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OBESITY TECHNOLOGY

Engineering Approaches to Energy Balance and Obesity: Opportunities for Novel Collaborations and Research

Report of a Joint National Science Foundation and National Institutes of Health Workshop

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Abstract

Energy balance disorders account for a large public health burden. The obesity epidemic in particular is one of the most rapidly evolving public health problems of our day. At present, two-thirds of American adults and one-sixth of American children and adolescents are considered either overweight or obese. Public health concern about obesity is high because of the increased risk and increased mortality of cardiovascular disease, Type 2 diabetes, many forms of cancer, gallbladder disease, and osteoarthritis. These risks increase with the severity of the obesity. Excess adipose tissue, representing fat storage, ultimately derives from an imbalance between energy intake and energy expenditure. Conversely, undesirable and inadvertent loss of body weight and muscle mass, as seen in aging and cachectic states of chronic diseases such as heart failure and cancer, have serious clinical and functional consequences without satisfactory clinical or behavioral solutions. Innovative engineering technologies could help to address unresolved problems in energy balance, intake, and expenditure. Novel sensors, devices, imaging technologies, nanotechnologies, biomaterials, technologies to detect biochemical markers of energy balance, mathematical modeling, systems biology, and other approaches could be developed, evaluated, and leveraged through multidisciplinary collaborations. Engineers, physical scientists, and mathematicians can work with scientists from other relevant disciplines who possess expertise in obesity and nutrition. Furthermore, the possibility of re-engineering the "built environment" to encourage higher levels of physical activity has been suggested as another promising and important approach to which engineers can contribute (see http://www.obesityresearch.nih.gov). Ultimately, systematic application of the "Engineering Approach" can help in developing the needed technologies and tools to facilitate research and eventually support therapeutic advances and behavioral change. This article summarizes important public health concerns related to disordered energy balance and describes research priorities identified at a recent National Science Foundation-National Institutes of Health workshop. Research funding opportunities are described as posted on the NIH Guide to Grants and Contracts (see http://www.nih.gov/grants/guide).

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Abbreviations: (BMI) body mass index; (DR) dietary or caloric restriction; (EE) energy expenditure; (GEI) Genes and Environment Initiative; (MEMS) micro-electromagnetic systems; (PA) Program Announcement; (PAR) Program Announcement with Review; (PCA) principle component analysis; (RFA) Requests for Applications; (SBIR) Small Business Innovative Research; (STTR) Small Business Technology Transfer; (WBC) Walkable and Bikable Communities Project

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Introduction

This report summarizes background information and discussions for a workshop held in June 2006, entitled Engineering Approaches to Energy Balance and Obesity: Opportunities for Novel Collaborations and Research. The meeting was convened by the National Science Foundation and the National Institutes of Health to identify and prioritize important and under-studied research topics in energy balance that could be addressed through innovative engineering approaches.

The Public Health Challenge: Problems of Positive and Negative Energy Balance

General Population: Overweight and Obesity

At present, ~65% of American adults are either overweight (body mass index (BMI) ≥25 kg/m^2) or obese (BMI ≥30 kg/m^2), and ~16% of American children are similarly categorized (by age-and sex-adjusted percentiles of BMI).[1] This worrisome situation reflects the high energy efficiency of American life, where little physical effort is needed for work and recreation, and where the national diet is abundant in low-cost, energy-dense food. Popular approaches to weight control have been generally unsuccessful, despite public awareness of the problem and considerable individual efforts at weight loss. Furthermore, the United States is not alone in facing this issue; rates are also rising worldwide in both developed and developing economies.[2]

The public health consequences related to obesity are already serious and are expected to worsen. Type 2 diabetes rates are starting to rise across the age spectrum[3,4] and the potential for a substantial obesity-driven increase in morbidity and mortality from multiple forms of cardiovascular disease (e.g. coronary heart disease, stroke, and congestive heart failure) also is of concern.[5] Overweight and obesity also may increase the risk of several forms of cancer (such as breast, colon, and prostate cancer), arthritis, and digestive diseases (such as gallbladder disease and non-alcoholic steatohepatosis). Even risk of congenital heart defects has been tied to maternal overweight, perhaps due to the presence of early stage and undiagnosed Type 2 diabetes.[6,7] Ultimately, resolution of the obesity epidemic at the population level will depend on individual behavioral changes that take place within the larger societal environment. Such changes may be facilitated in some individuals through medical therapies such as drug treatment and surgery. However, new technologies and tools are also needed to monitor behavior and achieve treatment goals for diet and activity.

