Human Obesity
Exploding the Myths

Discussant
DAVID S. WEIGLE, MD

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DAVID S. WEIGLE, MD*: Several misconceptions about obesity have hampered health care for the obese in recent years. Although the popular press and diet faddists have contributed to these misconceptions, the medical profession has often failed to provide a balanced view of the physiology of body weight regulation and the health hazards of obesity. Four commonly held beliefs underlie much of the confusion in this area. The first is that one's body weight is not a physiologically regulated variable but, rather, is set by acquired food habits and conscious or unconscious desires. A corollary of this misconception is that by choosing the right diet, a person could set his or her body weight to any desired level without incurring adverse health consequences in the process. A third misconception is that weighing more than a certain tabulated standard constitutes a sufficient health hazard in all persons that efforts to lose weight (usually by diet) should be undertaken. Finally, it is not commonly appreciated that body shape, which reflects the location of the dominant fat deposits, may have a much more important influence on a person's health than his or her overall weight. To develop rational guidelines for dealing with obese persons, it is important to address these four misconceptions.

Body Weight Regulation

Although a large body of empiric evidence argues convincingly that body weight is a regulated variable, it is useful to consider two general observations bearing on this issue. The first is that in most people body weight is either stable after adolescence or increases slowly over the lifespan.[1-3] Fox, whose average self-reported weight varied by less than 1.4 kg (3 lb) over a 19-year period, suggests that the mean annual weight gain of most Western populations is no more than 0.23 kg (½ lb) per year.[1] This degree of weight stability implies a precise match between energy intake and energy expenditure over prolonged periods. Even an 83.6-kilojoule (20-kilocalorie) excess in daily energy intake, the caloric content of a single soda cracker, would result in a 0.9-kg (2-lb) per year rate of weight gain. This precision in balancing daily energy intake and energy expenditure would be difficult to achieve on a purely volitional basis. It is more reasonable to postulate that energy balance reflects the operation of a physiologic regulatory, or homeostatic, mechanism.

Several excellent studies of body weight inheritance provide a second argument for body weight regulation. Studies of monozygotic and dizygotic twins suggest that a large portion of the variance in body weight among different family members is genetic in origin.[4,5] To elucidate whether this apparent inheritability of body weight is genetic or reflects the shared environment of family members, Stunkard and co-workers examined the body weights of Danish adoptees who had been separated from their biologic parents shortly after birth.[6] They found that the body weights of the adoptees correlated more closely with the weights of their biologic parents than with those of the foster parents in whose home the adoptees were raised. A direct explanation for these observations would be that one or more critical peptide molecules whose level(s) are determined by definable genes are in some way responsible for a person's body weight.

The usual body weight that a person maintains without conscious effort may be referred to as his or her "set point" weight. As weight deviates from this set point, restorative forces begin to operate to return the person to the set-point weight.[7] An increase in weight leads to increased energy expenditure and decreased appetite, whereas a decrease in weight leads to decreased energy expenditure and increased appetite. The power with which these restorative forces operate depends directly on the degree to which a person's weight has varied from the set point. On a day-to-day basis, the operation of these forces may be unnoticeable, whereas after a binge of holiday eating or the fasting associated with a transient illness, a person may experience pronounced satiety or hunger. Those in whom the restorative forces operate strongly experience relatively little variation in their daily or weekly body weights. Persons with a weaker regulatory response have greater weight fluctuations. It is important to note that both normal-weight and obese persons experience the same restorative changes in appetite and energy expenditure after a sufficient change in body weight. Thus, the regulatory system operates independently of the factors that actually determine the set point.

The set-point theory of body weight regulation is based on a large body of empiric evidence, only a small portion of which can be presented here. Considering appetite first, the work of Sims and associates showed that overfeeding normal-weight persons sufficiently to cause an 8% to 10% increase in body weight led to marked sensations of satiety or even nausea.[8] The satiety, and consequent suppression of voluntary food intake, observed by Sims and colleagues persisted until the body weight of each experimental subject returned to its previous baseline value. Overfeeding obese

*Assistant Professor, Division of Metabolism, Endocrinology, and Nutrition, Department of Medicine, Harborview Medical Center and University of Washington School of Medicine, Seattle.

Reprint requests to Department of Medicine, RG-20, University of Washington School of Medicine, Seattle, WA 98195.

