Metabolism
Clinical and Experimental

VOL 44, NO 2, SUPPL 2 FEBRUARY 1995

Introduction

Theodore B. VanItallie

DURING THE 1980s, many physicians had high hopes that their obese patients could be treated successfully in professionally supervised, multidisciplinary weight-control programs. These hopes might have been justified if only patients enrolled in such programs had continued to adhere to the dietary and exercise practices so diligently taught them during treatment. But, unfortunately, after achieving a substantial weight loss, a majority of those who completed and then left the programs were unable to sustain the newly learned eating and exercise behaviors that would have enabled them to remain indefinitely at their reduced weights. Indeed, during the last 5 years, the early euphoria generated by the conspicuous short-term success obtained by many weight-control clinics has been followed by the sobering realization that within months or, at best, a few years of having shed many pounds, most of the initially successful patients regained much or all of their lost weight.

In principle, responsible weight-control programs were (and are) correct in making strenuous efforts to help patients acquire better control over diet and physical activity. But, as it turned out, the initial expectations of both therapists and their patients were unrealistic. Now, with expectations scaled back, it is possible to regard achievement and maintenance of modest to moderate improvements in weight status—for example, a loss of 10% to 15% of pretreatment weight—with a modicum of satisfaction. The satisfaction, limited as it is, is justified only because recent studies suggest that even a relatively small degree of weight loss can yield tangible health benefits: for example, some reduction in blood pressure, alleviation of hyperglycemia and hyperinsulinemia, and a decrease of plasma low-density lipoprotein cholesterol and triglyceride concentrations.

Despite the restricted success obtained by many weight-control programs, the overall state of treatment of obesity remains unsatisfactory. The prevalence of this condition, along with its adverse effects on health and longevity, is on the increase, notably among children and adults in the United States, in other industrialized societies, among the poor and disadvantaged, and ironically in many developing nations. It seems unlikely that better nutrition education or more intensive exercise training, even if widely instituted during the early years of school, can do much to stem this ever-rising tide of obesity. Nor is it realistic to expect the food environment to change in such a way as to promote a reduced energy intake among members of subgroups of the population most vulnerable to obesity. Finally, there is little hope that most adults will voluntarily increase their physical activity, even if they believe such an increase can be beneficial to health.

A remaining (perhaps the only) alternative would be to develop safe pharmacologic agents that can modify or overcome the behavioral and metabolic characteristics that, in a calorie-laden, sedentary society, render so many people vulnerable to excessive fat storage. Viewed from this perspective, it is evident that new developments in the pharmacotherapy of obesity are potentially important and merit close attention.

The symposium herein introduced includes consideration of a new pharmacologic approach to treatment of obesity, but it also covers several other consequential themes.

First, in his background discussion of the energy balance equation, Felber (University of Lausanne) reviews the metabolism of body fuels in relation to level of energy expenditure. In his analysis, Felber focuses on the effect of obesity on regulation of nutrient metabolism. In obese individuals, the enlarged fat depot gives rise to an overall increase in free fatty acid (FFA) release and consequently fat oxidation. The increase in fat oxidation is associated with inhibition of hepatic glycogen breakdown and glucose oxidation in skeletal muscle. Insulin resistance of metabolic origin may occur early in obesity (with an augmented

From the Department of Medicine, Columbia University College of Physicians and Surgeons at St Lukes-Roosevelt Hospital Center, New York, NY.

Address reprint requests to Theodore B. VanItallie, MD, 1678 Jose Gaspar Dr, PO Box 775, Boca Grande, FL 33921-0775.

0026-0495/95/4402-2013$03.00/0

insulin response to hyperglycemia), in part because of "the excess of lipids as an energetic substrate . . . at the expense of glucose." As obesity continues and becomes more severe, hyperglycemia develops, presumably as a compensatory mechanism to overcome resistance to glucose storage. In obese patients, the onset of clinical diabetes occurs when blood glucose has not returned to the basal level in the early-morning fasting state. Although basal insulin secretion remains elevated, the magnitude of the insulin response to a glucose load decreases progressively and eventually becomes minimal.

According to Felber, an appropriate treatment for non–insulin-dependent diabetes mellitus (NIDDM) is to increase energy expenditure, preferably by means of more exercise. Apart from weight reduction, another approach could be to administer insulin or drugs that stimulate its secretion. This method of treatment "uses the stimulatory effect of insulin on glycogen synthase activity to overcome the feedback inhibition of glycogen synthesis." Also, by decreasing basal glycemia, insulin will decrease the inhibitory effect of hyperglycemia on hepatic glycogenolysis, thereby "restoring the anterograde function of the glycogen cycle."

