

# OBESITY IS CELLULAR OXYGEN DEFICIENCY: THE DYS-OX MODEL OF THE MUSCLE AND FAT CELL DYSFUNCTION

**Majid Ali, M.D.**

**Professor of Integrative Medicine,  
Capital University of Integrative Medicine, Washington, D.C.**

Chemicalized foods, chronic anger, fatigue that prevents exercise, and bad science of nutrition — put them together and you have a prescription for an obesity epidemic. Two thirds of American are overweight at present. For that tragedy, I hold responsible the gurus of weight control industry who engage in frivolous debates about low-carb, low-fat, and other dieting plans, and ignore the real causes of obesity given above. And the high priests of 'nutrition science' at the American Medical Association, the National Institutes of Health, *The New England Journal of Medicine*, and Food and Nutrition Board? None of them has the courage to speak out against those chemicalize our foods, pollute our environment, or victimize overweight individuals with toxic information.

## OUTLINE

- |       |   |        |   |
|-------|---|--------|---|
| I.    | Introduction  | XII.   | Neurotransmitter and Hormonal Regulation of Energy Homeostasis  |
| II.   | The Obesity Epidemic and the Academicians                             | XIII.  | The Oxidative-Dysoxygenative Insulin Dysfunction and Obesity  |
| III.  | The Obesity Epidemic and the Ghostwriters of the Weight Loss Industry | XIV.   | The Inflammatory Theory of Obesity  |
| IV.   | Persistent Obesity Is Cellular Toxicity                               | XV.    | The Oxidative Theory of Obesity   |
| V.    | The Spreading Epidemic of Obesity                                     | XVI.   | The Oxygen Theory of Obesity: The Adipomyocytic Dysoxygenosis Model                                   |
| VI.   | The Spreading Epidemic of Mitochondrial Dysfunction                   | XVII.  | The Oxygen Model of Obesity Explains Its Link to Heart Disease, Diabetes, Cancer, and Other Disorders |
| VII.  | The Travesty of Food Pyramids   | XVIII. | Optimal Weight for the Life Span  |
| VIII. | Low-Fat Weight Loss Programs Are Fattening                            | XIX.   | Upregulation of Fat-Burning Enzymes   |
| IX.   | Low-Carb Weight Loss Programs Are Fattening                           | XX.    | Limbic Exercise   |
| X.    | Energy Homeostasis and Adaptive Thermogenesis                         | XXI.   | Concluding Comments   |
| XI.   | Obesity Genomics  |        |   |

## I. INTRODUCTION

Misinformation about the science of health, eating depleted and denatured foods, and chemicalization of our cells — put them together and you have a very effective prescription for causing a massive epidemic of obesity. All those factors eventually lead to dysoxygenosis in adipocyte and myocytes. That, simply stated, is the tragedy of epidemics of obesity and diabetes that we witness today. If we wish to understand the links between obesity and many other disorders, again we need to consider the basic scientific aspects of oxygen homeostasis, cellular energetics and energy homeostasis in the body.

In 2004, in an article entitled "Hypothesis: Obesity Is Adipomyocytic Dysoxygenosis," I introduced the concept that excess body weight that cannot be lost by ordinary efforts of reduced caloric intake and increased physical activity is a cellular oxygen deficiency state caused by impaired mitochondrial function (the dys-ox state) in adipocytes and myocytes.<sup>1</sup> In that "adipomyocytic dysoxygenosis (AD) model," the fundamental electron transport enzymatic pathways that initiate metabolic events and sustain a robust metabolism — and an optimal weight — are injured by toxic foods, toxic environment, toxic emotions, and toxic thinking. In persistent obesity, adipocytes are increased in number and distended with fat. More importantly, the mitochondria are dysfunctional and the cells have impaired oxygen utilization. That, simply stated, is the root cause of the spreading epidemic of obesity in the United States and elsewhere in the world. For the general readership, I also published a second article entitled "Oxygen Is Cellular Oxygen Deficiency State," to provide a rational and scientifically sound approach to achieving and maintaining an individual's optimal weight.<sup>2</sup>

### Three Furies of Obesity

Excess fat in the adipocyte is oxidizing. Excess oxidation in the adipocyte impairs cellular oxygen utilization. Adipocyte dysoxygenosis so produced evokes "molecular inflammation" in the cell. Molecular inflammation in adipose tissue activates macrophages and vascular endothelial cells, and so sets the stage for cellular inflammation. Adipose inflammation so produced further stokes the oxidative fires in adipocytes. More fat, more oxidation, more oxygen dysfunction, more inflammation — the cycle

perpetuates itself, increasing the degrees of oxidosis, acidosis, and dysoxygenosis (the three furies of obesity). That, simply stated, is the inflammatory theory of obesity.

The adipomyocytic dysoxygenosis model of obesity is distinct from the views of obesity held by purists in the fields of clinical bariatrics, energy homeostasis, and genomics on the one side and the authors of weight control books, who with uncommon exceptions are mere ghost writers for the enormously rich weight control industry. The adipomyocytic dysoxygenosis model of obesity — in my view — is superior to other prevailing notions for the following six principal reasons:

1. It holds the cellular energetics and energy homeostasis in the muscle and fat cells as its two centerpieces, which simply cannot be optimally maintained without daily physical exercise.<sup>3</sup>
2. It focuses on the issue of altered cellular metabolism as the *primary* phenomenon in the causation of obesity, rather than on gene mutations currently in fashion among academics.<sup>4-8</sup>
3. It makes a sharp distinction between foods and ecologic factors that preserve cellular oxygen homeostasis and those elements that put it in jeopardy, rather than engage in meaningless low-carb/low-fat debates.<sup>9-17</sup>
4. It addresses the critically important factors of food allergy and related adverse food effects, as well as large variations among individuals in their requirements for nutrients. Those factors are taken into account neither by promoters of various weight loss diets nor by the academics.<sup>18-22</sup>
5. It has a strong explanatory power for molecular pathways that link obesity to coronary heart disease, cancer, and other disorders discussed in a later section.
6. It provides sound scientific basis of integrative plans to effectively address the problem of obesity, rather than the use of drugs like leptin, dexfenfluramine (taken off the market) and sibutramine (modulators of serotonin), and others, none of which have proven safe and effective in the long run.<sup>23-27</sup>

## II. THE OBESITY EPIDEMIC AND THE ACADEMICIANS

As for the academicians preoccupied with genomics of obesity, I do not foresee they are going to be very helpful to two thirds of Americans who are overweight. Those academicians seem not to have learned yet that food fuels the furnace of human metabolism and exercise stokes it fires. Lest some reader think I am overly dramatizing my case, consider the following quote from *The New England Journal of Medicine*:

The January 7, 1865, issue of *Harper's Weekly* published instructions on weight loss that are not so different from the advice offered by sensible physicians today. Advances in the treatment of obesity have been made since then, but we must acknowledge that they are not sufficient. In contrast to these pallid therapeutic advances, our understanding of the mechanisms of obesity has improved substantially in the past 20 years. In the early-to-mid-1980s, revolutionaries such as Stunkard published convincing data that human obesity had an inherited component and sparked an explosion of research on the genetic and biologic underpinnings of obesity.<sup>28</sup>

*Advances in the treatment of obesity have been made since then!* That is a misstatement if there ever was one on the subject. What the *Journal* considers advances in the treatment of obesity have utterly failed in the United States, where three out of every five persons now are overweight or obese. Not only has the mainstream medicine — essentially a medicine of pharmacologic blockade — not brought forth any benefits, in my view it has significantly contributed to the problem by ignoring the real issues and injudiciously prescribing drugs that slow down the metabolism.

Now consider the following quote in a recent review of obesity in *Nature*:

The global epidemic of obesity results from a combination of genetic susceptibility, increased availability of high-energy foods and decreased requirement of physical activity in modern society.<sup>29</sup>

Amazingly, *Nature*, one of the most, if not the most, prestigious science journals in the world completely fails to address the elements that threaten redox equilibrium and oxygen homeostasis — related to highly processed foods, environmental pollutants, and emotional stresses — that impair or block enzymes of Krebs and other catabolic pathways. The case of peddlers of 'obesity drugs' is the same. Consider the following quotes from *Nature*:

Whatever happened to leptin? Just five years ago, it seemed that a single protein might reverse the rising tide of obesity. What worked for mice has not yet translated to people.... By any reckoning, US\$20 million is a lot to spend on a protein. But in May 1995, Amgen of Thousand Oaks, California, paid just that for the commercial rights to leptin, a hormone that made fat mice slim. Identified only six months earlier, leptin could be injected into grotesquely obese, leptin-deficient mice where it curbed their voracious appetites and boosted their metabolic rates. Within a month, and with no apparent side-effects, these mice lost almost half of their excess weight.<sup>30</sup>

Leptin, of course, was touted as the wonder drug fully capable of killing the dragon of obesity.<sup>31,32</sup> Now, nearly ten years later, it is clear that script was written to divest gullible investors of their hard-earned retirements. Clinical trials so far have failed to show any merits of the hormone.

As for links between obesity and chronic diseases—the cardiovascular diseases, diabetes, cancer, and others —consider the following quote from *Nature Insight-Obesity*:

For reasons that are not fully known, obesity is associated with an increased risk of hypertension, heart disease, diabetes, and cancer.<sup>33</sup>

It seems safe to predict that preoccupation with obesity genes will not reveal the fundamental links between obesity and any of the diseases mentioned in the above quote. Nor will that be achieved by loud quarreling among enthusiasts of low-carb and low-fat

diets. Obesity, at its core, is a problem of molecular energetics. And molecular energetics, at its core, is a matter of redox equilibrium and oxygen homeostasis. I return to this crucial issue in a later section.

### III. THE OBESITY EPIDEMICS AND THE GHOSTWRITERS OF THE WEIGHT LOSS INDUSTRY

The authors of popular low-carb, high-protein, low-fat, and other diets, with uncommon exceptions, have been mouthpieces of the rich and enriching weight control industry. *They did not write about what they actually observed in their patients over years and decades.* Rather, they were driven by the profit motive, not by any passion to guide people back to health. The marketers of those books have rendered an enormous disservice to overweight and obese individuals in three ways: (1) they have kept the focus away from the central issue of daily physical exercise, without which optimal weight simply cannot be achieved or maintained; (2) they have essentially ignored the issues of depleted and denatured foods, and the impact of food allergy and adverse reactions caused by the altered states of bowel ecology; and (3) they disseminated misinformation about the roles of carbohydrates, proteins, and fats in cellular energetics and energy homeostasis in the long-term.

Some are merchants extolling the virtues of their potions or diet bars. In decades of clinical work I have not seen patients who stayed on any of those weight loss programs for years and later were thinner and healthier. Invariably, they initially lost weight on those diets but ended up heavier and sicker in the long run.

There have been good books written about improving health, speeding up the metabolism, and losing unwanted weight. But truth generally has few takers. Rich companies were not interested in promoting those books because they could not see any profitability in the sound health information contained in those volumes. Recently I learned that someone I know (who has great passion for giving good health information) was banned from the public TV channels because he had spoken strongly about the health hazards of sugar. Health information on TV is nearly always delivered by those paid — albeit indirectly — by drug companies. They know they cannot bite the hands that feed them.

### IV. PERSISTENT OBESITY IS CELLULAR TOXICITY

*Persistent obesity is cellular toxicity caused by cellular dysoxygenosis!* This may surprise some readers, but only because they would not have reflected on the energetic-molecular basis of obesity. Excess weight accumulation generally begins with lack of exercise, habitual overeating, consuming highly processed foods, and using food to cope with anger. But what turns that initial mild weight gain into persistent obesity? That question has not been critically addressed in the field of energy homeostasis.

Since oxygen is the organizing influence of human biology and nutrition sustains oxygen homeostasis, it follows that weight gain and obesity, at a fundamental level, must be related to oxygen homeostasis in the body. That, indeed, is the case. Obesity — in my view — cannot be understood without a clear understanding of cellular dysoxygenosis. (Cellular oxygen dysfunction and dys-ox are the terms I use for patient education.) Nor can obesity be prevented and reversed without effectively addressing the central issue of cellular dysoxygenosis.

I believe much light on that question can be shed if the problem of energy dyshomeostasis in obesity is seen in light of cellular oxidative- dysoxygenative models of various clinical disorders. In a series of previous articles, I have presented the crucial aspects of altered cellular energetics and impaired oxygen utilization in fibromyalgia,<sup>34,35</sup> atopic disorders,<sup>36</sup> insulin dysfunction and diabetes,<sup>37</sup> cancer,<sup>38</sup> mercury-related illness,<sup>39</sup> dysautonomia,<sup>40</sup> coronary artery disease,<sup>41</sup> and other degenerative disorders.<sup>42</sup> Indeed, the adipomyocytic dysoxygenosis (AD) model of obesity is rooted in my earlier models of those disorders.

*In adipomyocytic dysoxygenosis, cellular fat itself becomes oxygen-depriving and fattening.* I concede that direct experimental evidence for some aspects of my view is not yet forthcoming. However, the preponderance of direct and indirect lines of evidence for my core concept of cellular dysoxygenosis is so overwhelming that I am certain when my hypothesis is put to experimental test, it would be borne out. I discussed this subject at length in *The Ghoraa and Limbic Exercise*.<sup>43</sup> Brief comments about mitochondrial energy dysfunction in a subsequent section will also shed some light on my view.

*Adipomyocytic dysoxygenosis is the primary mechanism of incremental cellular fat storage!* That may also seem far-fetched to some and too simplistic to be of clinical value to others. Yet others might be amused by it because they find it flaunting the thermodynamic principles. I believe a careful review of relevant facts of pathobiology of obesity and deeper reflection on the pandemic of obesity in many countries of the world will show that my view has considerable merit.

## V. THE SPREADING EPIDEMIC OF OBESITY

Consider the following quote from a recent issue of *Science News*:

The United States is big, and getting bigger each year — at least around its collective waistline. Federal statistics indicate that as of 2001, one in five U.S. adults was obese. That's roughly 45 million people. Almost twice that many fall into the next category, overweight. Some 15 percent of children, ordinarily the most active and trim segment of population, are also too heavy.<sup>44</sup>

The federal statistics also tell us that in one decade — from 1991 to 2001 — the number of obese people in the country *increased by 74 percent*. To make matters worse, the largest increase in obesity-related disabilities was observed in the age group expected to be most productive in the society — those between 30 and 49 years. But obesity is not merely a problem of the rich West. Consider the following quote from *Nature*:

Obesity is now so common within the world's population that it is beginning to replace undernutrition and infectious diseases as the most significant contributor to ill health. In particular, obesity is associated with diabetes mellitus, coronary heart disease, certain forms of cancer, and sleep-breathing disorders. Obesity is defined by a body-mass index (weight divided by square of the height) of 30 kg m<sup>-2</sup> or greater, but this does not take into account the morbidity and mortality associated with more modest degrees of overweight, nor the detrimental effect of intra-abdominal fat.<sup>45</sup>

Obesity has been considered by most to be largely a disease of post-industrial society. But this broad generalization is misleading. For example, the prevalence of obesity in highly advanced Sweden is less than that in the United States.<sup>46</sup>

## VI. THE SPREADING EPIDEMIC OF MITOCHONDRIAL DYSFUNCTION

The subject of obesity cannot be separated from that of mitochondrial function. Mitochondria are the organelles of cellular energetics as well as the seat of lipid metabolism. Thus, it should not surprise us that there is close parallelism in the rising incidences of obesity and mitochondrial dysfunction. And that is so even though clinicians, with rare exceptions, do not investigate the possibility of mitochondrial dysfunctions in their clinical practices.

The November 3, 2003, issue of *U.S. News & World Report* ran a story titled "Energy Crisis." Following are some excerpts from that article:

Failing 'power plants' inside cells give rise to debilitating diseases ...Researchers have also uncovered intriguing clues suggesting that mitochondrial failure may play a role in Alzheimer's disease, stroke, diabetes, and heart disease, among other age-related ills. Although therapies remain elusive...This month, Naviaux and some of his colleagues petitioned the National Center for Health Statistics, a division of the Centers for Disease Control and Prevention in Atlanta, to officially recognize nearly 400 newly described mitochondrial disorders.