Elderly and Chronically Ill Population: Sarcopenia and Cachexia

Defects in nutrient and energy metabolism are major contributors to the deleterious changes in body composition and associated metabolic disorders observed with aging.[8] This includes loss of lean body mass (sarcopenia), as well as cachexia (weight loss with increased degradation of muscle protein). Approximately 45% of the older United States population is sarcopenic.[9] The reduced protein stores inherent in sarcopenia leave the elderly with decreased ability to cope with illness or injury, and can have a profound impact on health status. Reduced muscle mass increases the risk for chronic diseases, notably Type 2 diabetes, and leads to the onset of physical functional problems.[10] Indeed, the estimated healthcare cost for sarcopenia-related disability in the United States in 2000 was $18.5 billion.[11]

Even relatively healthy, high-functioning individuals will experience age-related declines in metabolic rate, muscle mass, energy intake, and energy expenditure. Furthermore, chronically inactive individuals have insufficient muscle mass in proportion to weight, with deleterious consequences for health.[12] However, many aged individuals are characterized by existing poor function, an ever-increasing propensity to adverse unpredictable events (such as falls and sudden illness), and impaired response to such events. Aged individuals also are less likely than younger persons to be able to restore body weight after a period of impaired intake, perhaps due to age-related blunting of compensatory effects on appetite. Prediction of the propensity to such events, and detection of early stages of impaired adaptive responses, is needed in order to preserve functional capacity.

The combination of increased fat stores and decreased muscle mass results in a body composition status described as "sarcopenic obesity". This means that obesity in the elderly can be masked by loss of muscle mass, osteoporosis, dehydration, or other body composition changes that result in net weight loss. This condition cannot be assessed readily by anthropometry or other traditional indirect body composition methods. Other situations are also associated with disproportionate and undesirable loss of muscle mass. Notably, some weight reduction programs may carry the risk of significantly reducing protein stores or disturbing water homeostasis. Monitoring changes in body composition, and not just in body weight, is required in these cases.

Cachexia in association with illness represents a situation of persistent negative energy balance that often is accompanied by diminished appetite, disproportionate loss of muscle tissue, weakness, and steady deterioration of physical function. Cachectic states carry a dire prognosis and often herald the final stages of chronic diseases such as heart failure, chronic obstructive pulmonary disease, and cancer. Overall, little is known about how best to reverse cachexia once it develops; methods for detecting the onset of such periods would be useful. To better characterize the relationships between energy imbalances, body composition and risk of chronic diseases and disability, it is important to be able to have accurate assessments of energy intake and expenditure (mainly physical activity) in older adults.

Engineering Challenges in Studying Energy Balance and Obesity

The ability to measure states of energy balance and the components of energy balance – dietary intake, energy expenditure, body composition – is a critical public health need. However, these measurements are remarkably difficult to perform in satisfactory fashion. Also, the inconvenience, expense, and relative inaccuracy of current methods are a persistent and serious barrier to progress in understanding the etiology of significant weight gain and loss and to progress in managing weight. Engineering approaches have the potential to help overcome these limitations, but represent a relatively untapped area of scientific expertise for tackling the research issues and practical aspects of the obesity epidemic.

The Engineering Approach

The "Engineering Approach" is a powerful method that involves the application of knowledge of physical and biological sciences and mathematics to address specific practical problems, in this case energy balance and obesity. The approach incorporates specific elements in a systematic way, which is summarized below.

1. *System Identification* is the clear identification of the system under investigation, including its boundaries and its interactions with neighboring systems. In the present context, a system may be identified at the molecular, cellular, organ, or whole body levels.

2. *Understanding of Physical Behavior and Response* is gained by careful laboratory experiments. Such experiments are designed to elucidate the behavior of the system in response to internal or external stimuli, such as by interaction with other systems.

3. *Mathematical Modeling of Relevant Physics* involves the application of first principles to describe the observed physical behavior taking place within the system. In the present context, one example is the development of models for physio-chemical interactions that result in exchange of mass and energy between the system and its surroundings.

4. *Simulation of Physical Behavior* is enabled by integration of mathematical models into computational tools that perform rapid and efficient solution of the governing physical models, allowing prediction of the behavior or response of the system in terms of changes in its most relevant parameters. Simulators can be used for real time feedback and control scenarios in the laboratory.

5. *Experimental Validation* refers to the comparison of the measured behavior or response of an experimental phantom or subject system to the predicted behavior as obtained by simulation. This is a necessary step for developing confidence in the underlying models. No simulator can be certified for use without appropriate validation.

As illustrated by these elements, the Engineering Approach offers the capability to create physics-based mathematical models and validated physical simulations based on empirical evidence, which can ultimately be applied to design useful devices and processes. In the present context of obesity and other problems of energy balance, the engineering approach might provide a consistent and systematic methodology for developing large, computationally intense models of complex metabolic and energy exchange processes, and a framework for understanding the processes for which models are deficient and therefore require empirical investigation. Such a modeling and simulation framework could enhance the usefulness of clinical observations.

