Obesity:
Fat Cells — Not Fat People
New Therapeutic Goals

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AMONG AFFLUENT technically developed societies, an abundance of high caloric foods is conveniently available in tempting variety. This circumstance, coupled with a wide proliferation of labor-saving devices, has resulted in progressive increases in the endogenous storage depots of fat among greater numbers of children as well as adults. Practical methods to assess the degree of "fatness" among these patients have generally been less than satisfactory. Direct techniques to estimate lean body mass and total body fat are not convenient enough for routine clinical use. Accordingly, physicians have tended to rely on indirect measurements such as skin-fold thickness,[1] various indices of body weight[2,3] or, more commonly, biodata tables published by insurance companies.[4]

With this last criterion, current estimates suggest that as much as 30 percent of the United States population exceeds what is termed ideal weight* by 20 percent or more[5]—the relative weight generally accepted as defining obesity.[6]

Unfortunately, these direct or indirect methods fail to estimate the total number of adipose cells within which total body fat is distributed. Because metabolic abnormalities such as insulin resistance, hyperlipidemia and hyperglycemia correlate primarily with the enlargement of adipose cells rather than with their number or total body fat,[7,8] valid reasons exist for reevaluating the definition of

obesity. In this article an attempt is made to redefine obesity on the basis of new information concerning developmental, structural and physiological characteristics of the adipose organ as well as upon data relating to epidemiological aspects of its relation to coronary risk. Evidence will be reviewed refuting the prevailing general definition of obesity as an excessive amount of total body fat and supporting a more precise definition of obesity as *an excessive amount of fat per adipose cell.*

The Adipose Cell Theory
Evidence for Two Major Forms of the Obesity Syndrome

The concept of two major forms of clinical obesity is based on the following reported observations of Hirsch and co-workers[9,10] and Björntorp and co-workers.[11,12]

Normal Adiposity

The number of adipose cells in adults is constant whether weight increases[13] or decreases.[9] Patients of normal insurance-table weight average about 26×10^9 cells, which contain about 25 to 35 pounds of total body fat. For example, a normal man with a height of 68 inches would weigh approximately 68 kg (150 pounds), of which 54.4 kg (120 pounds) is the lean body mass and 13.6 kg (30 pounds) consists of fat (Figure 1). Since 13.6 kg represents approximately 14×10^9 μg, the average quantity of fat per cell is, therefore, approximately 0.6 μg per cell.

Hypertrophic Obesity

Patients with adult-onset obesity have the normal fixed number of fat cells. Therefore, the extra 13.6 or 27.2 kg (30 or 60 pounds) of fat is dis-
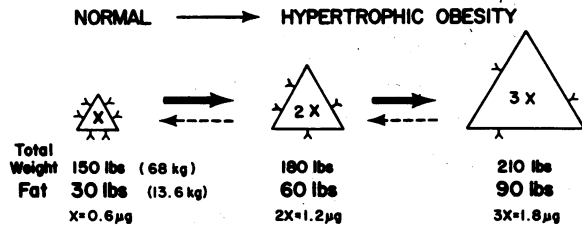
Figure 1.—Characteristics of normal and hypertrophic adipocytes. >——— represents insulin receptors on cell membrane; X represents the average triglyceride content of the normal fat cell.

tributed within their 26×10^9 cells, resulting in enlarged or hypertrophied cells containing an average of 1.2 μg or 1.8 μg of fat per cell, respectively (Figure 1).

Hyperplastic-Hypertrophic Obesity

During childhood, all cells of the body, including the adipose tissue, are able to grow in number as well as size. Adults whose obesity developed in childhood are observed to have an increased number of fat cells as well as increased fat per cell. Indeed, they are reported to have two to four times the normal number of adipose cells with each averaging two or three times the normal fat content.[8,10] Consequently, instead of a normal amount of total body fat (13.6 kg, 30 pounds), they have from 54.4 to 122.4 kg (120 to 270 pounds) of fat, making a total body weight of 108.8 to 176.9 kg (240 to 390 pounds). This type of obesity is characterized as mixed hyperplastic-hypertrophic (see Figure 2).

