Diet, Drugs, Surgery: The Skinny on Weight Reducing Therapies

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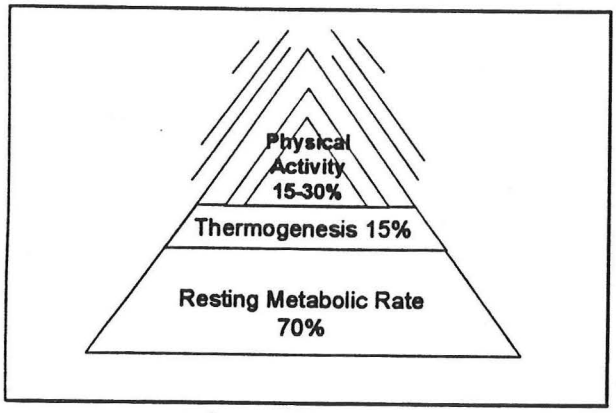
Weight-loss drugs may harm brain cells, scientists sa

Recently, the National Bureau of Health Statistics reported disappointing news: Americans are getting fatter[1]. The latest survey shows that a 25 yr old man weighed 8 pounds more in 1991 than he did in 1980. Not only are people heavier, but the weight distribution is skewed, with more people than ever falling into weight categories of overweight, obese, and morbidly obese. This gain in weight has occurred despite a brisk $30 billion per year industry of weight loosing therapies. Since weight gain is the result of imbalance of energy supply and demand, I will begin this medicine grand rounds by reviewing the demand side of the energy equation.

Percent of Americans Meeting WHO BMI Criteria for Excess Weight

overweight	25-29.9	31%
obese	30-39.9	18%
morbidly obese	>40	3%



Requirements for Energy

Energy requirements are determined by three components: resting metabolic rate, thermogenesis, and physical activity

Resting Metabolic Rate.
The majority of our daily requirement -- up to 70% -- is accounted for by our resting metabolic rate[2]. This is the amount of energy needed to sustain life without consideration for eating or physical activity. Resting metabolic rate is lower in women, declines with age, and increases with increasing body weight.

Resting metabolic rate in kcal/d can be estimated by the Harris-Benedict Equation:

$$\text{men} = 66 + (13.7 \times W) + (5 \times H) - (6.8 \times A)$$
$$\text{women} = 655 + (9.6 \times W) + (1.8 \times H) - (4.7 \times A)$$

Where W = weight in kg, H = height in cm, and A = age in years.

Plugging some numbers into this equation can be instructive. For a 5'7", 35 year old, 150 lb man, resting caloric requirements are 1610 compared to 1449 for a similar age and size woman. A 20 year old 5'10", 190 lb man requires 1998 calories, but a 70 year old same sized man only 1658 calories. The most striking effect is that of obesity: a 5'3", 45 year old woman weighing 115 lbs requires 1230 kcalories, but a 200 lb woman requires 1602 kcalories.

Resting metabolic rate is subject to individual variability of 11-20%. Most of this variability (83%) is accounted for by differences in fat free mass[3]. Individuals who are heavier have more fat free mass and therefore higher resting metabolic rates than individuals who are lean. Although variation in resting metabolic rate may appear substantial, beyond the influence of body weight and fat free mass, individual differences in resting metabolic rate are in the range of 100-400 kcal/d[4].

Thermogenesis.

A relatively fixed component to our daily energy requirements is thermogenesis. Thermogenesis accounts for up to 15% of daily energy requirements. Part of our requirements are obligatory -- maintaining body temperature. Part is facultative -- maintenance of normal body temperature during exposure to cold, and elevation of body temperature in response to metabolic stress.

Several dietary factors alter thermogenesis. Caffeine, an appetite suppressant, increases thermogenesis by 14% for several hours after ingestion.[5] Ketogenic diets increase thermogenesis by 3 -12%, depending upon whether the diet was eucaloric or hypercaloric.[6]

Physical Activity.

The final and most variable component of our daily energy requirements is physical activity. Physical activity accounts for 15% of energy demands during bed rest, 18% while watching television[7], and on average 30% of total daily caloric requirements. In healthy, free living men, energy expenditure from physical activity has a day-to-day variation of 10%[8]. Estimating television watching as burning 30 kcal/hr, compare other leisure activities from the following compilation by Holt[9].

Approximate Energy Expenditures of Recreational Sports

Activity	*Kcal per hour**
Baseball/softball	
All except pitcher	280
Pitcher	450
Basketball	360-660
Bicycling	
5 mph	240
8 mph	300
10 mph	420
11 mph	480
12 mph	600
13 mph	660
Calisthenics	
Light	360
Heavy	600
Golfing	
Powercart	240
Pulling bag cart	300
Carrying clubs	360
Handball	
Social	600
Competitive	660
Rowing machine	840
Running	
5 mph (jogging)	600
6 mph (jogging)	750
7 mph (moderate)	870
8 mph (moderate)	1,020
9 mph (fast)	1,130
10 mph (very fast)	1,285
Upstairs, uphill	1,000
Skating (ice, roller)	
Leisurely	420
Rapidly	700
Skiing	
Downhill, light	500
Downhill, vigorous	600
Cross country, 2.5 mph	560
Cross country, 4 mph	600
Cross country, 5 mph	700
Cross country, 8 mph	1,020
Swimming	
Leisurely	360-500
Crawl, 25-50 yard per minute	360-750
Backstroke, 25-50 yard per minute	360-750
Breaststroke, 25-50 yard per minute	260-750
Butterfly, 50 yard per minute	840
Sidestroke, 40 yard per minute	660
Tennis	
Doubles	360
Singles	480
Volleyball	
Noncompetitive	300
Competitive	480
Walking	
Level road, 1-2 mph (strolling)	120-150
Level road, 3 mph (leisurely)	300
Level road, 3.5 mph (brisk)	360
Level road, 4 mph (fast)	420
Level road, 5 mph (very fast)	480
Downstairs	425
Upstairs	600-1080
Uphill, 3.5 mph	480-900
Downhill, 2.5 mph	240

