

# American Diabetes Association Annual Meeting, 1999

## Diabetes and obesity

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This is the third of eight reports on the American Diabetes Association Annual Meeting and Scientific Sessions held in San Diego in June. It covers topics related to the association between diabetes and obesity and to new understandings of effective treatment of obesity. Interesting related presentations at meetings held recently in New York will also be discussed.

Gerald Bernstein, New York, NY, gave the American Diabetes Association President's Address at the annual meeting, citing such accomplishments of the past year as the United Kingdom Prospective Diabetes Study publications and increased efforts by people such as Nicole Johnson, a woman with type 1 diabetes who was selected as Miss America in 1998, to publicize diabetes. He stated, however, that "in spite of all we are doing, many out there do not get it. Why are we facing a worldwide pandemic of diabetes, and what are we going to do about it?" Bernstein quoted Shakespeare's Cassius: "The fault, dear Brutus, lies in ourselves," and then suggested that it is "ironic that prosperity has created the environment where diabetes will flourish." The "thrifty gene" advantage led to adaptations that cause diabetes, and "today that group of genetic faults is rapidly progressing" because of obesity, physical inactivity, and aging. "We cannot," he asserted, "wait for evolution to rid society of type 2 diabetes."

Worldwide, diabetes prevalence will increase 42% in the developed world and 172% in the developing world during the next 30 years. The frequency of diabetes in the U.S. will increase from 16 to 30 million with a predicted cost of "a trillion dollars—that's right—a trillion dollars." Bernstein stated that public health interventions can make a difference by focusing on overeating and lack of physical activity.

Judith Stern, Davis, CA, discussed the implications of excess weight in diabetic patients. Stern defined obesity as mild with BMI >30, moderate with BMI >35 and severe with BMI >40 kg/m<sup>2</sup>, and, she pointed out that additional information is gained by measurement of waist circumference for those with BMI <35 and that abdominal obesity is present for men and women with waist circumference >102 and 88 cm (40 and 35 inches), respectively. Data from the second National Health and Nutrition Examination Survey (NHANES II) show that 15–25% of individuals with BMI >35 have diabetes. There are currently 63 million overweight Americans who constitute 35% of the adult population. Health costs for obese individuals are \$70–100 billion/year. Obesity affects 80% of patients with diabetes and 70% of patients with cardiovascular disease (CVD), and is associated with gallbladder disease, dyslipidemia, hypertension, sleep apnea, and a number of malignancies. Stern cited the discouraging

measure of the increase in portion sizes over the past two decades: the size of dinner platters has increased in response to changes in eating patterns. Physical inactivity is strongly associated with obesity. Children face environmental distractions, such as the television and computer, a decrease in the availability of safe outdoor play areas, and less emphasis on physical activity in schools, although the social stigma against overweight children is worse than that against overweight adults. In the context of our inability to help overweight patients attain normal weight levels, Stern reviewed several new definitions of success for treatment of obesity, which have become increasingly more important as third-party payers refuse to fund weight loss interventions. Weight loss of 5–10% of initial body weight represents a successful intervention, although this does not fulfill the expectations of patients entering weight loss programs. Certainly, the maintenance of attained weight loss is crucial to successful dietary intervention, but the prevention of weight gain may also be considered a success, as would be the amelioration of hypertension, dyslipidemia, or diabetes. "We have learned," Stern pointed out, "that chronic diseases require chronic treatment [...], that weight loss is modest, that weight regain is common, [and] that one treatment does not work for all patients."

Khan et al. (abstract 1348) showed that nondiabetic patients enrolled in a long-term weight management protocol using diet, exercise, behavioral modification, and appetite suppressant therapy lost 8.0 vs. 4.8 kg for patients with diabetes and that weight loss decreased in patients with more advanced diabetes disease stages (abstract numbers refer to the Abstracts of the 59th Annual Meeting and Scientific Sessions of the ADA, Diabetes 48 [Suppl. 1]:1–A550). The important role central obesity plays in diabetes and the atherosclerotic process was addressed by Boras et al. (abstract 1632), who showed that among 102 individuals with type 2 diabetes and the metabolic syndrome characterized by waist-to-hip ratio (WHR), BMI, and levels of serum triglycerides, serum HDL cholesterol, microalbumin

