The Obesity Pandemic: Where Have We Been and Where Are We Going?

Jesse Roth†‡, Xiaoling Qiang†‡, Sharon Lee Marbán¶, Henry Redelt, Barbara C. Lowell†*

Abstract

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Obesity, a new pandemic, is associated with an increased risk of death, morbidity, and accelerated aging. The multiple therapeutic modalities used to promote weight loss are outlined with caution, especially for patients who are very young or old. Except for very rare single gene defects, the inheritance of obesity is complex and still poorly understood, despite active investigations. Recent advances that have shed light on the pathophysiology of obesity are the recognition that 1) excess fat is deposited in liver, muscle, and pancreatic islets; 2) fat tissue secretes a large number of active signaling molecules including leptin, adiponectin, and resistin, as well as free fatty acids; and 3) activated macrophages colonize the adipose tissue. Other candidates for key roles in the causes and consequences of obesity include 1) metabolic programming, where food acts as a developmental regulator; 2) the constellation of defects known as the "metabolic syndrome;" 3) cortisol overproduction in the adipose tissue; and especially, 4) insulin resistance. The possible etiologies of insulin resistance include cytokine excess, elevated free fatty acids, and hyperinsulinemia itself, as with transgenic overproduction of insulin in mice.

Key words: pandemic, adiposity

Introduction

Obesity has captured headlines and spurred research as its incidence and prevalence have exploded. Professionals worldwide in academia, government, and industry are devoting increasing resources and energy to combating obesity and its consequences worldwide. Despite much new data, obesity is still very mysterious, even to the experts.

Serious Consequences of Obesity

Mortality

For both men and women, there is a progressive increase in risk of death (1) as adiposity increases above normal (Figure 1). With BMI as the measure of adiposity, the graph of the increase in mortality appears to curve upward. The increase in mortality seems to be, in large part, caused by the increase of fat mass. Typically, a 20% or so increase in body weight above normal results in a 100% increase of total body fat. This has significant implications for obesity treatment, as will be discussed later.

The cause of the increase in mortality with low body weight in humans (Figure 1) is not well understood and has not been reported in experimental animals. The plateau observed in the "normal" weight range (Figure 1) suggests that there are actually two competing processes that meet to form the plateau. Also, this highlights some of the imperfections of BMI. For example, in elderly people, as fat mass increases and muscle mass decreases, the BMI underestimates adiposity. Also in the elderly, height decreases, artificially raising the BMI. There is also another interesting age effect (2). As the age of the population rises, the whole curve shifts up and to the right (2). Additionally, the excess risk imposed by obesity varies with age (Figure 2) (3). Young men (age, 25 to 34 years) with morbid obesity (BMI $>$ 40 kg/m^2) have a 10-fold excess mortality compared with their normal weight counterparts. Whereas the absolute risk for death increases with age, the excess relative risk diminishes with age, but the excess does persist even beyond age 65 years.

Accelerated Aging and Illness

Obesity markedly accelerates aging processes, especially when coupled with diabetes. Except for osteoporosis (where

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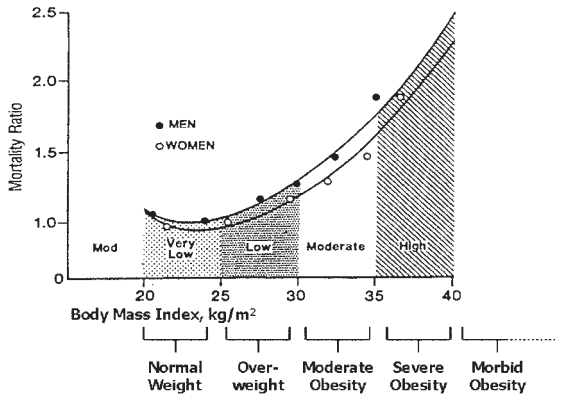

Figure 1: Risk of mortality in both men and women increases with increases in the degree of obesity. Note that the curve is J-shaped, with an upturn at the low end of BMI. At older age ranges, the J moves up and to the right. Reproduced from Bray et al. West J Med 1988;149:429–41 with permission of the BMJ Publishing Group (1).

it is protective), obesity speeds the onset, increases the prevalence, and intensifies the severity of all of the major diseases of old age (4–7).

Among the cardiovascular disorders that have been associated with obesity, which are well documented, are hypertension (8,9), myocardial infarction (10), and stroke (11,12). Hypertension, for example, occurs at almost twice the rate in obese individuals compared with normal weight men and women (13).

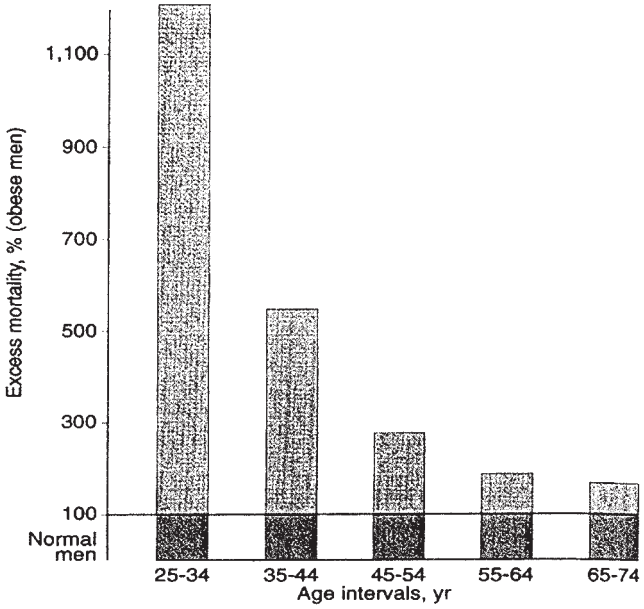

Figure 2: Excess mortality among men with morbid obesity as a function of chronological age. Adapted from Drenick et al. (3).

Type 2 diabetes is also a well-established consequence of obesity (14,15). Recent data have suggested that the frequency of type 1 diabetes is also increased by the presence of obesity (16,17). A special concern has been that the coexistence of obesity with chronic hyperglycemia, due to impaired glucose tolerance or frank diabetes (18,19), magnifies the risks related to the common forms of cardiovascular disease.