**—Caloric consumption is based on a person weighing 70 kg (150 lb). There is a 10 percent increase in caloric consumption for each 7 kg (15 lb) over this weight and a 10 percent decrease for each 7 kg under 70 kg.*

Weight Maintenance and the Respiratory Quotient

Another way to examine energy requirements is to evaluate how efficiently the body utilizes fuel. Body composition is maintained by a continuous process of storage and breakdown of carbohydrate, protein, and fat. Theoretically, if the fuel consumed does not match the fuel oxidized, an imbalance in one of the compartments could occur and obesity could result. The amount of CO_2 produced divided by the amount of O_2 consumed (Respiratory Quotient) and 24 hour urinary nitrogen excretion measures fat, carbohydrate, and protein oxidation. Similarly, calculations can be made for foods by measuring how much oxygen is consumed during food oxidation. (Carbohydrate has a food quotient of 1.0, whearas fat has a food quotient of 0.7).

At a typical fasting respiratory quotient of 0.80 to 0.85, it has been estimated that 50% of the body's energy needs are being met by fat oxidation, 40% by carbohydrate oxidation, and the rest by protein oxidation[10]. It has been proposed that respiratory quotient measurements made during and following a meal should predict fat balance. Studies tracking respiratory quotient in groups of subjects from the fasting to the postprandial state have documented that the respiratory quotient changes after a meal, with values ranging from 0.79 and 0.91. High carbohydrate feeding was found to increase the respiratory quotient, suggesting that fat from fat stores continues to be oxidized despite ingestion of a meal. On the other hand, high fat feeding did not lower the respiratory quotient and therefore did not appear to promote oxidation of fat from fat stores in excess of that provided by the diet[11].

A theory developed that high fat diets promoted the deposition of fat in fat stores, and high carbohydrate diets promoted the oxidation of fat stores[12].

This theory has turned out to be naive. Stores of protein and carbohydrate are limited and their concentrations are tightly regulated[13]. Fat stores are not regulated but remain in equilibrium with the total calories fed. The respiratory quotient not only reflects the current oxidation status of fuel, it also reflects the status of total body energy stores. The respiratory quotient increases when a person is overfed, when a meal is high in carbohydrate, when glycogen stores are maximally repleated, and when the adipose tissue stores are large.

Studies relating the respiratory quotient to obesity have observed that individuals with a high respiratory quotient are more likely to gain weight than those with a low one. The initial interpretation of this finding was that persons with high respiratory quotients are burning less fat, thus making them

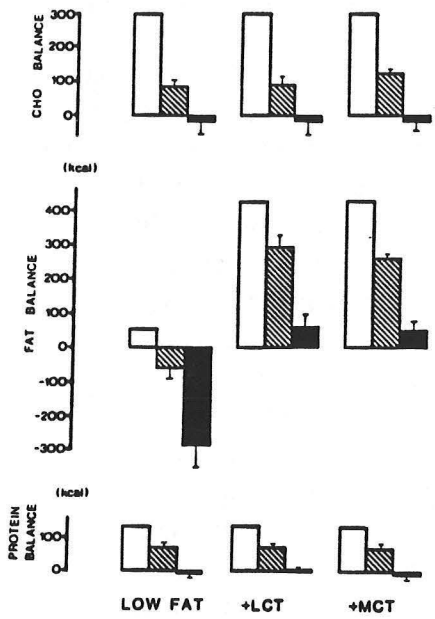


Figure 4. Carbohydrate (CHO), fat, and protein balances immediately after (white), 4.5 h after (hatched), and 9 h after (black) ingestion of the low fat LCT- or MCT-supplemented test meals. (Means±SE; n = 7.)

susceptible to weight gain. However, an equally valid interpretation is that persons with a high respiratory quotient are at risk for obesity because they are overfed and have repleted glycogen stores. Since the respiratory quotient accounts for only 10% of the variance in subsequent weight gain, and since the meaning of a high respiratory quotient is unclear, the theory that consuming fat promotes storage of fat has not gained favor as a major explanation of why people become obese.

Is Obesity a Genetic Problem? Heritability of Body Mass Index

The body mass index of twins from the Swedish Twin Registry who were reared together vs reared apart have been correlated to see how much of body weight is heritable[14]. In this study population, the mean body mass index was 25 and few of the subjects were obese. The BMI of 93 pairs of identical twins reared apart were compared to 154 pairs of identical twins reared together, and 218 pairs of fraternal twins reared apart were compared to 208 pairs of fraternal twins reared together. The correlation of body mass index among the monozygotic twins was 0.66 - 0.74, suggesting that approximately 2/3 of the variance in body mass index among lean individuals may be genetic.

Twins Reared Together and Apart

	BMI (Men)	Intrapair correlation	BMI (Women)	Intrapair correlation
monozygotic				
together	24.8±2.4	0.70	24.2±3.4	0.66
apart	24.2±2.9	0.74	23.7±3.5	0.66
dizygotic				
together	25.1±3.0	0.15	24.9±4.1	0.25
apart	24.6±2.7	0.33	23.9±3.5	0.27

Heritability of Energy Requirements

Motivated by a search for a genetic cause of obesity, the heritability of resting metabolic rate has been extensively studied. It has been estimated that 11% of the variability in resting metabolic rate not accounted for by lean body mass can be attributed to familial inheritance[15]. Specifically, in a study of 53 Pima Indian families, the mean adjusted resting metabolic rate between families varied by 500 kcal per day, but the mean variation within families was only 60 kcal per day . Since fat free mass determines so much of the variance in resting metabolic rate, some investigators have wondered whether there are genetic determinants of fat free mass. In a recent study of 80 families participating in the Quebec Family Study, the familial inheritance of fat free mass was estimated to be 45 - 50%[16]. A major gene is postulated[17]. Summing this with the variability independent of fat free mass, perhaps as much as 60% of the variability in resting metabolic rate is inherited.