ABBREVIATIONS USED IN TEXT

BMI = body mass index
CHD = coronary heart disease
CT = computed tomography
HDL = high-density lipoprotein
NIH = National Institutes of Health
V:S ratio = ratio of visceral to subcutaneous fat

persons to cause a significant deviation above baseline weight leads to a similar decrease in appetite (R. Leibel, MD, Rockefeller University, oral communication, November 1989). The extreme increase in appetite that occurs with fasting to a subnormal weight in nonobese persons has been extensively documented by Keys and co-workers in a study of experimental semistarvation.[9] The intense hunger and preoccupation with food experienced by the subjects of this study persisted throughout the refeeding period until the baseline body weight was again achieved. The similar increase in appetite that occurs when obese persons lose weight by dieting contributes to the difficulty in maintaining weight loss experienced by reduced-obese persons.

The effects of deviations from set-point weight on energy expenditure also have been studied extensively. As early as 1902 Neumann recognized that body weight did not increase indefinitely despite the ongoing consumption of calories in excess of baseline weight maintenance needs.[10] Neumann reasoned that at body weights sufficiently above baseline, energy requirements were increased such that the excess calories were no longer stored as body fat. Sims and associates noted a similar leveling off of subjects' body weights despite the ongoing feeding of a caloric level significantly above baseline requirements.[8] Various other studies have shown that in both normal-weight and obese subjects, energy expenditure increases progressively as weight deviates above the set point for each person.[11-14] This increased energy expenditure, much of which occurs in the compartment of the resting metabolic rate, acts to limit further weight gain.

When food consumption is reduced such that body weight falls below the set point, both normal-weight and obese persons have a reduction in resting and total daily energy expenditures.[15-18] Leibel and Hirsch demonstrated this homeostatic energy-conserving response with an obese subject group that had an average weight of 152 kg and a daily energy requirement of 15.3 MJ (3,651 kcal).[15] After reducing to a mean final weight of 100 kg, the energy requirement of this group fell to 9,075 kJ (2,171 kcal) per day, which was actually less than the 9,530-kJ (2,280-kcal)-per-day requirement of a group of lighter control subjects at their mean baseline (set point) weight of 63 kg. Geissler and colleagues made similar observations in a group of reduced-obese and normal-weight women studied at several different levels of activity.[16]

To better define the mechanism of energy conservation with weight loss, we did two studies of obese and reduced-obese persons.[19,20] In the first of these studies we confirmed that the weight-stabilizing caloric intake—a measure that reflects total daily energy expenditure—and the resting metabolic rate of a group of men and women decreased substantially with stable weight reduction.[19] The resting metabolic rate, which was proportional to fat-free mass at baseline weight, showed exactly the same relationship to the reduced fat-free mass after weight loss. A second study of obese men before and after weight loss was designed to determine the degree to which the reduced energy cost of physical activity at the lower body weight contributed to the energy savings of the reduced-obese state.[20] To this end, five obese men were placed on an energy-restricted diet until a mean 23% weight loss was achieved. A matched group of five subjects on the same diet wore a specially tailored vest into which flat lead weights could be placed. The subjects were weighed twice a week, and weights were added to the vests at each weighing session to exactly compensate for body weight lost on the diet to that point. Subjects wore the vests under their usual clothing for 16 hours per day. A comparison of the energy expenditures of the two subject groups before and after weight reduction revealed that weight replacement, by keeping the energy cost of physical activity comparable to baseline values, cancelled about half of the fall in energy expenditure of the vest-wearing group. Control subjects had a 3,829-kJ (916 kcal)-per-day (29% of baseline) fall in energy expenditure, whereas weight-replacement subjects had only a 1,689-kJ (404 kcal)-per-day (12%) decrease. Thus, the reduction in energy expenditure that occurred with a 21% to 23% weight loss represented both a metabolic adaptation and a roughly comparable biomechanical energy savings.

These observations regarding the operation of the body weight regulatory system can be incorporated into a model as shown in Figure 1. The central nervous system, responding to both internal and environmental appetite cues, initiates eating. Food intake occurs until signals arising largely from the gastrointestinal tract are interpreted by the central nervous system to produce the subjective experience of satiety.[21] This short feedback loop principally regulates the size of a meal. On a longer term basis, the ingestion of calories in excess of immediate needs leads to an expansion of the adipose mass. A signal or signals, the level of which is proportional to the excess adipose store, then increase in the circulation and augment the experience of satiety elicited by the gastrointestinal factors in the central nervous system.[22,23] The average meal size would consequently be reduced until the adipose mass returns to its baseline value. As the adipose mass expands, the total body weight increases, leading on a biomechanical basis to a partially compensatory increase in activity-related energy expenditure. The increase in fat-free mass that accompanies increasing adiposity results in a higher resting energy expenditure. Circulating factors proportional to the adipose mass could also modulate energy expenditure directly. The net effect of decreasing food consumption and increasing energy expenditure would be to reduce the adipose mass towards its baseline value. When a deficient caloric intake leads to contraction of the adipose mass, a regulatory response opposite to that discussed above tends to restore the adipose reserve to baseline.

