Diabetes Mellitus Interagency Coordinating Committee Meeting
Co-Sponsored by the
National Institute of Diabetes and Digestive and Kidney Diseases and
National Heart, Lung, and Blood Institute

Leveraging the Investment in Obesity Initiatives To Advance Diabetes Programs

National Institutes of Health
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Summary Minutes

Opening Remarks

Dr. Saul Malozowski, Executive Secretary of the Diabetes Mellitus Interagency Coordinating Committee (DMICC) welcomed the attendees and expressed the Committee's appreciation in having Dr. Jeffrey Flier and Dr. Lawrence Green present to open the scientific discussion on "Leveraging the Investment in Obesity Initiatives To Advance Diabetes Programs." Dr. Malozowski is Senior Advisor for Clinical Trials and Diabetes Translation, Division of Diabetes, Endocrinology, and Metabolic Diseases (DDEM), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH). Dr. Jeffrey S. Flier is Chief Academic Officer, Research and Academic Affairs, Beth Israel Deaconess Medical Center, Boston, and Dr. Lawrence W. Green is Director, Office of Science and Extramural Research, Public Health Practice Program Office, Centers for Disease Control and Prevention (CDC), Atlanta.

Dr. Malozowski explained that following Dr. Flier's and Dr. Green's presentations, members of NIH and other Federal agencies would present their organizations' obesity initiatives. He then introduced Dr. Allen M. Spiegel, Director, NIDDK.

Dr. Spiegel welcomed the participants and stated that DMICC is an important group that reflects the coordinated aspect of the Federal Government's approach to diabetes and, as illustrated by the day's topic, its focus on obesity, given the unequivocal evidence that obesity is driving the current type 2 diabetes epidemic. As examples of this evidence, he noted that more and more is being learned about how mechanistically obesity leads to insulin resistance and that results from the Diabetes Prevention Program (DPP) showed that even relatively modest weight loss can reduce the incidence of diabetes in those at risk.

As co-chair of the NIH Obesity Task Force, along with Dr. Barbara Alving, Acting Director of the National Heart, Lung, and Blood Institute (NHLBI), Dr. Spiegel announced that the Task Force has framed a comprehensive strategic plan for obesity research based on its vision of creating a true interdisciplinary approach to this multi-dimensional problem. He observed that the group was fortunate to have for this meeting two speakers who are outstanding leaders in their respective areas of obesity research. Dr. Spiegel explained that Dr. Flier has been a leader in aspects of the study of leptin and its various actions and is co-author of two articles in the April 2, 2004, issue of *Science*, including "The Fat-Brain Axis Enters a New Dimension" with Dr. Joel Elmquist (Science 2004 304(5667):63-64). For the first time (albeit in mouse models), it has been shown that leptin and similar factors can control brain

"wiring," raising very important issues in terms of intrauterine environmental effects and questions about the biological underpinnings that lead to obesity. Not that these are fully deterministic in the same way that genes are deterministic, but there is evidence of a powerful biological force that may be driving some of these aspects as has been suspected.

Dr. Spiegel noted that Dr. Green has been active in smoking cessation efforts, translational research, and public health approaches and is highly knowledgeable of the importance of behavioral, lifestyle, and environmental factors in these efforts. Dr. Spiegel concluded by saying that, in keeping with the Obesity Task Force's vision, he hoped that in the future there would be a blend of these two distinguished scientists' expertise as a hybrid or interdisciplinary approach to research on obesity. This hopefully would break down the false dichotomy that the causes and answers are all biological or all environmental. Dr. Spiegel then introduced his co-chair and NHLBI's Acting Director, Dr. Alving.

Dr. Alving reiterated Dr. Spiegel's statement that when a major problem needs to be addressed, not only the NIH institutes but other Federal agencies coalesce and bring their individual initiatives forward to be shared. In addition to the NIH Obesity Task Force, there is a Food and Drug Administration (FDA) Task Force on Obesity and a Secretary's Task Force (i.e., U.S. Department of Health and Human Services Secretary Tommy Thompson). Their efforts are interactive, rather than duplicative. She explained that the initiatives being put forth by the NIH Task Force will include bioengineering, to get a better feeling for measuring energy in/energy out; the built environment (the buildings, spaces, and products created or modified by people, such as schools, land use, transportation); prevention of childhood obesity, both in primary care settings and in daycare centers; prevention of obesity in the workplace; and new treatment options. In addition to the trans-NIH effort, individual institutes have their own commitments to obesity, such as the Women's Health Initiative. Dr. Alving said that the latest trial results on use of estrogen-alone, which would be published in the April 14, 2004, issue of the *Journal of the American Medical Association (JAMA)*, show that for these women, whose mean age is now 70, their average BMI is 30, indicating that the problem spans all ages.

Meeting Agenda

The meeting's agenda provided presentations and discussions on the diabetes epidemic and its relation to obesity; the nature of obesity and the obesity epidemic; factors that tend to lead to obesity, including genetic, biological, and environmental factors; therapeutic approaches currently available; lessons learned from public health efforts in smoking cessation and other national health crises; challenges in studying obesity; and possible future directions in obesity research. Current and planned obesity research initiatives sponsored by the trans-NIH Obesity Task Force and by NIDDK, the National Cancer Institute (NCI), and NHLBI and obesity activities of the Veterans Administration (VA), FDA, CDC, and U.S. Department of Agriculture (USDA) were presented by agency representatives. Presenters' slides can be seen at http://www.niddk.nih.gov/federal/dmicc/meetings.htm

Presentations and Discussions

Obesity Research and Relationship to Type 2 Diabetes
Jeffrey S. Flier, MD, Chief Academic Officer, Research and Academic Affairs, Beth Israel Deaconess Medical Center, Boston

Dr. Flier opened his presentation by noting that the press worldwide has published the news of the rising tide of diabetes, a disease that encompasses a group of syndromes with hyperglycemia of multiple etiologies, linked to specific complications that are heavily, but not entirely, related to vasculature. More than 17 million Americans have diabetes, of whom 90 percent have type 2 diabetes. This country now has States where 8 percent of adults have diabetes and many others where the incidence is greater than 6 percent. Whereas overall mortality for cancer seems fairly stable, and cardiovascular disease is declining, the diabetes mortality rate is alarmingly on the increase—it has become the sixth leading cause of death in the overall U.S. population and the third leading cause of death in some minority groups. Dr. Flier said that it is known that type 2 diabetes has a mixture of causes related to genes and the environment, with the genetic component being stronger in those with clinical onset at an early age. MODY (maturity-onset diabetes of the young) disorders are now quite well defined genetically, largely involving genes that impact on the beta cell and insulin secretion. Genes are still important in the late onset of the disease, but environmental factors have a correspondingly greater role.

Dr. Flier stated that the genetics of type 2 diabetes has been intensely studied, continues to be intensely studied, and can be divided into two general categories: the so-called monogenic forms, where it is easy to identify a specific genetic determinant, and the polygene category. The monogenic are the minority of cases (less than 5 percent). They involve a subgroup of mitochondrial genetic disorders (1 percent), the MODY disorders (2-3 percent), and then some rare disorders (0.5 percent) that involve either the insulin receptor or PPARγ, for example. The vast majority of the genetic influences are in the polygene category. Although there are continuing efforts in this area, in Dr. Flier's opinion, the majority of the important polygenes that contribute to type 2 diabetes are as yet unidentified.

As an example of the critical relationship of type 2 diabetes and obesity, Dr. Flier presented information from the Nurses' Health Study, where the age-adjusted relative risk for type 2 diabetes is highly correlated to body mass index (BMI), one of the gold standard ways of looking at body fat content and obesity. Given obesity defined clinically as a BMI of 30 and above, even in the range of body weights that formally are not called obesity, between 25 and 29.9 BMI, the Nurses' Health Study showed a very important, powerful relationship to the risk of diabetes. Dr. Flier suggested that "If we didn't have obesity, if everybody were lean, type 2 diabetes would virtually disappear." He added that it would be hard to argue against the premise that treating obesity would be a powerful treatment of type 2 diabetes that would probably be unrivalled by any other kind of therapy.

While obesity is an excess of adipose tissue, Dr. Flier said there is no precise cutoff between normal and abnormal in terms of the distribution of body weight and body fat. Obesity is defined medically by a linkage to morbidity. It could be defined differently, depending on how the term is used. However, there are relationships between body fat and morbidity that are not linked just to having a BMI over 30.

The rate of obesity among U.S. adults has been steadily growing. According to the CDC's Behavioral Risk Factor Surveillance System (BRFSS), more than 20 percent of the adult population was obese in 2000. Relatively speaking, the problem is worse in children. Dr. Flier said that, interestingly, the dramatic change in the prevalence of obesity does not imply that people are 40 pounds heavier now than they were 10 years ago. Between 1990 and 1998, the average body weight of adult males increased by 7.8 pounds; the average body weight of adult females, 8.3 pounds. The reason that this gradual increase translates into such a change in obesity is the distribution of weights in the population. The mean is close to obesity, so

just a few more pounds, and a person goes from non-obese to obese. A slight shift in weight crosses the threshold from overweight to obesity.

Dr. Flier and Dr. Jeffrey Friedman (The Rockefeller University, New York) have pointed out, in talking about what causes this diabetes/obesity epidemic—what causes this shift in weight, how does one relate the genes to the environment, and so forth—it must be remembered that whatever the environment is that everyone is in, it permits a major fraction of individuals to remain lean, as well as a major fraction to become obese. Dr. Flier added that this is a worldwide event. While, for this meeting, the critical aspects of the morbidity of obesity are diabetes-related, there is no less concern regarding hypertension, dyslipidemia, atherosclerosis, cancer, and a variety of other medical syndromes.

Dr. Flier raised the question of how obesity and increased body fat have such a significant impact on health, especially diabetes, but other disorders as well. A major change in the scientific community's thinking and a major enhancement of its understanding comes from the realization that the fat cells, the fat tissues, are an extremely active, communicative tissue, organ, cell type. Not only do these cells produce leptin, which is a critical regulator of energy balance, appetite, energy expenditure, and neuroendocrine function, but fat also produces a whole variety of circulating molecules that are either cytokines, or hormones, or in some cases, metabolites. A theme that has emerged is the clear understanding that some of these factors can actually enhance insulin action and resist coronary artery disease, and others promote insulin resistance and probably promote some of the vascular findings that are a concern, as well. This central principle—that the adipose cell, adipose tissues, and endocrine organs can be influencing systemic biology—is probably the most transforming aspect of the field in the last 10 years, and it is "picking up steam."

Next Dr. Flier addressed the general aspects of the pathogenesis of obesity. Like diabetes, like hypertension, like everything else, there are genetic components and environmental components. The genes that are influencing obesity, just as for diabetes, are of the monogenic variety and the polygenic (susceptibility) category. It has been pointed out, and seems to be true, although still surprising, that for some people the genetic determination of body fat and obesity is as strong as the genetic determination of height. It seems counterintuitive to many people, but that is what the studies show. Just like body fat and body weight can be influenced by starvation, famine, war, and so forth, so of course, can height, and to about the same degree.

A few of these monogenic causes are known and illustrate the fact that genetic determination of body weight can exist in very powerful forms in specific cases. That has been exceptionally important in understanding how the system is wired and how it works. In the vast majority of cases, these monogenes have not been identified and almost certainly there also is a category of multiple genes creating susceptibility to particular environmental factors.

Environmental factors are also of obvious critical importance. They relate to the availability and the composition of diet, the amount and nature of physical activity, and other factors that influence energy expenditure. In Dr. Flier's opinion, the science does not currently exist to recommend specific kinds and amounts of nutritional support for people in the community. The role of different carbohydrate and fat compositions in the diet are not yet adequately known. He added that this lack of knowledge is obvious to the public and should be viewed as a very important subject for further study.

Dr. Flier brought up the increasing portion size of food, described in a paper in *JAMA* in 2003, as one contributing environmental factor [Nielson SJ, JAMA, Jan 22, 2003]. For example, when the calories in a sugared soft drink are calculated and one looks at the size of the portions ingested, the effect in shifting that weight curve is obvious.

Dr. Flier stated that our genes were honed over millions of years of evolution and perhaps not prepared for the recent environment. Although, it should be pointed out that even tens of thousands of years ago, there was likely to be obesity in some subset of individuals, assuming that they were not truly starving all the time. From a physiologic point of view, obesity is a disorder of energy balance. If energy intake exceeds energy expenditure for a prolonged period of time, there is no other place for energy to be stored, in any significant amounts, beyond fat, and therefore, obesity results. Leanness is a greater threat to survival than obesity, in terms of the speed with which it can cause death; thus, it is not surprising, that there are multiple, redundant systems in place, genetically and physiologically, to resist the consequences of inadequate caloric intake. The same genetic and physiologic systems that have these consequences promote obesity in environments such as those that we live in today.

Dr. Flier explained that the first principle to understand is that the central nervous system (CNS) plays an extremely critical role in orchestrating the decision to eat, to be hungry, to go after food, and to regulate metabolism. It does this through effects, of course, on behavior, on autonomic outputs (things we are not aware of on a day-to-day, minute-to-minute basis), and neuroendocrine functions. These behaviors are integrated, in part, through very discrete centers in the brain that receive information from the periphery and bring about a variety of behaviors and physiologic changes.

Some of the metabolic feedbacks (for example, glucose) have been known for a long time. If a person's blood glucose was lowered, the person would get hungry and various things would happen to his/her autonomic output and other functions. However, the critical physiologic regulators that provide information related to body energy stores really were not known until 10 years ago, with the discovery of the ob (obese) gene and its product, leptin. These can be categorized theoretically into acute and chronic feedback signals.

Dr. Flier cited Dr. Friedman's observation that the gene responsible for the ob/ob mouse was a gene encoding a protein, mainly made in fat, that circulates in the blood and is a cytokine-like molecule. If the molecule is replaced in a deficient mouse, the disease essentially goes away in virtually all ways that it can be measured. This was a true landmark event in the field. Then Dr. Steve O'Rahilly and his group in Cambridge found the first family where there was an ob gene mutation—no functional leptin being made in two cousins. It was clear that the cousins had a severe dysregulation of appetite. From shortly after birth, they were always hungry. They became profoundly obese, but they could be cured with leptin therapy. Today they are essentially lean. This study shows the effects of recombinant leptin in a fully leptin-deficient child—massive obesity as an inborn error of metabolism can be cured by replacement therapy.

Dr. Flier stressed that to look at an individual who has this leptin-deficient disease in the untreated state and to say that the problem is the environment, it is the diet, is of course, absurd. To take the mother away from the child because the mother is thought not to be a good mother, as has happened on a number of occasions in cases like this, is totally unreasonable. As we learn about a pathway and a process, we have to change our understanding of the social implications as well as the medical implications.

The broader context of this, Dr. Flier pointed out, is that not only is the fat tissue (in this case, the fat cells) producing a hormone called leptin, in the absence of which a person has an overwhelming desire to eat, but it also produces a whole group of other factors. Fatty acids are more interesting than they used to be. They are not just fuel. They are also signaling molecules in a variety of ways. It has been known for years that active estrogen can be made in fat tissue, but researchers are just beginning to learn all the implications of that. Much is being learned about various complement factors, cytokines, factors that draw macrophages into fat, factors that regulate the vascular system and thrombosis, factors recently discovered that influence insulin sensitivity, and enzymes that can make local factories for the production

of a classic hormone like cortisol. Dr. Flier added that he is certain that there are many more factors that have not yet been identified.

Downstream targets of products released from fat cells include sex steroid and glucocorticoid-dependent processes, inflammation and immunity, glucose and lipid metabolism, vascular tone, thrombosis, appetite (of course), autonomic nervous activity and all of its manifestations, and neuroendocrine function. For example, if the person's cells do not make leptin, there can be no sexual maturation. Leptin replacement therapy will allow sexual maturation to take place. Dr. Flier spoke of recent studies in review now at Beth Israel showing that in a group of women with the common reproductive disorder of idiopathic hypothalamic amenorrhea (absence of regular menstrual cycles) who have low leptin levels and are lean, if they are given leptin therapy, their reproductive system reactivates. These are examples of the powerful effect of fat on areas that formerly it was not known directly responded to signals from fat. This also includes neural development, an area Dr. Flier's group has been interested in, in which observations suggest, that in the absence of leptin, in the rodent at least, there are major abnormalities of brain development.

Dr. Flier next discussed adiponectin, the molecule identified by a number of groups that is produced very heavily by fat cells, if not uniquely by fat cells. It is a secreted molecule—actually a group of molecules—that circulates in high concentrations. They are an oligomeric species of different kinds that are just now being worked out. This group of molecules can be measured in the blood. It has been shown that with obesity (and to a significant degree, diabetes), the levels of this circulating protein or proteins are reduced. In the last year or two, there are direct demonstrations that adiponectin or one or more of its species will directly increase insulin sensitivity, increase lipid oxidization in tissues such as liver and probably muscle as well, and have major actions on what Dr. Flier called vascular protection. The exact mechanisms by which these effects occur are still being examined.

A recently published paper states that adiponectin has direct effects on targets in the brain that regulate energy expenditure, distinct from the targets regulated by leptin. This provides another part of the loop that directly regulates energy expenditure through the brain through specific receptors, a couple of which have been identified. At least one of them seems to activate AMP kinase enzyme, which is a very important enzyme for metabolic integration. In addition, drugs that increase insulin sensitivity and have other salutary effects, such as the thiazolidinediones that were observed several years ago, also induce the expression and levels of adiponectin. Dr. Flier noted that these are examples of areas of previously unknown biology that can be explored and potentially taken advantage of for therapeutic purposes.