Unresolved Issues in Studying Energy Balance

The Causes of Obesity

Obesity is a complex problem of energy balance, where intake exceeds expenditure and adipose tissue stores accumulate to excessive and detrimental levels. This situation reflects the high energy efficiency of American life, where little physical effort is needed for work and recreation, and where food is abundant, inexpensive, and energy-dense. Obesity results from an imbalance between energy expenditure and energy intake that occurs on a genetically susceptible background. At one level this relationship is accurately described by the first law of thermodynamics but at another level, the problem is better understood as a derangement in a feedback system that has economic and hedonic overrides.[13] Feedback systems can be used to understand the workings of natural physiologic homeostatic systems for regulating food intake and body weight over the short-term and long-term. Once foods arrive in the body, then gastro-intestinal signals provide important input to the brain, mainly through the vagus nerve.[14] Most of this information serves to inhibit further food intake, and to coordinate timing of hunger and the onset of the next eating occasion, partly through the actions of an array of hormones released from the gastrointestinal tract. Adipose tissue also releases hormones that appear to act in longer-term control systems, again through interactions with the central nervous system and other organs. All of these factors interact with other overrides, which may be behavioral modulators of energy balance, such as level of physical activity; environmental and psychosocial factors related to food, such as proximity, convenience, nutrient values and preparation techniques; financial costs; and hedonic factors, such as taste preferences.

Assessing the Components of Energy Balance

Apart from body weight, which can be easily and accurately determined, obtaining accurate measurement of other components of energy balance is difficult at the present time. The very concept of energy balance is in fact somewhat tenuous, as the concept only has meaning in the context of a particular time span of interest (e.g. days, weeks, months, years). In the most obvious sense, an individual is in balance if they do not gain or lose weight. However at the physiologic or biochemical level, we do not know what the best measure of balance may be, whether the mass of various tissues or organs (such as adipose tissue) or a biochemical marker of energy availability or use, as yet undefined.

Assessment of human energy balance, the net difference between energy intake (by diet) and expenditure (by work and heat), is a key component of obesity research, prevention, and treatment. The importance of accurate measurement of states of energy balance can be appreciated by considering average weight gain in middle-aged adults (~10 lb/decade). This significant gain in weight generally results from very small, persistent excesses of intake over expenditure of approximately 0.2-0.3% of the daily calorie consumption.[15] This imbalance is well below the level of perception for most individuals. Similarly, energy expenditure from physical activity must be quantified accurately in order to understand the dose effects of exercise on body weight and other aspects of health, such as blood pressure. Weight loss programs often encourage behavioral changes leading to ~5% increments of expenditure and ~20% decrements of intake. Research aimed at quantifying changes in energy intake or energy expenditure in response to weight loss or behavioral interventions often fails to detect significant differences between groups, probably because of the inability to accurately detect small changes.

Measurement of each component of the energy balance equation presents unique challenges. For example, the difficulty of ascertaining food intake with acceptable levels of accuracy is well known to nutritionists. Standard recall techniques (such as self-report questionnaires) can provide valuable data on dietary patterns, and can be improved by electronic information technologies and by judicious use of results from cognitive process research.[16] These approaches are time-consuming and inconvenient. Furthermore, considerable under-reporting of total energy intake is typical, with this error more severe in overweight than non-overweight individuals.[17] At the other extreme of precision and cost is the research technique of providing a controlled diet with all food intake measured and defined by chemical analysis. Use of this controlled feeding method generally is limited to hypothesis-testing physiology research and therapeutic investigations, because of high cost, small sample size, and demands on participants that restrict enrollment to highly motivated individuals.[18,19] Therefore, new and improved methods of determining energy intake are critically needed for research as well as practical purposes.

Measuring physical activity is also difficult outside of the laboratory. Measurement devices must be convenient, cost-effective, suitable for short-term and habitual activity, and valid for an array of circumstances and states of health and fitness. None of the available methods (pedometers, accelerometers, electronic load transducers, foot contact time monitors, or heart rate monitoring) are fully satisfactory, because they only capture a fraction of needed information.[20] They do not yield data that are easily understood, particularly by the lay public, nor can they easily detect changes in behavior. An exception to this situation is the pedometer, which yields data in terms of steps and in some situations can foster behavior change (i.e. more walking). However, the data yielded by these devices are not of sufficient reliability and precision, and do not readily translate into calories expended over the entire course of a day, to allow comparison to energy expended. Therefore, it is difficult to obtain and express information about both energy intake and energy expenditure in the same units.

We currently do not have accurate techniques for the assessment of total energy expenditure that can be used on a widespread basis. Doubly-labeled water is well-accepted as the "gold standard" method for determining total expenditure, but is fairly expensive, involves the use of stable isotopes, and is most suitable for basic research.[21] Recently improved research tools include room calorimeters with floor-mounted force plates to study movement energetics and global positioning transponders to track outdoor activity patterns. The overall state of body energy stores also cannot be easily ascertained, particularly at the individual level, because data outputs are usually based on group-derived algorithms. However, there has been some recent progress in techniques used to estimate energy stores (e.g. bioelectric impedance for percent body fat; MRI-quantified adipose depots to define metabolically active compartments). Ultimately, we need to be able to estimate directly and with good accuracy and precision whether and to what extent an individual is in energy balance, deficit, or excess.

