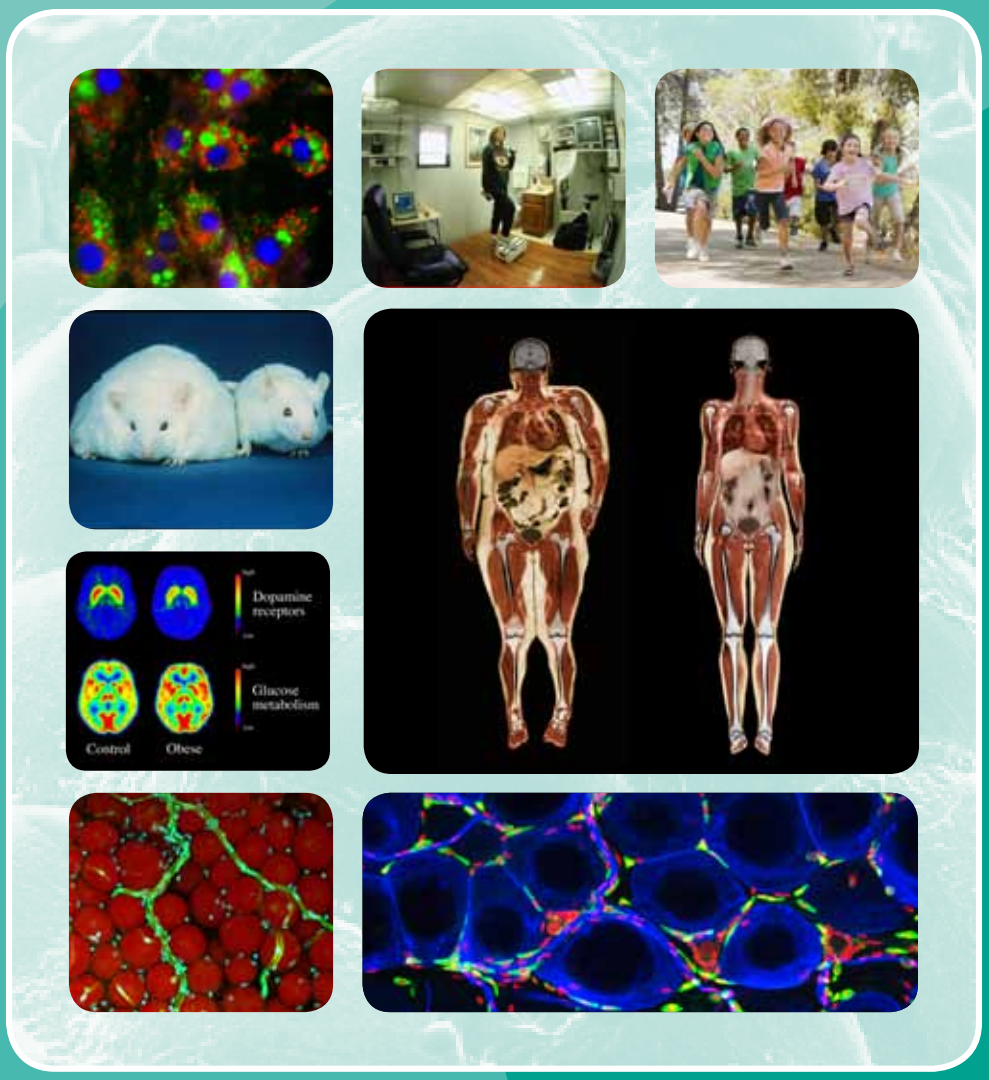

Research on obesity and its relationship to diabetes spans fundamental research on fat cells and the brain to clinical research strategies to prevent or treat this condition *(Image credits and information: Top row, left: Microscope image of brown fat (e-BAT, or engineered Brown Adipose Tissue) created by adding a key control switch to skin cells of mice. Presence of green-stained objects (droplets of oil stored in the cell) confirms the skin cells have been converted to brown fat-producing cells. Blue objects are cell nuclei. Image courtesy of Dr. Shingo Kajimura, Dana-Farber Cancer Institute. Top row, middle: Image courtesy of Dr. Kong Chen, NIDDK. Top row, right: Jupitor images/creatas (RF)/Jupiter images. Middle row, top left: Normal and obese mouse. Jackson Laboratories. Middle row, bottom left: Measuring dopamine receptor (top) and glucose metabolism (bottom) in brains of obese and non-obese humans. Image courtesy of Dr. Gene-Jack Wang, Brookhaven National Laboratory. Reprinted from The Lancet, 357, Wang GJ, Volkow ND, Logan J, Pappas NR, Wong CT, Zhu W, Netusil N, Fowler JS, Brain Dopamine and Obesity, 354-7, Copyright (2001), with permission from Elsevier. Middle row, right: Images created by Wei Shen and Steven Heymsfield, New York Obesity Research Center, St. Luke's-Roosevelt Hospital, Columbia University, New York. Bottom row, left: Fat cells (stained red) that make up adipose tissue can't grow without blood vessels (stained green) to nourish them. (red stain=adipocytes, green stain=vasculature, blue=DAPI). Image courtesy of Dr. David Burk, Pennington Biomedical Research Center. Bottom row, right: The swarm of inflammatory cells in obese adipose tissue: Microscopic image of abdominal adipose tissue from an obese mouse. Fat cells (blue) are surrounded by a large number of macrophages (green). These inflammatory cells infiltrate fat and form clusters around areas of dead fat cells. These macrophage generate inflammatory factors that disrupt the normal function of fat cells and enter the circulation to generate low grade chronic inflammation in other organs. A large number of other cells are also found in obese fat (nuclei are stained red) that interact with macrophages and fat cells to produce a pro-inflammatory environment in adipose tissue. Image courtesy of Dr. Carey Lumeng, University of Michigan.)*

OBESITY

contents:

INTRODUCTION

Obesity is a major risk factor for the development of type 2 diabetes and insulin resistance. It is also a major cause of morbidity and mortality in the United States in its own right. Obesity is commonly assessed using the body mass index, or "BMI," which is a calculated ratio based on an individual's weight and height. By this measure, over one-third of U.S. adults are considered obese (11). Obesity disproportionately affects some racial and ethnic minority populations—for example, 43 percent of Hispanic American women and over 49 percent of African American women meet the criteria for obesity (11). Moreover, the levels of childhood overweight and obesity have escalated in the past several decades, such that obesity now affects approximately 12 percent of children 2 to 5 years old and 17 percent of children and teens ages 6 through 19 (12)—alarming statistics matched only by the increase in type 2 diabetes in youth. Efforts to combat type 2 diabetes are inextricably linked to research to understand, prevent, and effectively treat obesity.

In understanding the role of obesity in diabetes, the broad spectrum of problems associated with obesity must also be realized. For example, the effects of obesity on morbidity and mortality differ across ethnic groups. Moreover, the effects of obesity on morbidity and mortality depend not only on total fat mass, but also on fat distribution. Central abdominal obesity ("apple shape" body type) is associated with a much greater health risk than peripheral obesity ("pear shape" body type). However, at molecular, genetic, and cellular levels, these important differences have yet to be fully explained. Physical activity and fitness are related to the risk of obesity, but may also influence type 2 diabetes independently of obesity. Finally, obesity is related not only to the risk of type 2 diabetes but also to insulin resistance, hyperlipidemia, hypertension, accelerated atherosclerosis, and coronary heart disease. Clearly, these associations create much of the heath hazard of obesity, even in the absence of full-blown diabetes.

Obesity results from an imbalance between energy intake and energy expenditure. A sustained "positive" energy balance will lead to storage of extra calories as fat, potentially leading to overweight and obesity. The delicate coordination of energy intake and expenditure occurs through a variety of external factors (social and environmental) and internal functions (endocrine and neural signals that emanate from adipose tissue, various regions of the brain, the endocrine system, and gastrointestinal tract). There has been tremendous progress in defining these complex pathways. Research has demonstrated that obesity is not simply due to overeating, but is the result of misregulated pathways that normally control the balance between appetite and energy expenditure. Progress is being made to understand the factors that disturb these pathways and how they can resist being reset to "normal." Research is also revealing molecular and behavioral links between metabolism, appetite, and the circadian rhythm, as well as how social and physical environments influence the regulation of energy balance.