Dr. Flier summarized several studies to illustrate key points about different regions in the hypothalamus that are important in the central circuitry for regulating energy balance. A critical area for hypothalamic regulation and integration is in the arcuate nucleus of the hypothalamus, particularly in the leptin-target neurons in this region. Leptin, by one means or another, gains access to this arcuate nucleus region. Dr. Flier focused on two classes of cells in the nucleus. One expresses two neuropeptides, AgRP (agouti-related protein) and NPY, anabolic or orexigenic products. Putting these neuropeptides into this region of the brain will induce animals to eat and to gain weight. Leptin will suppress the activity of these neurons through binding to its receptor on these neurons. Very nearby, an anatomically and genetically distinct population of cells express pro-opiomelanocortin (POMC) and something called CART; these are catabolic or anorexigenic products. When they are put into the brain, animals will eat less and will lose weight. Leptin activates these neurons.

Secondary targets of the leptin-target neurons are neurons expressing melanocortin (MC4R) receptors in other regions of the brain, which respond to mutually antagonistic ligands. One region called the PVH/VMH that has neurons that have the MC4R receptor on it receives input from these neurons in the form of a peptide called α-MSH (alpha-melanocyte-stimulating hormone) and leptin drives this part. At

the same time that leptin is driving this part, it is suppressing another peptide that is an antagonist. So there is a yin-yang on this receptor, an agonist and an antagonist. Leptin drives the agonist and inhibits the antagonist; therefore this set of neurons is activated not only by leptin but also by a variety of other factors that are of interest to energy balance. Dr. Flier said that the target of these neurons is, of course, a matter of great interest. By using genetic techniques available to modulate these pathways and individual neurons, researchers are learning about what these neurons do, where they go, and how that wiring system works.

A further part of the pathway involves an area called the lateral hypothalamus. All of this is taking place within a few millimeters of physical space in the hypothalamus. The lateral hypothalamus was previously known to be an area where, if you put a lesion in it, the animal would not want to eat. Now it is known that there are several neuropeptides, but the most preeminent is melanin-concentrating hormone or MCH. When MCH is put into the brain by infusion, the animals will eat more and will get obese. If it is genetically knocked down, they will be lean. If it is genetically overexpressed, they will be prone to obesity. There are direct projections that go from the leptin-target neurons in the arcuate nucleus to MCH neurons in the lateral hypothalamus. This is highly complex, but Dr. Flier assured the group that researchers are confident that this is the underlying biology of the core system, based on results from various genetic experiments.

The current April 2, 2004, issue of *Science* cited earlier includes a sketch by Dr. Flier depicting three different models of how leptin affects these neurons in the arcurate nucleus. (A fourth model is under development at Dr. Flier's laboratory.) In the first model, which is the classical approach, leptin receptors turn the neurons on or off and change electrical activity and the expression of various neuropeptides such as NPY and POMC. The second model, which came from a paper published by Dr. Friedman and others, demonstrates that, in fact, not only is leptin acting on these neurons directly through receptors, but in the ob/ob mouse that does not have any leptin, the actual synaptic connections to these neurons can be drastically altered. In some cases, there are more of these synapses; in some cases, less. Even more interesting is the fact that giving leptin to a leptin-deficient animal over a course of 6 hours will make these synapses form again. Although it is not yet understood just where these synapses are coming from and how they are regulated, they can be rapidly regulated by leptin and presumably by other factors, such as nutrition.

The third model is based on the work of Dr. Richard Simerly and his group (at the Oregon Primate Research Center in Beaverton), who have developed observations made earlier at Beth Israel. This earlier research showed that in the ob/ob mouse, its brain weight is reduced and evidences of neural development are suppressed in various regions of the brain. These could only be partially restored by giving leptin to an adult animal. There are important physical projections from these neurons to the paraventricular nucleus. Dr. Simerly very elegantly has shown that in the ob/ob mouse the paraventricular connections are drastically reduced in number and giving leptin to a fully adult ob/ob mouse only partially restores these connections. However, if leptin is given at a critical postnatal period, one at which Dr. Flier had previously shown there was a surge of leptin in the blood, possibly for developmental purposes, the connections are rapidly restored. These developments lead to a need to consider not just nerve activity or the amount of various neural peptides, but how these wiring diagrams are actually formed; the genetic, nutritional, and hormonal influences over their formation; and how they may account for some of the biological facts that are observed, including the effects of early nutrition on later biology.

Dr. Flier emphasized that thus mutations in a CNS pathway clearly can cause obesity in man, whether they are mutations in leptin, in the leptin receptor, in the POMC molecule itself that leads to α-MSH, in a processing enzyme needed to make this maturation take place, or in the melanocortin (MC4R) receptor. If these mutations exist in mice or men, the result is obesity. Most of these cases are, however, rare. On the other hand, as many as 6 percent of relatively young people with severe obesity will have a loss of

function mutation at the MC4R locus. It is like the situation in the mouse, where loss of a single MC4 receptor allele will cause substantial degrees of obesity. It is a tightly regulated pathway that cannot be modified very readily without having substantial effects on body weight.

From the viewpoint of obesity in general, the problem is that most persons do not have any of these defined mutations. They have high levels of leptin proportional to their body fat and they have, not only by inference but by direct study, various degrees of leptin resistance. One of the things that researchers at Beth Israel are most convinced of and that they work on is the premise that there is a real biological fact of leptin resistance, and that leptin resistance is not total, is not global, but is highly specific for certain functions and certain locations in the body. Identifying the mechanisms for leptin resistance is currently their single greatest focus. The two molecules that have been heretofore defined as playing a role in leptin sensitivity are PTP1B, a tyrosine phosphatase, and SOCS-3, suppressor of cytokine signalling 3, a member of the cytokine signaling gene family. Dr. Ben Nneel and Dr. Barbara Kahn, as a by-product of studying PTP1B as a modulator of insulin signaling, were able to show a couple of years ago that a genetic knockdown of PTP1B will cause an animal to be more sensitive to leptin or resistant to obesity. Dr. Flier announced that a paper will hopefully be published soon that will show the role of the SOCS-3 in regulating leptin sensitivity. He is sure more information will be coming out in these areas over the next several years.

Dr. Flier said that another major area of excitement in the obesity domain that also will have great relevance to diabetes is the fact that leptin actions that researchers were initially focusing on rather selectively are seen as integrated with signals regulating meal size. This biology and physiology, in general, was known for a long time. If one expands the stomach and puts food in the stomach, elements go through nerves and inform the brain of something that should limit how much one will eat related to that individual meal. What has emerged is a flurry of work extending earlier studies with the intestinal peptide cholecystokinin (CCK) to now include PYY and ghrelin (PYY coming from the small intestine and ghrelin largely from the stomach). These molecules converge on this same limited region of the hypothalamus. Ghrelin promotes feeding and then PYY released after a meal inhibits appetite. There are still some controversies and sorting out of all the facts regarding this, but Dr. Flier thinks these will be important factors. Even though their primary focus has been on their role in making a person less hungry 10 to 15 minutes after starting eating, these same signals are converging on the pathways regulated by leptin. One thing that is known is that in the absence of leptin, these signals simply do not have a functional impact on the brain. Children, for example, who do not have leptin, will eat until their stomachs are extremely distended because there is no signal that causes them to lose their drive to eat. At the more usual level of leptin and leptin signaling, it is not known exactly how these signals interact.

With regard to the enzyme called 11 beta hydroxysteroid dehydrogenase 1 (11 beta HSD-1), the focus has been on its role in fat as a generator of local glucocorticoid cortisol. The context of this is shown by a 46-year-old male patient who has prominent abdominal obesity, hypertension, and glucose intolerance, a common profile in the obesity, diabetes, and coronary artery disease clinics. He did not have other cardinal signs of Cushing's syndrome such as muscle weakness and striae, and tests for glucocorticoid overproduction were negative.

For years, many endocrinologists, among them Dr. Flier, wondered whether there was something still going on in this type of patient related to glucocorticoid. Most of the studies, and increasingly now, that are looking at the activity of the 11 beta HSD-1 enzyme, which activates the inactive cortisol to become active cortisol within a tissue, indicate that this activity increases when measured in the fat of people as they become more and more obese. Obese individuals have more of this cortisol-activating activity in fat, and they have more of it in visceral fat.

In transgenic mice that have an increase in the activity of this enzyme selectively, the degree of the increase is similar to what is seen in obese individuals. Dr. Flier's laboratory created mice that had local cortisol excess in fat, the genetic-initiating event. The mice developed obesity, especially visceral obesity. Interestingly, they also ate more and developed glucose intolerance, diabetes, and when put on a high-fat diet, insulin resistance, hyper-triglyceridemia, a variety of altered adipocyte-derived circulating factors, hypertension, and fatty liver. They had the whole gamut of the metabolic syndrome—just by tuning up this enzyme about three-fold in adipose tissue. The implications of this are that local glucocorticoid reactivation in fat can cause visceral obesity and its complications. It appears that at least many obese humans have something like this. Inhibition of this enzyme might have beneficial effects on obesity and the metabolic/vascular complications of obesity. This is one of the major drug targets in the pharmaceutical field right now. The initial developments seem to be focused on application to diabetes. Dr. Flier's viewpoint is that a really effective compound—and there is still some question as to which companies, if any, may have a really effective compound—would actually benefit the whole syndrome. This will only be known when a good compound can be tested in people.

Dr. Flier briefly mentioned several other areas of excitement within obesity research that will have larger implications for the whole metabolic field. One is the realization that, just as glucose is both a fuel and a signal, it is not surprising that lipids are a fuel, a substrate for storage, and also a signal for many mechanisms, one of which, for example, would be actions to modulate various nuclear receptors like the PPARs. Another way that they may act would be to focus on their role in the hypothalamus to regulate metabolism. All of the details of this are not known. Dr. Flier presented a slide by Dr. Luciano Rosetti, demonstrating that if long-chain fatty acids in the hypothalamic regions regulate body weight, then increasing these long-chain acetyl CoAs could have the biological consequence of inhibiting food intake and glucose production by the liver. This phenomena that Dr. Rosetti described by a pharmacologic addition of compounds is consistent with a whole variety of other manipulations, both in his lab and other laboratories, that influence these pathways either by modifying fatty acid synthase or the CPT-1 enzyme that modulates fatty acid fluxes into the mitochondria. All these pathways and others suggest that somehow these long-chain acetyl CoAs may bring about signaling changes in the hypothalamus that do modify food intake and metabolism.

Another slide from Dr. Rosetti demonstrated one part of the picture. It depicted a blow up of the arcuate nucleus, the same area that responds to leptin, and showed that there are nuclei there that respond to the addition of long-chain CoAs by a variety of mechanisms—one possible one by the action of these long-chain CoAs to influence K_{ATP} channels in various neurons by either activating or suppressing them. These second-order neurons send out signals that go to find brain areas that will influence metabolism. Some of this same kind of biology has been shown with fatty acids and also with insulin given directly into the brain. These findings modify the view that insulin has direct actions on all these peripheral organs, but it also has indirect actions in the hypothalamus through nerves to bring about some of the same actions. There is greater complexity and greater redundancy of the mechanisms.

Another frontier discussed by Dr. Flier in the pathogenesis of diabetes and obesity is the role of inflammation. It is now known that, just as in various atherosclerotic states, there are inflammatory markers in both obesity and diabetes. They are increased in obese individuals and, in some cases, even in early states in the evolution of the disease. Increasingly, these inflammatory biological factors are linked to the pathogenesis and the complications. One example is the role of cytokines in the pathogenesis of insulin resistance. These cytokines are produced in fat tissue, and very recently several groups have demonstrated that in obesity, macrophages infiltrate, occupy, and are obviously doing something within fat tissue. Just as macrophages are in the vessel wall, there are actually a lot of them in fat tissue. In fact, most of the cytokines that are in fat and are increased in fat tissue in obesity, contrary to what was originally supposed, are coming from resident macrophages. There are signals coming from fat cells to

draw in those macrophages. Dr. Flier's laboratory and those of others are now doing genetic experiments to modify factors that bring macrophages in to see what the consequences of that might be.

Dr. Jerry Shulman at Yale has been focusing on the availability of fatty acids in various peripheral tissues, liver or muscle. Using a modified slide from Dr. Shulman, Dr. Flier showed that a transport protein, FATP1, is required to get fatty acids in high concentration into the cell and then back into the fatty acetyl CoA, the same kind of molecule that seems to be operating in the brain. There are still many mechanisms being invoked, whether through a particular PKC species or through various JNK1/IKKB pathways. Whatever the exact mechanism, there is activation of serine kinase cascades that suppress insulin signaling, among other things.

SOCS-3 is definitively involved in insulin resistance. Inflammation through cytokines will induce SOCS-3 in a variety of brain and peripheral tissues through several mechanisms that will lead to a suppression of insulin signaling. Dr. Flier's point was that all of this information about fatty acids, inflammation, leptin sensitivity, and other factors is starting to come together in a common set of pathways related to obesity and diabetes.

Other evidence about mechanisms and links between obesity and diabetes is contained in recent research by Dr. Mary Elizabeth Patti and others demonstrating that expression of mitochondrial oxidative metabolism genes is reduced in many humans who have insulin resistance in diabetes. Dr. Flier acknowledged this would include many, many people, of course, with obesity. The two most important papers to make this point recently were by the Patti group at the Joslin Diabetes Center (Patti et al., PNAS, July 8, 2003) and by Dr. Vamsi Mootha at Whitehead (Mootha et al. Nat Genetics, July 2003). This observation, that there is a common reduction in the expression of genes involved in oxidative phosphorylation in tissues of people with diabetes or even pre-diabetes, has now also led to an increasing focus on the pathway that may regulate the oxidative phosphorylation gene program, especially on the molecule PGC-1, discovered by Dr. Bruce Spiegelman. PGC-1 is a nuclear co-activator protein that, among other things, will interact with PPARγ, the receptor for the thiazolidinedione drugs. Dr. Flier stated that it appears that the biology of PGC-1 is going to play an essential role in some aspect of the altered energy expenditure and metabolic fluxes in both diabetes and obesity.

Dr. Flier remarked that there are other aspects of the pathogenesis and biology of diabetes and obesity that could be discussed before moving on to the therapeutic approaches to obesity that are available today. There is a great amount of effort, money, and concern about what to tell people about their diet, their exercise, and their behavior modification. Although not an expert in these areas regarding public health recommendations, Dr. Flier thinks that realistically not enough is yet known to comfortably be able to tell everyone what to do. The available drugs are weak, offering modest benefits along with some complications. Meridia (sibutramine), a centrally acting drug, is of relatively limited efficacy, and there is concern regarding side effects. Xenical (orlistat) reduces a mild state of a malabsorption of fat. There is a variety of over-the-counter preparations. Approximately 120,000 gastric operations are being done this year with some very major benefits but also some concern about resorting to surgery as a major therapy for obesity and diabetes.

Dr. Flier referred to the ongoing debate between the two major positions on therapeutic approaches for obesity. Position 1 says that since the recent major increase in obesity is surely caused by the environment (i.e., diet and exercise), not due to a change in genes, treat obesity by attacking the environment. People adamant about this position believe there is basically no point in studying pathways on a molecular level for the purposes of developing drugs. Just change the environmental factors.

Position 2, which is a version of Dr. Flier's view, is that the environmental approach is good, please go ahead and try to accomplish it, but we really do not know how to do this right now; therefore, from a

public health perspective, trying to develop safe and effective medications makes sense, at least until effective social, environmental, and nutritional ways can be found. The scientific community would be happier if it could avoid the drugs for treating coronary artery disease, but at present, lacking another effective approach, we use statins. Likewise, if "statins" that hit the pathway in a relevant way for obesity can be found, it would be unreasonable to not use them.

There are trials to prevent and delay the progression from impaired glucose tolerance to type 2 diabetes, some of them heavily supported by NIH and showing success through dietary and lifestyle approaches. These include the Diabetes Prevention Program, the Malmo Study, the Da Qing study, and the Finnish Diabetes Prevention Study. The Malmo Study, for example, showed a 63-percent risk reduction for type 2 diabetes after 5 years of intervention. Dr. Flier agreed that there is a definable, clear, and obvious benefit regarding diabetes from these lifestyle changes. His question is: "Are we able to press a button and have these lifestyle changes affect this epidemic?" Obviously, we must try. Meanwhile, the scientific approach of studying the problem at the pathways levels is also essential. Both scientific approaches are needed.

The pharmaceutical industry is also studying various possibilities. Dr. Flier believes 10 to 15 percent of obese persons could be successfully treated with leptin sensitivity enhancers; however, studies would need to show this. Axokine, a neurocytokine based on CNTF (ciliary neurotropic factor), which was all the way through a phase III study, was eliminated by antibodies. There are many questions about its mechanism of action. Melanocortin 4 receptor agonists are extremely logical but they are hard to develop because they are agonists and they have to work in the brain; also they have some side effects that are related to a Viagra-like action. This may or may not decrease the market for them if they work for obesity. These are still being developed. Beta 3 agonists, a long-standing effort, are mainly limited by the inability to get a really good drug that is bioavailable and selective for the beta 3 receptor in humans.