Cardiovascular risk factors and cerebrovascular disease both significantly predispose to dementia; these findings complement recent reports that hyperglycemia and obesity may also magnify the risk of dementia (19,20). When 392 Swedish nondemented elderly adults were studied for 18 years (from 70 to 88 years of age), investigators found that an elevation in BMI of one unit was associated with a 36% increase in Alzheimer's disease in women. However, this association was not seen in the men (20).

Obesity also increases the risk of cancer. This is especially true of cancers of the breast and endometrium. Traditionally, this increase in risk has been ascribed to the influence of estrogen produced in excess by the fat tissue (21,22). Recent research has indicated that many other common (non–estrogen-dependent) cancers, such as those of colon and kidney, are also more prevalent among overweight individuals (23).

Many other organ systems are affected. The hepatic steatosis ("fatty liver") associated with obesity can lead to hepatic dysfunction and cirrhosis. This disorder is now diagnosed more often, because health care practitioners have become more aware of it, and diagnostic techniques have improved (24,25). Pulmonary disorders are more common and more severe in obese individuals, particularly sleep apnea and asthma (26–28), both of which have seen an upsurge in diagnosis in recent years. Other well-recognized associations with obesity include osteoarthritis (29–31), gallstones (32), complications during and after surgery (33–36), problems with fertility, pregnancy, and delivery (37), and an increase in depression and suicide (38–40). Social acceptance, quality of life, and career trajectories are all compromised (40,41), largely because of society's discrimination against the obese.

Genetics of Obesity

Classic studies have concluded that obesity has a strong but poorly defined genetic basis. The adiposity of adopted children tracks the adiposity of their biological parents rather than their adoptive parents (42). The concordance in body weight is much greater among monozygotic than dizygotic twins; the latter have been indistinguishable from non-twin siblings (43).

Monogenic defects that cause severe obesity, first recognized in rodents several decades ago, have now been discovered in humans (44,45), but are quite rare. The list of single-gene defects that are responsible for human obesity is

growing, but only two will be presented here, those that cause leptin deficiency and melanocortin 4 receptor malfunction (44–48). Each has been associated with overeating caused by loss of an important turn-off signal. Leptin deficiency, which causes early onset of extreme obesity, should not go undiagnosed because it is highly treatable, although the treatment, daily injections of leptin, is quite expensive (44,45). Melanocortin 4 receptor mutations, the most common of the monogenic obesities, have recently been shown to be highly associated with binge-eating (46-48). With the explosion of information about the molecules that contribute to regulation of energy intake and energy expenditure (49), we can anticipate the recognition of new mutant genes associated with obesity and new syndromes. We anticipate that the new knowledge of the regulation of energy intake, metabolism, and weight maintenance from research on obesity will lead to insights not only into weight-loss disorders in young adults but also into those associated with chronic illnesses and old age.

For most patients, obesity is a complex disorder resulting from the interaction of multiple *susceptibility genes* with *environmental factors* over *time.* Progress has been made with the "candidate gene" approach, which combines shrewd guessing, good luck, and hard work. Early examples from our studies at the NIH and Johns Hopkins are mutant genes with a modest effect on obesity: those in the β_3-adrenergic receptor and in the peroxisome proliferator-activated receptor $\gamma 2$ (50–52). Positional cloning, an elegant and powerful method for elucidating single gene defects, has failed thus far to elucidate genes for common disorders with complex genetics, such as obesity and type 2 diabetes.

Epidemiology

The epidemic of obesity has become pandemic, defined as an epidemic occurring over a wide geographic area and affecting an exceptionally high proportion of the population. The obesity epidemic was first noted in the U.S. and has now spread to other industrialized nations; it is now being seen even in developing countries. First noted in adults, it has now spread to adolescents and children. Most worrisome has been the sudden emergence and rapid increase of a new medical condition, type 2 diabetes in children (53). Household pets (54) in America and wild bears that forage outside fast food establishments in the American West have also become obese (55). For the first time in the history of our planet, the number of people who are overfed has overtaken the number of the underfed (56).

We present U.S. population studies over the last 40 years to document the progressive increase in adiposity. Particularly disturbing is the very large jump in the percentage of men and women in the severely obese and morbidly obese group (Figure 3) (49,57). Studies in the U.S. by Mokdad et al. (30,58) have further shown the rapid spread and worsening of the pandemic that has spread globally (Figure 4).

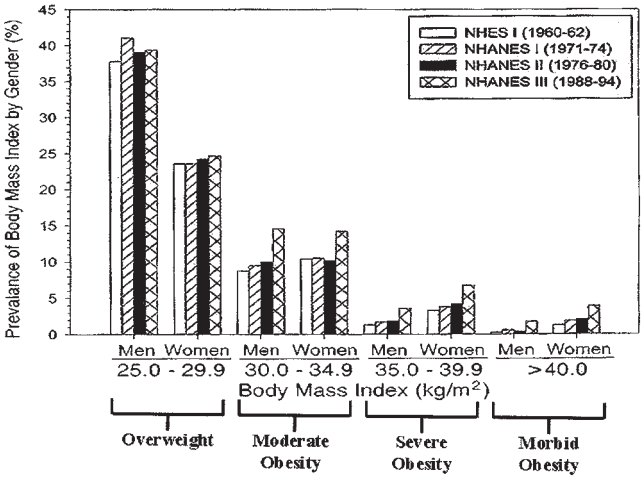

Figure 3: Comparison of four national health surveys. Notice the increase, especially in the most recent survey, in the prevalence of increased BMI in all categories of obesity, but especially with severe and morbid obesity. Adapted from Flegal et al. (57) and Dananberg et al. (49).

Pathophysiology

Fat Deposits

Concepts about fat storage have evolved over time. Older research dealt with excess weight as simply that—a person was "carrying around too much weight," which was assumed to be fat in fat cells. However, fat can be deposited elsewhere in the body, outside of the adipocytes; this is termed metastatic fat (59). The deposition of metastatic fat generally occurs when fat tissue is already heavily laden with fat. The metastatic fat deposits may compromise or damage the deposit site. Hepatic steatosis is one example (24,25), familiar to many in the food *foie gras* (literally fatty liver), prepared from the liver of an overfed goose or duck. Fat can also be deposited in muscle (60); cutting into a high-quality lean-appearing steak often results in the release of a torrent of molten fat. The β-cells of the pancreas may also accumulate fat deposits that interfere with insulin secretion (59).

