"Weapons of Mass Destruction: Pandemic Lipotoxicity in the U.S."

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Internal Medicine Grand Rounds
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This is to acknowledge that Dr. Unger has disclosed any financial interests or other relationships with commercial concerns related directly to this program. Dr. Unger will not be discussing off-label uses in his presentation.

Hedonophagia (eating for pleasure):

Origin: Until 1765, eating for pleasure was restricted to the European elite who, as far back as ancient Rome, maintained elaborate culinary facilities employing the best of chefs. Since refrigeration was unknown, the odor of decaying food had to be masked by delicious sauces. The general population ate only to assuage hunger. Meals varied very little from one another, their composition determined more by availability than by choice. Restaurants did not exist until 1765, when A. Boulanger, a soup vendor, opened a business in Paris, with a sign above his door advertising "restoratives," or in French, "restaurants." This term referred to soups and broths, which apparently were considered to have the same therapeutic value as today's chicken soup.

From French Food to Fast Food: In 1789, the French Revolution destroyed the royalty, the nobility, and the landed gentry, suddenly idling hundreds of superb chefs. Many of these chefs opened their own eating establishments, also referred to as restaurants. Boulanger's restaurant became the first public place offering a menu with a choice of dishes. By 1804, Paris had more than 500 restaurants, producing some of the great chefs of history in creating many famous dishes and a cuisine that still reigns supreme throughout the world. During the Napoleonic era, leading restaurants would list on their menu a dozen soups, two dozen fish dishes, 15 beef entrees, 20 mutton entrees, and many side dishes. Some of these early restaurants such as Le Grand Vefour and Maxim's, are still in business today (Figure 1).

Figure 1. *A famous Parisian restaurant circa 1890. Truncal obesity is apparent in the waiter.*

The restaurant concept spread throughout the world. In the United States, several variations developed. In 1849 during the California gold rush, the cafeteria first appeared in San Francisco. This was a precursor of other accelerated eating places, such as the drugstore counter and, more recently drive-through restaurant where patrons are served in their automobiles. With the development of Interstate highways, the familiar fast-food companies proliferated throughout the country, McDonald's established a single restaurant in Des Plaines, Illinois in 1955, but within 40 years had 15,000 such restaurants. Kentucky Fried Chicken was founded in 1956 and Pizza Hut in 1958. Processed food products, calorically enhanced by government-subsidized corn products, replaced traditional foods, as mass production reduced the cost of a calorie to historically low levels. These unnatural diets were often accompanied by artificial sucrose-enriched soft drinks.

World's Largest and Longest Clinical Research Project:

Effectively, by 1954, the stage had been set for the largest "clinical research project" in world history. Table 1 describes its specific aims, subjects, and experimental design.

TABLE 1

LARGEST CLINICAL RESEARCH PROJECT IN WORLD HISTORY

Specific Aim: To determine the effects of lifelong caloric excess on body weight and health of a nation.

Subjects: 250 million Americans.

Experimental design:

A. **Restrict physical activity through motorized transportation and sedentary work and leisure.**

B. **Promote consumption of calorie-dense diets through aggressive advertising, ubiquitous food availability and very low cost per calorie.**

C. **Determine effects on BMI and health of the population.**

D. **Results:**

D. Results:

The results of this unplanned study are shown in Figures 2 and 3 They indicate that the changes in the American diet, in a setting of reduced physical activity, led within two generations to widespread somatic metamorphosis in more than half of Americans. By the turn of the millennium an unprecedented health care crisis had been created. Although genetic and even viral causes have been invoked to explain the obesity explosion in the U.S., no known nonenvironmental factor could possibly explain how 65% of an entire nation could become overweight within a span of 50 years. Nor could it explain why obesity is so rare in every part of Japan, except for the island of Okinawa, where the American military made the American diet available to the local inhabitants, who are now the fattest Japanese.

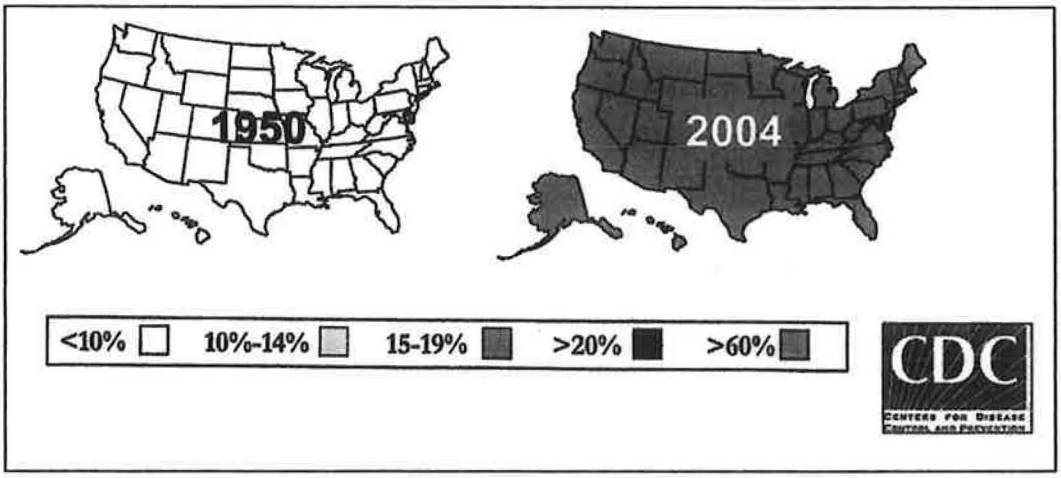

Figure 2. *Percent of Americans with BMI <or> 26.*

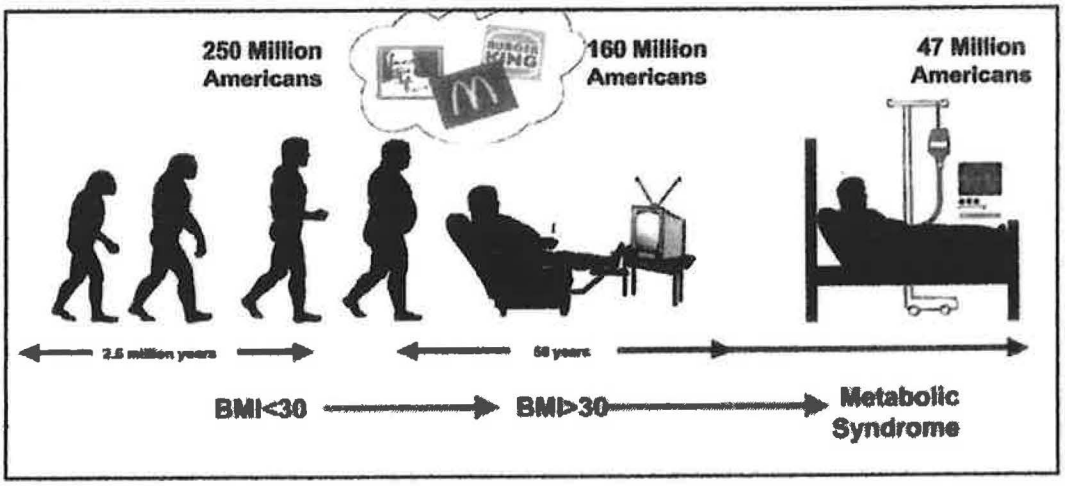

Figure3. *Overweight Americans with metabolic syndrome.*

Health Consequences: The health consequences of the obesity pandemic have already surpassed those of tobacco. The risk of death from all causes at all ages rises once the body mass index (BMI) exceeds 24.9. Death is due to components of the metabolic syndrome (Table 2) plus cancer. Although cancer is not generally thought of as a complication of obesity, 20% of all cancer in women and 14% in men is associated with obesity (cancer of the esophagus, colon and rectum, liver, gall bladder and kidney, and non-Hodgkin's lymphoma and multiple mycloma) (Calle et al, 2003). There was also increased mortality from the cancers of the stomach, prostate, breast, uterus, cervix, and ovaries. Although the precise link between obesity and cancer is unknown, it has been suggested that LKB-1α component of the AMP activated protein kinase kinase (AMPKK), which is mutated in the Peutz-Jeghers Syndrome (Su et al, 1999) might be involved (Fernandez et al, 2004).

TABLE 2

Normal Liporegulation

Provides sufficient lipids to meet cellular needs (membrane bilayers, signaling molecules and fuel)----even during famine.

Prevents lipid overload of nonadipose tissues---even during overnutrition---by partitioning surplus lipids into adipocytes.

Even without the excess cancer mortality in obesity, the morbidity and mortality and costs of the metabolic syndrome itself, the main complication of overweight, is staggering. In 2002 over 47 million of the 160 million overweight Americans had metabolic syndrome (Ford et al, 2002) (Figure 3). If we analogize this clinical predicament in terms of our national security, we are under a 50-year-long attack by devastating biological weapons, created in the United States and deployed by Americans into American bodies, where they are poised to attack vital organs. The irony is that we understand completely how to thwart this attack, and yet for complex reasons we fail to do so. Even though we could eliminate weapons of lean body mass destruction by lifestyle change at absolutely no cost, we prefer to spend billions in a search for a pharmacologic substitute for self-discipline. The American tragedy is that we are all co-conspirators in this attack on the American lean body mass.

