

New Insights in Obesity

ZACHARY T. BLOOMGARDEN, MD

This is the sixth in a series of reports on the American Diabetes Association (ADA) 61st Scientific Sessions held in Philadelphia, PA, in June 2001. It covers topics related to the treatment of type 2 diabetes.

Childhood obesity

At a symposium on childhood obesity, William Dietz (Centers for Disease Control, Atlanta, Georgia) gave an overview of obesity and the consequences of childhood obesity in the U.S. The prevalence of obesity showed a progressive increase in this country from 1991 to 1999, with a concordant increase in diabetes (1). Next to tobacco use, low levels of physical activity and poor dietary habits are the major factors in the U.S. leading to increases in mortality (2). Dietz reviewed epidemiological data for children from the 1960s through 1990s, which suggested that obesity has particularly increased during the past decade in both the U.S. and other countries. Complications of overweight occurring during childhood include its effects on growth, psychosocial difficulties, hyperlipidemia, hepatic steatosis, and abnormal glucose metabolism, as well as persistence into adulthood, leading to a myriad of further complications.

Over the past 20 years, fast food consumption has increased to account for >40% of income spent on food, with 25% of daily calorie intake among children being from snacks. Dietz noted that schools look to food as a "revenue generator," which leads to more fast food and soda being consumed. Annual per capita consumption of soft drinks increased from 27 gallons in 1972 to 44 gallons in

1992. Supermarkets "may have the same impact on people as a buffet," by exposing purchasers to a variety of foods, increasing weight gain. Another potential driver of obesity is portion size, which has shown a particular increase among older children.

In the Netherlands 30% of all trips are made by bicycle, whereas in the U.S. 1% are made by bicycle. During the past few decades, daily participation in physical education decreased from 45 to 35% among high school boys, and from 38 to 30% among girls. The majority of children of previous generations walked to school, whereas now fewer than one-third of U.S. children living within a mile of school walk to school, leading Dietz to suggest that we need "to make physical activity an easier choice." A principal cause of inactivity for children is television viewing, which increased from a median of 2 h/day among adolescents in 1970 to 4.8 h/day in 1990, with 34% watching >5 h. There is a direct relationship between hours of television-watching per day and obesity.

Dietz suggested several obesity prevention strategies. An increase in breastfeeding appears to decrease the likelihood of childhood obesity by 15–25% (3). Increases in physical activity may have substantial benefit. Particularly important are noncompetitive activities, which lead to more than twice as much actual physical activity as formal physical education approaches. Efforts to decrease children's television viewing are effective (4). Dietz suggested that we need to create "incentives for parents to turn off the television set."

Leann L. Birch (University Park, PA) discussed parent-child interactions determining the development of obesity. Childhood obesity doubled from 1980 to 1994, reaching 24% in the "overweight" (>85th percentile) and 11% in the obese (>95th percentile) category, with overweight parents a particular risk factor for overweight children. Parents provide the genes, but also, Birch pointed out, the environment, which she suggested "is more like the weather: people talk about it but nobody does very much [research] about it." Parent weight status and eating behavior may influence children's weight and eating. Infants have predisposition to sweet and salty rather than sour or bitter flavors, and to the rejection of new foods. They learn to like or dislike foods. An important change is the transition from depletion-driven eating driven by hunger and satiety to that controlled by a variety of other cues as the child develops from infancy to childhood. From very early on, parents shape the child's eating environment. Breast milk transmits different food tastes. Parental dieting also has impact on children.

Children learn food preferences. Two dimensions underlie these judgments, sweetness and familiarity, the latter a characteristic of the child's experience rather than of the food. With repeated exposure, many initially rejected foods will be accepted. Children show varying preferences for high-fat foods, and this preference predicts fat intake and child weight status, with linkage to parental weight status. She suggested that parents clarify the concept of food "restrictions," teaching appropriate portion size and refraining from giving or withholding foods as a reward or punishment. Many young children understand concepts of dieting, including restrictive eating and increasing activity, particularly when the mother is currently dieting and when there is a family history of obesity.

Food portion size has an important effect. For young children, food intake is constant, whereas older children show an increase in food intake with larger portion servings. Birch noted that the size of a typical Coca Cola and French-fried potato serving has tripled over the past 20 years. She showed evidence that portion size is

Zachary T. Bloomgarden, MD, is a practicing endocrinologist in New York, New York, and is affiliated with the Diabetes Center, Mount Sinai School of Medicine, New York, New York.

