LEPTINS

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THERE'S MORE TO THE STORY: A LEPTIN PRIMER

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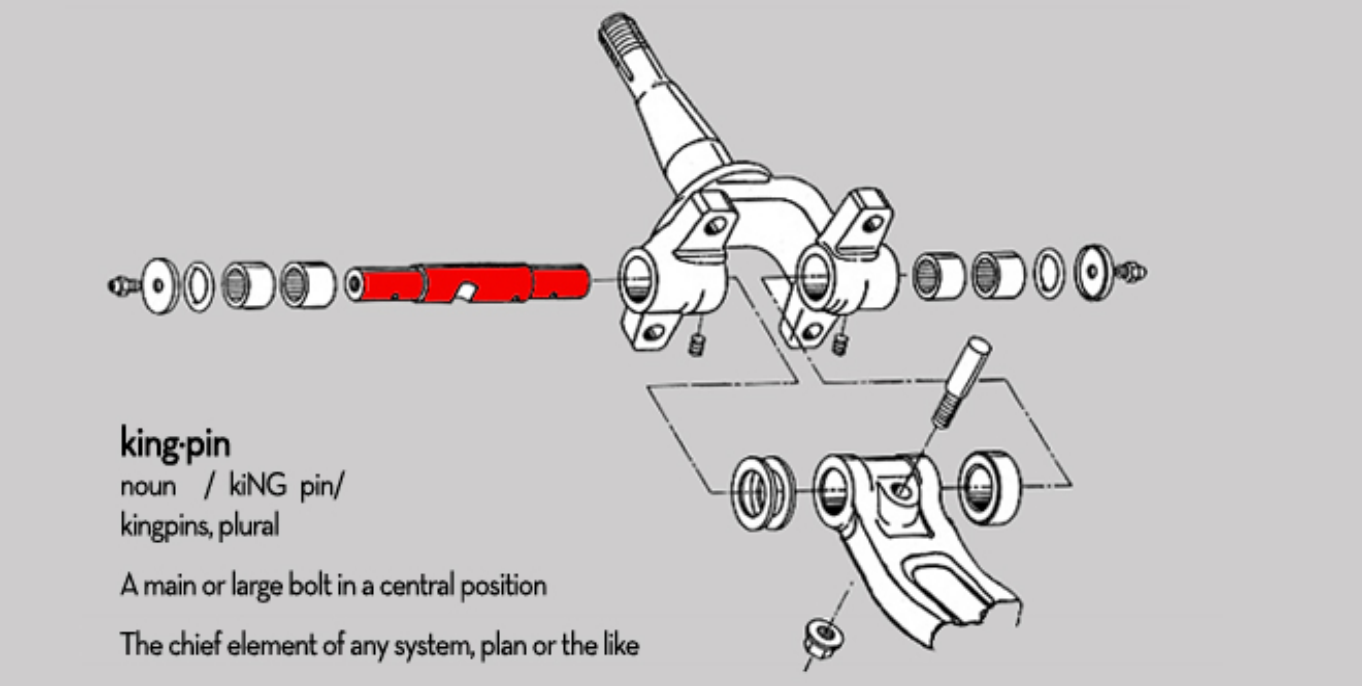

Our bodies have complex regulatory mechanisms for food intake and energy expenditure, and the complexity continues to confound scientists seeking to understand these relationships. However, a little over 15 years ago, the discovery of a hormone called leptin, and a growing appreciation for its central role in managing both how much you eat and how much you move, has somewhat clarified the very muddy waters.

Why We Get Fat

Yes, we stole that from Gary Taubes. Taubes, among scores of science writers and actual scientists, has written extensively about the central role that the hormone insulin plays in the storage of body fat. It's a well-established "fact of life" that insulin functions to let calories (i.e., energy, including carbohydrate and fat) into your cells for immediate usage, and/or storage for *future* usage. Limited amounts of carbohydrate can be stored in the liver and muscles in a form called *glycogen*, but it can be converted into an even more "compact" form for longer-term storage: fat.

See, body fat is not a bad thing. It's what allows us as a species to survive long periods of food shortage. It's what allows us to not eat for a couple days when we have the flu, and it's what allows athletes to perform such amazing feats like running from New York to Los Angeles. But our bodies are pessimists. **Our DNA always expects, despite the surplus of readily-available energy *right now*, that food will run out soon, and therefore, the only way to survive this coming famine is… store some energy as fat.** It's as natural as breathing.

But, of course, for those of us in the developed world, there *is* no famine. Ever. We've practically forgotten what it's like to even be hungry, much less to be actually (temporarily) deprived of food. It *almost* seems like we (us Westerners) believe we have an inherent *right* to not be uncomfortable, feel pain, be hungry, or otherwise experience biology's more unpleasant realities. "Rising above" the realities of nature is a dangerous – and foolhardy – trajectory. But we digress.

As fat is a storage depot for energy, it is important that your body have a way to measure how much fat you have at any given moment, and to control your behavior (primarily, eating and activity) accordingly.

Enter Leptin

Leptin is a fascinating, powerful hormone that was only discovered in 1994. As such, the research into leptin's regulatory role is in its relative infancy. However, there are a few things that we do know:

1. **A primary function of leptin is to act as a messenger from stored fat to the brain** to provide feedback about how much fat is in storage (i.e., the status of our "reservoir" of stored energy). Leptin is secreted into the bloodstream by fat cells (adipocytes) in proportion to the amount of fat mass. **More fat, more leptin secreted.**

2. **Leptin also acts as a** satiety **signal**, blocking orexigenic hormones like NPY and AgRP that typically tell us to eat more (and move less). Higher levels of leptin (after meals) register in our brains to say that we've eaten enough – for now – and it's okay to stop eating. Leptin also suppresses ghrelin, another "hunger hormone". Getting the picture?

3. **Leptin is structurally and functionally similar to a family of chemical messengers called cytokines**. These cytokines – including leptin – regulate important aspects of **immunity** and **inflammation**. Leptin can be considered one of the inflammatory (i.e. immune-stimulating) cytokines that fat cells secrete. **More fat** = **more inflammatory cytokines** secreted.

4. Leptin registers in the brain at the arcuate nucleus of the **hypothalamus**, a central controller of both **appetite** and **activity level**. **Key point: in order for leptin to deliver its message, it must *register* with the appropriate neurons in the hypothalamus. And that doesn't always happen.** [Storm clouds brewing.]

5. Leptin, like **insulin**, is secreted after we eat, and elevated insulin levels cause the secretion of **more leptin**. Remember which macronutrient tends to drive insulin levels up the most? That's correct: **carbohydrate** – particularly energy-dense, nutrient-poor carbohydrate sources like sugar, processed foods, grains and some dairy. Think a highly insulinogenic diet might contribute **chronically elevated leptin levels**? We do. Interestingly, in normal pancreatic cells, leptin tends to suppress insulin secretion. In the context of a high-carb diet, that could contribute to post-prandial (after eating) periods of prolonged elevated blood glucose. [More storm clouds.]