Next, food consumption patterns in Germany (paradigmatic for other developed countries) are described from both the standpoint of the epidemiologist (Heseker et al, Justus-Liebig University) and that of the clinician (Hepp, Krankenhaus München-Bogenhausen). The study reported by Heseker et al (derived from the German Nutrition Survey) disclosed an increase in prevalence of overweight (body mass index [BMI], 25 to 30 kg/m^2) with age, from 15% in the group aged 18 to 24 years to 50% in the group aged more than 55 years. Prevalence of severe overweight (BMI, 30 to 40 kg/m^2) increased from 3% to 17% in the same age groups. In terms of nutrients consumed, a high BMI was associated with a higher intake of fat and protein and a lower intake of carbohydrate. On average, 5.5% of the study population obtained more than 20% of total energy intake from snacks. In his report, Hepp points out that during the five decades after World War II, West Germans consumed increasingly more calories, fat, cholesterol, alcohol, and sugars, and less dietary fiber. In 1980, approximately one third of the West German health budget and approximately one fifth of the indirect costs arising from loss of productivity, invalidism, and premature death were ascribed to nutrition-derived disorders. However, Hepp emphasizes that the connections between this burden of healthcare costs, the high prevalence of overweight, and the unhealthy diet consumed by so many Germans need to be defined with greater care and clarity.

In his report, Schoeller (University of Chicago) discusses the substantial limitations of self-reported dietary intake data as disclosed by concurrent measurement of energy expenditure with the doubly-labeled water method. As Schoeller points out, "The bias is greatest in obese individuals, and there is no indication that valid estimates of dietary energy can be obtained by self-report in subjects over 12 years of age. . . . Even in the non-obese where bias is minimal, the ability to measure dietary energy intake in individuals is marginal." Schoeller properly advises that because of the bias in self-reported intake, data on dietary intake derived from self-reported dietary records should be interpreted with caution.

In the setting of these epidemiologic and methodologic observations, this symposium issue focuses next on a series of studies of the effect of dexfenfluramine (dF) in certain rodent models of obesity, as well as its effects on ingestive behavior and metabolism in overweight humans with and without NIDDM.

Using the JCR:LA corpulent rat—a useful laboratory model for the obesity-diabetes dyslipidemia syndrome—Brindley and Russell (University of Alberta) have found that dF treatment can decrease an array of obesity-associated coronary heart disease risk factors.

In another rat model of obesity—induced by a high-fat diet—Rebuffé-Scrive and DePodesta (Yale University) report that compared with a pair-fed group, dF-treated obese rats exhibit lower fat-pad weights and smaller fat-cell sizes in all major fat depots. These data suggest an effect of dF on body fat content that is independent of its action on energy intake.

Blundell and Lawton (University of Leeds) summarize published experiments suggesting that in both animals and man dF treatment may induce a selective decrease in intake of dietary fat. They theorize that the antagonistic effect of dF on fat consumption could occur via "sensitization or priming of serotonin- (and [cholecystokinin] CCK)-mediated fat-induced satiety signals." As Blundell and Lawton point out, the inhibitory effect of CCK on food intake can be antagonized by serotonin blockers, an action that involves the same serotonin (5-HT$_{2c}$) receptors implicated in the mediation of dF-induced suppression of eating. (The finding reported by Blundell and Lawton that under certain experimental conditions dF selectively decreases fat intake needs to be reconciled with previous observations in both animals and human subjects indicating that dF administration is followed by a preferential decrease in ingestion of carbohydrate-rich foods.)

Björntorp (University of Göteborg) summarizes recent research on the neuroendocrine abnormalities associated with visceral obesity in man. According to Björntorp, levels of a serotonin metabolite (5-hydroxyindoleacetic acid) and corticotropin-releasing factor are lower than normal in cerebrospinal fluid of women with visceral obesity. This finding suggests the need to explore possible links between abnormalities of serotonin and corticotropin-releasing factor concentrations in the central nervous system on one hand and certain metabolic and endocrine perturbations in the periphery on the other. Examples include increased cortisol turnover and reduced secretion of sex steroid hormones and growth hormone. Abnormalities of steroid hormone secretion could contribute materially to the already-discussed insulin resistance that may result from an increased flow of FFA from enlarged fat stores. Björntorp also postulates that the centralization of body fat stores in visceral obesity could be caused by the pattern of endocrine abnormalities described earlier.

