CHAPTER 15

THE LEPTIN FACTOR

Obesity is a symptom . . . not a diagnosis!

Crack open your morning newspaper, these days, and the odds are high that you'll soon find yourself reading an alarming health story about "the growing obesity epidemic in America."

Unfortunately, most of those breathless, page-one stories are all too accurate. Take a look around; the proof is there. The "American Waddler" is all too commonly sighted in public places and doctor's offices. If you missed seeing the Waddler on the streets, you will see him on the Evening News, rippling past the camera, arms swinging wide over the layers of belly-rolls and thunder thighs. You don't need a Ph.D. in human physiology to understand that Americans (and especially American *children*) are getting fatter with each passing year.

How bad is the U.S. "obesity problem" today, and why is it becoming increasingly worse?

This bad: According to the latest data from the number-crunchers at the U.S. Centers for Disease Control and Prevention (CDC) in Atlanta, fully one-third of America's 280 million citizens are currently classified as medically overweight.

Even more ominous, say public health officials, is the fact that "clinical obesity" – a chronic disease with a variety of potentially life-threatening consequences – is now affecting more than 56 million Americans (about 20 percent of us), day in and day out. Just 10 years ago, the numbers were significantly lower.

Here's the bad news for Americans in the first decade of the new millennium: Although the CDC opinion released for public consumption is often wrong about medical issues and frequently distorts scientific research-findings for the sake of its own narrow political agenda, the agency is dead-on correct about the threat from the spreading obesity problem. What the CDC *hasn't* figured out yet, however, forms the heart and soul of this chapter – the startling fact that obesity is actually a chronic illness, either genetically based in abnormal leptin and insulin physiology or acquired in ways related to the immune responses that are part of other chronic, "biotoxin-associated" environmental illnesses of our day (such as Sick Building Syndrome). Indeed, the biggest news in weight-loss treatment right now is the recent discovery – based on research from the seemingly unrelated field of chronic biotoxin illnesses such as "Post-Lyme Disease Syndrome" – that there is a close link between our increasingly chemically polluted environment and a new family of biotoxin-linked ailments that often trigger both obesity and diabetes.

So far, only a few isolated researchers (and they're not in Atlanta!) have grasped the relationship between the fact that as our environment continues to change rapidly under the influence of the 70,000 industrial and agricultural chemicals pumped into air,

soils, rivers, estuaries and oceans each year, Americans are getting fatter and fatter. Nor have the "Medical Mandarins" at the CDC (or their counterparts in the largest and most prestigious university medical research departments) yet understood that obesity is an illness of *over-storage* of fat that has almost *nothing* to do with *"overeating*" alone . . . and *everything* to do with physiological resistance to metabolic hormones such as insulin and leptin. While we can't alter the genetic predisposition to leptin and insulin problems, we can *control* that resistance with new medications and the No-Amylose Diet. The role of other "new" obesity related hormones, including gherlin and neuropeptide Y, shows promise for additional interventions to defeat obesity in the future. But treatment of the obesity epidemic linked to hormone resistances is here now. (More on the exciting recent breakthroughs in leptin and insulin resistance and its links to inflammation from the hidden "environmental diseases" in a minute.)

Make no mistake: America's "fat epidemic" is rapidly spiraling out of control, and the negative impact on grownups and kids alike can be observed from the rocky coastline of Maine to the towering redwoods of California. Example: According to the latest health statistics, more than 300,000 Americans are now dying each year from diseases (such as diabetes, hypertension, sleep apnea, colon cancer and breast cancer) that have been linked directly to obesity. If heart disease is added to the toll (and many physicians believe it should be), there can be no doubt that obesity now ranks as our nation's biggest health threat. Even if the extra fat doesn't kill right away, the multiple impairments caused by obesity make life miserable, from the unnecessary pain from arthritic weight bearing joints, reduced ability to walk up a flight of stairs or even put on a pair of shoes. The derogatory attitudes about obesity in our society add to the misery, as many overweight people are regarded as self-indulgent gluttons. Being overweight is a sign of personal slothfulness in the eyes of many who view obesity as a "preventable illness." And who would list "obesity" on a job application as an important self-accomplishment that would help convince a personnel manager to offer employment?

These obesity-associated health problems cause untold anguish for the victims and their families, of course. But the carnage produced by obesity also hits America hard in her pocketbook, while adding more than $900 million per year to the cost of health care in this country. Alarmed by the surge in fat-related costs, no less a figure than the U.S. Surgeon General recently warned the nation that if the current trend continues, "Obesity may soon cause as much preventable disease as cigarette smoking." For those on the front lines of obesity treatment and research, his words need to be changed to reflect the real issue: obesity has a series of understandable mechanisms and it can be treated before it causes disease by understanding those mechanisms.