Lipid Homeostasis:

The father of experimental medicine, Claude Bernard, coined the term homeostasis in 1869 (Bernard, 1853). By that he meant constancy of the *internal milieu* or environment. Good health, he argued, requires constancy of intra- and extracellular environments because most cells tolerate very poorly any major deviations from an optimal range. Almost any activity or event in life will, to some degree, alter the internal environment of some cells, but in healthy organisms vigilant, highly responsive reactive systems restore rapidly any perturbation within the internal environment. For example, the hormones of glucose homeostasis, insulin and glucagon, are perfect examples of such a system; failure to maintain glucose homeostasis results in diabetes or hypoglycemia (Unger, 1975).

Liporegulation and leptin: Of all the vital homeostatic systems, liporegulation (see Table 2) has been virtually ignored. Failure of liporegulation, we propose here, is responsible for the so-called metabolic syndrome. The primary liporegulatory hormone is leptin, discovered by Jeff Friedman's group at Rockefeller University in 1994 (Zhang et al, 1994). Its discovery through positional cloning disclosed a mutation in the gene in obese mice known as *ob/ob* mice. The ob gene of Friedman encoded a protein, leptin, which, when injected into the *ob/ob* mouse, caused regression of the obesity (Halaas et al, 1995). It appeared that the physiologic role of leptin was to inhibit food intake and to prevent overnutrition and diet-induced obesity (DIO).

However, the problem with that idea was that the vast majority of obese Americans were hyperleptinemic (Kennedy et al, 1997), and leptin therapy did not reverse their obesity (Heymsfield et al, 1999). Most in the field concluded that the hyperleptinemia was secondary to leptin resistance associated with the obesity. However, in normal Sprague-Dawley rats leptin increased 4-fold on the first day that normal rats begin a high-fat (60%) diet, and increased

progressively as body fat increased (Figure 5). One possible explanation as to why endogenous leptin seems incapable of reducing food intake during overnutrition is that certain triglycerides impair leptin uptake by the brain (Banks et al, 2004). Another is that the overnutrition increases the endogenous ligands of the cannabinoid receptors, such as anandamide and 2-arachinodoyl-glycerol (2-AG) (Valenti et al, 2004) to bind to the cannabinoid receptors CB1 and CB2 (Ravinet Trillou et al, 2004; Di Marzo et al, 2001; Wenger and Moldrich, 2002) to interfere with leptin action. Whatever the cause of the prompt blockade by overnutrition of leptin's anorexic and weight-reducing activity, clearly the idea that leptin's function is to prevent obesity has become difficult to defend. Not only is there no evolutionary pressure to prevent it, but also every piece of experimental evidence disputes it.

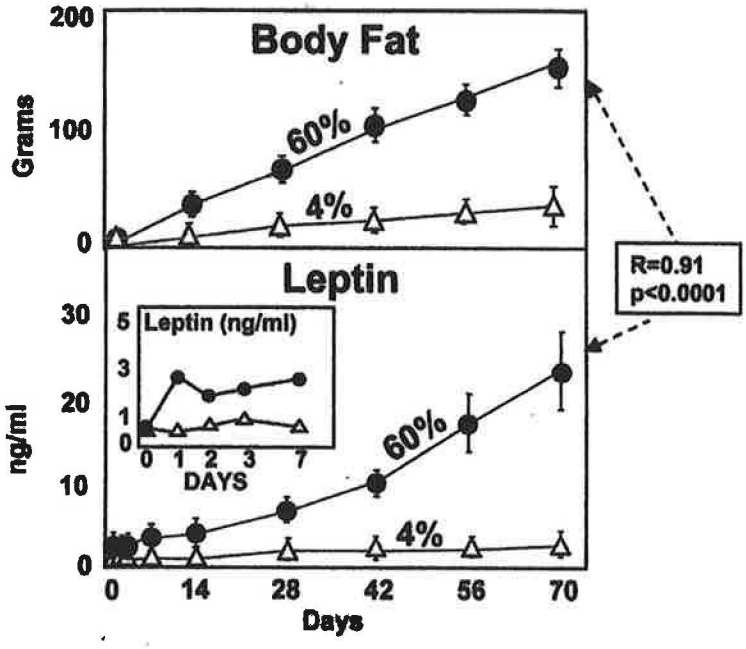

Figure 5. *Endogenous leptin levels rise in proportion to body fat and seemingly do not restrain either the appetite or the weight gain.*

How can one reconcile the anorexic, weight-reducing effect of exogenous leptin administered to leptin-deficient *ob/ob* mice and the normal lean rodents (Halaas et al, 1995)? The explanation involves a fundamental rule of experimental endocrinology. An endogenous increase in a hormone will be elicited by a homeostatic perturbation against which it defends (Figure 6A). Thus a rise in endogenous insulin is caused by an increase in blood glucose, which is restored to normal by the endogenous insulin (Figure 6A). However, if exogenous insulin concentration is administered experimentally in the absence of any physiologic demand for the hormone, it causes hypoglycemia (Figure 6B), while endogenous hyperinsulinemia does not cause hypoglycemia, but rather prevents or minimizes hyperglycemia after a meal (Figure 6B). The precise physiologic role of any hormone must, therefore, be assessed in the context of the physiologic perturbation that stimulates its secretion. In the case of leptin, exogenous hyperleptinemia causes anorexia and weight loss (Figure 6C), whereas endogenous hyperleptinemia, which occurs only during an increase in body fat (Figure 5), does not (Figure 6D).

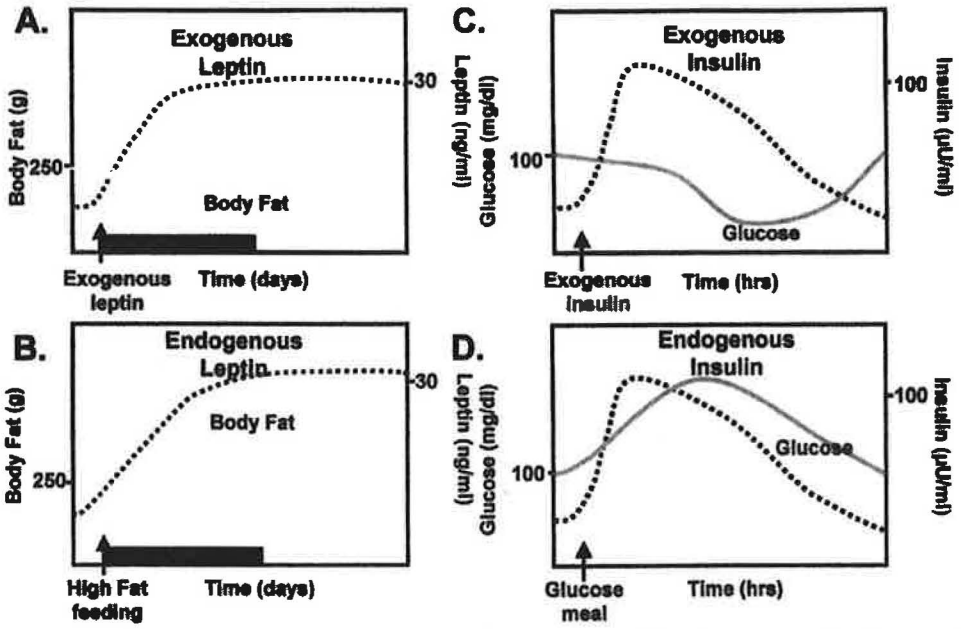

Figure 6. *Effects of endogenous and exogenous hormones differ because the former is responding to correct a physiologic perturbation while the latter is administered without any physiologic demand.*

To identify the role of endogenous hyperleptinemia, we carefully examined the physiologic context of the endogenous hyperleptinemia induced by overfeeding. In particular, we were struck by the distribution of the huge increase in body fat that had transpired within the 70-day period of overfeeding a high fat diet. We noted a 150-fold increase in adipocyte fat but only a trivial increase in non-adipocyte fat (Figure 7).

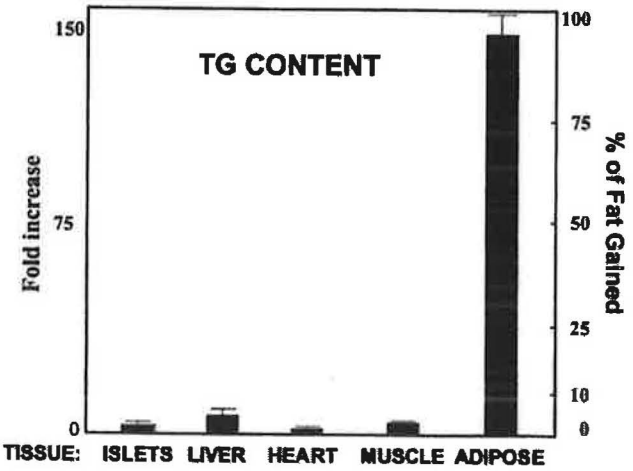

Figure 7. *Lipid partitioning in normal rats after 8 weeks of 60% fat diet (n=6).*

We wondered if this meant that the adipocytes, while storing the surplus calories given to these rats, were secreting leptin in order to protect non-adipocytes from the metabolic trauma that would be caused if they were to be inundated by the lipid surplus. In other words, if this idea of an antilipotoxic role for leptin were correct, the tissues of unleptinized rodents would be overloaded with fat. This was in fact, the case. The organs of *ob/ob* insulin-deficient mice, and of *db/db* mice and ZDF (*fa/fa*) rats, both of which are leptin-unresponsive, all had triglyceride contents ranging from 7 to 100 times normal, even though they were on a normal 6% diet (Figure 8) (Lee et al, 2001).