Dr. Flier briefly listed other approaches, including the MCH pathway and antagonists that published and unpublished data indicate are powerful anti-obesity drugs. It is unknown if they can successfully make it through the process required before treatment in human beings is approved. A large launch is being planned for the endocannabinoid receptor CB1 antagonist category of drugs that would, in theory, cause weight loss, reduce diabetes, and make it easier to give up smoking. More selective serotonin receptor antagonists and other interesting GPCRs (G protein coupled receptors) are being identified and may be important. The gut peptides (ghrelin antagonists, PYY agonists, GLP-1 pathway, CCK) and alternative gut approaches are leading to many therapeutic approaches. For example, the GLP pathway, which is anti-diabetic, is potentially on the pathway for regulating body weight, as well. The HSD-1 antagonists are being developed broadly by many companies. There are molecules such as DGAT 1, ACC2, and FATP1 antagonists that are directed at various aspects of fatty acid metabolism that are, in some cases, getting ready to be tested in humans in maybe a year. The JNK and JNK-related inflammatory pathways relate to obesity in diabetes and are being heavily mined. Nuclear receptors such as PPAR delta agonists seem to reduce obesity and cause fat burning and those are being studied. There is also the possibility of combination therapies.

Dr. Flier suggested he might have been a little provocative in some of his comments. He stressed, however, that there is no argument that the obesity epidemic and associated diabetes, coronary artery disease, and cardiovascular disease represent a major and increasing unmet medical need. Obesity and fat cell biology are at the core of much of the biology of the problem. New insights into the molecular basis for the regulation of energy balance and the periphery offer exciting targets for drug development. Modifications of the environment are worthy and should be pursued. It is Dr. Flier's opinion that, unfortunately, such attempts are unlikely to reverse the epidemic soon. The goal would be to enable everyone to tolerate the effects of the environment, as many lean people do without treatment, possibly because of their genes.

Discussion

Dr. Spiegel referred to an op-ed piece in the *Wall Street Journal* by Dr. David Katz, who heads a CDC-funded prevention center at Yale. The article entitled "The Scarlet Burger," basically took the position, in reference to a short story entitled "The Birthmark" by Nathanial Hawthorne, that our "birthmark" is the thrifty gene hypothesis that states humans were built to prevent starvation. Dr. Katz agreed with that hypothesis, that we will never be able to develop safe ways, or even effective ones, to block that system, because it is so intrinsic to us. In comparing an obesity-reduction drug to Dr. Flier's statin example, Dr. Spiegel said that although some people will take statins so they can eat steak all the time, very few people take statins for cosmetic reasons. On the other hand, any anti-obesity medication that turns out to be effective will be so massively overused and prescribed irrespective of any warnings put on them, that it will be the same as what happened with phen-phen. Not to say that there will be the same side effects, but individuals who want to lose a couple of pounds before their wedding will be prescribed the drug. The bar, in terms of safety, will have to be extraordinarily high.

Dr. Flier agreed that the bar should be high, but not exaggeratedly so. One cannot say that obesity is a huge public health problem that causes diabetes, hypertension, coronary artery disease, cancer, respiratory disease, and so forth, and we have to find a way to stop this growing epidemic, and at the same time say we must not use a drug because some people will take it to go from a BMI of 25 down to 21. Dr. Flier asked if there was a medication that had the same level of safety that a statin does, would it not be introduced to treat obesity because of concerns that a large number of people would want it just to be lean? The matter should be openly discussed, but as a physician, Dr. Flier would feel obligated to try to help those who could be helped by it. He also would do everything possible to ensure the drug's safety and prevent abuse of it. Dr. Flier added that although he did not endorse this, there is some biological evidence that the population would be healthier if the curve was shifted toward more people whose BMIs were 24, 23, or 22. If a pathway could be safely tuned up so that more people had these lower BMIs, as some healthy people do, it might be a health breakthrough. Dr. Flier stated that too much fear of how a drug might be misused by some people runs the risk of underplaying the beneficial effects of having a successful medication for those who need it. He believes it is possible to find elements of the pathway that can be "tweaked" to do this.

Some of Dr. Flier's colleagues and friends who, when they heard he was coming to speak at this meeting, urged him to make the point that they understood the interaction between genes and the environment—the biological position and the environmental position. At the same time as things are being discussed and tried to affect the environment, they are close to finding new ways of changing the pathways and hopefully finding an effective drug. Dr. Flier expressed his concern that this cannot happen if the community becomes excessively and prematurely concerned about the consequences of a drug being abused.

In response to a comment that some obese people are healthy and do not have glucose intolerance or diabetes, Dr. Flier responded that such persons may not need to be treated medically, but a question remains regarding what "health" is in an obese person. The number of people who are fully healthy at each degree of obesity is a complicated question. Granted that there are obese persons whose blood pressure and LDL are lower and their HDL higher than people who are much leaner than them, this is not surprising because the various hormones that influence pathways and result in complications have to be there in a certain form to be acted on. There are genetic variations and other kinds of variations that influence how any given obese person will respond to having low adiponectin and the level of adiponectin in some of these people will not be as low as it is in others. Dr. Flier added that we are beginning to better understand the heterogeneity between obesity and the complications of obesity.

Another comment concerned whether Dr. Flier had heard that the practice of treating obesity with thyroid hormone seems to be coming back into fashion. He replied that the problem with thyroid is that in the vast majority of instances where it has been studied and given to a non-hypothyroid individual, it does not cause much weight loss and it can cause adverse effects of hyperthyroidism. There is some interest in examining that model and trying to define agonists for thyroid hormone receptors that may be selectively able to stimulate aspects of energy expenditure, for example. That is a perfectly legitimate thing to do under clinical trial circumstances.

Dr. Judith Fradkin, Director, DDEM, NIDDK, asked what Dr. Flier thought NIH or other agencies represented at the table might do to foster development, other than continued support of the kind of basic research that he had discussed. Dr. Flier answered that he certainly would not underestimate this basic research. It is necessary to find the right balance between funding the excellent investigator-initiated studies that are looking at these hypotheses and bearing fruit and finding more effective ways to catalyze interdisciplinary research. The interdisciplinary approach, which Dr. Flier finds critical today, requires a greater degree of infrastructure than used to be required. To do first-class work in energy balance in a mouse today, a researcher cannot be a lone citizen setting up a lab and doing it on his/her own. The investigator needs the genetic models, the measurement equipment, and increasingly sophisticated ways to study behavior, and so forth.

Dr. Spiegel addressed these comments by saying that it is his perspective that NIDDK, while focusing on translational research, should not be either reinventing the wheel or doing what private industry can and should do, a lot of which is market-driven. The market here is so vast that there is no need for NIH to be heavily invested. Diabetes, cardiovascular disease, cancer, and so forth are not orphan diseases that tend to be neglected by industry. NIH investment led to aldurazyme, and even that required industry involvement. For mucopolysaccharidosis that affects a handful of people around the world, a case can be made for NIH involvement. For these other diseases in NIDDK's areas of responsibility, Dr. Spiegel is comfortable in investing heavily in the basic research that will illuminate targets, which industry could do, but will not necessarily. In addition, he believes in using innovative ways to foster an interdisciplinary focus. For example, the NIH Director, Dr. Elias Zerhouni, added monies for the Obesity Task Force's Fiscal Year 2005 budget and one of the initiatives from the Task Force is in the neurobiology of obesity. All the neuroscience institutes, along with NIDDK, will be invested together in this initiative. Dr. Spiegel said that clearly the convergence of neuroscientists as well as endocrinologists such as Dr. Flier is needed, and Dr. Flier agreed.

Dr. Spiegel went on to say that, however, the environmental and lifestyle approaches, by and large, are not going to be the provenance of the private sector. Nike may be interested in pushing physical activity, but the lifestyle or behavioral area is where NIH, both from basic support of economic approaches, policy approaches, and others, really needs to be, in conjunction with its sister agencies. Philosophically, that is how Dr. Spiegel would approach it.

Dr. David Acheson, Chief Medical Officer and Director of Food Safety and Security, Center for Food Safety and Applied Nutrition, FDA,, agreed with Dr. Spiegel that the incentives from industry to get involved in environmental research and change is not there because the area is not market-driven.

Dr. Spiegel also cautioned against glibness in addressing issues in this area. Food and beverages are not the same as tobacco, so pulling soda machines out of schools will not necessarily make everything fine. There are historical controls as well as parallel controls that can be compared with schools where an intervention is implemented, and the outcomes of such studies ultimately will inform policy. Rigorous science is needed, of course, and yet some things need to be implemented while the science is being developed. In regard to implementing measures for which there is not yet a rigorous evidence base, Dr. Spiegel explained that it comes down to a question of risk-benefit. If there is no risk to it, if it is

perfectly reasonable, then the evidence threshold does not need to be very high to implement. He added that we need to consider such values.

Dr. Flier agreed with a comment by Dr. Philip Smith, Deputy Director, DDEM, NIDDK, about molecules and pathways involved in individual differences in energy consumption and weight gain as a good area for research. Dr. Flier referred to a paper from the Mayo Clinic a few years ago that said if one took a group of people in a GCRC type of study and paid them to eat more by agreement and then studied the extent to which they gained weight, some people gained more, some people gained less. One correlation was non-exercise-associated thermogenesis, rather than basal metabolic rate. This was related to physical movements—posture, fidgeting, and so forth. Probably there are biological determinants in part over the extent to which this kind of a pathway is being engaged. It is also known from some of the genetic models, for example the MCH pathway, that leptin or other molecules may influence not only energy intake, but also behavior and physical movement, as in the way a mouse moves around a cage in various non-purposeful but energy-burning ways. These pathways are tied in together. Ultimately, thinking along these lines, we may well have drugs that modify appetite and, at the same time, in a favorable way, cause a person to be a little less of a couch potato. The fact that we do not understand why some people are perfectly happy to not move and others need to move a lot does not mean there is not a neurobiological underpinning there.

Translational Research: Lessons From Public Health Achievements of the Late 20th Century for Emerging Health Issues of the 21st Century
Lawrence W. Green, DrPH, Director, Office of Science and Extramural Research, Public Health Practice Program Office, Centers for Disease Control and Prevention (CDC), Atlanta

Dr. Green stated that, in keeping with the spirit of the theme of the meeting, he wanted to present a convincing case for leveraging the investment in obesity, since, until there is some success in controlling obesity, there is not much else other than the investment to leverage. As Dr. Flier said, the obesity epidemic would not be turned around quickly using environmental interventions, so he trusted that a pill might be found to assist with the problem. On the other hand, there are some very persuasive cases to be made for the experience gained in turning epidemics of this kind around through a combination of educational-behavioral and environmental interventions.

In the 20th Century, and the last third of the 20th Century in particular, there have been some commendable successes: the control of birthrates in developing countries with the family planning movement that began in the 1960s; the rise and then gradual decline in the use of cigarettes; and success with hypertension control and a 58-percent reduction in stroke deaths since the early 1970s. Half of what was lost in the first half of the century to smoking, automobile-crash deaths, and cardiovascular and stroke deaths was regained in the last third of the century. Automobile injuries, especially alcohol-related injuries, have decreased through success in road design, automobile design, and seatbelt usage, a combination of educational-behavioral and environmental interventions.

Dr. Green has been particularly involved in efforts to control birthrates in Bangladesh, the tobacco epidemic, and in hypertension control. Recently, he has undertaken a critical analysis of the tobacco experience. Dr. Green agreed with Dr. Spiegel that there is no easy parallel to be drawn with the obesity epidemic insofar as the industries that must be dealt with are very different, the private sector interests are different, and the product is very different. There is virtually no redeeming value in cigarettes, whereas people cannot live without food. The strategies used for the tobacco epidemic and other initiatives do have a story to tell, however, and one that Dr. Green believes can be usefully analyzed to leverage initiatives in obesity control.

Dr. Green proposed that seven lessons be drawn from these previous initiatives, beginning with an examination of the data on the tobacco epidemic and the events that surrounded the shifts in that curve over time. Some of those shifts were associated with economics. The Great Depression was one of the first points in time when there was a very palpable reduction in tobacco consumption. The end of World War II also shifted the economics, but more to the point, shifted people's social relationships around the product. The product access and availability was changed at the end of World War II. The first smoking cancer concern publication in the *Reader's Digest* caused a gigantic leap in public awareness of the connection between tobacco and their health, and a consequent drop in consumption that was even greater than the previous two. The first Surgeon General's report in the mid 1960's was the point in the curve where the corner was turned from the 65-year increase in tobacco consumption to the beginning of the decrease. Probably the most salient event in recent decades was the Nonsmokers' Rights movement. What parallel might be found in the obesity issue is a matter of conjecture and sometimes humorous speculation. Whether you can get into your airplane seat next to the person beside you may be a form of the Nonsmokers' Rights movement in relation to obesity. Seriously, it was the galvanization of public sentiment and concern around the effect that people who smoked were having not just on themselves but on other people that really accelerated and sustained the reversal of that epidemic.

The first lesson to be drawn is the imperative of surveillance. Tobacco control has had access to good data on a population scale. Surveillance data have given us the opportunity to conduct continuous and repeated natural experiments. Surveillance has been a key to establishing baselines and trend lines that can be projected to warn against neglect of an issue and to put an issue on the public policy agenda. Surveillance also has been the key to showing change in relation to other trends, policies, and program interventions and has been the key to comparing progress in relation to objectives and programs, over time and between jurisdictions.

Dr. Green's Seven Lessons

1. Surveillance and making better use of natural experiments
2. Comprehensiveness
3. Ecological Imperative
4. Threshold spending
5. Environmental influence and settings imperative
6. Education imperative
7. Evidence-based imperative and limitations

For example, the ongoing surveillance data in the 1990s on States' smoke-free indoor air legislation along with corresponding data on consumption in these States allowed the drawing of some inferences about the relationship. If there had been only one-time surveys of the independent and dependent variables, it would have been impossible to determine cause and effect. Did it mean that in States in which people were smoking less, they wanted more clean air legislation? Or was it that more clean air legislation was causing people to smoke less? Having surveillance data over time and between jurisdictions has helped track the order of events or trends and has been a powerful tool in several of the public health epidemics mentioned earlier.

As an example of how data between jurisdictions and over time were used to develop best practices, Dr. Green said that surveillance data were available for 48 states at 3 different points in time (1984-88, 1990-92, and 1992-96) showing no change in their rates of tobacco consumption. Two additional States, California and Massachusetts, showed major changes. California was the first off the mark, with an increase in tobacco taxes funding major campaigns and policy initiatives in the late 1980s, so that in the early 1990s, they showed a virtual doubling in the rate of decline in smoking compared with their earlier period and compared with the other 48 States. Massachusetts got a later start, so they showed no change during that 1980-90 period, but in the subsequent period, they virtually doubled the amount of money they were investing per capita in tobacco control and achieved a near tripling of the rate of decline in tobacco consumption in that latter period. What worked? The comprehensive programs of these two States, combined with their tax increases, resulted in two- to three-times faster declines in adult smoking prevalence, a slowed rate of youth smoking prevalence compared with the rest of the Nation, and

accelerated passage of local ordinances. There were similar, though later, changes in the same directions and of comparable magnitude associated with comparable program spending, in Oregon, Arizona, and in the youth population segment of Florida, where Florida conducted a similar type of program but specifically for youth.

Combined, these data gave a much better sense that something was working. What was it? The main lesson that had to be drawn when the data were examined was Lesson 2: the importance of comprehensiveness. There was no magic bullet, to be sure, in environment or in behavior. The components of tobacco control programs, when isolated, could not be shown to stand alone. There were many essential components; no one of them by itself could account for the changes that were observed in tobacco control. Also, any combination of methods was more effective than individual methods. Perhaps due to a dose effect: The more components, the better the results .The more components, the better the coverage. Dr. Green concluded that a lot can be said for comprehensiveness just from the standpoint of reaching different people with different methods, because different people will be responsive to different methods, different messages, and different environmental changes.

The Office of Smoking and Health at CDC put these lessons together from California and Massachusetts in a document entitled, "Best Practices for Comprehensive Tobacco Control Programs." Dr. Green noted this was different from many of the best practices guidelines that come out of the systematic reviews of randomized control trials because these were not randomized controlled trials. The Office did consult the randomized controlled trial literature, but the problem was that smoking cessation studies in clinical practices had not made much progress over the decades, whereas these large-scale State programs with their combination of policy, environmental changes, and mass media efforts to change public perceptions did produce massive changes.

The components of comprehensive tobacco control programs in the "Best Practices" manual included community programs; State-wide programs, because community programs without the back-up of State-wide support could not stand alone; work with the medical care sector in maintaining a relationship to the chronic disease treatment programs for people with diseases that had been associated with their smoking; school and worksite programs; enforcement of policies that were passed because failure to enforce new laws only made a mockery of policy changes; countermarketing in relation to what the tobacco industry was doing; cessation programs; surveillance and evaluation; and administration and management. These nine things were found to be essential components of a comprehensive approach to reversing that epidemic. Dr. Green suggested looking for parallel components in a comprehensive approach to obesity and diabetes control.

The dose-response response effect seen in the analyses of these data suggested a clear relationship between how much was spent in the programs per capita relative to the effect, aside from the effect of the price increases that went with the taxes in both California and Massachusetts. Somewhere around $6 per capita, there was a point where further expenditures per capita did not show a proportionate increment in the effect in behavior change at the population level. This point of diminishing returns can be compared with the threshold level of something like $2 per capita below which very little increase in the rate of declining tobacco consumption rates could be shown. More on the threshold level follows below.