Underlying the issues of energy balance is the fat tissue, or adipose tissue, itself. There are two major types of body fat, "white adipose tissue," which stores energy and comprises most body fat, and brown adipose tissue (BAT), which actually burns calories to help

maintain body heat. Scientific views on adipose tissue have undergone a fundamental change over the past 15 years. Rather than a mere storage compartment for triglycerides (fats), white adipose tissue is now recognized as an endocrine organ. The crosstalk between multiple different cell types, including adipocytes, endothelial, and immune cells, gives rise to a very active tissue that releases a large number of protein and lipid factors that profoundly influence systemic energy metabolism. As such, adipose tissue assumes center stage in the underlying etiology of type 2 diabetes. Moreover, there is accumulating evidence that BAT likely plays a role in adult metabolism, and hence may influence obesity and type 2 diabetes.

It has also become clear that obesity is associated with chronic inflammation that, when present, increases the risk of metabolic syndrome, diabetes, and atherosclerosis. Although the mechanisms linking obesity, inflammation, and metabolic dysfunction are incompletely understood, it is evident that cellular inflammation is a key mediator of insulin resistance. This effect is mediated in part by cellular inflammatory responses that block insulin signaling in tissues throughout the body. A key mediator of obesity-associated tissue inflammation involves the infiltration and activation of immune system cells called macrophages. Understanding this newly recognized relationship between obesity, inflammation, and insulin resistance may lead to new approaches to halt progression to type 2 diabetes.

Finally, research has also clearly implicated behavior, environment, policy, and social relationships and context in influencing patterns of eating, nutrition, and activity. For example, obesity has been inversely associated with socioeconomic status, and changes to the built and food environment have been shown to influence energy intake and activity. These in turn affect —and are affected by—a person's nutrition, which is essential for good health. Basic social and behavioral research findings are also yielding new and important insights about factors that influence diet and activity. For example, research regarding early childhood feeding, social networks, behavioral economics, sensory input, and sleep patterns as they relate to weight offer the possibility for some novel intervention targets for the prevention and treatment of overweight and obesity.

The increased prevalence of obesity—and hence, of type 2 diabetes—is influenced by a complex set of factors that include biology, behavior, social, and environmental influences. Often these influences involve complex interactions such as biology influencing behavior or behavior and environment influencing biology. This complexity makes research in this area both interesting and challenging. Cross-disciplinary research across a range of research modalities, from fundamental studies to clinical trials and epidemiological research, seems best poised to yield important findings in the future.

RECENT RESEARCH ADVANCES

In just the past decade, researchers have made great strides in understanding the molecular, genetic, brain, behavioral, and environmental factors underlying obesity and its role in promoting insulin resistance and diabetes, as well as in approaches to prevent and treat obesity. The following are some major examples of this research.

The Link Between Obesity and Inflammation: Research suggests that inflammatory mediators produced by activated macrophages are important factors underlying the synergistic relationship between obesity, insulin resistance, and metabolic dysfunction. First documented in adipose tissue, obesity-associated inflammation and macrophage accumulation have now been demonstrated in diverse tissues, including liver, skeletal muscle, vasculature, and brain. The macrophage represents a significant new target in developing therapies to break the link between obesity and diabetes.

Discovery of Hormones and Neural Circuits That Contribute to Energy Balance: While the existence of homeostatic systems that maintain body weight and adiposity at near-constant levels has long been appreciated, the mechanisms that underlie energy homeostasis have begun to be elucidated only recently. There is now a better understanding of the role of hormones, such as insulin, leptin, agouti-related peptide (AGRP), neuropeptide Y (NPY), melanocyte stimulating hormone (MSH), and melanin-concentrating hormone (MCH), that convey information related to energy storage in adipose tissue to homeostatic brain circuits. New evidence is emerging that these brain regulatory centers also modulate glucose production by the liver as part of an integrated response to energy availability. An appetite-stimulating hormone, ghrelin, and other peripheral signals of feeding and energy status have been identified. Within the brain, particularly in the hypothalamus, a number of neural circuits and neurotransmitters that respond to and mediate the effects of leptin and other metabolic signals have been identified. Collectively, these findings reveal that alterations in body weight provoke changes in these neural systems to produce a homeostatic response to defend body weight. In addition to providing new therapeutic targets, these discoveries are opening a new window to understanding human motivation to eat.

Mechanisms That Underlie the Dysregulation in Energy Homeostatic Systems To Promote and Maintain Obesity: While the key pathogenic change(s) are not yet known, a number of processes that may alter the function of the neural circuits that modulate energy balance have been identified. These include: molecular/signaling mediators and inflammatory mechanisms that may interfere directly with signaling by appetite-suppressing hormones and/or circuits; altered early development/wiring or later remodeling of the energy homeostatic circuitry in response to dearth or excess of nutrition (and their hormonal surrogates); and alterations in access of nutritional or hormonal cues to these circuits. Armed with this knowledge, scientists can now study how these mechanisms go awry and

potentially contribute to inappropriate weight gain and/or retention. Identifying key sites of susceptibility to environmental insult and the critical periods when these changes are likely to occur will have a significant impact on design of successful interventions to prevent obesity.

Implication of Mutations in *MC4R* as One Cause of Severe Obesity in Humans: Genetic studies in animal models led to the discovery of a novel hypothalamic pathway impaired in obese mice, and implicated members of the melanocortin receptor (MCR) family in the regulation of body weight. Dominantly inherited mutations in the MC4R gene (*MC4R*) were quickly recognized in some humans who are obese. At least 80 obesity-related mutations of *MC4R* have been reported, and a common genetic variation near *MC4R* has been associated with increased BMI. The major effects of mutations in the *MC4R* gene on obesity are conveyed by effects on food intake, in some cases resulting in extreme hyperphagia. These effects may be greater in children than in adults. Many of these mutations affect intracellular transport of the *MC4R* encoded receptor protein, suggesting that the development of suitable molecular chaperones could provide therapeutic benefit in obesity.

Bardet-Biedl Syndrome (BBS) Convergent Phenotypes Due to Mutations in Components of the Ciliary Body: A new avenue in obesity research has been opened through study of a rare genetic syndrome whose symptoms include not only obesity, but also preaxial polydactyly (thumb duplication), retinal degeneration, anosmia (inability to perceive odors), generalized decrease in peripheral sensation, and renal/hepatic cysts. Of 14 known causative BBS genes, eight encode known components of the primary cilium, a complex sensory organelle that may require up to 1000 proteins for function, is present in most mammalian cells, and plays a role in development, cellular maintenance, and key signaling and trafficking pathways (Wnt and Hedgehog). BBS proteins are required for leptin receptor signaling in the hypothalamus, and thus mutations in BBS genes could result in impaired regulation of energy balance through structural and/or signaling abnormalities in this key brain region. It is likely that all BBS results from complex combinations of partly functional genes (hypomorphic alleles) contributing to formation and activity of this complex cellular component. Unraveling the molecular genetics of this rare syndrome could provide the proof-of-principle that combinations of hypomorphic alleles of the components of a cellular structure, and presumably pathway, can result in obesity.

Genome-wide Scans for Genes Associated with Obesity: Genome-wide association (GWA) studies have enabled the detection of common genetic variants that are associated with specific common phenotypes. A sequence variant in the first intron of the fat mass and obesity associated gene (*FTO*) was originally identified as associated with type 2 diabetes in a study of over 30,000 well-phenotyped individuals and controls. However, controlling the original association for BMI eliminated the association of the genetic locus with type 2 diabetes, indicating that *FTO* was actually an obesity rather than a type 2 diabetes locus—a finding that has now been replicated in multiple independent cohorts. It is of note that a second gene, *FTM*, located close to the first exon of *FTO*, encodes a component of the ciliary body, and thus could account for the obesity-related phenotypes associated with this interval. Subsequent GWA studies for obesity have identified additional loci/genes (see Table 3 in the "Genetic Basis of Type 1 Diabetes, Type 2 Diabetes, Obesity, and Their Complications" chapter). As with most GWA

studies to date, the novel loci/genes are of relatively modest relative risk. However, these studies should lead to further discoveries of how genes interact with the environment and uncover heretofore unappreciated biological pathways that may provide novel insights into obesity and its treatment. (Advances in the field of genetics are more fully outlined in the "Genetic Basis of Type 1 Diabetes, Type 2 Diabetes, Obesity, and Their Complications" chapter.)