Engineers might approach issues of biological energy balance by considering the individual as a system, in this case, a complex bio-physio-chemical system. The modeling of the energy cascade, from intake to storage and expenditure is extremely complex, at all biological levels, including the all inclusive whole body level. To bring closure to models, the problems can be reduced to those of measuring thermodynamic quantities such as heat and mass transfer across system boundaries, work produced by the system, and the internal energy of fuel consumed by the system. For most engineering applications, measuring such quantities is well within the state of the art for "macro" devices used for generation or utilization of thermal, mechanical, or chemical energy, for example. However, because the system in this case is an individual person, such measurements are problematic: the system is mobile, produces multiple forms of work, consumes various types of complex fuels, and produces heat at wide-ranging rates and gradients along its boundaries. An added challenge is to make such measurements in a way that does not inconvenience the individual. With these complexities, novel applications of emerging and existing sophisticated technologies are needed to compute energy balance accurately and conveniently. At lower levels of the energy cascade, for example at the organ, or cellular level, experimental characterization of the transport processes pushes the state of the art. Newly emerging nano- and micro-technology could have breakthrough impact in the development of sensors at these small scales.

Assessing Body Composition

Body composition methods should be applied to the management of obesity, because obesity is not always easily identified or monitored. New ways of making body composition measurements are particularly needed for patients who are elderly and patients who are undergoing aggressive weight reduction treatments. The considerable physical and medical differences between these populations suggests the need for several categories of instrumentation: devices for reference measurements, and simple portable instruments for field measurements.

Reference measurements require whole body imaging methods and in vivo elemental analysis using neutron activation and fast neutron scattering.[22] The equipment necessary for these measurements is complicated, expensive and unavailable to users outside a handful of major research laboratories. However, the models used for the analysis are simple, direct and applicable universally to all types of patients. They serve as the "Bureau of Standards" against which other methods are validated.

Field measurements require small, inexpensive, portable devices and methods that can be used to monitor large numbers of subjects in their own free-living environments. Stable isotopes and bioelectrical impedance analysis for the assessment of water compartments are examples of this approach, although satisfactory accuracy and precision are an unachieved goal. It is an engineering challenge, however, to design field instruments that can monitor body composition changes rapidly and accurately, so that they can be used to track the progress and safety of obesity treatments. It is expected that, unlike reference methods, an array of instruments will have to be developed, each of them validated within their own target population.

Assessing Energy Balance in the Aging Population

There are unique aspects of developing imaging and sensor technologies suitable for the elderly. In this population, such tools are needed to assess rates of change in total energy intake, balance, and expenditure, and in the size and function of multiple metabolic compartments (especially muscle mass), over relatively long intervals and in response to rare but cumulative events. These technologies need to be able to distinguish between changes related to the physiological process of aging, as opposed to age-associated ailments and other changes reflecting the health and social experience of the aged population. The inclusion of non-invasive measurement techniques in prospective studies of risk factors for chronic disease can be a powerful approach in clinical aging research for determining the extent and severity of asymptomatic disease and potential future risk of disease development. Any methodology used for the elderly population must accommodate a spectrum of functioning ranging from the unusually fit, to the typical level of function, to the frail. Also, the information gathered should be translatable to research and/or practical applications related to preservation or impairment of ability to undertake activities of daily living. Assessment techniques and data analysis methods need to be able to distinguish between true capacity vs. elicited performance; these are highly variable among the aged, and are susceptible to measurement biases and errors. Human factors issues are particularly important for the elderly population, and must acknowledge participant burdens related to time (including that of caregivers/assistants), transportation, cognitive capacity and effort, discomfort, and physical capabilities (such as vision, hearing, strength, and mobility).

(Note: The report of a July 2004 workshop held by the National Institute on Aging and the National Institute of Biomedical Imaging and Bioengineering on this topic is available at: *http://www.nia.nih.gov/ResearchInformation/ConferencesAndMeetings/ImagingSensorTechnology.htm*)

Improving Energy Expenditure Measurements

The current gold standards for measuring human energy expenditures (EE) are indirect calorimetry chamber (whole-room respiratory chamber) and doubly-labeled water for laboratory and free-living conditions, respectively.[23] Metabolic chambers are capable of measuring rates at 1-minute to 15-minute intervals (depending on the individual chamber designs) of EE prospectively for hours to days. The major advantages of the chamber methodology are: its ability to differentiate EE into its components (sleeping, resting, thermic effect of food, and activity); measurement of substrate oxidation of fat, carbohydrates, and protein (with total urinary nitrogen); good resolution; accuracy; and high reproducibility. However, a metabolic chamber is relatively costly to build and operate, and its use also limits the variability inherent to free-living physical activity. The doubly-labeled water method is well-suited for measuring the sum of EE over a period of time from 5 to 28 days. The non-invasive and non-intrusive nature of the technique makes it well-suited for free-living assessments. However, it is expensive and low in resolution (specificity). Since physical activity-related EE represents the largest source of variability both intra-individually and inter-individually, the ability to measure this component accurately is critical.