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Abbreviations: AgRP, agouti-related peptide;  $\alpha$ -MSH,  $\alpha$ -melanocyte-stimulating hormone; B3A,  $\beta_3$ -adrenergic; B3AR, B3A receptor; BAT, brown adipose tissue; CRH, corticotropin-releasing hormone; CT, computed tomography; CVD, cardiovascular disease; ICV, intracerebroventricular; MAPK, mitogen-activated protein kinase; NEP, norepinephrine; NMR, nuclear magnetic resonance; NHANES, National Health and Nutrition Examination Survey; NPY, neuropeptide Y; PAI, plasminogen activator inhibitor; PDE, phosphodiesterase; PI3K, phosphatidylinositol-3-kinase; PIP3, phosphatidylinositol 3,4,5-triphosphate; POMC, proopiomelanocortin; PPAR- $\alpha$ , peroxisome proliferator-activated receptor- $\alpha$ ; PVN, paraventricular nucleus; SC, subcutaneous; SNS, sympathetic nervous system; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ ; UCP, uncoupling protein; VMH, ventromedial hypothalamus; WAT, white adipose tissue; WHR, waist-to-hip ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

minuria, and hypertension, only age and WHR showed significant independent association with carotid artery intima media thickness. Lemieux et al. (abstract 1335) measured height; weight; waist girth; hip girth; visceral adipose tissue (by means of computerized tomography); fasting plasma insulin, triglyceride, and HDL cholesterol levels; and plasma insulin and glucose responses to a 75-g oral glucose tolerance test in 273 men and 299 women aged 18–72 years. Waist girth tertiles showed similar visceral adipose tissue area in nonobese (BMI first or second tertile) patients and noncentrally obese (BMI third tertile, but waist girth first or second tertile). Using the WHR to similarly define noncentral obesity, however, this group had substantially greater visceral adipose tissue than the nonobese group, suggesting that classification based on waist girth is more effective than classification based on WHR.

A number of presentations at the June ADA meeting discussed new understanding of factors that control food intake and obesity, focusing in particular on leptin, knowledge of which, according to Dan Porte, Seattle, WA, “has revolutionized the study of obesity and body weight regulation.” Stephen Woods, Cincinnati, OH, discussed the regulation of energy intake by leptin. A basic concept is that adipocyte signals, such as leptin, act to regulate sensitivity to the much more rapidly changing meal-related signals. Hormonal regulators of adiposity include leptin and insulin, both of which inhibit food intake. Both leptin and insulin are large peptides secreted from peripheral sites. However, there are differences in their peripheral effects: leptin deficiency is associated with weight gain, and insulin deficiency causes weight loss. Low-dose intracerebroventricular (ICV) insulin decreases food intake in nonhuman primates in a dose-dependent fashion that is similar to the effects of leptin. Like leptin, insulin enters the brain via receptor-mediated saturable transports; an important site of action for both peptides is the arcuate nucleus of the ventromedial hypothalamus (VMH). Subsequently, leptin inhibits neuropeptide Y (NPY)-secreting cells, which synthesize and secrete agouti-related peptide (AgRP). Both NPY and AgRP increase food intake. In addition, leptin stimulates secretion of proopiomelanocortin (POMC), the precursor of  $\alpha$ -melanocyte-stimulating hormone ( $\alpha$ -MSH).  $\alpha$ -MSH leads to decreased food intake, with  $\alpha$ -MSH agonists and antagonists decreasing and

increasing food intake. Additional hormones affecting intake are corticotropin-releasing hormone (CRH) and oxytocin, which are produced in the paraventricular nucleus (PVN) and tend to reduce food intake and increase energy expenditure, and the orexins and melanin-concentrating hormone, which are produced in the lateral hypothalamus and tend to increase food intake. These signals seem to be integrated in the brainstem. There is also synergy between peripheral signals. For example, cholecystokinin, a satiety signal that enters in the brain stem, and leptin, an adiposity signal that enters in the arcuate nucleus, act together in the brain to decrease body weight.

A number of studies presented at the ADA meeting addressed the interrelationships between hypothalamic factors and food intake. Matsuda et al. (abstract 114) used magnetic resonance imaging to monitor hypothalamic function after oral glucose intake in 10 obese and 10 lean nondiabetic individuals. After glucose ingestion, lean but not obese subjects showed decreased signals in the PVN and ventromedial nucleus, and the time taken to reach maximum inhibitory response correlated with fasting plasma glucose and insulin concentrations in both lean and obese subjects. McMinn et al. (abstract 269) showed ICV  $\alpha$ -MSH decreased food intake by 40% initially and by 11% over a 6-day period with a 4% decrease in body weight and a 29% decrease in plasma insulin. cFos-like immunoreactivity, a measure of neuronal activation, increased 250% in the PVN and 200–1,000% in the supraoptic nucleus, the central nucleus of the amygdala, and the parabrachial nucleus of the brainstem, all of which are part of hindbrain pathways associated with satiety. Liu et al. (abstract 110) infused rats with  $\alpha$ -MSH ICV for 6 h while insulin was clamped at 65  $\mu$ U/ml. The amount of glucose required to maintain euglycemia decreased because of increased gluconeogenesis, which suggests that activation of the hypothalamic melanocortin pathway accounts for some of the metabolic effects of leptin. In a complementary study, Satoh et al. (abstract 111) administered ICV SHU9119, an  $\alpha$ -MSH antagonist, to transgenic mice overexpressing leptin, which have increased glucose metabolism and insulin sensitivity. Food intake, body weight, and blood glucose levels increased with decreased hypoglycemic response to insulin, suggesting that both the satiety