Limits in the Ability of Adipose Tissue To Expand in the Face of Excess Calories May Drive the Accumulation of Fat in Other Tissues, Leading to the Morbidities Associated with Obesity:

Many of the adverse effects of obesity can be traced to accumulation of fat in organs such as liver, muscle, pancreas, and blood vessels. Research has shown that mice capable of expanding adipose tissue through adipocyte proliferation without concomitant inflammation become obese, but do not redirect fat deposition to organs other than adipose tissue. These mice appear metabolically healthy, with normal insulin sensitivity and blood lipids. Similarly, clinical data have highlighted the potently protective nature of some fat pads, and epidemiological studies have revealed correlations between plasma levels of adipokines and systemic insulin sensitivity, diabetes, cardiovascular risk, and many additional disease states. Data from pre-clinical models further corroborates these correlations, and in many instances directly implicate the dysregulated adipokine in the development of insulin resistance. These findings provide new clues that may allow disruption of the link between obesity and type 2 diabetes and may explain the "fit-fat" conundrum by clarifying how fat accumulation in some depots is more deleterious than when it is stored in others.

Environmental and Policy Approaches Show Effectiveness in Increasing Physical Activity and Improving Eating Behaviors:

Healthy eating and physical activity are important for preventing excess weight gain and producing weight loss across the lifespan. Research supports environmental and policy approaches to increasing physical activity and improving eating behaviors in both adults and children that could lead to significant public health benefit. Establishing local policies and practices for creation of, or improved access to, places for physical activity and healthful foods, and reducing exposure to social and environmental triggers to eat and remain sedentary can be effective in facilitating increased levels of physical activity and improved eating behaviors. Environmental and policy approaches have also shown promise as cost effective means for population-based weight management. Improved understanding of social, environmental and policy influences on physical activity and eating will guide future clinical and population-based health interventions.

Bioimaging Provides New Insights into Fat Tissue:

Rapid technical developments in medical imaging, particularly in nuclear magnetic resonance imaging (MRI), have spurred new advances in obesity research. These techniques have enabled researchers not only to further explore anatomy and morphology of different tissues and organs, but also to examine their dynamic functions with increasing accuracy and reduced invasiveness in humans as well as animals. As a result of these developments, researchers can now use MRI to quantify visceral and subcutaneous adipose subdepots, and use MR spectroscopy to investigate the role of ectopic fat in muscles and liver in the pathogenesis of

insulin resistance. Functional MRI also has enabled researchers to study brain responses to food stimuli noninvasively, and also extend studies to elucidate the role of peripheral hormones, such as insulin, in the brain. PET/CT scanning has revealed the presence of significant depots of brown adipose tissue in adult humans and suggests that it could play a role in response to metabolic challenges such as cold exposure (see next Advance). These studies provide a bridge between mechanistic, but invasive, studies in animal models, and an understanding of behavior and metabolism in humans.

Brown Adipose Tissue and Energy Metabolism: The potential importance of BAT in human energy metabolism has resurfaced. The conventional wisdom that the importance of BAT in energy metabolism is limited to small mammals and human neonates has been challenged by recent evidence: Scientists have found that BAT is detectable in a substantial subset of adult humans (although not primarily in the interscapular area typical of rodents and newborn humans), that BAT can be rapidly activated by cold exposure and other stimuli in many individuals, and that this response shows gender difference, is attenuated in individuals who are obese, and may be blocked by drugs such as beta-blockers. Furthermore, obesity-resistant strains of mice have been shown to have more BAT in unusual locations, such as embedded in leg muscle. These insights set the stage for studies to determine whether reduced BAT thermogenesis (heat production) contributes to obesity pathogenesis, and whether pharmacological or other strategies to activate BAT might be therapeutically useful. It has been shown that some BAT depots appear to be derived from precursors that are shared with skeletal muscle, whereas others may be more closely related to the lineage that gives rise to white adipose tissue. The discovery of key genes and growth factors that control BAT differentiation provides new opportunities for fundamental research in this area. Further clinical investigation will be necessary to define the potential role of BAT in pathogenesis, prevention, and treatment of obesity.

Impact of Bariatric Surgery on Body Weight and Glucose Metabolism: Bariatric surgery is the most effective available treatment for extreme obesity. One frequently performed operation, Roux-en-Y gastric bypass (RYGB), causes profound weight loss that, unlike other modalities, seems not to activate compensatory responses to weight loss that lead to weight regain, at least in some individuals. This procedure can also induce a complete normalization of euglycemia via mechanisms that appear, at least in part, to be independent of weight reduction. Potential mechanisms underlying this effect include increased secretion of intestinal hormones (e.g., glucagon-like peptide-1), neuroendocrine changes induced by excluding ingested nutrients from the upper intestine, compromised ghrelin secretion, altered intestinal nutrient sensing, or other as-yet unidentified processes. These findings have opened a new research avenue that may lead to new diabetes treatments (see also the "Type 2 Diabetes As a Multi-Dimensional Disease" chapter and the "Clinical Research and Clinical Trials" chapter).

KEY QUESTIONS AND FUTURE DIRECTIONS FOR RESEARCH

The 1999 report of the congressionally-established Diabetes Research Working Group (DRWG), *Conquering Diabetes: A Strategic Plan for the 21st Century*, recognized the importance of obesity in diabetes and as a critical problem in its own right, emphasizing the need for enhanced basic, clinical, and behavioral research in this area. In the intervening years, the surge in prevalence of both obesity and diabetes in the United States has made research to combat these twin health problems increasingly urgent. Indeed, the NIH established an Obesity Research Task Force in 2003 to bring greater focus to the wide array of research needs in obesity. The research challenges posed by obesity cut across many fields and disciplines. Described below are research questions and opportunities to pursue in the next several years to reach the goal of understanding, preventing, and effectively treating obesity with special emphasis on mitigating it as a risk factor for type 2 diabetes.

Obesity, Inflammation, Insulin Resistance, and Macrophage Function

Understanding the role of obesity in development of diabetes will require further study to understand the relationship between fat and inflammation. Many questions remain regarding the role macrophages play both in peripheral tissues and in the central nervous system (CNS) in mediating disordered energy intake and storage, especially in response to consumption of a high fat diet. Conversely, more needs to be done to understand macrophages and inflammation as an outcome of obesity leading to insulin resistance and other complications, such as atherosclerosis. Clarifying both the mechanisms underlying, and consequences of, tissue-specific inflammation induced by obesity is a key priority for future research.

Key Questions

- **At the cellular level, what mechanisms link exposure to excess nutrients to activation of inflammatory signaling, and how do these responses cause insulin resistance?**
- **Does hyperinsulinemia exacerbate this problem by forcing the uptake of nutrients into insulin-resistant cells?**
- **What role does macrophage activation play in the deleterious metabolic and cardiovascular responses to obesity? What signaling molecules are involved?**
- **How does hypothalamic inflammation affect energy homeostasis? How do inflammatory mediators influence the relationship between microglia (the macrophages of the brain) and neural systems governing energy balance and peripheral metabolism?**
- **How does body fat distribution affect inflammatory responses observed in obesity?**

Future Directions

➤ **Determine whether inflammatory pathways can be targeted effectively in the prevention and treatment of obesity and its metabolic sequelae, and if so, which specific molecules are best suited as therapeutic targets.**

At the cellular level, inflammation induced by nutrient excess and obesity can involve multiple organelles (e.g., mitochondria, endoplasmic reticulum) and signal transduction pathways (e.g., IKKbeta-NFkappaB, JNK) depending on the cell type. Optimal strategies for limiting this type of inflammation may therefore vary across tissues, and further studies are warranted in this area.

- **Establish whether the beneficial impact of exercise on metabolism involves an attenuation of cellular inflammation induced by nutrient excess.**

To meet the demands of physical exercise, increased rates of substrate oxidation are required. At the cellular level, this process can favor the mobilization of nutrients that might otherwise accumulate and promote inflammatory responses. Thus, the effect of exercise to mobilize stored nutrients may contribute to its ability to improve metabolic function, and efforts to quantify this effect and its therapeutic potential are warranted.

