Pathophysiology of obesity[1,2]

George A Bray

ABSTRACT Individuals weighing > 100 kg represent a small fraction of the population and yet pose a major health risk to themselves. It is proposed that individuals be classified according to their body mass index (BMI). Class 0 individuals have a BMI of 20–25 kg/m^2 and are not obese; Class I individuals have a BMI of 25–30 kg/m^2 and are at low risk from their obesity; Class II individuals have a BMI of 30–35 kg/m^2 and have moderate risk; Class III individuals have a BMI of 35–40 kg/m^2 and have high risk associated with their obesity; Class IV individuals have a BMI of > 40 kg/m^2 and are at very high risk for illness. Class IV is the primary group for surgical consideration. The pathophysiologic consequences of excess weight result in large part from increased food intake and/or decreased physical activity. Individuals in Class IV have additional problems related to their weight, including cardiomyopathy, Pickwickian/sleep apnea syndrome, pituitary/gonadal dysfunction, acanthosis nigricans, and significant osteoarthritis. *Am J Clin Nutr* 1992;55:488S–94S.

KEY WORDS Risk, classification of obesity, body mass index

Introduction

Individuals weighing > 150 kg are a small subset of the adult American population (1, 2). Data from the National Center for Health Statistics (NCHS) are plotted in **Figure 1** and show that such individuals represent < 0.1% of the population, ie, those weighing < 110 kg (240 lb) comprise 99.9% of the population. We thus have little information about such individuals from census tract studies because too few are included in any of the studies by the NCHS. It is recommended that in future studies, the NCHS overrepresent this group in their sample.

Several terms have been used to describe this top 0.1% of the weight group (1). The surgeons have frequently used the term morbid obesity to define a group of people in whom medical complications justify surgical intervention. This group has also been called corpulent, jumbo, extreme, massive, malignant, gross, or super obese. Many of these same individuals have what may be described as progressive obesity, a syndrome in which individuals exceeding 150 kg by age 30 have an increment in weight gain that is relatively constant from year to year (2). Individuals who gain on average slightly > 4.5 kg/y (10 lb/y) year after year weigh > 140 kg (300 lb) by the age of 30 when the incidence of untoward complications associated with this progressive form of obesity increases. It is this group who will be the major focus of this paper.

Evaluation and classification of obesity

Evaluation of body fat and its distribution

Accurate measurement of body fat requires sophisticated techniques (**Table 1**) that are often expensive and require special equipment (3–5). These techniques include measurements of body density; determination of water by isotopic or chemical dilution measurement of total body conductivity or bioelectric impedance, the measurement of the naturally occurring isotope of potassium (^{40}K); and the determination of specific body components with neutron activation or dual-photon (or x-ray) absorptiometry. The assessment of regional fat and its distribution can be done by computed tomography or nuclear magnetic resonance imaging.

Careful measurement of height and weight is currently the initial step in the clinical assessment of overweight. Overweight, as distinct from an increase in percent fat called obesity, has frequently been defined in relation to tables of desirable weight, which have generally been prepared by life insurance companies. The Diet and Health report has provided a critique of this approach (6). A better approach to defining healthy or good weight ranges is to use weights that are associated with the most favorable mortality experience (6). **Table 2** is a list of good or healthy body weights adapted from the Dietary Guidelines (7).

The degree of overweight can be expressed in several ways, but the most useful is the body mass index (BMI). This index is the body weight in kilograms divided by the square of the height in meters [wt/(ht)^2] and can be obtained from the nomogram in **Figure 2** (8, 9). Good weight is defined as a BMI between 19 and 25 kg/m^2 for men and women between 19 and 34 y and 21–27 kg/m^2 for those over 35 y (Table 2). Overweight is a BMI of 25 or 27–30 kg/m^2 and is associated with low risk. A BMI > 30 kg/m^2 is almost always associated with an increase in body fat and is synonymous with obesity, except in body builders and other athletes.