and antidiabetic effects of leptin are mediated through the hypothalamic melanocortin system. Ebihara et al. (abstract 1369) showed that AgRP administration increases food intake and reverses leptin injection-induced satiety, suggesting that dysregulation of hypothalamic AgRP production by leptin could be a mechanism of leptin-resistance. Sindelar et al. (abstract 112) studied streptozotocin-induced diabetic mice deficient in NPY, showing these animals decreased food and water intake in comparison with those with normal NPY levels. Although it is not required for transient fasting hyperphagia in this model, NPY is required for the sustained hyperphagia induced by diabetes. Havel et al. (abstract 288) showed that rats with streptozotocin-induced diabetes had an 80% decrease in hypothalamic POMC mRNA and a 60% increase in AgRP, which indicates that there are additional mechanisms that induce their hyperphagia. The change in POMC, but not in AgRP, was partially reversed by insulin treatment. Diabetes increased hypothalamic NPY by 60% and decreased CRH by 30% with normalization by insulin treatment. Uncoupling protein (UCP)-3 expression was increased by 10-fold in gastrocnemius muscle from diabetic rats, and this effect was prevented by insulin treatment. These responses may contribute to the effects of uncontrolled diabetes on energy metabolism and fuel partitioning. Zhang et al. (abstract 212) showed that chronic norepinephrine (NEP) infusion into the VMH in rats induced hypertriglyceridemia, abdominal fat accumulation with increased lipogenesis in isolated adipocytes, hyperinsulinemia, insulin resistance, and glucose intolerance. Elevated endogenous VMH NEP is present in obese glucose-intolerant animals and may contribute to their metabolic condition. Nakagawa et al. (abstract 302) showed that brain-derived neurotrophic factor, which decreases blood glucose levels in mice lacking the leptin receptor, potentiated the hypoglycemic action of insulin and increased liver and the muscle insulin receptor phosphorylation.

Clifton Baile, Athens, GA, described the relationship between leptin and apoptosis. Adipocyte apoptosis is increased in malignancies and may be mediated by tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) (1). Interestingly obesity increases TNF- $\alpha$ , although not to levels seen in malignancy, and stimulates adipocyte apoptosis, which can be inhibited by insulin. However, leptin does

not increase circulating TNF- $\alpha$  levels. Leptin administration decreases adipocyte mass below the levels in pair-fed control subjects, with a particular decrease in adipocyte number. Moreover, recovery of body weight after discontinuing leptin is delayed in comparison to control subjects (2). ICV leptin causes adipocyte loss by apoptosis, which is not seen in pair-fed rats and is maintained even after hypophysectomy. These observations suggest that mediation is by neural rather than endocrine mechanisms (3). The rate of brown adipose tissue (BAT) apoptosis in mice is decreased by cold exposure under control of noradrenergic and dopaminergic stimuli, which may, in part, be stimulated by leptin.

In a related talk, Leslie Kozak, Baton Rouge, LA, discussed the relationship between leptin and UCP, both of which regulate energy expenditure and body weight in obese and diabetic subjects. Early studies showed that, even with restriction of food intake to 80% of that given control animals, the body weights of ob/ob mice increased above control levels in association with increased body fat. Leptin increases adipocyte sympathetic nervous system activity and increases thermogenesis by inducing both white and brown fat mitochondrial UCP-1 fivefold. UCP-2 also increases in association with increased adipocyte fatty acid oxidation, decreased lipogenesis, and increased peroxisome proliferator-activated receptor- $\gamma$  (PPAR- $\gamma$ ) levels and PPAR- $\gamma$  activity (4,5). The main function of BAT is thought to be nonshivering thermogenesis, which is under sympathetic nervous system (SNS) control. BAT can appear in white adipose tissue (WAT) deposits under SNS stimulation with cold exposure or  $\beta_3$  adrenergic (B3A) treatment. Kozak noted the relevance of these studies to human obesity, pointing out that "the white adipocyte in humans starts as a brown adipocyte. The challenge is to reactivate [brown adipose tissue-like thermogenic activity]." Further understanding of the control of adipocyte UCP and apoptosis may allow development of new treatment strategies for obesity.