Although alternatives to the scheme diagrammed in Figure 1 can be envisioned, this model shows that body weight is set at the point of balance of the various feedback loops that regulate the adipose mass. The genetic influence on body weight could be mediated primarily through differing levels of expression of the long-term circulating satiety factor(s) or its receptor in the central nervous system. Persons who express the active factor or its receptor at low levels would have to gain relatively more adipose tissue until the decrease in appetite and increase in energy expenditure are sufficient to result in energy balance. Body weight regulation would then occur around this elevated set point. The critical circulating factor or factors proposed in Figure 1 remain to be discovered. Porte and Woods have suggested that insulin, the circulating level of which is proportional to

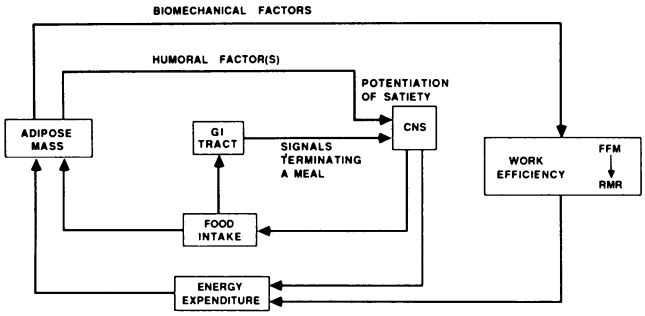

Figure 1.—The schema is of a model for the body weight regulatory system. See text for explanation. CNS = central nervous system, FFM = fat-free mass, GI = gastrointestinal, RMR = resting metabolic rate

body fat content, could be an important long-term physiologic satiety factor.[24] The recent discovery of adipsin, however, suggests that adipose tissue itself could secrete peptides that function to regulate body weight.[25] This is an area of intense current research interest.

Several arguments have been offered against the existence of body weight regulation.[7] It has been suggested that the notable variability of body weight among different persons is inconsistent with a real homeostatic mechanism. This argument is no more compelling than the suggestion that interindividual differences in blood pressure disprove the existence of blood pressure regulation.[7] Body weight set point, if determined by the level of expression or activity of one or more gene products, would be expected to vary in a population unless the resultant phenotype led to impaired reproductive success. The slow upward drift in adiposity that occurs with normal aging has also been offered as an argument against the existence of body weight regulation. This objection may be addressed by comparing the energy imbalance implied by a typical yearly weight gain with the total caloric flux occurring over a similar period of time. Thus, a yearly weight gain of 0.2 kg^1 represents an energy excess of only 7,524 kJ (1,800 kcal) per year. This figure constitutes less than 0.2% of a typical yearly intake of 1 million calories. This "failure" of body weight regulation could simply reflect an age-related decline in the synthesis of a critical regulatory factor (Figure 1), much as cardiac and renal performances decline with normal aging. Finally, the observation that body weight can be influenced by the hedonic qualities of food has been cited as evidence against a regulatory system. Again, this observation has no more relevance than the observation that a high salt intake can lead to an increased blood pressure.[7] Were it not for the usual stability of body weight, the transient increase in weight occurring after a binge of holiday eating would go unnoticed. The degree to which indiscretion in eating affects a person's weight depends only on the strength of the counterregulatory responses in that person and his or her discomfort in the face of satiety. As a population exposed incessantly to a surfeit of prepared and convenience foods, we probably always exist close to a maximal tolerable weight above the set point.

The Dubious Value of Diet Alone in Managing Obesity

If a person's body weight were set by habit or desire, then voluntary dietary energy restriction should provide a "cure" for obesity. The long-term maintenance of weight loss achieved through diet alone, however, is poor in most persons. Drenick and Johnson reported that only 7 of 121 morbidly obese subjects who had lost weight on a regimen of fasting followed by semistarvation remained below their starting weights at a mean of 7.3 years' follow-up.[26] Pavlou and co-workers, and other investigators who have employed less draconian diets, have reported comparably poor long-term results.[27] This general outcome of dietary therapy is not surprising in light of the strength of the body weight regulatory system discussed above. The task of keeping a person's weight considerably below its set-point value through dietary energy restriction is comparable to attempting to maintain a significantly elevated serum osmolarity through voluntary restriction of free water intake. Only persons with incredibly strong will power or the ability to tolerate physical discomfort are likely to be successful in this attempt to defeat a homeostatic mechanism. The degree of physical and emotional discomfort induced by dietary energy restriction depends primarily on the degree to which body weight deviates below its set point.[9]