6. Over-consuming food (even temporarily) will create an **inflammatory state**. This inflammation increases leptin secretion, leading to elevated levels of leptin in the blood (**hyperleptinemia**). Overeating quickly makes you leptin resistant. Of course, since (over)eating acutely triggers leptin secretion, **grazing like an antelope will cause frequent rises in leptin levels. You are a not an antelope.** And "all leptin, all the time" is not a good plan.

7. **Chronically increased leptin levels cause the hypothalamus to become desensitized** to the leptin signal, creating **leptin resistance**, much like other cells can become insulin resistant in the presence of chronically high levels of insulin. **Leptin resistance means that the satiety signal is not registering at the brain, which drives ongoing overconsumption of food, and reduces the amount of activity we are inspired to undertake**. Furthermore, it turns you into a "sugar burner", making it difficulty to access body fat for fuel. It also increases the proportion of fat intake that is stored as body fat. It's like quicksand.

8. There is a **diurnal rhythm** (daily cycle) to leptin secretion, and dysregulation of this pattern can create or exacerbate leptin resistance. **(Translation: when you eat matters, too.)** For those of you familiar with cortisol's importance as a stress hormone, you might find this interesting: leptin's rhythm has pretty much the opposite pattern from normal cortisol secretion, though **leptin is tied to when you eat** and **cortisol is tied to the light/dark cycle**. So their patterns are the same, but different.

9. **Smart people like Robb Wolf have long talked about how elevated cortisol levels will make weight loss incredibly difficult, and that is unequivocably true. However, we believe that the mechanism for this phenomenon is actually via leptin dysfunction. Elevated cortisol in the blood means more leptin is secreted (i.e. hyperleptinemia). More leptin secreted, over time, leads to pancreatic beta cell leptin resistance, so leptin no longer suppresses insulin secretion, leading to blood glucose volatility and likely insulin resistance. [The rain starts.] Worse yet, your hypothalamus becomes leptin resistant, no longer accurately registers how much body fat you have, and tells you to eat all the time, especially at night (since it thinks you're not fat enough to survive). And… it doesn't register properly even when you've eaten a large meal, so you overeat then, too. [Full-on hurricane.]**

Now, this discussion has already stepped beyond what you really *need* to know about leptin, but many folks (ourselves included) really want to know the whys and hows. These points explain a few of those things – but there is so, so much more. Adiponectin, NPY, Agouti-related peptide, ghrelin, orexin, interleukin-6, TNF-α… the list is long. We've read literally hundreds of studies that have contributed to our understanding of this stuff, and will continue to learn as new research is published. We're not going to throw down a comprehensive physiology lesson here (partly because we don't know everything), but we wanted to share some of our thoughts on leptin as a kingpin of metabolic regulation.

Leptin – A Kingpin?

So, based on the thousands of leptin studies in the last decade-and-a-half, leptin seems to be a pretty central player in regulation of metabolism. (And don't think that drug companies don't want to figure out how to use leptin to treat obesity. They are scrambling to find a way. There's *big money* in people being fat – and trying to get unfat.) But all that being said, why are *we* writing about leptin?

We Think It's Important

We also think that there is no one "right" reason for why we get fat. Do highly-rewarding foods promote overconsumption? Unquestionably. Do foods that promote chronically elevated insulin levels tend to drive the deposition of body fat? Sure do. Do foods that promote increased gut permeability (and thus inflammation) play a role in leptin resistance and the pathogenesis of obesity? We think so.

But it's not just food that makes you – or keeps you – fat. Sleep plays an important role, too. **And chronic stress is a surefire way to create leptin resistance.** (Cortisol potentiates leptin secretion, for those of you who care about the how.) Creating excessive inflammation via over-exercising (or, as we prefer, under-recovering) can further disturb leptin and insulin signaling.

There Is No Easy Button

We're not the only people who view altered leptin signaling as a central problem in the pathogenesis of both obesity and other metabolic conditions, including thyroid dysfunction and some eating disorders. But as central as proper leptin function is, **it is not the cure for all your woes**. It will not be the "quick fix" to *finally* getting lean. We observe many trends in our online fitness/health community, and *lots* of people are writing about leptin these days. **But please understand that this is only *one* aspect of the underlying mechanisms that make each of us healthy… or not as healthy as we could be.** It's not that easy. Sorry. (Yes, we're #paleobuzzkills.)

In order to optimally integrate all these factors into a life that is healthier in the future than it was in the past, you have to address *all* the components. Unfortunately, simply eating a healthy Paleo-ish diet and exercising smarter-not-harder cannot undo all the damage that your old habits caused. **The route from B to A is not always the same as it was from A to B.**

INSULIN, LEPTIN, DIABETES, AND AGING: NOT SO STRANGE BEDFELLOWS

Source: Ron Rosedale, MD (January 2008)
http://www.diabeteshealth.com/read/2008/01/13/5617/insulin-leptin-diabetes-and-aging-not-so-strange-bedfellows/

Ron Rosedale, M.D., is an internationally renowned expert in nutritional and metabolic medicine and a specialist in the biology of aging. Dr. Rosedale has helped thousands suffering from so-called incurable diseases regain their health. He is the author of the recent books, The Rosedale Diet, and Insulin and its Metabolic Effects. He is currently chief medical officer at Advanced Metabolic Laboratories in collaboration with the University of Colorado and lives in Denver, CO.

To successfully treat any disease, one must know what disease to treat. Treating only a symptom of the disease will leave the underlying disease unchecked and possibly worse. For example, we evolved the "runny" nose to help us clean out upper respiratory infections. So taking a decongestant to eradicate the symptom of a "runny" nose is actually counterproductive for the underlying disease.

Symptoms are the way that evolution has taught us to deal with disease. What are normally called diseases - heart disease, diabetes, obesity, osteoporosis, autoimmune diseases, arthritis and cancer - are all chronic symptoms of aging. The biology of aging is teaching us that aging itself, though not curable, is treatable.

If you are not treating aging, you are treating a symptom, and you do not know if the treatment will be worse than the "disease" that you are trying to treat. It matters very little if 10 studies show that a drug improves risk for heart disease if it also increases risk for cancer or other diseases of aging. What you really need to know is its effect on mortality rate and, therefore, aging.

Cultivating Longevity

Much of what we know about longevity is derived from studies of humans and animals who have broken the age barrier for their species. The longest lived flies may survive only a few days, mice a couple of years, and dogs for one or two decades, depending on their size. Humans currently have the potential to live at least 120 years, but few actually do. The average life expectancy today is around 80 years, which is impressive but nowhere near our full potential.