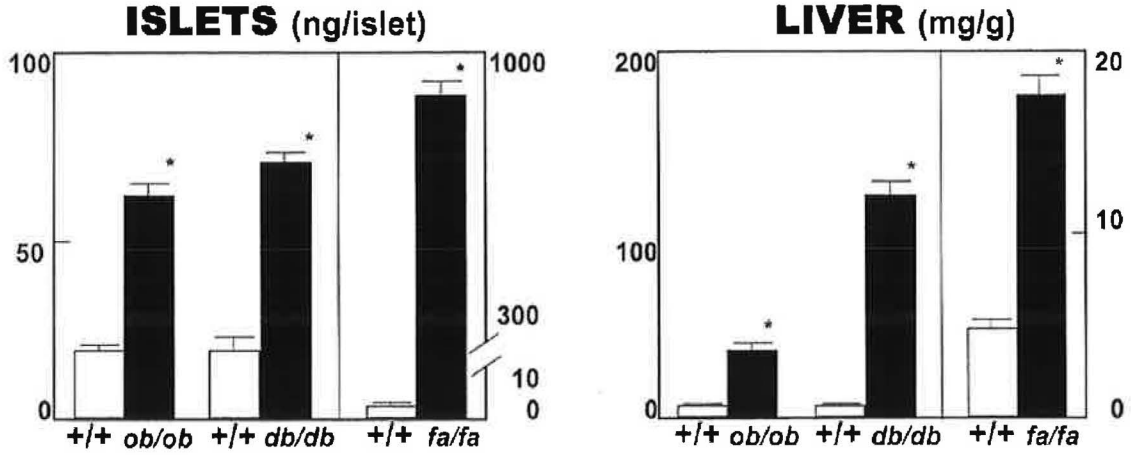

Figure 8. *Triglyceride content is high in nonadipose tissues of unleptinized rodents ■. Ob/ob mice have no leptin while db/db mice and fa/fa rats have no leptin response.*

In other words, their tissues contained far more lipids on a normal diet for 3 months than those of normal rats after 7 months on a diet with 10 times the normal fat content (Figure 9).

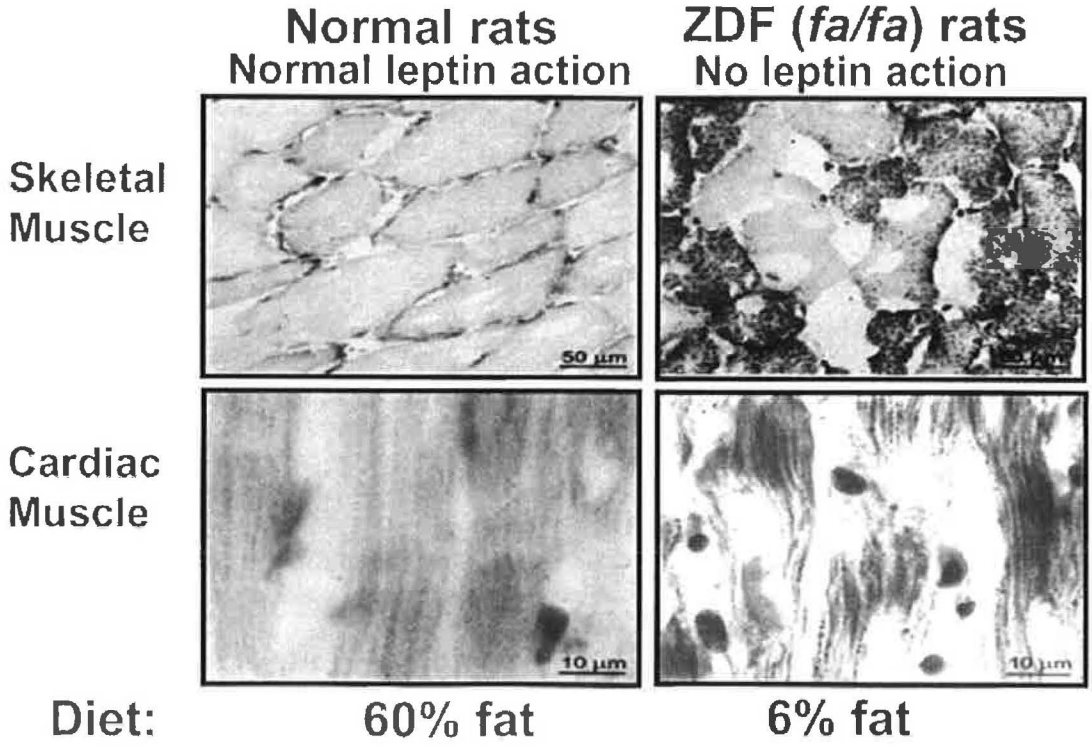

Figure 9. *Oil red O stain for lipids. Ectopic lipids are absent even on a high fat diet (60%) when leptin action is normal. However, severe steatosis occurs when leptin action is absent-even on a normal diet (6%). Courtesy of Lelio Orci.*

Moreover, the unleptinized rats exhibited the clinical features of the human metabolic syndrome (Grundy et al, 2004) (Figure 10), raising the possibility that the metabolic syndrome was caused, not by insulin resistance, but rather by leptin resistance and/or relative hypoleptinemia.

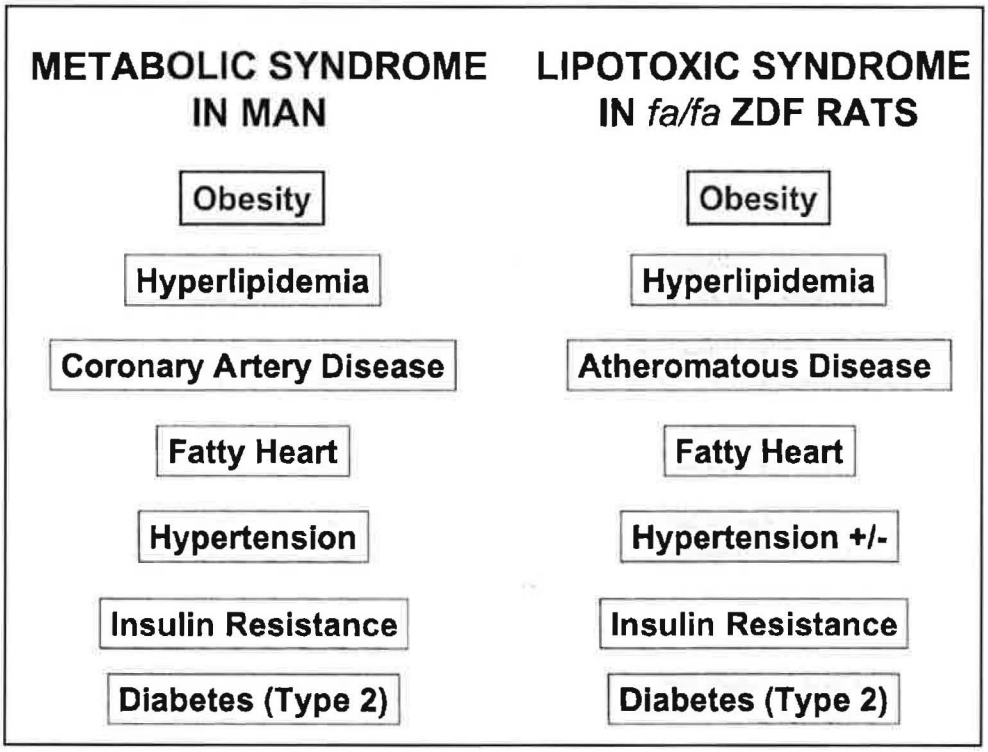

Figure 10. *Comparison of human metabolic syndrome and rodent lipotoxic syndrome.*

Central Obesity: Central obesity is associated with leptin levels that are higher than those of normal lean subjects (Abate et al, 1995; Kanesova et al, 2002; Gautier et al, 1998; Miyazaki et al, 2002; Staiger et al, 2003), but they are below those of patients with subcutaneous obesity. Since metabolic syndrome is far more common with visceral obesity (Ruderman et al, 1981), we infer that the subcutaneously produced hyperleptinemia was protecting against metabolic syndrome by maintaining a level of leptin sufficient to overcome any peripheral leptin resistance, i.e. centrally obese patients may have "relative hypoleptinemia." It is important for clinicians to keep in mind that individuals with a normal BMI but a "potbelly," (Ruderman, 1981) may be at higher risk for metabolic syndrome than overtly obese individuals, since they lack the subcutaneous adipocytes that appear to protect against that complication. It is noteworthy that patients with severe, third-degree burns, in which subcutaneous fat is consumed by fire, often develop a fulminating metabolic syndrome precipitated by hyperalimentation. A full list of conditions in which metabolic syndrome is a feature appears in (Figure 11). The fat distribution pattern in all but the lipodystrophic group is generally one of increased truncal relative to peripheral fat tissues.