Recent technical advances have made accelerometers into a reliable technique to measure physical activity in the free-living. However, their accuracy for predicting EE is currently poor, mostly because they were neither initially designed nor well-validated post-hoc to estimate EE. There is an urgent need to improve portable techniques for measuring EE accurately (±50 kcal/day), specifically (activity types and intensities), reliably (data storage over days to months), and practically (inexpensive, non-invasive, worn without affecting their daily living). Three areas of needed EE research include: 1) Hardware: developing miniature and nano-sized sensors, power supplies, data storage devices, and wireless communication tools. The accelerometer can provide a viable base for new developments. Physiological measurements, such as heart rate, cardiac output, ventilation, skin and core temperatures, regional heat flux, sweating, glucose levels, lactate levels, and others may be combined with accelerometers to further improve the accuracy and specificity of the measurement of EE in sedentary activities where accelerometers are insensitive. 2) Models: predicting EE from these parameters needs to be systematically validated in relevant populations (obese, children, elderly), developed using criteria measures such as the metabolic chamber, and tested for various activity types and intensities. The models should consider the non-linear nature of human physiology, as well as simplicity for stability and generalizability. 3) Validation: the development of the hardware and models needs to be validated in the free-living situation, using doubly-labeled water as a criteria measure. In addition, EE for sedentary (lower intensity) types of daily activity, rather than only exercise in the moderate to vigorous levels, and EE in children, obese, and elderly, needs validation. Accurate and non-invasive measurements for organ or tissue specific EE are also needed.

Metabolic Markers of Energy Balance

An individual's nutritive state with respect to calories reflects at least five factors: 1) calorie intake; 2) calorie usage; 3) calorie balance; 4) individual genetics and physiology; and 5) environmental influences. Unfortunately, measurement of each of these is associated with substantial limitations and uncertainty. An alternative approach to accurately assessing these is to try to build biomarker profiles that reflect the functional caloric state of an individual.

In animals, the question can be approached using biomarkers based on metabolomics. Dietary or caloric restriction (DR) is the most potent and reproducible known means of reducing cancer risk in mammals. For example, in the case of breast cancer, animal models of DR experience fewer propensities to develop tumors or cancers even in the presence of susceptible genetic background or carcinogen exposure. Likewise, increased body mass index is associated with a two-fold increase in post-menopausal breast cancer risk in humans. A biochemical profile reflects the DR metabolome.[24] Exploratory studies identified many redox-active small molecules from sera (measured by

HPLC coupled with coulometric detector arrays) with potential to distinguish dietary groups in both male and female rats. Classification power was addressed using mega-variate data analysis approaches. The compounds weakly distinguished ad libitum versus DR samples by principal components analysis (PCA) due to noise resulting from inter-cohort sampling. Soft Independent Modeling of Class Analogy, which builds independent PCA models of each class of interest, distinguished groups with 95% accuracy. Partial Least Squares Projection to Latent Structures Discriminant Analysis, a projection method optimized for class separation, in contrast, builds models with >95% accuracy in distinguishing groups without obvious cohort interference. Data processing choices of transformation, scaling, and winsorizing (outlier removal) each affected strength of the models, and, in some cases, revealed distinct metabolites to be of importance in building these models, often in gender-specific ways. Computational biology-based approaches suggest that the models have potential for >99.5% accuracy in larger cohorts. Diets varying in extent and duration of DR were used to develop models for intermediate caloric intakes, which are more relevant for human studies. The markers have also passed analytical tests in humans.

In conclusion, metabolic markers should be robust, flexible (multiple applications per marker), validated, and built from "off-the–shelf" components. Thermal heat imaging for assessing heat loss should be re-examined. Technologies for personal assessment, which have profound implications for military medicine and monitoring status in soldiers, could include blood or saliva testing for estimating caloric intake, caloric expenditure, fat stores, changes in energy balance, microtechnology, and mouth-based sensing.[25,26,27,28]

Novel Engineering Approaches

Non-invasive Sensors, Recorders, and Feedback Devices

The possibility of using sensors to measure human physiological variables should be considered. These sensors should be usable by ambulatory humans, acquire data outside the laboratory setting, be convenient, small, and non-invasive, and store data for up to a month for later downloading. The systems should provide feedback to the subject in real time, so that the feedback can be used to modify behavior. An inconspicuous skin-attached device for recording menopausal hot flashes is an example of a convenient instrument for collecting data for post-event analysis. Optimal utility would include providing real-time feedback that might be used to arrest or mitigate the event, for example by delivering a drug dosage. Opportunity exists for further development and miniaturization of such *in vivo* sensors for obesity studies. Their impact may be greatest if integrated into a real-time feedback and control system. Sensors for studying obesity could include: accelerometers to measure motion, sensors to measure foot force, electrodes to measure cardiac output by impedance cardiography, electrodes to measure muscle activation by electromyography, electrodes to measure sweating by skin electrical conductance, and pulse oximeters to measure hemoglobin saturation by light absorption.[29, 30]