Growing in ranks, yet still few in number, are the exceptional group of people who live to be 100 years old and more. Scattered throughout the world, these centenarians are providing scientists with a

living laboratory from which they can unravel the secrets of longevity. If we can figure out why these folks managed to live so long, we can use this information to extend the life span for everyone.

It would be easy to dismiss longevity merely as a function of luck, that is, simply a matter of winning the genetic lottery, but we know that this isn't exactly true. That's a good thing, for it means that we may be able to control our own destiny. We have been controlling the longevity destiny of laboratory animals for decades.

Laboratory animals put on calorie-restricted, nutritionally complete diets provide an equally rich source of information on longevity. Since the 1930s, dozens of species have been fed calorie-restricted diets, including microscopic tiny worms, assorted rodents, and more recently, rhesus monkeys - fellow primates that are closely related to humans. These animals virtually always live longer than normal - 30 to 300 percent. Assuming a "normal" human lifespan of 80 years, this would be the equivalent of a human living to be 104 to 240 years old.

Of Mice and Men

At first glance, human centenarians would appear to have very little in common with calorie-restricted animals. After all, humans can eat what they want when they want, and many centenarians did just that. There is no evidence that centenarians followed a particular diet or even had particularly healthy life styles. Some centenarians smoked, some did not; some exercised regularly, some did not; and some were careful eaters, and some ate whatever they felt like.

Despite the obvious differences, there are some striking similarities between caloric-restricted laboratory animals and free-living centenarians. Centenarians and calorie-restricted animals share a particular bio-metabolic profile that distinguishes them from their peers who die younger and sicker. **We now know the common denominators that are found in almost all living beings - whether they are worms, mice, monkeys or humans - that defy the odds and live beyond their expected life span. In nearly every study, the longest lived animals share the following traits:**

- **Low fasting insulin levels**
- **Reduction in fasting glucose**
- **Lower body temperature**
- **Low percentage of body (visceral) fat**
- **Reduced thyroid levels**
- **Low triglycerides**
- **Low fasting leptin levels** (Leptin is so new that it has only recently been measured in centenarians, but it has been measured in calorie-restricted animals. Since leptin correlates with and even controls these other biomarkers in humans, this is also probably true in centenarians.)

Why are these factors shared among long-lived individuals in all species? A very important finding of the various genome projects, including the human genome project, is just how similar our genes are to virtually all other animal species above bacteria. All of the important basic metabolic processes necessary for life are shared among nearly all species. That means that we have virtually the same genes as the ones that allow laboratory animals to live to twice their usual age or more.

The major differences among species, and particularly within a species, stem from which genes are allowed to be read, or "expressed," rather than from what genes are present. We have virtually all of the genes that a worm has, but we don't slither along the ground because we keep those worm genes under wraps, or "silenced." Many genes, however, can be turned on or off, and this mostly depends on their nutritional environment. Perhaps the most important of these genes regulate aging.

Virtually the same genes appear to regulate the factors that determine longevity in nearly all forms of life, including humans. Caloric-restricted animals may not have been born with the profile of longevity, but their diet enabled them to express the genes that recreate it. In other words, eating less has reprogrammed their genes to extend their lives.

You too can create a favorable genetic environment that is likely to not only extend your life, but help to keep you "disease"-free for as long as possible. You can actually make your body decades younger and turn back the clock to a time when you weren't weighed down with all that extra fat, or when you didn't have diabetes or heart disease...and you don't have to live in a cage on a caloric-restricted diet to do so.

Why We Age

Before we talk about how we age and the mechanisms that appear to control it, we should talk first about why we age. It takes energy to make babies - or in this case, new cells - lots of it. Throughout life's history, energy has been very precious and very limited. **Just as you budget your bank account, every living thing must decide how its energy currency is to be spent.**

The primary choice is between maintenance and repair, on one hand, or reproduction on the other. This is similar to the process of caring for your car. You must decide whether it is cheaper to keep repairing your car or whether it would be more economical to buy a new one. Furthermore, it makes no sense to waste energy making babies (new cells) when there's not enough energy available to be successful. You can't buy that new car if you can't pay for it.

Instead, it seems that virtually all living forms can "switch gears," actually switch genes, in times of food shortage. They can direct energy away from reproduction and toward mechanisms that will allow them to "hunker down" for the long haul and wait to reproduce at a future, more nutritionally opportune time.

In other words, nature will allow you to live longer to accomplish its primary directive of reproduction. It does this by turning on maintenance and repair genes. When you are in maintenance and repair mode, the body's "fix-it shop" is fully staffed and ready to go. Calorie-restricted animals and centenarians have measurably higher levels of key chemicals that extend life and promote repair, including antioxidants such as glutathione, catalase and SOD. These chemicals protect cells against damage inflicted by free radicals, which can accelerate aging and promote disease.

Calorie-restricted animals and centarians also have higher levels of very important proteins called heat shock proteins, which protect other vital proteins from being damaged and misshapen. Proteins communicate with other cells by "touch," much the same the way a blind person uses Braille. When a protein is misshapen, it will give bad instructions to other cells, which will interfere with the normal functioning of the body. The up-regulation of heat shock proteins is vital for a long, healthy life.

DNA repair is also bolstered. This all happens when you restrict calories in animals, and has been shown convincingly over 70 years of research to greatly extend their lifespan. Thus, there is a powerful link between energy stores, cell reproduction and longevity. One could guess that there must be signals that indicate energy stores and regulate the genetic expression of longevity genes.

One would be guessing right.

Our health and life depend on how accurately instructions are conveyed to our cells, so that they can act in harmony. It is the communication among the individual cells that determines our health and our life. The communication is carried out by hormones. Arguably therefore, the most important molecules in your body, the ones that ultimately decide your health and life, are hormones.

Many would say that genes and chromosomes are the most important molecules. Once you are born, however, your genes pretty much just sit there. Hormones tell them what to do, whether to act or not. Certainly, the most important message that our cells receive is how and what to do with energy, for metabolism and therefore life cannot take place without that. **The two most important hormones that deliver messages about energy, and therefore control metabolism and aging, are insulin and leptin.**

Two Critical Hormones

Metabolism can roughly be defined as the chemistry that turns food into life. Insulin and leptin, therefore, are critical to health and disease. Insulin and leptin work together to control the quality of metabolism (and, to a significant extent, the rate of metabolism).

Insulin works mostly at the individual cell level, telling the vast majority of cells whether to burn or store fat or sugar and whether to utilize that energy for maintenance and repair or reproduction. This is extremely important, because, at the individual cell level, turning on maintenance and repair equates to increased longevity. Turning up cellular reproduction, on the other hand, increases the risk of cancer.

Genetic studies in simple organisms have convincingly shown the link between energy stores, reproduction and aging to be at least partially mediated by insulin (which in simple organisms also functions as growth hormone) When insulin signals are kept low, indicating scarce energy availability, whether or not, in fact, energy is scarce, lifespan can be greatly extended.