The terms described above to label the top 0.1% of overweight individuals have pejorative connotations. Some individuals with a BMI > 40 kg/m^2 are not morbid in the sense of being deathly ill nor do they have progressive obesity. Likewise, the terms gross and superobese are unflattering, unkind terms. Massive and severe obesity are somewhat less jarring to the ear, but are similarly pejorative.

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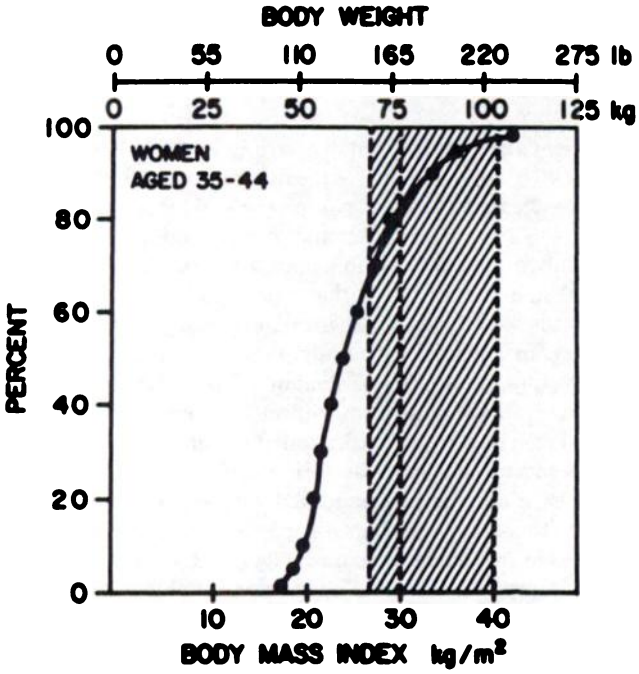

FIG 1. Cumulative percentage body weight. By using NCHS data, the cumulative percentage of weight for various categories of BMI is plotted. Less than 0.1% are > 110 kg (232 lb).

As an alternative to pejorative terms to describe obesity, I would propose that the BMI be used to classify obese individuals. This classification is shown in **Table 3**. BMI is used to divide weight categories from 20 kg/m^2 to > 40 kg/m^2 into subgroups of five BMI units. Following the American Heart Association, the use of Classes 0, I, II, III, and IV has been proposed (10–12), although the alternative European system of grades 0, 1, 2, and 3 could also be used (13).

The relative risk associated with this grouping by BMI is shown below (**Fig 3**). Such a system for classification avoids the pejorative connotations of all of the secondary terms described above. It also provides a way of providing a risk assessment associated with obesity. I would thus suggest that we replace morbid, severe, and extreme obesity by Class IV obesity, meaning individuals with a BMI > 40 kg/m^2.

Regional fat distribution

Localized distribution of fat can be evaluated by measuring skinfold thicknesses on the trunk and extremities, by measuring the circumference of the abdomen (waist) and the circumference of the hips and taking the ratio, the waist-to-hip ratio (WHR), or with computed tomography or nuclear magnetic resonance imaging (3). The abdominal or waist circumference is measured with a flexible tape placed in a horizontal plane at the level of the natural waist line or narrowest part of the torso as seen from the anterior view. The hip circumference is measured in the horizontal plane at the level of maximal circumference, including the maximum extension of the buttocks posteriorly.

It has long been noted that people differ with respect to the location of fat (14). Men tend to have more abdominal fat, giving them the android or male pattern of fat distribution. Women, on the other hand, tend to have greater amounts of gluteal fat and thus have larger hip circumferences, giving them the so-called gynoid or female pattern of fat distribution. The relative preponderance of one pattern or the other may be expressed by the abdominal-gluteal, android-gynoid, or waist-to-hip ratio. The relationship of WHRs to overall risk is shown in **Figure 4**.