Disturbing facts about the epidemic, its cost and its consequences? You bet. Even more disturbing, though, is the clear failure of all "medically accepted" attempts to defeat the epidemic with lifestyle changes. Our National Fat Attack has been taking place during an era dedicated to "physical fitness" . . . during an era in which most of us are bombarded daily with powerful propaganda about the vital importance of "eating right and getting plenty of exercise," if we wish to enjoy healthy, vigorous lives and stay slim. For reasons you have already read and more to come, the "eat less and exercise more" idea is worse than worthless for the vast majority of overweight people. When the "American Waddler" finally gets up the gumption to go out in the cold and rain four times a week to walk before the sun comes up, and he cuts back on everything enjoyable

at the dinner table, he still doesn't lose much weight and he certainly never keeps it off. Now add worsened self-esteem from his failed weight loss attempt to his ongoing weight problem. Why did the Waddler fail? Could it be that the reason for his obesity has nothing to do with trivial amounts of exercise or elimination of foods unrelated to weight gain from his diet… and a great deal to do with his daily consumption of fat-generating food?

The experts have a ready answer for the Waddler's failed weight loss attempt: *he* is the reason for the failure, not the "eat less, exercise more" model. Just try to find an obesity expert who doesn't explain the failure of the "eat less and exercise more" strategy by blaming the patient. "Well, Mr. Jones joined the fitness club, but only went there three times last year. And he never stopped having the French fries and the triple cheeseburgers." But Mr. Jones *did* his exercise and he *ate* the low fat, low cholesterol meals, with salads, pasta and whole wheat as he was instructed. He did what he was told, but he still failed.

The wrong entity is being blamed! In medicine, the failure of an accepted idea to explain what we observe usually means the idea is tossed out, like garbage bound for the landfill. In other words, we learn more in medicine by observing what intervention didn't work, and adjusting our model to accommodate the treatment failures, than we do by only observing what did work. If the model doesn't explain what actually happens, then the model, like "eat less and exercise more," is wrong.

In spite of our continuing obsession with "avoiding dietary fat" and jogging or walking at least 30 minutes each day," the remarkable fact remains: Americans are fatter now than ever before in their history. Somehow, our model of treatment of obesity that is based on devotion to the ideas from the Greek goddess of health, Hygeia – the patron saint of the "hygienic" approach to health, which insists that the key to curing illnesses is to "clean up" our bad lifestyle-habits, such as overeating and lack of exercise – hasn't succeeded in overcoming our national predilection for getting fat and staying fat**.**

The obvious question becomes, "*Does that mean that the treatment for obesity has little to do with lifestyle*?" Other questions follow immediately, once we realize that Hygeia doesn't have our answers:

Why do most people who become overweight tend to *remain* overweight . . . even if they do manage to shrug off a few pounds now and then, before promptly gaining them back again? And why are some people able to eat all they want, meal after meal, while remaining wonderfully, infuriatingly slender? Even more challenging is the question: "Why do many people gain weight that they never lose, while eating less than their slender counterparts?" Finally, "What can we do that will work to control the chronic disease of obesity?"

As a veteran family physician who's helped thousands of obese patients lose weight (and *keep* it off) during the past 25 years, I've spent many hours studying the latest research from around the world . . . while also conducting countless patient-interviews and medical examinations aimed at solving the mystery of why so many people tend to remain fat in spite of their frequent and courageous efforts at dieting and exercising. Obesity, like any chronic disease, needs a proper diagnosis. We don't blame the patient for having hypertension, we find out what is wrong, look for acquired blood pressure problems (we can cure those), and if we find the problem is one of unknown cause ("essential hypertension" is the medical term), possibly genetic (Did your parents

have hypertension, Mr. Jones?), we treat it, without complaining that the patient isn't doing something to prevent his illness. Sure, we will try modifying diet, exercise, salt consumption, stress, and other lifestyle factors, but when the Hygeia approach predictably doesn't work, we use medications. Treatment of obesity should be no different.

Imagine my surprise years ago, when my treatment of obese patients – along with my continuing inquiries on the causes of the disease- demonstrated a remarkable fact: the mechanisms that underlay obesity shared many of the same physiologic principles involved in chronic, biotoxin-associated illnesses. It was crystal clear that a proper diagnosis of obesity involved looking at interactions of genetics and hormones like leptin and insulin, as well as the chemical messengers called cytokines (more on inflammation and cytokines coming up) that help white blood cells monitor and manage our internal immune defenses. The same disturbances in cytokines and leptin, many with a genetic basis, which were operating in Sick Building Syndrome, were the active players in obesity, too! Here was the new information, based on rock-solid science, needed to challenge the "conventional wisdom" on obesity that has ruled American medical opinion for the past several decades. Imagine the mixture of exhilaration and wonderment I felt, when I analyzed the latest data on human biochemistry from obesity literature and seemingly unrelated fields of neurotoxicology and cytokine physiology, and began to realize*: We've been wrong about fat from the very beginning!*

It became increasingly clear that the weight-loss advice from popular diet books such as *Sugar Busters*, *The Zone* and *The New Diet Revolution* was either incomplete or was simply wrong. As heretical as this may sound, today's ongoing Obesity Epidemic provides incontrovertible evidence for the fact that even Dr. Robert Atkins – the legendary "guru" of weight-loss in America since the 1970s – had failed to incorporate into his work the complex biochemical, hormonal and genetic factors that actually cause most people to become overweight and stay overweight!