Levels of insulin are largely determined by glucose (and amino acid from protein) levels. In many people with diabetes, insulin levels are also determined by how much insulin they are taking. Many have been told that what they eat does not matter as long as they take enough insulin to cover it.

This couldn't be further from the truth. Consider two people with equivalent blood sugar levels but who are taking different amounts of insulin. The person taking higher amounts of insulin will likely age faster and accumulate the "diseases" associated with aging, such as heart disease, obesity, and even diabetes itself. Yes, that person's diabetes will get worse. Why? Because most cases of type 2 diabetes are caused by overexposure to insulin.

Just as you become unable to smell the odor in a smelly room after having been there awhile, your cells become unable to "smell" the essential messages from insulin (and leptin) after they have been

exposed to high levels of these hormones. Your body responds to this inadequate signalling either by producing higher levels of insulin and leptin or by requiring more to get the message across, contributing to a vicious cycle.

In short, low insulin is very healthy and good for you as long as its message is being heard. Most treatments for type 2 insulin-resistant diabetes, however, involve drugs that raise insulin or utilize injections of insulin itself. Treatment of type I diabetes also generally requires excessive quantities of insulin.

The tragic result is that conventional medical treatment for diabetes contributes to the manifest side effects and the shortened lifespan that people with diabetes experience. The major cause of poor results from conventional diabetes treatments is not that people with diabetes are inadequate students who simply need more education. The major problem is actually what is being taught, and this needs to be changed.

If you have lost the ability to smell an odor in a room, the best way to smell it is not to make the smell stronger (analogous to taking or making more insulin). What you should do is walk out of the room to re-sensitize your nose. When you walk back in, you can smell the odor well again, even if it has been reduced.

This is how diabetes needs to be treated. We need to reduce, not increase, the levels of insulin, so that your cells can "smell" it better. You need to reduce not just your blood sugar, but also your insulin, and the only way to do that is to get "more bang out of each insulin buck" by increasing insulin sensitivity. Contrary to what you have been told, there are no insulin sensitizing drugs. Only changing what you eat (combined perhaps with supplements that augment the dietary changes) can do this. Fortunately, changing diet does this very well, well enough to reverse most cases of type 2 diabetes completely.

Combating Glycation

Remember the laboratory changes seen in caloric-restricted diets. The longest-lived animals and people share the following traits:

- **Reduction in fasting glucose**
- **Low fasting insulin levels**
- **Lower body temperature**
- **Low percentage of body (viceral) fat**
- **Reduced thyroid levels**
- **Low triglycerides**
- **Low leptin**

Let's examine this further.

Your grandmother probably told you, "Sugar is bad for you," and she was absolutely correct. Why do the longest living humans and animals have low blood sugar levels for their age? First, high blood levels of sugar from nonfiber carbohydrates and excess protein send leptin levels soaring,

causing leptin resistance and obesity. It's also well known that high glucose also raises insulin, and it's well documented in laboratory animals that high insulin accelerates aging. Glucose literally AGEs you.

In a process called **glycation**, glucose reacts with protein, resulting in sticky, sugar-damaged proteins called advanced glycated end products (AGEs). When protein is damaged, it cannot function properly or communicate properly with other cells. AGEs also promote inflammation and free radical oxidation throughout the body. AGEs cause skin to wrinkle, and wrinkling and damage to the lining of arteries contributes to plaque and heart attacks. It can promote the formation of cataracts, macular degeneration, and eventual blindness.

The glycation process has also been linked to the destruction of protein and nerve cells that can lead to Alzheimer's disease, memory loss and various neuropathies. Heating of starches (especially frying them, like french fries and chips) can produce a type of glycated protein called acrilamides, which are potent carcinogens.

Glycation, along with free radicals from oxidation, are two of the major molecular mechanisms whereby damage accrues, disease occurs and death results. A good analogy is making caramel, where you add sugar to cream - a form of glycation in which fat oxidizes and turns rancid. As we age, we "caramelize" and turn rancid. I prefer to minimize that.

High blood sugar can suppress your immune system, making you more vulnerable to infection and cancer. Glucose is very similar in molecular structure to vitamin C, confusing white blood cells and impairing their ability to gobble up invading bacteria, viruses and cancer cells. Highly aggressive cancers outpace the availability of oxygen and therefore use an anaerobic fuel - glucose. Elevating glucose just feeds this.

Insulin's Real Purpose

What about insulin? If there is a known single marker for life span, as they are finding in the centenarian and laboratory animal studies, it is low insulin levels. **What is the purpose of insulin? It is not to lower blood sugar, as is believed by the general public and the medical profession alike. That is a relatively trivial side effect, as it is also the function of other hormones such as glucagon, epinephrine, cortisol and growth hormone.**

Insulin's evolutionary purpose is to store excess energy for future times of need. It lowers blood glucose levels for the purpose of storing it away, not regulating it.

Our ancestors were forced to survive for days, weeks, or even months on little food. High glucose was not a big problem back then! Insulin helped our ancestors store away nutrients for the proverbial rainy day when they would need it.

Today, high glucose is the norm, not the exception. As a result, our insulin levels are typically much higher than they were among our ancestors. When your cells are constantly bombarded with insulin, they become insulin resistant; that is, they stop hearing insulin's important message. Moreover, excess insulin can damage your cells. In fact, insulin resistance may be a defense mechanism on the part of cells to protect against the toxic effects of excess insulin and to keep glucose, and therefore glycation,

inside cells and in check. High insulin creates a hormonal derangement that has a catastrophic effect on your metabolism.

High insulin contributes to making you fat. Why? Firstly, high insulin is telling your cells to store fat rather than burn it. More importantly, repeatedly high levels of insulin cause insulin resistance. This wouldn't be so bad if it were uniform, but the major problem, once again, is a loss in the orchestration of the signals. Not all cells become insulin-resistant at the same time.

A possible scenario follows. Liver cells may be among the first to become insulin resistant. Since one of insulin's effects is to suppress production of sugar by the liver, if the liver is no longer listening to insulin, it is going to make a lot of sugar. Eventually muscle cells will become insulin resistant too. Then they can't burn the sugar that was manufactured by the liver, so your blood sugar levels keep rising. Your fat cells are among the last to become insulin resistant, which is a real problem because insulin promotes the making and storage of fat. Thanks to insulin, all that excess sugar that hasn't been burned off is now socked away as fat!

Deranged Signaling

One could consider obesity to be the price one is paying to keep from becoming diabetic. **Unfortunately, diabetes is still being defined by blood glucose and not by the derangement in hormone signaling that it should be.** Eventually, your fat cells will become insulin resistant, and you can then stop making all that fat. But then you have no place to put the excess sugar and it starts building up in your blood, and you finally will be diagnosed with diabetes.