Lesson 3, the ecological imperative, was the need to address the problem at multiple levels—individual, organizational, institutional, community, State, regional, national, and international. These levels of intervention needed to be mutually supportive and complementary. There needed to be connections between the State and the community, the State and Federal initiatives, and Federal initiatives with other national and non-governmental State efforts. The MATCH model developed by Dr. Bruce Simons-Morton and colleagues has attempted to articulate how this ecological approach can play out in the planning process. The model starts at Phase 1 by defining objectives or goals in relation to health status.

Phase 2 is intervention planning and has three sub-phases: (1) selecting the intervention objectives at levels of healthful behavior and policies, communities, and organizations to support the behavior through initiatives and changes in professional practices and policies; (2) identifying and selecting channels and mediators such as community leaders, community norm shapers, organizational decisionmakers, and individuals at risk; and (3) selecting the intervention approaches and target strategies to influence governments, communities, organizations, and individuals. Phases 3 and 4 are development and implementation, respectively. Phase 5 is evaluation at several levels: process, impact, and outcome evaluation. Dr. Green explained that this model was mostly built on the natural experiments provided by surveillance data.

Dr. Green said that another way to look at levels of intervention is not from the individual to organizations and communities and States and Nations but in an upstream/downstream sense of the causal chain. This premise starts with the people who are afflicted with the complications and to whom tertiary prevention initiatives are applied to prevent them from dying from their complications. Moving upstream to those who are afflicted, but without complications, secondary prevention is employed to prevent them from developing complications. Next upstream are the vulnerable populations for whom primary prevention is tried to prevent them from becoming afflicted in the first instance. This is where the obesity control efforts have their most promising contribution. Even further upstream, a strategy that might be called targeted protection is used to intervene with potentially vulnerable populations and create safer and healthier environments for those populations to prevent them from becoming vulnerable. This is where the environmental approach has its potential benefits.

General protection might be trying to improve adverse living conditions that limit people in their ability to pursue the healthful lifestyles recommended. Dr. Green presented one example that is playing out very saliently, which is the recent recognition that most people who live in relative poverty have very little access to fresh fruits and vegetables. The grocery stores to which they have access do not carry these products. So even if people are convinced that they should be eating fresh fruits and vegetables, they are having a hard time acquiring them.

The spectrum in carrying out this dynamic ranges from the work done by health professionals, particularly medical and public health policy, to the public work that needs to be done in collaboration with the educational sector, the private sector and employee programs, and activities in collaboration with other sectors of society to develop healthy public policy that will lead to more healthful environments.

Dr. Green stated that some of this is exactly what the Division of Diabetes Translation is attempting to do through its State-wide Diabetes Prevention and Control Programs (DPCPs). A study of some of these CDC model programs by Dr. Judith Ottoson and her colleagues has suggested that they could be conceptualized as follows. At the State level, the DPCP attempts to affect and strengthen the 10 public health essential functions or services. It does so initially and primarily through the environment and through its work with partners and stakeholders. In so doing, it hopes to create or to mobilize community interventions, health communications, and health system actions. These, in turn, are seen to affect the more proximal determinants of health outcomes through policy changes, system changes, and behavior changes, all of which cumulatively affect national objectives.

In addition to the point of diminishing returns and expenditure, and the dose-response effect observed in per capita spending to bring about some of these reversals of epidemics, Dr. Green said there is also an understanding that there is a threshold level of spending necessary to get any effect, which is Lesson 4. First, a critical mass of personal exposure is needed for individuals to be influenced. Second, a critical mass of population exposure is necessary to affect a detectable community response. Third, a critical distribution of exposure is necessary to reach segments of the population who are less motivated. Looking at the various States in relation to their relative success, Oregon, Arizona, and California, in a step-wise

fashion, spent $2 to $4.50 to $5 per capita. Massachusetts was spending over $11 per capita, and the effects that California and Massachusetts got relative to these expenditures have a correlation of nearly one.

Lesson 5 is about environmental influence and the settings imperative. Environments provide opportunities and cues and enable choices. Social environments reinforce positive behavior and punish, or can be organized to punish, negative behavior. Legal penalties and financial incentives can be built into environments. Settings can be seen or understood as the best social definition of environments, insofar as it is within social settings that most interventions are organized and implemented. Dr. Green pointed out that worksites and schools are the best examples, because they are distinct from the medical care settings where people normally think of intervention taking place. However, worksites and schools are set up in relation to their own objectives, which usually do not include health except as an instrumental value.

Environments had the opportunity in the tobacco epidemic to intervene specifically on things like smoke-free ordinances in workplaces and restaurants and some that applied to both workplaces and restaurants. There was a gigantic leap in the number of localities that were passing such ordinances in the early 1990s. There was also the move to control the availability of vending machines that had tobacco in them. Vending machines that have high-fat/high-sugar foods in them in schools is perhaps too obvious a parallel, but they are a potential target.

For Lesson 6, the educational imperative, Dr. Green listed public awareness of risks and benefits as necessary to gain public support for change. Public interest in lifestyle options is necessary to engage people in changing their own behavior. The public needs to understand the behavioral steps to take in order to change. Public attitudes toward the options and the steps must see them as do-able. Public outrage at the conditions that have put people at risk or in danger is needed. Finally, public support of the personal and political actions that may be necessary to change environments and behavior is key, which requires a well-informed electorate supporting the actions necessary.

For Lesson 7, the evidence-based imperative, Dr. Green noted that because the evidence is so weak at this moment in time with respect to the obesity epidemic, several bridges will be necessary. Best practices indicated by research will need bridges for their application in practice in underserved areas, because the research, at least until now, has mostly been done in relatively more affluent populations. Best practices from research will also have to be bridged to appropriate adaptations for special populations. The success of individual behavior changes of the affluent will need to be bridged to the system changes needed to reach the less affluent and the less educated. Finally, a bridge is necessary between university-based, investigator-driven research to practitioner- and community-centered research to make the necessary adaptations and tailor interventions to fit the vast cultural and social differences across communities in this country.

Dr. Green offered a vision for future effectiveness- and community-based best practices that would emphasize control by practitioners, patients, clients, communities, or populations to address the many variations referred to earlier. He called for emphasizing the need for local evaluation and self-monitoring as much as Nation-wide surveillance. There is a need to synthesize research other than just randomized controlled trials, because so much of what we are trying to get a handle on in this arena does not yield easily to randomization or other experimental control. He saw research on tailoring and new informatics technologies as holding a growing potential to overcome the essential limitation of mass media, with its homogenization of messages for masses, and using new technologies to tailor the information to specific sub-populations and even down to the individual level.

Dr. Green recommended more transdisciplinary systematic study of place, setting, and culture by engaging anthropologists, social geographers, economists, and others who understand the relationship between place or setting and organization and the changes that may be necessary in the various environments to control obesity. He considers "best practice" as a process to combine and adapt packaged interventions as opposed to the tendency to apply interventions homogenously across a whole population. Packaging programs and asking communities to mount them in a public health sense at the community level simply is not working. Dr. Green recommended that packaged interventions be pulled apart and repackaged to fit the community using a population-based diagnostic planning and evaluation cycle. "Best practices" understanding has to be based not just on the evidence for the intervention having demonstrated its efficacy in one or more studies, but its effectiveness when taken to other populations. A second set of handouts on definitions of translational research and some concepts in that area were distributed to attendees in their meeting packets and went more deeply into these issues. (See From Efficacy to Effectiveness to Community and Back from Clinical Trials to Community: The Science of Translating Diabetes and Obesity Research, January 12-13, 2004, Bethesda, Maryland, http://www.niddk.nih.gov/fund/other/Diabetes-Translation/LawrenceGreen.pdf

Dr. Green proposed that a "matching, mapping, pooling, and patching" process take place. He stated that evidence will have its limitations, inevitably and forever, in relation to such moving targets as population behavior. What he is hoping to find is a way of structuring the evidence and filling the gaps in the evidence that is more systematic than what has been attempted in the past. He recommended starting by *matching* levels of intervention with evidence-based best practices, as illustrated by the MATCH model he described earlier. Next, more systematic ways of *mapping* the changes against theory is needed to identify where the empirical evidence is insufficient, since it always will be insufficient, and how theory generated from research on related behavior or problems can be applied deductively. Theory is one of the tools that social and behavioral scientists have to bring to bear in their work with populations. Third, *pooling* experience from model programs that have not yet been submitted to extensive evaluation will help fill the gaps in evidence and theory. Looking at model programs that seem to be working, even though their evidence is not entirely in, is a necessary part of the process of building programs at the community level. Lastly, Dr. Green cited *patching* the remaining gaps with local experience, indigenous wisdom about local experience in that population. Finally, there needs to be a commitment to evaluate the resulting innovations as part of the process of matching, mapping, pooling, and patching.

Summary. In summary, Dr. Green suggested that good surveillance is the initial key to leverage the initiatives in obesity, based on leveraging the successes in birth control, in injury control, in hypertension control and the reduction of the stroke epidemic, the cardiovascular disease experiences, and changes in public health epidemics in the last third of this past century. Surveillance is needed on food consumption, BMIs, and obesity, and on the policies and practices of agencies and governments. Through good surveillance, there can be better use of natural experiments.

Secondly, a comprehensive approach to this problem is required. There will be no magic bullets. Even if Dr. Flier and his colleagues are successful in developing drugs to help with obesity control, there will be problems in getting people to use them properly. All of which then brings into play the principles from the other lessons to be learned from the achievements of the late 20th century: the ecological imperative—the need to attack difficult problems at multiple levels; threshold spending—the need to get to at least a critical mass of investment before expecting to see any effect; the environmental and settings imperative—the need to adapt our strategies to different settings and to work with other sectors to do so; the educational imperative—the need to build an informed electorate and an aware public, if not an outraged public; and the evidence-based imperative and limitations that lead us to pool the data we have and to fill the gaps in those data with strategic and creative, innovative, and evaluated interventions.

Dr. Green complimented Dr. Spiegel and his colleagues for their leadership at NIH in addressing translational research issues. He congratulated NHLBI for its long history in translation research, especially the National High Blood Pressure Education Program, which he saw as a model to be emulated. He also extended his congratulations to the National Cancer Institute (NCI) for its efforts in tobacco control.

Discussion

Dr. Spiegel told the group a Senator had asked about parallels between smoking and obesity, indicating this is on congressional leaders' minds, as well. He observed that fundamentally the situation is more complex than "you don't have to smoke to live" versus "you have to eat to live." With smoking, although there are pipes, cigars, smokeless tobacco, and filters, fundamentally the issue is smoke versus no smoke. With obesity, we are talking about diets of various macronutrient composition—Do you count calories or not?—and degrees of physical activity—What kind? It is much more complicated and difficult to convey any specific kind of message.

To continue the comparison between smoking cessation and obesity control, Dr. Spiegel referred to the issue of secondhand smoke and the Nonsmokers' Rights movement, arguably a crucial inflection point, versus such issues as airline seats. This leads to the stigma issue. There is certainly far less societal hesitation in stigmatizing smoking and smokers. Given these differences in the two problems, the question is "Is there any parallel?" Dr. Spiegel suggested two worth considering. One is advertising to children, because that has some parallels in the tobacco use situation such as Joe Camel-type messages. Even here, there is tremendous resistance on the part of industry. Associated with advertising is the issue of TV watching, for which there are controlled studies, including an NHLBI one which is not yet reported but in the final stages. There appears to be efficacy to reducing children's TV watching, but it is unclear; the larger study may illuminate whether the efficacy is attributable to decreased sedentary behavior, the effect of the ads, or eating while watching TV. The industry response is that it is strictly a matter of parental choice and responsibility.

Dr. Spiegel gave health insurance as the second parallel because an economic case can be made that obesity, like smoking, leads to increased health care costs. This brings up issues of implementation and again, stigmatization. Should obese people have to pay more for health insurance? These comparisons raise very difficult issues.

Dr. Spiegel also brought up the issues of public perception and education. Dr. Green had pointed out the need for comprehensiveness and spending to inform the public. Currently, Americans are spending some $33 billion on various forms of weight control. This clearly indicates that there is a strong perception of a problem in the public's mind. The paradox is that it is focused on cosmetic aspects. This may be counterproductive in terms of unrealistic expectations of an ideal weight and how much weight loss is necessary to get where an individual wants to be as opposed to the more modest amount that would make an actual health difference. In this sense, in terms of the Surgeon General's report on smoking and public perception, the parallel here may be to focus on the health imperative to balance unrealistic images of slimness portrayed by the TV and print media.

Dr. Green responded that the same reservations regarding aggressively tackling the industries supporting smoking were expressed about tobacco control very early in that experience. The peak in 1966, with the Surgeon General's report, was preceded by a period in which nobody would touch the tobacco industry. It was followed by a period in which there was still a lot of reluctance to get tobacco use off the television screen, the radio, and the airwaves. The industry decided to take themselves off because of the high costs of their competitive advertising on mass media. They found they could be far more effective if they used billboards and more targeted media. The diffidence in being willing to potentially stigmatize obese people

was the same expression of diffidence about smokers at another time in our history. There was a great reluctance to restrain their rights to smoke, to stigmatize them if they were smoking in public places. Dr. Green said that in speaking of these reservations, he was not suggesting a direction that should be taken. He was simply making the historical observation that similar concerns were expressed before.

Dr. Green added that there is a term in the social and behavioral sciences applied to health called "blaming the victim." There is deep concern about this stigmatization problem, especially in stigmatizing people for outcomes of behavior over which they have little control. That is why it is felt that environmental conditions must aggressively be made more conducive to behavior change, rather than mercilessly issuing messages to try to change people's behavior unilaterally.

Dr. Fradkin commented that a fundamental difference, though, between smoking and obesity is the whole secondhand smoke issue and the fact that the behavior of a person who smokes really does have a harmful effect on the people around him or her, whereas there is not a comparable issue with regard to obesity. She also asked Dr. Green to elaborate about using surveillance to make use of natural experiments going on in society. She asked what conclusions could be drawn from the surveillance that has shown such massive increases in obesity and in diabetes over the past decade in terms of the inadequacy of current public health interventions and what types of interventions should be tested in that kind of a paradigm.

Dr. Green replied that it is not yet possible to connect the changes in obesity relative to changes in practices, programs, or policies because the right practices, programs, and policies to affect obesity have not yet been identified. As practices emerge and are tried by various State governments or communities, having the surveillance in place and having the multiple baselines such surveillance provides will enable us to detect shifts in the prevalence of the problem in relation to the changes occurring down the line. For example, communities are beginning to work with the built environment. Will that make a difference? We do not have good data yet, but getting such data requires building the surveillance systems to track it.

Dr. Spiegel added that despite NHANES (National Health and Nutrition Examination Survey) and other surveillance systems, it appears that precise quantitative measures of either caloric intake or of energy expenditure do not exist. Basically, all that we have is inadequate and suspect self-reports. This fuels a debate in which the food industry can say, "It's all lack of physical activity, of being sedentary," and vice versa. He asked Dr. Green if this was true or an overstatement of the case. Dr. Green replied that there is an enormous effort underway in various sectors to get better measures, to validate self-reports and diary-based reports and so forth, on consumption and physical activity, but we are not there yet.

Dr. Rachel Ballard-Barbash, Associate Director, Applied Research Program, Division of Cancer Control and Population Sciences, NCI, stated that NCI's Applied Research Program has a major focus on developing improved measures in diet, weight, and physical activity. This is a huge challenge that she considers distinctly different than the challenge faced in tobacco. As demonstrated by Dr. Green, it can only be addressed with increased focused research. With regard to surveillance, Dr. Ballard-Barbash noted that improvements are being made to NHANES such as using an accelerometer together with self-reporting data on physical activity. Even recognizing that accelerometers only give us one part, it will be possible to have a more objective measure of how the situation changes over a 4-year period. There are other techniques that can be implemented to examine data and do better surveillance of the various issues as we move forward. She agreed with Dr. Green that we need to build surveillance systems to understand what is happening in terms of interventions and policies around the country and to be able to link them to the surveillance data that we have on health behaviors. There may be a point where we will have to recognize that some of the self-reporting just does not work in this field. Hopefully, better technologies will let us find cost-effective ways to improve on that. Regarding this, Dr. Spiegel said there is an NIH bioengineering initiative to develop such technologies.

Dr. Spiegel remarked that the BRFSS data for diabetes and obesity routinely shows, State-by-State, a direct inverse correlation between education status and the severity of either obesity or diabetes. It does not track socioeconomic status, although it may be that education here is a surrogate for socioeconomic status. Dr. Adam Drewnoski claims that, at least in the state of California, there is a surveillance system for obesity and diabetes that is similar to the United States Renal Data System, which geographically across the entire country identifies by ZIP Code, county, and so forth, the extent of hemodialysis and transplantation. The California system shows that in Malibu there is very low obesity. In Alameda County, near Oakland, there is very high obesity. This again shows an inverse correlation with socioeconomic status. Dr. Green alluded to this with regard to adapting programs for the affluent versus the underserved. Dr. Spiegel recommended that there be more definitive research on the economics of this and, if it is real, ask if it reflects differences in the environment—the fact that there is a lot of Whole Foods stores in Malibu—or is it genetics. It does not have to be either/or.