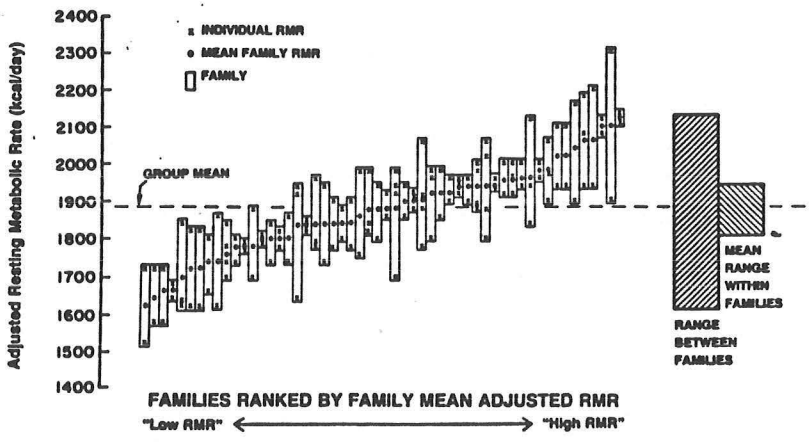


Figure 2. Mean Family (●) and Individual (×) Resting Metabolic Rate (RMR), Adjusted for the Covariates of Fat-Free Mass, Age, and Sex.

The adjusted resting metabolic rate was calculated as the residual from the regression model with the covariates only plus the mean resting metabolic rate for the whole sample. The families (□) are ranked according to adjusted resting metabolic rate. The range of the mean family adjusted resting metabolic rate and the mean range within families are depicted by the hatched bars on the right.

The Problem begins with Weight Gain

Weight gain occurs when energy intake exceeds demand. Weight gain can be easily produced in clinical research projects by overfeeding study participants. In a novel experiment in identical twins, 12 lean adult male twin pairs were overfed 1,000 kcal/d for 84 days during a 100 d period[18]. The initial correlation within twin pairs for body weight was not provided, but typically this correlation is on the order of 0.7. Mean weight gain during the study was 8.1 kg, with a range of 4.3 to 13.3 kg. One third of the weight gained was fat free mass. There was three times more variance in weight gain among pairs than within pairs, but only 25% of the variability in weight gain from overfeeding could be attributed to genetics.

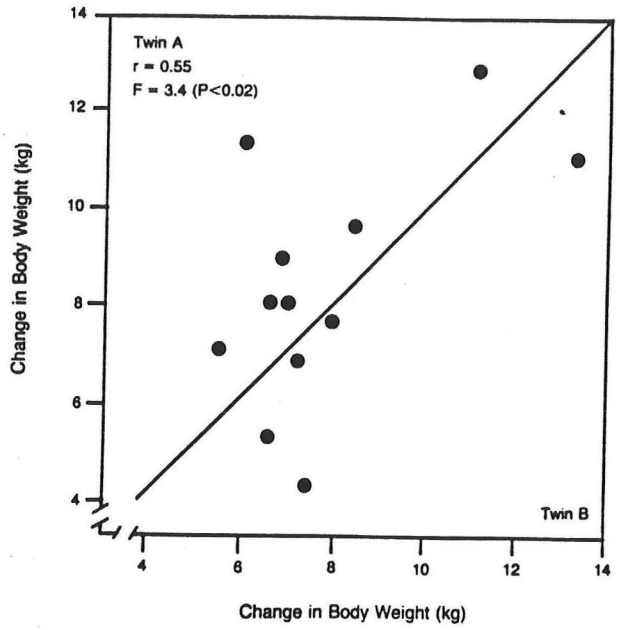


Figure 1. Similarity within Pairs with Respect to Changes in Body Weight in 12 Pairs of Male Twins in Response to 100 Days of Overfeeding.

Each point represents one pair of twins (A and B). The closer the points are to the diagonal line, the more similar the twins are to each other.

Several studies have tried to identify predictors of weight gain. Prospective, longitudinal studies of Pima Indians are under way to evaluate if weight gain can be predicted from baseline metabolic parameters. In preliminary studies after four years of follow up, individuals with low resting metabolic rate, individuals with low level of spontaneous physical activity, individuals with high respiratory quotient, and individuals with high insulin sensitivity gained weight[19]. In the Baltimore Longitudinal Study in Aging, where more modest gains in weight were observed over a 10 year period, high respiratory quotient was a weak but significant predictor of weight gain[20].

Changes in metabolism with weight gain

Cross sectional studies comparing the metabolic parameters of obese and lean individuals have consistently found that obese individuals require more calories than lean individuals to maintain their weight. In a classic experiment, Hautvast and colleagues studied 47 women age 20-47 in an 8 d experiment which included 80h in a room calorimeter. Women with a BMI < 25 kg/m^2 were classified as lean and those >25 were classified as overweight.

Baseline Characteristics

	lean	obese
age	29	33*
BMI	21	34**
% bodyfat	24%	42%**
weight	58.8 kg	93.7 kg**
fat free mass	47.7 kg	51.9 kg**

*p < 0.05
**p < 0.001

The average of the 3 day energy expenditures were calculated and compared. Obese subjects took in more calories and expended more calories than lean subjects. Assessing their resting energy expenditure per kg body weight, obese subjects expended less energy than lean subjects. However, when expressed per kg of metabolically active tissue (ie., fat free mass) there was no difference in resting energy expenditure between the two groups. When energy expenditure was measured for specific physical activities, obese individuals expended incrementally more energy than lean individuals during sleeping, sedentary activity, and bicycling .