With regard to fat-containing fat cells, the idea slowly developed that not all fat tissue and fat cells are identical. One shift has been from a focus on total excess weight to fat distribution, as manifest in body shape (pear vs. apple; gynoid vs. android; waist vs. hip ratios). Peripheral fat deposits are now distinguished from central deposits, subcutaneous from visceral, and "good" fat from "bad" fat (61).

Fat as a Secretory Tissue

The major advance that unites many of these diverse theories is the recognition that adipose tissue secretes

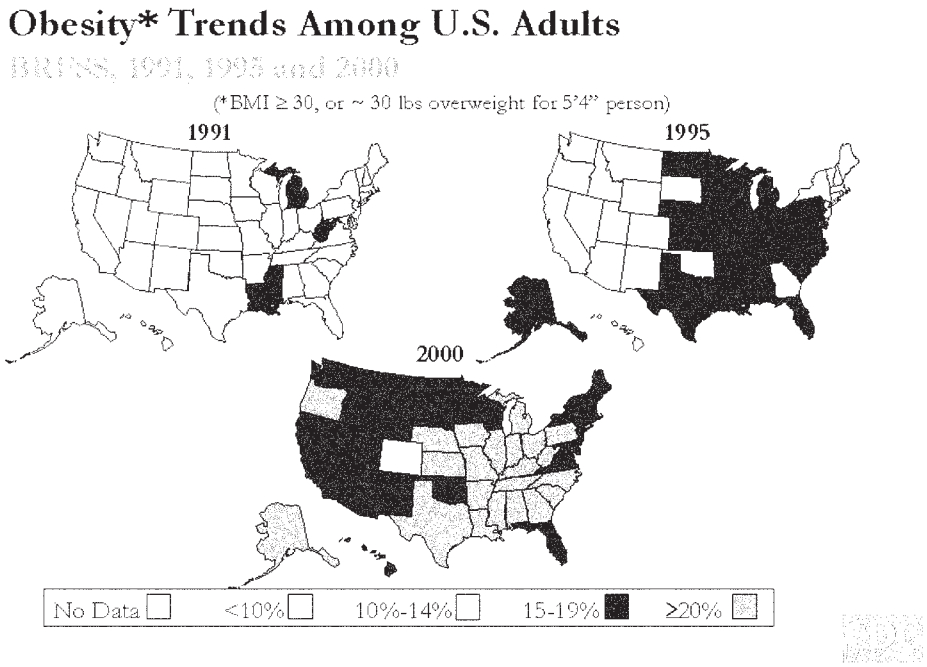

Figure 4: Increase in prevalence of obesity in the United States. Data from Mokdad et al. (30,58) and CDC Behavioral Risk Factor Surveillance System. Image modified from images available from the CDC at http://www.cdc.gov/nccdphp/dnpa/obesity/trend/maps/index.html.

a trove of signaling molecules (62). The menu of signaling molecules released (Figure 5) is the signature that determines the character of that fat depot. Fat deposits whose secretions at that moment in time support normal metabolism, e.g., acute secretion of insulin, insulin sensitivity, and enhanced glucose use, are referred to as "good" fat. Fat

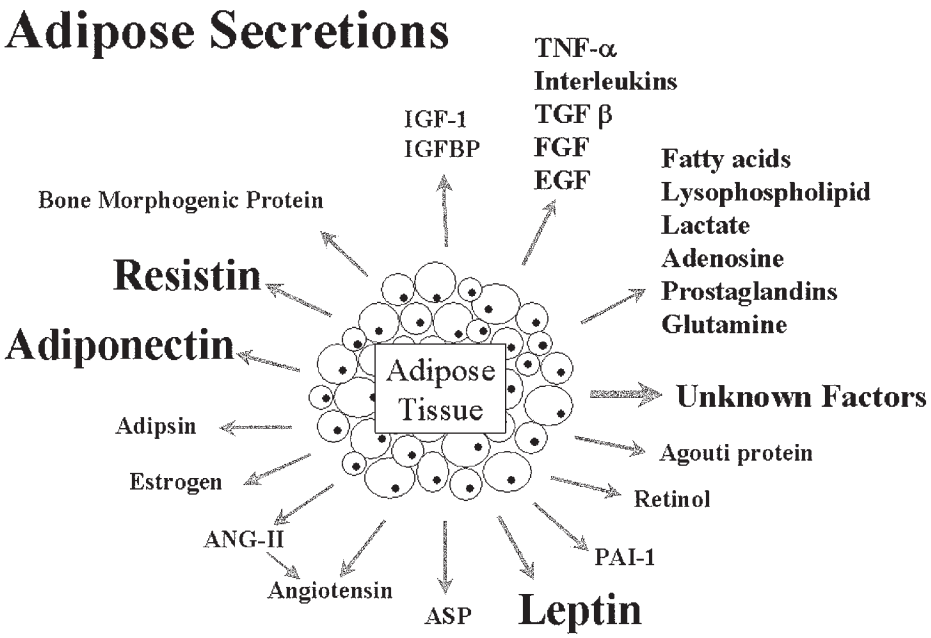

Figure 5: The secretory products of adipose tissue. Adipose tissue secretes leptin, adiponectin, and resistin, peptides that are not known to be produced elsewhere. In addition, adipose tissue is responsible for the secretion of a large number of other signaling molecules. Adipose tissue contains adipocytes and activated macrophages, which are both secretory cells (68,69). Reproduced with the permission of Dr. Steven Smith.

depots whose secretions promote the opposite are referred to as "bad" fat (61).

The concept of fat as a secretory tissue dates mostly from the discovery of leptin ~10 years ago (63). In Figure 5, the many secretions of fat tissue are catalogued. Three of the most important peptide products (49,64–66) are leptin (which regulates satiety and appetite among other processes), adiponectin (which heightens sensitivity of target cells to insulin), and resistin (which heightens resistance to insulin). All three are produced only in fat tissue, whereas many of the other adipose-derived signaling molecules are also produced in other tissues. Adiponectin has been considered to be beneficial because it improves sensitivity to insulin and promotes the disposal of glucose (64). The designation "good" fat may depend largely on how much adiponectin the fat tissue is secreting. It is still not known which secretory products define "bad" fat, but tumor necrosis factor-α (TNF-α),[1] resistin, and free fatty acids are strong candidates (67).