Dr. Flier said there probably are some genetic elements, but probably more social and environmental elements. This situation illustrates the fuzzy border between freewill and determinism here. There are social factors that powerfully influence motivations to be lean and at the margins those operate on behavior. They are influenced by cultural norms and other factors.

Dr. Spiegel continued that if the data supports it and a case could be made that the access to fresh fruits and vegetables is a crucial determinant, then making them affordable in neighborhoods and communities where they are not, might be a very positive thing. In contrast to the tobacco situation, the food industry could be given positive incentives to ensure more nutritious, healthy food was available. Dr. Drewnoski showed a graph at a recent meeting depicting caloric density (energy density) versus cost. Items that are massively energy dense are also inexpensive, and that has been a success of the food industry. This is an area where policy and positive incentives could be effective.

Dr. Ballard-Barbash said that NCI has looked at economic costs in cancer and the variety of factors related to it and recognizes the need for similar research in the obesity area. NCI is therefore developing a program announcement for economic research in this area, with probably a number of institutes joining in this effort. Dr. Spiegel noted that it has been found that persons on food stamps simply cannot afford the 5-a-Day (now 9-a-day) program. Incentives might spur the food industry to change that.

With regard to the best practices issue, Dr. Spiegel said that NIDDK partially supports the National Weight Control Registry being managed by Dr. James Hill at the University of Colorado and Dr. Rena Wing at Brown Medical School. This is a registry of several thousands of individuals who have lost at least 10 percent body weight and maintained the weight loss for at least a year, with the average doing so for several years. What is intriguing is that these are persons who were obese (an initial requirement for participation), which may mean that genetically and within their environment, they are on the left side of the bell curve, and were not part of a group expected to lose and maintain weight loss, yet they have done so. What can be learned from these people? The registry is not rigorously built because of how people are accrued. How can the registry be leveraged? Can accrual be enhanced? Dr. Spiegel added that virtually none of these people are on a low-carb diet; however, he understands that there is not some inherent bias in the way cases are accrued that would select people who are on Atkins.

Dr. Denise Simons-Morton, Director, Clinical Applications and Prevention Program, Division of Epidemiology and Clinical Applications, NHLBI, added that a major factor for persons who are successful in losing weight and keeping it off is that they dramatically increase and maintain their physical activity levels at twice what the CDC recommends (i.e., twice the 30 minutes a day, 5 days a week, moderate intensity). The recommendation to do a higher level of physical activity than is recommended for overall health is being incorporated into guidelines for losing weight and maintaining the loss. The question is how to get people to do it or help them do it.

Dr. Ballard-Barbash stated that Dr. Simons-Morton had made a key point, and hopefully with better objective data from NHANES, there will be a clearer sense of what level of physical activity actually exists in the population, since there is a big problem with self-reported physical activity, particularly in terms of estimating actual levels.

Dr. Malozowski added that Dr. Flier had made a very strong statement that he fully agreed with, that we do not know exactly what foods to eat, in spite of diets probably being the earliest research in diabetes in the 1930s and 1940s. Unfortunately, there has not been much incentive to do research in that particular field. The issue of investment threshold in basic, clinical, and community research to move the field forward was raised in both Dr. Flier's and Dr. Green's presentations and needs to be carefully considered.

Dr. Gilman Grave, Chief, Endocrinology, Nutrition, and Growth Branch, Center for Research for Mothers and Children, National Institute of Child Health and Human Development, commented that exercise has to be a key element for those who maintained the weight loss, since it has been shown that people who lose weight actually lower their metabolism, so it takes even less food to keep them at a stable weight. He asked if this was for a finite period or does the change last for a lifetime.

Dr. Flier agreed that caloric restriction puts people in a starvation-type physiology. Not only do they typically get hungrier, but they become more efficient at burning energy. How long this lasts has not been studied. It would be expensive to do so for more than a matter of weeks.

Dr. Ballard-Barbash commented that there has been an extensive focus in obesity research on the fat cell and fat cell metabolism and somewhat less focus on the muscle cell and muscle cell metabolism, which must also play a large role. The genetic factors might not necessarily be the same as what is seen in obesity; there may be a whole different set of genes that govern that.

Dr. Flier answered her request for a summary on this research by saying that the muscle cell was a bit out of fashion at present. In earlier mouse knockout experiments, for example when they did a knockout of the insulin receptor for muscle, not all that much happened. The mouse did quite well. There is beginning to be an interest again because of the mitochondria research, a lot of which is focused on muscle, because muscle is quantitatively an important tissue for energy metabolism or oxidative metabolism. Studies in muscle have actually led to recent observations about a generally small, but highly reproducible, decline in many, many parts of the oxidative machinery. PGC-1 in muscle seems to be quite important in that regard. It is becoming clear that previously there was no knowledge of the degree to which tissues that were thought of as doing function "A" were actually also signaling to other tissues. The focus was on fat because there were very shocking models of lipoatrophy where it was not understood what was going on. Now this is becoming clear, and Dr. Flier believes the same thing is going to happen with muscle. For example, it is beginning to be shown that in the PPARγ muscle-specific knockouts, muscle is sending interesting signals. What the signals are is not known yet, but they are going to the liver and other places. The capacity of muscle to be oxidative, to burn fat, and to even change the overall phenotype, from slow to fast twitch, is under genetic control, and it is potentially under pharmacologic control with the various PPARs, such as Δ, versus α, versus γ. Dr. Flier added that a weakness in current understanding is knowledge about what the lipid-signaling molecules are that regulate the PPARs, that are so fundamental to cardiovascular and metabolic physiology. They are called fatty acid sensors, but, according to Dr. Flier, what the endogenous modulators are is not understood.

Current and Proposed Initiatives

NIDDK Obesity Initiatives
Philip F. Smith, PhD, Deputy Director, Division of Diabetes, Endocrinology, and Metabolic Diseases, NIDDK, Bethesda, Maryland

In 2003, Dr. Spiegel appointed Dr. Smith and Dr. Susan Yanovski, Director, Obesity and Eating Disorders Program, Division of Digestive Diseases and Nutrition, NIDDK, to coordinate the obesity research initiative efforts within the institute. Dr. Smith explained that to work across divisions represents a new paradigm within the institute and brings together Dr. Yanovski's very different set of expertise and perspectives and Dr. Smith's experience in basic science. In addition to the NIDDK obesity research initiatives that Dr. Smith would be discussing today, he referred the group to the consolidated website for the NIH obesity research initiative at http://www.obesityresearch.nih.gov. The website lists relevant open Requests for Applications (RFAs) and Program Announcements (PAs), notices of upcoming scientific meetings, and an archive of prior meetings. There is also information for the public, although that is not the primary purpose of the website.

For FY 2004 and 2005, NIDDK is offering a broad range of studies from the most basic and molecular to studies that are clinical and translational. In addition, there are several workshops planned to develop future initiatives. NIDDK's initiatives, along with those of NHLBI and NCI, represent a broad, comprehensive approach to fulfill the vision of the NIH Obesity Task Force. Dr. Smith explained that although he will be presenting NIDDK-led initiatives, many are joint initiatives with other institutes, a practice that has been going on for many years, even prior to the formation of the NIH Obesity Task Force.

Dr. Smith stated that one of the fundamental problems in obesity research, from the basic science perspective, is that a lot is known about how to treat diabetes and obesity in the mouse, but less is known about doing so in humans. One focus over the next few years will be to learn more about the physiology and molecular basis of obesity and energy balance in general in humans. To do that, NIDDK is proposing a range of initiatives that focus on using the human as an animal model. One of these is an RFA for ancillary studies for NIDDK's large clinical trials or clinical trial networks to study the mechanistic underpinnings of obesity in those particular trials or the mechanistic underpinnings of successful interventions in those trials. The five NIDDK initiative trials connected to this RFA are: Look AHEAD, the NASH Clinical Research Network, TODAY (which is a type 2 diabetes in adolescents trial), the follow-up of the Diabetes Prevention Program (DPPOS), and the Bariatric Surgery Clinical Research Consortium (BSCRC), which is a particularly promising model to understand the metabolic pathways involved in energy balance in humans. The National Institute of Aging (NIA) is a partner in this last initiative and one of their trials is participating. NIDDK has also provided funds for trials of pilot programs that might lead to ancillary studies. These will be on a smaller scale and designed to be very flexible and very rapid in terms of funding as opportunities arise within these trials.

Dr. Smith noted that Dr. Flier had alluded to the fact that there is lot to learn about diet composition and energy homeostasis and that there is a fair degree of controversy in the field about what we know and do not know about diet composition. NIDDK is soliciting studies in animals with well-defined diets under various exercise conditions and studies in humans under controlled dietary intake, not in terms of self-reports. The Oxygen-18 for Doubly Labeled Water for Research study will address energy expenditure and is an example of efforts to provide the scientific community with resources and reagents to do research.

To bring together a broad range of expertise in the behavioral, imaging, molecular, genetic, and physiology sciences to tackle the problem of energy balance systems within the body, Dr. Smith said NIDDK has issued a call for supplements to support the development of collaborative research teams. This RFA went out on the Internet the first week of April 2004 and quickly generated a lot of interest. Two major areas will be addressed by the RFA: (1) integrative approaches to energy balance and (2) proteomics, which will be necessary to identify biomarkers that might be good predictors of treatment efficacy or might provide clues to the linkage between obesity and comorbidities. There will be a follow-up, at least in the area of energy balance, with an RFA for consortia-type programs to bring resources in human capital together to examine energy balance in animal models, non-human primates, and primates. Another recent RFA involves the use of the zebrafish, C. Elegans, drosophilae, and the mouse as models to identify new pathways and potential new targets for drug discovery and for understanding the pathways themselves.

On the clinical side, one area of concern is the issue of translating short-term weight loss (for which we have many efficacious methods) to long-term weight maintenance. Studies recently have given us a clue that there are a number of hormones that drive us to regain weight. It is not just a matter of our metabolic set-point, but also hormones drive us to eat increased food. One investigator is looking at the possible role of leptin and leptin replacement after weight loss as a way of maintaining reduced weight and reducing the drive to eat, which shows some promise.

Following up on Dr. Flier's presentation, Dr. Smith said that over the last 10 years, dozens of new molecules secreted by fat or at sites of fat-associated cells have been identified, and there are many more yet to be understood. One of the things that is not clear is whether these molecules differ depending on where the fat is. Clearly, fat depots are not all the same. Lipodystrophy is a good model that demonstrates the fact that people lose fat specifically in certain parts of the body and not in others. There is the notion that certain fat, such as visceral fat, may be associated more with comorbidity than other types of fat, but no one knows why that is. NIDDK is hoping to stimulate investigations to understand the key factors produced by fat at different depots, what causes fat to position in different depots, and what is the underlying basis and association with mortality.

Getting back to the human as a model organism, Dr. Smith spoke of an initiative this year on ancillary studies for clinical trials such as pilot and feasibility studies. To take advantage of the enormous opportunity offered by the breadth of the scientific community to partner basic and clinical researchers and really move discoveries in animals into humans, NIDDK issued an RFA with a receipt date in July 2004 to encourage investigations in the humanism research model.

For FY 2005, NIDDK will look at the potential effects of the maternal, neonatal environment on the development of energy balance pathways. There is a growing body of literature that suggests that gestational diabetes, for example, can affect the risk of the progeny to develop diabetes later in life. The same can be said for birthweight, both low and high, and whether an infant breastfeeds or is fed with formula. Dr. Smith asked "What is the template for those effects?" He also cited two papers co-authored by Dr. Flier in *Science* the week of April 4, 2004, that reflect the potential effect of such factors on the obesity epidemic. A group in Oregon demonstrated that in the leptin-deficient mouse there is a significant arborization of the connections between the sensing for leptin in the arcuate nucleus and a primary site of output, the PVH described by Dr. Flier. For example, in the wild-type animal across development (postnatal days 10 and 16 through 60), the arborization of connections can be seen from the arcuate nucleus, which contains the POMC and NPY cells, to the PVH, which contains the cells with the melanocortin 4 receptors. In the ob mouse, the development of those same pathways is heavily deficient. If the adult animals are treated, there is only a modest recovery of this connection; however, animals treated in days 10 to 16, during that critical period of development, can have the entire pattern of arborization and connections restored.

In the same issue of *Science*, Pinto et al. in Dr. Friedman's lab have shown that the actual connections to the various cells in the arcuate nucleus (that is, the NPY, or food-intake driving neurons, or the POMC, or food-intake inhibition neurons) are modulated in the leptin-deficient mouse. The effects of glucose inputs are essentially reversed, going from high on the cells that drive inhibition of food to high on the cells that drive food intake. When the mouse is treated with leptin, this reverses in a very short period of time (i.e., 6 hours).

According to Dr. Smith, both of these pieces of data indicate that the energy balance system in the brain is plastic and can be affected during critical periods in development. What is not known is whether or not this is going to be a template for the kinds of effects that one would see in gestational diabetes in terms of the offspring. Clearly, this is going to require an initiative that does not just study mice. It gets at the issue of what happens in humans. Those are difficult studies to do but NIDDK is hoping to bridge into non-human primates to try to make that connection.

Dr. Smith described two groups of initiatives that are NIH-wide. One, which came from the NIH Obesity Task Force and will be led by NIDDK is the "Genetics and Genomics of Obesity." This is a multiple-component initiative that goes from discovery in model organisms all the way up to testing of candidates in human populations and perhaps long-term prospective studies on individuals before and after development of obesity, not looking at the effects of being obese, but at the possible causes of obesity. The second one is the "Neurobiological Basis of Obesity," which, depending on budget outcomes, will be a major trans-NIH effort supported by the Office of the Director for 2005. All of the neuroscience institutes will be keenly involved, as well many of the other institutes in the Obesity Task Force. It will focus, in the final analysis, on trying to understand the biological basis of human behavior or, in this case, human feeding behavior, a very difficult task. The approach will have to be broad and multidisciplined, requiring imaging studies in humans and studies in various animal models of behavior that relates to food intake and exercise. There will be broad participation of institutes and development of collaborative teams of investigators. NIH has a new mechanism that allows for recognition of contributions from multiple components of a team that will be implemented for the first time with this initiative. This recognition is expected to be a key component in bringing together collaborative teams.

Dr. Smith emphasized that the NIH Roadmap (http://nihroadmap.nih.gov) should not be ignored. It is a key piece of NIH's strategy to move forward in terms of translation of basic findings to clinical intervention. There are three major areas within the Roadmap that NIDDK is heavily involved in and that might be particularly relevant to obesity, as well as other areas. One area is the "National Technology Centers for Networks and Pathways," which will be hubs to develop proteomics technology. The long-range plan is that the hubs for technology and development would be surrounded by spokes that would be disease-relevant and supported by the institutes. NIDDK feels strongly that diabetes and obesity will be major areas within that. The NIDDK website (http://www.niddk.nih.gov) describes two current NIDDK initiatives that involve proteomics; these are not associated with the Roadmap, but will provide good partners with those technology centers.

In recognition that the bridging of disciplines is critical to moving science forward in terms of treating disease, the NIH Director, Dr. Zerhouni, has made the "Interdisciplinary Research Centers," area the centerpiece of the Roadmap. A number of models are being tried, beginning with P20 consortium planning grants in FY 2004. This has received a very large number of applications, many of them focused on obesity. This initiative is actually unlike many of the Roadmap initiatives, since it is intended to focus on a particular disease or condition. Dr. Smith was therefore pleased that so many investigators selected obesity as a significant and complex biomedical problem. His initial review indicates that NIH has been successful in capturing what was wanted—very, very different approaches to the problem, from the built environment to behavior. NIDDK is very involved in this Roadmap initiative and the potential of its impact.

NIDDK is the lead institute for the third Roadmap area in Dr. Smith's discussion, "Metabolomics of Steady-State, Site-Specific Tissues." Dr. Maren Laughlin is the program contact. Dr. Smith noted that although metabolomics is probably a generation behind proteomics in terms of technology development, in the area of lipids and other signaling molecules, it will provide a key piece of the information needed to phenotype individuals to a greater degree. The focus will be on technology development with hubs supported by multiple projects, R01-based or otherwise, that would then use that technology in a particular disease. Information on these initiatives is available at the Obesity Task Force website.

NCI: Optimizing Energy Balance To Reduce the Cancer Burden
Rachel Ballard-Barbash, MD, MPH, Associate Director, Applied Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute (NCI), Bethesda, Maryland

Dr. Ballard-Barbash stated that for the first time in a bypass budget presented to Congress, for the 2005 budget the NCI Director, Dr. Andrew von Eschenbach, included a chapter on energy balance titled, "Optimizing Energy Balance To Reduce the Cancer Burden." Surprisingly, despite probably 50 years of research in animal models and 30 or 40 years of research in humans, it is only recently that the lay public and health professionals have become aware that obesity influences cancer outcomes. Nutrition and diet have been a focus of research at NCI for many years, but only lately has there been a recognition of the fact that NCI has been funding obesity-related research, largely to understand how it influences cancer outcomes. More recently NCI has also funded research on the role of physical activity on cancer outcomes.

Dr. Ballard-Barbash explained that the term "energy balance" is used at NCI to refer to the intersects among diet, weight, and physical activity. Dr. von Eschenbach created a working group across NCI and called for the development of an energy balance initiative in July 2002, as had been done previously regarding tobacco. This group developed the statement that went into the bypass budget. The goals of this statement are three-fold.

- Understand the causes of adverse patterns of weight, physical activity, and diet in the population.
- Understand how these patterns contribute to cancer.
- Apply this knowledge to develop effective interventions for cancer prevention and control.