As I studied the research and examined my patients during the 1980s and 1990s, I was gradually discovering that the assumptions of medical science about how we store fat and gain weight were deeply flawed. And yet those same flawed ideas – which failed to pinpoint the biochemistry and genetics of hormone resistance as the real source of weight-gain, while blaming it on mere "lifestyle" factors such as overeating and "couch-napping" – had been repeated so often over the years that they'd become accepted as Gospel, all across the increasingly fat USA! The "thermodynamics" idea about weight, namely, calories in equals calories out, wasn't the right answer (Chapter 5); exercise wasn't the answer unless the overweight patient had 12 hours a week for intense activity (Chapter 11); eliminating all carbohydrates ignored the different effects of carbohydrates on blood sugar (Chapter 2); and permitting some starches was a prescription for failure for insulin resistant patients (Chapter 6). What really do we have to do to understand treatment of the chronic disease we call obesity?

But let's back up for a second. In order to understand why the conventional wisdom about fat is flat-out incorrect, we need to look at how the process of getting fat actually *works* . . . even as we ask ourselves the key question that will solve the fat-mystery once and for all:

Question: What would happen if we looked at obesity as a *symptom*, rather than as a diagnosis? In other words: "What's different about the biochemical process of fat

manufacture and fat storage in obese patients – when compared to fat manufacture and storage in those who *aren't* overweight? If we know that answer, then we know why obesity is a symptom telling us to look at genetic, environmental, biochemical, and hormonal factors.

To answer that question, we need to spend a few moments reviewing our notes from *The History of 20th-Century Fat, 101: Or, Why Low-Carbohydrate Diets Alone Failed To Keep America Trim.*

Obesity and Leptin: A Primer

When Dr. Robert C. Atkins appeared on the national scene in 1972 with the publication of his first "Diet Revolution" guide to weight-loss, the public quickly hailed him as a bold pioneer with a radically different approach to dieting. The Medical Establishment was horrified, however, by the idea that eating fat and rich food actually was a good idea. Remember, back then, and continuing today, the cholesterol argument influenced the weight argument: "Low fat and low cholesterol foods are good – that's all there is to it!" Until the arrival of the famous diet doc, whose books on "no-carbohydrate" eating would eventually be purchased by millions, most scientific thinking about weight-loss focused on the importance of measuring (and limiting) the intake of dietary fat and reducing total calories, along with the need for lots of vigorous exercise.

But the controversial Atkins had a different idea, one that opened the door for later challenges to the dietary dogma of obesity.

According to the dieting revolutionary, the *real* culprit in weight-gain wasn't fat or lack of exercise but carbohydrates – complexes of carbon and water molecules, found mostly in sugar and starches, which the human body rapidly stores in fat cells for future use.

Imagine the shock waves that must have rippled through the U.S. medical community, when Dr. Atkins began insisting that the best way to lose weight was to avoid all carbohydrates . . . and that eating moderate amounts of fat would *not* make most people gain weight!

Controversial or not, the Atkins approach turned out to be reasonably effective for millions of people, in the short run. By cutting back on "carbs," the adherents of the Diet Revolution collectively lost millions of pounds . . . even if the lost weight was almost invariably re-gained by the dieters within a matter of a few months. Regardless of these problems with "weight-maintenance," however, the Atkins strategy was generally declared to be a success and the weight-loss author became a household American name as a result.

But now let's flash-forward 30 years and take a look around.

Let's ask ourselves: What ultimately became of the "eat-no-carbohydrates" approach to dieting that had made Dr. Atkins so famous?

Answer: *Over the long haul, it simply didn't work.*

Why did it fail? Although the biochemical explanation is complex (we'll worry about the chemistry a bit later), the fundamental reason for the failure is easy to grasp. That reason is based on the fact that although Dr. Atkins did a great job of focusing national attention on issues of weight-loss, he and most of his fellow-researchers were using the wrong "model" with which to understand how human beings get fat.