24 hr Energy Expenditures (EE), ± SEM

	lean	obese
Intake	2365 ± 32	2709 ± 76*
24h EE	2052 ± 32	2558 ± 108*
EE/weight	35.1 ± .6	27.6 ± 0.5*
EE/fat free mass	46.0 ± 0.7	48.5 ± 1.5

*p < 0.001

Calories per minute expended

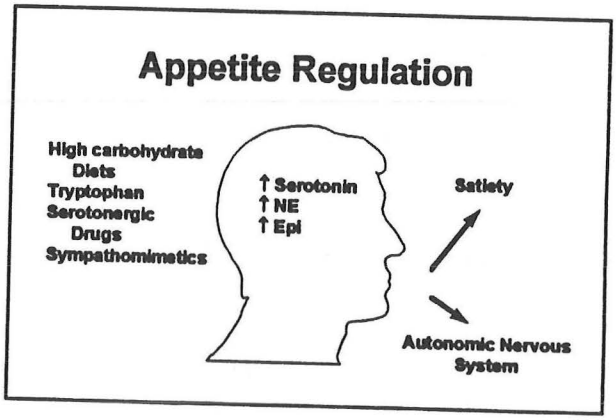
	lean	obese
sleeping	1.01 ± .02	1.2 ± .05
sedentary	1.33 ± .02	1.68 ± .12
bicycling	1.80 ± .04	2.30 ± .20

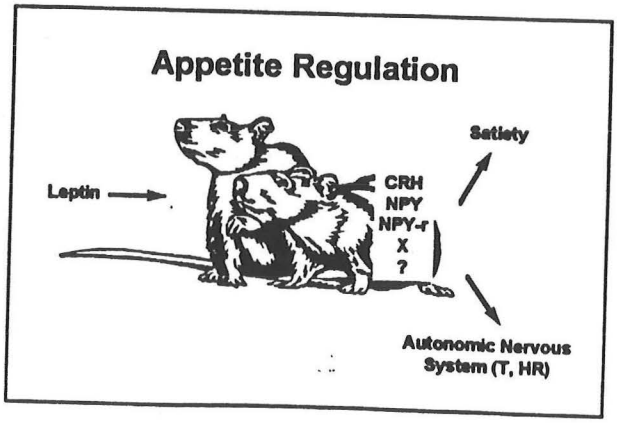
The association between weight gain and increased caloric requirements is causal. In the short-term overfeeding study of identical twin pairs described above, as weight increased, resting metabolic rate increased[21]. In a 42 d overfeeding study of six lean and 3 overweight young men, resting metabolic rate increased as body weight and fat-free mass increases[22].

Control of Overfeeding: Appetite Regulation

The regulation of appetite, which in turn controls energy intake, assumes a central theme in the treatment of obesity.

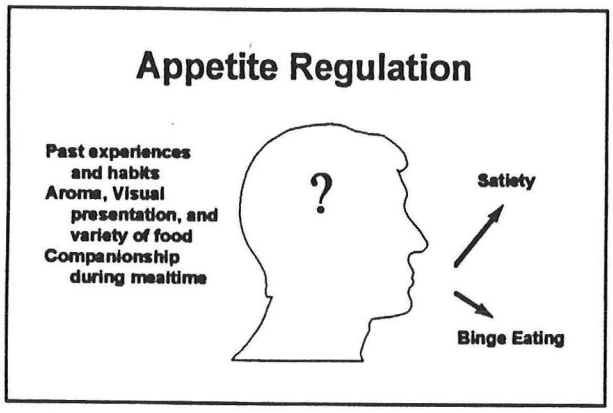
The pathophysiology of appetite in humans remains poorly understood at the molecular level. Classic experiments in rodents have shown that CNS levels of serotonin, epinephrine, and norepinephrine alter eating behavior[23] by shortening the duration of feeding time. Similar mechanisms have been postulated in man[24] and several serotonergic drugs have been developed which have some influence on the perception of appetite. However, the biologic triggers that stimulate brain release of serotonin have not been identified.





Exciting new advances have been come with the discovery of leptin, a peptide produced by fat ells. Leptin turns out to be a neurotransmitter and can act via at least five different pathways in the hypothalamus to terminate feeding behavior in

rodents[25] . It was initially speculated that obese humans would have low levels of leptin and that the lack of leptin caused the overfeeding syndrome of obesity. Measurements of leptin levels in humans have found the reverse -- obese humans have high levels of leptin -- and research is underway to untangle the meaning of this finding.



Although the neurobiology of appetite has yet to be fully elucidated, significant observations regarding eating behaviors have been made. The behavior of eating at a single meal is influenced by multiple environmental cues[26]. The time between the last meal and the size of the previous meal influence when and how large the next meal will be. The appearance and aroma of food stimulate appetite. Once tasted, appetizing food will be eaten in greater quantities than usual foods. Presenting a greater variety of food choices at the meal stimulates greater food intake. Protein containing foods may be more satiating than carbohydrate or fat containing foods[27]. Companionship during mealtime is also associated with longer meals and greater food intake.

Eating a single meal, the focus of current neurobiology, does not account for the complexity of eating behavior in man[28,29]. There is significant day to day and meal to meal variation in an individual's diet[30] and surprisingly, this variation is not reflected acutely by body weight. Among obese patients, a particular type of variation occurs called binge eating[31]. During binge eating, patients consume a large quantity of food to the point of physical discomfort. DSM-IV research criteria for binge eating have been proposed.

DSM-IV research Criteria for Binge Eating Disorder

A. Recurrent episodes of binge eating. An episode of binge eating is characterized by both of the following:
   (1) eating, in a discrete period of time (e.g., within any 2-hour period), an amount of food that is definitely larger than most people would eat in a similar period of time under similar circumstances: and
   (2) a sense of lack of control over eating during the episode (e.g., a feeling that one cannot stop eating or control what or how much one is eating).

B. The binge-eating episodes are associated with three (or more) of the following:
   (1) eating much more rapidly than normal
   (2) eating until feeling uncomfortably full
   (3) eating large amounts of food when not feeling physically hungry
   (4) eating alone because of being embarrassed by how much one is eating
   (5) feeling disgusted with oneself, depressed or very guilty after overeating

C. Marked distress regarding binge eating is present.

D. The binge eating occurs, on average, at least 2 days a week for 6 months.
   Note: The method of determining frequency differs from that used for Bulimia Nervosa; future research should address whether the preferred method of setting a frequency threshold is counting the number of days on which binges occur or counting the number of episodes of binge eating.