*Four hundred newly described mitochondrial disorders!* What might be the possible advantages of a classification system that establishes 400 discrete separate diagnostic labels? Such a system would be useful if it could shed light on what caused those 400 separate 'diseases.' That would open up some possibilities of disease prevention. The notion of 400 new 'diseases' could also be welcome if there were clearly delineated ways of treating those diseases. But that is not the case at all.

*Although therapies remain elusive!* Is that really true? Do therapies for prevention and reversal of heart disease, for instance, really remain elusive? Or those for diabetes? Or could it be that those 400 mitochondrial 'diseases' are, in reality, 400 different parts of the same 'elephant' of cellular oxygen failure?

Mitochondrial dysfunctions caused by chronic oxidative stress are the root causes of chronic energy deficit states labeled as chronic fatigue syndrome, fibromyalgia, environmental sensitivity syndrome, and persistent fatigue following chemotherapy.<sup>34,35,47-49</sup> The same holds for the Gulf War syndrome as well as 9/11-related illness and the chronic illness that will be undoubtedly encountered in the veterans of the second Gulf War. (*September Eleven, 2005*<sup>50</sup> for discussion.) But none of that justifies blind labeling of mitochondrial dysfunctions caused by incremental oxidative stress as specific 'disorders.'

## VII. THE TRAVESTY OF FOOD PYRAMIDS

I am puzzled why we physicians accept the claims of expertise from officials of the Department of Agriculture of the United States. They are not trained to be nutritionists. They do not practice nutritional medicine. They do not care for overweight individuals. Of course, they never speak about issues of impaired energy homeostasis. What drives them to design their frivolous food pyramids?, one wonders.

The folly of the first Food Pyramid foisted on Americans by the government bureaucrats led to an unprecedented epidemic of obesity. This is now universally recognized by the people in and out of the government. The statistics about the incidence of obesity cited earlier fully attest that. What continues to be ignored is that none of the government experts were qualified to provide any guidelines for food choices in the kitchen. They had no true-to-life experience with clinical nutrition.

While American citizens paid dearly for the bad advice they received from their government experts, the fast food industry profited enormously from it. The industry lobby made sure that those who spoke against the travesty of that pyramid were marginalized and vigorously excluded from the news media. Not too many Americans found out that the French fries they ate were laced with trans fatty acids. The meat they ingested delivered large doses of antibiotics and pesticides. People simply did not know how much

sugar was hidden in their foods, or how it clogged their arteries.

Here is what a professor at the Harvard Medical School has to say about the Food Pyramid:

A new theory threatens to upend the government's food pyramid, the nutrition bible that is used by dieters, taught to schoolchildren across the country and plastered on bread labels. The U.S. Department of Agriculture pyramid is outdated and doesn't reflect the latest food research, says Harvard professor Walter Willett, a top national nutrition researcher and author of a new book, *Eat, Drink and Be Healthy: The Harvard Medical School Guide to Healthy Eating*.<sup>51</sup>

The problem with the above statement from a Harvard professor is that he does not see any patients. He is in reality a ghostwriter for the government — an expert (in name only) too preoccupied with studies with mice and medical schools to try to go out on the field to listen to true-to-life experiences of persons gullible enough to follow the frivolous Food Pyramids put out by the Department of Agriculture..

Now consider the following quote from someone not motivated by financial rewards and interested in the truth regarding the government's food pyramid:

I also tried to find justification for The Food Pyramid in the studies hosted on the same government site that is seeding The Food Pyramid meme, but I couldn't find anything useful. Their studies on Obesity basically say, in aggregate: Most Americans are fat. Most Americans try to lose weight by cutting their fat intake. Most Americans are still fat and getting fatter. I also tried their section on Nutrition, but again it's just lots of studies that dance around the issues without actually supporting The Food Pyramid premises. Where's the basis?<sup>52</sup>

The second Food Pyramid promotes low-carb diet. Predictably, it will bring yet more obesity since it also ignores the real causes of obesity.

### VIII. LOW-FAT WEIGHT LOSS PROGRAMS ARE FATTENING

If there is less fat in the diet, the fat cells will accumulate less fat. That simplistic and simple-minded belief prevailed at the American Medical Association, the American Heart Association, the Nutrition Board, and other entities for decades. As pointed out earlier, the experts-in-name-only in those organizations advocated the low-fat diet for weight loss not because they had tested their programs and found them effective. They recommended their diets because they *thought* the diets should work.

The low-fat weight loss programs should be fattening — and, as a matter of fact, they are. The validity of that statement should be evident from the information presented in the preceding sections. Not unexpectedly, the first Food Pyramid — which ignored the essential issues of depleted and denatured foods and was based on the *opinions* of low-fat enthusiasts — brought forth an epidemic of obesity in the United States.

At a deeper level, I hold editors of prestigious medical journals accountable for the American epidemic of obesity to a greater degree. They summarily dismissed articles written by nutritionists about their true-to-life experiences with various diet programs. More damagingly, they equated nutritional medicine to quackery and environmental medicine as chicanery. Gradually over decades, their strong influence poisoned the minds of generations of young physicians against the use of nutrients to resolve problems of dysfunctional cellular energetics caused by increasing chemicalization of our foods and environment. Indeed, many of them published articles written by ghost writers on the payroll of drug companies as editorials. (See *RDA: Rats, Drugs and Assumptions* for specific citations.)

### IX. LOW-CARB WEIGHT LOSS PROGRAMS ARE FATTENING

Initially, people on low-carb diets lose weight. Then they get heavier and sicker. I cannot recall a single exception to that in hundreds of patients who were prescribed such diets and whom I saw months and years later. Amazingly, that happened to a large number of individuals on more than one occasion.' Once bitten, twice shy', seemingly does not apply to "low-carbers."

Recently, two studies of low-carb diets were published in *The New England Journal of Medicine*.<sup>10,11</sup>

Both studies were widely reported in the news media as establishing clear victory of low-carbers. The reality was totally different. Consider the following quotes taken from those articles:

Conclusions: The low-carbohydrate diet produced a greater weight loss (absolute difference, approximately 4 percent) than did the conventional diet for the first six months, but the differences were not significant at one year. The low-carbohydrate diet was associated with a greater improvement in some risk factors for coronary heart disease. Adherence was poor and attrition was high in both groups. Longer and larger studies are required to determine the long-term safety and efficacy of low-carbohydrate, high-protein, high-fat diets. At any given time, approximately 45 percent of women and 30 percent of men in the United States are trying to lose weight. Despite these efforts, the prevalence of obesity has doubled in the past 20 years and has become a major public health problem.

*But the differences were not significant at one year!* That essential message of the article was lost in the noise made by stakeholders in low-carb diet. *Adherence was poor and attrition was high in both groups!* That should have been the second message, but was not. The attention span of the TV audience was not sufficiently long.

Now, consider the conclusion of the second *Journal* article:

Conclusions: Severely obese subjects with a high prevalence of diabetes or the metabolic syndrome lost more weight during six months on a carbohydrate-restricted diet than on a calorie- and fat-restricted diet, with a relative improvement in insulin sensitivity and triglyceride levels, even after adjustment for the amount of weight lost. This finding should be interpreted with caution, given the small magnitude of overall and between-group differences in weight loss in these markedly obese subjects and the short duration of the study.<sup>11</sup>

*This finding should be interpreted with caution, given the small magnitude of overall and*

*between-group differences!* The authors must have known that disclaimers of that kind are seldom remembered by merchants of medicine.

Another problem with those two studies published in *The New England Journal of Medicine* was the matter of high drop-out rates. In the first study, only 79 of the original 132 individuals completed the six months period of study,<sup>2</sup> and only 37 of 63 persons could stay on the diet for 12 months in the second study.<sup>3</sup>

In the accompanying editorial, the *Journal* expressed its reservations with the validity of the two studies with the following words:

In general, none of these methods are defensible in the typical clinical trial, given that those who drop out are likely to differ from those who remain in the study, and all of these methods are particularly suspect in the context of a diet trial.<sup>9</sup>

*In general, none of these methods are defensible!* If that was the case, why did the *Journal* bother to publish data obtained with indefensible methods? The *Journal* editorial continued:

The average weight loss was greater in the low-carbohydrate groups than in the low-fat groups, but the difference was no longer significant at 12 months in the trial in which follow-up lasted that long. Finally, the weight loss was small relative to the amount of excess weight carried by these obese subjects.

*But the difference was no longer significant at 12 months!* That disclaimer was hidden well in the end of the editorial, an area not too many readers were expected to reach.

### **Men of Money in Medicine and the Science of Obesity**

The financial stakes in the war between low-carb and low-fat diets are enormous. What might the men of medicine have had to do with the publication of those articles in the most influential medical journal in the United States? That question did not arise in my mind until much later when I read an article in *Nature* which reported that some large Wall Street investment firms had paid 800 million dollars for controlling

interest in Atkins Nutritionals.<sup>53</sup> With that kind of money riding on low-carb products, who can doubt that those investors were going to take any loss. Whose long-term health is jeopardized by low-carb (and, by definition, high-fat) diet? Who profited? The men of money in medicine do not engage in such questions.

The folly of the second low-carb pyramid of foods being foisted on Americans by the government bureaucrats now will not stem the tide of obesity in the country. This is safe to predict. In a major review of literature concerning low-carb diets published in *JAMA* in 2003, the authors found no evidence that restricting carbohydrates had any effect in the long run.<sup>54</sup> No surprise there.

The author of the second study in the *Journal* was quoted as saying, "We have moved it from quackery to science."<sup>55</sup> One wonders about the source of such snobbery and arrogance.

## **X. ENERGY HOMEOSTASIS AND ADAPTIVE THERMOGENESIS**

From a thermodynamic perspective, energy entering the human body as oxygen and food should be balanced by energy exiting it as work and heat.<sup>56</sup> Heat generation in that model occurs due to the exothermic nature of the forward reactions of energy metabolism — those catalyzed by the mitochondrial respiratory chain, those that consume ATP (Na<sup>+</sup>/K<sup>+</sup> ATPase, Ca<sup>++</sup>ATPase, actinomyosin ATPase), and those involved in other reactions. Such heat generation, of course, is essential for maintenance of body temperature.

If the human body were a simple thermodynamics black box, the work performed by it — cerebral and cardiac activities, breathing, walking, and others — plus heat released into the environment, should equal the amount of energy given off as heat measured in calories during 'physical combustion' of the total food consumed. That model led to the development of direct calorimetry methods to measure the energy expenditure at rest (basal metabolic rate) and the concept of thermogenesis. By contrast, indirect calorimetry methods were based on the measurement of consumed oxygen. In that 'black box thermodynamic' model, weight loss is expected when the energy intake is exceeded by energy output. Conversely, weight gain and obesity are expected when energy entering the body exceeds that exiting it.

But the human body is far from a black box thermodynamic system. The term adaptive thermogenesis — also referred to as facultative

thermogenesis — was coined to refer to altered heat generation in response to changes in environment as well as diet. For example, in rodents oxygen consumption increases from two- to four-fold following acute and chronic exposure to cold temperature (4° C).<sup>57,58</sup> Shivering induced by acute exposure to cold evidently contributes to extra heat generation; however, it disappears with time and is followed by increased adaptive thermogenesis in brown fat and possibly in other fats.<sup>59</sup> Not unexpectedly, adaptive thermogenesis in humans exposed to cold weather occurs to a lesser degree because of adjustments in clothing and other behavioral responses. Specifically, lowering the temperature from 28 to 22° C has been reported to cause only 7% increase in adaptive thermogenesis in identically clothed persons.<sup>60</sup>

### **Adaptive Thermogenesis Explains Failure of Dieting Programs**

For teleologic reasons alone, diet can be expected to profoundly affect thermogenesis. Caloric restriction sufficient to maintain a 10% reduction in body weight results in decreased energy expenditure.<sup>61</sup> More dramatically, starvation decreases resting metabolic rate by as much as 40%.<sup>62</sup> The survival advantage of such adaptive thermogenesis is self evident. Energy conservation is needed when the food supply is limited. In common parlance, *dieting slows down metabolism*. Those who sell protein bars and trade in stocks of weight loss industry have little interest in the true science of energy homeostasis.

### **Adaptive Thermogenesis in Adipomyocytic Dysoxygenosis**

More important than the above theoretical considerations of adaptive thermogenesis — in my view — are the adaptive responses (beneficial as well as adverse) in thermogenesis that might be expected in clinical states characterized by cellular dysoxygenosis and the attendant respiratory-to-fermentative shift in ATP production.<sup>34-37</sup> This critical issue is seldom considered in discussions of thermogenesis and etiology of clinically significant obesity. Below, I reproduce some text from *Dysoxygenosis and Oxystatic Therapies*, the third volume of *The Principles and Practice of Integrative Medicine* (pp 39-40) that sheds light on this critical issues:

### **Oxygen and Yeastization of Human Cells**

In health, human cells harness energy with an energy-efficient respiratory mode of ATP production. A yeast cell, by contrast, is engaged in an energy-inefficient anaerobic glycolytic mode of ATP production. A human cell generates about 28 moles of ATP per one mole of glucose, a yeast cell obtains only two moles of ATP from the same amount of sugar. What would happen if human cells were to be 'metabolically degraded' to the level of yeast cells? Evidently, that means such cells would be extremely energy-deficient. But does that ever happen? Indeed, it does—and does so with regularity in chronic energy disorders, such as fibromyalgia, chronic fatigue syndrome, environmental sensitivity syndrome, severe autoimmune disorder, and in subjects receiving chemotherapy agents. The concept of oxidative regression to primordial (glycolytic) mode of energy production evolved during my work with nearly 5,000 healthy volunteer subjects and patients with a host of chronic energy disorders. I investigated the phenomena of chronic oxidosis and dysoxygenosis — as well as the clinical consequences of those states—with high-resolution phase-contrast and darkfield microscopy and analysis of urinary excretion of organic acids which would be expected to accumulate during glycolytic mode of cellular energetics. In 1998, I elaborated that concept in an article entitled "Oxidative Regression to Primordial Cellular Ecology (ORPEC).

I use the expression "yeastization of human cells" to explain, in simple terms, to my patients the essential nature of the cellular metabolic shift in ORPEC. Specifically, that phrase allows me to explain the dire energetic consequences of that shift in chronic energy states. Oxidosis, I elaborate for them, is the state of energy loss through excessive loss of electrons. Chronic oxidosis impairs or inactivates enzymes involved with the physiological respiratory ATP generation, and so initiates the process of 'human-to-yeast' shift of cellular energetics. Unrelenting oxidosis eventually affects genes responsible for

those enzymes, making that process self-perpetuating. That is the real explanation of why the recovery of patients with fibromyalgia, chronic fatigue syndrome, and related energy disorders can be disconcertingly slow.

There are yet other important aspects of adaptive thermogenesis. Specifically, I call into question the long-term clinical relevance of the prevailing method of defining obesity in terms of body-mass index (BMI). Does the weight in kilogram divided by square of the height in meters truly matter when the critical issue is body weight that might be deemed ideal for *healthful life and longevity*?

### Caloric Restriction and Life Span

Some aspects of the classical knowledge about the effect of caloric restriction on the life span of model organisms also sheds light on the subject of adaptive thermogenesis. Briefly, caloric restriction extends life span in many species and is the only established way of increasing the life span of mammals. Since Clive McKay's early classical work on effects of undernutrition (not malnutrition) on aging at Cornell University, an enormous body of literature has accumulated validating the direct relationship between caloric restriction and longevity.<sup>63-65</sup> This linkage has been documented in yeast, mosquitoes, flies, and rats. To cite a specific example, the life span of *Saccharomyces cerevisiae* increases by 25% when the glucose level in the culture is reduced from 2% to 0.5%.<sup>22</sup> Similarly mosquitoes on caloric restrictions live longer than those with ad-lib (unrestricted) feeding.

In experimental conditions, life span can not only be extended by limiting glucose availability, it can also be prolonged by reducing the activity of the glucose-sensing cyclic-AMP-dependent kinase (PKA). Such lifespan extension in mutant yeast requires both Sir2 — a regulatory protein with regulatory influences — and nicotinamide adenine dinucleotide (NAD).<sup>66-68</sup>

## XI. OBESITY GENOMICS

Rapid progress is being made in elucidating altered expressions of genes affecting essential aspects of metabolism, aging, and the species life span.<sup>91-98</sup> When viewed through the prism of oxygen homeostasis, many of those genes assume the functions of "body weight genes" and the same genes with altered expressions become the "obesity genes."