In a sentence: The Atkins model, like most others of his day, was based on analyzing and controlling the foods that people *eat* . . . rather than on understanding and then controlling (with medications, where appropriate) the human body's *response* to those foods during the processes of digestion, fat manufacture and fat storage. Those processes involve hormones, including insulin and leptin, genetics, inflammation and also discrete centers that regulate hunger and satiety in a part of the brain, the hypothalamus. The pivotal role of rapid rises of blood sugar after eating one common type of complex carbohydrate starch, amylose, and its effect on insulin-driven fat storage was also ignored. But all too soon**,** the lack of precision in defining "fat-causing carbohydrates" caused motivated patients to abandon the Atkins plan and others like it, because the dieters weren't allowed to eat the fruits and vegetables that are not only safe for a weight-loss plan, but also essential in order to maintain a reasonable "quality of life" while losing weight.

Dr. Atkins and his colleagues can't really be blamed for failing to understand that being overweight or obese is primarily a result of the patient's own unique biochemistry (that is, of the multiple interactions of his or her fat-regulating hormones) . . . and *not* a result of overeating or refusal to exercise. They simply didn't have the data on hormone interactions that in those days "belonged to the future" of obesity-treatment. But that future is now here, creating a model for understanding new treatments based on molecular biochemistry, and not on total calories or fat grams. The powerful new model of obesity, one that includes multiple factors, tells us that managing our weight successfully is primarily a matter of understanding and then manipulating hormones – based on their efficiency (or lack thereof) at transporting and transforming nutrients during the process of digestion and fat storage.

Sounds a bit complicated, you say?

Not really. All you really need to know in order to take advantage of the molecular research that has radically changed our understanding of obesity in recent years is one simple fact: Weight-loss is actually about *hormones* (such as insulin and leptin) . . . and specifically about defeating the "resistance" to the effect those hormones normally produce. It is hormone mechanisms gone awry that cause us to become fat, prevent us from losing much fat when we try, and make us gain weight – even when strictly observing the same "lower total-calorie diets" being eaten by those without hormone abnormalities! Obviously, those same hormone defects are also the root-cause of today's failure to achieve maintenance of fat loss, among millions of struggling "yo-yo" dieters.

The bottom line: If you're one of the millions of Americans whose "genetic inheritance" prevents your fat controlling hormones (and especially leptin) from working efficiently because of hormonal resistance, the good news is that medicine can now *fix* that problem with a new arsenal of medications (such as "leptin-modifying" drugs) designed to overcome the resistance and help you eliminate fat safely and eat good food without fear of re-gain.

For dieters everywhere, the future of weight-loss and weight-maintenance has finally arrived! In the wake of the latest obesity research, it's now possible to reliably correct the problems of excess leptin due to leptin resistance, and the problems of excess insulin due to insulin resistance. This simple fact is going to completely revolutionize the way we treat obesity in the future.

Earlier in this book, you learned that leptin is a key factor in controlling your weight because of the way it turns on the brain's "stop-eating center" – also known as the "satiety center." You may also recall from Chapter 14 that this process occurs in the hypothalamus, the area of the brain that regulates functions such as hunger, temperature and moods.

Now, here's where the recent research on hunger and hormones gets *really* interesting. Remember those exciting photos of genetically fat mice that didn't make leptin? When they were given leptin supplements, they all lost weight. At first glance, you might expect that a heavyset patient (let's call him "Mr. Overweight") who's suffering from leptin resistance (and thus from a shortage of leptin *effect* in the hypothalamus, even though there's plenty of leptin moving through his system that normally would do its job) could be coaxed into losing his excess poundage, simply by giving him periodic doses of leptin, right?

Wrong. Extra leptin just makes Mr. Overweight fatter. Although research shows that this approach works effectively on mice, our "leptin replacement strategy" doesn't translate to Mr. Overweight. Why not? Once again, the answer lies in biochemistry . . . in the fact that hormones can only do their work in human cells by first binding to "receptors" (think of them as cellular "docking stations") that must function normally to carry the hormone message across cell membranes.

Key point: If the patient has leptin resistance, leptin doesn't work properly to connect with its "docking station" – and the hormone never initiates all the later effects (we call them a "cascade") that result in both turning off hypothalamic hunger centers and burning fat directly in fat cells.

Surprisingly, the major breakthrough in our understanding of how leptin resistance helps to make people fat came from a study recently completed by our research group in Maryland. For several years now, our group has been investigating and publishing scientific articles on a threatening new family of chronic "biotoxin-associated" illnesses linked to recent alterations in the rapidly changing human environment.

Interestingly enough, our research group – which includes Environmental Protection Agency neurotoxicologist Ken Hudnell, Ph.D., along with Dennis House, the statistician at the Center for Research on Biotoxin-Associated Illnesses – recently discovered a key fact that affects leptin resistance. What we learned was that the immune responses to toxins released by microbial organisms such as those involved in chronic ailments like fibromyalgia, Sick Building Syndrome, and Post-Lyme Disease Syndrome *also* have a powerful negative impact on the body's leptin receptors!