- **Determine whether specific nutrients (e.g., saturated fatty acids, fructose) exert pro-inflammatory effects in obesity that are independent of energy balance per se.**

Although chronic consumption of nutrients in amounts that exceed bodily requirements induces deleterious effects on tissues throughout the body, the extent to which these effects are driven by an overall excess of calorie ingestion versus increased exposure to specific nutrients is an open question. Saturated free fatty acids are implicated as having pro-inflammatory effects, and diets high in saturated fat content seem to promote systemic inflammation more effectively than diets rich in mono- or polyunsaturated fats; indeed, foods rich in omega-3 fatty acids may have anti-inflammatory effects. Identifying the molecular mechanisms responsible for these differences and disarticulating energy excess from responses to specific dietary components is a key research goal.

- **Investigate mechanisms whereby hypothalamic inflammation is induced by systemic inflammatory stimuli and assess their consequences for energy homeostasis.**

Like many other tissues, the hypothalamus is susceptible to inflammation induced by nutrient excess. Unlike other tissues, however, this hypothalamic response has the potential to favor weight gain, in addition to simply being its consequence. This hypothesis is based on evidence that leptin and insulin are "adiposity negative feedback" signals that convey afferent input used by the hypothalamus to control energy balance, and that neuronal inflammation causes resistance to both hormones. This effect, in turn, is hypothesized to predispose to weight gain until circulating insulin and leptin levels increase sufficiently to overcome the neuronal resistance. Thus, it is proposed that a vicious cycle can exist in which nutrient excess itself favors excess weight gain in genetically susceptible individuals. Accordingly, drugs that disrupt this vicious cycle may be effective in obesity treatment and prevention.

- **Determine the impact of macrophage activation phenotype on insulin sensitivity and assess its potential as a therapeutic target.**

As obesity-induced tissue inflammation progresses, immune cells are recruited, further exacerbating the inflammatory response. Adipose tissue macrophages are clearly increased in both number and pro-inflammatory activation in individuals who are obese,

and data from both genetic and pharmacological intervention studies implicate these macrophages in obesity-induced insulin resistance. A key event in this pathological cascade is the induction of a pro-inflammatory phenotype of macrophages in insulin-sensitive tissues (so-called "classical activation" or M1 phenotype). Yet, macrophages can also be induced to exhibit anti-inflammatory properties ("alternative activation" or M2 phenotype), and available evidence suggests that induction of this macrophage phenotype switch ameliorates obesity-associated inflammation and insulin resistance. Thus, therapeutic interventions that favor the M2 over the M1 macrophage phenotype warrant study as novel strategies for the treatment of obesity-associated metabolic disease.

➤ **Determine the mechanisms whereby macrophages are recruited into different tissues during obesity, and whether body fat distribution affects this process.**

The mechanism(s) underlying obesity-associated accumulation and subsequent activation of macrophages in insulin-sensitive tissues is an area of intense scientific focus. Some argue that this effect is mediated by the release of chemokines that promote recruitment of circulating monocytes into tissues, while others invoke obesity-associated cellular necrosis as a key signal driving this process. Clarifying the underlying mechanisms may lead to new approaches to ameliorating obesity-associated metabolic dysfunction.

Mechanisms Underlying Energy Homeostasis: Impact on Obesity Pathogenesis and Treatment

Defining the mechanisms that contribute to the onset and maintenance of obesity will require a thorough understanding of the hormonal and neural controllers of energy balance. Each constituent of the energy balance system and each mechanism that may act on the energy balance system to promote positive energy balance in obesity represents a potential target for therapeutic intervention. Energy homeostatic circuits exist within a complex and intertwined network, and a myriad of processes regulate each circuit in distinct ways. Adding further complexity, neurons and their networks are capable of adapting organizationally and functionally in the face of changing conditions, engaging in so-called "neuronal plasticity." Scientists have only just begun to unravel the complex neural networks that modulate energy balance and their roles in responding to environmental perturbations, let alone their potential dysregulation in obesity. Even less is known about the impact of genetic, intrauterine, and acquired factors on these neurocircuits and how they may predispose to childhood obesity. Crosstalk from the gut that could affect these circuits is also under study, due to rapid metabolic improvements seen in some bariatric surgery patients prior to significant weight loss (see chapters on "Type 2 Diabetes As a Multi-Dimensional Disease" and "Clinical Research and Clinical Trials"). To identify targets for the generation of potential therapies, the nature of these systems and the mechanisms governing their function and dysfunction will need to be more precisely defined. Also, the potential of drug combinations needs to be explored more thoroughly to determine if targeting multiple components of this regulatory system can yield additive or even synergistic effects on body weight.

Key Questions

- **What are the neural systems that respond to and control energy balance?**
- **What are the mechanisms by which the energy homeostasis machinery responds to altered energy balance?**

- **What are the mechanisms that alter these systems to promote or maintain obesity?**
- **How do cognitive inputs, such as learning and social cues, interact with these pathways?**
- **Are there inherent differences in brain connectivity and chemistry that increase susceptibility to obesity?**
- **Do nutrients, adiposity hormones, or gut peptides induce neuronal plasticity?**
- **What are the critical developmental periods (prenatal and postnatal) for the biological predicates of obesity? By what mechanism(s) are such effects conveyed?**
- **Does nutrient signaling in the brain play a major role in the pathogenesis of obesity and related metabolic disorders?**

Future Directions

➤ **Develop a more complete understanding of the neural systems, along with the molecular mediators in these systems, that regulate energy balance by sensing and responding to signals of energy status.**

While the recognition of hypothalamic arcuate neurons and their roles in sensing and responding to perturbations in nutritional and energy status has provided important insight into mechanisms regulating energy balance, a number of lines of evidence suggest that other important systems contribute. It will be crucial to identify and study these other important energy homeostatic circuits. Obstacles to this goal include the lack of pharmacologic, molecular, or genetic tools to study many of these neural circuits. Some hypothesis-generating studies will be required to identify such tools and to thereby permit the analysis of these poorly-understood but important circuits. The taste and smell of food can also influence the energy balance equation; additional information is needed to clarify cellular and molecular mechanisms whereby this afferent information is processed and communicated to brain areas involved in food intake regulation.

➤ **Understand the mechanisms by which the neural circuits responsible for maintaining energy balance mediate adaptive responses to environmental challenges.**

While some aspects of the adaptive response to decreased energy stores, such as changes in gene expression of arcuate nucleus neuropeptides, have been well-studied, scientists' understanding of many other mechanisms that may contribute is less robust. For example, the control of neuronal cell membrane potential and the mechanisms that govern the establishment and plasticity of afferent and efferent neural circuit contacts remain poorly understood and should be studied. Similarly, a number of molecular and cellular systems (including signaling pathways and metabolic processes) in the brain that modulate or mediate energy balance have been identified, but the cells and/or circuits in which many of these exert their effects remain unclear. The complexity of the heterogeneous and intertwined neural systems presents many challenges. It is also likely that the same intracellular mechanisms have different, or even opposing, effects in distinct sets of neurons. Thus, it will be important to examine these parameters in a cell-type-specific manner, an approach that may require the generation of new technologies. Finally, in addition to determining the response to hormonal and nutritional challenges, it will be important to define the response to exercise. Beyond determining how distinct mechanisms operate during the adaptive response to altered energy balance, it will

also be crucial to examine the relative contribution of each mechanism to the overall adaptive response.

- **Understand how the systems that control energy balance may be altered to promote and maintain positive and/or negative energy balance in obesity.**

In addition to understanding the mechanisms by which the systems that control energy balance mediate physiologic adaptive responses, a greater appreciation is needed of how these processes are altered or become maladaptive to promote or maintain states of obesity and how they may be reversed to promote weight loss. It will be necessary to understand changes that occur with obesity, and how events occurring early in development (e.g., *in utero* or early postnatal) may program neural circuits to affect later metabolic fate. Determining whether the neural circuitry can be reprogrammed later in life, and whether exercise, modifying dietary intake, or other activities can induce or influence this reprogramming, will also be crucial. For each of the diverse set of circuits that regulate energy balance, the role of transcriptional, molecular, inflammatory, neurophysiological, synaptic, and other fundamental processes will need to be elucidated. In addition to the challenges presented by the complexity and diversity of these neural systems, generalizing the results obtained in experimental animals to humans will require the development of new technology. Another key area of study will be to determine whether the re-setting of the defended level of body weight involves fixed changes in wiring of energy homeostasis circuits due to neuronal plasticity or other mechanisms.