Genomics in considerations of obesity are thought to have two roles. First, investigations of rare mutations in animal models and humans provide fundamental insights into complex pathophysiological processes that initiate, amplify, and perpetuate obesity. Second, genetic information complements population-based studies that seek to unravel primary etiologic factors of obesity. Recent years have indeed brought forth remarkable progress on both fronts. Most of the previously recognized mutations in genes of model organisms that segregate as Mendelian traits have been cloned. Several homologous mutations have also been discovered as rare causes of human obesity. Mice and men share many phenotypes, and homologous obesity mutations show deep conservation of the underlying pathways. However, examination of specific characteristics in some obese individuals show aspects of energy homeostasis that appear to be unique to human physiology. Undoubtedly, a faster pace of advances in functional genomics can be forecast.

Geneticists have been a hardy bunch, considering the precious little clinical benefits their work has brought to date. Notwithstanding, they have not been shy forecasting great leaps forward. Consider the following quote from *Nature*:

Although the quantitative genetic and Mendelian approaches differ in primary goals, they may yet converge in both substance and application. New mutations in mouse obesity will provide material for candidate gene analyses, and the fraction of common human obesity genes that cause monogenic obesity when knocked out in mice could be substantial. Regardless of whether polygenic culprits turn out to be monogenic suspects, the approaches may intersect at the therapeutic level. One might imagine, for example, an array of therapies based on different single-gene disorders, each of which can be tested empirically on subsets of obese patients identified by allele sharing. Thus, genetically based treatments for common human obesity could begin while efforts continue towards molecular identification of the underlying genes. It would be surprising if the rate of progress made this past decade is not outpaced in the next one.<sup>99</sup>

I do not share the enthusiasm of the author of the above quote. The enormous value of genomics to

our understanding of the health/dis-ease/disease continuum is not contestable. However, it is one thing to delineate a plethora of genetic pathways to obesity and an altogether different thing to turn that into gene therapies for longer life span (except in a few instances of rare genetic disorders. I addressed this subject at length in *Oxygen and Aging*.<sup>100</sup>

### Obesity, Mutations, and DNA Repair

It seems certain to me that the endogenous and exogenous mutagenic factors play important roles in the causation of the obesity epidemic we are witnessing now. Such mutagens are expected to adversely affect the expression of genes that regulate the structure and function of the fat and muscle cells. To my knowledge, this crucial issue has not been investigated so far. Lacking specific information on the subject, I include below some general comments about DNA injury and repair to underscore my concern about the crucial importance of those factors in the etiology of obesity.

As is the case with other actively metabolizing cells, deoxyribonucleic acid in adipocytes and myocytes is under unrelenting assault from disruptive influences. Fidelity in its structure and during its duplication is evidently crucial to cellular structural and functional integrity. That is assured by a stunning array of cellular enzymes that detect and repair deletions, additions, and translocations in DNA threads. Such enzymes not only remove damaged segments, but also rapidly reconstitute the DNA threads in areas of gaps left by the damaging agents. One would expect that the efficiency of such enzymes would diminish with age. That, indeed, turns out to be the case. At a basic level, this expectation is borne out by the observed rising incidences of various cancers with increasing age. That is clearly a reflection of things going awry in DNA repair.

Species	DNA Repair (relative)	Life Span** (Logarithm)
Man	5	2
Indian elephant	4.3	1.9
Cow	4	1.5
Golden hamster	2	0.6
Norwegian Rat	1.8	0.5
Field Mouse	0.8	0.38
Long-tailed shrew	0.5	0.2

\* All values are included as close approximations for the sake of simplicity. See *Oxygen and Aging* for further discussion.

\*\* Life span is given as logarithmic value of the maximum species life span.

The efficiency of DNA repair enzymes can be assessed by measuring the rate of consumption of such enzymes added to DNA damaged under control conditions (in which nucleotides are exposed to various DNA-damaging agents). That was the approach taken by Hart and Setlow in the early 1970s.<sup>101</sup> They measured rates of DNA repair in fibroblasts from a number of species and plotted it as a function of the maximum life span of the species. Table 3 shows data for DNA repair in humans, Indian elephant, cow, golden hamster, Norwegian rat, field mouse, and long-tailed shrew. The numbers have been rounded to simplify the presentation of data. True to its complementarian and contrarian disposition, Nature has also built elaborate systems to repair the systems that restore injured DNA. This subject is discussed in *Nature's Preoccupation with Complementarity and Contrariety*, the first volume of this textbook.

## XII. NEUROTRANSMITTER AND HORMONAL REGULATION OF ENERGY HOMEOSTASIS

The subject of neurotransmitter and hormonal regulation of energy homeostasis is enormously complex. The major factors of interest are listed in Tables 1 and 2. Indeed, this is the second most important reason why I do not believe there will be a

single drug to cure obesity. (The first most important reason is that none of the neurotransmitters and hormones can effectively address the twin intensifying global problems of environmental pollutants and chronic anger.) The thyroid is an important endocrine gland involved in energy homeostasis and I address that subject in *Pathobiology by Microecologic Cellular and Macroecologic Tissue-Organ Ecoosystems*, the eight volume of this series. A full treatment of the subject is clearly outside the scope of this chapter. Below, I briefly outline the complementarian and contrarian roles of an ever-increasing number of native regulatory molecules involved in energy homeostasis.

Tables 1 and 2 also show orexigenic (promoters of increased energy intake) and anorexigenic (molecules that oppose increased energy intake) characteristics of the principal neurotransmitters and hormones involved in energy homeostasis. Nearly all, if not all, significantly influence insulin and leptin dynamics.<sup>69</sup>

**Leptin and Energy Homeostasis**

In 1995, Friedman and colleagues discovered an adipocyte-derived molecule that exerts regulatory influences on key energy homeostatic centers in the hypothalamus.<sup>31,32,70</sup> Reduction in the body fat leads to lower serum levels of leptin and higher energy intake. The converse also obtains. Increased body fat raises serum levels of the hormone which, acting on hypothalamic centers, decreases energy intake. Thus, leptin serves as an important energy homeostatic hormone.

Factor	Regulatory Signals
Neuropeptide Y (NPY)	9
Agouti-related protein (AGRP)	9
Melanocortin	9
Orexin (hypocretin) A	9
Orexin (hypocretin) B	9
Galanin	?
Noradrenaline	?

\*Adapted from reference #69

Factor	Regulatory Signals
"-melanocyte-stimulating hormone (" -MSH), pro-opiomelanocortin (POMC)	8
Corticotrophin-releasing hormone (CRH)	8
Thyrotropin-releasing hormone (TRH)	8
Cocaine- and amphetamine-regulated transcript (CART)	8
IL-1 $\beta$	8
Serotonin	98
Glucagon-like peptide	?
Oxytocin	?
Neurotensin	?
Urocortin	?

\*Adapted from reference #69

Obese individuals have higher serum leptin levels than thin persons.<sup>31</sup> Decreased leptin levels evoke hormonal responses characteristically encountered in the starvation state.<sup>32</sup> Not unexpectedly, mutations that alter leptin levels lead to massive obesity in rodents as well as humans.<sup>71,72</sup> The leptin neural pathway includes several key molecules that either facilitate or oppose effects of leptin. Among the former are neuropeptide Y (NPY) and agouti-related protein (AGRP), whereas the latter include "-melanocyte-stimulating hormone (" -MSH) and cocaine- and amphetamine-regulated transcript (CART).<sup>73-75</sup>

In view of Nature's preoccupation with complementarity and contrariety, a hormone that influences energy homeostasis would not be expected to have other important roles on nutritional physiology. And, indeed, this is so. Leptin exerts important roles on the immune, reproductive, connective tissues, and other tissues.<sup>31,32,70</sup> Beyond that, even in matters of fat homeostasis, one would not expect leptin to follow the script any more than other hormones. It is well established that intrinsic leptin sensitivity (of hypothalamus and other tissues) is variable, and obese individuals are generally leptin resistant.<sup>76,77</sup> To add to that complexity, leptin-related neural circuits are also influenced by certain uncoupling proteins and other effector molecules. An example of the latter is PGC-1

(a co-activator of peroxisome proliferator-activated receptor- $\alpha$  (PPAR- $\alpha$ ), which is a key regulator of thermogenesis.<sup>78</sup> Another example is pro-opiomelanocortin (POMC), which serves as a pro-obesity molecule.<sup>79</sup>

Of greater importance from the standpoint of the proposed adipomyocytic dysoxygenosis are the influences on leptin-related neurocircuitry of diverse environmental factors, including xenobiotic oxidants and disruptors of oxygen homeostasis that have been associated with cellular dysoxygenosis.<sup>48-51</sup> It seems safe to predict that many more of such molecular disruptors will be identified as our environment is increasingly chemicalized.

The story of leptin is further complicated by its myriad interactions with other bioactive peptides. Notable among them are orexin A and orexin B (also called hypocretin A and B respectively.<sup>80</sup> Those peptides are produced in lateral hypothalamic area (LHA, the so-called 'hunger center'), zona incerta, and perifornical area (PFA) of the hypothalamus. These peptides increase food intake as well as cause generalized arousal behavior when administered centrally. *A point of considerable clinical significance in these considerations is that hypoglycemia is a powerful stimulator of orexin release.* Thus, an effective clinical strategy to normalize the orexin-related energy dyshomeostasis might be diligent regulation of blood sugar levels by avoiding rapid hypoglycemic-hyperglycemic shifts.

### Monoamine Neurotransmitters and Obesity

Norepinephrine, dopamine, serotonin, and related neurotransmitters play complex roles in food intake and energy homeostasis.<sup>81-89</sup> Most of them interact among themselves, as well as with other regulatory hormones, such as leptin.<sup>82,83</sup> For example, leptin inhibits the release of norepinephrine from terminal areas in the brain.<sup>82</sup> Mice with *ob/ob* m profile show increased levels of norepinephrine in the hypothalamic paraventricular nucleus (PVN, the so-called 'satiety center').<sup>83</sup>

Injection of norepinephrine into the PVN increases food intake and serial injections cause significant weight gain, as is the case with injection into PVN of neuropeptide Y.<sup>84</sup> (Norepinephrine is synthesized in the dorsal vagal complex, locus ceruleus,

and other regions of brainstem.) Evidence for critical dependency of caloric intake on CNS dopamine signaling is provided by experiments in which profound feeding deficits occur following pharmacologic depletion of the neurotransmitters,<sup>85</sup> as well as genetic disruption of dopamine synthesis.<sup>86</sup> There are also other important considerations concerning the role of dopamine in energy homeostasis. For example, mesolimbic dopamine pathways appear to contribute to the 'rewarding' aspects of ingesting palatable foods.<sup>87</sup> (Mesolimbic pathways comprise neurons in substantia nigra and ventral tegmental areas.)

The serotonin system comprises cells in the caudal brainstem, including the dorsal raphe nuclei, that project broadly throughout brain parenchyma. This system is the primary target for pharmacologic agents that have been tried for control of obesity, such as dexfenfluramine and sibutramine. Such drugs putatively enhance serotonin-receptor signaling and so suppress appetite, while their antagonists oppose those actions.<sup>88</sup> Specifically, the 5HT<sub>2c</sub> serotonin-receptor subtype has been implicated in this process, as evidenced by the fact that knockout animals for this receptor exhibit markedly increased food intake and weight gain.<sup>89</sup>

### XIII. THE OXIDATIVE-DYSOXYGENATIVE INSULIN DYSFUNCTION AND OBESITY

One of the principal hormones involved with cellular energetics and energy homeostasis is insulin. So some comments about the role of insulin in obesity are necessary here.

The epidemics of diabetes and obesity in the industrialized countries seem to grow in parallel. This is abundantly clear from epidemiological and observational studies. However, there is also an epidemic of diabetes in poor countries that is associated with low body weight. Thus, the prevailing theories concerning the causation of the two epidemics in the West do not hold for the low-body-weight diabetes. In 2000, in an article entitled "Beyond Insulin Resistance and Syndrome X: The Oxidative-Dysoxygenative Insulin Dysfunction (ODID) Model," I marshaled evidence for my view that the common denominators in the etiology of obesity and diabetes are redox dysequilibrium and oxygen dyshomeostasis. Below, I reproduce the abstract of that article to provide a framework for my elaborating my adipomyocytic model of obesity:

Oxidative-dysoxygenative insulin dysfunction (ODID) is defined as impairment of any or all aspects of insulin production and metabolism caused by oxidative injury to any or all molecular pathways in which insulin serves any pathophysiologic roles. This definition reaches beyond the prevailing concepts of insulin resistance, syndrome X, and diabetes mellitus. Specifically, it integrates into a global view of insulin dysfunction myriad molecular interrelationships of insulin pathways to those of exercise, nitric oxide, NF-6B, TNF " , leptin, peroxisome proliferator-activated receptor-( PPAR( ), resistin, IGF-1, IGF-2, and glutamic acid decarboxylase (GAD). Equally important are the diverse counterregulatory signaling pathways involving glucagon, adrenal hormones, hypothalamic factor(s) and related molecular species that contribute to glucose/lipid homeostasis in health and disruptions of that in pathophysiologic states. Beyond that, the ODID model covers many "non-insulin-gluco regulatory" phenomena in the bowel, blood, and liver ecosystems that significantly contribute to epidemics of insulin resistance, syndrome X, and diabetes mellitus and yet are seldom, if ever, included in discussions of those disorders. Furthermore, the ODID model addresses the core issues of epidemics of rapid hyperglycemic-hypoglycemic shifts and brisk glucose-insulin-adrenergic responses in persons with chronic disorders characterized by accelerated oxidative molecular injury, such as chronic fatigue syndrome, fibromyalgia, multiple chemical sensitivity syndrome, Gulf War syndrome, and related autoimmune disorders.

Dysoxygenosis (dysfunctional oxygen metabolism) is defined as a state of sustained impairment of cellular enzymatic functions involved with oxygen metabolism. The ODID model is based on the following fundamental aspects of glucose and insulin pathophysiology: (1) essential oxidative nature of glucose metabolism (oxidative phosphorylation and oxidation of hydrogen atoms released during glucose

degradation); (2) incremental hyperglycemic oxidative stress (oxidosis) in the circulating blood caused by chronic and cumulative sugar overload, oxidative endproducts of glycation, and sensitivity of antioxidant enzyme systems to incremental oxidosis; (3) vulnerability to oxidosis of insulin receptors and other proteins involved in insulin signaling; (4) direct cellular glucose toxicity associated with cumulative intracellular glucose burden; (5) spreading epidemics of obesity-associated type 2 diabetes mellitus in the Western countries and low-body-weight-associated type 2 diabetes in the Orient; (6) association of derangements of glucose and insulin metabolism in clinical states characterized by accelerated oxidative molecular injury; and (7) reversibility of ODID state with measures that control oxidosis and dysoxygenosis.

The ODID model offers a unifying concept for disparate biochemical, genetic, and clinical observations concerning hyperinsulinemia, rapid hyperglycemic-hypoglycemic shifts, insulin resistance, syndrome X, and diabetes mellitus. Beyond that, it encompasses myriad "non-gluco regulatory" aspects of insulin pathophysiology, such as overproduction of androgens in women with polycystic ovaries as well as interactions of insulin pathways with major mediators of the inflammatory and immune responses. This model also has a strong explanatory power for normalization of insulin functions with "non-insulin therapies" that primarily address issues of the bowel, blood, and liver ecosystems.<sup>90</sup>

#### XIV. THE INFLAMMATORY THEORY OF OBESITY

Inflammation, I learned in 1958, is the process by which injured tissues heal. Years later, my reflections on redox equilibrium and oxygen homeostasis in the human body led me to the conclusion that life is an unending injury-healing-injury cycle.<sup>102</sup> Viewed from that perspective, inflammation is *utterly integral* to the process of living. So I recognize

*molecular* inflammation must be present when *any or all* threats to redox equilibrium and oxygen homeostasis in human cells are posed by any nutritional, ecologic, and lifestyle stress factors. Of necessity, that view of "molecular inflammation" requires that obesity also be considered in that light.