Banks et al. (abstract 258) studied the leptin receptor, which is a type 1 cytokine receptor that exists in multiple alternately spliced isoforms, the "long form" of which is critical for leptin action. Activation of the leptin receptor results in activation and autophosphorylation of a receptor-associated tyrosine kinase with autophosphorylation of tyrosine residues of the intracellular

tail of the receptor and the transmission of downstream signals. Commins et al. (abstract 19) studied rats lacking the enzyme responsible for synthesizing NEP and epinephrine from dopamine and rats lacking the leptin receptor. They found that leptin regulates its own expression in WAT and regulates UCP-1 expression in BAT through hypothalamic leptin receptors that lead to increased sympathetic outflow. Furthermore, they showed that the B3A agonist CL316-243 increased UCP-1 expression in BAT and reduced leptin mRNA in WAT. Richelsen et al. (abstract 18) described a dose-related stimulatory effect of insulin *in vitro* on muscle expression of mRNA for mitochondrial UCP-2 and -3 after 2 h of treatment. Muscle contraction stimulated UCP-3 but not UCP-2 after 6 h, whereas the  $\beta$ -adrenergic agonist isoproterenol, triiodothyronine, and leptin had no acute effect on UCP-2 or -3, suggesting that insulin influences acute energy expenditure. Saker et al. (abstract 20) used family-based association methods to study the B3A receptor (B3AR) and UCP genes in 170 parent-offspring trios. B3AR, UCP-1, and UCP-2 had no direct influence on susceptibility to type 2 diabetes, but several UCP-3 promoter variants were found, one of which was associated with increased WHR in parents and was possibly related to the development of diabetes. Portocarrero et al. (abstract 21) studied effects of conjugated linoleic acid, naturally occurring isomers that improve glucose tolerance in Zucker diabetic fatty rats and activate PPAR- $\gamma$  response elements *in vitro*. Expression of UCP-2 but not UCP-1 mRNA in gastrocnemius muscle was increased by dietary supplementation. Jucker et al. (abstract 22) noted that quiescent skeletal muscle utilizes ~45% of whole-body oxygen consumption and that this is controlled in part by UCP-3, which is expressed primarily in muscle and is encoded in a chromosomal region linked to hyperinsulinemia and obesity. Thus, UCP-3 may play an important role in regulating energy expenditure and body weight. They assessed mitochondrial energy uncoupling in skeletal muscle of awake rats by combining  $^{13}\text{C}$  nuclear magnetic resonance (NMR) to measure rates of mitochondrial substrate oxidation with  $^{31}\text{P}$ -NMR to assess unidirectional ATP synthase flux. Acute administration of the mitochondrial uncoupler 2-4-dinitrophenol decreased energy coupling ~80%, and chronic administration of triiodo-L-thyronine decreased energy coupling by

~60% with an increase in UCP-3 mRNA and protein expression. This approach may allow better study of *in vivo* regulation of UCP activity to determine its role in energy metabolism and obesity. However, it is not certain that these approaches will produce clinical benefit. Rave et al. (abstract 486) administered the B3A agonist UL-TG 307 for 2 weeks to 13 men with type 2 diabetes without improvement in insulin sensitivity or secretion or levels of free fatty acids, fructosamine, or glucose.

Michael Ashford, Aberdeen, Scotland, discussed fascinating data that showed that leptin, complementing its effects of decreased food intake and increased energy expenditure, opens the  $\beta$ -cell  $K_{\text{ATP}}$  channel and thereby decreases stimulus-induced insulin secretion. Leptin also inhibits insulin secretion by decreasing protein kinase C levels, cAMP levels, insulin gene expression, and intracellular calcium concentrations. Leptin has effects on angiogenesis, immune function, and reproductive function and on insulin secretion and action; many of these effects may also involve  $K_{\text{ATP}}$  channels, which is known to be true of leptin's action on the hypothalamus. In studies of the  $\beta$ -cell, Ashford showed that leptin causes a slow hyperpolarization of the cell membrane that can be reversed by the sulfonylureas tolbutamide and glyburide. Leptin's effect is not seen when ATP is depleted; leptin appears to activate specific kinases. Tyrosine kinase inhibitors, however, mimic many aspects of leptin's action, suggesting that it involves dephosphorylation of tyrosine in specific intracellular structures. The phosphoinositide signaling pathway includes multiple phosphorylated intermediates. Phosphatidylinositol-3 kinase (PI3K) is the main regulator, but intermediaries before PI3K, such as phosphatidylinositol 4-5-bisphosphate, which blocks ATP action, and phosphatidylinositol 3,4,5-triphosphate (PIP3), which mimics the action of leptin, are not affected by PI3K inhibitors. Insulin itself reverses the effects of leptin in the  $\beta$ -cell with a slow time course, but inhibitors of mitogen-activated protein kinase (MAPK) have no effect, and protein kinase B, which is stimulated by insulin in a PI3K-dependent fashion, is not affected by leptin. Ashford hypothesized that leptin may activate PI3K via PIP3, which changes the actin cell cytoskeleton conformation from filamentous to globular and activates the  $K_{\text{ATP}}$  channel.