As noted in Chapter 14, these biotoxin-linked diseases cause their multiple persistent symptoms (fatigue, headaches, muscle aches, blurred vision, short-term memory loss, and many more) because of the way they instantly set off alarm bells within the body's disease-fighting immune system. When the "alarm" sounds, the system quickly begins to churn out some powerhouse chemicals (known as "pro-inflammatory cytokines") designed to help neutralize and eliminate the toxins. Illness symptoms continue when genetically susceptible patients can't stop the cytokine response.

So far, so good. But even as the inappropriate release of cytokines is causing many adverse health effects (Remember your last bout with the flu? Those muscle aches, headaches, fatigue, fever and maybe some cognitive changes, too, were due to an appropriate release of cytokines in response to the virus. When the virus was

successfully repelled, the cytokine response was stopped and the symptoms cleared up.), our "biochemistry plot" suddenly takes another astonishing twist. The twist occurs when the continuous bombardment of inflammatory agents begins damaging the receptor for leptin (it is a cytokine receptor too) in the hypothalamus – thus preventing the leptin receptors there from doing their proper job of allowing the hormone to turn on the satiety center!

You can imagine the reaction among the members of our research group, when we realized that we were confronting a completely new concept in weight-loss and weight-maintenance – the notion that much of the resistance to leptin (and other hormones such as insulin) was actually due to cytokine-damage resulting from exposure to environmental toxins!

At first we were in shock. But when we stepped back and reflected on our find, we came to the startling realization that a high percentage of the patients who were overweight because of insulin/leptin resistance had actually *acquired* their resistance as a result of exposure to biotoxins from the environment. As matter of fact, there is now convincing evidence to show that about one-third of all leptin resistance is "environmentally acquired" in this fashion; the remaining two-thirds is the result of "endogenous" internal genetic factors, inherited from birth. A simple, non-invasive bedside test of visual contrast sensitivity (VCS) can separate patients with environmental sources of leptin resistance from those who were born with genes guaranteeing excessive fat storage

Exciting? You better believe it. Based on our studies of thousands of affected patients, three obesity-related discoveries were now crystal-clear.

First: Being overweight or obese is not about food or "overeating"; it's about resistance to fat-related hormones, which shuts down the effect of leptin on the brain's satiety center, among other effects, so that it fails to tell the patient: "Stop eating!" For 98 percent of weight-loss patients, this scenario is a major reason why they can't lose weight and keep it off.

Second: For about two-thirds of these resistance-linked weight-loss patients (and that's about 60 million people!) internal genetic flaws related to insulin resistance and leptin resistance account for the body's excessive fat storage and inability burn fat properly.

Third: For the remaining one-third, the resistance – and the failure to activate the satiety center – is "exogenous" . . . meaning that it's actually caused by biotoxins left behind by chronic, environmentally acquired illnesses such as Sick Building Syndrome and the Post-Lyme Syndrome.

The implications of our research seem far-reaching, to say the least. For one thing, we're now exploring an entirely new approach to the pro-inflammatory cytokine syndrome that underlies not only obesity but also diabetes . . . to say nothing of cholesterol-linked atherosclerosis caused by similar cytokine-triggered cell membrane failures. Inflammation is the new buzzword in heart disease- and those same effects are felt to be critically important in many of our "modern diseases."

For weight-loss patients, of course, these implications are far-reaching, as well. What we read about fat and weight loss in the best-selling books didn't include the causative role of inflammatory effects, controlled by genes, on fat manufacture and fat storage. No wonder the "eat less and exercise more" idea didn't work. As if willpower

had anything to do with inflammation or genetics! We are left with one crucially important fact: If we can defeat the inflammatory basis of leptin and insulin resistance and control the genetic basis of those hormone resistances, we can defeat obesity!

In order to understand exactly why, let's review a little bit more of our "Biochemistry 201" review. (Hang on; we're almost there.)

In recent chapters of this book, you've heard me talking repeatedly about the benefits of my "No-Amylose diet" for the large number of patients who are overweight primarily because of insulin resistance. But now I'm going to expand on that concept . . . by telling you how the same No-Amylose regime will benefit those heavyset patients who suffer from *leptin* resistance, as well. We are going to put the hypothalamus and inflammatory cytokines backstage for a minute.

Let's start our discussion by remembering that leptin is made from fat cells, and it is released into the bloodstream after we eat fat. Normally, the rising leptin will tell the satiety center that we have had enough to eat. In the case of the leptin resistant patient, however, the effect of fat consumption isn't to turn off hunger; in this case, the "turn-off" signal is simply ignored. But the key thing to emphasize here is that more leptin is still being made by fat cells in response to ongoing eating. All that extra leptin affects weight-gain in *two* important ways. First, the hormone works to prevent uptake (storage) of fatty acids in fat cells, keeping them suspended (free) in the blood. Second, the leptin prevents normal fat cell burning of the fatty acids it has already collected.