### Microscopic Inflammation and Fat Necrosis

Histologically, adipose tissue is largely composed of adipocytes, with sparse stroma that includes macrophages, vascular endothelial cells, and stromal cells. During my pathology work, in obese individuals brought to autopsy and in surgical specimens removed from overweight patients, I often saw scattered areas of increased vascularity in which the number of macrophages and lymphocytes was increased above that commonly seen in nonobese persons. Furthermore, in my clinical work with obese patients, it is not unusual for me to palpate small, usually nontender, nodularities. I consider those as lesions of focal panniculitis. Those lesions, in my view, are the precursor of the clinical entity called panniculitis, which is characterized by the development of painful, tender, and erythematous nodules in the subcutaneous tissues of obese women. Uncommonly, I have palpated similar subcutaneous lesions in men beginning vigorous exercise programs. The pathogenesis of such 'inflammatory foci' in adipose tissue in this context is not difficult to understand, since excess intracellular fat is oxidizing and disrupts cellular oxygen homeostasis. What implications might those morphologic observations have in understanding the molecular nature of obesity?

### Obesity Is Molecular Inflammation

Considerable experimental evidence now exists to provide strong support for my view that obesity is molecular inflammation. A large number of reports of the investigation of the molecular and cellular links between the inflammatory response have been published during the last few years. Many obesity researchers are pregnant with the hope that their findings will lead them to the development of drugs that will forever cure the scourge of obesity. That, I am certain, will not happen for the simple reason that normalization of the adipocyte function is simply not possible without normalization of the myocyte function, which requires daily physical exercise. Still, I present below a brief survey of the ever-growing body of the "obesity-inflammation link" literature for the general interest of

the reader, beginning with the following quote from a recent article in the *Journal of Clinical Investigation*:

Obesity and the associated metabolic pathologies are the most common and detrimental metabolic diseases, affecting over 50% of the adult population. These conditions are associated with a chronic inflammatory response characterized by abnormal cytokine production, increased acute-phase reactants, and activation of inflammatory signaling pathways. This association is not an inconsequential one, at least in experimental models, and is causally linked to either obesity itself or closely linked diseases such as insulin resistance, type 2 diabetes, and cardiovascular disease. A very interesting feature of the inflammatory response that emerges in the presence of obesity is that it appears to be triggered, and to reside predominantly, in adipose tissue, although other metabolically critical sites may also be involved during the course of the disease.<sup>103</sup>

A large body of evidence now supports the view that adipocytes and various types of immune cells—macrophages, T cells, and vascular endothelial cells—share many biologic roles in inflammatory pathways, such as inflammatory cytokine production and complement activation.<sup>104-108</sup> Adipocyte precursors have considerable pleuripotential capability and can be transformed into macrophages (with histiocytic functions) in response to oxidative stimuli.<sup>109</sup> Not surprisingly, stimulated macrophages also express many genes that are essential for adipocytic functions, including those encoding transcription factors, cytokines, inflammatory molecules, fatty acid transporters, and scavenger receptors.<sup>110,111</sup> It seems safe to predict that future research will reveal that macrophages recruited by adipocytes under duress are able to assume *all* molecular functionalities of the fat cells. For instance, leptin was originally reported as an anti-obesity protein. But it is also an angiogenic factor.<sup>112</sup> Angiogenic factors, of course, are molecular Dr. Jekyll/Mr. Hydes, and promote both healing and unabated inflammatory responses. One may raise an interesting question here: Will the use of leptin (or leptin-like molecules to be discovered in the future) lead to progression of cancers harbored by the treated obese individuals? Such are the vagaries of life outside the petri dishes!

### An Essential Shift

Inflammation, I often hear these days, is 'hot' in medicine today. *The focus on inflammation is a step in the right direction in pursuit of a clear understanding of the fundamental mechanisms of molecular and cellular injury. But inflammation is initially triggered by redox events. So hopefully the current focus on inflammation in understanding obesity will shift to issues of redox equilibrium. The disruptions of redox equilibrium are initially triggered by problems of oxygen homeostasis. One hopes that in the not too distant future, the focus on understanding the fundamental errors in energy homeostasis will shift to oxygen homeostasis, rather than be fixed on its inflammatory consequences. Then the true nature of obesity will be clearly understood by everyone.*

### XV. THE OXIDATIVE THEORY OF OBESITY

In 1983, in *Spontaneity of Oxidation in Nature and Aging*,<sup>113</sup> I put forth the view that spontaneity of oxidation drives all metabolic processes and is the primary regulatory mechanism in healthful aging, as well as in all diseases. In a series of articles I marshaled extensive clinical, morphologic, biochemical, and epidemiological evidence to support that view.<sup>34-42,114-118</sup> The oxidative theory of obesity is simply an extension of that theory, since all anabolic and catabolic drives in energy homeostasis are, first and foremost, provided by the phenomenon of spontaneity of oxidation.

In an article entitled "The Oxidative-Dysoxygenative Model of Aging,"<sup>119</sup> I briefly reviewed the existing theory of aging to underscore the point that oxidative-dysoxygenative injury is the common thread in all of them. On a deeper reflection, all the mechanisms of cellular aging proposed so far also shed light on the causation of persistent obesity.

### Food Intake, Oxidative Stress, and Obesity

Food is essential for life. That is self-evident. Chronic starvation threatens life — and eventual leads to death. Food also increases oxidative stress. That should be self evident as well, since all metabolic processes involved in digestion and utilization of food substances are oxidative in nature. It follows that excess food intake can be expected to result in chronic oxidosis and shortened life. That, as indicated earlier, has been proven to be true in all species in which it has

been investigated. In humans, actuarial work done by the insurance industry attests that as well.

Specifically, it is now known that caloric restriction extends life by both increasing resistance to reactive oxygen species (ROS) and by diminishing the production of ROS. A similar paradox also exists in the relationship between caloric restriction. Initially, caloric restriction leads to negative energetic homeostasis with loss of fat. However, fasting also triggers molecular responses that lead to increased energy intake and gain of fat. It may also be reiterated here that recent dissections of the genetic and molecular pathways of aging in *Saccharomyces cerevisiae* that revealed the existence of the fermentative-to-respiratory shifts also shed light on the cellular energetics of obesity. I briefly include here the above-mentioned aspects of food intake to not only show that obesity is oxidative in nature, but also to provide a framework for considering obesity as the cellular oxygen deficiency state.

### Oxidative Injury, Protein Cross-linking and Obesity

In 1955, Johan Bjorksten proposed his cross-linking theory of aging.<sup>120</sup> According to this theory, the basic aging process involves accumulation of damaged and insoluble (cross-linked) proteins, DNA, fats, and other large-sized molecules, such as vitamin A. Such cross-linked molecules cause aging by impeding or blocking the actions of enzymes, vitamins, and other substances. The process of cross-linking may be illustrated as follows: The structure of many healthy proteins resembles long threads of different sizes. Under heat or chemical stresses, individual molecules are bent, turned and twisted into many different shapes. Such misshapen molecules quickly regain their original shapes when the stresses subside. The term cross-linking means that such turned and twisted molecules get permanently disfigured because of excessive stress. Thus, such molecules are torn apart and, when the ends unite, they get tangled with each other and form crooked protein molecules. Cross-linked molecules are two molecules wrapped around each other in such a way that neither can function normally. Since Bjorksten first proposed it, the cross-linking theory of aging has been fully validated. Again in the context of obesity, all factors related to protein cross-linking also are expected to impede regulatory mechanisms involved in energy homeostasis.

### Free Radical Injury and Obesity

In 1956, Denham Harmon proposed his free radical theory of aging.<sup>121</sup> According to this theory, the aging process involves molecular and cellular injury caused by free radicals. Free radicals are highly unstable, extremely reactive atoms or molecules that form during normal metabolism, as well as during cellular injury caused by chemicals, microbes, radiation, and other types of injury. Needless to say, lipolytic enzymes in adipocytes and myocytes are not any more immune to oxidative stress than other functional proteins with complex structures. Since its introduction, the basic tenet of Harmon's theory has been supported by an ever-growing body of data. Indeed, until recently, the case for this theory as being the primary theory seemed ironclad. Again in the context of obesity, all factors related to free radical injury also are expected to impede regulatory mechanisms involved in energy homeostasis.

Since I proposed my oxidative-dysoxygenative theory of aging in *Oxygen and Aging*<sup>100</sup> in 2000, a number of elegant experiments involving varying growth conditions, gene deletions, and transcription factors have been performed to explore the roles of oxygen homeostasis and free radical dynamics involved in the aging phenomena. The major genetic pathways involving hundreds of genes in this context include the Sir2 family, cytochrome c1, and the transcription factor HXX2. The results of those investigations provide direct and strong evidence to support the oxidative-dysoxygenative model of aging. All of those molecular pathways that affect aging also intersect with the pathways of energy homeostasis.

#### Cytochrome C1

Further evidence for the role of oxygen in life extension was marshaled by experiments involving interruption of electron transport in *S. cerevisiae*, which was expected to abrogate life extension under the experimental conditions.<sup>66-68</sup> That turned out to be the case as well. Yeast strains with deletion of the gene encoding cytochrome c1 (CYT1) failed to show life extension, indicating that metabolic shift to respiratory ATP production was a prerequisite for life extension under the experimental conditions.

Finally, as indicated earlier, direct evidence against the free radical-induced aging process, at least in the context of aging of *Saccharomyces cerevisiae*,

may be drawn from experiments showing that the lengthening of life span of the yeast with caloric restriction is associated with increased resistance to reactive oxygen species.<sup>24</sup> This should not come as a surprise, since the free radical theory completely ignores the myriad roles of oxygen in redox regulation and oxygen homeostasis.

The recent studies of the fermentative -to-respiratory metabolic shift in yeast shed new light on the phenomenon of oxidative regression to primordial cellular ecology, and by extension on impaired energy homeostasis of obesity. When I initially described that phenomenon, I was preoccupied with the consequences of the respiratory-to-fermentative metabolic shift occurring in healthy human cells subjected to unrelenting oxidosis, acidosis, and dysoxygenosis.<sup>34-39</sup> I had not fully appreciated that clinically significant metabolic shift in the opposite direction — ferro-respiratory shift — could also take place under certain conditions. The finding that *Saccharomyces cerevisiae* rapidly shifts to fermentative mode of ATP production in the presence of ample supplies of glucose is of considerable importance to clinicians like me. We have repeatedly observed how rapidly sugar or excess starches in the diet can trigger abdominal bloating, cognitive difficulties, and other symptom-complexes — symptomatology that may be readily explained on the basis of increased fermentation in the gut.

### XVI. THE OXYGEN THEORY OF OBESITY: THE ADIPOMYOCYTIC DYSOXYGENOSIS MODEL

Suppose the matrix surrounding the adipocyte and myocyte becomes static and stagnant, and excess organic acids accumulate in it. How would it affect the cellular energetics in those cell types? Evidently, cells deprived of support and nurturing from a dysfunctional matrix will not metabolize oxygen well.

Next, suppose that the living, breathing membranes of adipocytes and myocytes were replaced with impervious plastic material? What would happen to the energy homeostasis of such cells? The membrane then could neither breathe nor respond to any of the ligands of a host of receptors on its surface. Nor could its ion channels function well and keep out ions that, when in excess, can paralyze the cell. Nor could it prevent the cell innards from leaking out. What would be the energetic consequences of such membrane

plasticizing?

Next, suppose the mitochondria in the cells could not respire well because of stagnant matrix fluid and plasticized cell membrane? Evidently, the electron transport chain would become sluggish. The coupled webs of cellular energetics would become uncoupled. Cellular energetics would fail.

Stagnant matrix, plasticized membranes, and clogged mitochondria — that in simple words, is the beginning of the adipomyocytic dysoxygenosis state and the consequent persistent obesity.

To provide a framework of reference for elaborating the adipomyocytic dysoxygenosis model of obesity, below I briefly outline the fundamental aspects of cellular energetics. The abstracts of two previous articles entitled "Oxidative Regression to Primordial Cellular Ecology" and "Dysoxygenosis" are especially relevant to this discussion, and have been included in an earlier chapter entitled "A Personal Perspective of Integrative Medicine." I urge the readers to read those abstracts, if they have not done so already, to gain a clearer view of the adipomyocytic dysoxygenosis discussed below.

If there is any mystery about the cause of obesity, it is locked up in the workings of two cells: the myocyte and the adipocyte. The core of that mystery — it seems to me — concerns the workings of oxygen in those cells.

The myocyte (muscle cell) is the cell where the action begins and adipocyte (fat cell) is where it ends. The study of these two types of cells reveals the true nature of obesity. It is through an understanding of the structure and function of the two cells that we can begin to discern the marvels of biology that keep us lean and energetic. It is also through an understanding of these two cells that we clearly see the utter irrationality of the prevailing ideas of dieting for weight loss. Life span foods nourish these cells; aging-oxidant foods paralyze their life-sustaining enzyme systems. Fat-burning exercises energize their fat-burning enzymes; sugar-burning exercises energize their sugar-burning enzymes. Antibiotics, pesticides and fungicides destroy their enzymes as do toxic metals and industrial pollutants.

Obesity is a problem of oxygen-deprived cells — of emaciated myocytes and bloated adipocytes. Obesity is not a problem of the mind. Dieting is not a

solution to the problem of obesity. Those who choose to diet do not know the biology of these cells (or do not choose to learn about these cells for reasons only they understand).

### The Adipocyte

An adipocyte is a tiny cell packed with triglyceride fat. There are approximately 30 billion adipocytes in the human body. Nature designed the adipocyte as a tiny packet of stored energy. Energy is stored in an adipocyte as a tiny droplet of triglyceride fat, about 0.5 microgram in weight (A teaspoon can hold roughly 6 million micrograms of sugar). An average adult carries about 15 kg (33 pounds) of fat in his 30 billion adipocytes. Since one gram of fat contains 9 calories, it follows that an average adult has 135,000 calories stored in his adipocytes. This depot of energy can sustain an adult through a 40-50 day fast.

The term triglyceride refers to a molecule formed by three fatty acids linked together by a single molecule of a specific type of alcohol called glycerol. The types of fatty acids included in triglycerides in adipocytes reflect the composition of fatty acids in the diet. Life span foods fill the adipocytes with unspoiled, unoxidized fatty acids; aging-oxidant foods lead to the storage of oxidized fatty acids. Studies have shown that diets rich in life span oils such as oleic acid (olive oil is an important source of this oil) lead to a higher quantity of healthful fatty acids in adipocytes.

### The Cellular Intelligence of the Fat Cell

The fat cell is an intelligent cell. The wisdom of this cell shows itself in how it orchestrates the workings of the molecules that reside on its surface and those that live within it. There are molecules on its surface that it uses as hooks. It literally fishes for molecules it needs from the soup of life fluids that bathes its surface. These molecules include various hormones and other important "intelligence" molecules of the body. It has its own enzymes, and it has messenger RNA molecules that it uses to make daughter enzyme molecules.

### The Adipocyte Cell Membrane

The adipocyte cell membrane is a marvel of biology. It:

- \* Separates internal order from external disorder.

- \* Serves as the principal clearing house for the cellular intelligence data.
- \* Transforms intelligence data into physical energy and molecular changes.
- \* Keeps under surveillance the intrinsic cellular self-destruct mechanisms.
- \* Alters its own image and structure to respond to changes in its environments.
- \* Serves the cell as its skin, its bowel, its kidneys, its lungs, all rolled in one.
- \* Influences the regulatory mechanisms for cellular growth, differentiation and reproductive potential.

In essence, the adipocyte membrane "thinks" for the cell. The adipocyte watches out for dangers. It fends for itself. It has sentinel molecules. It has gatekeeper molecules. It has builder molecules and scavenger molecules. It has molecules which it is willing to sacrifice and others which it guards with its life. It has slave molecules and master molecules. It has spies and messengers. The adipocyte has clear ideas of its internal organization, and it is capable of responding and adapting to preserve that order.