Joe Beavo, Seattle, WA, discussed an additional aspect of leptin regulation of the  $\beta$ -cell and reviewed leptin's effects on  $\beta$ -cell phosphodiesterase (PDE) activity. There are >40 different PDEs, which metabolize cAMP and cGMP to 5'-AMP and 5'-GMP. PDE3B is expressed at high levels in the  $\beta$ -cell. Beavo proposed that while  $\beta$ -cell insulin receptors are expressed at low levels, there are high levels of IGF-1 receptor expression. In this schema, insulin decreases levels of its own receptor but increases IGF-1 receptor levels, leading to increased  $\beta$ -cell PDE3B, which lowers the cAMP pool and decreases insulin release. Leptin may have a similar effect in increasing  $\beta$ -cell PDE3B, which, as predicted, leads to decreases in levels of cAMP. This effect is blocked by PDE3 but not by PDE4 inhibitors, which shows that specific intracellular cAMP pools are involved. Leptin also inhibits insulin release by cAMP analogs, which are substrates of PDE3B, further suggesting the involvement of a PDE pathway. Ahren and Havel (abstract 15) reported that leptin inhibits insulinoma secretion induced by such agents as GLP-1 and the PDE inhibitor isobutyl-methyl xanthine, which act via cAMP but do not affect basal insulin secretion or cholinergic or phorbol ester-stimulated insulin secretion, both of which act via protein kinase C.

Luciano Rossetti, Bronx, NY, discussed the role of leptin in regulation of hepatic glucose metabolism. The initial observations of leptin acting at the hypothalamus to decrease food intake with abnormalities associated with obesity also showed evidence of complementary metabolic effects with animals that lacked leptin showing increased tissue triglyceride levels. Weight gain is associated with increased ability to oxidize fat, and leptin administration increases insulin levels, causing increased glucose uptake and potentiating insulin-induced decreases in hepatic glucose production. Furthermore, leptin administration selectively decreases visceral fat to an extent similar to that seen with marked caloric restriction. However, some hepatic insulin effects are antagonized by leptin. Studies with labeled lactate and glucose show increased gluconeogenesis and decreased glycogenolysis with leptin administration, leaving net hepatic glucose production stable. Similar hepatic effects are seen with ICV leptin administration, suggesting that the process may be neurally mediated. ICV leptin also decreases hepatic acetyl CoA and malonyl CoA levels, thereby favoring fatty

acid oxidation over triglyceride synthesis.  $\alpha$ -MSH receptor blockers interfere with these effects, suggesting that leptin acts by stimulation of hypothalamic POMC. This does not, however, "exclude that there is a redundant effect in the periphery." Rossetti also noted that leptin action is "extraordinarily prone to [downregulation]," which perhaps explains the resistance to high leptin levels seen in obesity. In another study from this laboratory, Wang et al. (abstract 273) showed that systemic but not ICV leptin administration decreased leptin expression in fat and induced its expression in muscle with insulin levels  $\sim 60 \mu\text{U/ml}$ . High fat feeding for 3 days decreased muscle leptin expression by 50%, and 3 days of food restriction blocked leptin's feedback inhibition on adipose tissue leptin expression. Barzilai et al. (abstract 207) compared food restriction, the B3A agonist CL-316-243, and leptin treatment. All decreased visceral fat and caused similar improvement in insulin action on hepatic glucose production, but only leptin stimulated insulin-mediated peripheral glucose uptake, mainly because of increased glycogen synthesis. In a further study of peripheral action of leptin, O'Doherty et al. (abstract 204) studied the effects of leptin on glycogen metabolism in the absorptive state and the fed-to-fasted transition in rats treated with a recombinant adenovirus encoding rat leptin. Glycogen in fasting muscle, but not in liver, was decreased, and hepatic glycogen increased 2- and 10-fold in association with decreased glycogenolysis 4 and 10 h, respectively, after glucose feeding. Buettner et al. (abstract 100) produced a sustained moderate increase in plasma leptin by administration of a recombinant adenovirus containing the leptin cDNA to rats fed a high-fat diet that causes increased visceral fat mass and intramuscular triglycerides and elevated levels of plasma glucose, insulin, triglycerides, and free fatty acids. As a result, visceral adipose mass decreased by 40%, and intramuscular triglyceride, insulin-stimulated skeletal muscle glucose uptake, and normal plasma glucose and insulin levels decreased by 60%.

Yuji Matsuzawa, Suita, Japan, discussed adipose tissue as an endocrine organ and cataloged the large number of hormonal factors other than leptin secreted by adipocytes. Computed tomography (CT) scanning allows differentiation between subcutaneous (SC) and visceral obesity, the latter of which is associated with dyslipidemia, diabetes, and hypertension, leading to the concept that portal rather than