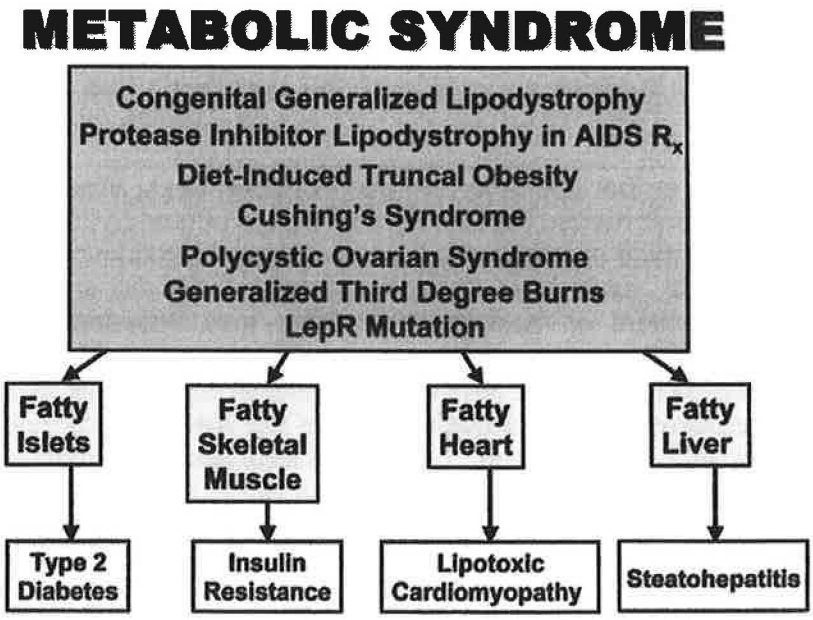

Figure 11. *Disorders in which the metabolic syndrome cluster occurs: relationship to ectopic lipid disposition*

Leptin is an antilipotoxic hormone:

Is leptin really a liporegulatory hormone that can prevent lipotoxicity (metabolic syndrome)? To test that hypothesis, we have transgenically overexpressed the functional leptin receptor (OB-Rb) in the liver (Lee et al, 2001), (Wang et al, 1998 and 1999), and the pancreatic islets, of ZDF rats that are completely unresponsive to hyperleptinemia because of a mutation in their OB-Rb. When these organs overexpress a normal leptin receptor, a dramatic reduction in their lipid content rapidly occurs, suggesting that leptin-receptor interactions reduce TG content of congenitally unleptinized tissues towards normal (Figure 12).

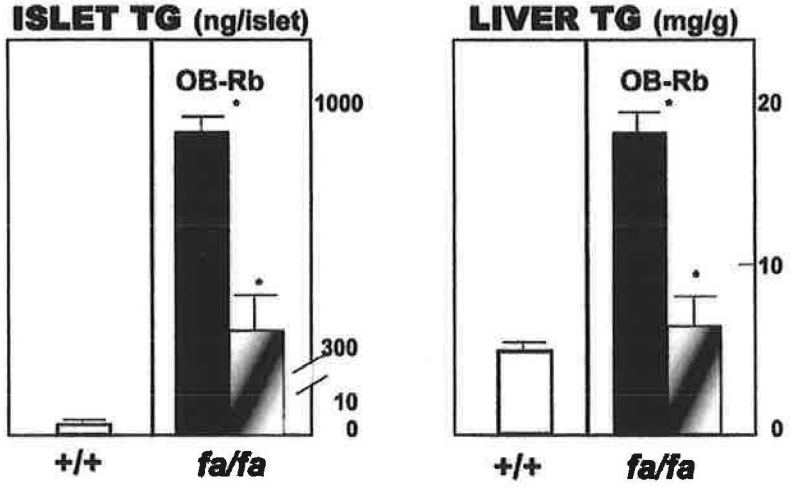

Figure 12. *Normal leptin receptor (OB-Rb) □ lowers TG content of unleptinized ■ fa/fa tissues.*

But the effect of a hormone in correcting its own deficiency state may not necessarily reflect its function in normal animals without the hormone deficiency. For this reason, we searched for

a normal animal model in which we could test the hypothesis that leptin is an anti-lipotoxic liporegulator.

In 2001 Chiu et al. in the laboratory of Jean Schaffer, M.D., Washington University of St. Louis, created a transgenic mouse expressing acyl CoA synthase (ACS) on the αMHC promoter (Chiu et al, 2001). The mice overexpressed the enzyme, which is involved in vectorial transport of long-chain fatty acids, exclusively in cardiomyocytes. By the age of 4 weeks a striking increase in the TG content of their cardiomyocytes was demonstrable, both histologically through oil red O staining and electron microscopy, and by biochemical assay of triacylglycerol (TG). While the esterification of the fatty acids to neutral fat probably renders them harmless, the increased TG content provides a useful index of the extent of the mismatch between fatty acid availability and fatty acid oxidation. Unoxidized fatty acids, are therefore available to enter pathways that are more damaging than esterification to TG (Figure 13). One such pathway is the ceramide pathway, which begins with condensation of palmitoyl CoA and serine. Ceramide, a mediator of apoptosis was increased in the ACS-transgenic hearts. TUNEL staining and cytochrome C extrusion assays, indices of apoptosis, both were increased, indicating that apoptosis was abnormally high. Thus the severe lipotoxicity and lipoaptosis resulting from the lipid excess caused a loss of functioning cardiomyocytes, which led to dilated cardiomyopathy, congestive failure and premature mortality.

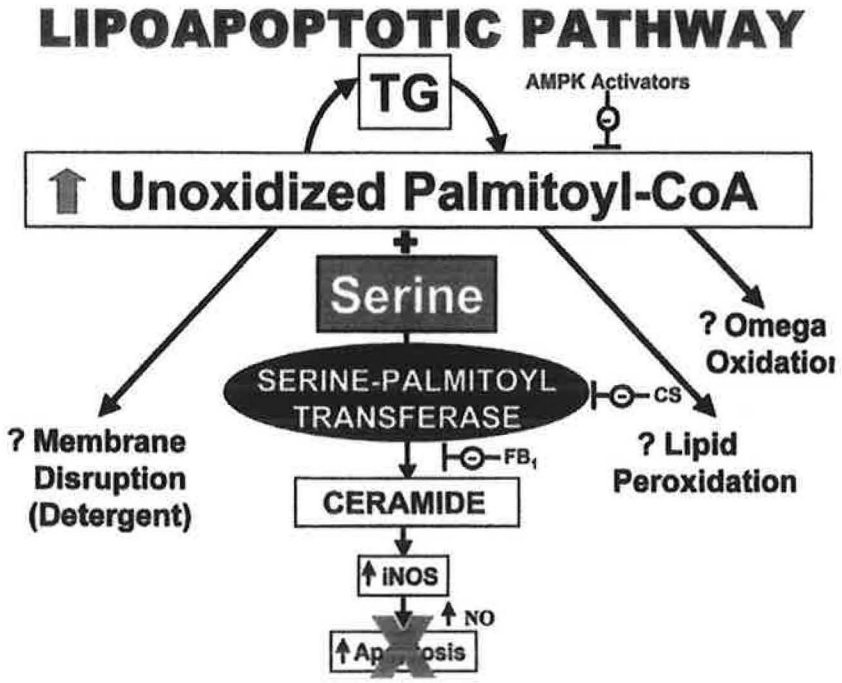

Figure 13. *Lipoapoptotic pathway. Apoptosis is blocked by lowering unoxidized palmitoyl CoA or inhibiting serine palmitoyl transferase with cycloserine (CS) or fumonisin B_1 (FB_1).*

Since these mice were lean, and their leptin levels were in the normal range (below 2 ng per ml). If, as proposed (Unger et al, 1999), the function of the hyperleptinemia of obesity is to prevent the overaccumulation of lipids in lean tissues and thus protect against lipotoxicity and lipoaptosis, these nonobese transgenic animals would be completely unprotected. To determine if raising their leptin levels to the hyperleptinemic range of diet-induced obesity, which ranges between 10-25 ng per ml, would prevent the phenotype of the ACS-transgenic mice, we induced obesity-level hyperleptinemia (Figure 14) by infusing them with recombinant adenovirus containing the leptin cDNA.

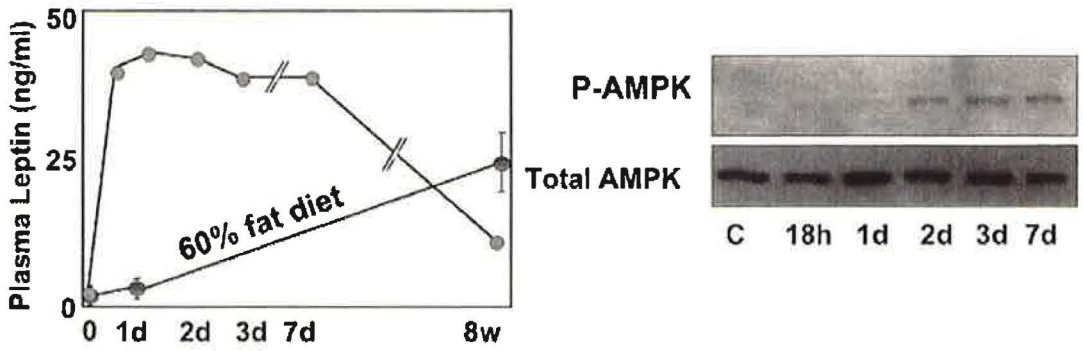

Figure 14. *Plasma levels (left panel) and myocardial P-AMPK in normal mouse heart induced by treatment with AdCMV-leptin. Levels of native leptin in diet-induced obese rats (60% fat diet) are shown for comparison.*

The treatment was given to 6-week old mice, in which the cardiomyopathic phenotype had already begun. Two months later, at the age of 14 weeks, they received echocardiograms and blood tests prior to sacrifice. Leptin levels at that time averaged ~10 ng per ml. The echocardiographs of the hyperleptinemic mice were indistinguishable from normoleptinemic wild-type animals and contrasted sharply with the extreme abnormality of untreated transgenic mice (Figure 15). The TG content of the hearts of hyperleptinemic mice was slightly below that of the wild-type hearts (Figure 15). There was no evidence of the apoptosis present in untreated transgenic hearts (Figure 13).