Björntorp points out that in addition to the endocrine

abnormalities associated with visceral obesity, there seem to be less well-defined disturbances in the central regulation of the sympathetic nervous system: "This multiple abnormal regulation of peripheral endocrine and nervous events strongly suggests a central neuroendocrine dysregulation." He goes on to say that cross-sectional evidence supports the notion of ". . . a coupling between the neuroendocrine abnormalities discussed, and psychosocial and socioeconomic handicaps, leading to a stress-reaction of poor coping."

As reported by Van Gaal et al (University of Antwerp), when dF or placebo was given to severely obese outpatients (32 premenopausal women who were euthyroid and nondiabetic) maintained on a 760-kcal high-protein diet for 3 months, dF appeared to help prevent the decrease in glucose-induced thermogenesis (GIT) normally associated with marked energy restriction. On a per-kilogram-body-weight basis, mean GIT increased slightly in the dF group but decreased significantly in the placebo group. (GIT measurements were made between days 16 and 90 of treatment.)

This finding suggests that in addition to its action on ingestive behavior, dF could augment therapeutic weight loss by limiting the adaptive decrease in metabolic energy expenditure that ordinarily accompanies prolonged calorie deprivation.

In their contribution, Drent and Koppeschaar (Free University Hospital, Amsterdam) report on results of a study in which eating patterns of three groups of obese subjects studied at different times were compared. Dietary history and/or dietary diaries were used to estimate energy and macronutrient intake. One of the groups (study III) was made up of obese "snackers" (those who consumed more than five snacks per day providing more than 500 kcal or who consumed more than 25% of total daily energy intake as snacks). It was observed that more total calories (from both fat and carbohydrate) were consumed by snackers than by nonsnackers. These findings held for both men and women.

Surprisingly, the mean BMIs of male and female snackers were not significantly greater than those of participants in the other two studies. The investigators acknowledge that some differences observed between snackers and groups that displayed a more structured eating pattern could have resulted from methodologic errors (see Schoeller, this issue). On the other hand, in study II in which energy intake was estimated by diary and by dietary recall, the two methods yielded similar results for the most part.

According to Cugini et al (University of Rome), the daily pattern of hunger sensation (HS) is subject to chronobiometric analysis because this pattern is characterized by ". . . a well-structured circadian rhythm whose mean level and oscillatory extent can be precisely measured and timed." Cugini et al have used such a chronobiometric approach to study daily HS patterns in 60 patients (20 men and 40 women) with "essential obesity" (namely obesity attributed to a "primary disorder of eating behavior"). Three different HS patterns (chronotypes) were identified in these patients—normal, excessive, and poorly perceived. Interestingly, patients with normal and poorly perceived ("low sensation of hunger") HS patterns did not refrain from overeating. This observation implies that eating behavior in patients who exhibit these two chronotypes is not mediated by excessive HS. Administration of dF resulted in a decrease in the daily mean level of HS in all three chronotypes. However, dF treatment did not alter the diurnal recursiveness of HS in patients who initially showed a normal HS pattern. In contrast, dF normalized the HS pattern in obese patients who had exhibited an excessive HS pattern (characterized by persistence of the hunger signal until late into the night, high HS amplitudes, together with other differences from the normal chronotype).

The final report by Greco et al (Catholic University of St. Cuore, Rome) deals with the acute and chronic effects of dF administration on blood glucose and FFA turnover and oxidation in 11 obese middle-aged women with NIDDM and a relatively high waist to hip ratio (mean, 0.91). They report a lower fasting blood glucose after acute administration of dF (30 mg orally) than after placebo (86.5 ± 5.1 *v* 114.3 ± 8.6 mg/dL). Long-term administration of dF also resulted in a significant decrease in blood glucose levels, even though the amount of weight lost during the 15-day treatment with dF was only 0.50 ± 0.12 kg.

FFA turnover and oxidation were both significantly greater after acute and long-term dF administration than after placebo. Thus, control of glycemia improved during both acute and long-term treatment with dF despite the concurrent increase in FFA turnover and oxidation rate. The investigators consider these metabolic events to be related to a primary effect of the drug and not attributable to weight loss. They also suggest that these responses may occur because of an improvement in insulin sensitivity induced by dF—a phenomenon that has been described by other investigators. They point out that in their series, the simultaneous increase in both FFA turnover rate and FFA oxidation associated with dF administration resulted in an equilibrium of (no change in) FFA concentrations. Moreover, the lack of change in insulin levels in the same series suggested that dF had exerted a weight-independent effect on glucose uptake by cells without increasing insulin production.