The major complications of obesity, including cardiovascular disease, diabetes mellitus, hypertension, and hyperlipidemia are associated with increased abdominal fat (14, 15). Although this fat distribution pattern is more common in men, both men and women show increased risk of heart disease with greater abdominal fat. Men may be considered at increased risk if the WHR is > 0.95 and women if the WHR is > 0.80.

TABLE 1
Techniques for estimating body fat and its distribution

	Cost*	Ease of use	Accuracy	Regional fat
Height and weight	$	Easy	High	No
Skinfold thickness measurements	$	Easy	Low	Yes
Circumferences	$	Easy	Moderate	Yes
Density				
Immersion	$$	Moderate	High	No
Plethysmograph	$$$	Difficult	High	No
Water				
^3H_2O	$$	Moderate	High	No
D_2O or $^{18}O\ H_2$	$$	Moderate	High	No
Potassium (^{40}K)	$$$	Difficult	High	No
Conductivity (TOBEC)	$$$	Moderate	Moderate	No
Impedance	$$	Easy	Moderate	No
Fat-soluble gas	$$	Difficult	High	No
Neutron activation	$$$$	Difficult	High	No
Computed tomography	$$$$	Difficult	High	Yes
Ultrasound	$$$	Moderate	Moderate	Yes
Magnetic resonance	$$$$	Difficult	High	Yes
Dual Photon (or x ray) absorptiometry	$$$	Moderate	High	No

* $, low cost; $$, moderate cost; $$$ = high cost; $$$$, very high cost.

TABLE 2
Good body weights for adults*

Height†	19–34 y Average	19–34 y Range	Over 35 y Average	Over 35 y Range
In pounds				
5'0"	112	97–128	123	108–138
5'1"	116	101–132	127	111–143
5'2"	120	104–137	131	115–148
5'3"	124	107–141	135	119–152
5'4"	128	111–146	140	122–157
5'5"	132	114–150	144	126–162
5'6"	136	118–155	148	130–167
5'7"	140	121–160	153	134–172
5'8"	144	125–164	158	138–178
5'9"	149	129–169	162	142–183
5'10"	153	132–174	167	146–188
5'11"	157	136–179	172	151–194
6'0"	162	140–184	177	155–199
6'1"	166	144–189	182	159–205
6'2"	171	148–195	187	164–210
6'3"	176	152–200	192	168–216
6'4"	180	156–205	197	173–222
6'5"	185	160–211	202	177–228
6'6"	190	164–216	208	182–234
In kilograms				
152	51	44–58	55	49–62
155	53	46–60	58	50–65
157	54	47–62	59	52–67
160	56	49–64	61	54–69
163	58	51–66	64	56–72
165	60	52–68	65	57–74
168	62	54–71	68	59–76
170	64	55–72	69	61–78
173	66	57–75	72	63–81
175	67	58–77	74	64–83
178	70	60–79	76	67–86
180	71	62–81	78	68–88
183	74	64–84	80	70–90
185	75	65–86	82	72–92
188	78	67–88	85	74–95
191	80	69–91	88	77–99
193	82	71–93	89	78–101
196	85	73–96	92	81–104
198	86	75–98	94	82–106
BMI (kg/m^2)	22	19–25	24	21–27

* Without clothes. Derived from National Research Council, 1989.
† Without shoes.

Fat cell size and number

The number and size of fat cells can be measured on a sample of adipose tissue obtained by needle biopsy, although this is not a common clinical procedure. A presumptive diagnosis of hypercellular obesity may be made on clinical grounds when the individual is > 75% above the desirable weight (BMI ~35 kg/m^2) (16, 17). On the other hand, when the onset of obesity is during adult years or during pregnancy, it often involves mainly enlargement of adipose tissue cells with lipid. This type of obesity is referred to as hypertrophic obesity and tends to correlate with an abdominal or android fat distribution. Obesity with enlarged fat cells is often associated with metabolic disorders such as glucose intolerance, hyperlipidemia, hypertension, and coronary artery disease.