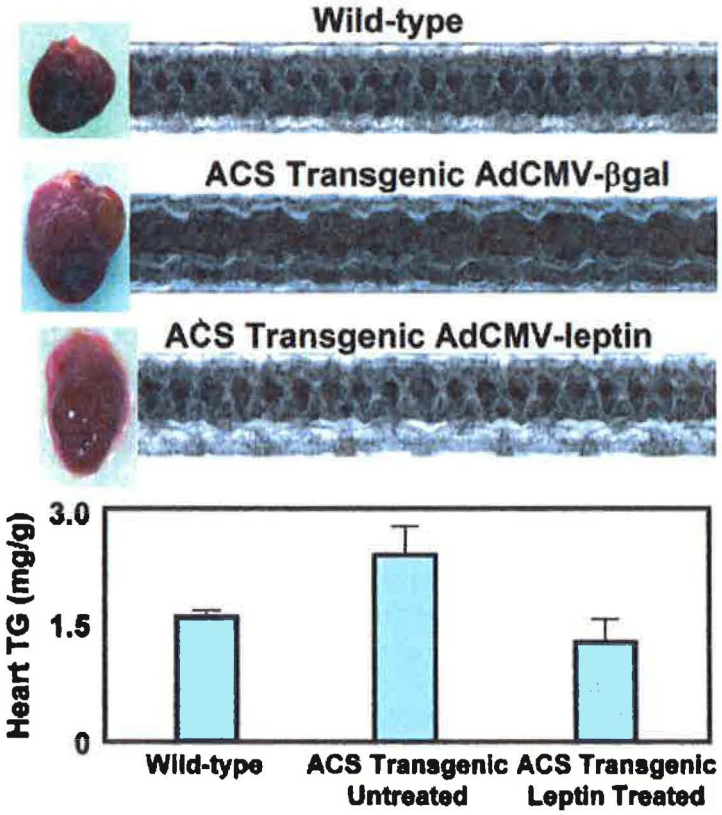

Figure 15. *Obesity-level hyperleptinemia induced by AdCMV-leptin treatment prevents lipotoxic cardiomyopathy in MHC-ACS transgenic mice. Echocardiogram and triglyceride content are completely normal in the hyperleptinemic mice.*

The interstitial fibrosis and endocardial adipocyte infiltration that characterized the untreated transgenic hearts was completely absent in the hearts of hyperleptinemic transgenic mice (Figure 16). In other words, all of the damaging consequences of the increased FA import into cardiomyocytes had been completely abrogated (Lee et al, 2004, in preparation). This provides extremely powerful evidence that the role of obesity-induced hyperleptinemia is to prevent the overaccumulation of lipids in lipid-intolerant nonadipose tissues. Teleologically, this permits overnutrition to take place without metabolic damage to the nonadipose tissues.

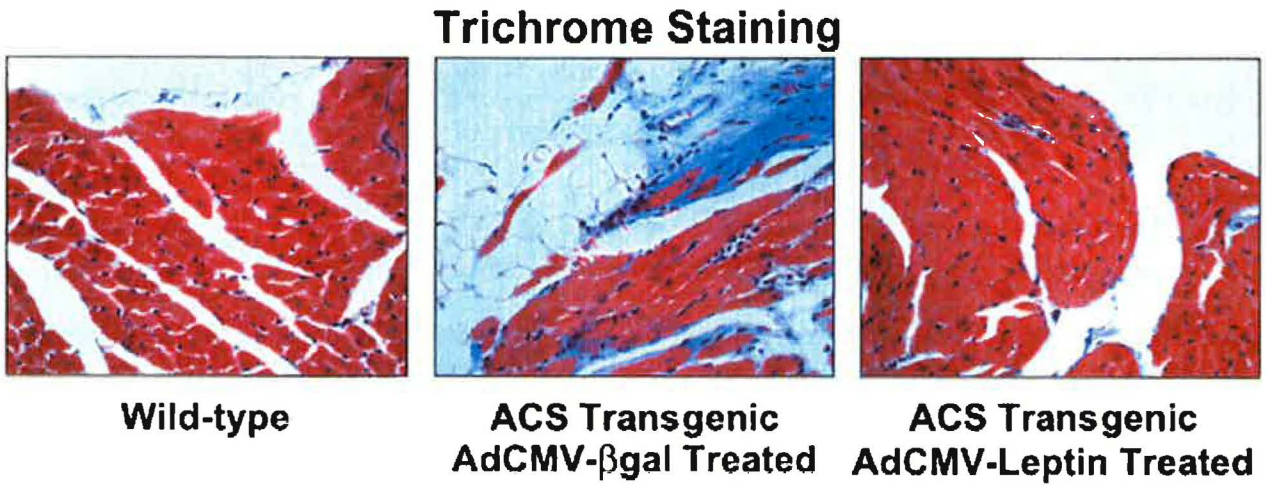

Figure 16. *Obesity-level hyperleptinemia induced by AdCMV-leptin treatment prevents interstitial fibrosis and lipotoxic cardiomyopathy.*

Mechanisms of leptin's antisteatotic effect:

A. Compensatory Oxidation: Two possible mechanisms for leptin's antisteatotic effect come to mind: 1) a compensatory increase in uncoupled fatty acid oxidation and 2) an increase in reverse fatty acid transport. There is strong evidence suggesting a compensatory increase in fatty acid oxidation is induced by leptin, at least in nonadipose tissues such as the islets of Langerhans (Shimabukura et al, 1997; Zhou et al, 1997). Figure 17 shows the effect of leptin on fatty acid oxidation in isolated islets. There is substantial evidence that leptin increases the activity of the "fuel gauge," AMP kinase (Hardie, 2004), by increasing its phosphorylation. AMP kinase inactivates the enzyme acetyl CoA carboxylase (ACC), which produces malonyl CoA, the first committed step in lipogenesis. McGarry and Foster showed in 1978 (McGarry et al, 1978) that malonyl CoA inhibits carnitine palmitoyl transferase-1 (CPT-1), the rate-limiting enzyme of fatty acid oxidization. By inhibiting ACC, leptin would block lipogenesis and stimulate fatty acid oxidation, thereby lowering fatty acid availability. Its ability to induce the expression of uncoupling proteins 1 and 2 implies that the oxidation is uncoupled and the energy generated dissipated as heat (Zhou et al, 1997). In addition, leptin is a powerful inducer of the coactivator peroxisome proliferator activated receptor γ-coactivator 1 (PGC-1α) (Kakuma et al, 2000), which induces mitochondrial biogenesis (Puigserver and Spiegelman, 2003). Thus leptin appears to act on nonadipose tissues to increase the number of mitochondria, and their lipooxidative activity, while "wasting" the energy as heat. All in all, this would provide a rather effective protection against steatosis.

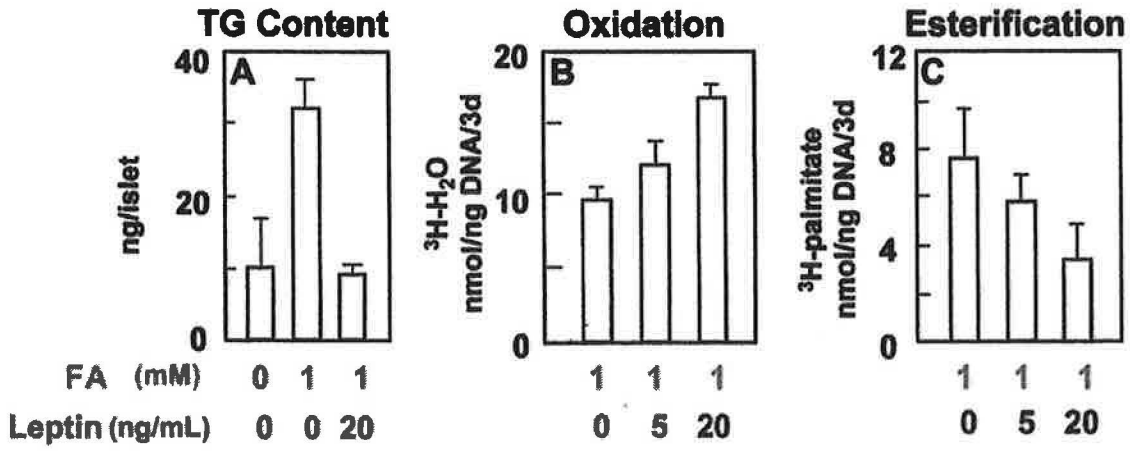

Figure 17. *Leptin prevents lipid overload in nonadipose tissues (isolated rat islets) by increasing oxidation and decreasing esterification of fatty acids (FA).*

B. Reverse fatty acid transport: Conventional dogma holds to a one-way trip for fatty acids. Certainly fatty acids flow from adipocytes to nonadipose tissues during periods of fasting and exercise when insulin levels are low. Recently, however, Park and co-workers (2004, submitted) have demonstrated for the first time a reverse flux of FA out of nonadipose tissues whenever FA oxidation has peaked and cannot be further enhanced. The efflux of long-chain fatty acids was demonstrated *in vitro* in cultured cardiomyocytes, *ex vivo* in the isolated perfused heart (Figure 18), and *in vivo* in lipodystrophic mice without any adipocytes. The efflux from cardiomyocytes appears to involve the fatty acid transporter CD36/FAT and fatty acid binding protein (FABP), both of which are translocated through insulin action to the plasma membrane of the cell. Although the direct effect of leptin on this process has not been demonstrated, leptin action greatly enhances insulin effectiveness, which would be consistent with an indirect leptin-mediated enhancement of fatty acid efflux from cells.