### **Cellulitis: The Graveyard of Dead Adipocyte**

There is an absolute limit to how much any cell can suffer. And so it is with fat cells. When toxic cyclic and trans fatty acids and fat peroxides coat a fat cell, the cell suffocates and slowly dies. Why does it happen? It happens because the cell cannot breathe through the plastic layer of these denatured fats on its surface membrane. The molecules it needs cannot come in. The molecules it wants to rid itself of cannot go out. The molecular menagerie of the cell, the ever-changing kaleidoscope of life, comes to a standstill. The fat cell dies. Then another cell dies, and then another. The dead bodies of these cells coalesce to form the chunks of dead fat we call cellulite. Think of dying and dead fat cells next time you see a child being fed french fries soaked with toxic oils and a greasy hamburger cooked with toxic fats. And then think of what dieting can do to the graveyards of dead fat cells. Dead fat cells in the body cannot be brought back to life by starving the whole body with dieting. Next, look at the label of the frozen foods that dieting experts package for you. Denatured, oxidized oils are not hard to spot. One clue: Almost all cholesterol-free items in these foods are made with processed oils contaminated with toxic fats. So stay away from cholesterol-free fats.

### **Oxygen and Excess Cellular Fat Share Mutual**

### **Disrespect**

Oxygen spoils to damage fats. Excess intracellular fat spoils to hurt oxygen homeostasis. Oxygen plays its "lipophobic" card readily by oxidizing fats and turning them rancid. Excess cellular fat, by contrast, does not have ready weapons to disrupt oxygen metabolism. However, it employs clever molecular means to not only protect itself from oxygen but also to blunt the weapons of oxygen against other molecular species. The fat cells produce and release into blood a number of potent proinflammatory substances, such as tumor necrosis factor (TNF- $\alpha$ ). When well nourished and larger in numbers, the fat cells produce those substances in larger quantities. In obesity, the production of those factor is markedly increased. Adipocytes and myocytes are the principal sites where oxygen and excess cellular fat engage each other in their destructive conflict. That, in simple word, forms the core of the adipomyocytic dysoxygenosis model of obesity.

### **Oxygen, Mitochondria, and Cellular Energetics**

Under idealized thermodynamic conditions of cellular energetics, electron transfer chains, ATP synthesis, and ATP use represent coupled reactions in which fixed amounts of reactants produce stoichiometric amounts of products at each step. For instance, fixed amounts of NADH and FADH<sub>2</sub> are generated during conversion of glucose to C<sub>2</sub>. Fixed number of protons are pumped across the mitochondrial inner membrane during oxidation of NADH and FADH<sub>2</sub>. Fixed amounts of ATP are regenerated by the re-entry of protons by means of ATP synthase. Fixed amounts of ATP are used during enzymatic steps performing cellular work. Theoretically, for thermogenesis to increase, the degree of 'coupling' at one or more of those coupled steps must change.<sup>122</sup> A second possibility would be that some of the cellular work done through ATP reactions would have to be 'undone' — a circumstance that essentially would mean ATP wasting as a part of futile cycling. Examples of conditions in which futile ATP cycling occurs include protein degradations and ion leakage — Na<sup>+</sup> in and K<sup>+</sup> out across the plasma membrane, and influx of Ca<sup>++</sup> from extracellular stores into cytosol. Specific inner membrane proteins called uncoupling proteins (UCP-1, UCP-2, and UCP-3) also participate in cellular energetics. For example, one established site of uncoupling is the leakage of protons back across the mitochondrial inner membrane, bypassing ATP

synthase and converting energy stored within photomotive force.<sup>123,124</sup>

In reality, however, energy homeostasis would be expected to be far from idealized in the presence of heavy metals and some xenobiotics that act as uncoupling agents. This is where the central phenomenon of adipomyocytic dysoxygenosis comes into play. Below, I reproduce some text from a previous paper to illustrate the point:

### **Spoiled Boys at a Picnic Table**

What are the fundamental dynamics of energy deficits in dysoxygenosis? That is the second critical question. The second analogy addressed that question. Some overweight undisciplined teenagers attack the food table at a picnic, dropping many items on the ground, and laying waste large portions of foods others cannot now eat. They do so partly driven by their ravenous appetites and partly because they are insensitive to the possibility that there may not be enough left for others. No one at the picnic seems to be able to discipline the teenagers. The result: First, the total energy yield of the food is diminished because much is wasted; Second, rapid eating by some spoiled boys leads to some individuals being deprived of sufficient food energy. In tribal cultures, the food-consuming traditions were such that all available food was consumed completely with full energetic yield. There were no loose teenagers ravaging the food supply.

Human energetics may be discerned in the same light. In health, all communities of cells and tissues in the highly complex multicellular human body primarily employ respiratory ATP-producing pathways with a much larger energetic yield. The allocation of energy to the various communities of cells is orderly and based on need to assure the goodness of the whole. Furthermore, healthy cellular communities execute maximal efficiency in extracting energy from the metabolism of food. Excess production and urinary excretion of metabolic intermediate organic acid is kept to the minimum—much like the

minimal exhaust of an efficient automobile engine. By contrast, the total energetic yield in the glycolytic pathways is two moles of ATP per mole of glucose metabolized.

Now, let us consider the wanton metabolic waste of a deviant community of cells in a malignant neoplasm. A cancer cell hates oxygen and loves acid, I often say to help my patients with tumors understand the metabolic attributes of their cancers. In choosing a fermentative ATP-producing pathway, the actions of a cancer cell are as wanton—and the metabolic consequences as energetically wasteful—as undisciplined spoiled boys at a picnic table. The same holds in noncancerous clinical situations in which the bowel, blood, and liver ecosystems are seriously disrupted and there are varying degrees of regression from the respiratory to fermentative ATP-producing pathway. This subject, as indicated earlier, is presented at length in the article entitled "Oxidative Regression to Primordial Cellular Ecology."

It may be mentioned here that the main body of the classical concepts of evolutionary biology is grounded on the assumption of trade-offs between the survival characteristics of the species. Notwithstanding the value of those assumed structures for constructing useful heuristic models, those efforts yielded only working hypotheses that were of limited clinical relevance. Those concepts cannot be uncritically applied in clinical medicine. It is important to recognize that the sick do not follow 'all or none' models that are often presented in medical textbooks. In clinical medicine, the 'respiratory-to-fermentative shift' is forever changing in degrees and clinical consequences. Of course, effective therapies that address the underlying causes of dysoxygenosis restore the respiratory ATP-producing pathway.

### **A Clogged Automobile Engine**

The symptom-complexes of energy disorders are extremely diverse. All subjects with persistent and debilitating fatigue eventually develop

most of the following symptoms: myalgia; disorders of mood, memory, and mentation; temperature dysregulation; tachycardia, cardiac arrhythmias, and racing of the heart—a feeling of urgency in the heart experienced by the patient but not always clear to the physician; abdominal discomfort, distension, cramps, and irregular elimination; menstrual disorders, lack of libido, dry skin and eyes, and a sense of oxygen hunger. How may one search for the cause of such diverse symptomatology, except by invoking a *global* phenomena that can affect every cell type in the body? Indeed, that was one of the core questions which eventually led me to propose the dysoxygenosis hypothesis.

The term oxygen disorder appears throughout this book. Below, I explain the basic oxygen disorder of the September canaries (9/11-related illness) with a simple analogy: A car engine mixes fuel and oxygen to produce energy. A properly maintained engine performs without generating excessive toxic exhaust. An engine clogged with soot produces less energy and more toxic fumes. The basic difference between the two is that fuel is completely burned in the first instance, leaving no toxic residue behind, whereas in the second car incomplete combustion leads to generation of excess toxic residue. Like the good engine, a healthy person uses oxygen to extract clean energy from his meal. By contrast, a human canary with an oxygen disorder cannot do so without producing excess toxic waste which, in turn, causes fatigue and immune weakness.

Cellular overproduction and retention of organic acids in dysoxygenosis—the result of regression of the respiratory to fermentative ATP-producing pathway—in essence, result in choking of all cell types in the body. Hence, the diverse symptom-complexes which do not fit into any of the established 'disease categories' in medical textbooks. Indeed, in my view, this is the primary reason why the energy disorders are poorly understood by many clinicians. Of course, the measurements of 24-hour urinary excretion of organic

acid is only infrequently done by the main body of physicians.<sup>125</sup>

Excess fat causes dysoxygenosis because the lipids in the cells are largely proinflammatory molecules. Fat and oxygen share mutual disrespect for each other. Oxygen tries to damage fats that it spoils to hurt fats as soon it sees them. Fats, on the other hand, do not have ready weapons to destroy oxygen, but employ clever molecular means to not only protect themselves from oxygen but also blunt the weapons of oxygen against other molecular species.

JNKs are *c*-JUN amino-terminal kinases which interfere with insulin action and are activated by free fatty acids as well as inflammatory cytokines, including TNF- $\alpha$ . In both dietary and genetic (*ob/ob*) models of obesity, total JNK activity is markedly increased in the liver, muscle, and adipose tissue.<sup>126</sup>

#### **XVII. THE OXYGEN MODEL OF OBESITY EXPLAINS ITS LINK TO HEART DISEASE, DIABETES, CANCER, AND OTHER DISORDERS**

The human nutritional science can be understood through a clear comprehension of oxygen homeostasis. Beyond that, the clinical practice of integrative nutritional medicine must be grounded on that understanding. In the preceding volumes of this book, I have marshaled evidence for my view from a large body of epidemiological, experimental, and empirical clinical data. The central importance of nutrients in maintaining redox equilibrium and oxygen homeostasis is inescapable whether one focuses on antioxidants—ascorbic acid, uric acid, cholesterol, sulfur, selenium, and others—or prooxidant molecules, such as copper, iodine, fluorine, mercury, pesticides, and others. The readers might consult *Toxic Metal Load and Toxicity*, the seventh volume of this series, in which I dwell deeply into oxidative-dysoxygenative molecular and cellular injury caused by mercury, and show all known symptom-complexes of mercury can be explained by the oxidative-dysoxygenative model. Next, I present strong arguments for why oxystatic nutrient and herbal prescriptions must be considered as the foundational therapies for mercury chelation regimens.

In this volume, my focus is on presenting nutritional prescriptions for a large number of clinicopathologic entities without cumbersome digressions for an in-depth review of the chemistry of

redox dysequilibrium and dysoxygenosis for each entity included. Still, to provide a framework of reference, I include below some excerpts from previous publications concerning the larger subject of dysoxygenosis.

It has been estimated that the 50 percent survival rate—the age reached by one-half of the population — increased from about 22 years in ancient Rome to about 40 years in the middle of the nineteenth century. In the United States, that number reached 49 in 1900. The 50 percent survival then showed rapid increases in this country, reaching 67 years in 1946, 72 years about fifteen years later, and leveled off at about 74 years in the 1980s. It seems safe to attribute such rapid rises in the 50 percent survival to improvements in agriculture, availability of food, vaccination, and public health measures. Clearly, the aforementioned theories of aging during those decades had been of theoretical interest only, since no concrete measures were taken to extend life span according to the dictates of any of those theories.

The imperatives of the oxidative-dysoxygenative model of aging, by contrast, are compelling. The incidence of oxidative-dysoxygenative energy disorders—fibromyalgia, chronic fatigue syndrome, environmental illness, Gulf War syndrome, the September Eleven-related illness, and others — is rising in nearly all countries with epidemic proportions. Recently, the *Wall Street Journal* estimated that fibromyalgia now afflicts over eight million Americans. Nearly one of every six women and men sent to the Gulf War in 1991 are now fully or partially disabled. The energetic-molecular basis of none of those maladies can be understood within the context of the prevailing disease classifications. Beyond that, the incidence of Alzheimer's disease in the older individuals and of cognitive difficulties in younger persons is rising at a frightening rate. Below, I include some text from one of my articles published in *The Journal of Integrative Medicine* to show that we can learn much about dysfunctional oxygen metabolism from disappearing frogs, shrimp, oysters, and other living beings.

What do alpine meadows of Yosemite National Park, piney woods of South Carolina, and plains of Laramie, Wyoming, have in common? Answer: The warm summers there are unusually hushed. The reason for this is that the frog population in those areas\_and many

others in the world\_has been decimated. By some estimates, up to a third of the nation's amphibians\_frogs, toads, and salamanders\_have disappeared. In 1988, in Costa Rica on a Monteverde ridge, half of the 40 amphibian species simply vanished. Some wags have speculated that those amphibians were stolen by aliens\_a global whodunit!

In Chesapeake Bay, during some summers, nearly all Eastern oysters are parasitized by dermo. Up to one-half of the total population succumbs. Similarly, grass shrimp suffer from heavy parasitic infestation. In Alaska, ten years after one of the largest oil spills in history, the Valdez accident, species which have failed to recover include the common loon, cormorant, harbor seal, harlequin duck, and pigeon guillemot.

Marine biologists report "mass mortalities" among plants and aquatic life forms. Consider the following quote from a recent issue of *Science*.

In the past few decades, there has been a worldwide increase in reports of diseases affecting marine organisms. In the Caribbean, mass mortalities among plants, invertebrates, and vertebrates have resulted in dramatic shifts in community structure. Recent outbreaks of coralline algae lethal orange disease have affected Indo-Pacific communities on unprecedented scale.<sup>127?</sup>

### Excess Fat Causes dysoxygenosis

Excess intracellular fat causes dysoxygenosis because fatty tissue, by its very nature, is proinflammatory. Cells accumulate excessive fats when their oxygen-utilizing enzymes are impaired. This is not intended to trivialize a truly frightening problem. The epidemic of obesity in the United States is spreading at a frightening rate. Nearly two thirds of the general population is now believed to be overweight. In 2001, in an article entitled "Beyond Hyperinsulinemia and Syndrome X — The Oxidative-Dysoxygenative Insulin Dysfunction (ODID) Model," I marshaled extensive biochemical, epidemiological, and clinical evidence to link insulin dysfunction and obesity with impaired cellular oxygen utilization.<sup>20</sup>

The National Institutes of Health, in its 1985 consensus report, defined obesity as an excess of adipose tissue (body fat) that frequently results in significant impairment of health. As can be expected from a consensus report of nutrition "experts" who do not practice nutritional medicine, this is a statement singularly devoid of any merit. It is of no relevance to those who are serious about preventive medicine and health. First, how do we define excess of adipose tissue? The consensus report does not tell us that. Second, how do we know what this consensus report considers significant impairment of health? In classical medicine we think only of two states: a state of disease and a state of absence of disease, when our CAT scans and blood tests do not allow us to select a disease label for a given patient. I have never seen a medical textbook of medicine that dares to define health. There is a third problem with this statement. In preventive medicine, we do not wish to wait until significant impairment of health has occurred before we regard a particular weight as unacceptable from a life span perspective.

### **XVIII. OPTIMAL WEIGHT FOR THE LIFE SPAN**

In 1992, I introduced the term "Life Span Weight" to refer to the ideal weight that will allow an individual to live his expected life span lean, fat-free, fit, energetic and in perfect health.<sup>128</sup>

Life span weight is not simply a reduced weight. Children and adults become emaciated in many countries during periods of famine. Starvation consumes the muscle mass before it depletes the body fat stores. Thinness achieved through starvation has disastrous effects on the long-term health of an individual, whether it is caused by a famine or drought in an impoverished country or by famine of misguided dieting in an impoverished state of mind.

A thin, muscleless frame is not a healthy frame. It is not thinness that we should be after. It is a lean, fat-free and vigorous body that gives us life span weight and a life span perspective of health and life.

The epidemic of obesity deserves serious inquiry. Regrettably, this matter has been reduced to nonsensical low-carb, low-fat, or 'Food Pyramid' fads that are singularly devoid of any scientific merit. Consider the following quote from the cover story in a recent issue of *New York* magazine:

Alarmed by the surge in childhood obesity (and all too aware that they're judged by their children's appearance), New York's carb-obsessed parents are fixating on how to keep their children healthy — and perhaps more important — thin.<sup>129</sup>

A photograph of a little boy accompanied the article. It showed what appeared to be three pills on his plate, with one knife and one fork on either side of his plate, presumably to be used while ingesting the pills.