Macrophages in Adipose Tissue

Recently, two groups have shown that adipose tissue typically hosts macrophages that reside in clusters between the adipocytes (68,69). They have proposed that adipocyte secretions attract the macrophages as well as stimulate their maturation and activation. The density of macrophages in adipose tissue of obese humans and rodents is higher than in the fat tissue of their normal weight counterparts. It is not yet fully determined which molecules of the menu of secretions are from which cell type, but leptin and adiponectin in mice and humans are from adipocytes; resistin in mice comes from adipocytes, whereas in humans, it is a product of macrophages. One implication of this work is that the activated macrophage in fat tissue is a potential contributor to the behavior of "bad" fat and generates pro-inflammatory stimuli characteristic of obesity. Interestingly, evidence has accumulated pointing to pro-inflammatory cytokines as important contributors to insulin resistance and as mediators of pathology in obesity, diabetes, atherosclerosis, and aging (60,68,69). Multiple recent studies by us and others have shown that insulin at biologically relevant concentrations can dampen the release of cytokines (Figure 6) (70,71). Recent studies have shown that, in the *ob/ob* (leptin-deficient) mouse, known to be very insulin resistant metabolically, the secretory processes of their macrophages are "resistant" to the suppressive effects of insulin (72). Thus, it seems that insulin and pro-inflammatory cytokines intersect to regulate insulin sensitivity at iconic target cells as well as at cytokine-secreting cells of the innate immune systems (72) (in addition to effects of cytokines directly on insulin secretion).

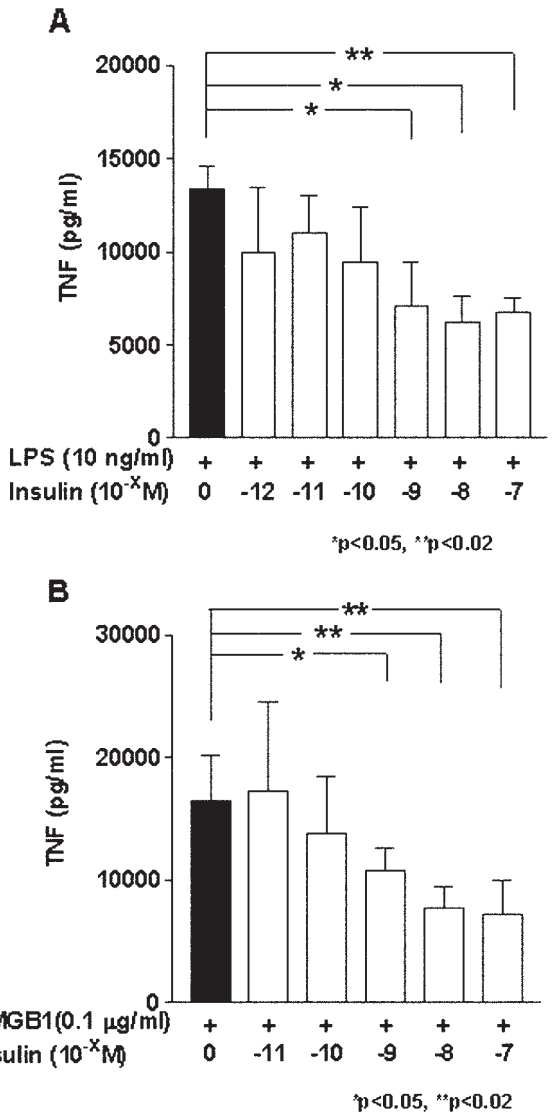

Figure 6: Insulin-mediated dampening of cytokine release. (A) Lipopolysaccharide-stimulated cytokine (TNF) release is a model of early stages of sepsis. (B) HMGB1-stimulated TNF release is a model of later stages of sepsis. In these experiments (70), mouse macrophage-like RAW cells were incubated with (A) lipopolysaccharide (10 ng/mL) or (B) HMGB1 (0.1 μg/mL) in the presence or absence of the indicated concentration of insulin for 6 hours. The TNF level in the supernatant was measured by ELISA (70). Data represent mean ± SE of three independent experiments performed in duplicate (*$p < 0.05$, **$p < 0.02$).

Free Fatty Acids as Signals

Another feature of obesity is the overabundance of free fatty acids, released from adipocytes. Plasma free fatty acids presented to the pancreatic β-cell—through intracellular metabolism (like glucose) and through newly described cell surface (G-linked) receptors (73)—enhance insulin release, which in turn, at the adipocyte, dampens lipolysis, enhances reesterification of fatty acids, and reduces plasma-free fatty

[1] Nonstandard abbreviations: TNF-α, tumor necrosis factor-α.

acids to more normal levels. Between meals, fatty acids are a major regulator of the level of basal insulin secretion (74), which in turn is a significant determinant of whole body "insulin sensitivity." Elevated levels of free fatty acids also have direct effects on metabolism in muscle and liver, again to dampen the effect of insulin (60,75,76). Thus, the hypertrophied fat mass produces an oversupply of fatty acids in blood that contributes in multiple ways to the metabolic disturbances in obesity.

Is Weight Loss Beneficial?

Because obesity is typically associated with heightened morbidity and mortality, we presume that weight loss will always ameliorate both, but studies have been inconsistent on this point (77–81). A recent study may shed light on this issue. Investigators from the Centers for Disease Control and Prevention interviewed >6000 overweight and obese individuals over 35 years of age and followed up on their vital status 9 years later (81). They found that weight loss was associated with a significant decrease in mortality rate when it was intentional, whereas unintentional weight loss was associated with a higher mortality rate, possibly because of comorbid conditions and unhealthy behavior patterns. In comparison with those who expressed no intention to lose weight, those who attempted weight loss had lower mortality, whether or not they actually lost weight. Similar conclusions have emerged from their study of 1000 overweight patients with diabetes (82). Possibly, the declared intention to lose weight is associated with other health-promoting activities, such as exercise and blood pressure control.

Management of Obesity

There is now a strong body of evidence on which the management and treatment of obesity in adults under 65 years of age can be based. Nonpharmacologic therapy (diet and exercise) should be emphasized, both for weight loss and for the retardation of the onset of diabetes (83,84). Diet and regular exercise are the linchpins of every program.

Drugs

Medications to treat hypertension, hyperlipidemia, and hyperhomocysteinemia are often very appropriate in the treatment of obese adults, as are medications for diabetes, depression, and other complications of obesity. Often diet and exercise prove to be inadequate. Polypharmacy, the use by the patient of a very large number of medications, may be unavoidable, because each of these conditions may require more than one drug. On the other hand, medications to promote weight loss per se are loaded with caveats and are recommended only in highly selected patients on an individualized basis (85).