- **Determine the role of nutrient signaling in the brain in obesity.**

Nutrients affect the activities of AMPK, glucokinase, mTOR, and enzymes involved in lipid metabolism in ways that affect feeding, as well as peripheral glucose and lipid metabolism. However, questions remain about how nutrients enter the brain to engage neuronal circuits, how nutrients specifically regulate neurotransmission in the hypothalamus and elsewhere, and whether experimental results based on central injection of nutrients are physiologically relevant.

- **Investigate CNS mechanisms potentially underlying pathogenesis of childhood obesity.**

Numerous environmental perturbations (such as exposure to environmental toxins, nutritional surfeit or deficiency, and altered endogenous metabolite or hormone levels) during fetal development and early childhood affect the predisposition to obesity later in childhood and beyond. Mechanisms by which early environmental perturbations may lead to obesity include programming of the brain systems that modulate energy balance. The CNS exhibits enhanced plasticity during fetal and early childhood development; this plasticity subsequently diminishes, so that the conditions experienced during early development ultimately provoke fixed changes to program later CNS function. Such programming may be mediated by epigenetic modifications of the genome, by the modulation of neurogenesis and/or apoptosis (programmed cell death), or by altered developmental "wiring" of the neural systems that contribute to the regulation of energy balance. Indeed, environmental influences modulate each of these processes during CNS development. Important future research goals in this area include defining the permanent changes produced by environmental factors during development and directly examining the causal links between such alterations in

CNS function and subsequent metabolic outcomes, such as obesity.

➤ **Identify CNS mechanisms that underlie weight loss in inflammatory, infectious, and neoplastic disorders.**

Pathological anorexia with disproportionately elevated energy expenditure leads to severe loss of both lean mass (cachexia) and fat mass in common wasting diseases, and involves incompletely understood alterations of the same neuroendocrine control systems that govern body weight in normal-weight individuals and people who are obese. Thus, clarifying the underlying mechanisms may ultimately identify novel targets for weight loss therapy, as well as for the treatment of wasting illnesses.

Central Nervous System Control of Thermogenesis

In addition to the control of food intake, integrative neurocircuitry in the brain also regulates energy expenditure in the service of energy homeostasis. Although progress in understanding the biological pathways and networks involved in regulation of thermogenesis has been substantial, the connection among the hypothalamus and endocrine and autonomic pathways that control diverse functions associated with energy expenditure, including basal metabolic rate, the thermic effect of food, nutrient partitioning, and control of physical activity, remains undiscovered. While studies in many model organisms are revealing new biological targets and pathways, challenges researchers face include the limitations of rodent models to fully reflect the complex control of energy expenditure in humans and how it contributes to weight maintenance and obesity. New technologies are needed to explore these pathways and to look for their correlates in humans.

Key Questions

- **Does impaired thermogenesis contribute to "common" obesity?**
- **How are neural, behavioral, and endocrine determinants of thermogenesis coordinated?**
- **Do brown adipocytes play a significant role in energy homeostasis in humans?**

Future Directions

➤ **Determine if reduced energy expenditure contributes to "common" obesity.**

Individuals who are obese have high circulating leptin levels and reduced leptin sensitivity. In rodents, leptin resistance can affect the control of thermogenesis as well as energy intake. Quantitative, long-term energy balance studies are needed in both animal models and humans to identify the relative contributions of increased intake and reduced energy expenditure to obesity pathogenesis. Also, because energy expenditure varies as a function of body size, metabolic rate must be adjusted for this effect when comparing lean to obese animals. Optimal strategies for this normalization step are highly debated and need to be established.

➤ **Understand bioenergetics in the etiopathogenesis of obesity.**

The relative contributions of energy intake and expenditure to obesity in any individual may vary, and current technologies cannot accurately assess these parameters over significant periods of time. To be informative, research in this area should be conducted in individuals prior to the development of obesity and/or in response to weight perturbations, because, at stable weight and body composition, obese individuals

are in energy balance and do not differ from non-obese individuals in their energy expenditure or intake normalized to metabolic mass.

- **Long-term measurements of energy intake:** The doubly-labeled water technique can quantitate energy expenditure over several weeks, but equivalent measures of energy intake are not available. Highly accurate measurements of body composition could be combined with measures of energy expenditure to calculate intake by difference.
- **Responses to weight perturbation:** Individuals who were formerly obese and those who have never been obese display comparable responses in energy expenditure to imposed weight gain and loss. The response to weight loss includes reduction in energy expenditure beyond that explicable by reduced metabolic mass, as well as diminished satiety in meal-testing paradigms. These combined phenotypes are sufficient to account for the very high recidivism to obesity. Understanding the molecular mechanisms that mediate these changes could lead to effective strategies for the maintenance of reduced body weight that might be quite different from those used to induce weight loss per se.
- **Role of brown adipose tissue in mediating inter-individual differences in energy expenditure and responses to weight perturbation:** The ability to assess the mass and activity of brown adipose tissue in humans using PET/CT scanning can be used to explore the role of this tissue in the development of obesity and the response to weight reduction. It is possible that a portion of the reduction in energy expenditure accompanying weight loss is due to diminished activity of brown adipose cells.
- **Relating differences in energy homeostasis to genetic variation:** The strong evidence for genetic contribution to susceptibility to obesity and increasing numbers of implicated genes have not yet provided clear insights regarding the mechanisms by which these genes predispose to obesity (see the chapter on "Genetic Basis of Type 1 Diabetes, Type 2 Diabetes, Obesity, and Their Complications"). Such insights will be gained by prospective application of the techniques described above to individuals before and after the development of obesity.

Discovering Genetic and Intrauterine Determinants of Obesity Susceptibility That Predispose to Developing Diabetes

Genes unquestionably play a major role in susceptibility to obesity and diabetes and may influence treatment response. The genes conveying susceptibility to obesity appear, in general, to be distinct from those mediating susceptibility to diabetes. However, obesity of any etiology constitutes a stress on beta cell function and can unmask individual genetic differences in beta cell mass and function, leading to the development of overt diabetes. Heritability estimates from studies of identical and non-identical twins indicate a strong genetic contribution to both metabolic problems. Other studies, such as recent GWA scans in large numbers of people, suggest that there are a large number of genes with relatively small effects for obesity and type 2 diabetes; whether there are rare alleles (population frequencies of less than about 5 percent) with high functional/physiological impact remains to be seen. Discovery of genes relevant to obesity will continue to direct researchers to molecular pathways that may be helpful both in understanding the pathophysiology of this condition and in identifying molecular targets for the development of drug therapies. If the genetics of

obesity and/or type 2 diabetes are ultimately shown to be dependent on the aggregate impact of many genes of small effect, the clinical utility of these genes in predicting individual susceptibility may not be great, but they could be helpful in selection of specific therapies for people who have these conditions or for those at risk. Virtually any of the genes identified in such searches will be strongly influenced by other genes as well as by developmental, behavioral, and environmental factors. The ability to account for the contribution of specific genes will ultimately enable better understanding of the mechanisms by which environment, development, and other genes mediate disposition to obesity. Growing evidence also suggests that, during pregnancy, maternal metabolic dysfunction can lead to developmental and/or epigenetic changes that can predispose offspring to obesity, insulin resistance, and type 2 diabetes in adulthood. Mechanisms linking changes in the intrauterine environment to such outcomes are poorly understood, as is their relationship to genetic and environmental factors that influence these outcomes. (See also the chapters on "Genetic Basis of Type 1 Diabetes, Type 2 Diabetes, Obesity, and Their Complications" and "Special Needs for Special Populations.")