Complicating factors

A patient's age is important in determining the risk from obesity. Age 40 is a dividing line, as the risk for a comparable degree of obesity seems to be greater in people < 40 y of age than in those > 40 y of age (2). Duration of obesity and its progression are also important and may influence the associated risks. Longitudinal studies have shown that weight gain confers a greater risk of cardiovascular disease than an unchanging level of obesity (6). Thus, an attempt at determination of the age of onset of obesity is important in the evaluation of an obese patient. Sex is another variable with great impact on the development of obesity. From puberty onward, women are fatter than men, and women tend to gain more fat during adult life than men. Yet women have a lower risk associated with any degree of extra body fat. This may be explained partly by differences in fat distribution. In one study an extra 20 kg of fat was needed by a woman to produce the same impairment in glucose tolerance or blood pressure as in a man.

Functional associations

Detection and description of the functional impairments associated with obesity is important from both a clinical and prog-

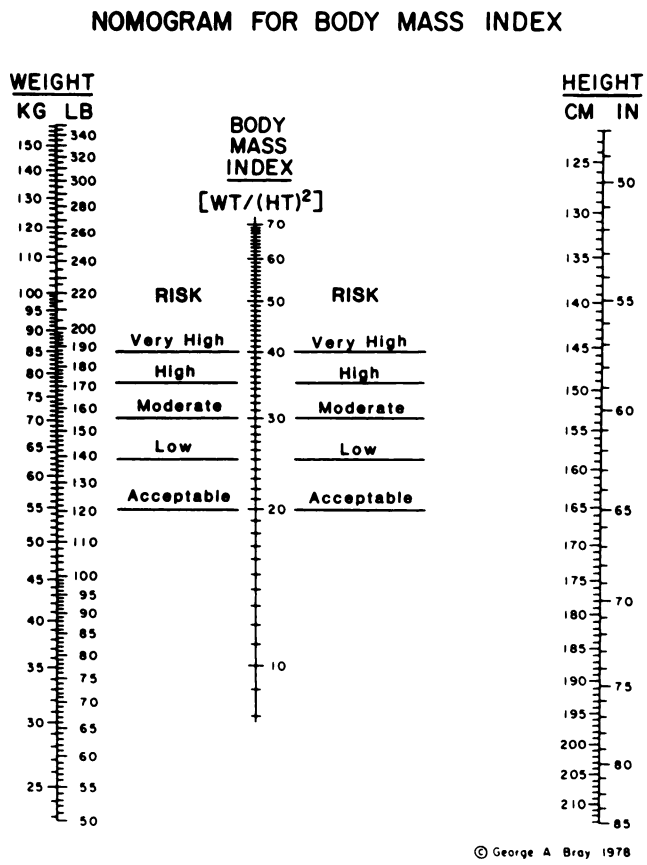

FIG 2. Nomogram for determining BMI. Lay a straightedge across between weight and height. The point where it crosses the BMI line is the BMI in metric units (kg/m^2) (Copyright 1978 George A Bray, MD; reproduced with permission).

TABLE 3
Proposed classification of obesity

BMI (kg/m²)	20–25	25–30	30–35	35–40	>40
Class	0	I	II	III	IV
Grade	0	1	2	2	3
Risk	Very low	Low	Moderate	High	Very high
Fat cell no.*	Normal	Normal	Normal or ↑	↑	↑

* ↑, increased.

nostic point of view. It is well established that obese individuals have an increased frequency of high blood pressure, diabetes mellitus, and coronary artery disease (14). It is important to delineate the presence of any cardiac risk factors such as hypertension, hyperlipidemia, glucose intolerance, and cigarette smoking. If history warrants, evaluation of the gall bladder by ultrasound or oral cholecystography and measurement of pulmonary function may be performed. Menstrual disorders, including irregular bleeding and amenorrhea, are common among obese females. Although some studies have shown that obesity is associated with osteoarthritis, others have not and the role of excess body weight in the etiology of this condition remains controversial. Finally, obese people have been found to suffer from psychological and social problems and these should be identified. Body image may be severely distorted in people with childhood-onset obesity and obese people may be discriminated against in school and the workplace. A prospective study from