E. The binge eating is not associated with the regular use of inappropriate compensatory behaviors (e.g. purging, fasting, excessive exercise) and does not occur exclusively during the course of Anorexia Nervosa or Bulimia Nervosa.

Note. From American Psychiatric Association (1994). *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., p. 731). Washington, DC.

An association between binge eating and obesity is well supported[32]. 20-30% of obese patients seeking treatment for obesity report binge eating behaviors. The severity of adiposity is also associated with the prevalence of binge eating -- whereas 10% of women with BMI 25-28 describe binge eating behavior, 40% of women with a BMI of 31-42 report this behavior. Evaluations of the long term success of very low calorie diets suggest the binge eaters are more likely to drop out of the treatment program than non-binge eaters[33]. Thus, binge eating is likely a significant contributor to excess weight in obese persons.

Although the presence of binge eating may suggest that obese persons have underlying psychiatric disease, studies have repeatedly shown that obese persons are no more likely to have a psychiatric illness than the general population. However, the presence of a psychiatric illness can reduce the effectiveness of a weight loss program[34], and studies evaluating individual vs group counseling have found that individual counseling results in better long term success than group counseling[35].

Irrespective of the presence of binge eating, behavioral therapy is an important component to all weight loss programs. The goals of behavioral therapy are to restore a normal eating pattern by teaching people to identify and modify external triggers which may cause them to overeat[36]. Behavioral therapy provided before a weight loss program is less successful than one provided during weight loss; follow up visits after weight loss has been completed to reinforce behaviors improves long term success[37].

Exercise.

Rather than focus on energy intake, some have focussed on energy expenditure as treatment for obesity. Aerobic exercise programs per se have had little success at producing large amounts of weight loss[38,39], amounting to only a few kg of loss over a 6 month trial. Resistance training programs result in no net weight loss, but increases of 1-2 kg of fat free mass have been observed.

When exercise is added to a weight loss program, the loss of fat free mass is reduced from 2.9kg/10kg weight loss to 1.7 kg/10kg weight loss[40,41]. This difference in fat free mass may explain why exercise is a predictor of successwith long term weight loss[42]. In a voluntary follow up study of 102 participants in liquid formula diet study, reported exercise predicted long term weight loss[43].

Calories/wk Exercised vs Long Term Weight Loss

no exercise	up to 1,000 cal/wk	> 1,000 cal/wk
–5.6	–9.3	–17.5

Treatment of the Cause of Weight Gain: Therapies to Reduce Food Intake

Dietary Therapy.

The obvious treatment of obesity remains simple caloric restriction. The rapidity of weight loss from dietary modification is directly related to the caloric deficit achieved by the diet. Two general approaches have been tried -- very-low-calorie or low calorie.

The very-low-calorie-diet is a diet providing 400-600 kcal/d primarily as protein. A multivitamin is provided to ensure micronutrient adequacy of the diet. Very-low calorie diets are typically structured -- often the patient is only allowed to consume a liquid formula diet. Some variations exist, including a liquid supplement plus one meal[44]. For patients who have difficulty controlling their eating behavior, the very-low-calorie diet offers a strict program with definite rules. Weight loss from a very-low-calorie diet is highly predictable and depends upon the duration of the diet [45,46]; typical weight loss is 21 kg after 16 weeks[47]. However, many patients have difficulty with the transition to a natural food diet after their goal weight is achieved, and weight gain following these diets is very common[48].

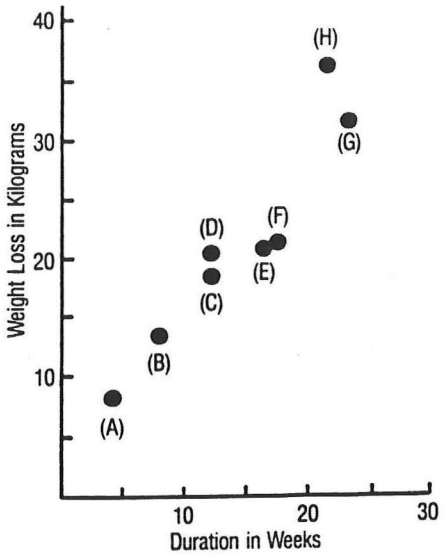


Figure 4.—The amount of weight loss in relation to duration of treatment is presented for several very-low-calorie diets. The letters in parentheses represent specific programs described by Wadden and co-workers.[25]

Low-calorie diets provide 1,000-1,500 calorie a day using natural foods. To many patients, low calorie diets provide less definitive restrictions than liquid formula diets, and extra time must be spent instructing the patient on how to achieve a calorie reduction within the confines of his or her lifestyle. This drawback can be addressed by using frozen TV-dinner style meals [49], but it remains to be seen whether providing the diet during weight loss result in better long term success of weight loss. In a study comparing a 6 month program of a counseled diet with weekly meetings, meetings with a structured meal plan and grocery list, meetings with food provisions at cost or free to the participant, no difference in the success of weight loss was seen between the plans that provided a definitive structure for the diet[50]. Since the caloric restriction is not as great as with a very-low-calorie diet, a patient must stay on the diet longer to achieve the same weight loss. Typical weight loss is 10-12 kg at 26 weeks[51]. Because weight gain is so common following a very-low-calorie diet, low calorie diets may be as effective as very-low-calorie diets at one year[52,53].

Regarding dietary composition, strong opinions have been voiced that high fat diets promote weight gain and obesity[54,55]. As discussed previously, some of this enthusiasm has been fueled by the mistaken interpetations that these diets "burn fat." In a study comparing a low fat ad libitum carbohydrate diet with a low calorie-low fat diet, the low calorie diet participants lost more weight because they consumed fewer calories [56]. The majority of dietary studies comparing high vs low fat weight loss diets suggest that a calorie is a calorie and reductions in calories from any source promote weight loss[57].