Abbreviations: AgRP, agouti-related peptide; CART, cocaine-amphetamine-regulated transcript; CHD, coronary heart disease; CHO, carbohydrate; CVD, cardiovascular disease; ERK, extracellular signal-related kinase; GABA, γ -amino butyric acid; GLP-1, glucagon-like peptide 1; ICV, intracerebroventricular; IL, interleukin; IRS, insulin receptor substrate; LHA, lateral hypothalamic area; MAPK, mitogen-activated protein kinase; MSH, melanocyte-stimulating hormone; MUFA, monounsaturated fatty acid; NPY, neuropeptide Y; PDE, phosphodiesterase; PET, positron emission tomography; PI, phosphatidylinositol; PKA, protein kinase A; POMC, proopiomelanocortin; PUFA, polyunsaturated fatty acid; PVN, paraventricular nucleus; STAT3, signal transducer and activator of transcription 3; TNF- α , tumor necrosis factor- α ; UCP, uncoupling protein.

positively related to energy intake and body weight in both 2- to 3- and 4- to 5-year-old children. In a longitudinal study, the greatest increases in children's BMI and skinfold thickness from age 5 to 7 years are in members of "obesogenic families" that consume diets particularly energy-dense and that have low activity levels. Another important factor is television watching, which correlates with snacking frequency and causes inactivity.

Thus, children learn food preferences and aversions, appropriate portion sizes, controls of food intake, responsiveness to internal and external cues, snacking patterns, and body satisfaction. To foster healthy diets, Birch suggested that we help children eat foods that are nutrient-dense but not energy-dense and that we teach understanding of portion size and meal patterns.

Adam Drewnowski (Seattle, WA) gave what he characterized as an "absolutely different" assessment of taste and food preferences in children, asking Why do children prefer some foods, what has taste to do with it, do such choices lead to obesity, and can these preferences be changed? Children's food choices are determined, he pointed out, by factors including genetic traits, brain neurotransmitters, age, sex, obesity, restraint, and self-efficacy, as well as by environmental factors. He suggested taking a consumer approach, looking at taste, cost, convenience, health, and variety, recognizing that energy density is not perceived by consumers *per se*. One must recognize that children like sweet and reject bitter tastes, that children prefer energy-dense foods to those of low energy density, and that energy-dense foods are both more palatable and, often, less expensive in dollars per kilocalorie.

The taste system is mature at birth and robust into extreme old age, with the exception of bitter taste, and plays a central role. Neonates show reflex taste responses with grimacing to bitter and smiling to sweet. Perception of bitter and sweet tastes involves multiple receptors and different transduction mechanisms. Taste receptors are organized on the tongue and on the palate. Bitter taste is highly complex, with 40–80 distinct bitter taste receptors, and with genetic and heritable traits for certain bitter tastes, whereas there are only 2–3 receptors for sweet taste. Bitter tastes can be masked with salt, sugar, or fat. Rejection of bitter

tastes is an innate human trait, which presumably has survival advantage in avoiding toxins. Children like sweet tastes. Infants select intensely sweet sucrose solutions over water and prefer sucrose to lactose or glucose, which are less sweet. Sweet taste preferences decline somewhat between adolescence and adulthood, but, Drewnowski pointed out, "You cannot eliminate sweet taste from the diet, and any attempt to do so will result in failure." Taste preferences are modifiable but cannot be changed altogether, particularly in children. Thus, when we impose food preferences on children, we need to mask bitter tastes, allowing them, say, to eat fruit rather than vegetables. Palatability and energy density of foods are linked, again most markedly in children.

Energy density of food is directly driven by decreasing water and increasing fat content, with carbohydrates (CHOs) playing a minor role. There is, however, a strong association between sugar consumption and obesity. Added sugars account for 12–20% of daily energy, and soft drinks provide 35% of added sugars in children. Children are consuming less fruit juices and milk, and more soft drinks. Sucrose is, however, one of the least expensive foods available, providing 19,000 kcal/dollar at current world prices, whereas foods rich in "natural sugar" are considerably more expensive. "Healthy diets," Drewnowski said, "cost more," and diet quality is linked to socioeconomic status. Thus, he suggested that, in certain ways, obesity may be primarily an economic issue, and it may be important to address it as such.

Jack Yanovski (Bethesda, MD) discussed the consequences of obesity in children. Orthopedic effects include slipped capital femoral epiphysis, occurring at a rate of 3.4 per 100,000 children, with 50–70% of affected children being overweight; neurological effects such as pseudotumor cerebri, with 90% in overweight children; asthma, with as much as 80% of severely overweight children having abnormal pulmonary function with exercise; and abnormal sleep, described in more than one-third of obese children, which may lead to impaired learning and school performance. Gallstones are infrequent but almost always occur in obese children, as does hepatic steatosis. Social consequences include effects of obesity on self-esteem, the ability to have friends, lower college acceptance rates, and higher

poverty rates. Effects on growth include advancement in skeletal and pubertal maturation in children with obesity. There are decreased growth hormone levels in obese children, but IGF-1 levels are normal, and as IGF binding protein 1 and 3 levels are decreased in obese adolescents, free IGF-1 levels are increased. Low levels of sex hormone binding globulin may explain the association of gynecomastia with obesity. Polycystic ovarian syndrome is another association, which in turn is linked to dysregulation of glucose metabolism. Hyperinsulinemia, increased risk of type 2 diabetes developing by age 30 years, hypertension, increases in triglycerides, and decreases in HDL cholesterol are other important associations.