The National Institutes of Health, in its 1985 consensus report, defined obesity as an excess of adipose tissue (body fat) that frequently results in significant impairment of health. As can be expected from a consensus report of nutrition "experts" who do not practice nutritional medicine, this is a statement singularly devoid of any merit. It is of no relevance to those who are serious about preventive medicine and health. First, how do we define excess of adipose tissue? The consensus report does not tell us that. Second, how do we know what this consensus report considers significant impairment of health? In classical medicine we think only of two states: a state of disease and a state of absence of disease (when our CAT scans and blood tests do not allow us to select a disease label for a given patient). I have never seen a medical textbook that dares to define health. There is a third problem with this statement. In preventive medicine, we do not wish to wait until significant impairment of health has occurred before we regard a particular weight as unacceptable from a life span perspective.

Some nutrition experts consider an increase in weight of 20% (or more) over the ideal body weight as a health hazard. Again, they do not tell us what the ideal weight is. In our life span perspective, we are oriented toward optimal health with vigorous energy for the duration of our expected life span. We are not merely focused on narrow issues of health hazards.

Life span weight is the specific weight for a person that gives him the best chance for living his full life span in perfect health. Good health for an individual is not what a professional can determine by consulting his computer charts and graphs. It is a weight that a person must determine by himself by limbically listening to his body tissues. A knowledgeable professional is necessary for guidance in making good food choices and for outlining optimal programs for exercise and self-regulation. Basic knowledge of human

biology and energy dynamics is essential for increasing muscle mass, decreasing body fat, and achieving and maintaining life span weight. Commonly used weight tables (prepared by the Metropolitan Life Insurance Company or other sources) are also valuable as a general guide. But the true determinant of what constitutes the life span weight for a person has to do with his sense of energy, vitality, fluidity of motion, and ability to enjoy his work and personal time in full health. The key issue here is a perspective of his life span, not simple-minded efforts to lose weight by starving his tissues. The distinction between the two is critically important.

In *The Butterfly and Life Span Nutrition*, I defined the term catabolic maladaptation and indicated that obesity is a visible reflection of the deeper catabolic problems included in this term. I described that further detail aspects of this maladaptation in *The Ghoraa and Limbic Exercise*. The catabolic maladaptation includes all those energetic-molecular events that threaten health and life span. Specifically, it includes dysfunctions that cause fat-burning muscle fibers to become emaciated, fat-burning enzymes to become sluggish, fat cells to become bloated with toxic fats. That, in simple words, is one description of adipomyocytic dysoxygenosis.

Some nutrition experts consider an increase in weight of 20% (or more) over the ideal body weight as a health hazard. Again, they do not tell us what the ideal weight is. In our life span perspective, we are oriented toward optimal health with vigorous energy for the duration of our expected life span. We are not merely narrowly focused on issues of health hazards.

Life span weight is the specific weight for a person that gives him the best chance for living his full life span in perfect health. Good health for an individual is not what a professional can determine by consulting his computer charts and graphs. It is a weight that a person must determine by himself by limbically listening to his body tissues. A knowledgeable professional is necessary for guidance in making good food choices and for outlining optimal programs for exercise and self-regulation. Basic knowledge of human biology and energy dynamics is essential for increasing muscle mass, decreasing body fat, and achieving and maintaining life span weight. Commonly used weight tables (prepared by the Metropolitan Life Insurance

Company or other sources) are also valuable as a general guide. I have included suggested guidelines at the end of this chapter. But the true determinant of what constitutes the life span weight for a person has to do with his sense of energy, vitality, fluidity of motion, and ability to enjoy his work and personal time in full health. The key issue here is a perspective of his life span, not simple-minded efforts to lose weight by starving his tissues. The distinction between the two is critically important.

In *The Butterfly and Life Span Nutrition*, I defined the term catabolic maladaptation and indicated that obesity is a visible reflection of the deeper catabolic problems included in this term. I describe in further detail aspects of this maladaptation in the chapter, *On the Nature of Obesity* in that volume.

The catabolic maladaptation includes all those energetic-molecular events that threaten health and life span. Specifically, it includes dysfunctions that cause fat-burning muscle fibers to become emaciated, fat-burning enzymes to become sluggish, fat cells to become bloated with toxic fats, and health-preserving molecular pathways to be thrown into roller coaster

No cell can preserve its health and integrity without a layer of healthful fats in its covering membrane. I sometimes wonder why nature would make fats in food so necessary for satiety if not to assure a healthy supply of fats for the cell membranes. The fat cell and its fat-processing enzymes know how many healthy fats it needs to store and how many unwanted fats it must burn to maintain a lean, fat-free, fit body. The muscle cell and its fat-burning enzymes know how much energy they need and whether they need it fast (generated by burning sugars) or whether they need it in a slow and sustained fashion (generated by burning fat). What we need to do is to understand this and respect the wishes and actions of the catabolic control.

The person feels "not healthy," tired, and depleted. He begins to add layers of fat over his thinned-out muscles. Each pound of additional fat feeds the catabolic disorder. Misguided efforts to lose fat only worsen the problem. Tissues loaded with toxic fats are tired tissues. The cells in these tissues are bloated, their enzymes sluggish. The cells have diminished energy levels. They are slow in producing energy, slow in their work, slow in ridding themselves of toxic wastes, and

slow in recovery from injury. Fat cells are tired cells that cannot burn fat; instead they hoard yet more fats.

The catabolic regulation for maintenance of life span weight is a molecular and cellular function, primarily located within the fat and muscle cells and not in the hypothalamus in the brain as our obesity experts think. In the chapter entitled "On the Nature of Obesity" in *The Butterfly and Life Span Nutrition*, I present scientific evidence to dispel the myth that there is a hypothalamic set point for weight control and describe how molecular and cellular intelligence at the levels of fat and muscle cells determines whether we remain lean, fit and energetic or become obese, fatigued and listless.

Tired tissues have tired metabolism. Tired metabolism makes people tired. It is not our purpose to lose weight to reach any arbitrarily determined body weight, and in the process become thin, flabby, tired, slothful and unhealthy. Our goal should be to eat well, to attain and maintain our life span weight with more energy, less weight, better looks, improved health and longer life.

### Weight and Height Tables

Physicians are often asked by their patients questions considering desired weights according to their heights and the general body structure. In Tables 1 and 2 given at the end of this discussion, I include weight and height charts for males and females so that such questions may be answered, though I believe the data given in those tables is of limited value to a given individual.

### XIX. UPREGULATION OF FAT-BURNING ENZYMES FOR WEIGHT LOSS

From the information presented above, it should be evident that the rational, logical, and scientifically sound approach to the prevention and treatment of obesity must effectively address the underlying causes of adipomyocytic dysoxygenosis. The single most important hurdle in pursuing that goal is the misinformation disseminated by marketers of the weight loss industry.

Sometimes it is argued that when prevention fails, obesity is a chronic and costly disease that, like other medical conditions, requires pharmacologic treatment of the disorder. Because obesity can rarely be cured — that line of reasoning continues — obesity

drugs had to have significant impact on appetite, caloric intake and body weight. I see two problems with such thinking: (1) it totally neglects the issue of chemicalized foods; and (2) it assumes that overweight individuals can play little, if any, roles in this aspect of the health.

This section has two essential messages: (1) For achieving and maintaining the life span weight, an individual needs to address *all* relevant issues that cause and perpetuate adipomyocytic dysoxygenosis; and (2) adipomyocytic dysfunction cannot be reversed without a long-term, noncompetitive, meditative physical exercise.

### XX. LIMBIC EXERCISE

In the early 1990s, for my patients I developed a program for non-competitive meditative exercise for a lifetime fitness which emphasized some of the ancient Chinese and Indian concepts of physical fitness. I introduced the term *limbic exercise* for that program to underscore its spiritual aspects, and specifically excluded the prevailing no-pain-no-gain-huffing-and-puffing schedules are in vogue in the United States at present. In 1993, in *The Ghoraa and Limbic Exercise*, I defined the following terms:

1. Cortical and Limbic Exercises;
2. Type I (slow twitch) and Type II (fast twitch) Fibers;
3. Lipolytic and Glycolytic Exercises;
4. Energy, Fatigue and Stress Molecules;
5. Cortical and Limbic Pacing;
6. Cortical Greed and Limbic Gratitude;
7. Cortical Clutter and Limbic Openness; and
8. Limbic Breathing

Below, I include some text from *The Ghoraa and Limbic Exercise*, for the general information of the reader.

#### Cortical Exercise

Cortical exercises are intense, competitive, and goal-oriented. These exercises are of the stop-and-go type which focus on technique, style, duration and results. The best examples of cortical exercise are competition sports and athletics such as wrestling, bodybuilding, football, tennis, basketball and soccer. Sharply focused, highly intense and meticulously analyzed cortical exercises are evidently essential for such sports.

#### Limbic Exercise

Limbic exercises are continuous, non-intense, non-goal oriented, noncompetitive exercises. There is

no hyperventilation or perspiration. When done *limbically*, exercise ends with more energy than that with which it began. The essence of limbic exercises is the absence of focus. When we run limbically, we do just that — we simply run. There is no effort made to run well, to run at some predetermined speed, to run for some defined distance or to run to solve the problems of the day. When we walk, we simply walk. We make no attempt to solve our problems or sit in judgment on how we walk. Limbic exercises are done with abandonment, with total disregard of all the demands of the thinking head.

Cortical exercises are performed while taking commands from the thinking mind. Limbic exercises, by contrast, are exercises done while we take counsel of our tissues, counsel from muscles that contract to produce motion, counsel from tendons that carry the commands from the muscles to the bones, counsel from the ligaments that hold the bones together and counsel from bones that provide muscles their scaffolds. We take counsel from lungs that bring air into the body and from the heart that pumps the blood to spread nourishment to the body tissues. A period of listening to body tissues (and dismissing all demands from the thinking mind — the cortical monkey) is a necessary prelude to limbic exercise. It generally requires several minutes before we begin limbic exercises. With continued limbic exercises comes what I call "limbic openness." Limbic openness is a period of inner reflection, meditation, prayer and deep visceral stillness. There is no rush of cortical thoughts. There is only a limbic flow of limbic perceptions past one another. This subject is discussed at length later in this section.

### **Type 1 (Slow Twitch) Muscle Fibers**

Slow twitch muscle fibers burn fats to generate energy, much like a candle burns wax to generate light slowly but for a long time. These muscle fibers are rich in mitochondria — and the oxidative enzymes contained in them. They are designed to break down fats and utilize the fatty acids liberated from fats by their oxidative enzymes.

### **Type II (Fast Twitch) Muscle Fibers**

Type II muscle fibers burn sugar to generate quick bursts of energy, much like a piece of dry paper burns to produce sudden heat with a flash but only for a few moments. These muscle fibers have fewer mitochondria and are poor in mitochondrial oxidative enzymes. Unable to use fatty acids for energy, they follow the path of less resistance and burn whatever sugars are available to them (the glycolytic or sugar-burning molecular pathways for energy generation).

### **Lipolytic Exercise**

Lipolytic exercises are fat-burning exercises. In these exercises, Type I muscle fibers *burn fat in a slow and sustained* fashion; the flame of the candle is subdued but it lasts for long periods of time. So it is that exercises that require a low but sustained supply of energy are predominantly lipolytic. Again, the myocyte (muscle cell) senses the energy needs and acts accordingly. In general, fat-burning exercises are limbic exercises.

### **Glycolytic Exercise**

Glycolytic exercises are sugar-burning exercises. In these exercises, Type II muscle fibers burn sugars fast; the flame of the paper is bright but it dies out within moments. So it is that exercises that require rapid bursts of energy for short periods of time are predominantly sugar-burning. The myocyte knows it, is quick to sense the requirements for energy and acts accordingly. In general, sugar-burning exercises are cortical exercises.

### **Energy, Fatigue, and Stress Molecules**

One of the principal energy molecules in the human frame is ATP (adenosine triphosphate), while lactic acid is one of the principal fatigue molecules. Adrenaline and its cousin molecules catecholamines are the principal stress molecules. Although cortical exercises have many health advantages, when it comes to prolonging one's life span, the effects of cortical exercise are not as beneficial as those of limbic exercises. Cortical exercises *deplete* the body of its ATP energy molecules and increase the number of fatigue (lactic acid and others) and stress (adrenaline and others) molecules. Limbic exercise, by contrast, has the opposite effect: The number of lactic acid and adrenaline molecules is reduced and the number of ATP molecules is increased.

### **Cortical Pacing**

Cortical pacing is the common method for determining the type, technique, speed and duration of exercise. This type of exercise pacing is highly goal-oriented, much like keeping a tight schedule at work. It includes the commonly used methods of "pushing the distance of the run," measuring the "pulse peak" and counting the breathing rate.

### **Limbic Pacing**

Limbic pacing is a mode of exercise whereby a person allows himself to simply follow his inner "limbic voice." This voice may wish him to walk slowly or quickly, run with arms swinging from the

shoulders or just hanging by the side; it may urge him to continue or stop.

### **Cortical Greed**

Cortical greed is the irrepressible desire to "do autoregulation right." The core idea of autoregulation is to listen to the tissues by overcoming the unrelenting cortical demands for knowing what was, is and will be happening within our body tissues. These cortical demands negate the very idea of autoregulation. This is a point of enormous practical significance. Unquestionably, this has been the most common obstacle encountered by those patients of mine who have tried to learn autoregulation.

### **Limbic Gratitude**

Limbic gratitude describes the sense of gratitude with which we accept whatever responses we receive from our tissues when we do autoregulation. Autoregulation, I reiterate, is about *listening to body tissues*; it is not putting demands on them. Limbic gratitude is gratitude in receiving, at a nonintellectual, limbic level.

### **Cortical Clutter**

Cortical clutter is a term I use to convey the unending chatter in which we engage with our cortical minds. It is living in the head, an unremitting case of head fixation. It consists of all the What if, Why couldn't it, Why not, Why me and all of the other favorite lines we use for punishing our tissues. Unfortunately, canceling the cortical clutter is easier said than done.

There are other less threatening forms of cortical clutter, for example planning your day during your walk, or examining somebody else running on the same track, or simply not wanting to do exercises because it is Sunday or Saturday or the 4th of July. Most people who walk, run or cycle for fitness know what cortical clutter is, though the term may be unfamiliar to them: it is all the thoughts that cross their minds while exercising, all the problem-solving, head-clearing and goal-setting.

Anger and hostility are the first casualties of autoregulation. Walking or running without autoregulation is not nearly as effective in dissolving these serious threats to health and fitness as the same exercises when they are combined with autoregulation.

### **Limbic Openness**

Golfers know what it is to be "on the greens." For tennis enthusiasts, it is being "on the courts" and for fishermen, "on the water." In autoregulation lingo, the term limbic openness describes a comforting limbic state in which there is no thought activity, no anger, no hostility, no desire to excel and no judgmental overview. It is a state of calm communion between what is under our skin with what is outside it. There is a consciousness of an openness, a wide, limitless, comforting limbic openness. In a more advanced state, there is a consciousness of a larger presence, a state totally free of any desire to map out, define, understand or know this presence. The presence is simply there.

I don't know if achieving the full depth and breadth of limbic openness is possible for most people during limbic exercise. Perhaps not. What I know from both personal experience and that of some of my patients is that limbic openness in some form or other is attainable by most people through limbic exercise. At the very least, most people who practice limbic exercise learn to allow themselves an escape from cortical clutter without much difficulty. For many individuals, it may indeed require considerable practice.

### **Motivation for Limbic Exercise**

The subject of motivation fascinates me, and I find motivation "experts" to be fascinating people. Consider the following quote from

The purpose of this article is to examine movement science research on personal and social-environmental motivational influence in physical activity contexts. Motivation is defined as a process in which internal and external factors direct and energize thoughts, feelings, and actions. Motivation is described as a consequence of meaning, which is derived from a combination of personal and social factors, including personal goals or incentives, expectations of personal efficiency, movement-related perceptual and affective experience, and social and physical features of the environment.<sup>1,30a</sup>

### **Short Versus Long Bouts of Exercise**

There is an active debate among the exercise experts as to how many minutes one should exercise to get the most benefit. Alas, the numbers again! Why is it that we Americans must ruin the fun in everything by putting some numbers on it?