Our national preoccupation with dieting might be excusable if dissatisfaction were the only adverse consequence of this rather ineffective approach to the treatment of obesity. Dieting carries certain risks, however, that must be considered when making individual therapeutic or public health recommendations. The use of severely energy-restricted or unbalanced diets has been associated with deficiency syndromes, arrhythmias, and sudden cardiac death.[28,29] Fortunately, the collagen hydrolysate diets that were associated with many of these cardiac complications have been removed from the market.[29] Even balanced energy-restricted diets invariably lead to chronic fatigue, impaired concentration, cold intolerance, and malaise as the body weight drops progressively below its set point. These symptoms are associated with a decrease in fat-free mass and objective decreases in muscle strength and endurance.[27] Impaired peripheral conversion of thyroxine to triiodothyronine with dietary energy restriction may also contribute to these symptoms. Welle and Campbell have shown that the replacement of triiodothyronine in subjects consuming a low-caloric diet partially restores their energy expenditures towards normal.[30]

Several adverse psychological outcomes of dieting are important. Because attempts to maintain weight loss achieved through diet usually fail, many persons put themselves through repeated cycles of dieting. Repeated failures with diets may lead to low self-esteem and reinforce the erroneous notion that the person is to blame for his or her own obesity. Frustration with energy-restricted diets may lead a person to ignore more useful dietary guidelines aimed at preventing hyperlipidemia, diabetes mellitus, and colonic diseases. Obsession with dieting on a population basis may contribute to the increasing incidence of anorexia nervosa and bulimia in this country.[31] Finally, unrealistic expectations of dietary therapy for obesity by health care providers may delay the institution of effective pharmacologic therapies for the obesity-associated conditions of diabetes mellitus, hypertension, and hyperlipidemia.

Ernsberger and Haskew have proposed that some of the health complications that have been associated with obesity may actually be caused by energy-restricted diets or the acute realimentation that follows dietary failure.[32] These authors cite, among other studies, the epidemic of hypertension and congestive heart failure following the Siege of Leningrad in 1942 as a large-scale demonstration of the danger of refeeding after caloric deprivation.[33] The pronounced peripheral edema that often develops in patients with anorexia nervosa during treatment also illustrates the potential harm of cycles of energy restriction and refeeding. This sodium and fluid retention is presumably due to enhanced renal sensitivity to mineralocorticoids that develops

during caloric restriction and the abrupt increase in the insulin level that follows realimentation.[34] On the basis of limited studies in animals and humans, it appears that cycles of weight loss and regain may lead to a reduction in daily energy requirements.[35,36] This enhanced metabolic efficiency would, in turn, promote further weight gain with each new cycle of dieting. Although this potential adverse effect of "yo-yo" dieting is both plausible and worrisome, more research is needed to verify these preliminary observations.

The set-point theory of body weight regulation has been viewed with great pessimism precisely because it implies the futility of dieting.[37] A more optimistic alternative view, which has ample precedent in medical research, is that only when a problem is reduced to its physiologic roots is it possible to find a meaningful solution. With molecular biologic techniques, the critical regulatory factor(s) postulated to exist in Figure 1 is likely to be identified long before the complex psychodynamics offered by some as an "explanation" for obesity are unraveled. Perhaps the best course to take while awaiting a more fundamental biochemical insight is to recommend the use of energy-restricted diets as a treatment of obesity only in situations where the potential benefits clearly exceed the risks. Such situations might include ventilatory failure associated with obesity or when preparing a morbidly obese person for an elective surgical procedure. As will be discussed later, a general public health recommendation for weight reduction through dieting cannot be supported strongly with existing data.

The proper food choices and regular aerobic exercise have at least as much to offer in the treatment of obesity as dietary energy restriction. Exercise programs, either used alone or in combination with mild caloric restriction, have been shown to enhance the successful long-term maintenance of weight loss.[27] Regular exercise may lower the set point for body weight regulation.[7] Certainly when the body weight is dropped below the set point by exercise, the total daily energy expenditure remains appropriate for the new weight, in contrast to the notable fall in energy expenditure observed when the same amount of weight is lost by diet alone. Additional benefits of regular exercise include improved cardiovascular fitness, a greater sense of well-being, and improvements in blood pressure, carbohydrate tolerance, and lipid profile. Perhaps most important is the growing evidence that exercise is associated with increased longevity in a variety of study populations.[38,39]

The Overstated Health Hazards of Moderate Obesity

Compared with the health hazards of smoking, hypertension, diabetes mellitus, and certain hyperlipidemias, the adverse health consequences of moderate obesity are relatively mild.[40] Nevertheless, the panel of the 1985 National Institutes of Health (NIH) Consensus Development Conference stated that "weight reduction should be recommended to persons with excess body weight of 20% or more above desirable weights in the Metropolitan Life Insurance Company tables."[41] Given the potential adverse consequences of dieting discussed earlier, it is important to examine the data on which such a sweeping public health recommendation is based.