Key Questions

- **Are there rare, high impact alleles of known or unknown genes that increase or reduce susceptibility to obesity or type 2 diabetes or their sequelae?**
- **How many genes will be required to account for substantial ordinary risk variance for these phenotypes?**
- **What (if any) are the genetic substrates for the apparent impact of intrauterine and neonatal exposures to nutritional "stress" on subsequent risk of obesity and type 2 diabetes?**
- **Are there genes that moderate the effectiveness of various environmental, social, behavioral, and physiological/pharmacological interventions to prevent and control obesity and type 2 diabetes and that define population subgroups that will respond more or less to those interventions?**

Future Directions

➤ **Conduct prospective analyses of genetic contributions to obesity-related phenotypes and intervention responsiveness.**

Once obesity and/or derangements of insulin and glucose homeostasis occur, it is difficult to disarticulate cause from effect in terms of underlying molecular physiology. The identification of genes and gene-gene interactions relevant to obesity and type 2 diabetes has made it possible to examine individuals at high risk for these health problems by virtue of genotype at ages and periods of development prior to the occurrence of any major medical phenotype. Careful prospective metabolic/behavioral study of such individuals and/or those exposed to different interventions should greatly enhance understanding of the basic biology underlying obesity and type 2 diabetes in humans. For example, brain imaging techniques (fMRI, PET) could be used to characterize responses to food and other stimuli in individuals identified as having one or more alleles of susceptibility genes prior to any increase in body fat. These prospective studies can also address the issue of so-called "critical periods" in the development of obesity and the contributions of genetic differences to such

periods. Characteristics that mark genetic risk of illness (even in the absence of illness), or endophenotypes, could be useful, and the use of tissue-related gene expression array data may be of great interest in this regard. Prospective analysis of such phenotypes in individuals at risk of obesity—insulin resistance, for example—could provide mechanistic insights not necessarily apparent once the systemic phenotype is established. Similarly, the potential role of genes in moderating the effects of different interventions could help identify the population subgroups to be targeted by specific interventions. For example, a particular allele may identify particular subgroups of participants who respond to a greater or lesser extent to a specific intervention. Such genetic analysis might also enable prediction of weight gain responses to specific antipsychotic drugs (see also the "Special Needs for Special Populations" chapter). In addition to conducting such studies *de novo*, an effort should be made to identify longitudinal data sets that might lend themselves to relevant *post hoc* analyses, especially those that allow examination of "naturally-occurring" or planned interventions. A very important challenge in this context is the lack of accurate measurements of energy intake in free-living humans. More satisfactory measures of energy expenditure and body composition are now available; these could be combined to calculate energy intake over extended periods of time.

- **Investigate copy number variation (CNV) as a source of inherited or sporadic phenotypes related to obesity and diabetes.**

In addition to the widely recognized effects of sporadic duplications/deletions of whole chromosomes in causing human disease, it is clear that subtler, transmissible alterations in copy number of contiguous genes can have effects on complex phenotypes. Such copy number variants (CNVs) are not necessarily associated with "syndromic" phenotypes, hence their potential contribution(s) to a complex phenotype cannot be reliably ascertained clinically. The degree to which such variants contribute to phenotypes related to obesity and diabetes cannot be adequately assessed without high resolution maps of their locations and access to suitable quantitative assays. In addition to contiguous gene deletions/duplications, the extent to which intragenic deletions/duplications generate mutations in genes causing monogenic forms of obesity or type 2 diabetes has not been systematically addressed. The newer genotyping arrays provide the data on common CNVs and exome sequencing can be used to identify rare events.

- **Identify additional genetic variations and understand their role in pathways that contribute to obesity.**

Although 17 SNPs have been shown by GWA studies to be associated with obesity, most of the genetic effect on adiposity has yet to be accounted for. This may be because the SNPs identified so far are not the functional variants, because there are rare variants with much greater phenotypic impact that have yet to be discovered, or because of complex interactions between genes within pathways or between genes, behavior, and the environment. Better tools are needed to investigate the effects of environment on the impact of predisposing genetic variants.

- **Investigate developmental "imprinting" *in utero*.**

Poor metabolic control in women who have gestational diabetes leads to increased fetal mass/adiposity, apparently increasing subsequent risk of obesity.

Obesity per se in pregnant women who do not have diabetes appears also to predispose their offspring to obesity. Such effects—sometimes referred to as "metabolic imprinting"—are conveyed by unknown mechanisms. It is likely that placental biology and the intrauterine environment are affected by metabolic consequences of maternal obesity, and that such changes could influence aspects of brain, adipose tissue, and pancreatic islet development in a fetus in ways that would predispose to obesity and type 2 diabetes. Studies are needed to determine whether the genetic status of the fetus interacts with such environmental effects, in a manner similar to what is likely to occur in the extrauterine environment. Pursuit of these studies will require very sophisticated experimental models and clinical/epidemiological analysis.

Allele-specific differential methylation of DNA during gametogenesis, or "genomic imprinting," can affect the levels of expression of specific alleles in offspring; histone acetylation may influence this process and/or have independent effects on the expression of specific alleles. Environmental effects, such as maternal metabolic state and diet, may play a role in this process. The extent to which such phenomena modulate otherwise classical genetic and environmental influences on susceptibility to obesity in humans is unknown. Systematic comparisons of gene methylation (and CNV) status in identical twins discordant for obesity could provide important insights.

Adipose Tissue Biology

More than just innocent bystanders, adipocytes are present in close physical proximity to all major organ systems and as such can influence neighboring cells. Understanding how to properly manipulate these cells and enhance their metabolic flexibility is key for a successful therapeutic approach for diabetes. Brown fat represents an unappreciated and potentially significant metabolically active tissue that may contribute to overall energy balance. In addition, the variability in brown fat mass or function may underlie some aspects of susceptibility to excess caloric intake. Important areas for future research include study of the mechanisms that determine adipocyte number and size and those that determine the relative size and function of different white fat depots, and developing improved tools for measuring these end points; investigation into the link between the anatomy of body fat deposition and metabolic sequelae; epidemiological analysis of the effect of fat distribution on metabolic risk; and study of the mechanisms governing adipose tissue development *in vivo*.

Key Questions

- **What mechanisms determine adipocyte number and size? Can improved tools be developed for measuring these end points?**
- **What mechanisms link variation in body fat deposition to metabolic sequelae?**
- **What mechanisms govern adipose tissue development and distribution *in vivo*?**

Future Directions

➤ **Discover factors that control the adipogenic and mature adipose gene expression profiles in different fat pads, and determine how these factors are affected by metabolic cues.**

Differential gene expression is achieved through regulation of distinct "modules" in which groups of genes are coordinately regulated. These programs are regulated differentially between males and females, are characterized by unique combinations of these modules in different fat pads, and are regulated by adipocyte cell size, the local microenvironment, and systemic signals.

A better understanding of the cellular machinery regulating gene expression in these programs—nuclear receptors, their co-activators, and co-repressors—will be essential for this process.

- **Identify the molecular events that maintain functionality of expanding adipose tissue.**

Biological responses underlying adipose tissue expansion include the process of angiogenesis, as well as recruitment and local proliferation of pre-adipocytes, and studies are needed to identify "local triggers" that promote adipocyte expansion versus differentiation.

- **Characterize additional key lipid and protein factors released by adipocytes.**

Hepatocytes (liver cells) and adipocytes share in common numerous secreted factors, such as acute phase reactants. Additionally, adipocytes are likely to release many important lipids, but the identity of these mediators awaits further study. Lipidomics and proteomics can be employed to identify adipocyte contributions to systemic levels of these factors under different conditions. Adipocytes may well signal to other tissues, such as muscle and other fat depots, and may receive information from liver, muscle, brain, gut, and other tissues through as yet undiscovered signaling moieties that underlie connections between obesity and diabetes through their contribution to the coordinated response to changes in energy availability among tissues.

- **Investigate heterogeneity of white adipose tissue in different fat depots.**

It has been recognized for over 20 years that central obesity produces a high risk of diabetes and metabolic syndrome, whereas peripheral obesity is not associated with such a risk and may even be protective against metabolic disease. Both BMI and adipose distribution, as measured clinically by waist-hip ratio, are strongly genetically determined, but what specific genes are involved has been unknown. Studies have begun to identify the genes involved in fat distribution and indicate that these genes exhibit large difference in expression even in cells in the preadipocyte stage—i.e., before differentiation to fat. These findings raise the possibility that white fat is more heterogeneous than previously thought. Defining the factors that program this heterogeneity may provide new insights into the link between obesity and metabolic disease.