Novel noninvasive devices and pattern recognition methods can also be used to perform studies of human food intake behavior in order to produce objective estimates of volumetric and caloric food intake. Such monitoring devices could monitor obese patients as a part of their therapy, and potentially improve their quality of life and decrease their morbidity and mortality. Pattern recognition methods, such as artificial neural networks, "fuzzy" logic, and other statistical methods, could be used to automatically identify periods of food intake based on chewing and swallowing pattern. Additional validation studies could be performed later to test the system's calibration.

Computational Modeling and Systems Approaches

Obesity is a complex problem; therefore we are not likely to find a single "magic bullet", (i.e. one target mediator, metabolite, etc.) that can capture the problem. Therefore understanding of the system (the whole body and organ subsets such as liver and adipose tissue) is necessary. This requires systems biology approaches[31] that will deliver improvements in: 1) methods to gather large data sets (genomics, proteomics, metabolomics; 2) management tools to organize, analyze and integrate large data sets; and 3) models, based on a biological framework or both, to simulate/predict the response of the body. A systems biology approach can ultimately identify multiple targets and allow rational design of diagnostic tests and combination therapies. These new approaches would be more likely to succeed than traditional reductionist approaches, which focus on single or limited sets of markers or pathways.

One computational model of human energy metabolism utilizes daily carbohydrate, fat, and protein intakes as model inputs and computes daily whole-body energy expenditure, macronutrient oxidation rates, respiratory exchange, de novo lipogenesis, and gluconeogenesis.[32] This model integrates a large quantity of published data and accurately simulates daily macronutrient imbalances and the resulting changes of body composition under a variety of controlled conditions, including underfeeding, overfeeding, and isocaloric changes of dietary composition. Models applying systems biology to obesity must be tailored to the appropriate time scale and spatial resolution.

For example, models can be constructed for heat exchange, mass transfer, molecular interactions, sub-cellular metabolic and biochemical networks, cells, organs, organ systems, or the whole body. Several unresolved issues in such modeling include how to: 1) validate models; 2) optimize parameters; 3) perform sensitivity analyses and 4) choose between modeling individuals or groups. The promise of computational modeling is initially to interpret and integrate existing data and eventually to validate new measurement techniques, design future studies, and develop therapeutic interventions for obesity.

Engineering at the Nano/Bio-Interface

Converging science, engineering, and technology at the nanoscale, and especially at the "nano-bio" interface is one of the scientific drivers for research funded by the NSF and the NIH. At the intellectual heart of the research activity is the ability to identify and characterize building blocks at the smallest scales of matter (i.e. atoms, molecules, and cells). Nanoengineering is emerging as the ability to manipulate and control structure so as to produce new properties and functions that are unique because of the scale. The area of nano-bio sensors, for example, could have a profound impact on obesity and energy balance issues. Such sensors often use nano-manipulation of surface properties to make their active elements sensitive to the presence of specific molecules or cells. Understanding and manipulating the interface between living matter, such as cells, or bio-molecules such as proteins and enzymes, and the non-living matter of sensor receptors could lead to the development of in-situ sensors for monitoring the markers that establish nutritive or metabolic state. Sensors of this type also could be used at the organ level to provide in-vivo monitoring and perhaps even neural stimulation in some controlled feedback loops in obesity applications. An emerging application of nanotechnology is in the efficient delivery of drugs via nano-containers such as vaults (capsules) or tubes. Nano-capsules could possibly be bio-molecularly engineered to preferentially attach themselves to certain types of cells or tissues, thereby providing highly localized drug delivery. These are but two examples of what might be possible outcomes of the application of nano-science and engineering to the obesity and energy balance problem. The interdisciplinary teaming of experts in nano-science and engineering with experts in obesity could lead to the application of the Engineering Approach from the bottom up rather than from the top down.

The Built Environment

An additional challenge is how to re-engineer the societal physical ("built") environment in ways that will return physical activity (i.e. energy expenditure) to daily life. There is little question that widespread incorporation of labor-saving and time-saving devices in daily life has produced a net decrease in energy expenditure, below the level that appears necessary for satisfactory regulatory matching of intake to output. The built environment encompasses all of the buildings, spaces, and products created or modified by people, such as buildings (housing, schools, workplaces); land use (industrial or residential); public resources (parks, museums); and zoning regulations. In addition, policies to encourage greater use and accessibility of public transportation systems or individual transportation that uses higher human energy cost can have profound impact on energy expenditure and long-term weight control. Modifying the built environment to encourage healthy lifestyles will require professional input from civil engineers and others with expertise in diverse fields such as transportation, architecture, structural engineering, and human factors engineering (*http://www.niehs.nih.gov/drcpt/beoconf*).