The Metropolitan tables, which have been published at intervals since the early 1940s, are an attempt to relate mortality experience to body weight in the insured population. An "optimal" (lowest mortality) weight is tabulated for three frame sizes in each height and sex category. Although the concept of an optimal weight may be sound in principle, several problems make the use of these tables as a cornerstone of public health policy risky.[42] Because most of the data on which the tables are based reflects the experience of white upper- and middle-class men, the tables may not be generalizable to the American population as a whole.[42] The average follow-up period of one of the central data bases from which the tables were formulated was only 6.6 years.[42] It is impossible to judge the effect of other important variables, such as cigarette smoking, on the tabulated data.[42] Furthermore, no explicit definition of frame size was built into the data bases from which the tables were drawn, and the important effect of subject age on the relationship between body weight and mortality is not incorporated into the tables at all.[43] Finally, tables of optimal weight for height give no information as to the rate at which mortality increases as weight deviates from the optimum. A steeply increasing relationship between mortality and weight would justify a more aggressive public health approach to obesity than would be justified by a less pronounced relationship.

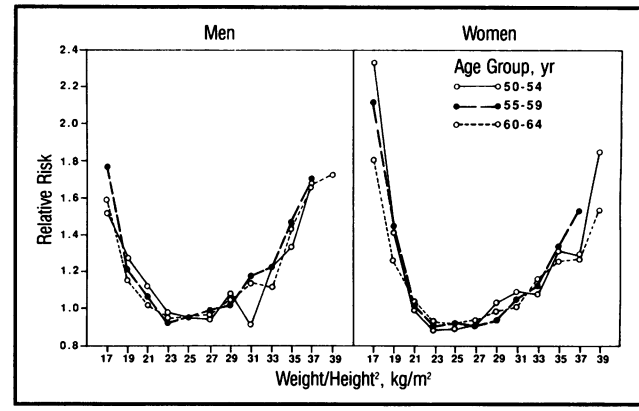

Figure 2.—The graphs show the relative mortality for three age groups according to the body mass index (ratio of weight to height squared) (from Waaler[44]).

Several studies have shown that the curve relating body weight and mortality from all causes is U- or J-shaped.[43-45] Mortality increases with a deviation either above or below a particular weight that increases with age.[43] In the largest study of body weight and mortality to date, 1.7 million Norwegians aged 15 years or older were observed for ten years.[44] As shown in Figure 2 for three age groups enrolled in this study, risk ratios for overweight persons varied between only 0.9 and 1.8 over a wide range of a body mass index (BMI). These risk ratios are considerably less than those associated with smoking, hypertension, diabetes mellitus, and certain hyperlipidemias.[46] As described by Waaler, "the curves are very wide at the bottoms, indicating uncertainty in the determination of an optimum, or in other words that a rather extensive overweight is required to give an excess mortality of any importance."[47] The 20% overweight guideline for weight reduction suggested by the NIH Consensus Development Panel corresponds to BMI values in the range of 25 to 27 kg per m^2.[41] As shown in Figure 2, the increased mortality associated with this degree of overweight is inconsequential.

In the United States, an American Cancer Society study of 750,000 men and women produced data comparable to those obtained in the Norwegian study.[45] The U-shaped curve relating mortality and body weight for all subject ages combined was again rather broad, with a maximum risk ratio of about 1.9 for both men and women greater than 140% of average weight. For weight categories as high as 120% of average weight, mortality ratios remained less

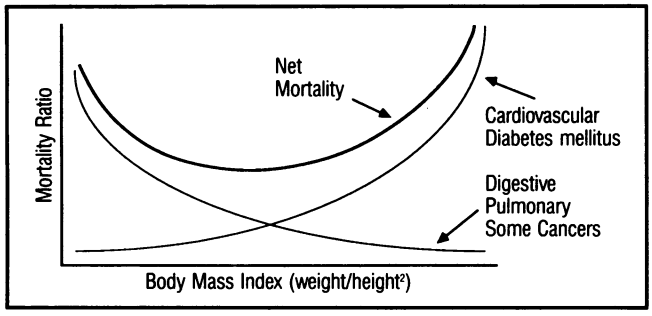

Figure 3.—The graph shows the origin of the U-shaped curve relating overall mortality to adiposity. Disease categories responsible for deaths at both low and high values of body mass index are noted.

than 1.2. It is important to note that in the American Cancer Society study, weights were expressed as percentages of the observed average weights rather than as percentages of ideal body weights. Because these weights were generally higher than those appearing in the 1959 Metropolitan tables, the risk ratios corresponding to the NIH Consensus Development Panel's treatment guidelines for obesity would actually be less than 1.2. On the basis of overall mortality data, it appears that general recommendations for the treatment of obesity should be targeted toward more overweight persons, particularly if treatment is ineffective or associated with its own morbidity.