Four specific objectives were defined and then milestones developed under each of these objectives. ***Objective 1*** is to discover how weight, physical activity, and diet, along with genetic and environmental factors, interact over a lifetime to influence carcinogenesis.

Dr. Green and others had discussed at this meeting the important issue that the working group formulated as ***Objective 2***: Monitor trends and determinants of weight, physical activity, and diet and their cancer-related consequences by expanding nationwide research, particularly the surveillance infrastructure. Given that the institute has had the SEER (Surveillance, Epidemiology, and End Results) Registry for many years, Dr. Ballard-Barbash noted that NCI's attention to population-level surveillance is much larger than that of other institutes. A large part of her program involves improving national and regional data on cancer control surveillance related to factors such as tobacco, diet, weight, screening, treatment, and cost of cancer.

Objective 3 is to develop improved measurement methods for weight and body composition, physical activity and fitness, and diet and bioactive food components, using self-reports and also advances in technology for objective reference measures. Finally, ***Objective 4*** is to accelerate research on energy balance-related behaviors and develop interventions to improve cancer-related health outcomes, especially in high-risk populations.

Objective 1 milestones focus on issues of improved understanding of the mechanisms of obesity and carcinogenesis. The first is to discover and characterize mechanisms leading to cancer by initiating transdisciplinary research centers in the areas of energetics, physical activity, nutrition, and genetics. The Transdisciplinary Research on Energetics and Cancer (TREC) RFA, modeled after the successful transdisciplinary research on tobacco cessation, is expected to be released in June 2004. Another milestone is to improve collection of self-reported and objective measures on all of the energy balance factors within existing population studies to explore potential mechanisms by which these factors affect cancer outcomes. A third milestone involves advancing an understanding of cancer mechanisms by conducting studies in the area of energy balance within existing NCI clinical metabolic and nutrition research units. NCI has supported extensive development of animal models relevant to cancer research. One new area of exploration is examining how animal models that have been developed for the study of obesity might intersect with animal models that have been developed for the study of cancer. Additionally NCI will support basic and clinical research using proteomics and molecular technology as tools for exploring that area further.

Objective 2 milestones focus on improving surveillance activities. The objective has an extensive list of milestones, indicating NCI's broad perspective on surveillance. Plans include expansion of nationwide surveys, most specifically within NHANES and also within NHIS (National Health Interview Survey). These efforts will improve self-report, biologic, and genetic measures within these systems that monitor health behaviors in major U.S. population groups. Because national surveys do not obtain sufficient data on smaller population subgroups, community surveillance through efforts such as the California Health Interview Survey (CHIS) are also supported. In addition, NCI supports a national survey on people's health communication needs related to cancer that will include a component about people's understanding of health recommendations in physical activity and nutrition. Other key aspects of health surveillance are obtaining representative data on healthcare providers' knowledge, attitudes, and practices related to weight control and developing research resources on legislative policies related to nutrition, physical activity, and obesity. NCI is developing a PA on economic factors related to diet, physical activity, and energy balance in at-risk populations. Dr. Ballard-Barbash noted that the U.S. Department of Agriculture (USDA) has an economics PA largely focused on diet. NCI's PA will broaden that focus to include physical activity and weight control. Finally, this objective highlights the need for training, at the national and international levels, to improve competency among future scientific leaders in this area, linking energy balance across the cancer continuum. This will include support of interdisciplinary or transdisciplinary training in basic sciences through population sciences.

Objective 3 milestones address research to improve measurement of the energy balance factors. This research includes reference biomarker research such as the OPEN (Observing Protein and Energy Nutrition) study to explore the extent of measurement error with existing self-report measures. Under this objective, NCI will expand validation research to include diet, physical activity, and fitness through the use of reference biomarkers and measures of physical fitness or activity within national and international cohort studies. NHLBI has been leading an effort promoting the development of innovative technologies, such as bioengineering and other measures to enhance accuracy of measurement; NCI has collaborated with NHLBI in this effort. Dr. Ballard-Barbash explained that one of the difficulties is that most methodologies for capturing these health behaviors have been developed in general populations. Another milestone focuses on the need to develop tools for diverse cultural populations. The last milestone under Objective 3 concerns developing better surrogate (intermediate) biomarkers as predictors of the effectiveness of diet and physical activity interventions.

Objective 4 milestones pertain to development of interventions. Given research suggesting that obesity may have an adverse effect on prognosis for breast and other cancers, NCI is supporting research on interventions that focus on weight control through diet and physical activity for cancer patients and for populations at high risk for cancer. Another milestone is to focus on the effect of sociocultural factors in

the adoption of recommended behaviors and to develop approaches to improve interventions in specific populations. This milestone will examine lessons learned from the tobacco control program and the 5-a-Day program. The potential for social marketing research to enhance the effectiveness of communication is reflected in a milestone to support formative communication research in this area. The effect of food labeling to support recommendations also will be considered under this milestone. Lastly, through the TREC RFA mentioned previously, transdisciplinary research on energetics and cancer will be a focus, not just on mechanisms of how obesity influences cancer outcome, but also to identify effective population-level interventions, particularly with children and adults during critical periods of weight gain.

Dr. Ballard-Barbash concluded by noting that to-date, NCI and all of NIH has traditionally funded research that has examined micro-level factors—individual physiologic, behavioral, and genetic factors influencing a variety of health behaviors or organism behaviors and outcomes and a subsequent disease. Within NCI's initiative on energy balance, examination of macro-level factors—contextual sociocultural, environmental, institutional, and policy factors—is also a key focus, as recommended by many of today's speakers.

National Heart, Lung, and Blood Institute Initiatives
Denise Simons-Morton, MD, MPH, Director, Clinical Applications and Prevention Program, Division of Epidemiology and Clinical Applications, NHLBI, Bethesda, Maryland

Dr. Simons-Morton opened her presentation with a discussion on how NHLBI obesity research fits into conceptual models of translation to inform clinical and public health applications. The first phase is etiologic and determinants research, which is needed to identify potential risk factors, influences, and modifiers. This is followed by randomized controlled trials to determine the *efficacy* of risk factor changes, which then leads to clinical and community trials of intervention *effectiveness*. The distinction between phases two and three is that efficacy is basically asking what NIDDK often calls "proof of principle," whereas effectiveness is what happens in real-life settings. Efficacy involves getting effects on health outcomes when implementing high-quality interventions, with high compliance, in an ideal population, in a research setting. Effectiveness of interventions is a function of efficacy and adherence and delivery in real-life settings. More and more the thinking is that another step is needed—dissemination and translation research, as it has been found that what has been learned is not being translated very well into public health or clinical practice. Now it is thought that we need to study approaches to achieve this final step. For example, given an effective intervention program, how can we get agencies and organizations around the country to adopt it? This means targeting not the patient population or the resident population, but the gatekeepers and organizational decisionmakers to implement such programs.

Next Dr. Simons-Morton described how the NHLBI portfolio addresses these four phases that inform clinical and public health applications. Under the etiologic and determinants research phase, there are observational studies in obesity, such as the National Growth and Health Study (NGHS) that focuses on the development of obesity in children; Framingham, which was the first study to identify obesity as an independent risk factor for cardiovascular disease and is examining additional questions today, including genetics and other mechanisms; and CARDIA (Coronary Artery Risk Development in Young Adults), an observational prospective study in young adults, 18- to 30-years-old at enrollment, that is examining obesity trends over time and relationships between diet, physical activity, and obesity on one hand and cardiovascular risk factors on the other.

NHLBI is funding a number of randomized controlled trials testing whether weight loss improves hypertension and hypercholesterolemia. The institute is working with NIDDK on the Look AHEAD (Action for Health in Diabetes) trial, which is an efficacy study testing whether intentional weight loss

reduces cardiovascular disease events in people with diabetes. There are several effectiveness studies, including Pathways, which was a school-based study of American Indian schoolchildren to prevent adiposity; GEMS (Girls Health Enrichment Multi-Site Studies), which is a program of several studies testing interventions to prevent the development of obesity in African-American adolescent girls; PREMIER, a recently completed study on multiple lifestyle interventions, including weight loss in the overweight participants, to improve hypertension control; and WML (Weight Loss Maintenance), which is testing approaches to maintaining initial weight loss.

Related to the dissemination and translation area, NHLBI has funded several studies under the Environmental Interventions RFA, on which NIDDK took the lead. There is currently a Worksite Obesity RFA to find studies to test intervention approaches in worksites that include changing the environment in the worksite. Dr. Simons-Morton noted that to date studies have not tested organizational change approaches for getting interventions into real-life practice, which is a direction NHLBI would like to move toward. The closest study to doing this is the Catch On Study, a follow-up to the Child and Adolescent Trial of Cardiovascular Health (CATCH). Catch On examined the implementation of the CATCH school-based intervention program in new schools and asked what it takes to get this program implemented in schools. The answer was that it takes a "change agent" in the school.

Dr. Simons-Morton reviewed another conceptual model, the "natural history of disease and levels of prevention" model, which she approached from the opposite direction from that used by Dr. Green when he discussed this same model. NHLBI wants to do primordial prevention to prevent risk factor onset, primary prevention to reduce risk factors when present and thus prevent disease, and secondary prevention when disease is present to prevent adverse disease outcomes. There is no clear demarcation, necessarily, in the continuum, but it is a useful way to think of things and apply the model to obesity.

There are determinants of obesity, which influence diabetes, hypertension, and cholesterol, which in turn influence cardiovascular disease. Dr. Simons-Morton placed the NHLBI studies described above into the research-related phases of this natural history model. The childhood observational and intervention studies (NGHS, Pathways, and GEMS) provide information on the development of obesity and on interventions to prevent obesity development in the first place. Once obesity occurs, the focus of observational and intervention studies is to reduce obesity and prevent hypertension (PREMIER) and to identify relationships between obesity and other cardiovascular risk factors and between obesity and cardiovascular disease (Framingham and CARDIA). Look AHEAD is examining the effects on cardiovascular disease of reducing obesity. In addition to these studies, NHLBI also is conducting a variety of mechanistic and biological studies and has a number of new initiatives in the pipeline.

Dr. Simons-Morton stated that there *are* successful lifestyle interventions for weight loss. They consist of a number of common factors:

- They include one-on-one individual sessions with participants, often with group sessions interspersed, or maybe primarily group sessions with some individual sessions interspersed.
- They target both diet and physical activity.
- The focus is on calorie balance, not necessarily low-carb or low-fat, or the macronutrient composition, but what is considered a healthy diet, which is relatively low-fat and varied in composition.
- They use behavioral approaches. Knowledge is necessary, but not sufficient, so they use things like self-monitoring, feedback, and individualized problem solving.
- In general, the more intensive initial intervention phase is followed by a less intensive maintenance phase.

PREMIER was a three-arm, randomized trial testing the effects of multiple lifestyle interventions on blood pressure level in people with elevated blood pressure. There was an "advice-only" group and two groups—an established and established plus DASH—that had weight loss components, reduced dietary sodium, and increased physical activity. The established plus DASH group also taught people how to eat the DASH (Dietary Approaches to Stop Hypertension) diet, which is 8 to 10 servings of fruits and vegetables a day, overall low in fat, and 3 servings of low-fat dairy. The DASH diet was proven in an efficacy trial to substantially lower blood pressure. Average weight at baseline was 97 kg. At 6 months, the established and established plus DASH groups lost 5 to 6 kg on average, which was significantly different than the advice group's average of 1 kg or less. At 18 months, there was still a large difference, but the established and established plus DASH group's loss had crept up to an average of 4 to 5 kg, while the advice group lost from 1 to 2 kg.

Dr. Simons-Morton pointed out that the Diabetes Prevention Program results followed the same weight loss pattern as that of PREMIER. Six months is when the lifestyle arm had their major weight loss of 6 to 8 kg, compared to the metformin arm's 2 kg and the placebo arm's less than 1 kg loss. Then the lifestyle group's weight gradually went up over a 4-year span to an average of a little less than 3 kg from their initial baseline. The same pattern was seen in the trials of hypertension prevention, which had a 3-year follow-up. This pattern has been seen in many studies. One could conclude that interventions only work for 6 months, but one could also conclude that interventions work as long as the intensive phase of the intervention is going on. Because what happened in all these studies is that when the study moved to the maintenance phase, people reverted somewhat back to their old behaviors. In NHLBI's current Weight Loss Maintenance trial, once the participants achieve a certain amount of weight loss, they will be randomized into three different intervention approaches for maintenance to test what works best.

Based on these and other studies, Dr. Simons-Morton summarized what has been learned to date. We know from randomized control trials (RCTs) that obesity is a risk factor for hypertension, dyslipidemia, and other CVD risk factors. We know from randomized trials and epidemiologic evidence that lowering hypertension and dyslipidemia reduces cardiovascular disease. We know from RCTs that obesity also is a risk factor for diabetes, which is a risk factor for cardiovascular disease (CVD). The relationship between diabetes and cardiovascular disease is only known from epidemiologic evidence so far. NHLBI is sponsoring the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial to test whether intensive control of blood glucose will reduce cardiovascular disease and provide RCT evidence.

Dr. Simons-Morton added that we also know that on the continuum of primordial to primary to secondary prevention, diet and physical activity are both important behaviors for energy balance, which influences obesity, and thus cardiovascular disease risk factors and cardiovascular disease. There is evidence for each piece of this causal pathway. We also know that educational and behavioral interventions can improve diet and physical activity, as was shown in PREMIER and DPP. Based on the evidence, NHLBI collaborated with NIH and external colleagues and developed the Obesity Education Initiative. NHLBI produced a Practical Guide that classified overweight and obesity into categories based on BMI ranges and disease risk relative to normal weight and waist circumference for men and women. The guide recommends clinical practices to address the problem. Information about the Obesity Education Initiative and guidelines for health professionals and for patients and the general public can be found at http://www.nhlbi.nih.gov.

Dr. Simons-Morton listed influences that affect the basic causal pathway that leads from diet and physical behaviors to energy imbalance to obesity to risk factors to CVD. There are intrapersonal factors (knowledge, attitudes, beliefs, and skills that influence an individual's behavior) that have yet to be fully tapped in terms of interventions for diet and physical activity behaviors. There are environmental, community, and societal factors that affect the intrapersonal factors. These include the built environment and the availability of healthy foods, rather than the inexpensive high-fat, high-calorie foods, and places

to be physically active. People are in a constant struggle against an environment that promotes a sedentary lifestyle and poor dietary intake, which we, as a human organism, have to fight. These things influence people's knowledge and their attitudes, beliefs, and so forth, but they also directly influence behaviors. There are physiologic factors such as satiety levels and taste that affect diet and physical activity and result in energy imbalance. Finally, there are biological determinants and mechanisms such as genetics and the pathways discussed by Dr. Flier that directly affect obesity and the other risk factors for CVD. It is a complex system. NHLBI supports research in these areas and efforts to implement guidelines for what we already know.

Individuals at risk for being obese are influenced by their families, by organizations in which they play and work, by the communities in which they live, and by society's norms and influences. Many people think that interventions to address the problem need to not only target individuals in terms of their health behaviors and adherence to recommendations, but, to be effective, interventions should also target organizations, communities, governments, and policies. Dr. Simons-Morton explained that the translational research she referred to earlier tests systems level and environmental level approaches to learn what works to influence organizations and communities to implement programs that have been found effective at the individual level.

Dr. Simons-Morton's stated that NHLBI hosted a Think Tank on Enhancing Obesity Research at the NHLBI to consider future research directions. The Executive Summary published in January 2004 recommended (1) more basic biological research examining issues related to etiology and metabolic consequences of obesity, including research in genetics, adipose tissue biology, critical periods in obesity development, and etiologic and metabolic issues related to diet and physical activity; and (2) developing effective, practical prevention and treatment interventions, particularly related to translation into practice, including research on environmental and social determinants of diet and physical activity, influences of family environment, and interventions that could be applied in clinical practice and community settings. NHLBI is currently analyzing its portfolio with respect to specifics for future initiatives based on these recommendations.

In summary, Dr. Simons-Morton listed the following conclusions:

- Obesity is an important and proven causal risk factor for diabetes and CVD.
- Lifestyle interventions can reduce obesity, which can reduce diabetes and other CVD risk factors.
- Successful weight loss interventions include behavioral approaches for both diet and physical activity. They do not generally sustain the initial weight lost, however. Also, they are intensive, and thus of limited utility for real-world settings.
- Therefore, environmental changes and multi-level approaches are probably needed to enhance the delivery and effectiveness of weight loss programs that we know work and to promote obesity prevention.

Dr. Simons-Morton added that people in intervention programs should not have to struggle against an environment that is constantly hampering and undermining them and influencing them to do different things than what they are being taught to do. She offered two quotes. The first is known as Occam's Razor or the law of parsimony as stated by William of Occam, a physicist who lived in the late thirteenth and early fourteenth centuries: "Entities must not be multiplied beyond what is necessary." For example, it is simpler to describe all the planets revolving around the sun than it is the sun and all the planets revolving around the Earth. The Occam's Razor of obesity is "Calories count, and if you want to prevent obesity, your calories in should not exceed your calories out, and if you want to reduce obesity, your calories out should exceed your calories in." Unfortunately, things are not that simple. When it comes to behavior and society, H.L. Mencken may have provided a more accurate and relevant statement: "For

every complex problem, there is a single solution that is simple, neat, and *wrong*." Dr. Simons-Morton stressed "There is not a single solution to the complex problem of obesity."