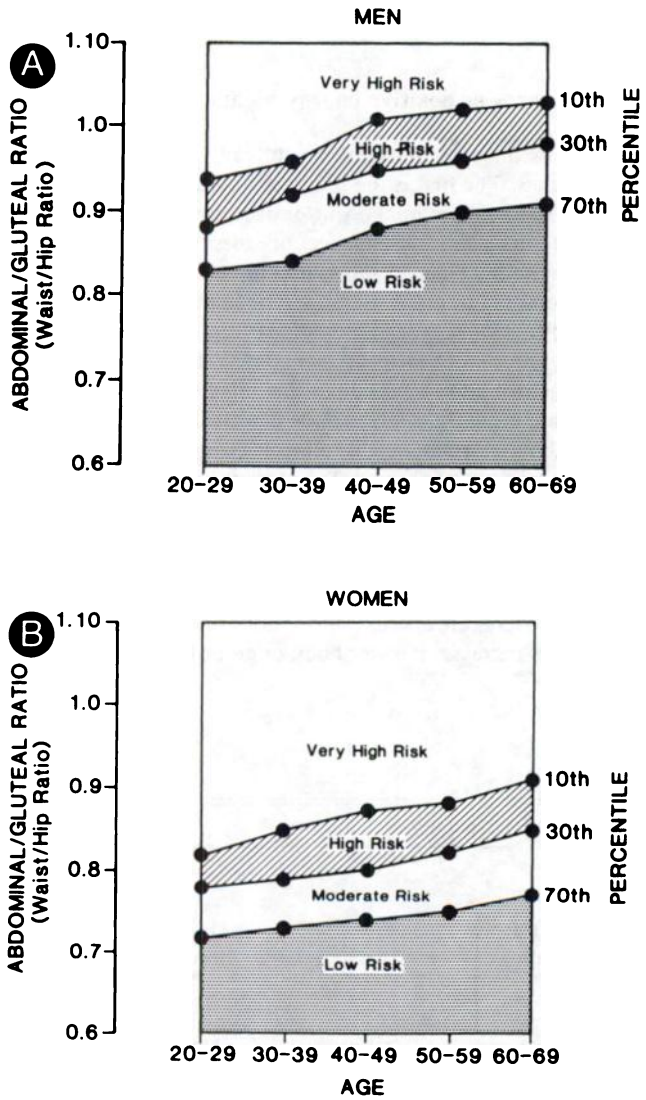

FIG 3. Distribution of waist-to-hip circumference ratios. This data is adapted from the Canadian Fitness survey. The estimates of risk are those of the author. A men; B women (copyright 1988 George A Bray, MD; reproduced with permission).