Clinical studies of obesity

Giammattei et al. (226-OR) found that of 126 boys and 128 girls in a survey of 6th and 7th graders, 52% of those from ethnic minorities, mainly Hispanics, but 29% of non-Hispanic whites watched ≥ 2 hours per night (abstract numbers refer to the Abstracts of the 61st Annual Meeting of the American Diabetes Association, *Diabetes* 50 [Suppl. 2]:1-A649). Of those who watched < 2 h of television daily, 28% had BMI ≥ 85 , and 12% had BMI ≥ 95 for age, considered to be overweight and obese, respectively. However, among those watching > 2 h of television daily, 52 and 28% were overweight and obese, respectively. Wilson et al. (816-P) found that men in the Framingham Study whose BMI at the time of first observation were < 25 , 25–30, and > 30 had 11, 17, and 32% cumulative diabetes rates after the age of 35 years, respectively, whereas women's respective diabetes rates were 8, 15, and 32%, so that BMI > 30 more than doubles the risk of diabetes. Of the cases of diabetes, 66% among women and 84% among men developed after the age of 60 years.

Obesity treatment

In a symposium on the role of fat intake, Beth Mayer-Davis (Columbia, SC) suggested that fat intake "does matter in metabolic control." Weight management is clearly of importance in view of the high prevalence of obesity in diabetes. The greater the weight loss, she stated, the greater the decrease in triglycerides and in HbA_{1c}. Studies with 2–4% weight loss in patients with impaired glucose tolerance

show that >50% of the patients developed normal glucose tolerance. Bariatric surgery decreases the risk of diabetes, hypertriglyceridemia, hypertension, and low HDL. Among patients with diabetes, decreased HbA_{1c} levels can be shown both with standard low-calorie and with very low-calorie diets. The role of dietary fat in weight management is, first, in aiding individuals to reduce caloric intake. Mayer-Davis pointed out that “it is extremely challenging to have weight loss maintained over time.” Lower-fat diets without calorie restrictions per se are associated with decreased caloric intake and with greater weight loss. Meta-analysis of such diets “under conditions of free choice for total calories” confirms this, and, among individuals successful in weight loss after a 1-year intervention, comparison of low-fat versus fixed-calorie diets again shows benefits of fat restriction.

Data from the St. Louis Valley Diabetes Study and from the Insulin Resistance Atherosclerosis Study of 421 and 437 adults with type 2 diabetes, respectively, who had diet assessment showed that ~50% of the patients had stable weight and 30% had weight loss of ≥ 5 lb over the previous year. Of the calories in the two groups, respectively, 39 and 36% were from fat. Total fat, adjusted for caloric intake and BMI, was significantly associated with LDL cholesterol. The triglyceride level was not significantly associated with fat intake, although patients with weight gain over the prior year showed an association of triglyceride levels with CHO intake. The type of fat ingested may affect lipids. With diets high in monounsaturated fatty acids (MUFAs), triglycerides tend to be lower and HDL cholesterol higher (5). “You certainly do not,” however, Mayer-Davis pointed out, “just pour oil,” particularly because MUFAs usually have little other nutrient content, and she concluded that it behooves patients with diabetes to “eat less fat.”

Frank Hu (Boston, MA) suggested “a different approach and a different perspective” on the interrelationships between dietary fat and glycemic control, looking at metabolic studies and preliminary results from the Nurses’ Health Study on the relationship between dietary fats and both obesity and cardiovascular disease (CVD) in diabetes. The new National Cholesterol Education Project guidelines consider diabetes a “CVD risk

equivalent,” with patients with diabetes without a history of coronary heart disease (CHD) having similar rates of CHD to those without diabetes and with a CHD history, both in Finnish data and, in the Nurses Health Study, in women who have had diabetes for ≥ 10 years. In addition to glycemic control, dyslipidemia is very important to CVD development in diabetes, with an important role of dietary factors. Hu presented data suggesting that hypertriglyceridemia and low HDL cholesterol are both approximately twice as common with diabetes in both men and women. A range of nonlipid and nonglycemic factors also play a role in CVD in diabetes.

Given over several-week periods, diets with 60% of energy from CHOs and 20% from fat, when compared with diets with 40% of energy from CHOs and 40% from fat, a large portion of which was MUFAs, resulted in 19% higher triglyceride and 4% lower HDL cholesterol levels. Fasting and postprandial plasma glucose levels were lower with the lower CHO and MUFA diets. Diets high in CHOs with a higher glycemic load (the product of CHO quantity and glycemic index) are associated with higher fasting triglyceride levels, particularly among overweight individuals, suggesting a relationship to insulin resistance. Diets high in fiber and low in saturated fat were associated with falls in LDL cholesterol, but with falls in HDL cholesterol as well. Hu suggested that some of the effects of differing diets may be mediated by changes in insulin sensitivity. To what extent high-fiber versus high-MUFA diets are beneficial has not been studied. Also, it is not known whether polyunsaturated fatty acids (PUFAs) are of similar or greater benefit than MUFA. Hu showed data suggesting that PUFAs may have important benefits in treating and, perhaps, in preventing diabetes. Looking at the relationship between fat intake and CHD incidence in women with diabetes in the Nurses’ Health Study, of the 1,700 women with diabetes at the beginning of the trial and the 3,000 women who developed diabetes, multivariate analysis with adjustment for age, cigarettes, and BMI showed no relationship between total fat intake and CVD, whereas higher polyunsaturated-to-saturated ratios were associated with decreased CVD risk, particularly among women with diabetes.