Incidentally, two of the most popular diabetic medications today, Actos and Avandia, wrongly claimed by their manufactures as being insulin sensitizers, actually work by multiplying fat cells, thereby creating more wastebaskets in which to store sugar as fat. They actually make you fatter and more leptin resistant, and they accelerate your rate of aging.

High insulin is a major contributor to cardiovascular disease. It results in the inability to properly store magnesium, causing blood vessels to constrict, elevated blood pressure, and coronary arterial spasm, all of which can result in a heart attack. Also, with low magnesium you can't properly metabolize important fatty acids such as EPA and DHA, which are vital to your heart and health in general.

Excess insulin causes retention of sodium, fluid retention, elevated blood pressure and congestive heart failure. Studies have shown that if you drip insulin into the artery of an animal, the artery will become blocked with plaque. Heart attacks are much more likely to happen after a high carbohydrate meal than after a high fat meal. The immediate effect of the rise in blood sugar after a high-carb meal is to raise insulin and leptin; that, in turn, triggers a "stress response" that can cause arterial spasm, constriction of the arteries, irregular heartbeat and even sudden death.

Elevated insulin plays an important role in osteoporosis. Insulin promotes the excretion of calcium in the urine. Much more importantly, if insulin is elevated and leptin resistance is telling your brain that you mustn't burn fat, then you have no choice but to burn sugar or foods that turn to sugar for fuel. Since we store very little sugar, you will crave it, and if you do not constantly eat it (such as when you are sleeping), then your body must break down lean mass, including muscle and bone, to supply its fuel needs.

This is a major source of osteoporosis and far exceeds in importance a lack of calcium in the vast majority of people. There is a high correlation between osteoporosis and calcification of arteries. In other words, most people with osteoporosis have the calcium - it's just in the wrong places. It is being given the wrong signals about where to go.

The Link to Cancer

In most species of calorie-restricted animals, life span increases primarily as a result of a reduction in cancer rates (cancer being the number-one killer in most animals). This is not surprising. Insulin is closely related to another hormone, IGF-1, or insulin-like growth factor. As its name implies, IGF's primary function is to promote growth and cellular reproduction. There is a strong link between IGF levels and cancer (which is basically excessive cellular reproduction).

Because of its molecular similarity to IGF, insulin can trigger the same genetic message, promoting cellular reproduction and cancer. IGF, derived from growth hormone, is normally low in calorie-restricted animals. Elegant studies have shown that bringing those IGF levels up to just average levels totally negates the benefits of caloric restriction on longevity.

Finally, and perhaps most significantly, the first, and perhaps the most powerful, genetic pathway that researchers (from the University of Colorado, Harvard, MIT, and the University of California) have been able to manipulate to greatly extend lifespan in many different species of laboratory animals is the insulin pathway. Genetically forcing insulin and its cousin, IGF, to remain low greatly extends lifespan.

As critical as insulin is to your health, leptin may even be more so.

New research is revealing that glucose and therefore insulin levels may be largely determined by leptin. Leptin, through the brain and hypothalamus, also controls thyroid levels and body temperature. It largely determines the accumulation of visceral fat and the ability to burn fat as indicated by triglyceride levels. It appears to control all of the other markers of longevity.

It had been previously believed that the insulin sensitivity of muscle and fat tissues were the most important factor in determining whether one would become diabetic or not. Elegant new studies are showing that the brain and liver are most important in regulating a person's blood sugar levels especially in type 2 or insulin-resistant diabetes.

It should be noted again that leptin plays a vital role in regulating the brain's hypothalamic activity which in turn regulates much of a persons "autonomic" functions; those functions that you don't necessarily think about but which determines much of your life (and health) such as body temperature, heart rate, hunger, the stress response, fat burning or storage, reproductive behavior, and newly discovered roles in bone growth and blood sugar levels. Very recent study reveals leptin's importance in directly regulating how much sugar that the liver manufactures via gluconeogenesis mostly from muscle and bone.

Many chronic diseases are now linked to excess inflammation such as heart disease and diabetes. **High leptin levels are very pro-inflammatory, and leptin also helps to mediate the manufacture of other very potent inflammatory chemicals from fat cells that also play a significant role in the progression of heart disease and diabetes.** It has long been known that obesity greatly increased

risk for many chronic diseases, including heart disease and diabetes, but no one really knew why. Leptin appears to be the missing link.

Leptin not only determines how much fat you have, but also where that fat is deposited. When you are leptin resistant, you put that fat mostly in your belly (your viscera), causing the so-called "apple shape" that is linked to disease. Some of that fat permeates the liver, impeding the liver's ability to listen to insulin and further hastening diabetes.

Leptin plays a far more important role in your health than, for instance, cholesterol, yet how many doctors measure leptin levels in their patients? How many know their own level, know that it can be easily measured, or even know what it would mean?

Leptin helps to control the brain areas that regulate thyroid levels and the sympathetic nervous system, which also has huge impacts on blood pressure, heart disease, diabetes, osteoporosis, and aging. Leptin's stimulatory effect on the sympathetic nervous system also helps determine the adrenal stress response, including cortisol levels.

The Link to Aging

As we have seen, leptin plays a significant role in obesity, heart disease, osteoporosis, autoimmune diseases, inflammatory diseases and cancer. These are the so-called "chronic diseases of aging." Could it perhaps affect the rate of aging itself? Scientists who study the biology of aging are beginning to look at that question.

Remember, there are two endeavors, two drives, that life has been programmed since its inception to perform successfully: to eat and to reproduce. If every one of our ancestors had not succeeded in eating and reproducing, we would not be here. All of your morphological characteristics, from your hair to your toenails, are designed to help you succeed at those two activities. That is what nature wants us to do.

Nature's purpose is not necessarily to have you live a long and healthy life, but to pass on the instructions, the genes, that tell how to perpetuate life. Even so-called "paleolithic" diets, though undoubtedly far better than what is generally eaten today, were designed by nature not to help us live a long and healthy life, but to maximize reproductive success. Nature does not care much about what happens to us after we have had a sufficient chance to reproduce. That is why we die. But there are clues as to how to live a long and healthy life. And that brings us once again to fat - and leptin, and how to control it.

The primary signal that indicates how much fat is stored is leptin, and it is also leptin that allows for reproduction, or not. It has long been known that women with very little body fat, such as marathon runners, stop ovulating. There is not enough leptin being produced to permit it. In fact, leptin was recently approved as therapy to allow skinny women to reproduce.

Leptin is also instrumental in regulating body temperature, partly by controlling the rate of metabolism via its regulation of the thyroid. Metabolic rate and temperature have long been connected with longevity. Almost all mechanisms that extend lifespan in many different organisms result in lower temperature. Flowers are refrigerated at the florist to extend their lifespan. Restricting calories in animals also results in lower temperature, reduced thyroid levels, and longer life. It should

be noted that reduced thyroid levels in this case are not synonymous with hypothyroidism. In the former, the body is choosing to lower thyroid hormones because it can, not because it has no choice.