One incredibly important result of keeping these free fatty acids in the bloodstream is the effect on insulin. Free fatty acids in the blood dramatically worsen the problem of insulin resistance if it is pre-existing, and make the resistance appear if it isn't–by shutting down the efficiency of insulin receptors on muscle cells, thereby reducing intake of sugar (glucose) by muscle. Faced with too much glucose, the liver responds by breaking down the extra sugar, to piece together and rearrange the sugar fragments into … more fatty acids! The liver did its job to prevent diabetes in the leptin resistant patient, only to make him fatter. The extra fatty acids, meanwhile, simultaneously drive up leptin release. When that happens, an overweight patient receives additional signals that it's "time to stop eating." Unfortunately, however, the leptin resistance – now combined with functional insulin resistance – prevents the body from turning off the spigot that's causing the flood of fatty acids. The key point: Fat storage, without fat-burn, is activated both by rising blood sugar *and* by rising fatty acid levels.

Without this normal "feedback control" on appetite, our leptin resistant Mr. Overweight just keeps on eating. At the same time, the resistance fouls up the storage system for fatty acids in the bloodstream. And the result? Poor Mr. O gets hit *twice*, as a result of his leptin resistance. He eats more, and his body does a great job of storing as fat the calories he takes in. And don't forget: The fatty acids already in fat cells that normally would be used for fuel are just sitting there, not being burned to release energy as they should be when we have stopped eating. Without the energy from direct fat cell burn of fatty acids, the leptin resistant patient who ate a sandwich (amylose in the bread) or a biscuit (more amylose) for breakfast will feel sluggish and tired about two hours later, when the sugar is gone and the fatty acids aren't mobilized to keep him going. So what does Mr. O do? He eats and "Stores!" some more.

Okay: We now understand the "double whammy" faced by those who struggle with leptin resistance. And now the plot thickens even further . . . when we remember that the development of leptin resistance is essentially no different than the development of insulin resistance: Both disorders are deeply affected by both genetic inheritance *and* the cytokines that result from the body's response to environmentally acquired toxins – with both impacting the brain's satiety center and the body's physiological fat-storage mechanism.

To understand why this happens, let's move in closer. When a leptin molecule goes into position on a receptor, lots of interesting things start to occur. First of all, the receptor activates a "second messenger," which promptly sends a bulletin to certain genes: *Get busy and make some new fat-controlling molecules!* But what happens if the receptor balks, due to resistance? In that ugly situation, the second messenger is never dispatched, and the new anti-fat molecules don't get manufactured. In the end, the entire biochemical cascade of effects – the process that should limit excessive fat-manufacture for the struggling Mr. O – gets shut down, and he winds up putting on more flab.

Question: Are you beginning to see, now, why "eating fewer carbohydrates and getting more exercise" simply won't get the job done – for 98 percent of those who are significantly overweight? If you do, welcome to the brand-new Leptin Resistance Era in American dieting!

But if our poor Mr. O has no chance to control his weight-gain through sheer "will power or exercise" what hope is there for him?

Enter now the fabulous Greek god Panacea (even as we say "Bye-bye" to Hygeia!), the inventor of medicines, who's carrying a very hopeful message for all of us: the recognition that, once we properly identify the *real* culprits in obesity, hormone resistance, genetics and inflammation, we can use appropriate drugs to rapidly offset their impact and restore a healthy biochemistry.

The really good news for all of us here is that these drugs will *work* – unlike the Atkins approach, which relied on people eating fat each day to activate their leptin production and thereby turning on the satiety center. (This was the *real* reason why Atkins sold all those books, by the way; his diet kept people from feeling hungry and miserable most of the time!) But Dr. Atkins's technique failed, in the end, because it didn't factor leptin resistance or insulin resistance or inflammation into the dietary equation for fat. Nor did he properly understand the crucial role played by amylose – the key carbohydrate that triggers a rapid rise in blood sugar and thus triggers both insulin and leptin resistance. (Sure, Atkins recommended that people stop eating carbs – but he failed to see the great importance of amylose as the carbohydrate that primarily sets off insulin resistance. Dieters of the world: Avoid amylose.)

Based on the latest discoveries at the molecular level, science now understands that the truly effective way to keep weight off is to *reduce leptin and insulin resistance*. For many people – those who own genes that cause the resistance – the solution to being overweight will likely mean taking a medication that blocks the overactive leptin response *and* the overactive insulin response every day, in order to overcome their flawed internal chemistry.

For those of us whose leptin resistance is an environmentally acquired, inflammatory illness, however (an office worker who's struggling with biotoxins from

the "Sick Building" where he or she works each day, for example), the solution to the weight problem begins with removal of the offending toxins from the bloodstream.

And what about the two percent of overweight patients who *don't* have either endogenous or acquired leptin resistance? For this tiny minority, the old rules still apply; to lose weight, they will have to eat less and exercise more!