Metformin deserves special mention. Metformin stands alone among current antidiabetic medications in that it promotes weight loss (rather than the weight gain characteristic of the others) (86–88). Some investigators have proposed that metformin be the preferred initial medication for diabetes and that it should be continued long term, even in combination with other oral agents and insulin, to minimize weight gain (87). In patients with impaired glucose tolerance, metformin also can retard the progress of the metabolic deterioration (84). Misbin (89), in a thoughtful review, has concluded that metformin is reasonably safe, provided it is used in accordance with printed guidelines and is avoided in patients who are very ill or suffering failures of major organ function. Metformin has also been recommended for weight loss in normoglycemic overweight postmenopausal women (90). Because of potential gastrointestinal side effects, experts have suggested starting initially with a minimum dose at dinner and working up to full doses by first adding more small doses with other meals (87).

Surgery

Bariatric surgery, both bypass and banding procedures, have increased in popularity (91). The results can be very favorable when there are meticulous preoperation selection and preparation, experienced surgeons, and attentive postoperation follow-up in both the short and long term. The surgical procedure typically shrinks the functioning volume of the stomach and creates some malabsorption. In addition, bariatric procedures may reduce circulating levels of ghrelin, a hunger-generating hormone produced in the stomach (91). More multicenter trials are very much needed.

Weight Loss in the Old and Young

For children and for the elderly, especially, there is a need for much more research on how to treat obesity. Whereas aggressive diets, such as the Atkins diet (92) and South Beach diet (93), are being used successfully and so far are probably safe in younger adult patients, we need to proceed cautiously in children and in the elderly. The traditional mantra for geriatricians with regard to treatment for the elderly, "start low, go slow," has an updated version, "start low, go slow, BUT GO." This is probably also the best advice regarding weight loss in the elderly obese patient (and probably for children as well). The flashing lights signaling caution are even more necessary for weight-loss medications (94–97) and for bariatric surgery in patients <21 or >65 years of age (98,99). In planning a weight-loss program for an obese elderly patient, recall that aging brings a diminution in the proportion of muscle tissue and an increase in body fat—the typical older patient has more adiposity for a given BMI. This may be partially offset because the height decreases seen with aging can produce an artificial increase in BMI, independent of any change in adiposity (2).

Achievable Goals

Some benefits of reduced intake of calories (and increased exercise) begin very quickly, even before any discernible loss of weight. Substantial benefits accrue with a modest exercise program and a 5% to 10% weight loss (84). Other interventions that improve blood pressure, plasma lipids, blood level of homocysteine, depressed mood, and sleep apnea can each ameliorate the risks associated with obesity. Often the improvements act synergistically to achieve a greater reduction of risk. Physicians and other health care providers who are successful with these patients stress the importance of sustaining positive interactions—with attitudes that are respectful, warm, and optimistic. In setting modest goals, recall that a body weight that is 20% above normal (e.g., BMI = 30 instead of 25 kg/m^2) has a 2-fold increase in body fat, mostly "bad" fat. With weight loss, the loss is mostly fat, and also mostly "bad" fat, so that moderate weight reduction can have substantial beneficial effects (100).

Calorie Balance

In planning individual programs, it is important to recall again that calories in equals calories out and that small differences in daily intake quickly add up. For example, with a 2000-calorie diet, a 1% excess of calorie intake equals 20 calories per day, or 600 calories per month. As a first approximation, this amounts to almost 1 lb of extra weight in 5 months. This balance is very subtle, and other factors may also need to be taken into account. Many medications also affect this balance, particularly antidiabetic and psychotropic medications and glucocorticoids (88,89,101). Endocrinopathies also need to be considered. Traditionally, the focus has been almost entirely on calorie intake, but new discoveries have also turned to the role of calorie expenditure, including lifestyle (TV watching, participation in sports), physiological components (basal metabolic rate, thermic effect of food, spontaneous activity, purposeful activity), and molecular components (β3-adrenegic pathway, uncoupling proteins). The uncoupling proteins, with their ability to uncouple oxidation from phosphorylation and thereby dissipate energy, hold exceptional promise as targets for therapeutic intervention (49,102,103).

Food Restriction and Longevity

Food restriction increases lifespan in rodents and monkeys, as well as in flies and worms (104–110). Recent studies in the worm *Caenorhabditis elegans* have shown that a full diet is associated with a short lifespan, whereas a restricted diet yields an extended lifespan. Interestingly, a full diet in an organism whose insulin receptor pathway has been disrupted is associated with longevity. This suggests that it is the signaling pathways associated with eating, in particular insulin pathways, rather than the excess food itself, that are associated with decreased longevity (111).

Metabolic Programming

Metabolic programming represents another new important shift in our perception of food. Until recently, food has been conceptualized only as fuel and as a provider of raw materials for the creation of other compounds. However, very recently, evidence has emerged that food also provides inter- and intracellular signals. Intact long-chain fatty acids, for example, have been shown (73) to directly influence, through cell-surface receptors, the pancreatic β-cell by amplifying glucose-induced insulin secretion. Research into "metabolic programming" has further amplified the actions of food as more than fuel and raw material (112). In rodents, both prenatal and postnatal manipulation of diet leads to physiological and anatomic changes that have a life-long effect on metabolism. Fetal undernutrition can lead to an insulin deficiency syndrome, whereas fetal overnutrition can lead, through gestational diabetes, to an insulin excess syndrome. Postnatal overnutrition, consisting of high-carbohydrate feeding for 24 days in place of lactation ("pup in a cup" model), leads to persistent hyperinsulinemia and heightened sensitivity to glucose. This metabolic programming may even have effects on subsequent generations, because offspring of the conditioned females continued to show metabolic abnormalities, even when fed a normal diet their whole life (112).

What are the biochemical mechanisms for the apparent Lamarckian inheritance of acquired characteristics? One possibility is glucose, which can act as a low-grade mutagen (113,114). Glucose is a suspect in the etiology of certain birth defects during the first trimester in the offspring of diabetic mothers (114). DNA methylation is another possible mechanism. A study in rats by Waterland and Jirtle (115) showed that dietary supplementation with folic acid, vitamin B_{12}, choline, and betaine, with its very rich content of donor methyl groups, resulted in the flipping of a transposon in the *agouti* gene. As a result, coat color in their offspring was changed. Transposable elements, such as were affected in the study of Waterland and Jirtle, constitute 35% of the human genome and are present in 4% of human genes (115). Collectively, these studies show that food has more in vivo effects than solely as a source of calories and molecular building blocks.