peripheral fatty acids affect hepatic lipid metabolism preferentially with excess adipose tissue in either location producing increased TNF- $\alpha$ , which contributes to insulin resistance in skeletal muscle. Matsuzawa described studies using expressed sequence tags to assess the profile of genes expressed by SC and visceral adipose tissue, although only about one-third of these genes encode known products. Visceral fat expresses cytokines and other peptides, including adiponin, apolipoprotein D, plasminogen activator inhibitor (PAI)-1, the IGF binding proteins, and lipoprotein lipase. In an obese rodent model produced by lesions of the VMH, PAI-1 mRNA was unchanged in SC fat but increased in visceral fat, which, presumably, contributes to CVD. Adiponectin, the most abundant secreted adipocyte gene product, which shows homology with several collagen subtypes, has a paradoxical decrease in secretion with obesity and is present at even lower levels in patients with CVD. Levels increase with weight loss in association with decreased leptin levels. Adiponectin decreases vascular smooth muscle proliferation, decreases TNF- $\alpha$ -stimulated expression of adhesion molecules by vascular endothelium, and decreases MAPK activity in endothelial cells, suggesting the potential for antiatherosclerotic effects. Thus, obesity may be characterized by decreased adiponectin and by increased free fatty acids derived from visceral fat and increased cytokines, including leptin, TNF- $\alpha$ , and PAI-1. Another set of adipocyte molecules, the aquaporins, have six transmembrane domains with intracytoplasmic COOH- and NH<sub>2</sub>-terminals and mediate water and glycerol permeability, which potentially offers a regulatory mechanism for fat and glucose homeostasis.

Understanding the regulation of obesity, including the actions of leptin, will be important in the treatment of diabetes. Donahue et al. (abstract 718) reported that insulin-mediated glucose uptake was negatively associated with leptin concentrations in men and women after adjustment for body fat, suggesting a relationship to insulin resistance independent of adiposity. Volk et al. (abstract 1278) compared 91 insulin-resistant with 91 insulin-sensitive offspring of patients with type 2 diabetes. Leptin was negatively correlated with insulin sensitivity among the former group only, although it correlated positively with body fat in both groups. Kazumi et al. (abstract 1601) reported a positive associ-

ation between blood pressure and fasting serum insulin and leptin, regardless of BMI or body fat. Dodt et al. (abstract 115) stimulated the lateral cutaneous femoral nerve with a microneurography electrode in nonobese and obese women and showed that interstitial glycerol release increased 68 vs. 22%, which suggests a neural lipolytic mechanism that is impaired in obesity.

Gary Foster, Philadelphia, PA, discussed cognitive-behavioral treatment of obesity, which is able to produce a sustained loss of 9–13% of body weight for >1 year, although only in selected patients. The challenge is to improve adherence by “assuming that patients lack planning or skills, rather than motivation.” Thus, the patient must be asked, “What got in the way?” and “How would you deal with the same situation in the future?” A successful weight loss intervention should be considered one with >5% weight loss sustained for >1 year. Few patients can achieve ideal body weight or maintain >15% weight loss. However, patients typically have unrealistic expectations of weight loss, typically desiring to lose one-third of their body weight and considering one-quarter the minimum they would accept. They need help to accept achievable goals and to focus on outcomes, such as improvement in glycemic control, lipids, blood pressure, etc. “What’s going to change,” stated Foster, “is that they’re going to be healthier.” More than three-quarters of morbidly obese patients feel that they are “always” or “usually” treated disrespectfully by the medical profession because of their weight (6). The physician must help the patient understand the rationale for change in behavior, which Foster termed the “Why?” aspect, strategies to be employed (“What?”), and specific behaviors to use (“Where?” and “When?”). Foster stressed exercise to protect long-term weight loss rather than to achieve short-term goals. In a relevant study, Holler et al. (abstract 1349) randomized 44 patients with type 2 diabetes to a 2-year period of intensive dietary counseling that emphasized reducing dietary fat but not carbohydrates and protein rather than a conventional approach to caloric restriction. Energy derived from fat decreased from 43 to 29% in the group who reduced dietary fat vs. 43 to 42% in the group relying on caloric restriction; energy derived from carbohydrates increased from 42 to 49% in the group who reduced dietary fat, whereas it decreased from 43 to 39% in the group who restricted caloric intake. At 1 year, the group who

reduced dietary fat and the group who relied on restriction of caloric intake lost 4.2 vs. 4.3 kg, respectively; at 2 years, they lost 3.6 vs. 4.1 kg, respectively, but body fat mass decreased 6.2 vs. 2.1 kg and 3.6 vs. 2.3 kg at 1 and 2 years. HbA<sub>1c</sub> levels fell from 10.2 to 6.8 and 7.1% at 1 and 2 years for those who adhered to a low-fat diet vs. 9.6 to 7.8 and 8.1% for those who adhered to conventional caloric restriction, which indicates that fat restriction with higher carbohydrate and fiber intake is a preferable diet for patients with type 2 diabetes.