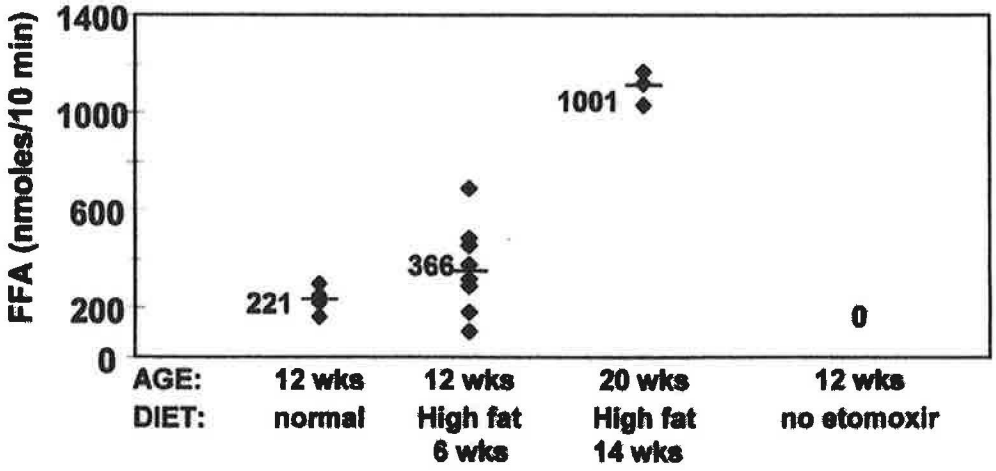

Figure 18. *FFA release from perfused hearts of normal lean rats whenever fatty acid (FFA) oxidation is blocked by etomoxir.*

Anti-apoptosis: leptin may also have an anti-apoptotic effect mediated by preventing fatty acid-induced suppression of Bcl-2 and an increase in its activity (Figure 19) (Shimabukura et al, 1998).

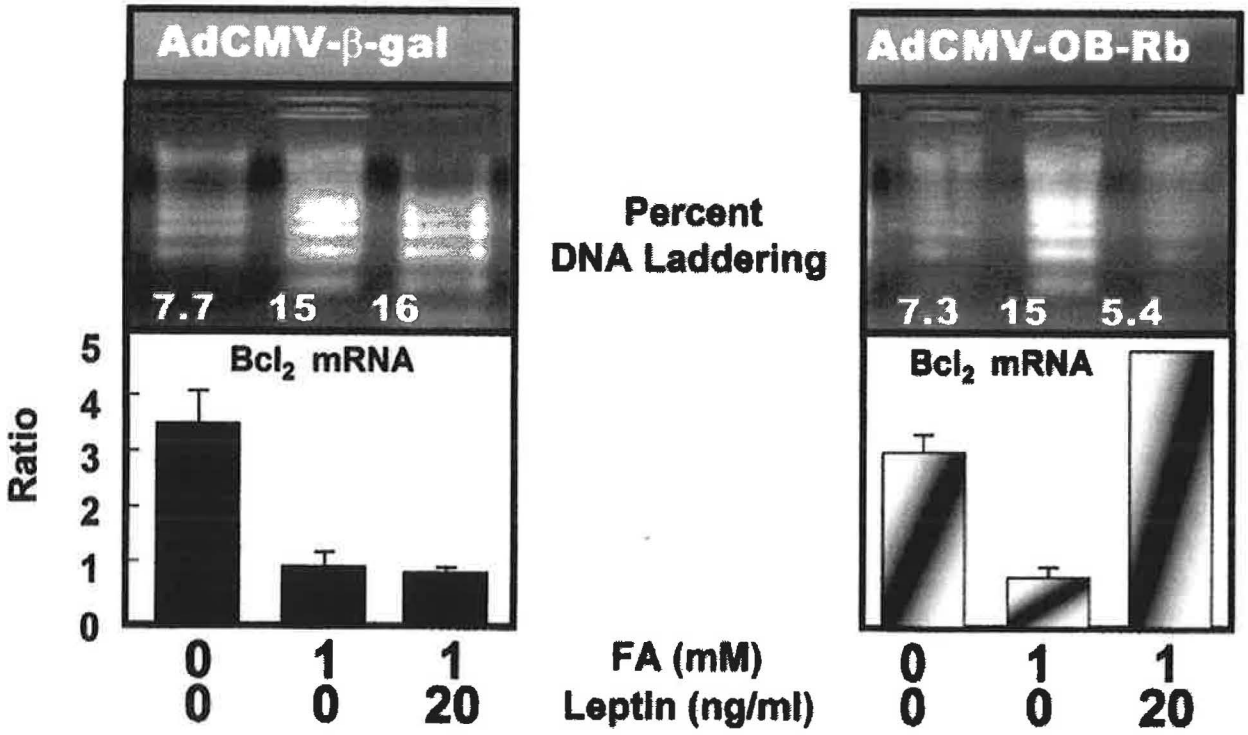

Figure 19. *Expression of the normal leptin receptor (OB-Rb) ■ restores leptin protection of fa/fa □ islets against fatty acid-induced apoptosis by Bcl_2 suppression. Left: Islets from fa/fa rats have nonfunctioning leptin receptors. Fatty acids (FA) suppress Bcl_2 expression and cause increased DNA laddering, an index of apoptosis. Right: AdCMV-OB-Rb treatment provides these leptin-unresponsive islets with functioning leptin receptors. Leptin (20mg/ml) now prevents fatty acid suppression of Bcl_2 and the increased DNA laddering is prevented.*

Is the human metabolic syndrome the same as the lipotoxic syndrome of rodents?

It is, of course, not possible to do the extensive lipid analyses in human tissues that have been done in the rats. Nevertheless, there is substantial circumstantial evidence suggesting that the metabolic syndrome is, like the lipotoxic syndrome of leptin-resistant rodents, the result of generalized steatosis, lipotoxicity and lipoapoptosis.

Fatty heart is a prominent feature of the metabolic syndrome of ZDF rats, but it is not considered a clinical diagnosis in humans, despite evidence that in human obesity, cardiac lipids are increased. Oil red O staining has been positive in the human hearts available for such studies (Figure 20).

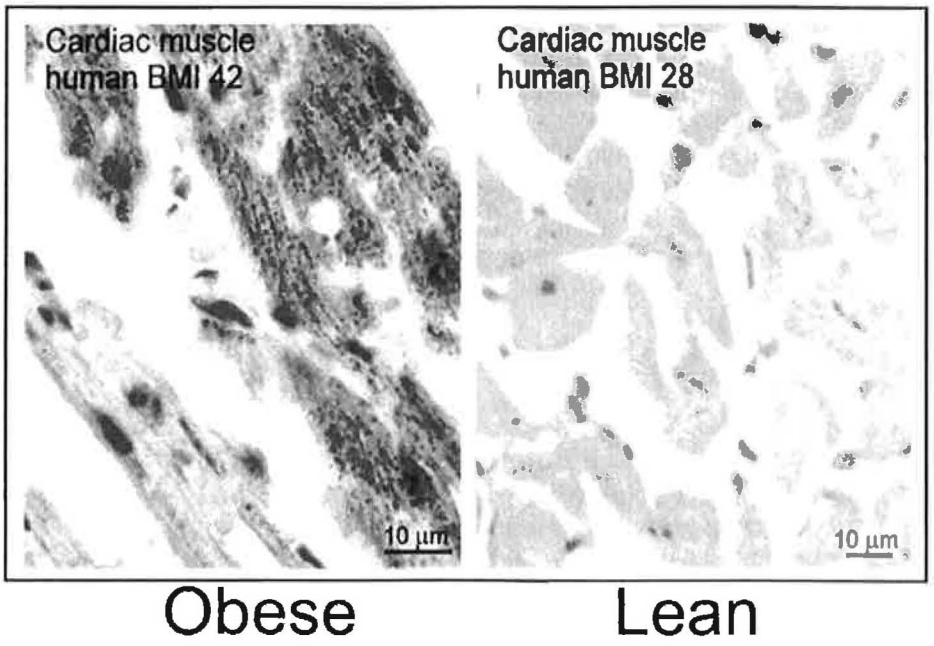

Figure 20. *Fatty heart of an obese human. Courtesy of Lelio Orci.*

Lidia Szczepaniak, Ph.D., of this institution, working in Ron Victor's group, has reported a correlation between body mass index and intracardiomyocyte TG by magnetic resonance spectroscopy (Szczepaniak et al, 2003). There was an inverse correlation between intracardiomyocyte lipids and myocardial function (Figure 21).