Meta-analysis of isocaloric high-MUFA versus high-CHO diets shows no

differences in weight gain, and studies of energy-restricted diets show similar decreases in body weight with high MUFAs and high CHOs, which, Hu commented, “supports the conventional wisdom that a calorie is a calorie whether from fat or from CHO.” In an outpatient setting, the high-CHO and high-MUFA diets showed similar weight loss at 6 months, but much less weight regain at 18 months with the latter diet. Indeed, there was a much greater degree of noncompliance with the former diet, suggesting high-MUFA diets to be more practical in the long-term, allowing more varied food sources. Hu also discussed the role of omega 3 fatty acids. Higher consumption of fish is associated with decreased CVD in the general population. Meta-analysis shows a decrease in triglyceride levels, a small increase in LDL cholesterol, and no change in glycemic control in patients with diabetes. In the Nurses’ Health Study, omega 3 fatty acids showed a similar inverse relationship to CHD in diabetic and nondiabetic participants. Formal trials comparing outcome of such dietary changes in patients with diabetes would be important.

“We ought to distinguish the type of fat rather than simply talk about total fat,” Hu summarized, emphasizing the need for studies to determine optimal PUFA intake for patients with diabetes. Similarly, the relationship between the type and quality of CHOs and diabetes should be assessed. Hu suggested that “we can combine good CHOs with good fats,” with the use of nuts and olive, canola, and soybean oils to replace “bad fats, the animal fats,” rather than increasing total calories. Thus, the “food pyramid” used to guide the population to eat more CHOs may be misleading, with many unhealthy foods high in processed CHOs being advertised as “low fat” and hence more healthy, leading the National Cholesterol Education Program guidelines to be recommending more moderate-fat rather than low-fat diets. Mayer-Davis stated, “I still am not at all convinced that the increase in triglyceride [with diets higher in CHOs] under short-term conditions really are significant,” pointing out the need for more long-term studies.

Davis et al. (82-OR) randomized 25 obese individuals with type 2 diabetes and HbA_{1c} >8% (mean 8.9%) to a diet with <45% CHOs and 36% total fat (12–19% from MUFAs) or a diet with >55% CHOs and <30% total fat. Their data

showed that the former diet markedly improved triglyceride levels, without significant differences in weight, HbA_{1c}, or HDL or LDL cholesterol levels. Takami et al. (83-OR) showed that 10 individuals with impaired glucose tolerance had similar decreases in body weight and fasting glucose with high-CHO and high-MUFA diets, with no change in insulin secretion, but they had greater insulin sensitivity and flow-mediated brachial artery vasodilatation, a measure of endothelial function, with the latter diet.

Krempf et al. (84-OR) treated 696 nondiabetic obese patients (BMI 35.6 kg/m²) with hypocaloric diet plus 120 mg orlistat before meals versus placebo for 18 months. The average weight was 97.0 vs. 97.7 kg initially for orlistat vs. placebo, but it was significantly lower with orlistat throughout the study: 89.9 vs. 93.3 kg at 6 months, 88.9 vs. 92.9 kg at 12 months, and 89.3 vs. 94.0 kg 18 months, for an overall weight loss of 9.2 vs. 6.9%. The fasting blood glucose fell by 2.9 vs. 0.8% for orlistat vs. placebo, and LDL cholesterol fell by 9.3%, compared with an increase of 2.3% with placebo. Shi and Zhu (404-P) described the effect of orlistat on weight loss and glycemic control in 85 overweight Chinese patients with type 2 diabetes or impaired glucose tolerance, a subgroup of a study of 444 overweight patients. HbA_{1c} fell 0.7% with orlistat vs. 0.1% with placebo, fasting glucose fell 2.1 vs. 1.0 mmol/l, and postprandial glucose fell 3.2 vs. 0.9 mmol/l. In the overall study, both 7.5 vs. 3.7% weight loss and 7.2- vs. 4.6-cm decrease in waist circumference were seen with orlistat vs. placebo. Bray et al. (427-P) compared 535 patients with obesity (BMI 28–43 kg/m²) and diabetes treated with insulin (HbA_{1c} 7.5–12.0%), who were put on a hypocaloric diet with orlistat versus placebo for 1 year. Weight loss averaged 3.8 vs. 1.2% for orlistat vs. placebo, and HbA_{1c} decreased 0.6% vs. an increase of 0.3%, whereas the insulin dose decreased by 8 vs. 2 units/day. LDL cholesterol decreased 9.1% vs. an increase of 0.8%, and waist circumference decreased 5.3 vs. 2.5 cm. Serrano-Rios et al. (526-P) randomized 237 patients with diabetes (BMI ≥27 kg/m² and HbA_{1c} ≥7.5%) with a hypocaloric diet with orlistat versus placebo. They found a 4.2 vs. 1.0% weight loss at 24 weeks, with HbA_{1c} falling 0.9 vs. 0.4%.