Fat-Cell Weight Versus Insurance-Table Weight

When a hypertrophic adult-onset obese person reduces to normal fat-cell weight of approximately 0.6 μg per cell, he has also reached the normal insurance-table weight since the number of fat cells in adult-onset obese patients is normal. In contrast, when the hyperplastic-hypertrophic obese patient decreases his weight during inpatient caloric deprivation or after a jejunal-ileal bypass operation, the amount of fat per cell would reach normal quantities long before insurance-table weight is achieved. Therefore, when the patient has reduced to 81.6 kg (180 pounds), the 27.2 kg (60 pounds) of total body fat is distributed within twice the normal number of cells so that there is pure hyperplasia of the adipose tissue without hypertrophy (Figure 2). At this point, despite
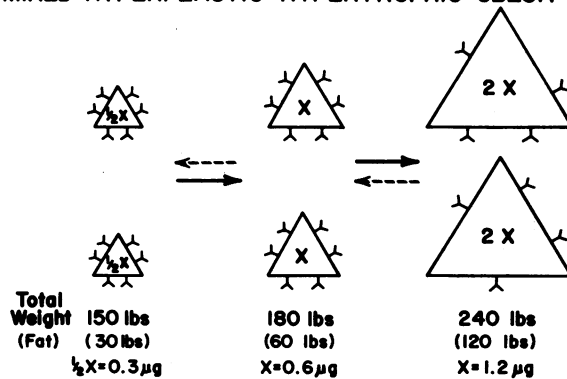

Figure 2.—Comparison of adipocytes in mixed hyperplastic-hypertrophic obesity at various levels of body weight (see Figure 1 for symbols).

total body fat being twice normal and insurance tables depicting a weight reaching 20 percent over the "ideal," the patient should not be considered pathologically obese because the amount of fat per adipose cell is normal and correlations with metabolic dysfunction have not been found when cell size is normal.[7,8]

Technical difficulty in obtaining adequate biopsy specimens of fat tissue from undernourished patients has resulted in inadequate data among thin patients. While all thin patients have reduced total body fat by definition, the adipose cell theory implies that adult-onset thinness would consist of the normal number of cells with hypotrophic adipocytes (for example, in anorexia nervosa developing after the age of 20). In contrast, undernourished children would have hypoplastic adipose tissue that could conceivably contain either normal quantities of triglyceride (if the undernourishment is treated) or hypotrophic cells as well. Therapy directed at restoring the hypotrophic cells to normal size would, in the case of the adult-onset form, produce a normal insurance-table weight. In contrast, among the childhood-onset type with hypoplasia, correction of the hypotrophic adipocytes would occur at a weight considerably less than that depicted as normal on insurance tables.

Some Metabolic Consequences of Hypertrophic Obesity

The circulating hormone insulin is particularly responsible for promoting as well as maintaining neutral fat within adipose tissue. A number of other hormonal and neural substances modulate this storage action of insulin by mobilizing these energy depots at times of caloric need. To initiate
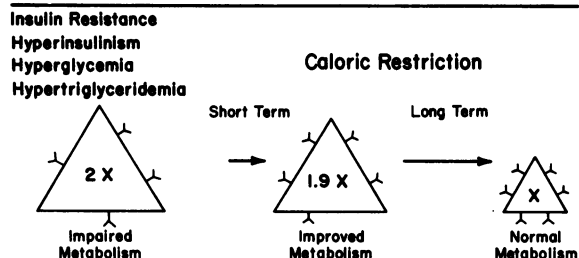
METABOLIC DYSFUNCTION OF HYPERTROPHIC OBESITY

Figure 3.—Restoration of insulin receptor concentration and correction of metabolic dysfunction in hypertrophic obesity after caloric restriction and weight reduction to normal triglyceride content of adipocytes (see Figure 1 for symbols).

its hormonal effect of clearing ingested foodstuffs from the blood and promoting and maintaining their storage, insulin binds to specific membrane receptors present on various target organs for insulin, including the adipocyte.[14,15]