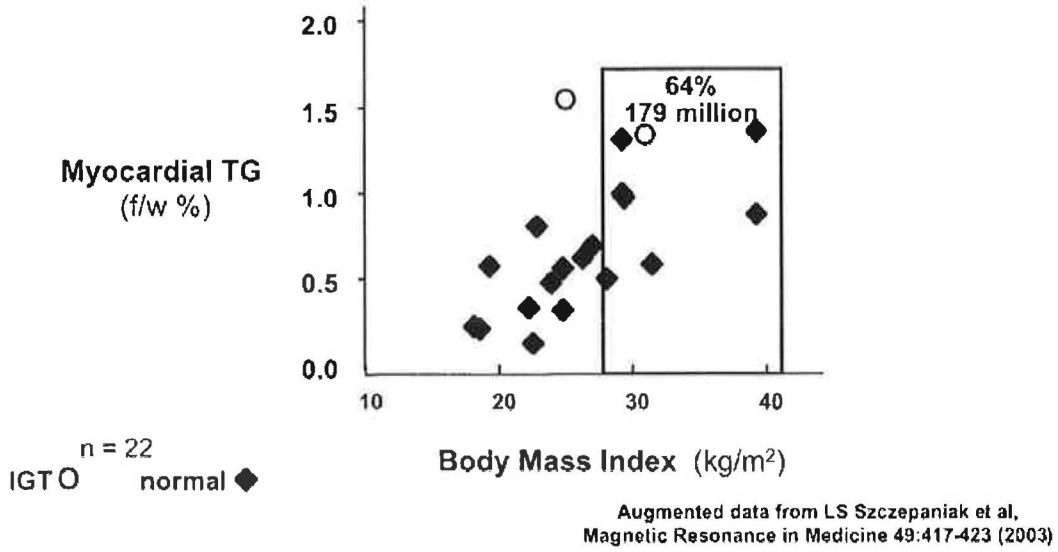

Figure 21*. Cardiomyocyte triglycerides measured by magnetic resonance technology in seemingly healthy subjects. Courtesy of L. S. Szczepaniak.*

Obesity is also well recognized to be the major cause of hepatic steatosis and is common in both rodent and human obesity. The steatosis of the pancreatic islets seen in unleptinized

rodents is, of course, impossible to prove in humans. Nevertheless, its relationship to obesity parallels that of the rats with lipotoxic beta-cell disease and it can be completely prevented in both leptin-resistant rats (Higa et al, 1999) and in humans (Nolan et al, 1994) by treatment with thiazolidiones and by caloric restriction (Ohneda et al, 1995).

Given the fact that rodent lipotoxicity and human metabolic syndrome are both associated with obesity, both comprise identical clinical derangements and both respond therapeutically to the same pharmacologic interventions, it seems reasonable to conclude that they are one and the same.

Aging and the Metabolic Syndrome

Obesity is not inheritantly unhealthy, as long as the surplus lipids are partitioned in the adipocyte compartment as the result of the action of leptin and perhaps other adipocytokines such as adiponectin. However, this action of leptin diminishes with age. Figure 22 compares the action of leptin on normal rats at the age of 6 weeks and rats at the age of 1 year. Leptin is less than 10% as effective as in the older rats (Wang et al, 2001). Age-related leptin resistance is believed to be the result of increased expression of suppressor of cytokine signaling (SOCS)-3 expression. In addition to leptin resistance, there may be relative hypoleptinemia due to a disproportionate increase in the visceral adipocytes relative to subcutaneous adipocytes. As mentioned, visceral adipocytes make less leptin than subcutaneous adipocytes.

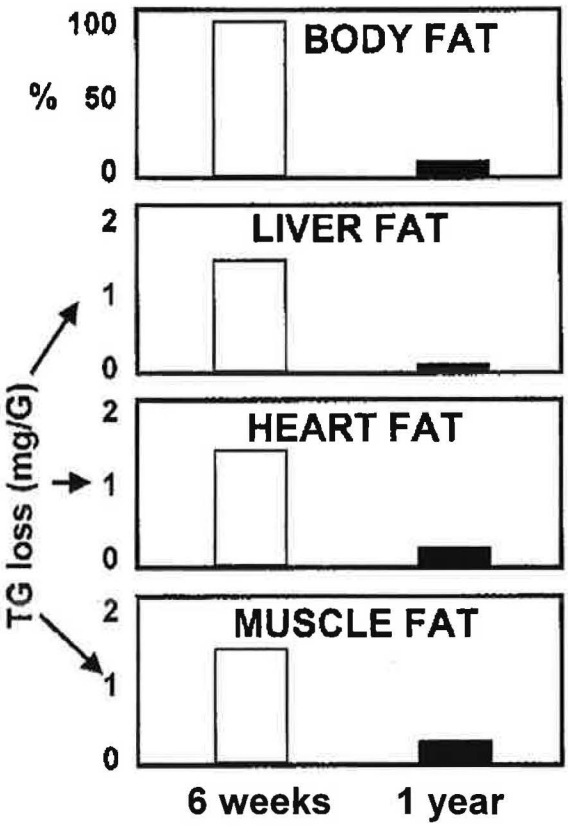

Figure 22. *Effect of aging on tissue fat content.*

MEDICAL TREATMENT OF OBESITY AND METABOLIC SYNDROME

Obesity and metabolic syndrome are polar opposites in terms of treatability. Obesity is very difficult to reverse once established, while prevention and reversal of metabolic syndrome is relatively easy, at least in its early stages.

Medical treatment of obesity: Medical treatment of obesity would include a long list of diets and drugs, none of which have been effective enough to take hold. The concept that a diet is a treatment for obesity is inherently counterproductive since it implies that a temporary alteration of life-long dietary habits and lifestyle may solve or ameleriorate the problem, which is almost never the case. What most patients and physicians fail to realize is that, once obesity is established, the caloric balance (food intake vs. energy consumption) are in a steady state. Only a substantial sustained negative caloric balance will reverse the obesity, given the fact that the function of the adipocyte is to retain its fat tenaciously, and to relinquish it only to promote survival in time of famine.

a. Cannabinoid receptor antagonist: Pharmacology of weight loss has been as dismal as the dietary approach, and the many ineffective agents will not be discussed. The current panacea *du jour* is a cannabinoid receptor inhibitor called SR141617 or rimonabant, which apparently is an antagonist to endogenous ligands, such as anandamide and 2-arachidoyl-glycerol (2-AG) (Valenti et al, 2004), which reacts with CB1 and CB2, the receptors that mediate marijuana action (Columbo et al, 1998; Ravinet Trillou et al, 2004). The results thus far have been extremely promising, and are in phase 3 clinical trials. Not only do they cause important loss of weight, but also they improve the abnormal lipid profile, while facilitating cessation of smoking (Cannon et al, 2004). Despres et al (2004) treated 1036 overweight, high cardiac risk patients with 20 mg for 1 year. They lost an average of 20 lbs, HDL rose 23% and TG fell 15%. The drug could be on the market by 2006.

b. Converting white adipocytes into brown adipocytes: Recent work from our laboratory has demonstrated that adenovirus-induced hyperleptinemia converts white adipocytes of normal lean rats from fat-storing cells into fat-burning machines that completely oxidize all body fat within 7 to 14 days (Figure 23A) (Orci et al, 2004). They do this uniquely by increasing FA oxidation within the white adipocytes and without exporting them to the liver as in other forms of weight loss.). Instead of containing fat, cytoplasm of the adipocytes is full of mitochondria (Figure 23B). This is mediated by an increase in PGC-1α (Figure 23C). UCP-1 and –2 expression, and AMP kinase activation were also increased (Figure 23D). Ironically, this effect of leptin does not occur once these normal rats overeat and develop diet-induced obesity. In other words, when the adipocyte senses a positive caloric balance and starts to increase its secretion of leptin, it becomes resistant to the autocrine action of its leptin in order to retain its fat-storing capability (Figure 24). Were it not for this leptin-hypersecreting leptin resistance, adipocytes would be incapable of storing fat because the leptin would induce a futile cycle in which FA would immediately be oxidized to produce heat rather than stored for future use during famine. Since our obese patients are unlikely to agree to a therapeutic "famine," it might be therapeutically useful it we could at least temporarily overcome the block of leptin activity in adipocytes, and induce the futile cycle by rendering exogenously administered leptin effective as a means of "pharmacologic liposuction." However, the predicted hyperthermia might preclude the approach.