Two new studies in mice have provided hints of additional mechanisms for "metabolic programming." Both studies have reported significant changes in the neural organization of hypothalamic nuclei in leptin-deficient (*ob/ob*) mice (116,117). One of the research groups found that acute replacement with leptin produced immediate changes in the organization of synapses in one brain region, even before food intake was affected (117). The other research group found that the disorganized neural pattern in the hypothalamus that they had observed was unaltered by leptin replacement, suggesting a permanent defect (116). The role of leptin, a hormone, is consistent with the growing

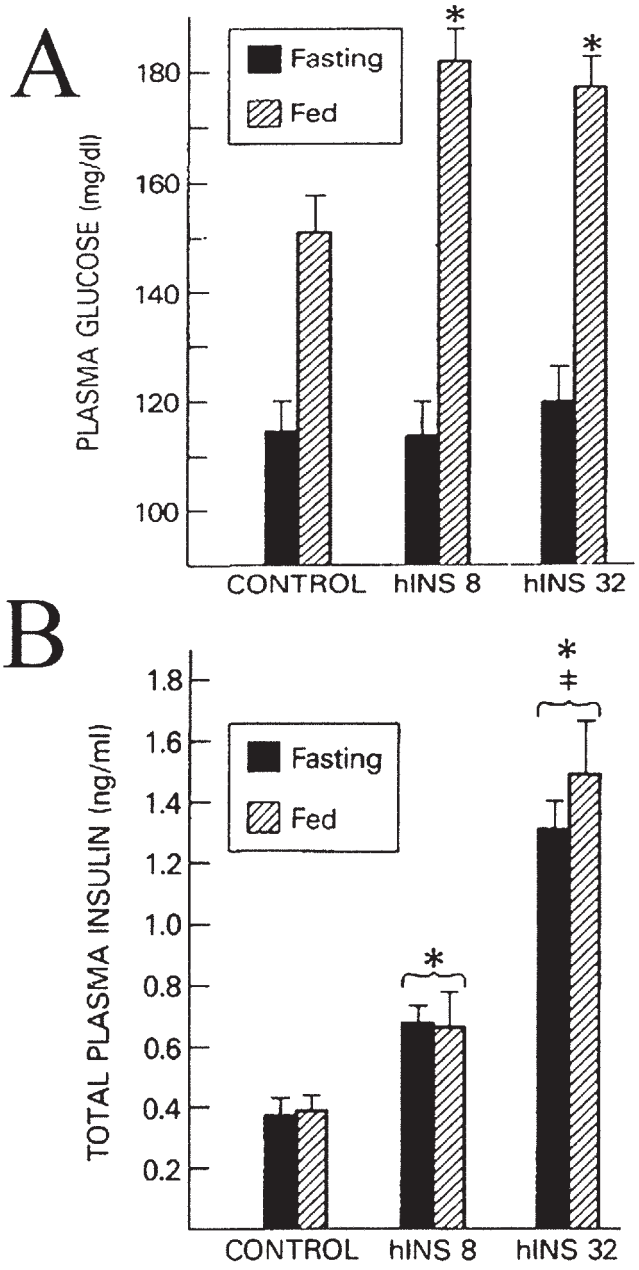

Figure 7: Plasma glucose (A) and insulin (B) in (thin) mice with transgenic hyperinsulinemia. The hINS 8 and hINS 32 mice have stably incorporated 8 and 32 copies, respectively, of the human gene for insulin. (A) Each plasma glucose point in fasting and fed states represent the mean ± SE for 13 to 25 individual determinations. Fasting glucose values were not significantly different between control and either transgenic line. However, in each of the three lines, the fed glucose level was significantly above fasting ($p < 0.001$). Both transgenic lines had fed glucose levels significantly above control (*$p < 0.004$ vs. fed control). (B) Plasma insulin was measured by radioimmunoassay. Each value represents the mean ± SE of 14 to 25 individual measurements. In each of the three mouse lines, there was no significant difference between fasting and fed values. Significant differences among the three groups are as indicated. *$p < 0.001$ vs. control. ‡$p < 0.001$ hINS 32 vs. hINS 8. Adapted from Marban and Roth: Transgenic hyperinsulinemia: a mouse model of insulin resistance and glucose intolerance without obesity, in Shafrir E (ed): Lessons from Animal Diabetes VI, p. 201–24, copyright Birkhauser, 1996, (127) with permission.

Table 1. Body weights of control and transgenic mice

	Male weight (g)	Female weight (g)
Control	43.5 ± 1.0	39.2 ± 0.8
hINS 8	42.7 ± 0.9	38.5 ± 1.1
hINS 32	42.4 ± 1.0	39.4 ± 0.9

Mice that harbor 0 (control), 8 (hINS 8), or 32 (hINS 32) copies of the human insulin gene secrete normal amounts, a 2-fold excess, or a 4-fold excess, respectively (127). The mice with the extra copies of the human insulin were glucose intolerant, insulin resistant, and hyperlipidemic, but remained thin. Numbers are mean ± SE of body weight for 24 male and 24 female mice in each group. Comparisons within each sex showed no statistically significant differences among the three groups (127).

recognition that signaling molecules, in addition to acute signaling, often mediate major events in development (118).

Insulin Resistance

Metabolic Syndrome

In 1988, Gerald Reaven (119,120) proposed that the cluster of insulin resistance (and hyperinsulinemia), impaired glucose tolerance, abnormalities of plasma lipids (commonly a raised level of free fatty acids), and hypertension were actually part of a single syndrome, which he dubbed "syndrome x" and which is now commonly called the metabolic syndrome. Two further developments are especially noteworthy. One relates to recent research in several laboratories (121,122), where components of the metabolic syndrome were linked to the local production of excess cortisol. Normally, cortisol, the active hormone produced by the adrenal gland, is converted to inactive cortisone by 11β-hydroxysteroid dehydrogenase type 2 produced in the kidneys. However, another form of 11β-hydroxysteroid dehydrogenase, type 1, produced in the adipocytes, transforms inactive cortisone to active cortisol. These researchers have proposed that the overproduction of cortisol in adipose tissue drives the metabolic syndrome, at least in some individuals.