Okay, time for the next *Big Question*: Does Dr. Shoemaker really have solid, convincing research data on which to base his recent claim that about one-third of all leptin-resistance comes from the chronic biotoxin illnesses that are now spreading rapidly across America? (I thought you'd never ask.)

The answer, of course, is a resounding "yes." Quite recently, Dr. Ken Hudnell, Dennis House and I presented an academic paper on Sick Building Syndrome in which we analyzed 21 SBS patients who were working in five different buildings crawling with toxic mold. After we documented the numerous symptoms of chronic, biotoxin-associated illness (see Chapter 14, if you want a review) – including chronic fatigue, high leptin levels and deficits in the special neurotoxicology test, VCS – we prescribed a toxin-binding and toxin-eliminating medication (cholestyramine, CSM) that would help them shrug off the poisons and restore their health, while also correcting their VCS deficit.

As we expected, the patients improved dramatically within a couple of weeks – and all experienced an immediate reduction of their leptin resistance, with resultant weight loss! In other words, as our published and scientifically verified findings presented at recent meetings of both the 83rd Endocrine Society (6/01) and the American Diabetes Association (6/02) made clear, these unhappy folks were actually being made *sick and tired and fat* by their toxic environments!

In order to test our hypothesis prospectively (this part of the study provides definitive proof of causation), we stopped the medication briefly in order to observe the effect of avoidance of the implicated building. The symptoms, VCS scores and leptin levels didn't change. We then watched as the patients returned to their toxic indoor environments, without CSM to protect them. Within three days, when we looked at them again, their biotoxin-illness symptoms had returned, their VCS scores had plummeted and their leptin resistance was soaring again. We then re-treated the patients, while they were still being exposed to the now-confirmed Sick Building, and saw a return to the baseline treated state, without symptoms, VCS deficits and overproduction of leptin.

The fact that we confirmed the leptin-changes within three days didn't surprise us, since we knew that the adverse effects on leptin receptors from cytokine responses to biotoxins occurs almost instantaneously. The rapid shifts in leptin were associated with changes in weight as well. Falling leptin, meaning reduced cytokine effects on leptin receptors, gave weight loss, with no changes in diet. Rising leptin, again without dietary changes, gave weight gain. Later, when these patients left their sick buildings behind and then flushed the biotoxins out of their bodies once and for all with CSM, they all lost impressive amounts of weight, without changes in diet. If our data on several thousand patients with biotoxin illnesses seems like a small number, remember our studies are only several years old and were performed in a rural area of Maryland. How many cases of Sick Building Syndrome are there if 10% of the workplaces and 15% of the schools in America have toxin-forming fungi as NIOSH stated several years ago? How many of those patients are part of the Obesity Epidemic that is currently being blamed on

sedentary lifestyle, self-indulgent eating and dietary excess? We won't know the answer if we don't know to ask the question.

All right, then: We're almost to the finish line now, in our effort to understand how controlling the body's hormone resistance (insulin, leptin) will help us to control our weight. But one obvious question remains: What medications can help us most here, and what's the basis for their effectiveness in shutting down resistance?

Panacea, may I have the envelope, please?

And the winner is . . . the thiazolidinedione family of medications, which we can simply call "TZDs," in order to avoid the horrors of pronunciation. These medications – they're commonly used to control diabetes, by the way – consist primarily of two key substances, pioglitazone and rosiglitazone, and they work by turning on a string of valiant, fat cell-based genes (known as "PPAR gamma") that produce many powerful organic compounds. TZDs block excessive inflammatory cytokine production, lower leptin, increase fatty acid uptake into fat cells and activate direct burning of fatty acids inside fat cells (Chapter 13). What more could an insulin/leptin resistant patient want? These compounds work effectively to help offset both leptin and insulin resistance, in other ways, too, but this time I'll spare you the complex chemistry. Of great interest for weight loss is the discovery that all these wonderful benefits from use of TZDs disappear when the patient begins to add amylose into his diet. Even worse, weight gain, some due to fluid retention, also occurs when TZDs are used in conjunction with a diet that includes amylose. Remember: If you are considering TZDs, you must use the No-Amylose diet, without fail.

In an earlier chapter, you read how we can use TZDs to help lower insulin resistance, and also control diabetes. Understandably enough, the U.S. Food and Drug Administration (which regulates the use of medicines in this country) long ago designated – or "labeled" – TZDs as a diabetes medication. This means that our use of the substance for weight-loss will have to be "off-label," as the doctors say . . . but so what? In fact, physicians prescribe such off-label usage of medications day in and day out: Such usage is strictly routine, and perfectly legal and ethical – provided only that the patient is properly informed of the "off-label" status. We always monitor liver function tests in our patients who take TZDs, just like we do with the statin cholesterol-lowering drugs, but especially because an earlier TZDs, troglitazone, was blamed for causing liver disease and was pulled from the market. No one, in my opinion, should consider using TZDs for targeted gene therapy of leptin resistance, insulin resistance and weight loss, until he has been evaluated carefully by a physician, found to have obesity refractory to standard measures and been shown to be able to stay on the No-Amylose diet. Then, following informed consent, the patient can take the drug under strict medical management.