Discussion

Dr. Simons-Morton agreed with a comment from Dr. Green that although there is a relapse in lost weight for the most successful groups, the curve does not seem to ever go back to the level of lesser weight lost by the other groups. The results can be viewed as a glass half-full or a glass half-empty. The important point is that the programs *do* work. They just do not work as well as they could because of the environment that people live in. She added that a number of things are needed, including a comprehensive, multi-level approach; biological, mechanistic research to improve medications; individual level health promotion and behavioral skill-building; and environmental changes. Obesity is such a complex problem, we cannot say that one thing or the other is all that is required. It needs to be addressed on all fronts, including primordial, primary, and secondary prevention. One difficulty is that there are other competing needs for NIH monies.

Dr. Kelly Acton, Director, National Diabetes Programs, Indian Health Service (IHS), heartily agreed with the need for translational research. It is not that decisionmakers are necessarily resistant to moving the research to the community. IHS is trying very hard to translate the best research findings such as those from DPP. It is a question of "how to" implement these interventions in Indian communities. It is not easy to sort out what part is unique to a clinical trial and what part of the intervention is applicable to day-to-day community practice.

Dr. Simons-Morton agreed and added that is what NIH is trying to resolve through their translational research efforts. The dilemma is that there are questions to be answered at the same time as action is needed to stem the epidemic. One cannot wait for the research to come up with all of the solutions. As suggested by Dr. Spiegel, we must do what we think works now and at the same time try to obtain more information.

Brief Overview of Ongoing Activities

Veterans Adminstration (VA), Richard Harvey, PhD, Assistant Director, Preventative Behavior, VA National Center for Health Promotion/Disease Prevention, Durham, North Carolina

Following a brief introduction to the VA in general, Dr. Harvey presented information on the VA's MOVE (Managing Overweight and Obesity for Veterans Everywhere) project, which was developed at the VA National Center for Health Promotion and Disease Prevention. The Veterans Health Administration currently treats more than 4.9 million patients a year. There are approximately 7 million enrollees in the system. The VA operates 162 medical centers and more than 1,300 community outpatient clinics. It is a very large system employing 184,000, including 15,000 MDs with an additional 25,000 affiliated MDs. The VA has strong academic affiliations throughout the country, and many of the Nation's health professionals have trained in the VA system at one level or another.

The VA patient population is generally older (49 percent are over 65), more ill, and of a lower socioeconomic status than the general U.S. population. The largely male population is roughly 73 percent Caucasian, 15 percent African American, and 6 percent Hispanic. The female population is rapidly growing, however, with females under age 50 now making up 22 percent of outpatients. In the last 5 or 6 years, the VA has gone from largely inpatient care to outpatient care delivery systems and has been moving from the clinic into the community and into the home, using technology to achieve care within veterans' homes.

Dr. Harvey explained that a major reason for developing the MOVE project was that limited data showed that 70 to 75 percent of veteran patients have a BMI greater than 25, BFRSS 2000 data indicated about 21 percent of those who use the VA fell into the BMI 30 or over obesity category, and the VA height and weight database collected from medical records indicated that actually 36 percent had a BMI over 30. With such a large group being overweight or obese, it was decided to develop a program for the entire VA system that would be based on the best evidence available to date, which included NIH clinical guidelines, NHLBI data and the Practical Guide developed by NHLBI for the Obesity Education Initiative, literature from the Agency for Healthcare Research and Quality's U.S. Preventive Services Task Force (USPSTF), and other current literature.

There are currently 17 limited-scope clinical trials going on, primarily researching the feasibility of standard interventions in primary care settings. Additional full-scale trials of possibly several thousand patients at each site are being planned to prevent additional weight gain and to reduce the BMI is those with ratings over 30 back down to 25. MOVE is a comprehensive program with a public health population-based approach emphasizing lifetime rather than episodic care. Most of the research and most of the current clinical programs fall into the category of an episodic care kind of a program lasting just 12 weeks, 6 months, or whatever. One thing that behaviorists know is people do not do or keep doing uncomfortable and unpleasant things unless they have a good deal of ongoing support. As Dr. Simons-Morton mentioned, without ongoing support and fairly intensive kinds of work, there will be regression. Therefore, lifetime care was built into MOVE, since these patients are in the VA system for a lifetime, which is an advantage the VA has.

MOVE will be carried out in primary care or ambulatory care settings within the VA system without increasing staff or resources. To do this, some tasks in the primary care setting were reallocated. Dr. Harvey said the VA wanted to ensure that the program did not increase load on the physicians, who are seeing half again as many patients as they did in 1996, while the overall number of employees has decreased significantly. MOVE is designed, therefore, to be operated by non-specialized, multidisciplinary staff such as nurses, nursing assistants, dieticians, psychologists, and physical activity specialists, with just a bit of encouragement from the physician. Fully scripted patient-staff interactions were created to implement the program.

Another important feature, according to Dr. Harvey, is immediate enrollment and immediate action on a patient's initial primary care visit. This is intended to avoid what happens with smoking cessation programs, when nearly half of the people do not show up. The program is a stepped care model, something that is imminently do-able, with an emphasis on health, not looks, again for veteran patients with a BMI of 25 or over.

At the trial sites, when a patient arrives for a routine primary care visit with their provider, their BMI is determined during the vital signs period, and those who are BMI 25 or over are advised of the scripted encounters and offered the opportunity to enroll in the MOVE program. Anyone who declines will be counseled and given a handout called, "So you're not ready yet?" which is itself a minimal intervention, but an intervention nonetheless.

Dr. Harvey said that those who are interested complete an on-line initial assessment questionnaire, which outputs tailored reports for the patient and the staff. The patient's report is similar to a wellness report from health-risk assessments, but is related specifically to weight and physical activity. The staff's report details the major features of the patient for the staff member, lays out some red flags to attend to, and details some ways that the staff might be able to assist the patient with his/her efforts. In addition to the individualized profile, the patient receives a package of handouts on reduction in caloric intake, increase in physical activity, and behavior modification strategies. There are also a number of optional tailored

handouts that relate to specific kinds of barriers or red flags that the patient has identified in the initial computerized assessment. These are not given out all at once because any given patient may qualify for 30 or so of them. They will be given over a period of time, as the patient is treated and is ready to deal with issue a, issue b, or issue c. Individuals who are able to walk and for whom walking may be recommended will be given a MOVE pedometer.

On this first visit, the patient receives brief counseling by the staff with regard to the handouts and the reports, agrees to one or two brief goals through a shared decision-making process, and is given a follow-up date, time, and method. The recommendations are for a follow-up a week later, and then every 2 weeks or so thereafter for as long as it takes to maintain the patient actively in the MOVE program. During follow-up visits, mostly done by telephone and about 5 minutes in length, progress is reviewed, barriers are addressed, information that the patient is ready to begin to deal with is sent to him or her, and reinforcement/encouragement is given. At some point, there will be a maintenance contact, maybe every 3 to 6 months, maybe more frequently, depending on the needs of the individual and other kinds of constraints. In any case, follow-up and support continue for the patient's lifetime.

The above described process is the basic Level 1 part of the program. Dr. Harvey added that since many patients benefit from group sessions, the VA has scripted 50 or 60 different group sessions that can be effectively conducted by an average nurse or individual who is not usually familiar with weight control strategies. In addition to these weekly group sessions, handouts, and telephone support, individual consultations may be conducted as well, in what is loosely termed Level 2. This would be a consultation with a dietician, a psychologist, a physical activity specialist, or other specialist as indicated.

In accordance with data about weight control interventions, pharmacotherapy might be added to either of the two levels. The VA will make FDA-approved medications available to the patients who need special assistance. The VA currently has one brief intensive residential program and plans to establish standards for such a program in every region. Lastly, of course, bariatric surgical procedures would be included, as well, for individuals who may need them.

The phone counseling is primarily behaviorally based on stages of change and includes motivational interviewing and shared decision-making techniques to address identified barriers with each patient. Caloric reduction is, of course, specified, but starvation diets are not recommended. No specific diet is recommended, based on the understanding that essentially any diet will work if there is a net caloric reduction. Patients are given examples such as typical American Heart Association and/or low-carb kinds of diets. Local practitioners may outline what they wish their patients to use.

Patients, including those with various types of disabilities, are encouraged to do any kind of physical activity that increases their overall level of activity. Given the disabilities amongst the VA population, some limitations do apply. The activity should be do-able and sustainable. Behavior modification is, of course, a major part of this largely behaviorally based program. MOVE encourages gradual change, lots of stimulus control alterations, substitute behaviors, skill building, knowledge enhancement, and cognitive and behavioral changes.

Dr. Harvey emphasized that MOVE is more than a clinical program. MOVE has an executive advisory committee, of which NIDDK's Dr. Susan Yanovski is a member. A VA steering committee is being formed to guide implementation of MOVE throughout the entire VA system. There will be a nationwide training initiative to train all primary care individuals in how to implement MOVE. A promotion campaign will address some of the environmental issues. Large posters and other items will be used to enhance awareness and motivation among staff and patients. Performance measures are being established, which, in Government, do drive change. A weight management directive will be issued, and VA/Department of Defense (DOD) clinical practice guidelines for the evaluation and treatment of

overweight and obesity will be established. Currently, there are about 60 different weight management programs within the VA that vary in quality and resources. The guidelines will help standardize the program throughout the system.

The National Center for Health Promotion will continue to support the development and the evaluation of the MOVE program. The office is also developing an ongoing research agenda in obesity, physical activity, and weight control issues. One idea has been to develop a peer coaching initiative to enhance motivation and, in a sense, increase the workforce for the MOVE program.

In summary, Dr. Harvey said that through MOVE, the VA will effectively address the obesity epidemic with a robust national program, exposing every overweight VA patient to some intervention, even if it is just a handout and a very brief counseling. It is expected that veterans' health status will improve as a result of this program, that their quality of life will improve, and that there will be long-term cost savings for the VA, given that these are long-term patients. When fully implemented, MOVE will become the largest weight management program associated with a national healthcare system in the country. The VA hopes MOVE will serve as a model for other national healthcare systems, such as that of DOD.

Discussion

Dr. Simons-Morton asked what the VA's plans were for evaluation of MOVE. She noted that there is very little in the research literature about whether this kind of program implemented in the healthcare setting makes a difference, in terms of, for example, BMI. Was the VA planning on having some comparison non-intervention sites, or was that not possible within the VA system? It would be interesting if sites could be randomized and have BMI outcomes measured.

Dr. Harvey responded that they would be doing some feasibility and some very brief outcome work with the 17 pilot trial sites. At a much larger trial to be implemented in several VA facilities in Florida, they will be doing some evaluation research, including outcome research. The plan is to collect similar data with sites that are not participating in the MOVE program. At present, there is no imperative that sites must implement the program, or to what degree it must be implemented. Dr. Harvey suggested that he discuss programs, and possible funding opportunities, with NHLBI.

Dr. Steven Yevich, Director, VA Center for Health Promotion/Disease Prevention, interjected that the evaluation is an important component of the MOVE program, which is constantly going to be evaluated and changed as needed. The program will be tailored so as to be culturally sensitive, because the VA is in 50 states plus some territories. For example, Native American veterans in the southwest region will receive different counseling and support than veterans in inner-city New York.

Food and Drug Administration (FDA), David W.K. Acheson, MD, Chief Medical Officer and Director of Food Safety and Security, Center for Food Safety and Applied Nutrition, College Park, Maryland

Dr. Acheson summarized the initiatives of the FDA's Obesity Working Group (OWG), which was formed in August 2003 by the Commissioner and charged to develop a clear, coherent, and effective public health message, outline a public health program, and see what could be done to enhance the food label. They were also to have a dialogue with the restaurant industry, facilitate development of more or better therapeutics, identify research gaps such as consumer behavior, and enlist the help of stakeholders to achieve their goals. The group was given a timeline of 6 months to prepare a set of recommendations to address these issues.

The FDA OWG held a series of meetings to engage stakeholders, beginning in October 2003 with a public meeting, and then in November with a workshop to explore the links between the food label and weight management. In December, they held a Health Professional Roundtable and a Consumer Roundtable. Public Docket No. 2003N-0338 was then submitted and received more than 100 comments.

Dr. Acheson said that the OWG's conclusions from all this input basically reflected statements heard at today's meeting—that obesity affects all segments of society. He emphasized that, whereas many things discussed at this DMICC meeting are outside of FDA's mission, the report of the working group addressed the issue from the perspective of FDA's mission; thus, there was a strong focus on labeling. The final report was released in March 2004 and includes both short- and long-range recommendations that are centered on the scientific fact that weight control is primarily a function of caloric balance. The full report can be found on the FDA website at http://www.fda.gov/oc/initiatives/obesity. For his summary, Dr. Acheson organized the recommendations into themes from individual working groups that independently studied the issues and then interacted with the overall team two or three times a week. These individual groups focused on labeling, enforcement, education, restaurants/industry, therapeutics, and research. Dr. Acheson then highlighted key elements in each category and referred the audience to the program handouts for further details.

The food labeling group's recommendations included publishing an advance notice of proposed rulemaking to seek comment on how to give more prominence to calories on the food label. Suggestions were simple items such as increasing the font size, including a percent daily value column for total calories, and eliminating the listing for calories from fat. A lot of these recommendations came out of focus group testing, in terms of what people actually understand and what is helpful. Dr. Acheson said that one of the things learned about the American public through limited focus group testing was to forget math. The label must be very clear, plain, and simple. One difficulty in improving the label is that there is not a lot of space on it. A second recommendation was to seek comments authorizing health claims on certain foods that FDA would deem appropriate. An example of a health claim might be "diets low in calories may reduce the risk of obesity, which is associated with type 2 diabetes, heart disease, and certain cancers." Among other recommendations, was one to get comments on additional columns to list quantitative amounts and percent daily values of an entire package. This was in response to the issue that, for example, a 20 oz. soda is shown as two servings, but clearly almost nobody consumes half the soda, puts it in the refrigerator, and then goes back and drinks the other half. The same is true of muffins and cookies and so forth. Although some of these would be problematic, there is a need to be more realistic of what is a serving and show the appropriate caloric content of the entire package.

Further labeling recommendations included comments on the amounts of foods that are customarily consumed and how that needs to be updated. There were several issues around carbohydrates, such as defining "low carbohydrate," "reduced carbohydrate," "carbohydrate free." The labeling working group wanted to encourage manufacturers to use dietary guidance statements. An example would be, "To manage your weight, balance the calories you eat with your physical activity," coming back again to the issue of it is input/output that is important. They also wanted to encourage manufacturers to take advantage of the flexibility of the current regulations on serving sizes, so as to label a single serving size with sodas.

Part of the enforcement working group's goal was to make sure that the nutrition fact panel (NFP) is accurate because the panel's accuracy is critical for consumers to monitor their intake in calories, particularly regarding serving sizes. The three recommendations of the group therefore included enforcement activities against those manufacturers who are inaccurately declaring serving sizes, highlighting in the Food Labeling Compliance Program enforcements against inaccurate declarations of serving sizes, and working with the Federal Trade Commission to target dietary supplement producers who offer false or misleading weight loss claims.

Dr. Acheson stated that just as the VA is planning a major education initiative through the MOVE program, the FDA also considers education an important part in influencing behavior. The education working group recommended that information on healthy eating choices support the bottom line FDA OWG message that "Calories Count." Specifically, the education group recommended establishing relationships with the private and public sectors to give consumers a better understanding of the food label. Since many people do read the food label, it is probably going to help to make it clearer and make it more specific to help consumers make healthier and wiser food choices. As part of this, FDA wants to pursue relationships and partnerships with youth-oriented organizations, such as the Girl Scouts and the 4H Program, to emphasize early on the importance of caloric balance and proper diet for weight management.

In considering goals for the restaurant and food industry, Dr. Acheson pointed out that American consumers are spending approximately 46 percent of their food budget on food consumed outside the home. Obviously, it is critical to address not just what should be put on the packages that people consume in their own homes, but to identify for them what they eat outside, particularly in quick-service restaurants. Recommendations of this working group were (1) to urge the restaurant industry to launch a nationwide, voluntary, point-of-sale nutrition information campaign for consumers and (2) to encourage consumers to request nutrition information when they eat out. It was suggested that a series of options be developed for providing standardized, simple, understandable nutritional information, including caloric information at the point-of-sale. One of the strategies tested in focus groups was, when one goes to a fast-food service restaurant, which would be most helpful—to have caloric intake posted next to the menu items or just high-calorie, medium-calorie, or low-calorie indicated? Generally, the consensus was that consumers at a fast-food restaurant want to know if the item they are about to eat contains 1,500 calories. Still, it comes down to educating consumers about the concept of caloric balance, which is obviously a critical element.

The therapeutic group approached the subject in a variety of ways, but recognized that there is a subpopulation of the obese and extremely obese who require medical intervention to reduce weight and to mitigate the associated diseases. Their recommendations were to pursue things further, to convene a meeting of standing FDA advisory committees to address these challenges, and to fill in some of the knowledge gaps about existing drug therapies for obesity, similar to much of what was heard earlier at this meeting. They recommended continuing discussions with the pharmaceutical and medical device sponsors about new products and revision and reissuing for comments of the 1996 draft "Guidance for the Clinical Evaluation of Weight-Control Drugs."