David Robbins, Washington, DC, discussed pharmacological approaches to weight loss at the ADA meeting, noting that the decrease in glucose levels in patients with diabetes treated with either orlistat or sibutramine is ~25–50 mg/dl, similar to that of accepted diabetes treatment interventions. Blood glucose, cholesterol, and triglyceride levels fall rapidly with initiation of diet treatment (7). Levels of weight loss, however, are typically lower in individuals with diabetes than in nondiabetic overweight individuals (8). Sibutramine induces satiety rather than suppressing appetite per se. In a 24-week study in patients with diabetes treated with sibutramine at a dose of 20 mg daily, the average weight loss was 4–5% with decreases in fasting glucose levels of 25 mg/dl and triglyceride levels of 50 mg/dl in those patients whose weight decreased >5%. Another study with sibutramine was presented by Heath et al. (abstract 1346), who administered sibutramine at a dose of 15 mg daily or placebo to 236 patients with type 2 diabetes. Of subjects who were administered sibutramine, 65 vs. 17% of control subjects lost >5% body weight, and 27 vs. 5%, respectively, lost >10% body weight with 0.4 and 0.7% falls in HbA<sub>1c</sub> levels of treated patients who lost >5 and >10%; however, there was no significant change in HbA<sub>1c</sub> levels in the overall group. Adverse effects of sibutramine include dry mouth, sweating, tachycardia, and increased blood pressure; consequently, as Robbins stressed, close monitoring of sibutramine administration is required.

Despres et al. (abstract 1344) reported effects of orlistat at a dose of 120 mg three times daily in 699 and placebo in 463 nondiabetic patients for 1 year. With administration of orlistat, there was 3.0 and 3.8 kg greater weight loss in men and in women, respectively, as compared with subjects who were administered placebo. In addition, decreased waist circumference, cholesterol,

LDL, HDL, and apolipoprotein B-associated cholesterol levels were seen, suggesting that orlistat has benefits for patients with abdominal obesity and dyslipidemia in particular. Hollander et al. (abstract 1356) administered orlistat at a dose of 120 mg times daily versus placebo to 321 obese patients with type 2 diabetes who were treated with sulfonylureas. There was, respectively, a 5.2 vs. 2.8% weight loss, and HbA<sub>1c</sub> levels decreased by 0.72 vs. 0.38%. LDL cholesterol levels decreased 5.6 and 8.7% in men and women treated with orlistat and increased 2.9 and 4.3% in men and women who were administered placebo. Moreover, triglyceride levels decreased 14.8 and 6.6% vs. 4.9 and 1.9%, which suggests that orlistat treatment in diabetic men and women effectively enhances long-term weight loss and improves glycemic and lipid parameters. In addition to sibutramine and orlistat, studies using metformin in overweight patients were presented. Lee et al. (abstract 1343) showed 8.4 and 7.2 kg weight loss with metformin at a dose of 1,700 mg daily and fluoxetine at a dose of 60 mg daily and 16.8 kg weight loss with the combination at 24 weeks in 32 obese women with glucose intolerance. Waist circumference, WHR, and levels of fasting glucose, HbA<sub>1c</sub>, triglyceride, and HDL and blood pressure showed similar patterns. Kurukulasuriya et al. (abstract 1379.5) treated seven patients with type 2 diabetes with a maximally tolerated dose of metformin (mean 1,200 mg/day) for 6 months. Weight decreased 4.1%, and visceral adipose tissue and SC adipose tissue, which were measured with CT and dual-energy X-ray absorptiometry scanning, decreased 15.7 and 5.8%, respectively. There was no change in waist circumference or WHR. Hanson et al. (abstract 979) further demonstrated the physiological importance of weight loss in obesity by comparing 93 obese nondiabetic Pima Indians who lost an average of 7 kg with 53 who gained an average of 8 kg over a 2.4-year period, showing that a 10% weight loss or gain respectively leads to an ~25% improvement or worsening in glucose disposal with low-dose insulin infusion.

Steven Weinstein (Knoll Pharmaceutical, Parsippany, NJ) discussed the treatment of obesity in patients with diabetes on 13 May 1999 at the Mount Sinai Diabetes Conference. Data from the NHANES III show that of the 176 million adults in the U.S., 58 million are overweight (BMI 25–29.9 kg/m<sup>2</sup>) and that 39 million are obese (BMI > 30

kg/m<sup>2</sup>) (9). The Nurses Health Study of 114,281 women aged 30–55 years followed from 1976 to 1990 showed that both BMI and the change in weight were major predictors of diabetes with a 20-fold increase at BMI 30 and a 100-fold increase at BMI 35 in comparison with BMI 22 and with a 20-kg weight gain, which increases risk 30-fold for all but the highest initial weight group (10). The Health Professionals Study in 1986 of 51,529 men aged 40–75 years showed 7- and 42-fold increases in risk of diabetes at BMI 30 and 35 with a 6- to 10-fold increase in risk in individuals who gained >11 kg since they were 21 years old (11). Similar results were reported from the NHANES epidemiological follow-up study (12), and according to the findings of these studies, more than half of type 2 diabetes in the U.S. has been attributed to obesity (13). Weinstein reported on a study of 175 patients with type 2 diabetes treated with placebo versus sibutramine at a dose of 20 mg daily and observed 0.5 vs. 3.5–4.0% weight loss, respectively, at 24 weeks. The overall group showed little change in fasting glucose or HbA<sub>1c</sub> levels, but slightly less than one-third of patients treated with sibutramine lost at least 5% body weight and showed decreases in fasting glucose levels of 25 mg/dl and triglyceride levels of 51 mg/dl and a non-significant decrease in HbA<sub>1c</sub> levels of 0.5%. Many of the issues raised by these studies will be addressed by the Study of Health Outcomes of Weight Loss trial, a 9-year study of 6,000 individuals anticipated to begin enrollment in September 2000 and sponsored by the National Institutes of Health. The study will assess whether lifestyle and pharmacological weight loss interventions in obese individuals with type 2 diabetes actually improve health status, particularly in terms of CVD. Assessment of the benefits and risks of these interventions in comparison with those of the diabetes and obesity themselves will be undertaken.