Generally, obese patients are relatively insensitive to the action of insulin and require exaggerated insulin levels to clear a glucose load.[16]

Recent studies have emphasized that this insulin insensitivity and hyperinsulinism with their associated delayed clearance of glucose and triglycerides *in vivo* correlate primarily with fat-cell size rather than with either fat-cell number or total body fat.[7,8,17] Similarly, measurement of insulin-binding to receptors on the surface of adipocytes has shown there to be decreased binding only in hypertrophic adipose cells but not in normal-sized adipocytes.[15] This observation could explain those occasional patients with childhood-onset obesity in whom hyperinsulinism is minimal or absent and insulin-binding to fat cells is not decreased despite a pronounced excess of total body fat.[15,18] Fasting and postprandial hyperglycemia are quite rare in obese children, as compared with obese adults who often have mild degrees of diabetes mellitus. One protective factor in this regard may be the ability of adipocytes to replicate during childhood in response to overfeeding, thereby minimizing hypertrophic changes.

Adults with predominantly hyperplastic obesity are rare because, presumably, the stimulus to develop hyperplastic adipose tissue is associated with overfeeding, which continues to produce excess fat as adipocytes mature to the adult nonreplicating form. When hypertrophy is present, whether accompanying the normal number of cells (Figure 1) or associated with hyperplasia, a number of metabolic cardiac risk factors appear which im-

prove with caloric restriction and disappear once weight reduction corrects the hypertrophy (Figure 3).

While the exact mechanism of insulin-resistance in hypertrophic adipocytes is not clear, it appears that an overdistended fat cell may directly resist further entry of glucose and triglycerides because of intrinsic regulatory mechanisms. In addition, the associated hyperinsulinemia results in "down-regulation" of insulin receptors. Figure 3 shows the short-term effect of caloric restriction, wherein a reduced stimulation of beta cells results in reduced circulating insulin levels. This ameliorates "down-regulation" of receptors, which thereby partially restores the concentration of insulin receptors on the surface of the fat cell. With further weight reduction, the normal-sized adipocyte regains its normal responsiveness to insulin and is no longer associated with elevated levels of circulating glucose, triglycerides or insulin.[19,20]

Identifying Type of Obesity and Relevance to Prognosis

At present, techniques for accurate fat-cell sampling, cell counting and quantification of triglyceride content are complicated and seldom available clinically. In addition, numerous biopsy studies may be required to characterize fat-cell morphometry accurately in a single patient. One group has reported as much as 100 percent variation in cell size during consecutive sampling from adipose tissue in the same patients.[21] From the foregoing comments, it is obvious that a vigorous research effort to develop improved morphometric methods would be most worthwhile. Meanwhile, reliance on certain clinical features of obese patients may assist in the differentiation: Those patients with a childhood history of obesity, characteristically centrifugal in distribution, and who weigh more than 113 kg (250 pounds) are most likely to be hyperplastic-hypertrophic types;[22] those who develop more of a centripetal type of obesity, occurring after adulthood, and who weigh less than 90.7 kg (200 pounds) are less likely to be hyperplastic.[22] A clinical indicator of fat-cell hypertrophy in either obese group would be the presence of hyperinsulinism, impaired carbohydrate tolerance and hypertriglyceridemia.

From the epidemiological standpoint, risk of myocardial infarction primarily relates to metabolic consequences of obesity, such as hyperlipidemia and hyperglycemia, rather than to the obe-

sity itself.[23,24] Since these factors relate particularly to fat-cell size, this suggests a medical indication for therapy only when the fat cell is enlarged. There is no known treatment for excessive numbers of fat cells, and, if they are of normal size, they should not disturb metabolic measurements despite their association with increased total body fat. Attempts to reduce total body fat to an insurance-table norm in patients with increased numbers of adipocytes are extremely difficult, possibly because the resultant semistarved condition of individual fat cells induces compensatory forces stimulating appetite as well as reducing basal metabolic rate. Also, insulin-receptor concentration may conceivably increase to supranormal quantities in the shrunken adipocyte. All of these responses would lead toward restoring fat within the reduced fat cell. If these normal compensatory mechanisms are forcibly suppressed, physical disability and psychological depression are likely to occur, as reviewed by Stunkard and associates.[25] Their evidence included the Rockefeller University report that, after 16 weeks of inpatient dieting in ten patients with childhood-onset hyperplastic-hypertrophic obesity, severe psychological depression developed as their total body fat approached normal, but in five adult-onset obese patients there was an enriched sense of well-being when body weight was brought to normal levels.[26]