- **Investigate mechanisms underlying the causes and impact of sexual dimorphism on specific adipose depots.**

Women differ from men both in regional patterns of fat distribution and in extent of adiposity. Individuals of either gender also show marked differences in pattern of white fat distribution, and this pattern can further change during periods of weight gain or loss and with aging. Delineating the mechanisms involved, as well as the critical periods in which patterns diverge, is essential for a better understanding of how different adipose depots affect metabolic function and diabetes risk.

- **Explore the potential for therapeutic manipulation of specific fat depots to reduce morbidity associated with certain depots.**

As a better understanding of depot-specific characteristics of adipose tissue emerges, tissue specific gene expression, cell ablation, or other methods can be utilized to modify those characteristics predisposing to metabolic dysfunction. Modest expansion of certain fat depots could be explored as an intervention that

ameliorates organ dysfunction by reducing fat deposition in muscle, liver, and other non-adipose tissues.

- **Investigate mechanisms for maintaining fully functional mitochondria in adipocytes.**

Accumulation of damaged mitochondria over time, especially in an oxidative environment, may contribute to pathological consequences of adiposity. Methods to stimulate mitochondrial biogenesis and repair may contribute to improved metabolic outcomes.

- **Accelerate technology development, including the use of noninvasive tools, such as magnetic resonance spectroscopy and labeled substrates, to investigate adipose tissue biology *in vivo*.**

These tools are essential both to translate discoveries made in animals into a better understanding of human biology and to monitor efficacy of novel therapeutics.

Obesity Prevention and Treatment

Behaviorally based lifestyle interventions in adults show efficacy for modest weight loss, and large scale trial data—such as results of the landmark Diabetes Prevention Program—clearly show that this modest weight loss reduces the incidence of type 2 diabetes in high-risk individuals. In overweight children and adolescents, lifestyle interventions with a focus on diet, physical activity, sedentary behavior or behavior change can produce clinically meaningful reductions in weight. Although the strongest weight control efficacy data for children is for family-based interventions, these interventions have not been translated into widespread practice. Theory-driven prevention programs in schools and other community settings have demonstrated some efficacy for preventing weight gain in population-based samples of children and adolescents. However, there is considerable room to improve both prevention of unhealthy weight gain and achievement of sustained weight loss across the lifespan, especially in populations disproportionally affected by obesity and type 2 diabetes. The impact of dietary composition and choices needs to be better understood to allow for evidence-based recommendations related to serving size and content in relation to the cost and availability of food. Research on the determinants of energy expenditure should include identifying factors that promote or deter physical activity, as well as understanding the link between fitness (aerobic and anaerobic) and metabolic disease independent of obesity. Research uncovering the behavioral mechanisms of obesity, and how they are driven by, or interact with, both biological and social and physical environmental factors, could point to novel approaches to treatment and prevention at the individual and population levels. Research on the safety and efficacy of non-surgical methods (e.g., structured meal plans, pharmacotherapy, and lifestyle) for weight control and diabetes improvement for those with extreme obesity (BMI of 40 or greater) is also needed, given that only a small fraction of eligible people seek or can obtain bariatric surgery. Preventing weight gain, maintaining weight loss in weight-reduced individuals, and promoting weight loss may each require strategies that are at least somewhat distinct, and research can help identify what works best for each of these types of weight management.

In addition to beneficial changes that can be implemented at the individual level (e.g., lifestyle management, therapeutics, bariatric surgery), strategies for inducing energy balance changes at the community/population level (e.g., education, environmental, economic, or policy interventions) are required. Translation and implementation are key challenges for research on how best to apply existing, effective

approaches in real-world settings. Finally, integrated research is needed to uncover biological (e.g., genetics, sensory or neural processing), cognitive, and behavioral factors for obesity as they interact with family/cultural and other social and physical environmental influences across the lifespan.

Key Questions

- **What strategies, methods, and approaches most effectively prevent inappropriate weight gain across the lifespan?**
- **How do prevention and treatment interventions work most effectively, individually and/or in concert, at multiple levels of influence (e.g., individual, social, policy, and environment)?**
- **What are the most "potent" modifiable behavioral, social, economic, physical environment, and policy influences on obesity, eating, and physical activity?**
- **How do patterns of eating, physical activity, and sedentary behavior develop and contribute to obesity and prevention of obesity in children and adolescents?**
- **How do developmental factors interact with biological, social, and physical environmental factors to contribute to obesity and prevention of obesity in children and adolescents?**
- **How are the processes of achieving weight loss versus maintaining weight loss versus preventing excess weight gain biologically and behaviorally distinct?**
- **How can technology and other innovations be used to translate findings from efficacy studies of obesity prevention and/or treatment to larger populations in real-world settings?**
- **What are novel targets (e.g., drug, behavior, and social and physical environments) for obesity management that can improve weight loss outcomes and reduce risk of developing type 2 diabetes?**

Future Directions

➤ **Develop multi-level obesity prevention interventions across the lifespan, especially those at the organizational level (health systems, schools, government, worksites, industry, and media).**

Intervention studies are needed to test novel approaches for preventing excess weight gain during high-risk periods for obesity development with the goal of reducing overall obesity prevalence, as well as disparities across racial, ethnic, and socioeconomic groups. Examples of approaches to investigate include interventions that modify the food, physical activity, sedentary behavior, or other environmental factors for children from infancy through young adulthood; systematic primary care or community-based interventions with pregnant women; social marketing of healthful foods and physical activity; behavioral economics strategies to promote more healthful eating and activity patterns; and increased opportunities for physical activity in schools and worksites. Approaches that simultaneously target multiple levels of intervention are promising, including modification of individual behaviors, family context (e.g., household availability, feeding practices), neighborhood environments (e.g., density of fast food restaurants or physical activity outlets), and societal-level factors (e.g., social networks, food advertising). Research on effective multi-level and systematic approaches to eliminating

disparities in obesity among minority and socially disadvantaged populations are needed. Studies to determine effective policy approaches to promote healthy weight in children and adults could inform population-wide approaches to prevention. Future dissemination of evidence-based obesity prevention programs would be enhanced by study design and measures that support evaluation of intervention implementation, generalizability, and costs.

- **Identify non-biological determinants of obesity and obesity prevention and build further evidence of key interacting influences on eating, sedentary behavior, physical activity, and obesity.**

More research is needed to understand how biological, cognitive, behavioral, social, and physical environmental factors interact to influence obesity-related behaviors and development of obesity. Differences and high-risk periods across the lifespan and across vulnerable populations also need to be explored. Measurement of the full range of potential determinants in both observational and experimental studies would enhance research in this area. For example, developmental neurobiological aspects and eating behaviors related to excess energy intake might be studied in conjunction with interactions among food preferences, dietary composition, household food environment, parental feeding, and food marketing influences. At the social and physical environmental levels, studies to identify neighborhood factors, media exposure, and social networks and their interactions with individual behaviors, cognitions, and motivations could reveal additional influences on obesity development and prevention.

- **Examine methods to improve long-term weight loss maintenance.**

Methods for long-term weight loss maintenance should be guided by a better understanding of the behavioral and biological context after weight loss in children and adults. Basic information is required about the reduced-obese state, such as assessments of physiological, nutritional, cognitive, affective, behavioral, and socio-cultural and physical environmental factors that affect an individual's predisposition to regain weight or maintain weight loss. Studies comparing before and after weight loss and/or successful versus non-successful weight loss maintainers could be informative. These may allow for identification of protective individual, social, or environmental factors that reduce risk for weight gain and inactivity in an otherwise obesogenic environment. Intervention studies are needed to examine the efficacy of various weight maintenance approaches (e.g., behavioral, pharmacological, environmental, combination) after a minimum of a 7 to 10 percent weight loss.