One of the mandates for the FDA OWG was to identify applied and basic research needs that include the development of healthier foods and a better understanding of consumer behavior and motivation. In this regard, the research working group recommended supporting and collaborating, as appropriate, with other obesity-related research groups, including NIH and the USDA. One suggestion was to collaborate with USDA on their national obesity prevention conference to be held in October 2004. The group also recommended the following five areas of obesity research: (1) information to facilitate consumers' weight management decisions; (2) the relationship between overweight/obesity and food consumption patterns; (3) incentives for product reformulation; (4) the potential for FDA-regulated products unintentionally to contribute to or result in obesity; and (5) the extension of basic research findings to the regulatory environment.

The overall result of the FDA Obesity Working Group's efforts was made clear in FDA Deputy Commissioner, now Acting Commissioner, Dr. Lester M. Crawford's statement: "We're going back to basics, designing a comprehensive effort to attack obesity through an aggressive, science-based, consumer-friendly program with the simple message that 'Calories Count'."

Centers for Disease Control and Prevention (CDC), Rodolfo Valdez, PhD, MSC, Epidemiologist, Division of Diabetes Translation, Atlanta, Georgia

Dr. Valdez stated that after 40 years of tracking public health epidemics, CDC agrees that it is time to move beyond surveillance and to establish programs to more effectively bring research findings to the community. CDC is sponsoring several such projects. The Division of Nutrition and Physical Activity has developed a comprehensive State-based program to help States maximize their efforts to prevent obesity by improving nutrition and physical activity. A PA published in the *Federal Register* in January 2003 resulted in 58 applications, of which 20 were selected for funding in FY 2003, 17 at the capacity-building level and 3 at the basic implementation level. These 20 programs have as their objectives to provide the population with the knowledge, skills, and motivation to modify their environments and provide opportunities for access to healthy eating and more physical activity. The interventions foster healthier behavior by mobilizing multiple levels of the social structure to achieve a balance between individual and environmental approaches for healthier lifestyles. CDC has provided a "Resource Guide for Nutrition and Physical Activity Interventions To Prevent Obesity and Other Chronic Diseases." Topics in the Guide include caloric intake and expenditure; increased physical activity; improved nutrition, including breastfeeding and increased consumption of fruits and vegetables; and reduced television time.

A second program briefly described by Dr. Valdez was the Steps to a HealthierUS initiative proposed by Secretary Tommy Thompson of the U.S. Department of Health and Human Services (DHHS). The goal of this program is to help Americans live longer, better, and healthier. A centerpiece of the program is a 5-year cooperative agreement that provides States, cities, and Tribal entities with funds to implement chronic disease prevention efforts. The focus is on reduction of diabetes, overweight and obesity, and asthma through interventions addressing three related risk factors: physical inactivity, poor nutrition, and tobacco use. In FY 2003, approximately $14 million was distributed to fund applicants representing 15 small cities or rural communities, a Tribal consortium, and 7 large cities. These 23 communities will implement action plans to reduce health disparities and promote quality health care and prevention services in the States of Arizona, California, Colorado, Florida, Louisiana, Massachusetts, New York, Pennsylvania, Texas, and Washington, and the Intertribal Council of Michigan.

In December 2000, Congress mandated that CDC develop a media campaign to improve the health of our Nation's youth. The resulting "VERB: It's what you do" was launched in October 2002 as a 5-year strategic effort to promote physical activity through research, the media, partnerships, and community activities. It uses communications designed by the best youth advertisers and marketers and involves the teens themselves at all stages of planning. Dr. Valdez emphasized that the campaign is "by kids and for kids." The campaign employs television, the Internet, and print and radio ads to reach youth 9- to 13-years-old, as well as their parents and other adults who influence youth. Messages are informational and motivational and customized to appeal to diverse populations. A recent evaluation showed that the campaign is receiving 70 percent recognition among children, so it has been very successful. Dr. Valdez stated that partnerships are critical to the success of the campaign. Through VERB, CDC's Division of Adolescent and School Health (DASH) provides lessons and funds to 42 states, 4 territories, 15 local agencies, and 8 national organizations to initiate or expand in-school, after-school, and community programs to increase the availability and quality of physical activities for youth and reinforce the messages of the campaign.

Dr. Valdez's group, the Division of Diabetes Translation, is studying how to implement the results of the DPP. Currently, they are asking States to assess and evaluate what programs they have now to prevent obesity and diabetes. Some pilot studies are being conducted in some States to determine just what type of efforts are needed. The Division also co-sponsors with NIDDK the National Diabetes Education Program and its "Small Steps" campaign. CDC is collaborating with the Look AHEAD project and also with environmental modifications to prevent obesity. A lot of effort is being put into screening to identify

the people at risk for diabetes, and that, of course, includes identifying those who are overweight or obese. One part of the screening effort is to identify persons who have diabetes and do not know it; the other part is to identify people termed pre-diabetic, which is an important target population for implementing lifestyle changes to help them reduce weight and other risk factors and prevent the development of diabetes.

Discussion

Dr. Fradkin asked if there is any additional evaluation of VERB beyond recognition of the campaign, such as information about attitudes or behavior. Dr. Valdez answered that there is and a report has been prepared on that. In response to a question from Dr. Malozowski regarding the pilot programs, Dr. Valdez said that CDC is receiving many calls from States asking what to do. They know that a healthy diet and increased physical activity have been shown to help prevent diabetes, but they want something specific to do to implement these findings. CDC has had to hold them back a little and say, "It's not that easy. We have to do something more." For instance, they are told the DPP shows that to prevent one case of diabetes in a high-risk population, one has to do intervention on seven people, so that is a massive intervention effort in a community. Currently, CDC is asking the States to first assess what resources they have in order to do prevention. For example, do they have a Department of Chronic Diseases? CDC has DPCs (Diabetes Prevention Centers) in all the States and territories, but usually they are quite small, and need to evaluate the research that they have. This assessment phase is primarily what is being done now.

U.S. Department of Agriculture (USDA), Joseph T. Spence, PhD, Acting Associate Deputy Administrator, Agricultural Research Service, Beltsville, Maryland

Dr. Spence explained that USDA is organized into mission areas such as the Research, Education, and Economics (REE) mission area and the Food, Nutrition, and Consumer Service mission area, which administers the Food Assistance Program. People tend to think about farms when they think about USDA, but it is largely a food assistance organization. Unlike NIH, the extramural and intramural research entities are separate. The Cooperative States Research, Education, and Economics Service (CSREES) is the extramural arm and the Agricultural Research Service (ARS) is the intramural arm. The bulk of research at USDA is being done by ARS. The Economics Research Service (ERS) has become very interested in obesity research and risk analysis, including research on determinants of why people make the food choices that they do based on economic issues. ERS also evaluates the food assistance programs in terms of effectiveness.

The ARS Human Nutrition Research program is basically divided among six Human Nutrition Research Centers, which Dr. Spence would be describing individually. In addition, for approximately 10 years, ARS has funded the Lower Mississippi Delta/Nutrition Intervention Research Initiative. This is a partnership of seven institutions throughout Louisiana, Arkansas, and Mississippi, dealing with the rural poor in one of the most economically disadvantaged parts of the United States and developing interventions to improve individuals' health status and diet. Fruits and vegetables are usually unavailable unless they grow these crops themselves. No amount of fat is ever wasted; it is consumed. Fast food to them is truck stops. This is a very important project for ARS, and they are beginning to see some successful interventions.

The overall mission of the ARS Nutrition Program is to define "what is a healthy diet?" Approximately 60 percent of information in the dietary guidelines process is generated by ARS; therefore, ARS is very active in doing research on dietary components. The agency has consistently had a foods-based approach to the study of nutrition. Even though centers may be doing molecular biology, the concentration is on food. Each of the centers has metabolic facilities to do between 8 and 20 in-house, long-term feeding

studies, including clinical beds for in-patient studies and the ability to do large out-patient studies. The Beltsville Center in Maryland can feed about 120 people per day indefinitely. For studies, ARS typically provides all of the meals for each individual while in the study. They receive breakfast, a packed lunch, and come back for dinner, including all their weekend meals. The mission of each of the centers involves nutritional needs over the entire lifecycle, from childhood through old age. Beltsville traces its ancestry back to Dr. Wilbur Atwater and has a longstanding interest in calorimetry and body composition.

Dr. Spence stated that ARS and USDA stayed away from direct research in obesity until recently, partly because NIH's investment in this area is so significant that they felt they would be small players. However, the compelling nature of the problem demands that USDA get involved. Another reason for their involvement is that, as the Nation's department of food, USDA has a lot to offer regarding a food-based approach toward studying obesity.

Each of the ARS research centers has its own mission, which is given in the program handouts. The Arkansas Children's Nutrition Center in Little Rock is relatively new. It works with women and children, emphasizing the effects of dietary factors on the prevention of atherosclerosis. This center is particularly interested in how diet affects cognitive development and immune function.

The Beltsville Center is the largest, most comprehensive, and oldest of the centers. Its mission is involved with diversity in the American population, and it has several studies intimately linked with obesity, particularly the influence of physical activity on long-term food intake and body weight and the beneficial effects of dietary fibers. As discussed today, it is very difficult for people to lose weight and keep it off. Rather than have participants go on a yo-yo dieting pattern, ARS is looking at diets, foods, and dietary consumption patterns that may not result in weight loss, but may be inherently healthier. Some of the work that the center has been doing on various plant fibers has borne this out.

The Beltsville Center is intimately involved in nutrition monitoring. The agency is working with the National Center for Health Statistics and is responsible for the dietary component of NHANES, including improving its accuracy. Because the system is not inherently accurate, Dr. Spence strongly disapproves of how people often use the data such as reporting values for calcium intake down to the nearest tenth of a milligram when the data may be only 10 to 20 percent accurate. The National Nutrient Databank is maintained at Beltsville as well. In community-based interventions, including ones related to diabetes, the center has worked with such supplements as chromium picolinate and some naturally occurring components in spices, particularly in cinnamon, which has been investigated by Dr. Richard Anderson.

The Children's Nutrition Research Center is part of an ARS cooperative agreement with the Baylor College of Medicine, Department of Pediatrics. This center is studying obesity, particularly related to children, looking at genetic and environmental factors contributing to childhood obesity, biological influences on children's diets, eating patterns, athletic self-concept and behavior, after-school physical activity, dietary intervention for children and families, and infant feeding patterns. They are examining how feeding patterns early in life affect children's susceptibility to chronic diseases, including diabetes and atherosclerosis later on. Dr. Thomas Baranowski, one of the scientists there, has some innovative studies using computer games for children to pick up healthy eating habits. Since children do not prepare their own foods, a lot of work is being done with families, especially prevention work.

The Grand Forks Nutrition Center is USDA's trace element center. Although they are currently doing little in the obesity area, they have an important role to play. As people are encouraged to consume reduced calorie diets, Dr. Spence emphasized that it is important to ensure that those diets are adequate in their content of the traditional known nutrients. Because of its location, the Grand Forks center is becoming more and more involved in Native American nutrition and Native American health. They have

a mobile van that they take out to the reservations, the Northern Plains Indian Reservations, and they are becoming more and more interested in community nutrition.

The Human Nutrition Research Center on Aging, the Jean Mayer Center at Tufts University, is also a cooperative agreement. This group is conducting a number of studies related to chronic disease, obesity, and diabetes and cardiovascular disease. The major focus, in terms of obesity, is the obesity that occurs at midlife. Dr. Spence noted that people lead a healthy lifestyle and then something happens; growth hormone stops being produced and there is a propensity to gain weight. The center is studying lipoproteins and nutrition in aging (particularly Dr. Alice Lichtenstein and Dr. Ernest Schaefer), aging adipocyte and systemic metabolism, body composition and nutritional assessment in the elderly (Dr. Susan Roberts), nutritional genomics, epidemiology applied to problems of aging and nutrition, and improving cardiovascular health with diet. They are also participating in the Geisinger rural aging study, sponsored by the Geisinger Clinic in Pennsylvania. This center is very interested in the determination of energy and insulin regulation and in body composition as are some of the other centers.

The Western Human Nutrition Research Center at the University of California–Davis campus moved from the Presidio about 3 years ago. They are in the process of building a new facility. Their mission is to study nutritional interventions and the methodology associated with them. Dr. Lindsay Allen is the new center director. Dr. Allen has been involved in international nutrition and is very enthusiastic about the possibility of being involved in some nutritional interventions in the United States. The center has major ongoing projects looking at internal and external factors affecting food intake and body weight such as energy restriction, mineral homeostatis, and functional outcomes. Again, the emphasis is on maintaining a healthy intake of essential nutrients while encouraging people to lose weight.

The Nutrition Research Center Directors have been encouraged by the Secretary of Agriculture to come up with a new initiative in obesity research. They are very cognizant of the work being done at NIH and other Federal agencies. Dr. Spence remarked that it had been very helpful to hear the discussions today. He would be sharing with his colleagues at USDA what the various groups were doing and suggesting they find ways to collaborate.

Dr. Spence said that USDA's broad outline of a plan emphasizes obesity prevention, rather than treatment of obesity. The agency is interested in helping populations at risk for gaining weight by developing effective processes and interventions. USDA is committed to a foods-based approach. They will work with plant producers and animal breeders to develop new foods, new varieties of foods, and incorporate these into diets, and then hopefully get the food producers and the food industry to adopt some of these. In fact, some of them are on the market now and are very successful. USDA will conduct research that provides the scientific basis for sound food assistance programs, which is highly important to the Department of Agriculture. USDA has been accused by some people of responsibility for the obesity epidemic because some foods are too cheap or because the agency is thought to be pushing the wrong kinds of food and so forth. It is true that one cannot produce inexpensive food that is high in calories and then be suddenly surprised that people are gaining weight. Of course, as has been said repeatedly at this meeting and elsewhere, this is a multifaceted problem, but USDA does want to have its food assistance programs based on the best available scientific evidence.

At the Secretary's request, the Nutrition Research Center Directors put together a draft proposal that Dr. Spence outlined for the audience. The Directors recommended that there be a long-term, longitudinal study, similar to Framingham. Phase I would establish community cohorts to determine risk factors in vulnerable population groups; determine behavioral and lifestyle influences on food choices, meal patterns, purchasing, family environments, and so on; determine effects of participation in food assistance programs on choices and behaviors; and establish and refine methods to assess dietary practices and

quality. Basically in Phase I, the objective is to understand why people make the food choices that they do.

Phase II is a longitudinal follow-up study of Phase I participants, who will be children, to determine how factors identified in Phase I predict weight change and body composition over time. Phase III will test intervention strategies over time. From the work USDA has done, it is known, for instance, that children can be brought into an environment where they become very interested in nutrition and, as a result, they will change their food-eating habits. Whether that continues from, say, preschool, elementary school, into high school and beyond, is another question to be answered. This phase will test various intervention strategies and follow the participants long-term to learn what works and what does not work.

Dr. Spence noted that there are similarities in what USDA is proposing and in what NIDDK and NHLBI are doing and proposing. He said he would welcome the opportunity to sit down and talk about long-term plans. The USDA can offer expertise in the food area that could be helpful to several other Federal agencies in their obesity reduction and prevention initiatives. Dr. Spence stressed that it is important to have a dialogue, because if there were ever a problem that requires thinking outside the box, obesity is that problem. Strategies need to be developed to come up with something new and fresh and make an impact on this epidemic.

Discussion

Dr. Fradkin asked Dr. Spence if ARS collects data on a State-by-State basis in terms of food purchases that could be analyzed to evaluate the impact, for example, of a CDC State-based initiative or a public health message about healthier food choices. He responded that they do collect that kind of data based on disappearance of products from shelves, which does not necessarily reflect what people are consuming. The disappearance data includes fast-food venues, but again, not what is being consumed, just what leaves the outlet. The Ag Marketing Service, which is another agency, keeps their own set of data on what is being purchased, what is being consumed, or what is being put into products on the periphery. It tracks the raw commodities. Within the data collected in NHANES, everything is broken down to raw commodities, so if somebody said they had a slice of pepperoni pizza, one can see how much wheat they consumed, how much tomato, how much meat, and so forth. The raw commodities data is compared with the disappearance data, which could provide some reasonable estimates of a change in people's food choices, and although it would not be entirely accurate, it would be worth examining.

Dr. Malozowski commented that in the area of the main supermarkets, one knows what is being purchased. He asked if such a system is in place in closed communities as a double check. Dr. Spence answered that in Delta communities or rural communities, there is not the tracking that is available in a place like Washington. For example, in Arkansas, the disappearance data provides some data that you would not normally get because it collects how many dairy products went off of the shelves back to the warehouse, not at the individual grocery store. In rural communities, this is very difficult. They do not have the infrastructure in place.

Dr. Malozowski asked Dr. Spence if he was aware of the National Children's Study managed by the National Institute of Child Health and Human Development (NICHD) as this could be a good match with USDA's Phase III plans regarding following up children's nutrition and development. Dr. Spence replied that they had learned about the project somewhat after the fact, but that Dr. Dennis Bier, the Director at Houston, has been working with NICHD's Dr. Gilman Grave to become involved in the project.

Dr. Spiegel thanked all those present for coming to the meeting and expressed his appreciation to the speakers. He deemed this had been a very helpful session. Dr. Malozowski thanked Drs. Susan Yanovski, Brian Hoover, and Philip Smith for their assistance in organizing the meeting.

The meeting was adjourned at 4:05 p.m.