There is growing evidence for the role of physical and social factors on health outcomes. Neighborhood and the built environment, for example, are linked to the epidemic rise in obesity among adults and, increasingly, children. To understand the connections between environmental factors, individual wellness, and population health, there needs to be accurate, valid, and relevant spatial and environmental data; methods in multilevel spatial analysis; and the tools for data collection, storage, management. Spatial informatics is an emerging field for improving and advancing public health surveillance, epidemiological investigations, and prevention initiatives. Spatial informatics provides the theoretical and methodological frameworks to characterize *neighborhood*. This discipline uses individual-level units of observation, measurement, and analysis derived from micro-scaled socio-physical data. Readily available from land parcel records, these spatial data can serve to create personal or place-specific environmental profiles through geoprocessing techniques. This observational research approach has significant advantages over area-based analyses that depend on such administrative units as census units, zip codes, or counties. Spatial informatics increases the precision of analyses, simplifies statistical modeling, and facilitates the interpretations of results. One example of how these approaches can be used effectively in the research setting is the Walkable and Bikable Communities Project (WBC), supported by the Centers for Disease Control and Prevention in Atlanta. The project addressed environmental supports of walking at health-enhancing levels, based on a survey of randomly selected respondents and objective measures of environment taken for each individual respondent. Additional technologies under development for environmental sensing include: assessing a building (house, school, office) *in toto*; measuring energy expenditure; measuring food intake; using event logging (e.g. visits to a basketball court) to assess interventions; utilizing GPS and cell phones as potential tools; and creating validation concepts for interventions.[33,34,35]

Future Research: Priority Topics and Funding Opportunities

Most techniques for measuring either side of the energy equation are costly, cumbersome, and suitable primarily for research use. They do not address the critical issue of overall energy balance, nor do they take advantage of new knowledge of biochemical markers. Moreover, the available devices are not sufficiently precise or specific for guiding individual behavior, and their measurement errors may be greater than the treatment effect. Devices designed for use by the public are particularly hampered by these problems. At present, we do not have the equivalent of a "magic wristwatch" that can readily convey whether the wearer has exceeded an intake goal or fallen short on expenditure. New approaches might provide accurate, convenient, easily understood, and inexpensive devices to foster research and improve clinical management of adults and children. Greatly needed are devices and information-driven technologies suitable for populations relatively unfamiliar with the metric system measurement units that scientists use to study heat and mass.

The consensus of the speakers and attendees at the workshop was that there is a critical need to develop and validate new and innovative engineering approaches to address clinical problems related to energy balance, intake, and expenditure (**Table 1**). The greatest scientific need is for improved methods to achieve short-term and long-term measurements of energy, such as total intake, expenditure, exchange, and balance. Also needed are methods for measuring specific components of energy balance such as resting and basal metabolic rate, physical activity, and thermic effects of food, as well as body composition and metabolic compartments. These measurements must be developed for various physiologic conditions and activities, including work, sleep, and leisure activity. The use of micro-electromechanical systems for biomedical applications (BioMEMs) to measure appropriate biomarkers of energy balance may be of great benefit. Since many materials exhibit novel and unique properties at the nano level, their use might represent a new approach for precise measurements of energy status and metabolic activity.

Novel sensing and imaging technologies to detect biochemical markers of energy balance should be developed and evaluated by collaborating engineers, physical scientists, mathematicians, and scientists from other relevant disciplines with expertise in obesity and nutrition. The goal is to increase the number of useful technologies and tools available to facilitate research in energy balance and health. Eventually, these research tools should facilitate therapeutic advances and provide feedback to foster behavioral changes.

Numerous federal agencies are highly committed to encouraging new research and application efforts on the issues discussed in this article. Descriptions of identified research priorities for the NIH can be found in the NIH Obesity Research Strategic Plan[36] (also see *http://www.obesityresearch.nih.gov*). The research community is encouraged to take note of multiple active NIH solicitations for investigator-initiated research grant applications (**Table 2**).

Appendix:

Workshop and Interagency Program Planning Committee

National Institutes of Health, Bethesda MD:

National Heart, Lung, and Blood Institute: Abby Ershow, Sc.D., Tim Baldwin, Ph.D.

National Cancer Institute: John Milner, Ph.D., Sharon Ross, Ph.D.

National Institute of Diabetes and Digestive and Kidney Diseases: Maren Laughlin, Ph.D., Arthur Castle, Ph.D.

National Institute on Aging: Winifred Rossi, M.A., Chhanda Dutta, Ph.D.

National Institute on Biomedical Imaging and Bioengineering: Brenda Korte, Ph.D.

National Science Foundation, Arlington VA:

Directorate for Engineering: Alfonso Ortega, Ph.D., Michael Plesniak, Ph.D., Semahat Demir, Ph.D., Patrick Phelan, Ph.D., William Schultz, Ph.D.