A regimen of moderately intense exercise for periods of 30 minutes three times per week is very popular with many researchers studying methods for increasing exercise training and functional capacity. Indeed, the 30-minute duration seems to have assumed divine rights among our exercise experts.

The exercise gurus at the American Heart Association have pronounced that we can get some physical benefits out of exercise only if we do it for a minimum of 30 minutes. The preoccupation of exercise experts with numbers generated by their ergometric exercise, in my view, has not done much to improve the health of Americans. Consider the following quote from the *American Journal of Cardiology*:

Thus, multiple short bouts of moderate-intensity exercise training significantly increase peak oxygen uptake. For many individuals short bouts of exercise training may fit better into a busy schedule than a single long bout....To evaluate the "threshold" of exercise duration required to produce training effects we compared...The solid state recorder enabled accurate quantitation of the exercise regimen for both groups.<sup>131</sup>

### **Limbic Lipolytic and Cortical Glycolytic Exercises**

Energy in foods exists as a chemical bonds. Living bodies require electromagnetic, thermal (heat) and mechanical forms of energy. The purpose of metabolism is to convert the chemical bond energy of foods to those other forms of energy for the performance of various life functions.

In the catabolic maladaptation of obesity, the primary dysfunction is that of energy generation. The enzymes essential for energy are either very sluggish due to disuse and loss of muscle mass, or are poisoned by denatured and toxic foods, pesticides and herbicides, environmental pollution, allergic reactions, oxidizing molecules of stress and various forms of radiation. All these factors lead to the collection of excess fat and toxic fatty substances in the fat cells.

How can we reverse this catabolic maladaptation? In *The Butterfly and Life Span Nutrition*, I describe strategies for preventing enzyme inactivation and toxicity with food choices. When a bodybuilder exercises, he does so to build his muscles. For this purpose, by and large, he needs short bursts of high-energy output. The muscle cells that respond are primarily of the Type II (fast twitch) myocytes, which predominantly burn sugars to produce quick bursts of

energy. These myocytes are poor in fat-burning mitochondrial oxidative enzymes. The very nature of exercise undertaken by the bodybuilder puts him into a sugar-burning catabolic mode. The bodybuilders know how quickly they lose muscle mass and become flabby and obese when they stop their bodybuilding exercises.

When a marathon runner runs, the muscle fibers that primarily respond to his activity are of Type I (slow twitch) myocytes, which are rich in fat-burning oxidative mitochondrial enzymes. These enzymes burn fat at a slow and sustained rate, very much like a candle does, slowly and for long periods of time.

If an overweight person says he loves his exercise time, he is probably being polite. His fat-burning enzymes are sluggish (often totally exhausted). He is not likely to find much pleasure in beating up on the tired enzymes and tired tissues. If a slim, energetic person says the same thing, the chances are he means it. His enzymes are charged, his tissues energized.

The problems of the bodybuilder when he stops exercising and of the overweight person *are not problems of the mind*. These are problems of sluggish enzymes and neglected Type I myocytes. The advantages of the runner and those of the slim, energetic person *are also not advantages of the mind*. These are physiologic advantages of charged enzymes and pampered Type I myocytes.

## **XXI. CONCLUDING COMMENTS**

Obesity is an alarming global epidemic. To date, some countries like Sweden appear not to have suffered as much as others like the United States. That is just a matter of time. People in those countries are fundamentally not less vulnerable to nutritional, environmental and life style stressors that cause adipomyocytic dysoxygenosis and set the stage of persistent obesity.

The cost of obesity in terms of higher associated incidences of hypertension, heart disease, diabetes, cancer, and other oxidative-dysoxygenative states is being increasingly recognized. Obesity-associated disability has not been in equally sharp focus. Obese people are often stigmatized socially. The cost of that is essentially known only to them.

There is much enthusiasm among the obesity researchers that the true answer is close at hand. Consider the following quote from *Nature*:

But major advances have now been made in identifying the components of the homeostatic system that regulates body weight, including several of the genes responsible for animal and human obesity. A key element of the physiological system is the hormone leptin, which acts on nerve cells in the brain (and elsewhere) to regulate food intake and body weight. The identification of additional molecules that comprise this homeostatic system will provide further insights into the molecular basis of obesity, and possibilities for new treatments.<sup>132</sup>

I do not share *Nature's* enthusiasm. My reason for that is simple: Those researchers are not addressing the real underlying issues in obesity. Available information about obesity hormones and obesity genes makes this abundantly clear that pharmacologic therapies on blockade of single hormones and genes will not yield good long-term results. The same will hold for drugs designed to facilitate actions of other obesity hormones and genes.

What is needed is long-term true-to-life studies of individuals in their eighth and ninth decades of life who have maintained their optimal life span weights for several decades. I base the adipomyocytic dysoxygenosis model of the cause of obesity on my studies of redox equilibrium and oxygen homeostasis. I have attempted to base my recommendations for achieving and maintaining life span weight *primarily* what my octogenarian and ninogenarian patients have taught me.

What is needed even more is a clear recognition of the fact that obesity begins in utero life and is compounded during childhood.<sup>132</sup> Specifically, reduction in sugar intake and consumption of cafeteria-style "obesogenic" fats during the childhood years of development can significantly reduce the incidence and its serious health sequelae during later decades of life. This has been conclusively shown by careful studies in experimental animals.<sup>133</sup> For instance, reduced cell signaling by insulin-like peptides increases the life span of nematodes, flies, and mice.<sup>134</sup> It is highly significant in the context of the adipomyocytic model of obesity discussed in this chapter that lengthening of life spans by reduced insulin and insulin-like signaling has been attributed to oxidative damage. It may also be pointed out here that JNKs are *c-JUN* amino-terminal kinases which interfere with insulin action and are activated by free fatty acids as well as inflammatory cytokines, including TNF- $\alpha$ . In both dietary and genetic (*ob/ob*) models of obesity, total JNK activity is markedly increased in the liver, muscle, and adipose tissue.<sup>135</sup>

There is an enormous potential for the *right* kind of intervention that can reduce the incidence and consequences of obesity related to in-utero life and childhood. Sadly, this subject is all but ignored for lack of public funding. Here I draw a sharp contrast between the financial resources allocated to public health measures and that committed to drug development. It is noteworthy that the entire process of a compound emerging from a chemistry lab as a drug in use in the clinic typically costs \$900m and takes 15 years.<sup>136</sup> One can only wonder what clinical results may be expected if 900 million dollars were allocated to obesity education by practicing nutritionists (not by ivy league theorists with voracious appetites for public funds who never see any patients). What would just the cost of bringing out a *single* blocker drug — which the society can do well without — would do in right hands?

Rapid fluctuations observed with the commonly used weight loss program not only diminish the probability of long-term success, such changes actually increase morbidity and shorten the life span of the individual. The evidence on that important issue is clear. I cite below two quotes from the *American Journal of Epidemiology*<sup>137</sup> and *The New England Journal of Medicine*<sup>138</sup> respectively that support my case:

These results support the concept that large changes in weight during young adulthood increase the risk of coronary disease and cancer.<sup>137</sup>

First, weight fluctuation was most strongly associated with adverse health outcomes in the youngest cohorts (age 30 through 44 years).<sup>138</sup>

The oxidative-dysoxygenative model of obesity has three strengths: (1) It has a strong explanatory power for a host of observed phenomena concerning the spreading epidemics of obesity, as well as hyperinsulinemia, syndrome X, and diabetes; (2) It provides rational and scientific basis for all sound molecular underpinnings of newly emerging patterns of biologic derangements in wildlife; and (3) It calls for a sharp focus and vigorous efforts to undertake public health measures to preserve and/or restore redox and oxygen homeostasis to prevent disease and extend life span. The recently documented fermentative-to-respiratory metabolic shift in yeast calls for a careful assessment of our existing notions of man-microbe relationships, especially those observed in chronic oxidative-dysoxygenative energy disorders, such as fibromyalgia, chronic fatigue syndrome, environmental illness, Gulf War syndrome, the September Eleven-related illness, viral activation syndromes, chronic fatigue after chemotherapy for malignant tumors, and others.

<b>Table 1. WEIGHT AND HEIGHT TABLE FOR MALES</b>			
<b>Height</b>	<b>Small Frame (+-3)</b>	<b>Medium Frame (+-5)</b>	<b>Large Frame (+-6)</b>
5'2"	128	132	140
5'3"	130	134	143
5'4"	132	136	145
5'5"	134	138	148
5'6"	136	141	151
5'7"	139	144	154
5'8"	141	147	158
5'9"	143	150	161
5'10"	146	153	165
5'11"	148	156	168
6'0"	150	159	173
6'1"	155	163	176
6'2"	158	167	180
6'3"	162	170	185
6'4"	166	175	190
<b>Range</b>	<b>(+-7)</b>	<b>(+-8)</b>	<b>(+-12)</b>

<b>Table 2. WEIGHT AND HEIGHT TABLE FOR FEMALES</b>			
<b>Height</b>	<b>Small Frame (+-4)</b>	<b>Medium Frame (+-6)</b>	<b>Large Frame (+-7)</b>
4'10"	105	112	120
4'11"	106	114	123
5'	107	116	125
5'1"	110	119	128
5'2"	112	122	131
5'3"	115	125	135
5'4"	118	128	138
5'5"	121	131	142
5'6"	124	134	145
5'7"	127	137	149
5'8"	131	140	152
5'9"	133	143	155
5'10"	136	146	157
5'11"	139	149	161
6'0"	144	152	164
<b>Range</b>	<b>(+-4)</b>	<b>(+-6)</b>	<b>(+-9)</b>

## References

1. Ali M. Hypothesis: obesity is adipomyocytic dysoxygenosis. *J Integrative Medicine*. 2004;9:19-38.
2. Ali M. Oxygen is cellular oxygen deficiency state. *Aging Healthfully* 2004;7:2-5.
3. Barsh GS, Farooqi S, O'Rahilly S. Genetics of body-weight regulation. *Nature*.2000;404:644-651.
4. Comuzzie, A. G. & Allison, D. B. The search for human obesity genes. *Science*. 1998;280: 1374-1377.
5. Lander, E. & Kruglyak, L. Genetic dissection of complex traits: guidelines for interpreting and reporting linkage results. *Nature Genet*. 1995;11:241-247.
6. Comuzzie, A. G. et al. A major quantitative trait locus determining serum leptin levels and fat mass is located on human chromosome 2. *Nature Genet*. 1997;15:273-276.
7. Hager, J. et al. A genome-wide scan for human obesity genes reveals a major susceptibility locus on chromosome 10. *Nature Genet*. 1998;20:304-308.
8. Perusse, L., Chagnon, Y. C., Weisnagel, J. & Bouchard, C. The human obesity gene map: the 1998 update. *Obes. Res*. 1999;7:111-129.
9. Ware JH. *Interpreting Incomplete Data in Studies of Diet and Weight Loss*. Volume 2003;348:2136-2137.
10. Foster GD, Wyatt HR, Hill JO, et al. A randomized trial of a low-carbohydrate diet for obesity. *N Engl J Med* 2003;348:2082-2090.
11. Samaha FF, Iqbal N, Seshadri P, et al. A low-carbohydrate as compared with a low-fat diet in severe obesity. *N Engl J Med* 2003;348:2074-2081.

12. Larosa JC, Fry AG, Muesing R, Rosing DR. Effects of high-protein, low-carbohydrate dieting on plasma lipoproteins and body weight. *J Am Diet Assoc* 1980;77:264-270.
13. Serdula MK, Mokdad AH, Williamson DF, Galuska DA, Mendlein JM, Heath GW. Prevalence of attempting weight loss and strategies for controlling weight. *JAMA* 1999;282:1353-1358.
14. St Jeor ST, Howard BV, Prewitt TE, Bovee V, Bazzarre T, Eckel RH. Dietary protein and weight reduction: a statement for healthcare professionals from the Nutrition Committee of the Council on Nutrition, Physical Activity, and Metabolism of the American Heart Association. *Circulation* 2001;104:1869-1874.
15. Kennedy ET, Bowman SA, Spence JT, Freedman M, King J. Popular diets: correlation to health, nutrition, and obesity. *J Am Diet Assoc* 2001;101:411-420.
16. Westman EC. A review of very low carbohydrate diets for weight loss. *J Clin Outcomes Manage* 1999;6(7):36-40.
17. Westman EC, Yancy WS, Edman JS, Tomlin KF, Perkins CE. Effect of 6-month adherence to a very low carbohydrate diet program. *Am J -Med* 2002;113:30-36.
18. Eades MR, Eades MD. Protein power lifeplan. New York: Warner Books, 2000:434.
19. Atkins RC. Dr. Atkins' new diet revolution. New York: Avon Books, 1992.
20. Eades MR, Eades MD. Protein power. New York: Bantam Books, 1999.
21. The truth about dieting. *Consumer Reports*. June 2002:26-32.
22. Freedman MR, King J, Kennedy E. Popular diets: a scientific review. *Obes Res* 2001;9:Suppl 1:1S-40S.[ISI][Medline]
23. Blackburn GL, Phillips JCC, Morreale S. Physician's guide to popular low-carbohydrate weight-loss diets. *Cleve Clin J Med* 2001;68:761, 765-6, 768.
24. Bray, G. A. *Current and Contemporary Management of Obesity*. 1998. Newtown, PA. Handbooks in Health Care.
25. Bray, G. A. & Greenway, F. L. A review of current and potential drugs for treatment of obesity. *Endocr. Rev.* 1999;20:805-875.
26. Rolls, B. J., Shide, D. J., Thorwart, M. L. & Ulbrecht, J. S. Sibutramine reduces food intake in non-dieting women with obesity. *Obes. Res.* 1998;6:1-11.
27. Astrup, A., Breum, L., Toubro, S., Hein, P. & Quaade, F. The effect and safety of an ephedrine/caffeine compound compared to ephedrine, caffeine and placebo in obese subjects on an energy-restricted diet. A double-blind trial. *Int. J. Obes. Relat. Metab. Disord.* 1992;16:269-277.
28. Bray GA, Tartaglia LA. Medicinal strategies in the treatment of obesity. *Nature*.2002;404:672-677
29. Kopelman PG. Obesity as a medical problem. *Nature*.2000;404:635-43. p635.
30. Chicural M. What happened to leptin? *Nature*. 2000;404:538-40.
31. Friedman, J. M. & Halaas, J. L. Leptin and the regulation of body weight in mammals. *Nature*. 1998;395:763-770.
32. Ahima, R. S. et al. Role of leptin in the neuroendocrine response to fasting. *Nature*. 1996; 382:250-252.
33. Friedman JM. Obesity in the new millennium. *Nature*.2000;404:632-4.p633.
34. Ali M: Fibromyalgia: an oxidative-dysoxygenative disorder (ODD). *J Integrative Medicine* 1999; 3:17-37.
35. Ali M. Dysoxygenosis. *J Integrative Medicine*. 2002;6:1-34
36. Ali M. The oxidative-dysoxygenative perspective of allergic disorders. *J Integrative Med*. 2000; 4:1-17
37. Ali M. Beyond insulin resistance and syndrome X: The oxidative-dysoxygenative insulin dysfunction (ODID) model. *J Capital University of Integrative Medicine*. 2001;1:101-141.
38. Ali M. Carcinogenesis: The Oxidative-Dysoxygenative Model. *J Integrative Medicine* 2001;5:9-32
39. Ali M. The oxidative-dysoxygenative mercury-related-illness model. *J Integrative Medicine*. 2002;6:35-100.
40. Ali M. Oxidative-dysoxygenative parasympathetic dystrophy: Frequency of diminished high-frequency parasympathetic outflow in subjects with chronic oxidosis and dysoxygenosis. *J Integrative Medicine*. 2002;6:101-107.
41. Ali M. Beyond the cholesterol and inflammatory theories of coronary artery disease: The oxidative-dysoxygenative coronary disease (ODCAD) model. *J Integrative Medicine*. 2002; 7:1-19.
42. Ali M: Darwin, oxidosis, dysoxygenosis, and integration. *J Integrative Medicine* 1999;3:11-16.
43. Ali M. *The Ghoraa and Limbic Exercise*. 1993. Denville, New Jersey, Life Span Books.
44. Raloff J. Inflammatory fat-unraveling the injurious biology of obesity. *Science News*. 2004;165:139-140.
45. Kopelman PG. Obesity as a medical problem. *Nature*. 2000;404:635-643. p 45.
46. World Health Organization. *Obesity: Preventing and Managing the Global Epidemic*. 1998. Geneva. World Health Organization.
47. Elston T, Wang H, Oster G. Energy transduction in ATP synthase. *Nature* 1998;391:510-513.
48. Noji H, Yoshida M. The rotary machine of the cell, ATP synthase. *J Biol Chem* 2001;276:1665-1668.
49. Chinnery PF, Turnbull DM. Epidemiology and treatment of mitochondrial disorders. *Am J Med Genet* 2001;106:94-101. Also: Holt IJ, Harding AE, Morgan-Hughes JA. Deletions of muscle mitochondrial DNA in patients with mitochondrial myopathies. *Nature* 1988;331:717-719.
50. Ali M. *Oxygen and Aging*. 2nd ed. 2004. New York, Canary 21 Press.
51. Eat, Drink and Be Healthy: The Harvard Medical School Guide to Healthy Eating.<sup>51</sup> (Simon & Schuster, \$25). <http://www.usatoday.com/news/health/2001-07-26-food-pyramid-usat.htm>
52. Webb B. [www.brandyn@sifter.org](http://www.brandyn@sifter.org).
53. Butler D. Slim pickings. *Nature*. 2004;428:252-3.
54. Yeo, G. et al. A frameshift mutation in MC4R associated with dominantly inherited human obesity. *Nature Genet*. 20, 111-112 (1998).
55. Harris, R. B. S., Kasser, T. R. & Martin, R. J. Dynamics of recovery of body composition after overfeeding, food restriction or starvation of mature female rats. *J. Nutr.* 1986;116:2536-2546.
56. Lowell BB, Spiegelman BM. Towards a molecular understanding of adaptive thermogenesis. *Nature*. 2000;404:652 - 660.
57. Hart, J. S., Heroux, O. & Depocas, F. Cold acclimation and the electromyogram of unanesthetized rats. *J. Appl. Physiol.* 1956;9: 404-408.