- **Evaluate novel technologies and tailored methods of weight control interventions.**

Research is needed to examine the stand-alone or added efficacy of using technologies (e.g., ecological momentary assessment, smart phones, texting, social networking applications, devices to track physical activity and dietary intake) and other innovative strategies to facilitate diffusion and use of empirically validated strategies (e.g., self-monitoring) with less face-to-face contact. These technical approaches could support individualized and tailored delivery of interventions outside of the clinical setting. Research should also evaluate technology-based and/or tailored interventions delivered in locations where people already convene for other purposes (e.g., worksites, places of worship). Studies could assess the relative efficacy of various technologies (alone or in combination) or tailored

messages and/or the minimal dose of face-to-face contact required for clinically beneficial weight loss.

Improving Clinical Investigative Tools

Technological advances in instrumentation are allowing scientists to characterize body composition and mechanisms of body weight regulation, such as energy intake and expenditure in humans, and begin to establish links between obesity, diabetes, and metabolic syndrome. In clinical research centers, investigators can modify energy and nutrient intake in well-controlled environments and quantify changes in energy expenditure, body composition, and related physiological parameters. Because some of these changes can be very small, measurement is only possible with the improved precision and dynamic range of newer generation whole-room calorimeters, dual-energy x-ray absorptiometry scanners, MRI, and other specialized instruments. This increased measurement capacity and precision allows clinical studies in well-controlled environments to quantify small but significant between-individual differences or within-individual changes in energy balance that may be important to body weight regulation. These measurement techniques also allow researchers to examine differences under varying conditions (e.g., over or underfeeding, exercise, sedentary states, and pharmaceutical interventions). Further development of clinical tools and measures is needed to continue to facilitate and simplify these studies.

Objective, unobtrusive, relatively simple, and cost-efficient measures, monitors, and sensors are particularly needed for use in free-living and population-based research. Portable sensors and monitors are increasingly useful for continuous monitoring of an individual's physical status, including heart rate, blood glucose level, hydration, body and ambient temperatures, physical activity, posture, geo-location, sleep, pain, environmental lighting, and many other factors. Developments in this area are fueled by advances in sensors, processors, memory storage, wireless communication, and Web-based data transport, processing, and sharing. For example, in the area of dietary assessments, emerging technologies are exploring the use of cell-phone cameras and Web-based imaging recognition software for energy intake determinations. Further research and refinement are needed to improve the accuracy, reliability, acceptability, and efficiency of these tools. Likewise, validation and testing are needed to develop brief assessment tools that capture relevant and immediately useful information on risks for obesity and weight-related behaviors across the lifespan in medical settings, particularly primary care. A particular need is for measurement approaches that can be used in children.

Key Questions

- **What are the best ways to measure individual variability and improve classification of various obesity phenotypes (e.g., cognitive, behavioral, metabolic, and body composition)?**
- **How can existing and emerging technologies be used to improve the accuracy and efficiency of assessment in intensively controlled laboratory or clinical research?**
- **What technologies can be harnessed or developed to bring accurate, acceptable, and low-cost assessments of energy intake, energy expenditure, physiological responses, and body composition into real-world settings with free-living humans, such as medical clinics, schools, and communities?**

- **What new tools, methods, and technologies are needed to assess nutrient intake, specifically the amounts and types of foods and beverages consumed over discrete periods in free-living humans?**

Future Directions

➤ **Improve measurement accuracy, sensitivity, and feasibility of clinical obesity research tools for phenotyping.**

Improved tools for both short- and long-term monitoring of body composition, energy intake, energy and substrate utilization, physical activity and fitness, diet composition, and behavioral assessment in human studies are needed. These tools are needed across the lifespan, from infancy throughout adulthood. Body composition measurement for use in both research and practice settings is a particular area of research opportunity. While BMI is a good general estimate of overweight and obesity in a population, it is not ideal for understanding individual body composition status or changes and is not necessarily equivalent across all sex, age, or race/ethnic groups. Improvements in the capacity to measure body composition accurately in all age groups in clinical settings would allow research studies of the relationship between body composition and clinical features, and would facilitate translation to medical management in real-world situations. Additional priorities include brain imaging by functional MRI and PET scanning, measures of adipocyte, muscle, bone, macronutrients (lipids, carbohydrates, and protein) and their metabolite turnovers and depositions, and heat generation and dissipation in tissues and organs. Clinical research centers (such as those supported by Clinical and Translational Science Awards) are an example of a good venue for supporting both mechanistic (bench-to-bedside) studies and the creation of reference standards for free-living clinical and population research.

➤ **Establish and reduce cross-center (laboratory) variability in the same measurements.**

Despite using the same techniques and instruments (even from the same manufacturer), assay results often differ across different research sites. Standard operating procedures and references need to be established that include strategies to correct for instrument variability and thus improve the accuracy and/or consistency/agreement in data collected across multiple sites.

➤ **Improve free-living assessments.**

Development is urgently needed for measurements in free-living humans of diet (energy intake, macro and micronutrients, body water content, appetite, satiety, and eating patterns), physical activity and inactivity (frequency, intensity, type, duration, and social context), living and working environments (including sleep), and stress (physical and emotional), as well as population-level assessment tools of social networking and the built environment. This area of research will require the development of new data collection and analytic tools designed to enhance information derived from clinical and population-based studies.

➤ **Develop assessment tools for clinical settings.**

It is important that inappropriate weight gain trajectories or weight fluctuations be identified earlier in primary care settings. Many clinicians in primary practice frequently do not record or plot BMI values or address weight gain trajectories, even in people who are overweight by BMI criteria. Development of brief, cost effective and predictive obesity risk

assessment tools for assessing and monitoring weight and weight-related behavior that are validated for use in clinical settings and trials would represent a crucial step toward rectifying these practices. In addition to validity and reliability, the needs of health care providers, their patients, and participants in clinical studies are important to consider in developing these tools. Assessment tools are needed across the lifespan that address quantitative nutrient, caloric, and energy expenditure information, as well as qualitative dietary and activity habits, such as frequency of eating at restaurants or fast food establishments, excessive consumption of sweetened beverages, consumption of excessive portion sizes, and bouts of sedentary (e.g., screen time) and non-sedentary behavior.

- **Overcome limitations in current brain and metabolic tissue imaging techniques.**

MRI and single photon emission computed tomography (SPECT) reflect changes in blood flow to the brain as a surrogate for direct assessment of neuronal activity. PET technology permits direct assessment, but the repertoire of suitable reagents is limited, and radiation exposure reduces applicability. Access to the anatomy of connections among neuronal groups can be provided by diffusion tensor imaging. Research is needed on complementary *in vivo* electrophysiology (e.g., EEG) and techniques for integrating all such measures with sophisticated quantitative and qualitative assessments of ingestive behaviors. New, relatively noninvasive technology is also needed to enhance the ability to monitor the incidence of BAT in the human population, and to measure BAT mass, metabolic activity, and its contributions to overall energy balance.

IMPORTANCE OF RESEARCH GOALS AND STRATEGIES: HOW TRANSLATING RESEARCH OUTCOMES MAY LEAD TO IMPROVEMENTS IN HEALTH

Obesity is the major driver of the increased rates of type 2 diabetes worldwide and a serious sequela of intensive insulin therapy in type 1 diabetes. Thus, reversing the trends toward weight gain both in the general population over time and in individuals over their lifetimes is key to conquering diabetes. The past decade has seen huge gains in understanding of the exquisite and intricate regulation of energy balance and of the mechanisms by which excess nutrient intake and inadequate physical activity exert their deadly effects. This information, as well as knowledge yet to be developed, creates opportunities to intervene. One such prospect involves breaking the links between obesity, inflammation, and altered metabolism. Another entails restoring optimal energy balance through re-setting of signaling networks that regulate appetite or inducing increased peripheral energy expenditure. Alternatively, the ability to modulate the development of fat or direct deposition of nutrients to specific locations could turn out to be potently protective against obesity-associated health problems. This potential strategy will entail understanding how to enhance adipogenesis in a way that reduces inflammation, which could have a positive impact on all tissues. A better understanding of genetic contributors to obesity and type 2 diabetes may identify new therapeutic targets and help tailor therapeutic strategies for people at risk. Likewise, developing and testing multiple approaches to help diverse populations avoid inappropriate weight gain across the lifespan will boost efforts to prevent type 2 diabetes and its health complications in the United States. New technologies and tools could help health care providers detect weight issues sooner and help clinical investigators tackle the challenges of how biological, behavioral, and environmental factors affect weight loss and gain in real world settings.