This is not to say that dietary composition has no influence on weight loss. Diets low in carbohydrate promote loss of total body sodium and water[58]. Patients following a low-calorie, high-protein, high-fat diet augment the weight loss induced by a hypocaloric diet with a sodium diuresis. High-protein, high-fat diets such as the Adkins diet are well received by patients because they achieve rapid results. However, the greater weight loss achieved by such diets is in fact no greater fat loss than that achieved by an equal restriction of calories from a balanced diet. These

diets are unduly restrictive and teach patients to avoid fruits, grains, and vegetables -- the very foods whose consumption has been associated with lower rates of cancer and coronary disease[59]. For these reasons, high protein, high fat diets cannot be recommended.

Another once popular diet for weight loss was the ketogenic diet. Ketogenic diets were thought to promote weight loss because of their ability to increase thermogenesis. Ketogenic diets are no longer recommended for the treatment of obesity because of they are no more efficacious than a nonketogenic diet[60] and because they cause impairment of higher cognitive functions[61].

Longterm Risks/Benefits Unique to Dietary Therapy

Dietary therapy is safe. Very-low-calorie diets can occasionally induce cholelithiasis. This can be prevented with drug therapy if rapid weight loss is medically indicated.

Although dietary therapy gets at the very cause of obesity -- energy imbalance -- the fact remains that over 70% of patents who participated in a low calorie diet regain at least half of the 10-14 kg weight loss within two years of stopping the diet[62]. In a 3 yr followup study of 192 patients who followed a 12 week very low calorie diet, 42% were within 4.5 kg of their initial weight. 20% weighed 4.9-13.5 kg less than and 13% weighed 4.9-13.5 kg more than their initial weight. These disappointing long term results stimulate search for other treatments of obesity.

Drug Therapy

Catecholamine centrally acting appetite inhibitors (Noradrenergic, amphetamine-like drugs)

It has been known for some time that sympathomimetics such as amphetamine, reduce appetite. Several drugs had been marketed for this purpose (amphetamine, trade name Benzedrine; d-amphetamine, trade name Dexedrine; Obetrol). Besides weight loss these drugs produce a euphoric state that promotes drug addiction. In addition, amphetamines are associated with significant cardiovascular side effects such as an acute arrhythmia, chest pain, and in long term use cardiomyopathy[63]. For these reasons, the FDA has classified these drugs as class II, and has narrowly restricted their use, including clear language that these are not to be prescribed in the United States as appetite suppressants[64].

Phentermine is a noradrenergic drug that produces anorexia through stimulation of catecholaminergic pathways. Phentermine is classified as a stimulant and can cause insomnia, nervousness, irritability, and headache. Increased blood pressure and tachycardia may also occur[65]. Phentermine does not have the addiction potential of amphetamine. Phentermine (trade name Fastin, Phentrol, Adipex-P, OBY-CAP) or Phentermine Resin (trade name, Ionamin) has been used available as a schedule IV drug in the United States, and is licensed for short term use (12 weeks). Phentermine has been shown to cause greater weight loss compared to placebo (10 kg vs 4.4 kg, respectively)[66], and produces an equivalent weight loss compared to dl-fenfluramine[67].

Non-catecholamine sympathomimetic amines (serotonergic Drugs; SSRI)

D-fenfluramine an amine but not an amphetamine, has been extensively studied for its effect on appetite[68]. D-fenfluramine and the racemic mixture, dl-fenfluramine, suppress appetite and cause feeding behavior to be prematurely terminated. Minor adverse side effects of fenfluramine include diarrhea, polyuria, dry mouth, sleep disturbance, and somnolence. The FDA has classified d-fenfluramine as class IV and has approved the use of dl-fenfluramine and d-fenfluramine as a single agent to suppress appetite for short term use (12 weeks) and d-fenfluramine for long term maintenance (1 year). The class IV designation may be based on initial confusion as to whether d-fenfluramine was in fact an amphetamine. It now appears clear that d-fenfluramine can be classified as a Selective Serotonin Reuptake Inhibitor (SSRI). Evidence that d-fenfluramine increases metabolic rate is unsubstantiated, as the weight loss achieved can be entirely explained by reductions in caloric intake[69].

Another serotonin reuptake inhibitor, fluoxetine (trade name Prozac) has been shown to have significant appetite suppressant effects in normal volunteers. This drug alone might produce a 4 kg weight loss among obese subjects; the weight loss can be increased by an average of 10 kg if a diet and behavior modification program are included[70].

Drugs blocking Absorption of Nutrients

A drug soon to be released by the FDA, Orlistat, inhibits gastric and pancreatic lipase and has been shown to produce weight loss on the order of 5-10%[71]. The main side effects of orlistat are gastrointestinal.

Combination Therapy

Bray and colleagues have suggested combining different classes of appetite suppressants to see if greater weight loss could be achieved[72]. Although no greater efficacy with combination therapy of a sympathomimetic and a SSRI have been observed, combination therapy has allowed the administration of lower doses of each drug and fewer side effects than a single agent alone[73].

A long term study designed to address the efficacy, safety and addiction potential was conducted by Weintraub and colleagues at the University of Rochester School of Medicine[74]. The efficacy achieved are similar to other studies[75,76,77]. The study is presented here in detail because the authors attempted to answer many of the questions that practioners face when prescribing these drugs.

Weintrab and colleagues recruited 121 obese subjects at 130-180% of the ideal body weight according to the 1983 Metropolitan Life tables. Subjects began a 6 week run in period of behavior modification which included instructions from a dietician for modest caloric restriction (1500-1800 calories/d for men and 1000-1200 calories/d for women) as well as an exercise prescription to expend 300 kcal over and above the usual activities at least three times per week.

During this six week period, participants lost on average 3 kg.