58. Davis, T. R. A., Johnston, D. R., Bell, F. C. & Cremer, B. J. Regulation of shivering and nonshivering heat production during acclimation of rats. *Am. J. Physiol.* 1960;198:471-475.
59. Foster, D. O. & Frydman, M. L. Tissue distribution of cold-induced thermogenesis in conscious warm- or cold-acclimated rats reevaluated from changes in tissue blood flow: the dominant role of brown adipose tissue in the replacement of shivering by nonshivering thermogenesis. *Can. J. Physiol. Pharmacol.* 1979;57:257-270.
60. Dauncey, M. J. Influence of mild cold on 24 h energy expenditure, resting metabolism and diet-induced thermogenesis. *Br. J. Nutr.* 1981;45:257-267.
61. Leibel, R. L., Rosenbaum, M. & Hirsch, J. Changes in energy expenditure resulting from altered body weight. *N. Engl. J. Med.* 1995;332:621-628.
62. Blaxter, K. *Energy Metabolism in Animals and Man.* 1989. Cambridge. Cambridge Univ. Press.
63. McKay CM. *Chemical Aspects of Aging and the Effect of Diet upon Aging.* In: Cowdry's Problems of Ageing. 3rd ed. 1952. Eds. Al Lansing. New York. Williams and Williams. p139.
64. Weindruch W. Walford RL. *The Retardation of Aging and Diseases by Dietary Restriction.* Thomas, Springfield, Illinois, 1998.
65. Yu BP. *Modulation of Aging Processes by Dietary Restriction.* CRC Press, Boca Raton, Florida, 1994.
65. Also: Roth GS, Ingram D K, Lane MA. Calorie restriction in primates: will it work and how will we know? *J. Am. Geriatr. Soc.* 1999;47:896-903
63. Lin SJ, Defossez PA, Guarente L. Requirement of NAD and SIR2 for life-span extension by calorie restriction in *Saccharomyces cerevisiae*. *Science* 2000;289: 2126-2128.
64. Imai S, Armstrong C M., Kaerberlein M, et al. Transcriptional silencing and longevity protein Sir2 is an NAD-dependent histone deacetylase. *Nature* 2000;403:795-800.
65. Landry J. et al. The silencing protein SIR2 and its homologs are NAD-dependent protein deacetylases. *Proc.*
69. Schwartz MW, , Stephen C. Woods SC, , Daniel Porte D, et al. Central nervous system control of food intake. *Nature.* 2000;404:661-671. p 664
- x1. Friedman, J. M. & Halaas, J. L. Leptin and the regulation of body weight in mammals. *Nature.* 1998.395, 763-770 .
70. Friedman JM. Obesity in the new millennium. *Nature.* 2000;404:632-634.
- x. Ahima, R. S. et al. Role of leptin in the neuroendocrine response to fasting. *Nature.* 1996;382:250-252.
71. Zhang, Y. et al. Positional cloning of the mouse obese gene and its human homologue. *Nature.* 1994;372:425-432.
72. Montague, C. T. Congenital leptin deficiency is associated with severe early-onset obesity in humans. *Nature.* 1997;387:903-908.
73. Stunkard, A. J., Harris, J. R., Pedersen, N. L. & McClearn, G. E. The body-mass index of twins who have been reared apart. *N. Engl. J. Med.* 1990;322: 1483-1487.
74. Erickson, J. C., Hollopeter, G. & Palmiter, R. D. Attenuation of the obesity syndrome of ob/ob mice by the loss of neuropeptide Y. *Science.* 1996;274:1704-1707.
75. Fan, W., Boston, B. A., Kesterson, R. A., Hruby, V. J. & Cone, R. D. Role of melanocortinergic neurons in feeding and the agouti obesity syndrome. *Nature.* 1997; 385:165-168.
76. Pelleymounter, M. A. et al. Effects of the obese gene product on body weight regulation in ob/ob mice. *Science.* 1995;269:540-543.
77. Maffei, M. et al. Leptin levels in human and rodent: measurement of plasma leptin and ob RNA in obese and weight-reduced subjects. *Nature Med.* 1995;1:1155-1161.
78. Puigserver, P. et al. A cold-inducible coactivator of nuclear receptors linked to adaptive thermogenesis. *Cell.* 1998;92:829-839.
79. Krude, H. et al. Severe early-onset obesity, adrenal insufficiency and red hair pigmentation caused by POMC mutations in humans. *Nature Genet.* 1998;19:155.
80. Sakurai, T. et al. Orexins and orexin receptors: a family of hypothalamic neuropeptides and G-protein-coupled receptors that regulate feeding behavior. *Cell.* 1998;92:573-585.
81. Schwartz MW, Stephen C. Woods SC, , Daniel Porte D, et al. Central nervous system control of food intake. *Nature.* 2000;404:661-671.
82. Brunetti, L., Michelotto, B., Orlando, G. & Vacca, M. Leptin inhibits norepinephrine and dopamine release from rat hypothalamic neuronal endings. *Eur. J. Pharmacol.* 1999;372: 237-240.
83. Oltmans, G. Norepinephrine and dopamine levels in hypothalamic nuclei of the genetically obese mouse (ob/ob). *Brain Res.* 1983;273:369-373.
84. 102. Leibowitz, S., Roossin, P. & Rosenn, M. Chronic norepinephrine injection into the hypothalamic paraventricular nucleus produces hyperphagia and increased body weight in the rat. *Pharmacol. Biochem. Behav.* 1984;21:801-808.
85. Salamone, J., Mahan, K. & Rogers, S. Ventrolateral striatal dopamine depletions impair feeding and food handling in rats. *Pharmacol. Biochem. Behav.* 1993;44:605-610.
86. Szczypka, M. et al. Feeding behavior in dopamine-deficient mice. *Proc. Natl Acad. Sci. USA.* 1999;96:12138- 12143.
87. Pothos, E., Creese, Hoebel B. Restricted eating with weight loss selectively decreases extracellular dopamine in the nucleus accumbens and alters dopamine response to amphetamine, morphine, and food intake. *J. Neurosci.* 1995;15:6640- 6650.
88. Leibowitz S, Alexander J. Hypothalamic serotonin in control of eating behavior, meal size, and body weight. *Biol. Psychiatry.* 1998;44:851- 864
89. Nonogaki, K., Strack, A., Dallman, M. & Tecott, L. Leptin-independent hyperphagia and type 2 diabetes in mice with a mutated serotonin 5-HT<sub>2C</sub> receptor gene. *Nature Med.* 1998;4:1152-1156.
90. Ali M. Beyond insulin resistance and syndrome X: The oxidative-dysoxygenative insulin dysfunction (ODID) model. *J Capital University of Integrative Medicine.* 2001;1:101-141.
91. Almeida, N. G., Levitsky, D. A. & Strupp, B. Enhanced thermogenesis during recovery from diet-induced weight gain in the rat. *Am. J. Physiol.* 1996;271:R1380-R1387.
92. Comuzzie, A. G. & Allison, D. B. The search for human obesity genes. *Science.* 1998;280:1374-1377.
91. Barsh GS, Farooqi S, O'Rahilly S. Genetics of body-weight regulation. *Nature.* 2000;404:644-651.p650.

93. Maes HH, Neale MC, Eaves LJ. Genetic and environmental factors in relative body weight and human adiposity. *Behav. Genet.* 1997;27:325-351.
94. Comuzzie, A. G. et al. A major quantitative trait locus determining serum leptin levels and fat mass is located on human chromosome 2. *Nature Genet.* 1997;15:273-276.
95. Hager, J. et al. A genome-wide scan for human obesity genes reveals a major susceptibility locus on chromosome 10. *Nature Genet.* 1998; 20:304-308.
96. Rotimi, C. N. et al. The quantitative trait locus on chromosome 2 for serum leptin levels is confirmed in African-Americans. *Diabetes.* 1999; 48:643-644.
97. Hixson, J. E. et al. Normal variation in leptin levels in associated with polymorphisms in the proopiomelanocortin gene, POMC. *J. Clin. Endocrinol. Metab.* 1999;84: 3187-3191.
98. Perusse, L., Chagnon, Y. C., Weisnagel, J. & Bouchard, C. The human obesity gene map: the 1998 update. *Obes. Res.* 1999;7:111-129.
99. West DB. Genetics of obesity in humans and animal models. *Endocrinol. Metab. Clin. North Am.* 1996;25:801-813.
100. Ali *Oxygen and Aging*. 1st ed. 2000. New York. Aging Healthfully Books.
101. Hart, J. S., Heroux, O. & Depocas, F. Cold acclimation and the electromyogram of unanesthetized rats. *J. Appl. Physiol.* 1956;9: 404-408.
102. Ali M. *Healing Miracles and the Bite of the Gray Dog*. 1997. Denville, New Jersey, Life Span Books.
103. Wellen KE, and Gökhan S. Hotamisligil GS. Obesity-induced inflammatory changes in adipose tissue. *J. Clin. Invest.* 2003 112: 1785-1788.
104. Weisberg SP, McCann D, Desai M, et al. Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest.* 2003;112:1796-1808.
105. Xu H, Barnes GT, , Qing Yang Q, et al. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *J. Clin. Invest.* 2003;112:1821-1830.
106. Hotamisligil, G.S. 2003. Inflammation, TNF[ $\alpha$ ] and insulin resistance. In *Diabetes mellitus*. D. LeRoith, S.I. Taylor, and J.M. Olefsky, editors. Lippincott-Raven Publishers. Philadelphia, Pennsylvania, USA. In press..
107. Hirosumi, J. et al. A central role for JNK in obesity and insulin resistance. *Nature.* 2002;33-336.
108. Hotamisligil, G.S., Shargill, N.S., and Spiegelman, B.M. 1993. Adipose tissue expression of tumor necrosis factor- $\alpha$ : direct role in obesity-linked insulin resistance. *Science.* 1993;259:87-90.
109. Uysal KT, Wiesbrock SM, Marino MW., et al. Protection from obesity-induced insulin resistance in mice lacking TNF- $\alpha$  function. *Nature.* 1997;610-614.
110. Rosen, B.S. et al.. Adipsin and complement factor D activity: an immune-related defect in obesity. *Science.* 1989;244:1483-1487.
111. Charriere, G. et al.. Preadipocyte conversion to macrophage. Evidence of plasticity. *J. Biol. Chem.* 2003;278:9850-9855.
112. Tontonoz, P., Nagy, L., Alvarez, J.G., Thomazy, V.A., and Evans, R.M. PPAR $\gamma$  promotes monocyte/macrophage differentiation and uptake of oxidized LDL. *Cell.* 1998;93:241-252.
113. Makowski, L. et al. Lack of macrophage fatty-acid-binding protein aP2 protects mice deficient in apolipoprotein E against atherosclerosis. *Nat. Med.* 2001;7:699-705.
114. Sierra-Honigmann, M.R. et al. Biological action of leptin as an angiogenic factor. *Science.* 1998;1683-1686.
115. Ali M. Oxidative coagulopathy in environmental illness. *Environmental Management and Health.* 2000;11:175-191.
116. Ali M. The oxidative-dysoxygenative perspective of allergic disorders. *J Integrative Med.* 2000; 4:1-17
117. Ali M. The oxidative-dysoxygenative mercury-related-illness model. *J Integrative Medicine.* 2002;6:35-84.
118. Ali M. Oxidative-dysoxygenative parasympathetic dystrophy: Frequency of diminished high-frequency parasympathetic outflow in subjects with chronic oxidosis and dysoxygenosis. *J Integrative Medicine.* 2002;6:101-107.
119. Ali M. The Oxidative-Dysoxygenative Model of Aging. *J Integrative Medicine.* 2003;7:21-30.
120. Harmon D. Aging: a theory based on free radical and radiation chemistry. *J Gerontol* 1956;11:298.
121. Bjorksten J. Crosslinking\_key to aging. *Chem and Engin News* 1955;33:1967.
122. Boss, O. et al. Uncoupling protein-3: a new member of the mitochondrial carrier family with tissue-specific expression. *FEBS Lett.* 1997;408: 39-42.
123. Vidal-Puig, A., Solanes, G., Grujic, D., Flier, J. S. & Lowell, B. B. UCP3: an uncoupling protein homologue expressed preferentially and abundantly in skeletal muscle and brown adipose tissue. *Biochem. Biophys. Res. Commun.* 1997;235: 79-82.
124. Gong, D. W., He, Y., Karas, M. & Reitman, M. Uncoupling protein-3 is a mediator of thermogenesis regulated by thyroid hormone, beta3-adrenergic agonists, and leptin. *J. Biol. Chem.* 1997;272: 24129-24132.
125. *The Principles and Practice of Integrative Medicine Volume III: Dysoxygenosis and Oxystatic Therapies.* 2003. Washington, D.C. Capital University Press (in collaboration with Canary 21 Press, New York). www.cuim.edu & www.Canary21press.com.
126. Hirosumi J, Tuncman G, Chang L, et al. A central role for JNK in obesity and insulin resistance. *Nature* 2002;420:333-336.
127. Ali M: Darwin, oxidosis, dysoxygenosis, and integration. *J Integrative Medicine* 1999;3:11-16.
128. Ali M. *The Butterfly and Life Span Nutrition.* 1992. Denville, New Jersey, Life Span Books.
129. Gardener Jr. R Tot Therapy. .New York Magazine. April, 2004. pp32-39.
130. Physical Therapy. 1990;70:808.
130. Ali M. *The horaa and Limbic Exercise.* 1993. Denville, New Jersey, Life Span Books 1993.
131. Am J Cardiol. 1990;65:010.
132. Hales CN, Barker DJP. *Br Med Bull.* 2001;60:5-20.
133. Ozanne SE, Hales CN. Catch-up growth and obesity in male mice. *Nature.* 2004;427:411-2.
134. Tartar M, Bartke A, Antebi A. *Science.* 2003;299:1346-1351.
135. Hirosumi J, Tuncman G, Chang L, et al. A central role for JNK in obesity and insulin resistance. *Nature* 2002;420:333-336.
136. *The Economist Technology Quarterly*, March 13, 2004 (citing a number from Tufts center for the Study of Drug Development).
137. *Am J Physiology.* 1989;129:312.
138. *N Eng J Med.* 1991;324:1839.