Workshop Speakers

James Hill, Ph.D., University of Colorado CO (Chair)

Dale Baker, Ph.D., University of California, San Diego CA

Francois Berthiaume, Ph.D., Harvard Medical School, Boston MA

George Bray, M.D., Pennington Biomedical Research Center, Baton Rouge LA

Kong Chen, Ph.D., Vanderbilt University, Memphis TN

Wilson Chiu, Ph.D., University of Connecticut, Storrs CT

Elizabeth Deakin, M.A., J.D., University of California, Berkeley CA

Karl Friedl, Ph.D., U.S. Army Research Institute of Environmental Medicine, Natick MA

Kevin Hall, Ph.D., National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda MD

Joseph Kehayias, Ph.D., Tufts University, Boston MA

Bruce Kristal, Ph.D., Burke Medical Research Institute, White Plains NY

James Levine, M.D., Ph.D., Mayo Clinic, Rochester MN

Edward Sazonov, Ph.D., Clarkson University, Potsdam NY

Randy Seeley, Ph.D., University of Cincinnati, Cincinnati OH

Anne Vernez-Moudon, Dr. es Sc., University of Washington, Seattle WA

John Webster, Ph.D., University of Wisconsin, Madison WI

Table 1.

Priority Areas for Research, Technology Development, and Technology Validation

- Diagnostic and therapeutic systems to monitor energy balance and appropriate biomarkers. Such systems may be used to provide appropriate feedback to stimulate behavior change or to administer appropriate agents.
- Biosensors, including intra-cellular and extra-cellular systems, for measuring calorie consumption and energy expenditure. Sensors which are non-invasive, minimally invasive, miniature, stable, and durable.
- Mathematical and computational models for predicting interrelationships between energy balance and weight control or obesity.
- Mathematical models using metabolic profiles to predict energy intake or energy expenditure.
- Implantable devices for monitoring and treating obesity and overweight.
- Engineering tools that integrate self-reported information with biologic and/or sensor measures of physical activity, diet/nutrition, and energy balance/obesity. This would include tools that measure this integrated information in real-time.
- Methodologies for imaging structure and function, blood flow, perfusion, and metabolism from the molecular/cellular level to whole organs for the purpose of measuring and studying energy balance, intake and expenditure, and weight control.
- Miniaturized non-invasive sensors to detect motion, thermal output, pressure/other mechanical forces, body position, geophysical location.
- Energy balance indicators, such as "smart" clothing, household or office furnishings that incorporate sensors, bar codes or other identifying technologies to calculate energy expenditure, detect motion, identify food characteristics, and assess portion sizes.
- Development of sensors to continuously measure physiological parameters/biomarkers that regulate or reflect appetite and metabolism (e.g. insulin, leptin, vagus nerve activity).
- Identification of new and accurate biomarkers that correlate with energy expenditure, calorie intake, physical activity, or total energy balance, and sensors to detect levels of these biomarkers, inasmuch as output from such sensors would provide needed feedback measures.
- Technologies specifically applicable to the study of energy balance aspects of gene-environment interactions.

Table 2.

Current National Institutes of Health Research Grant Solicitations

For details, see postings on the NIH Guide to Grants and Contracts (*http://www.nih.http://grants.nih.gov/grants/guide/index.html*).

Requests for Applications (RFA)

RFA HL-07-007: "Bioengineering Approaches to Energy Balance and Obesity"; Request for Applications for Exploratory and Developmental grants (R21 mechanism). (*http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-07-007.html*).

RFA-CA-07-032: "Improved Measures of Diet and Physical Activity for the Genes and Environment Initiative (GEI)"; Request for Applications for Cooperative Agreement grants (U01 mechanism). (*http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-07-032.html*).

Program Announcements (PA)

PAR-07-006: "Bioengineering Approaches to Energy Balance and Obesity"; Program Announcement with Review (PAR) for Research Project grants (R01 mechanism) (Release pending).

PA-06-055: "Bioengineering Approaches to Energy Balance and Obesity"; Program Announcement for Small Business Innovation Research (SBIR) grants (R43/R44 mechanism) (*http://grants.nih.gov/grants/guide/pa-files/PA-06-055.html*).

PA-06-056: "Bioengineering Approaches to Energy Balance and Obesity"; Program Announcement for Small Business Technology Transfer (STTR) grants (R41/R42 mechanism) (*http://grants.nih.gov/grants/guide/pa-files/PA-06-056.html*).

PAS-06-130: "Applications of Imaging and Sensor Technologies for Clinical Aging Research"; Program Announcement with Set-aside for SBIRgrants (R43/R44 mechanism). (*http://grants.nih.gov/grants/guide/pa-files/PAS-06-130.html*).

PAS-06-131: "Applications of Imaging and Sensor Technologies for Clinical Aging Research"; Program Announcement with Set-aside for STTR grants (R41/R42 mechanism). (*http://grants.nih.gov/grants/guide/pa-files/PAS-06-131.html*).

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