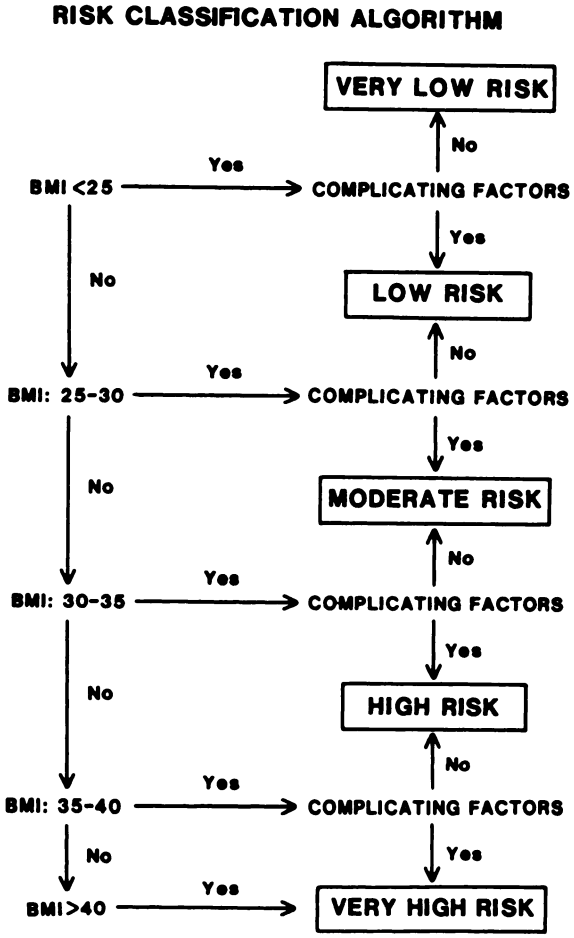

FIG 4. Risk assessment algorithm. After measuring the BMI, the individual risk is increased or decreased based on the presence of complicating factors. These would be age under 40, a high WHR (> 0.95 for men; > 0.80 for women), and male. (Copyright 1988 George A Bray, MD; reproduced with permission).

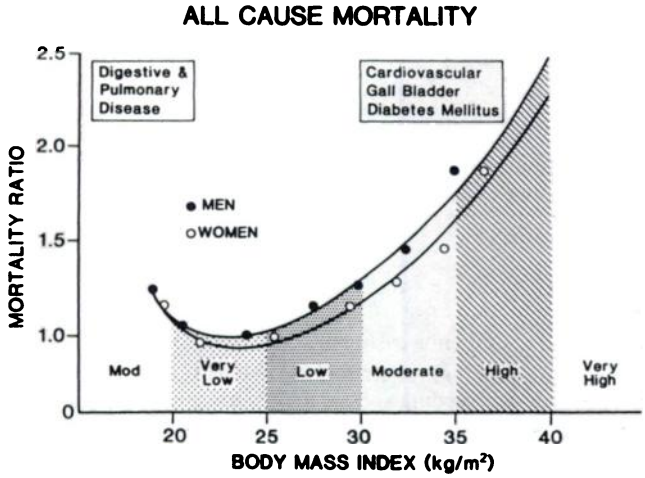

FIG 5. Relationship of BMI to risk. The curvilinear plot is based on data adapted from the American Cancer Society study. As BMI increases the excess risk rises. A healthy or good body weight range is between 19 and 27 kg/m^2.

Denmark showed that obese military recruits attained much lower social class status than lean recruits after an average 12.5 y of follow-up (18). Therefore, it is important to find out about these functional impairments and to measure blood pressure, blood cholesterol and triglyceride concentrations, and blood glucose.

Algorithm

Two algorithms are available to guide assessment of the obese patient (5, 19). The first can guide the selection of test procedures for the overweight patient (19). Once the workup for etiologic and complicating factors is complete, BMI, body fat distribution, sex, and age are noted and the physician is referred to the algorithm in **Figure 5** for risk classification (15). Those with BMIs between 25 and 30 kg/m^2 are placed in the low-risk class unless they have android obesity (WHR > 0.95 for males and WHR > 0.80 for females), are < 40 y old, have medical complications, or are male. These patients are placed in the moderate-risk class along with those who have a BMI between 30 and 35 kg/m^2. Patients with BMIs between 35 and 40 kg/m^2 are also placed in the moderate-risk class unless they have any of the above mentioned complicating factors. In this case they are placed in the high-risk class along with those who have a BMI > 40 kg/m^2. Because of increasing complications from obesity, more aggressive efforts at therapy should be directed at members of each successively higher risk classification. Based on this assessment of risk, a rational approach to treatment is presented in **Table 4** (10).

Pathophysiology of obesity

A curvilinear relationship between BMI and medical complications is well known (Fig 5) (2, 20, 21). The association of obesity with increased mortality, increased heart disease, increased risks of diabetes mellitus, and increased risk of gall bladder disease have been clearly described (10, 20, 21). These relative risks range from 2 to 8 when the BMI exceeds 35–40 kg/m^2. This contrasts with the low risk to health of weight in the healthy, or good weight category, which is a BMI of 19–27 kg/m^2.