Anything will dissolve faster in hot water than cold water. Extra heat dissolves, disrupts and disorganizes. It is commonly advised to "increase metabolism" and increase "thermogenesis" for health and weight loss. Yet how many of you would put a brand of gasoline in your car that was advertised to make your engine run hotter? What would that do to the life of your car? It is not an increase in metabolism that I am after; it is improved metabolic quality. That will be determined by the quality of your leptin signaling.

If it is poor, if you are insulin and leptin resistant, your metabolism is unhealthy and high in what I call "metabolic friction." If you then increase its rate, you will likely accelerate your demise. To increase the quality of your metabolism, you must be able to properly listen to insulin and especially to leptin. If your fasting blood serum level of leptin is elevated, you are likely leptin-resistant and you will not be healthy unless you correct it.

The Source of Resistance

How do people become leptin resistant? This is the subject of much research. I believe that people become leptin resistant by the same general mechanism that people become insulin resistant; by overexposure to high levels of the hormone. High blood glucose levels cause repeated surges in insulin, and this causes cells to become "insulin-resistant," which leads to further high levels of insulin and diabetes. It is much the same as being in a smelly room for a period of time. Soon, you stop being able to smell it because the signal no longer gets through.

I believe the same happens with leptin. It has been shown that as sugar gets metabolized in fat cells, fat releases surges of leptin. Those surges result in leptin-resistance, just as insulin over-exposure results in insulin-resistance. Insulin resistance leads to high glucose that then contributes to high leptin and leptin resistance, and they both conspire to make you fat and accelerate your rate of aging.

Normally leptin's function is to reduce appetite and induce fat burning (among many other functions). That is what high leptin signaling in a brain does. Low leptin in the brain is an indication to eat more and store more fat (that is, to successfully reproduce, and to live long enough to do so). **However, elevated leptin in a fasting blood sample indicates leptin resistance** and, probably, low leptin signaling to some parts of the brain while other parts of the brain get the full high signal. In other words, some of the brain hears only a whisper, while other parts (of the brain and periphery) get screamed at. Neither is good communication.

Low-leptin signaling to the appetite center of the brain induces the brain to want to make the body hungry, and it alters physiologic functions so as to store more fat. Ultimately, increasing fat stores

should manufacture more leptin to overcome the resistance. In the meantime, however, one continues to get fat and often obese. This is similar to insulin resistance: High fasting insulin indicates low activity in some parts of the body and a disruption in insulin signaling that is being compensated for by the pancreas, which makes more insulin. What is lost, however, is the orchestration of insulin levels among various tissues. If your liver is insulin-resistant, it continues to make sugar out of protein, and if your muscles are insulin-resistant, they cannot burn that sugar.

Until your fat tissue becomes insulin-resistant, however, it continues to "hear" the high levels of insulin that are caused by the elevated sugar. Insulin's signal to fat tissue is to take that sugar, make fat out of it, and then store it. You continue to gain weight until the adipose tissue ultimately becomes resistant.

Likewise, **when you become leptin-resistant as indicated by high fasting leptin, you lose the fine orchestration of hormone levels. As the appetite control center in the hypothalamus becomes leptin resistant, it cannot hear the message from leptin to curb hunger and stop storing fat.** It believes, therefore, that you do not have enough fat stores and must eat more and make more fat. Also lost is the knowledge of where to put that fat, so a preponderance of it is stored in the viscera. The communication regarding where to put calcium is also disrupted, and calcium is deposited in blood vessels instead of bone.

An Orchestral Breakdown

However, it appears that the master control center of the sympathetic nervous system in the brain does not become resistant, and it continues to hear the loud messages of elevated leptin, causing overstimulation of the sympathetic nervous system. This can cause diabetes, elevated blood pressure, increases in blood coagulation and inflammation, elevated T-3 and temperature, and heart disease. Hormonal resistance is bad mainly because of the loss of the intricate orchestration of those signals, and less so because of diminished signals that can be compensated for just by "yelling louder."

Leptin resistance plays an important role in osteoporosis. If leptin is telling your brain that you mustn't burn fat, you will have no choice but to burn sugar or foods that turn to sugar for fuel. Since we store very little sugar, you will crave it, and if you do not constantly eat it (such as when you are sleeping) then your body must break down muscle and bone matrix to supply its fuel needs. This is a major source of osteoporosis and far exceeds in importance a lack of calcium in most people. There is a high correlation between osteoporosis and calcification of arteries. In other words, most people with osteoporosis have the calcium - it's just in the wrong places. It's being given the wrong signals about where to go. Taking more calcium may then not be wise.

To summarize: normally leptin is secreted acutely in response to a meal or chronically in response to increasing fat stores. In a leptin-sensitive individual, leptin will reduce hunger, increase fat burning, and reduce fat storage. However, when one is leptin-resistant, as indicated by an elevation in fasting serum leptin, the part of leptin's message that would normally reduce hunger and fat stores, and increase fat burning does not get through to the brain (mimicking low leptin), so one stays hungry and stores more fat rather than burning it. However the message to increase sympathetic nervous system activity gets through all too loudly and clearly, so one stays hungry, continues to get fat, and gets elevated sugar, insulin resistance, high blood pressure, heart disease, and accelerated aging.

How to Restore Order

When one becomes more leptin sensitive after following my diet program, as indicated by a lower fasting leptin, suddenly the brain is able to hear leptin's messages much more clearly. The now louder and more accurate message to the appetite control center and other parts of the hypothalamus is to reduce hunger and get rid of stored fat, because now the brain realizes that you have stored far too much. The lower leptin reduces the volume that the sympathetic nervous system hears. The hormone is making less "noise," but instead is allowing the orchestra to play fine music.

The only known way to re-establish proper leptin (and insulin) signaling is to prevent those surges, and the only known way to do that is via diet and supplements. As such, these can have a more profound effect on your health than any other known modality of medical treatment. **When leptin signaling is restored, your brain can finally hear the message that perhaps should have been delivered decades ago.** High leptin levels can now scream to and be heard by your brain that you have too much fat and that you better start burning some off, for your life is in danger.

Your brain will finally allow you into the pantry where you have been storing your fat. Your cells will be fed the food from that fat and they will be satisfied. They will not know whether that food came from your belly fat or from your mouth, nor will they care. They will be receiving energy that they need and will not have to ask for more. **You will not be hungry. This also makes counting calories irrelevant, for the calories that you put into your mouth today are not necessarily what your cells will be eating: That will be determined primarily by leptin.**

Whether or not you put food into your mouth, your cells will be eating. If they cannot eat fat, they must eat sugar. Since little sugar is stored, that sugar will be obtained by making you crave it or by turning the protein in your muscle and bone into sugar. This contributes in a major way to weakness and osteoporosis. **Whether or not this lean tissue wasting happens is determined by your capacity, or incapacity, to burn fat. And that is determined by your ability to listen to leptin.**

A strategic diet that emphasizes good fats and avoids blood sugar spikes coupled with targeted supplements (as recommended in my Rosedale Diet), will enhance insulin and leptin sensitivity so that you can once again hear their music, allowing your life to be the symphony it was meant to be.