The role of pharmacotherapy in the treatment of obesity in diabetes was debated at the Metropolitan Diabetes Society, New York, NY, on 11 May 1999. Xavier Pi-Sunyer, New York, NY, spoke in favor of behavioral interventions. Genetic factors appear to explain about one-third of the risk of obesity, which, according to Pi-Sunyer, suggests that “there is a lot you can do about the environment” (14). Indeed, with a genetic predisposition but without appropriate environmental conditions, the obese phenotype is not expressed (15). Pi-Sunyer stressed that current approaches to obesity

encourage behavior modification to change diet and physical activity levels and are not psychotherapeutic treatments but lifestyle changes, which can be managed by any physician whose practice includes patients with obesity. Further, the emphasis should not be on the rarely attained goal of “ideal body weight” but on preventing the natural tendency of patients to progressively gain weight over time. Pi-Sunyer commented that “one of the things about behavior is that you have to have a patient who is ready to cooperate with you.” Thus, it is necessary to assess the patient’s attitude to losing weight, the patient’s ability to increase physical activity, the patient’s understanding of nutritional guidelines, and the patient’s levels of social and familial support. Rather than “put yourself in the position of [urging diet on] a patient who is not ready,” it is often better to just follow the patient and encourage them to become ready. Group therapy approaches are often appropriate for overweight patients and may be implemented within the context of a medical practice. Pi-Sunyer pointed out that patients who diet successfully lose 1–2 lb per week and plateau after 4–6 months, for a total loss of 8–12 lb. Because the average U.S. diet contains 36% fat and 18% simple sugars, modification of food choices, particularly with elimination of processed foods and sugar-containing beverages, is particularly useful. Caloric intake is proportional to the percentage of dietary fat with experimental diets of 15–20% fat leading to weight loss and diets of 45–50% fat leading to weight gain (16). Exercise is particularly important for maintenance with nonexercisers having a greater chance of regaining weight after dieting (17). Blood glucose levels rapidly decline with diet in patients with diabetes, showing maximal benefit after 12 days despite ongoing weight loss after this time (18). Weight loss correlates with the change in HbA<sub>1c</sub> level. Wing et al. (19) showed that patients who lost >6.9 kg or who had a loss of >5% body weight had a 1.6% decrease in HbA<sub>1c</sub> levels, whereas those with less weight loss had no significant change and those who gained weight had a 0.8% increase in HbA<sub>1c</sub> levels. As Pi-Sunyer commented, diet “clearly has an effect if you can prevail.”

Priscilla Hollander, Dallas, TX, spoke in favor of pharmaceutical interventions at the Metropolitan Diabetes Society debate, stressing the “feeling of hopelessness that patients cannot successfully do behavior modification.” Indeed, studies lasting

2 years show little sustained benefit (20,21). “Of course,” Hollander commented, “pharmacologic therapy has a rather storied past” with amphetamines associated with addictive potential and psychiatric illness, and fenfluramine and dexfenfluramine associated with primary pulmonary hypertension and valvular heart disease. Approaches to decreasing nutrient absorption date from the early 1900s, when diet treatment with “sanitized tapeworms” was widely advertised. Orlistat acts to decrease fat digestion in the small bowel lumen. Treated versus placebo patients show 10 vs. 6% weight loss at 1 year and 8 vs. 4% weight loss at 2 years, whereas patients who stop orlistat at 1 year return to the placebo level at 2 years (22). Among 163 vs. 159 patients with type 2 diabetes randomized to orlistat vs. placebo for a 1-year study, weight decreased 6.2 vs. 4.3% and HbA<sub>1c</sub> levels decreased 0.8 vs. 0.3% (23). Other studies with orlistat show decreases in LDL cholesterol levels over those expected from the degree of weight loss alone and prevention of progression from impaired glucose tolerance to diabetes. In regard to the findings surrounding agents such as orlistat, Hollander asked the following key questions: 1) “Are these agents that we would think of using for life?” and 2) “How little efficacy is acceptable?” Pi-Sunyer commented that “the important thing is the risk-benefit ratio. The change between the drug and the placebo is small.” He also mentioned the relatively high cost of these agents.

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