While these hyperplastic-hypertrophic patients have metabolic features of insulin resistance that clear when they reach a normal fat-cell weight, their excess of total body fat in the pure "hyperplastic" phase may continue to produce mechanical consequences such as arthritis of weight-bearing joints, breathing difficulty and greater postsurgical risk. Advantages of further weight reduction to improve these mechanical problems must be balanced against the possible psychological disadvantages and high failure rate of attempting to reduce adipocytes below their normal weight.

Redirection of Therapeutic Goals in Obesity

Therapy in obese patients is difficult enough without compounding the problem by indiscriminately grouping together two quite different clinical types. The more common hypertrophic, adult-onset obese patients generally have a more favorable prognosis for successful reduction to, and maintenance of, insurance-table ideal weight. This is in pronounced contrast to the hyperplastic-

hypertrophic patients in whom normal insurance-table weight is seldom achieved and virtually never maintained, despite repeated attempts to achieve this elusive goal.

For hyperplastic-hypertrophic patients, a more realistic aim is the elimination of their fat-cell hypertrophy to minimize the metabolic consequences of obesity, particularly hyperglycemia, hyperinsulinism and hyperlipidemia. Reduction of fat-cell numbers with present day techniques is as impossible as reducing body height or bone structure. Previous goals that did not consider cell number led to deterioration of self-concept and recurrent depression consequent to repeated futile attempts to reach and maintain a state of cellular starvation. Unfortunately, the therapy for obesity as reported in publications from university medical centers, practicing bariatricians or weight-reducing organizations has concerned itself mainly with the more conspicuous hyperplastic-hypertrophic obese patients. Presumably, their greater body mass as well as their refractoriness to weight reduction have resulted in their disproportionate concentration in these treatment centers, and the literature therefore emphasizes the high failure rate in achieving or maintaining ideal weight in obesity. As a result, the much more prevalent type of patient with adult-onset hypertrophic obesity has often been deprived of the metabolic and cardiovascular benefits of an energetic, intensive program of weight reduction because of this aura of "failure" associated with treatment of a different form of obesity.

It is hoped that awareness of the significance of adipose cell number and size will alleviate this tendency to nihilism and help redirect therapeutic goals in a more realistic and achievable manner.

Summary

Evidence exists for two distinct forms of the obesity syndrome, and enlarged "hypertrophic" adipocytes are common to both. It is their number that distinguishes each form: A normal number of fat cells characterizes adult-onset hypertrophic obesity; an increased number, the childhood-onset hyperplastic-hypertrophic type. In both, fat-cell hypertrophy accounts for the observed metabolic sequelae, including insulin insensitivity, hyperinsulinism, hypertriglyceridemia and delayed glucose clearance—all of which contribute to an increased cardiovascular risk. In those rare patients with excessive quantities of total body fat in whom

these metabolic features are normal, predominant hyperplasia is suggested.

Until improved techniques of adipocyte morphometry are available, therapeutic goals in managing obesity should be directed primarily at reducing the circulating levels of insulin, triglycerides and glucose to normal. With adult-onset hypertrophic obese patients this will coincide with attainment of normal insurance-table weight. By contrast, in hyperplastic-hypertrophic obese patients, normalization of these metabolic features occurs long before insurance-table weight is achieved.

Failure to consider these differences among patients categorized as obese based on indirect measures of total body fat has resulted in considerable frustration, unnecessary psychological despondency and a profoundly debased self-concept in patients with hyperplastic-hypertrophic obesity. An additional consequence has been the unfortunate presumption of hopelessness in treating adult-onset hypertrophic obese patients, leading to a lack of enthusiasm and motivation in both patient and therapist.

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