As shown in Figure 3, the U-shaped curve relating body weight and mortality from all causes can be explained by the occurrence of distinct categories of disease at opposite extremes of body weight.[32,44,45] Deaths due to obstructive lung disease, peptic ulcer disease, stomach cancer, lung cancer, and tuberculosis tend to be more frequent at lower body weights, whereas cardiovascular, cerebrovascular, and diabetes-related deaths are more common in obese persons. The excess deaths occurring at low body weights are not simply due to the preexisting disease causing weight loss or the association between smoking and reduced body weight.[32] Given the incidence of cardiac death in developed countries, the important public health question about obesity relates to whether an increased body weight constitutes a true risk factor for cardiovascular morbidity and mortality.

Univariate studies of the relationship between body weight and cardiovascular end points support the association of obesity with cardiovascular disease. Obesity, however, is also associated with hypertension, diabetes mellitus, hypertriglyceridemia, hyperinsulinemia, and low levels of high-density lipoprotein (HDL) cholesterol. Because each of these factors has been implicated as a risk factor for coronary heart disease (CHD), it is difficult to determine whether obesity is an independent risk factor for cardiovascular disease. It has been suggested that the tight association of all of these variables, along with the favorable response of hypertension and blood glucose and lipid levels to body weight reduction, makes the independence of obesity as a risk factor for CHD irrelevant. Counterarguments to this somewhat nihilistic point of view include the poor long-term outcome of most attempts to treat obesity, the morbidity associated with energy-restricted diets, and the more effective pharmacotherapy available for the "metabolic complications" of obesity. Perhaps most important, a better understanding of the relationship between body weight and coronary artery disease could lead to a more fundamental understanding of the causes and prevention of atherosclerosis.

Several studies have employed multivariate analysis in an attempt to identify any independent contribution of obesity to CHD morbidity and mortality. The results of seven of these studies are summarized in Table 1 according to an increasing duration of follow-up. The Japan-US study, which was designed principally to differentiate environmental and genetic influences on CHD risk factors, somewhat surprisingly found obesity to confer an independent risk for CHD after only two years of follow-up in the American cohort.[48] This result was not confirmed in the mainland Japanese cohort, perhaps because of the low incidence of obesity among these men. The Walnut Creek (California) Contraceptive Drug Study, one of the few large studies of cardiovascular disease in women, found a relative risk of 2.2 for myocardial infarction as a function of obesity.[49] This result was barely significant (χ^2 3.1) after adjusting for smoking, alcohol use, blood pressure, cholesterol level, and gallbladder disease. The Gothenburg, Sweden, and seven countries studies of men found no independent association between obesity and coronary heart disease despite follow-ups of 13 and 15 years, respectively.[50,51] Only subjects in the 40- to 59-year age range were enrolled in those studies, however. The Los Angeles Heart Study found obesity to confer a risk for CHD independent of serum cholesterol levels and blood pressure after 15 years of follow-up.[52] This effect of obesity was restricted to men younger than 40 years at enrollment. Because blood glucose, triglyceride, and HDL-cholesterol levels were not measured in the Los Angeles study, it is impossible to determine whether obesity conferred its risk through unfavorable changes in these variables. In the Manitoba study, 26 years of follow-up were required to show a significant effect of obesity on CHD morbidity and mortality.[53] As in the Los Angeles study, obesity was a risk factor only in men younger than 39 at

TABLE 1.—*Is Obesity an Independent Risk Factor for Coronary Heart Disease?*

Source	Study Population or Location	Patients, No.	Sex	Initial Age, yr	Follow-up, yr	Answer
Robertson et al, 1977[48]	Japanese and	1,963	♂	45-68	5	No
	American	7,705	♂	45-68	2	Yes
Petitti et al, 1979[49]	Walnut Creek, Calif	16,759	♀	18-54	6.5	Borderline
Larsson et al, 1984[50]	Gothenburg	792	♂	54	13	No
Keys et al, 1984[51]	Seven countries	11,579	♂	40-59	15	No
Chapman et al, 1971[52]	Los Angeles	1,859	♂	20-70	15	Yes*
Rabkin et al, 1977[53]	Manitoba	3,983	♂	15-64	16	No
					26	Yes*
Hubert et al, 1983[54]	Framingham, Mass	2,252	♂	28-62	12	No
		2,818	♀	28-62	26	Yes

♂ = male, ♀ = female

*Effect seen only in subjects younger than 40 years at enrollment.

enrollment. Because the only covariables included in the Manitoba study were age and blood pressure, little can be concluded about the independence of obesity as a coronary artery disease risk factor. Finally, after 26 years of follow-up, the Framingham study found obesity to confer a risk for CHD outcomes that was independent of age, cholesterol levels, systolic blood pressure, smoking, left ventricular hypertrophy, and glucose intolerance in both men and women.[54] Again, the adverse associations of body weight were most apparent in subjects younger than 50 at enrollment.