THIS HORMONE MAKES COUNTING CALORIES IRRELEVANT

Source: Ron Rosedale, M.D. (June, 2009)
http://articles.mercola.com/sites/articles/archive/2009/06/20/this-hormone-makes-counting-calories-irrelevant.aspx

It is amazing how the little twists and turns of researchers can have such a profound impact on what we generally come to realize as “scientific truth.” Let me share a recent fascinating example of how this impacted one of the most powerful hormones in your body.

The Ob mouse is a strain of mouse that has a genetic mutation that makes it obese and unhealthy. It has been used for many years as a model of obesity to do research on, though the reason that it was obese had eluded scientists.

This changed when, in 1994, Jeffrey Friedman discovered that this mouse lacked a previously unknown hormone called leptin, and when it was injected with leptin it became thin, vibrant, and very healthy within weeks. This made headlines around the world, "the cure for obesity found" and pharmaceutical companies started tripping over themselves with trillion dollar signs in their eyes to be the first to genetically manufacture leptin on a large-scale.

This did not last long. When people were tested for leptin, it was found that, unlike the Ob mouse, they did not lack leptin; on the contrary almost all overweight and obese people have excess leptin.
These people were "leptin resistant" and giving extra leptin did little good.

The financial disappointment was extreme and scientists working for pharmaceutical companies said that leptin wasn't important anymore since they could not find a drug to control it, and therefore the industry couldn't make money on it. To make big money in medicine one needs a patent and this generally means remedies which are not commonly or easily available -- that are not natural.
This illustrates two extremely unfortunate principles in modern medicine; only those therapies that will make lots of money (generally for the pharmaceutical industry or hospitals), ever get pursued and then taught to physicians (since most of medical education after medical school takes place by drug reps), and these therapies, almost by definition, will be unnatural.

This inhibition of extremely important knowledge is not only unfortunate, it is deadly, and is exemplified by how few people, including doctors, know anything about leptin, though I would consider it to be the most important chemical in your body that will determine your health and lifespan.

Two Hormones that are Vital for Optimal Health

Each and every one of us is a combination of lives within lives. We are made up of trillions of individual living cells that each must maintain itself. Even more significantly, the cells must communicate and interact with each other to form a republic of cells that we call our individual self.

Our health and life depends on how accurately instructions are conveyed to our cells so that they can act in harmony. It is the communication among the individual cells that will determine our health and our life.

The communication takes place by hormones. Arguably therefore, the most important molecules in your body that ultimately will decide your health and life are hormones.

Many would say that genes and chromosomes are the most important molecules, however once born your genes pretty much just sit there; hormones tell them what to do. Certainly, the most important message that our cells receive is how and what to do with energy, and therefore life cannot take place without that.

The two most important hormones that deliver messages about energy and metabolism are insulin and leptin.

Metabolism can roughly be defined as the chemistry that turns food into life, and therefore insulin and leptin are critical to health and disease. Both insulin and leptin work together to control the quality of your metabolism (and, to a significant extent, the rate of metabolism).

Insulin works mostly at the individual cell level, telling the vast majority of cells whether to burn or store fat or sugar and whether to utilize that energy for maintenance and repair or reproduction. This is extremely important as we shall see, for on an individual cell level turning on maintenance and repair equates to increased longevity, and turning up cellular reproduction can increase your risk of cancer.

Leptin, on the other hand, controls the energy storage and utilization of the entire republic of cells allowing the body to communicate with the brain about how much energy (fat) the republic has stored, and whether it needs more, or should burn some off, and whether it is an advantageous time nutritionally-speaking for the republic --you-- to reproduce or not.

What Exactly is Leptin?

Leptin is a very powerful and influential hormone produced by fat cells that has totally changed the way that science (real science, outside of medicine) looks at fat, nutrition, and metabolism in general. Prior to leptin's discovery, fat was viewed as strictly an ugly energy storage depot that most everyone was trying to get rid of. After it was discovered that fat produced the hormone leptin (and subsequently it was discovered that fat produced other very significant hormones), fat became an endocrine organ like the ovaries, pancreas and pituitary, influencing the rest of the body and, in particular, the brain.

Leptin, as far as science currently knows, is the most powerful regulator that tells your brain what to do about life's two main biological goals: eating and reproduction. Your fat, by way of leptin, tells your brain whether you should be hungry, eat and make more fat, whether you should reproduce and make babies, or (partly by controlling insulin) whether to "hunker down" and work overtime to maintain and repair yourself.

I believe I could now make a very convincing and scientifically accurate statement that that rather than your brain being in control of the rest of your body, your brain is, in fact, subservient to your fat -- and leptin.

In short, leptin is the way that your fat stores speak to your brain to let your brain know how much energy is available and, very importantly, what to do with it. Therefore, leptin may be "on top of the food chain" in metabolic importance and relevance to disease.

How Leptin Regulates Your Weight

It has been known for many years that fat stores are highly regulated. It appeared that when one tried to lose weight the body would try to gain it back. This commonly results in "yo-yo" dieting and in scientific circles one talks about the "set point" of weight. It has long been theorized that there must be a hormone that determines this.

Science points now to leptin as being that hormone.

In our ancestral history, it was advantageous to store some fat to call upon during times of famine. However, it was equally disadvantageous to be too fat. For most of our evolutionary history, it was necessary to run, to obtain prey and perhaps most importantly, to avoid being prey. If a lion was chasing a group of people it would most likely catch and eliminate from the gene pool the slowest runner and the one who could not make it up the tree -- the fattest one.

Thus, fat storage had to be highly regulated and this is done, as is any regulation, through hormones, the most significant being leptin.

If a person is getting too fat, the extra fat produces more leptin which is supposed to tell the brain that there is too much fat stored, more should not be stored, and the excess should be burned.

Signals are therefore sent to an area of the brain in the hypothalamus (the arcuate nucleus) to stop being hungry, to stop eating, to stop storing fat and to start burning some extra fat off.

Controlling hunger is a major (though not the only) way that leptin controls energy storage. Hunger is a very powerful, ancient, and deep-seated drive that, if stimulated long enough, will make you eat and store more energy. Asking somebody to not eat, to voluntarily restrict calories even though they are hungry, is asking the near impossible. The only way to eat less in the long-term is to not be hungry, and the only way to do this is to control the hormones that regulate hunger, the primary one being leptin.

How Leptin Resistance Leads to Disease

More recently, it has been found that leptin not only changes brain chemistry, but can also "rewire" the very important areas of the brain that control hunger and metabolism. I'm not aware of any other chemical in the body that has been shown to accomplish this "mind bending" event.