In the first phase of the study, subjects were randomized to receive either placebo or 15 mg phenteramine plus 60 mg dl-fenfluramine for 28 weeks[78]. During the treatment period, participants were asked to rate difficulty following diet, hunger and satiety. While the placebo group reported increasing difficulty following the diet, the drug treatment group reported an immediate reduction in difficulty following the diet. The intensity of reported appetite suppression diminshed after 8 weeks of drug therapy, remaining only slightly less than the placebo group. Body weight in the drug treatment group fell 15% or 14 kg compared to 5% or 4.6 kg in the placebo group. Most of the weight lost in the drug treated group occurred by week 16 of drug therapy, with no additional weight loss despite continuation of drug therapy.

After documenting that drug therapy was more effective than placebo, a second phase testing the optimum drug therapy began[79]. In this open-label phase, all 112 participants who completed the first phase received drug therapy. Those previously randomized to placebo were switched to active drug and all those who had at least 10% weight loss on active drug were randomized to intermittent therapy or continuous therapy. For those who had achieved less than 10% weight loss, the dose of the drug was augmented to see if the poor response could be improved with higher drug doses. During the first 26 weeks of therapy, those previously on placebo lost an additional 9 kg on drug therapy. Those on continuous therapy maintained their weight loss; those on intermittent therapy gained weight when off drugs but lost most of the regained weight when drug therapy was reinitiated. Despite higher dosages, those in the augmented group failed to show any additional weight loss.

Of the 100 participants who completed up to week 60 of the trial, subjects who had received placebo and then active drug were now added to one of three treatments: augmented, intermittent, and continuous therapy. During this time period, all three groups tended to gain weight in the order of 2, 5.7 and 3.2 kg, respectively. The intermittent group complained of some inconvenience each time the medication was reintroduced.

In Phase III of the trial, 77 of the initial 121 subjects continued the study to test the effects of individually tailored dose adjustment of drugs[80]. No differences in fullness, hunger and satiety were observed, but those on higher dosages of drugs reported greater "drug helpfulness". Unfortunately, despite the detailed dosage adjustment, not only was no additional weight loss observed, but all participants tended to gain 1-2 kg weight.

In Phase IV of the trial, 52 of the original 121 subjects remained in the trial, and another double-blind placebo/drug randomized trial began[81]. The efficacy of continued drug therapy was documented -- despite the fact that the drug treated group continued to gain an average of 4 kg, the placebo group gained 8 kg. Surprisingly, participants receiving placebo reported less difficulty following the diet than those receiving active drug. There were no differences in hunger or satiety experienced by the two groups.

In Phase V of the trial, 48 patients still enrolled in the trial stoppped all medications, and were observed. The previously drug treated group gained more weight than the previously placebo treated group, suggesting that the drug continued to have effects on appetite.

The Weintraub-trial suggests that drug therapy has a consistent but small benefit. Those who respond to drug therapy in the first few weeks do not receive benefit from higher dosages. Over time, despite drug therapy, the tendency is to gain weight. Patients who remain under treatment with drugs, however, gain less weight than those under treatment with placebo.

Longterm Risks/Benefits Unique to Drug Therapy

The success of drug therapy in the Weintraub trial reflects that of all other shorter trials of either single drugs or combination therapy -- the maximum average weight loss from drug therapy is 5-10%, even when combined with a diet, exercise and behavioral therapy program. In fact, this success is no better than that of dietary therapy. Less than one fourth of the original 121 subjects achieved and maintained at least a 10% weight loss for three or more years of the trial, and only one seventh derived "partial benefit" in that an overall reduction in weight by 0.1%- 9.9% was observed. Thus, 30% of participants had some loss of weight, but 70% received no long term benefit from therapy. This success rate is no better than that achieved by dietary therapy.

Although the minor side effects listed above appear inconsequential, two potentially serious side effects of therapy have been raised: the serotonin syndrome and primary pulmonary hypertension.

The serotonin syndrome may occur when a serotoninergic drug is combined with another serotoninergic drug or a mono amine oxidase inhibitor, a triclyclic antidepresssant, trazodone, buspirone, or lithium carbonate [82]. Disorientation, confusion, restlessness, agitation, myoclonus, tremor, rigidity, hyperreflexia, incoordination, fever, diaphoresis, shivering, tachycardia, tachypnea, pupillary dilattion, and diarrhea are characteristic. Severe cases may develop high fever, seizures, disseminated intravascular coagulation, rhabdomyolysis, coma and death. Although no reported cases of serotonin syndrome in patients with dexfenfluramine alone or in combination have been made, anecdotal reports have described in patients receiving dexfenfluramine with another serotinergic drug some aspects of this syndrome[83]. The use of fenfluramine or dexfenfluramine is contraindicated in patients receiving mono amine oxidase inhibitors or other serotoninergic drugs; its use with central acting agents should be avoided since the propensity for this syndrome is unknown.

Several case reports and two case control studies have found an association between the use of anorectic agents and primary pulmonary hypertension[84,85,86]. In primary pulmonary hypertension, patients present with dyspnea, decreased exercise tolerance, angina, syncope, and lower extremity edema. The incidence is 1-2 cases per million people per year, with estimated risk asociated with use of anorectic agents for more than 3 months increasing to 23-46 cases per million people per year. Whether anorectic agents per se cause primary pulmonary hypertension is unclear, because a maximum lifetime self-reported BMI of greater than 30 was also associated with an increased risk of primary pulmonary hypertension. Nevertheless, this association must be considered when assessing the risk/benefits of therapy.

Surgical Therapy

The surgical approach to obesity is an alternative approach that has gained favor for the treatment of morbid obesity[87]. Comparing the efficacy of surgical therapy vs medical therapy is difficult because surgical therapy is often reserved for the morbidly obese or super obese, and these patients have greater disturbances in eating behavior than those patients with lesser obesity [88]. There are several different surgical approaches to the treatment of obesity[89]. These approaches fall into two categories: surgical attempts to induce malabsorption and surgical attempts to mechanically limit the quantity of food that can be comfortably ingested.