Several explanations may be offered for the conflicting data regarding obesity as an independent risk factor for coronary artery disease. First, obesity could simply be a rather weak factor predisposing to atherosclerosis. This possibility is suggested by the appearance of an association between obesity and CHD outcomes only in subjects who were enrolled at earlier ages and followed for periods of 20 years or more. Andres recognized this important modulating influence of age on the risk associated with obesity and formulated a set of optimal weight for height tables in which age and height rather than sex, frame, and height are the index variables.[43] These tables indicate that in younger subjects, who would have exposure to any harmful effects of obesity for longer time periods, the weight associated with the lowest mortality is lower than in older subjects. A second explanation for the apparent ambiguity of obesity as a CHD risk factor could be that obesity is associated with a more important, but as yet unproved or unrecognized, atherogenic condition. Hyperinsulinemia may be one such condition.[55] Finally, as will be discussed, obesity may consist of several subgroups, some of which are associated with accelerated atherosclerosis and some of which are not.

The Importance of Body Fat Distribution

Vague in 1956 was the first worker to divide human obesity into either android (central) or gynoid (lower body) subtypes.[56] He noted that premature atherosclerosis, diabetes, gout, and uric calculous disease were more commonly associated with the android type of obesity. Vague attributed both android obesity and its complications to overactivity of the pituitary-adrenal axis. These early observations have been confirmed and refined by a large number of subsequent studies, only a few of which can be considered here.

In the Honolulu Heart Program, 7,692 men of Japanese ancestry were observed for as long as 12 years to determine the relationship between central body fat distribution and the occurrence of definite CHD (nonfatal myocardial infarction and CHD-related death).[57] A single measurement of subscapular skinfold thickness was used as an index of centrality, and the body mass index was used as a measure of overweight. When the data were analyzed by tertiles, subscapular skinfold thickness was found to be a stronger predictor of CHD than was the BMI. Within any tertile of subscapular skinfold thickness, the relationship between the BMI and CHD was not significant. Risk factors that showed a positive correlation with the subscapular skinfold thickness included total cholesterol, blood glucose, and triglyceride levels and blood pressure status. After adjustments were made for these risk factors as well as age, BMI, and the use of cigarettes, the relationship between subscapular skinfold thickness and CHD remained significant (relative risk for the highest versus the lowest tertiles of skinfold thickness, 1.5; 95% confidence intervals, 1.1 to 2.1). The significance of this independent association between central body fat distribution and definite CHD is particularly impressive because the subscapular skinfold thickness reflects overall body fat content almost as well as it reflects central fat distribution. A variety of studies that have used other techniques to measure regional body fat also suggest that the most overweight persons tend to be the most centrally obese. This relationship between degree of overweight and central obesity in study populations could certainly explain the apparent association between obesity and CHD outcomes noted in Table 1. As the authors of the Honolulu Heart Program report note, "The focus of attention on the independent predictive ability of obesity may be misplaced."[57(p823)]

TABLE 2.—*Percentage Probabilities of Myocardial Infarction and Death From Any Cause in Relation to Tertiles of Body Mass Index and Ratio of Waist to Hip Circumference**

Tertiles of Waist to Hip Ratio	Tertiles of Body Mass Index (Weight/Height²)		
	Lowest	Middle	Highest
Myocardial Infarction			
Lowest	0.9	0.0	0.0
Middle	1.1	0.9	1.5
Highest	3.8	0.0	3.5
Death			
Lowest	7.6	2.5	1.0
Middle	4.7	4.7	4.7
Highest	7.0	5.2	6.3

*From Lapidus et al.[58]

The Gothenburg longitudinal study of 1,462 women reached conclusions similar to those of the Honolulu Heart Program in a female population.[58] In this 12-year study, central body fat distribution, as reflected by an elevated waist-to-hip ratio, was more closely associated with a variety of cardiovascular end points than was the BMI or the sum of skinfolds (another index of general adiposity). As shown in Table 2, tertiles of increasing waist:hip ratio correlated with an increasing probability of either myocardial infarction or death in most tertiles of BMI. In contrast, within any tertile of the waist:hip ratio, there was no increase in the probability of either of these end points with increasing BMI. When a multivariate analysis was used to remove the confounding effects of age, BMI, smoking, total cholesterol and triglyceride levels, and systolic blood pressure, the association between the waist:hip ratio and myocardial infarction remained significant. As in the Honolulu study, the occurrence of the highest waist:hip ratios in the most overweight persons would have led to an apparent independent association between the BMI and CHD if considered out of context.