Consequences of positive energy balance

The consequences of excess weight can be presented under two headings. The first is the series of consequences associated with increased caloric intake and/or decreased physical activity and the second is the consequences of excess weight on a variety of organ systems. **Figure 6** shows that increased food intake can affect several major organ systems. The first is the effect on the storage of triacylglycerol in the adipose organ. As body weight increases, the size of fat cells increases. When the maximum size is reached, additional adipocytes must be recruited to accommodate more triacylglycerol. When BMI exceeds 35 kg/m^2 or 75% above normal weight, almost all individuals have the hypercellular form of obesity. One consequence of hypercellular obesity is an increase in lipoprotein lipase, which increases linearly as a function of the increase in BMI up to 50 kg/m^2. The deposition of triacylglycerol in subcutaneous or visceral depots is influenced by a number of factors. Increasing abdominal or visceral fat depots are affected by corticosteroids and sympathetic activity. An increase in lower body or gluteal fat depots is pro-

TABLE 4
A risk-benefit classification of obesity

			A classification relating risk to treatment*				
			Diet				
Class	Grade	BMI	840–3360 kJ/d (200–800 kcal/d)	>3360 kJ/d (>800 kcal/d)	Exercise	Drug therapy	Surgery
		kg/m²					
0	0	20–25.9	3	1	1	NA	NA
I	1	25–29.9	2	1	1	3	NA
II	2	30–34.9	1	1–2	2	2	NA
III	3	35–39.9	1	2	3	2	3
IV	3	>40	1	3	3	1	1

* 1, first choice; 2, second choice; 3, third choice in the author's list of preferences; NA, not applicable. Caloric intake is expressed in kcal/d.

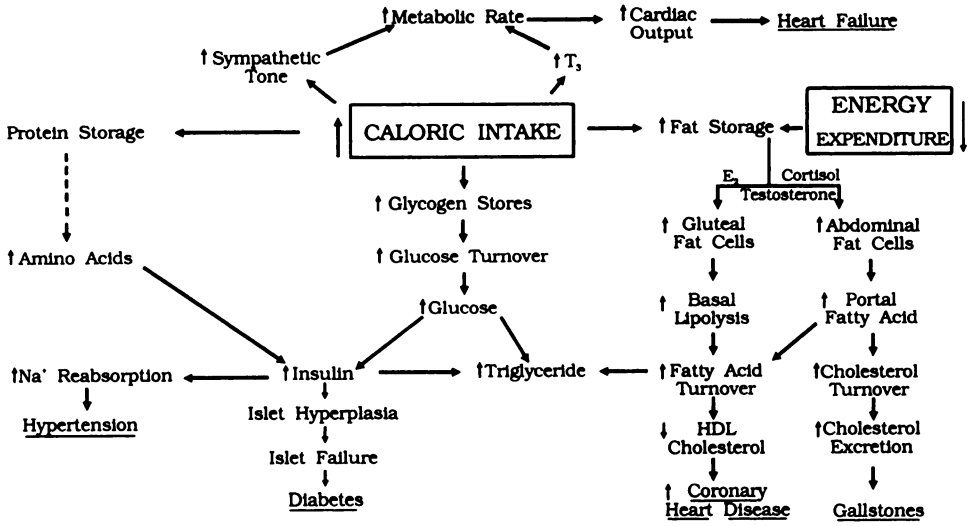

FIG 6. Consequences of increased food intake or reduced physical activity. The effects of increasing food intake and/or decreasing physical activity on the adipose tissue organ, on carbohydrate metabolism, the metabolism of protein and amino acids, and the control of metabolism through thyroid hormone and the sympathetic nervous system are shown.

moted by low concentrations of cortisol and high concentrations of estradiol relative to testosterone. The increase in triglyceride stores is associated with a linear increase in the production of cholesterol. Increased cholesterol production is in turn associated with increased cholesterol secretion in bile and an increased risk of gallstone formation and the development of gall bladder disease (2).