Regarding the first approach, the Roux-en-Y Gastric bypass is the most frequently used surgical procedure to produce malabsorption. It is often cited as an excellent operation for patients who crave sweets, since high simple sugar ingestion induces a dumping syndrome. Biliopancreatic bypass and other intestinal bypass surgeries that cause even greater malabsorption have fallen out of favor because of the malnutrition syndromes associated with their use.

Regarding the second approach, several techniques have been developed to reduce stomach size such as gastric banding, gastric resection, and vertical banded gastroplasty. While these procedures may appear safe, they are associated with other complications such as stricture, dehiscence of the wound at the suture site etc. The surgical treatment most commonly in use today is the vertical banded gastroplasty. Because the band is secured around an endothelial surface, it is more stable than other techniques of gastroplasty. The severity of restriction of gastric capacity should not be minimized. This procedure limits the capacity for a meal by 100 fold. The stomach pouch prior to the band can contain 14 ml; the band size is 5 cm with an interior diameter of 11-12 mm. More recently, surgeons have combined the gastroplasty procedure with a Roux-en-Y procedure, with anecdotally better success than either procedure alone.

Longterm Risks/Benefits Unique to Surgical Therapy

The weight loss results from surgical procedures is not well documented in the literature. There appears to be significant variation in the success of the surgeon, e.g., in one series of vertical banded gastroplasty surgical reoperations were 6% with complications less than 1% and in another series surgical complications were 45% [90,91,92]. Surgical treatment is successful in that gastric banding produces 10% of weight loss in 78% of the patients and a 25% weight loss in 45%. The average BMI fell from 46 to 36, with an average weight loss of 28 kg. Gastric bypass produced more dramatic results, with a fall in BMI from 50.2 to 34.1 at 18 months (67). It should be noted, however, that most patients remain obese following surgery. The major benefits of surgical therapy, as with drug therapy, is that the magnitude of weight loss is sufficient to reduce the long term complications of obesity[93].

Longterm Risks/Benefits to Weight Loosing Therapies: Is there harm in repeatedly trying therapies that do not work?

Patients who have participated in multiple attempts to loose weight often report that after each attempt to loose weight, they gain even more weight back than they have lost. This leads to the

popular believe that their previous efforts have "damaged", "tricked", or "slowed" their metabolism. There is, in fact, some truth to this claim. Weight loss acutely and chronically changes metabolism.

During rapid weight loss such as with very-low calorie diets, resting metabolic rate is acutely decreased on average 14%[94]. Despite the reduction in resting metabolic rate, the rate of weight loss remains constant as long as compliance to the dietary regimen is maintained[95]. Rate of weight loss of a very-low-calorie diet is correlated with total energy expenditure and not resting metabolic rate[96], so the importance of a 14% reduction in resting metabolic rate (100-300 kcal) on the bottom line -- weight loss -- appears to be little if any in the face of severe caloric restriction. Low calorie diets reduce resting metabolic rate only 1-2%, and thus have little effect on metabolism.

Does the acute change in resting metabolic rate from a very low calorie diet translate to permanent "damage" to the metabolic system? The effects of weight cycling can be measured in competitive wrestlers, who often use crash diets to achieve their weight class just prior to competition. In a prospective study, six lean college wrestlers who subjected themselves to at least five 4.5kg or greater weight gain-loss cycles per year were compared to six wrestlers who did not weight cycle and twelve physically active controls who did not wrestle[97]. Resting metabolic rate was higher in both groups of wrestlers compared to controls. Resting metabolic rate did not differ between the two types of wrestlers, suggesting that weight cycling had no long term effect on resting metabolic rate.

Similar observations in obese women suggest that dieting only acutely alters resting meabolic rate. The resting metabolic rates in 50 obese women who reported weight cycling were no different than predicted by equations using fat free mass[98]. Tracking resting metabolic rate in 14 obese children before, during, and after a hypocaloric diet, shows the initial reduction in resting metabolic rate is not sustained[99]. Another weight loss study in obese children found that changes in resting metabolic rate paralleled changes in fat free mass and not changes in caloric intake[100]. In a study of eight post-obese women who had lost on average 21.5 kg, energy expenditure at rest, during different daily activities, and following a meal was no different than that of age, height, body mass index and fat free mass matched controls[101]. In summary, individuals who have lost weight have metabolic rates indistinguishable from those who have stayed lean.

Regarding chronic changes in metabolic rate, because weight loss reduces fat free mass, loosing weight reduces the number of calories it takes to maintain weight. In other words, although obese persons need more calories than lean persons, post-obese persons need fewer calories than their obese counterparts to maintian weight. The changes in caloric expenditure are small and on the order of 100-200 calories per day. However, since body weight is tightly regulated, this amount of calories may be enough to cause weight gain if not compensated for by increasing energy expenditures.

Summary and Conclusions

The cause of obesity is overconsumption of calories. An obese person requires more calories than a lean person to maintain weight.

Food choices influence body weight because of their caloric content and not because of their protein, fat or carboydrate content. Very-low-calorie diets achieve a 21 kg weight loss at 16 weeks. Low calorie diets can achieve an 11 kg weight loss at 26 weeks. Dieting does not damage metabolism and is a safe form of weight control. The problem with dietary therapy is that weight regain occurs in over 75% of patients.

Drug therapy with anorectic agents may augment the weight reduction achieved by diet by 5-10 kg but is no more successful in the longterm than diet. Drug therapy may place an individual at risk for primary pulmonary hypertension. For these reasons, drug therapy should be reserved for those patients where weight loss serves as a therapy for an existing disease (e.g., hypertension, diabetes).

Surgical therapy may achieve a greater magnitude of weight loss than other therapies but is generally reserved for the morbidly obese. Even after surgical therapy, the majority of patients remain obese.

Until more effective therapies become available, the focus of physicians should be on the prevention of weight gain. The focus of patients should be on evaluating each eating occasion and making more often the choice "no, thanks".

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