Anderson et al. (85-OR) treated 327

individuals without diabetes (BMI 30–43 kg/m²) with placebo versus bupropion SR at 300 or 400 mg daily. They found a weight loss of 4.9, 7.0, and 9.4%, respectively, suggesting this antidepressant to be a potentially effective anorexic treatment. Geloneze et al. (453-P) performed vertical gastroplasty with Y-Roux bypass on 10 patients with type 2 diabetes, finding BMI decreasing from 54.1 kg/m² at baseline to 40.6 and 35.5 kg/m² at 6 and 12 months, respectively. HbA_{1c} decreased from 7.6% at baseline to 4.9 and 4.6% at 6 and 12 months, respectively, and insulin sensitivity improved 2.3- and 2.7-fold at 6 and 12 months, respectively, suggesting benefit of the procedure in improving glycemic control.

Adipocyte secretory products

A number of reports dealt with potential metabolic effectors produced by adipocytes. In a study of the cytokine interleukin (IL)-6, Trujillo et al. (48-OR) showed that IL-6 doubles leptin secretion and glycerol release from human adipocytes *in vitro*, suggesting a role of adipocyte IL-6 production in regulating adipocyte metabolism. Zhang et al. (50-OR) showed that tumor necrosis factor (TNF)- α doubled lipolysis by human adipocytes *in vitro*, with phosphorylation of extracellular signal-related kinase (ERK)-1/2. An inhibitor of an earlier portion of the mitogen-activated protein kinase (MAPK) pathway decreased TNF- α -induced lipolysis and ERK phosphorylation. Rosiglitazone decreased TNF- α -induced lipolysis without changing its effect on ERK, suggesting its effects to be downstream from the ERK pathway.

Huan et al. (31-LB) addressed the question of whether there is a direct adipocyte effect of leptin in a model with selective reduction of adipocyte leptin receptors after birth. Although showing normal food intake, the animals had increased adipocyte mass as well as liver and skeletal muscle triglycerides, with development of hyperinsulinemia and glucose intolerance, suggesting that leptin can directly regulate fat metabolism independent of its central nervous system effects. Larcher et al. (16-LB) developed transgenic mice overexpressing leptin ectopically from epidermal cells, showing a 25- to 30-fold increase in serum leptin, low body weight, and severe fasting hypoglycemia with low insulin levels at 4–6 weeks. Beginning at 12 weeks in males

and 18 weeks in females, however, body weight met and then exceeded control levels, suggesting the development of leptin resistance, subsequently causing insulin resistance and obesity. Arioglu et al. (3-LB) noted that leptin deficiency is seen in severe lipoatrophy, and that leptin replacement in a mouse model with lipoatrophy led to resolution of diabetes and dyslipidemia. In 5 women with generalized lipoatrophy or familial partial lipodystrophy, recombinant methionyl-human leptin treatment for 4 months increased serum leptin from 1.2 to 13.8 ng/ml, decreasing fasting glucose, HbA_{1c}, triglyceride, free fatty acid, and alanine aminotransferase levels, with a 35% decrease in liver volume.

Resistin, an adipocyte-derived polypeptide, was discovered because of its downregulation by thiazolidinediones and may in part explain the benefits of treatment with these agents. Steppan et al. (281-PP) reported that resistin antagonizes the action of insulin, decreasing glucose tolerance and increasing insulin action in normal mice, and that immunoneutralization improves glucose tolerance and insulin action in models of insulin resistance. Cao et al. (283-PP) showed a complex pathway of β -adrenergic induction of thermogenesis. β 3-Adrenergic signals activate cyclic AMP and protein kinase A (PKA), resulting in the phosphorylation of p38 MAPKs, with subsequent increase in uncoupling protein (UCP) 1 gene expression in brown adipocytes. Inhibitors of PKA and of p38 both prevent induction of UCP1 mRNA.

The adipocyte-derived peptide adiponectin potentiates the action of insulin, improving the insulin resistance of lipoatrophic mice, and protects mice fed a high-fat diet from developing obesity. Yamauchi et al. (282-PP) reported that both lipoatrophic diabetes and type 2 diabetes are associated with decreased levels of adiponectin, and that treatment with this peptide reverses the insulin resistance of the two conditions in animal models. Lacquemant et al. (14-LB) noted genetic linkages of chromosome 3q27, which contains the gene for adiponectin, to type 2 diabetes as well as to coronary disease, which is also associated with low adiponectin levels. Genotypes of 384 obese patients, 310 individuals with strong family history of type 2 diabetes, 189 individuals with type 2 diabetes, 223 nondiabetic individuals from families

with diabetes, and 377 nonobese nondiabetic control subjects showed an association of chromosome 3q27 with the presence of diabetes in obese subjects and with coronary disease among individuals with diabetes. Weyer et al. (1556-P) reported plasma adiponectin averaging 7.2 in 121 Pima Indians but 10.2 mg/ml in 23 Caucasians, and they reported levels of 5.5, 6.1, and 7.5 mg/ml in Pima Indians with diabetes and impaired and normal glucose tolerance, respectively. In multivariate analysis, adiponectin showed negative correlation with abdominal obesity and with fasting insulin, and it showed positive correlation with insulin sensitivity, suggesting adiponectin deficiency to be an important mediator of insulin resistance.