Increased levels of circulating triacylglycerol in obesity are associated with decreased concentrations of high-density-lipoprotein (HDL) cholesterol. The decreased HDL cholesterol and the increased work on the heart associated with supplying blood to peripheral organs may account for the increased risks for cardiovascular disease and heart attack in obese patients.

Weight gain is associated with an increase in insulin concentration, demanding increased insulin secretion from the pancreas. The enhanced insulin resistance and increased insulin demand may lead to pancreatic failure and diabetes mellitus in individuals who are at risk for pancreatic islet insufficiency. Similarly, hyperinsulinemia may be important in the sodium retention and hypertension associated with obesity. Increased insulin secretion may also result in part from the altered amino acid metabolism associated with obesity and weight gain. Several of the amino acids that are increased in obesity are those that enhance insulin secretion.

Finally, increased food intake and obesity may be associated with altered control of energy metabolism. Increased T_3 production from thyroxin is associated with the increased food intake of obesity. Similarly, the sympathetic nervous system may be altered by obesity and this along with the hyperinsulinemia may play a role in the increased risk of hypertension in this syndrome.

Consequences of excess weight

Excess body weight may carry its own consequences (22). The presence of Class IV obesity has long been known to be associated with an increased risk of sudden death. This observation was initially made by Hippocrates more than 2000 years ago (23) and it has been confirmed in numerous epidemiologic studies, including the Framingham and the Wadsworth Veterans Administration study. In the Wadsworth study, Drenick et al (24) noted sudden death to be increased 13-fold.

Class IV obesity is also associated with a number of pathophysiologic consequences, which are summarized in **Table 5**. Cardiomegaly with cardiomyopathy has been associated with extremes of overweight in a number of studies (25). Whether the increased requirements for circulation of the blood are sufficient to explain this or whether it reflects other components of the changes shown in Table 5 remains for future research. The Pickwickian syndrome with alveolar hypoventilation, plethora, and somnolence usually reflects the combination of Class IV obesity and sleep apnea (26). Because of the pulmonary hypertension associated with the hypoxemia, these patients can require acute hospitalization for respiratory or cardiac failure. In women, Class III and IV obesity are sometimes associated with hirsutism, which disappears when excess weight is lost. In men, Class IV obesity is associated with a lower concentration of sex-hormone–binding globulin and with a reduction below normal in the level of free testosterone (27). Acanthosis nigricans, blackening of the creases in the neck and skin over the extensor surfaces is seen in some individuals with Class IV obesity. Finally, the extra

TABLE 5
Pathophysiologic conditions related to body weight

1. Sudden death
2. Cardiomyopathy
3. Pickwickian/sleep apnea syndrome
4. Pituitary/gonadal dysfunction
5. Acanthosis nigricans
6. Osteoarthritis

weight poses serious problems on the joints with higher frequency of osteoarthritis (10).

Conclusions

Class IV obesity, defined as a BMI > 40 kg/m^2, is recommended as preferable to such pejorative terms as extreme, severe, massive, gross, super, progressive, malignant, or morbid obesity. It is recommended that the NCHS oversample individuals with a BMI > 35 kg/m^2 to provide a better epidemiologic picture of these individuals. Most pathologic changes in individuals with Class IV obesity result from a relative increase in food intake or decrease in physical activity. These have been identified by using a flow diagram. Some problems such as cardiomyopathy, obstructive sleep apnea, sudden death, hypogonadism, hirsutism, acanthosis nigricans, and osteoarthritis, however, may be related to the weight level per se of individuals in Class IV. More research into the pathophysiologic mechanisms and their treatment is needed to provide a coherent picture of Class IV obesity.

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