Recent studies employing computed tomography (CT) have further defined the relationship between central obesity and factors contributing to an increased CHD risk. Fujioka and co-workers determined the ratio of visceral to subcutaneous fat (V:S ratio) in 46 obese subjects by means of CT at the level of the umbilicus.[59] The mean V:S ratio of the subject group as a whole was 0.4. A V:S ratio of greater than 0.4 (but not the BMI or duration of obesity) identified subjects who were more likely to have non-insulin-dependent diabetes mellitus and higher values of fasting blood glucose, plasma glucose area after oral glucose loading, total cholesterol, and triglycerides when compared with those of subjects with a V:S ratio of less than 0.4. When multiple-regression analysis was used to remove any confounding effect of BMI and age, the correlation between the V:S ratio and the plasma glucose area, total cholesterol, and triglyceride levels remained significant.

Peiris and associates measured abdominal visceral fat by CT and total body fat by hydrostatic weighing of a group of 33 obese premenopausal women.[60] In multivariate analyses, visceral fat, as compared with total fat, accounted for twice the percent variance in blood pressure, insulin response to an oral glucose load, and the ratio of HDL to total cholesterol measured in the study subjects. After adjusting for visceral fat, there was no significant association between these CHD risk factors and the total body fat. In contrast, the association between visceral fat and risk factors remained significant after adjusting for total fat. The waist:hip ratio correlated less strongly with CHD risk factors than did visceral fat.

The balance of evidence suggests that the excess abdominal visceral fat of persons with central obesity predisposes to CHD both through traditional risk factors and other factors, such as hyperinsulinemia, that were not considered in the Honolulu and Gothenburg studies. Björntorp has hypothesized that the greater lipolytic activity of abdominal visceral adipose tissue may mediate the adverse metabolic effects of central obesity.[61] This enhanced lipolytic activity appears to be due to a higher ratio of β- to α_2-adrenergic receptors and lower insulin sensitivity of the adipose tissue depots that drain into the portal circulation.[62-64] A greater delivery of free fatty acids to the liver would tend to promote the synthesis of very-low-density lipoproteins and create insulin resistance with resultant hyperinsulinemia.[61] These derangements could lead to hyperlipidemia and diabetes mellitus in many persons. Hyperinsulinemia is also associated with hypertension, but the pathogenetic link between these two conditions is less clear.[61]

Human Obesity—What to Do Until More Answers Are Available

Although the cause or causes of human obesity are not yet known, several conclusions may be drawn from the evidence summarized above. Perhaps most important is the observation that obesity is not a disorder of body weight regulation. Most obese persons regulate their weight appropriately about an elevated set-point weight. This set point appears to be strongly influenced by the person's genotype. As hypothesized in Figure 1, diminished expression of, or a reduced ability to respond to, a circulating satiety factor, which signals the long-term status of the body's energy reserve to the central nervous system, may constitute the genetic lesion, resulting in a high set-point weight in some obese persons. This hypothesis is encouraging in that it implies a discrete defect that should be approachable through the techniques of molecular biology. The discouraging news, however, is that energy-restricted diets are a physiologically unsound means to achieve weight reduction. Energy restriction calls into play strong counterregulatory responses both in appetite and energy expenditure that almost invariably act to restore a reduced-obese person to his or her set-point weight. Exercise as a primary approach to weight loss may circumvent this counterregulatory response to some degree, while conferring other important health benefits.

The health hazards of moderate obesity may have been overstated to the American public. The mortality risk ratios of 1.1 to 1.2 that accompany BMI values in the 30- to 35-kg-per-m^2 range probably do not justify the widespread application of a therapy as ineffective and likely to cause adverse physical and psychological effects as the energy-restricted diet. To a large degree, obesity confers an enhanced risk for CHD through the associated risk factors of hypertension, diabetes mellitus, hyperlipidemia, and possibly hyperinsulinemia. Any significantly increased CHD risk conferred independently by obesity appears to be restricted to younger centrally obese persons.

Until a more detailed understanding of the physiology of body weight regulation is attained, several guidelines for the management of obesity seem justified:

- Target therapeutic efforts to younger patients with elevated waist-to-hip ratios (>0.95 in men, >0.85 in women).
- Dietary instruction should emphasize correct food choices as equal in importance to caloric restriction. Keep dietary weight loss goals moderate.
- Emphasize regular exercise in the therapeutic program for obese persons.
- Do not withhold pharmacologic therapy for the obesity-related disorders of hypertension, hyperglycemia, and hyperlipidemia in the face of unrealistic expectations for sustained weight loss.

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