Obesity and the brain

P. Antonio Tataranni (Phoenix, AZ) discussed positron emission tomography (PET) scan studies of the neuroanatomical correlates of taste, hunger, and satiation in humans. He pointed out that the discovery of leptin in 1994 and subsequent insights into its interaction with receptors in the brain has led to an expansion of research, from psychology and neurophysiology to biochemistry, in the mechanisms underlying the development of obesity. New understanding of leptin's direct activation of proopiomelanocortin (POMC) neurons and indirect effect in decreasing neuropeptide Y (NPY) and agouti-related peptide (AgRP), with the presence of ultrashort feedback loops regulating this system, is an example of this increasing sophistication in the understanding of eating patterns. The initiation of eating involves cross talk of the hypothalamus with the thalamus, amygdala, hippocampus, and several areas of the cortex, all of which have afferents to the NPY/AgRP neurons, suggesting this is an integrating system. Using PET with administration of positron-emitting radiotracers to measure regional blood flow responses to specific stimuli allows identification of regions of the brain, where changes in blood flow take place in response to those stimuli. He described studies of obese versus lean individuals after a 36-h fast, after initially tasting food, and after ingestion of 50% of a day's caloric requirement. Three-dimensional brain mapping shows that with the administration of a meal, there is increased activity in the frontal cortex and de-

creased neuronal activity in the hypothalamus, thalamus, and a large number of regions in the limbic and paralimbic system, hippocampus, and temporal cortex. Because the frontal cortex is involved in the inhibition of inappropriate responses, its activation may be related to the decrease in activity in other regions. With obesity, there was a less marked increase in blood flow in the prefrontal cortex and a lesser decrease in neuronal activity in the hypothalamus in the obese group. This has been confirmed with functional magnetic resonance imaging studies showing a decreased neuronal activity in the hypothalamus after glucose ingestion that occurred more rapidly in lean individuals. Preliminary studies of "successful dieters" show patterns similar to those seen in the lean group. Thus, the limbic and paralimbic areas may participate in a central orexigenic network modulated via feedback by areas of the prefrontal cortex, with differing responses in obese and lean individuals. It will be important to assess effects of antiobesity treatment on these patterns to see whether normal inhibitory processes are mimicked.

Hans-Rudolf Berthoud (Baton Rouge, LA) discussed neural systems controlling food intake and body weight, pointing out that ingestive behavior is more than the act of eating and is controlled by neural systems that go far beyond the hypothalamus, to include cortical areas. The initiation of food ingestion is based on both the internal state and the incentive value of the goal object and leads to a change in the drive state, which allows appropriate motor program selection for the phase of nutrient procurement. This is nonstereotypical and volitional behavior that requires foraging, with the organism needing to remember the location, abundance, and cost of a food source. During the phase of food consumption, stereotypic action occurs with rhythmic movements and with autonomic adjustments, including secretion of saliva, acid, insulin, and various accommodation and counter-regulatory responses. Finally, the meal is terminated, usually because of satiety, until the next initiation phase. Neurologically, information is gathered from associative learning for further use. Very little of this complex sequence can be explained in neurobiological terms. The "input-integration-output" model of behavioral control suggests that "internal input" is an important factor, stored from

previous experience, including information about food expectancies, reward/pleasure, emotional value, and the social and situational content of the meal. Thus, the behavior of starting and stopping food ingestion is mediated via complex neural pathways.

A myriad of internal and external sensory signals are available to the brain. The rostral nucleus of the solitary tract in the brain stem relays information from the mouth and tongue to the cortex and to the hypothalamus by two major pathways, and there is vagal input of data from the splanchnic bed, as well as input to the brain from bloodborne nutrients and hormones. There are two competing concepts: that the hypothalamus is an integrative center, and the idea of there being a "distributed system," also involving the autonomic nervous system, brain stem, and cortex. New knowledge of NPY, leptin, POMC, AgRP, orexin, and other peptides suggest important endocrine and paracrine regulation, which should be considered additional processes rather than the sole regulators of eating behavior. There are ~40 different interconnected hypothalamic nuclei. The arcuate nucleus contains neurons synthesizing NPY and AgRP with leptin receptors, with projection to the paraventricular nucleus (PVN) and other areas. The arcuate and retrochiasmatic area contain POMC and cocaine-amphetamine-regulated transcript (CART), with projection to the PVN and also the lateral hypothalamic area (LHA). The LHA also has orexin, melanin-concentrating hormone, CART, and other neurons. These neurons project to the cortex, limbic system, and thalamus and presumably are involved in cognitive, appetite processing, reward assessment, and other "higher" functions. They also have output to the brainstem and spinal cord, leading to oro- and locomotor control and to autonomic control of effectors in thermoregulation, adipose tissue, muscle, pancreas, liver, and gut.