The second new development is the shift from four (or more) components of the metabolic syndrome to a single focus on insulin resistance (119,120). In a longitudinal

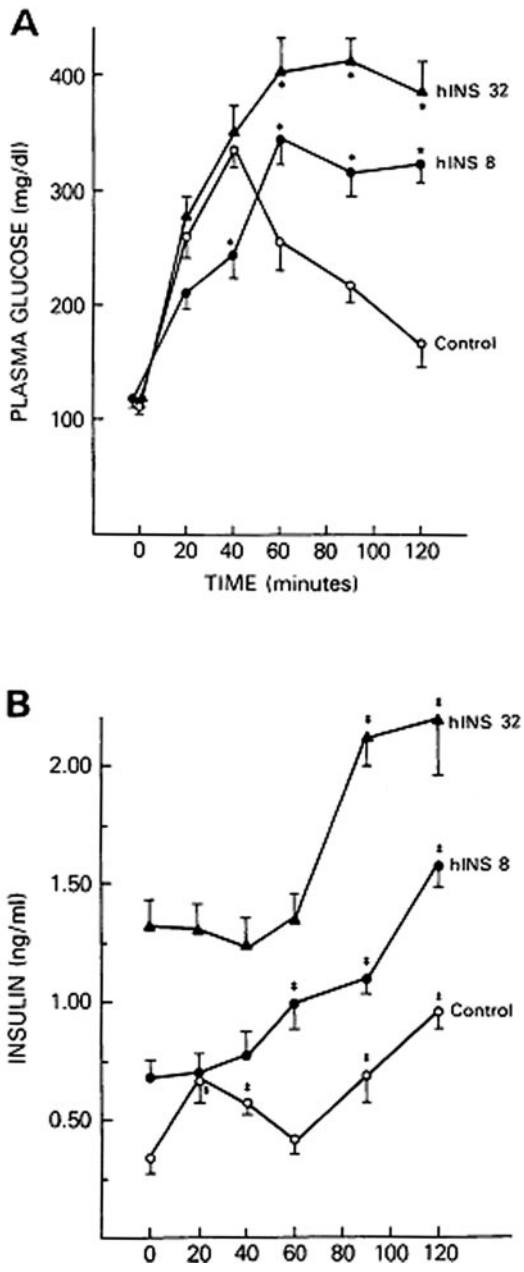

Figure 8: Glucose tolerance tests in transgenic hyperinsulinemic (thin) mice. After an overnight fast, animals were injected intraperitoneally with glucose (2 mg/g body weight). Blood samples were taken at time-points up to 120 minutes after injection for measurements of plasma glucose (A) and plasma insulin (B). Points each represent the mean ± SE of nine or more individual measurements (127). Adapted from Marban and Roth: Transgenic hyperinsulinemia: a mouse model of insulin resistance and glucose intolerance without obesity, in Shafrir E (ed): Lessons from Animal Diabetes VI, p. 201–24, copyright Birkhauser, 1996, (127) with permission.

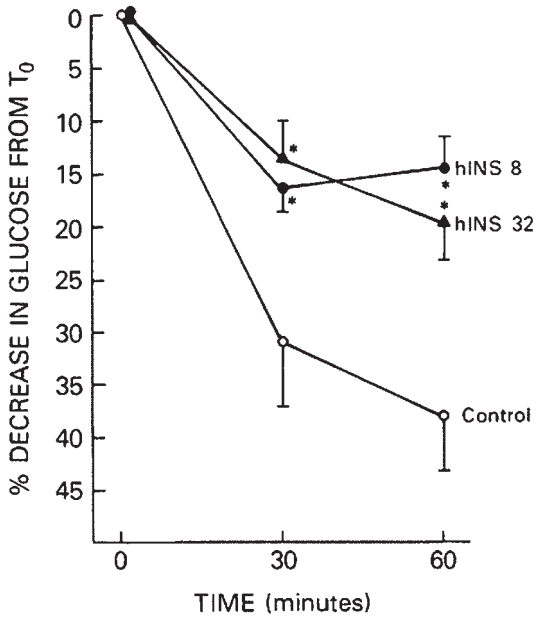

Figure 9: Insulin resistance in transgenic hyperinsulinemic (thin) mice. Mice were injected intraperitoneally with insulin (0.5 mU/g body weight). Blood for glucose determinations was drawn before and at 30 and 60 minutes after insulin injection. Each point represents the mean ± SE of 6 to 10 individual glucose determinations. $*p < 0.02$ vs. control (127). Adapted from Marban and Roth: Transgenic hyperinsulinemia: a mouse model of insulin resistance and glucose intolerance without obesity, in Shafrir E (ed): Lessons from Animal Diabetes VI, p. 201–24, copyright Birkhauser, 1996, (127) with permission.

study of 208 people over 4 to 11 years, Facchini et al. (123) have shown that insulin resistance is a dominant and independent predictor of major age-related diseases including cardiovascular diseases and cancer. Reavan et al., in effect, have moved from the concept of metabolic syndrome, where insulin resistance is one of four or more elements of the syndrome, to where insulin resistance is the single dominant factor predicting pathology (119,120).

Origins of Insulin Resistance

An acute rise in insulin is stimulatory, but persistence of an elevated level of ambient insulin desensitizes the target cells through a variety of mechanisms, including effects at the insulin receptor (124) and at several sites beyond the receptor (125,126). A sustained elevated level of insulin, immaterial of its origin, typically leads to generalized insulin resistance.