Welcome, then, to the Brave New Weight-Loss World of using TZDs to dramatically reduce leptin resistance and thus help overweight patients attack the *real* culprit behind their flabbiness. By using TZDs in combination with a No-Amylose diet, we can now achieve results that Dr. Atkins and his fellow fat-book authors only dreamed of: We can control body-weight almost at will, and without starving our patients half to death in the process!

This breaking news about the wonders of TZDs will be especially welcome among the estimated 30 million Americans whose overweight status is due to chronic, biotoxin-associated illnesses, such as Sick Building Syndrome and some cases of Chronic

Fatigue Syndrome. For these individuals, a few weeks of CSM therapy will kick off the complex process that underlies effective treatment. Once the toxins that are causing their leptin resistance are removed and the hypothalamic pathways that leptin activates are working normally again (sometimes, this is process quite complex), what we will see is a removal of the leptin resistance, which will then allow patients to shed their excess poundage quickly and painlessly**.**

The enormously hopeful news for overweight patients everywhere is that your hour of liberation is at hand. Instead of blaming yourselves (or being blamed by Dan Rather & Co. on national television) for your fat, and instead of blaming Burger Doodle for serving up too many triple-cheeseburgers, we're going to put the blame where it belongs: on human biochemistry, and on the insulin/leptin resistance which is the legacy of our biological evolution – as creatures whose forbears lived for countless millennia (as hunter-gatherers) under conditions of "feast or famine."

Make no mistake: The Obesity Epidemic isn't anyone's "fault"; it is simply a product of our history. Until the arrival of mechanized agriculture, only about a century ago, the human body had never been exposed to a continuous flood of sugars and fats – a flood that now never stops. For at least 200 centuries, and probably much longer, the human response to such sugars and fats had been: "Convert this stuff to fat, so that it will carry us through the next famine!" Remember: The famines prevented repetitive blood sugar-rises and blood fatty acid rises; during the long spells without much food, the fat storage process would slowly unwind, releasing stored energy, allowing primordial populations to survive winter and drought.

Is it any wonder, given this evolutionary reality, that many contemporary humans with hormonal resistance, both genetic and acquired, when exposed to an endless flood of excess nutrients, are turning into chunky, double-chinned folks who closely resemble our struggling Mr. O? And is it any wonder, given the explosion of buildings with indoor resident toxin-forming fungi, now bathing the HVAC with mycotoxins-of-the-day, that thousands and thousands of patients who work, live or go to school in these buildings are getting fat? Add in the many other biotoxin-forming organisms that seemingly are emerging from the mud each month, and we see the Obesity Epidemic in a whole new perspective: It isn't the calories we eat that counts, it is the calories that we store as fat. Cytokines are necessary for life; excess downstream cytokine effects cause excess weight that won't go away by using willpower and pushing away from the table.

Ladies and gentlemen, the Brave New World of Weight-Control has already begun. Armed with TZD and a new, rapidly growing understanding of molecular physiology in human beings, we're going to go far beyond the early contributions of Dr. Atkins and his fellow-authors. We're going to enter – have already *begun* to enter – a world in which losing excess weight and keeping it off will be about as difficult as having your teeth cleaned by the dental hygienist (we can't escape Hygeia altogether).

We're also about to enter a world in which fat people – folks like Mr. Overweight and the "American Waddler" – will no longer be denigrated as failures who couldn't control their own eating habits. Instead of being made cruel sport of, they'll be able to quickly and painlessly solve their weight-problems by asking a physician to measure their levels of insulin, leptin and cytokines, while also testing them with Visual Contrast Sensitivity and seeking symptoms that could be related to environmentally acquired, biotoxin-induced leptin and/or insulin resistance. (For more information about these

easily performed tests and the TZD- and cholestyramine-based therapies that will help overweight patients to lose their excess pounds rapidly and easily, visit www.chronicneurotoxins.com on the Internet.)

In summary, then: The bottom-line message of this chapter – and the message of LOSE THE WEIGHT YOU HATE – is that the Battle Against Fat has nearly been won. All that remains now is the process of educating ourselves about the actual physiology involved . . . and then taking the necessary steps to keep obesity at bay through the judicious use of effective medications such as TZD, while also remaining vigilant about over-consumption of those relatively few, amylose-based foods that also trigger hormonal resistance.

Dieters, rejoice: As this new world of molecular-based weight therapy takes off in earnest, you are going to live much better, healthier lives. You have nothing to lose but your flab!