There is a strong input from the prefrontal cortex to the lateral hypothalamus as well as from the insular cortex, which receives taste and visceral input through the thalamus. The amygdala also sends input to most of the hypothalamus, and the hippocampal complex also sends projections to various hypothalamic nuclei. There is feedback to the cortex from neurons containing orexin, and the reticular activating "arousal system" projects back

to the cortex. Certain neurons respond specifically to the taste of glucose or fat. Presumably, memory, including that of pleasure or displeasure derived from certain foods, and a variety of autonomic and endocrine parameters lead to further regulation. Berthoud summarized with the concept that there is a massive parallel processing network for the control of food intake. The central processor circuit consists of the frontal cortex, mediating polymodal association, the amygdala and nucleus accumbens, the hypothalamus, and areas of the brainstem including the nucleus tractus solitarius and the parabrachial nucleus.

Charles Billington (Minneapolis, MN) further discussed the regulation of food intake. The hypothalamus, with responsiveness to insulin and to leptin, shows some features of a closed feedback loop. Leptin absence, as seen in the *ob/ob* mouse and in rare human mutations, leads to obesity, suggesting that the hormone “represents a soluble fat mass signal to the brain.” One can suggest a simplified model, with the arcuate nucleus having input from leptin and to a lesser extent from insulin. These hormones inhibit NPY/AgRP and stimulate POMC and melanocyte-stimulating hormone (MSH). These act in the PVN, with NPY inhibiting and POMC/MSH stimulating the melanocortin receptor. Food ingestion is stimulated by the activation of type 1 and type 5 NPY receptors, and it is inhibited by activation of melanocortin receptors. The agouti mouse expresses an abnormal gene product that produces the agouti protein, which is associated with weight gain. There are multiple additional neuromodulators of energy metabolism. The classical modulators are norepinephrine, serotonin, and dopamine. NPY, opioids, galanin, cholecystokinin, corticotropin-releasing hormone, thyrotropin-releasing hormone, and bombesin were discovered subsequently, and most recently MSH/melanocortin receptors, urocortin, orexins, and glucagon-like peptide 1 (GLP-1) have been found to play complex roles. For example, serotonin has little effect alone but blunts the increase in food intake seen with NPY. In clinical use, serotonin agonists clearly may play a role in the treatment of obesity. NPY, opioids, orexin, galanin, and AgRP all increase food intake, and leptin, serotonin, melanocortin agonists, urocortin, CRH, and GLP-1 all decrease food intake. The set

point theory suggests that there should be a balance, with these acting as a homeostatic mechanism. In humans, however, this is not the case, and indeed the prevalence of obesity is increasing.

Billington proposed four explanations for the increasing human obesity. It is unlikely that pathological mutations similar to those in leptin-deficient states are present in 30–50% of the world’s population. Alternatively, humans may now be reaching their genetic body weight potential, previously not attained because of food shortages. Leptin action may be impaired in a broad spectrum of the population by acquired leptin resistance, due, perhaps, to toxic effects of excess dietary fat. Finally, the leptin/hypothalamic brain mechanism may be one of the brain mechanisms that coregulate appetite and body weight. Indeed, many brain sites are involved, in addition to the hypothalamic group (arcuate nucleus, lateral hypothalamus, PVN, and dorsomedial nucleus); the limbic system with prefrontal cortex; the amygdala, involved in attaching emotion to autonomic processes; the nucleus accumbens, attaching “reward;” and the brainstem with nucleus solitarius. Opioid effects appear to be important. The opioid antagonist naloxone particularly decreases consumption of sweetened food by food-deprived rats; sucrose ingestion increases naloxone-induced cFos activation in the central amygdala; and, when naloxone is directly administered into the amygdala, food intake is particularly blocked for diets liked by the individual rat. Opioid antagonists administered into the nucleus of the solitary tract also decrease food intake. Thus, the opioid system is related to overall “reward” mechanisms. Billington described dopamine as another “neural currency” for rewards of most kinds, including food, sex, drugs of abuse, and electrical self-stimulation, mediating some of the connection between the PVN and nucleus accumbens. There is little mechanistic knowledge of the role of the cortex, although in humans this must be of great importance in mediating education, behavior modification, and choice-making behavior. “In the explosion of obesity,” Billington noted, “our cortices are not able to supervise the [other] brain sites.”

Michael A Cowley (Portland, OR) discussed neuronal circuits regulating food intake, noting that leptin activates POMC

neurons through an integrated network of arcuate neurons. He proposed a “central processor” of adipostatic circuitry in the arcuate nucleus, with the MSH and NPY groups of neurons, projecting to the PVN of the hypothalamus, as a part of the disseminated network regulating food intake. By viewing blocks of hypothalamus under a dissecting microscope, it is possible to assess an opioid-specific current composed of functional POMC neurons. When leptin is applied, the resting membrane potential increases and there is a two- to fivefold increase in the firing rate of these neurons, in a dose-responsive fashion; without the presence of leptin, the POMC neurons do not produce MSH. Leptin appears to inhibit presynaptic γ -amino butyric acid (GABA) neurons containing NPY, which act to inhibit the POMC neurons, suggesting a complex feedback loop. Cowley showed that the growth hormone secretagogue peptide ghrelin increases the release of GABA onto POMC neurons threefold and decreases the firing rate of these neurons via both GABA and non-GABA pathways.