Transgenic Hyperinsulinemia

Studies in transgenic mice have shown this well (127). Each founder mouse permanently possessed 0, 8, or 32 extra copies of the human insulin gene, which resulted in plasma insulin levels that were normal or two or four times higher than normal, respectively (Figure 7). Surprisingly, the mice that overexpressed insulin were not obese (Table 1): body weight remained normal, and they developed no antibodies

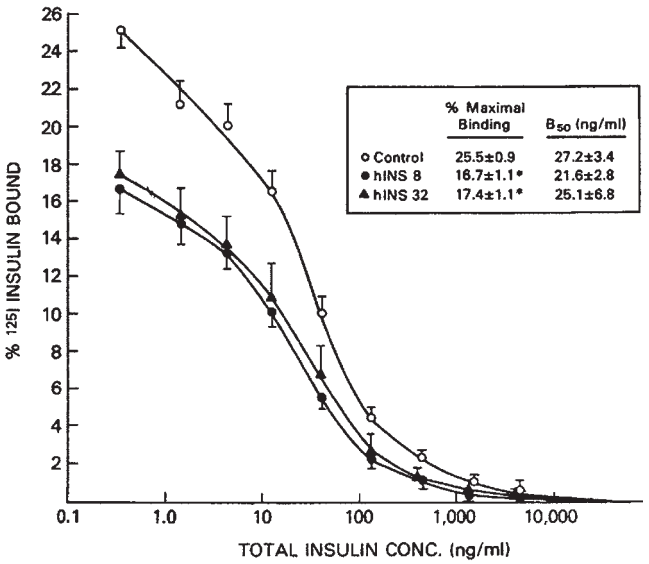

Figure 10: Diminished number of insulin receptors in liver from transgenic hyperinsulinemic (thin) mice. [^{125}I]-insulin binding to liver membrane preparations was measured in the presence of unlabeled insulin at 0 to 1.33×10^4 ng/mL. Nonspecific binding, defined as the labeled insulin bound in the presence of 1.33×10^4 ng/mL cold insulin, was 5% of maximal binding in all cases and was subtracted from total binding to obtain specific binding for each sample. All data were normalized as [^{125}I] bound per 60 mg of membrane protein. Each value is the mean ± SE of eight membrane preparations per group. As a measure of the receptor affinity for insulin, we used the B_{50}, which represents the concentration of unlabeled insulin at which 50% maximal binding occurred; there were no significant differences in the B_{50} values among the three mouse lines. Differences in the maximal binding values were significant at $p < 0.001$ vs. percent maximal binding for control (127). Adapted from Marban and Roth: Transgenic hyperinsulinemia: a mouse model of insulin resistance and glucose intolerance without obesity, in Shafrir E (ed): Lessons from Animal Diabetes VI, P. 201–24, copyright Birkhauser, 1996, (127) with permission.

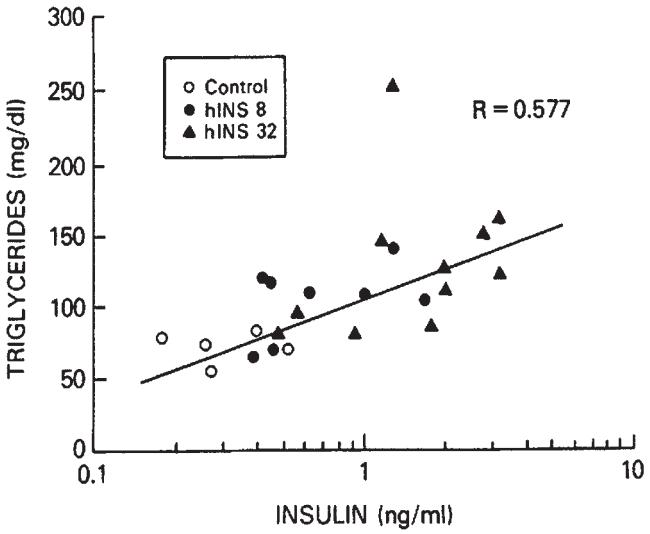

Figure 11: Plasma triglycerides as a function of plasma insulin in (thin) mice with transgenic hyperinsulinemia. Each point represents a single determination from an individual animal (127). Adapted from Marban and Roth: Transgenic hyperinsulinemia: a mouse model of insulin resistance and glucose intolerance without obesity, in Shafrir E (ed): Lessons from Animal Diabetes VI, p. 201–24, copyright Birkhauser, 1996, (127) with permission.

to insulin (data not shown). However, they exhibited elevated postprandial glucose levels (Figures 7 and 8), despite the extra insulin in the circulation. The hyperinsulinemia caused insulin resistance (Figures 7 to 9) and reduced insulin-receptor binding (Figure 10), as well as increased triglycerides (Figure 11). Thus, primary hypersecretion of insulin by itself in thin mice produced generalized insulin resistance and a metabolic state that resembles the early stages of diabetes (127). In essence, hypersecretion of insulin can be both *a cause of* and *a result of* insulin resistance.

Role of Fatty Acids

As discussed earlier, elevations of free fatty acid levels in obesity can lead to elevated insulin levels. The increased insulin leads to a reduction but not normalization of free fatty acid levels. A persistent drive by the free fatty acids toward hypersecretion of insulin develops, leading to generalized resistance to insulin (128–130). In addition to its effects on insulin secretion, elevated free fatty acid levels can produce insulin resistance in muscle and liver (75,76).

Irrespective of the original cause, steady-state hyperinsulinemia and insulin resistance coexist. The examples presented—transgenic hypersecretion of insulin, for one, and typical obesity, as another, as well as cortisol excess and growth hormone excess—have very similar patterns of insulin and glucose metabolism, despite the diverse etiologies.

Cytokines

Cytokines add to the complexity (5,70–72,131–134). For example, TNF-α can cause insulin resistance at the level of the target cells for insulin. Furthermore, insulin can dampen TNF-α secretion (Figure 6), and insulin resistance promotes cytokine hypersecretion (70–72). The insulin resistance of macrophages in *ob/ob* mice is associated with hypersecretion of cytokines, and the increased density of macrophages in fat depots strengthens the idea that cytokines play a major role.

Conclusions and Summary

The obesity pandemic is gaining momentum and will profoundly affect mortality, morbidity, and quality of life worldwide. While the role of genetics is widely appreciated,

there are emerging data that nutrient exposure in utero and in the early postnatal period ("metabolic programming") can have important life-long effects. Free fatty acids and hormone-like secretions from adipocytes and their associated activated macrophages are major regulators of metabolic processes. We have shown that resistance to insulin, a common characteristic in obesity and a harbinger of disease, can have many causes, including primary hypersecretion of insulin, hypersecretion of free fatty acids, and high levels of circulating cytokines. Both the free fatty acid hypersecretion and cytokine hypersecretion can be dampened by insulin. One key to the successful treatment of the obese patient is moderate calorie restriction and moderate exercise to yield a sustained 5% to 10% weight loss, along with prevention and treatment of the coexisting morbidities. Key to success are knowledgeable, committed, and sympathetic health care providers.

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