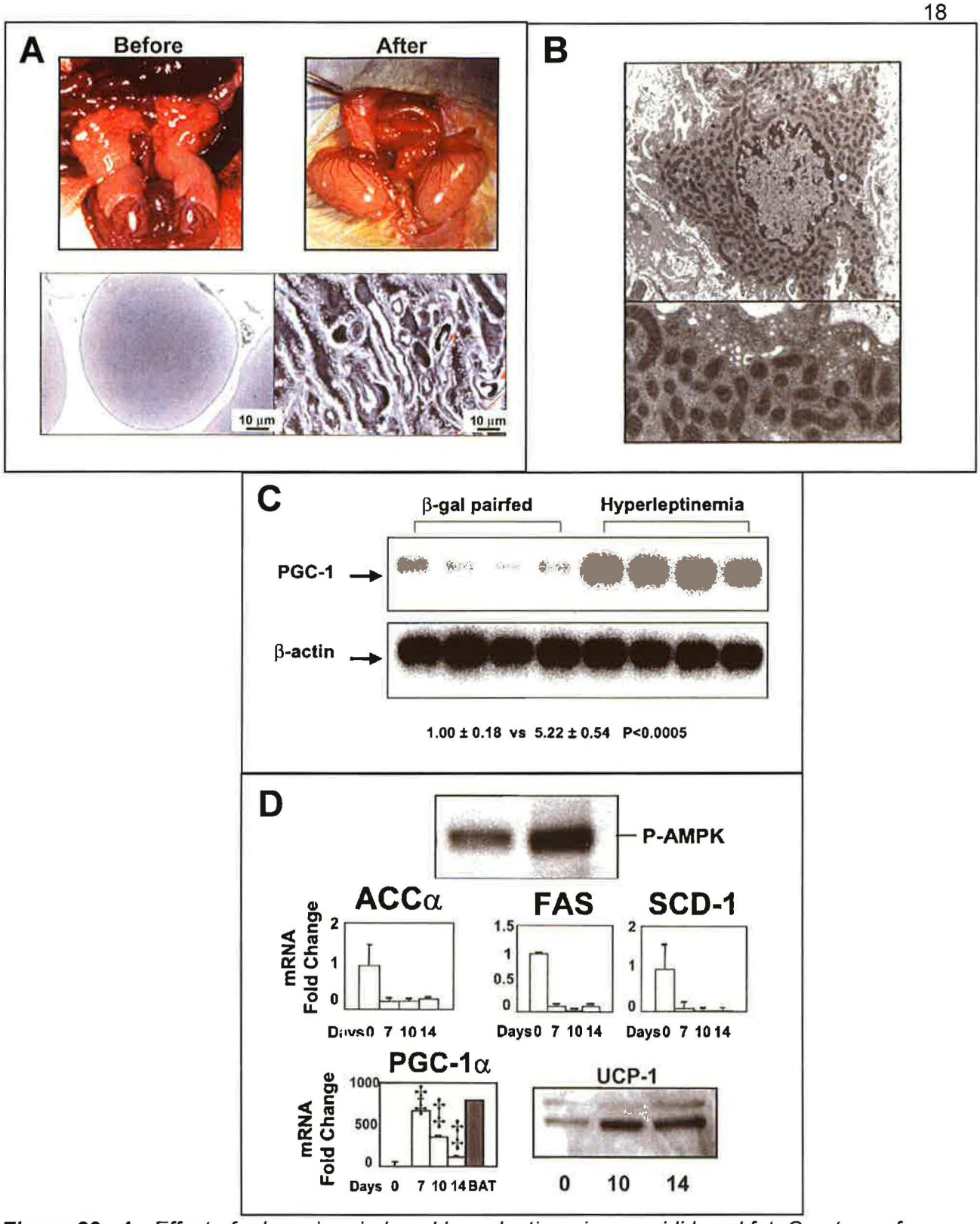

Figure 23. *A. Effect of adenovirus-induced hyperleptinemia on epididymal fat. Courtesy of Lelio Orci. B. White adipocytes after 14 days of hyperleptinemia, showing loss of fat and increased mitochondria. Courtesy of Lelio Orci.C. PGC-1 expression in white adipocytes during hyperleptinemia. D. Leptin-induced changes in normal adipocytes during fat disappearance, showing AMP-K activation and expression of genes involved in uncoupled oxidation.*

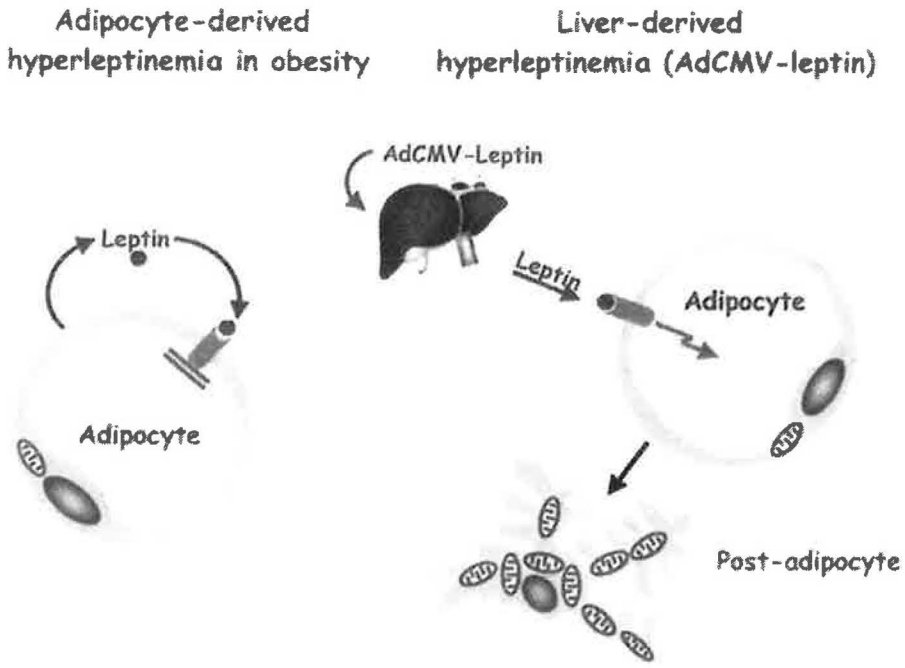

Figure 24. *Comparison of adipocytes-derived hyperleptinemia in obesity with liver-derived hyperleptinemia (AdCMV-leptin) in normal rats. The effects of endogenous adipocyte-derived leptin are completely blocked. Courtesy of Roberto Montesano.*

c. Inducing Adipocyte Apoptosis Through Prohibitin Targeting: In contrast to fat depletion of white adipocytes fat through their conversion to brown adipocyes phenotype, Kolonin et al (2004) report on depleting the adipocytes themselves by apoptosis. They use the peptide motif CKGGRAKDC to home in on prohibitin molecules that are displayed on white fat vasculature, which is estimated to be a mile long. The blood vessels of white fat tissue can be targeted with pro-apoptotic molecules that induce apoptosis in the adipocytes by synthesizing a hybrid molecule consisting of the CKGGRAKDC homing motif plus the apoptogenic molecule KLAKLAK2, which disrupts mitochondrial membranes and causes cell death. It had been used previously to induce apoptosis in tumors. Prohibitin is an ubiquitous mitochondrial protein of uncertain function widely expressed on intracellular membranes but not on plasma membranes. Iits expression of the surface of adipocytes endothelial cells anda nowhere else was completely unexpected.
The reversal of obesity in mice without side effects is promising, although unrestrained overeating in the absence of adipocytes could cause the lipodystrophic variant of the metabolic syndrome, unless the hyperphagia of leptin deficiency is prevented with by exogenous leptin replacement or accomplia rx.

Surgical treatment of obesity: Bariatric surgery is a common procedure that has been extensively reviewed elsewhere. Suffice it to say that it appears to reduce approximately 80 pounds of weight from massively obese people, the prime candidates for which the procedure is prescribed.

Treatment of the metabolic syndrome: The metabolic syndrome is relatively easy to prevent and to reverse, at least if intervention begins before the involved organs have been irreparably compromised. The simple regimen of caloric restriction and exercise will be beneficial even without any reduction in total body fat. The mechanism of these benefits are thought to be mediated by increased AMP in the tissues, which activates AMPK and inactivates ACC, all of which will enhance the oxidation of fatty acids (Figure 25).

There are several drugs that activate AMP kinase. Thiazolidinediones, metformin, and leptin, are the most extensively used AMPK activators in experimental animals. However, none of these agents have been examined in humans for clinical efficacy in preventing the features of metabolic syndrome other than type 2 diabetes.

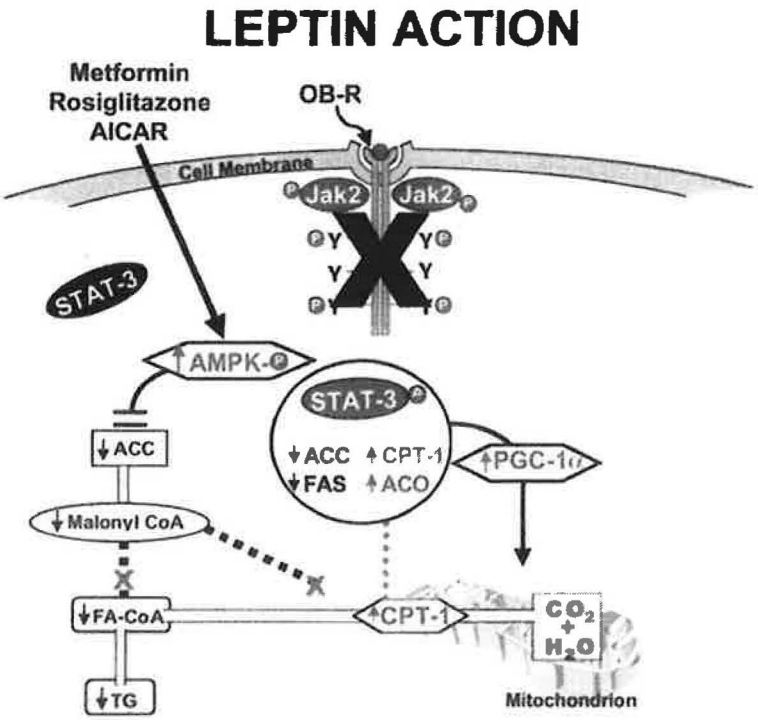

Figure 25. *When the leptin action pathway is blocked, AMP-K activating drugs can mimic to some degree the action of leptin.*

Summary:

There can be little question that the United States has fallen prey to a devastating attack on the national health. However unintentional this may have been, its goal was to alter the feeding habits of the nation in order to increase the consumption of calorie-dense, processed foods by aggressive promotion, ubiquitous availability, extremely low cost, and alteration of food preferences (attracting youngsters to such diets through gifts and playgrounds). These tactics have been very effective in altering food preferences in various parts of the world; in the Orient, where rice has been the staple of diets. American fast food is making important inroads and, for the first time, obesity has appeared.

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