In a study presented at the ADA meeting, Bingham et al. (55-OR) studied brain glucose metabolism using 18 fluoro-deoxyglucose PET in eight healthy male volunteers given somatostatin to suppress endogenous insulin. Their results show that basal insulin replacement increased total brain glucose uptake by 14%, with a particular increase in glucose uptake in the diencephalon, which includes the hypothalamus. They noted that this area has an increased density of insulin receptors with lessened blood-brain barriers, allowing easier penetration of insulin.

Niswender et al. (53-OR) administered intracerebroventricular (ICV) insulin with or without LY294002, an inhibitor of phosphatidylinositol (PI) 3-kinase, a metabolic signal of insulin action. Insulin increased mediobasal hypothalamic activity of insulin receptor substrate (IRS)-2 but not IRS-1 and -3. LY294002 did not affect basal food intake, but it but prevented the anorexia induced by ICV leptin, while not affecting anorexia caused by α -MSH, which mediates leptin action. Blockade of the non-metabolic intracellular insulin signaling MAPK pathway had no effect on leptin-induced anorexia. Morton et al. (25-LB) showed that the increase in food intake accompanying the inhibition of PI 3-kinase does not occur in mice lacking lep-

tin receptors and is restored after the microinjection directly into the hypothalamic arcuate nucleus of adenovirus expressing the leptin receptor. Carvalheira et al. (54-OR) pointed out that insulin and leptin are both secreted in proportion to body adiposity and have overlapping effects on hypothalamic control of energy homeostasis. Insulin signals through a receptor tyrosine kinase that phosphorylates and activates the docking proteins IRS, whereas the leptin receptor and its associated protein tyrosine kinase mediate phosphorylation and activation of the transcription factor signal transducer and activator of transcription 3 (STAT3). They showed that insulin induces phosphorylation both of the leptin receptor and of STAT3, a potential mechanism of the complementary effect of the two hormones. Zhao et al. (32-LB) reported that ICV leptin in rats tripled hypothalamic phosphodiesterase (PDE) 3B and quadrupled hypothalamic PI 3-kinase, while decreasing hypothalamic cAMP levels. A specific pharmacological inhibitor of type 3 PDE, cilostamide, completely blocked the satiety action of leptin, whereas this was not seen with an inhibitor of type 4 PDE. ICV cilostamide completely blocked the leptin-induced tyrosine phosphorylation of hypothalamic STAT3.

Obici et al. (56-OR) studied the peripheral effects of week-long ICV infusions of α -MSH versus the melanocortin antagonist SHU9119. Their results showed a decrease with α -MSH versus an increase with SHU9119 in visceral fat and potentiation, and there was a reduction with SHU9119 in insulin's effects on hepatic glucose output and on peripheral glucose utilization during hyperinsulinemic clamp studies, suggesting central coupling of energy intake and insulin action. Obici et al. (57-OR) also showed that ICV long-chain fatty acid administration with either oleic or palmitic acids inhibited hepatic glucose production, whereas this was not seen with the short-chain fatty acid octanoic acid. The ICV coadministration of either tolbutamide or glyburide blocked the effect of oleic acid, whereas the sulfonylureas alone did not have an effect, suggesting that the phenomenon requires the opening of ATP-sensitive K^+ channels, and that a hypothalamic pathway activated by fatty acids, leptin, and insulin links availability of nutrients to regulation of their production and intake. Shintani et al. (59-OR) noted that ICV administration of ghrelin, the endogenous growth hormone secretagogue present both in the stomach and the hypothalamic arcuate nucleus, in-

creases both food intake and hypothalamic NPY mRNA. Leptin decreases food intake and NPY, both effects blocked by ghrelin. Coadministration of an NPY antagonist blocks the ghrelin effect on food intake in a dose-dependent fashion.

References

1. Mokdad AH, Serdula MK, Dietz WH, Bowman BA, Marks JS, Koplan JP: The spread of the obesity epidemic in the United States, 1991–1998. *JAMA* 282: 1519–1522, 1999
2. McGinnis JM, Foege WH: Actual causes of death in the United States. *JAMA* 270:2207–2212, 1993
3. Gillman MW, Rifas-Shiman SL, Camargo CA Jr, Berkey CS, Frazier AL, Rockett HR, Field AE, Colditz GA: Risk of overweight among adolescents who were breastfed as infants. *JAMA* 285:2461–2467, 2001
4. Epstein LH, Valoski AM, Vara LS, McCurley J, Wisniewski L, Kalarchian MA, Klein KR, Shrager LR: Effects of decreasing sedentary behavior and increasing activity on weight change in obese children. *Health Psychol* 14:109–115, 1995
5. Garg A: High-monounsaturated-fat diets for patients with diabetes mellitus: a meta-analysis. *Am J Clin Nutr* 67 (3 Suppl.):577S–582S, 1998