This has really caught the attention of the scientific community. Further studies have now shown that leptin, or more correctly the inability of the body to properly hear leptin's signals, in other words leptin resistance, plays significant if not primary roles in heart disease, obesity, diabetes, osteoporosis, autoimmune diseases, reproductive disorders, and perhaps the rate of aging itself.

It helps to control the brain areas that regulate thyroid levels and the sympathetic nervous system which also has huge impacts on blood pressure, heart disease, diabetes, osteoporosis and aging.

Leptin's stimulatory effect on the sympathetic nervous system also helps determine the adrenal stress response including cortisol levels.

Leptin May Be Even More Critical Than Insulin

The importance of insulin in health and disease is becoming well-known. Aside from its obvious role in diabetes, it plays a very significant role in hypertension, cardiovascular disease, and cancer.

I was one of the first to speak publicly to doctors about insulin's critical role in health well over a decade ago (see the transcribed talk Insulin and its Metabolic Effects) and I am even more convinced now.

However leptin may even supersede insulin in importance, for new research is revealing that in the long run glucose and therefore insulin levels may be largely determined by leptin.

It had been previously believed that the insulin sensitivity of muscle and fat tissues were the most important factor in determining whether one would become diabetic or not. Elegant new studies are showing that the brain and liver are most important in regulating a person's blood sugar levels especially in type 2 or insulin resistant diabetes.

It should be noted again that leptin plays a vital role in regulating your brain's hypothalamic activity which in turn regulates much of a person's "autonomic" functions; those functions that you don't necessarily think about but which determines much of your life (and health) such as body temperature, heart rate, hunger, the stress response, fat burning or storage, reproductive behavior, and newly discovered roles in bone growth and blood sugar levels.

Another very recent study reveals leptin's importance in directly regulating how much sugar that the liver manufactures via gluconeogenesis.

Many chronic diseases are now linked to excess inflammation such as heart disease and diabetes. High leptin levels are very pro-inflammatory, and leptin also helps to mediate the manufacture of other very potent inflammatory chemicals from fat cells that also play a significant role in the progression of heart disease and diabetes. It has long been known that obesity greatly increased risk for many chronic diseases including heart disease and diabetes, but no one really knew why.

Leptin appears to be the missing link.

Could Leptin Also Affect How Fast You Age?

Leptin will not only determine how much fat you have, but also where that fat is put. When you are leptin resistant you put that fat mostly in your belly, your viscera, causing the so-called "apple shape" that is linked to much disease. Some of that fat permeates the liver, impeding the liver's ability to listen to insulin, and further hastening diabetes.

Leptin plays a far more important role in your health than, for instance, cholesterol, yet how many doctors measure leptin levels in their patients, know their own level, even know that it can be easily measured, or even what it would mean?

Leptin appears to play a significant role in obesity, heart disease, osteoporosis, autoimmune diseases, inflammatory diseases and cancer. These are the so-called "chronic diseases of aging".
Could it perhaps affect the rate of aging itself?

The Biology of Aging

Scientists who study the biology of aging are beginning to look at that question. There are two endeavors, two drives that life has been programmed, since its inception, to succeed at and to succumb to. These are to eat and to reproduce.

If every one of our ancestors had not succeeded in eating and reproducing we would not be here, and this paper would be moot. All of your morphological characteristics from your hair to your toenails are designed to help you succeed at those two activities. That is what nature wants us to do. Nature's purpose is not necessarily to have you live a long and healthy life, but to perpetuate the instructions, the genes that tell how to perpetuate life.

Even so-called "paleolithic" diets, though undoubtedly far better than what is generally eaten today, were not necessarily designed by nature to help us live a long and healthy life but, at best, to maximize reproduction. Nature appears to not care much about what happens to us after we have had a sufficient chance to reproduce. That is why we die.

But there are clues as to how to live a long and healthy life. And that brings us once again to fat--and leptin.

It takes energy to make babies; lots of it. Energy was and always will be a coveted commodity. Nature, and evolution, hates wasting it. It makes no sense to try and make babies when it appears that there's not enough energy available to successfully accomplish that goal.

Instead, it seems that virtually all living forms can "switch gears" and direct energy away from reproduction and towards mechanism that will allow it to "hunker down" for the long haul and thus be able to reproduce at a future more nutritionally opportune time. In other words nature will then let you live longer to accomplish its primary directive of reproduction.

It does this by up regulating maintenance and repair genes that increase production of intracellular antioxidant systems, heat shock proteins (that help maintain protein shape), and DNA repair enzymes. This is what happens when you restrict calories (without starvation) in animals, and that has been shown convincingly for 70 years to greatly extend the life span of many dozens of species. Thus, there is a powerful link between reproduction, energy stores, and longevity.

Genetic studies in simple organisms have shown that that link is at least partially mediated by insulin (which in simple organisms also functions as a growth hormone), and that when insulin signals are kept low, indicating scarce energy availability, maximal lifespan can be extended--- a lot; several hundred percent in worms and flies.

Glucose is an ancient fuel used even before there was oxygen in the atmosphere, for life can burn glucose without oxygen; it is an anaerobic fuel. The use of fat as fuel came later, after life in the form of plants soaked the earth in oxygen, for you cannot burn fat without oxygen.

The primary source of energy stores in people by far is fat, as many unfortunately are all too aware of. The primary signal that indicates how much fat is stored is leptin, and it is also leptin that allows for reproduction, or not.

It has long been known that women with very little body fat, such as marathon runners, stop ovulating. There is not enough leptin being produced to permit it. Paradoxically, the first pharmaceutical use of leptin was recently approved to give to skinny women to allow them to reproduce.

Leptin's Role in Improving Your Metabolism

Leptin also is instrumental in regulating body temperature, partly by controlling the rate of metabolism via its regulation of the thyroid.

Metabolic rate and temperature has long been connected with longevity. Almost all mechanisms that extend lifespan in many different organisms result in lower temperature. Flowers are refrigerated at the florist to extend their lifespan. Restricting calories in animals also results in lower temperature, reduced thyroid levels, and longer life.

It should be noted that reduced thyroid levels in this case are not synonymous with hypothyroidism. Here, the body is choosing to lower thyroid hormones because the increased efficiency of energy use and hormonal signaling (including perhaps thyroid) is allowing this to happen.

Anything will dissolve faster in hot water than cold water. Extra heat will dissolve, disrupt and disorganize. This is not what I try to do to make someone healthy. It is commonly advised to "increase metabolism" and increase "thermogenesis" for health and weight loss.

Yet how many of you would put a brand of gasoline in your car that advertised that it would make your engine run hotter? What would that do to the life of your car? It is not an increase in metabolism that I am after; it is improved metabolic quality.

That will be determined at the quality of your leptin signaling.

If it is poor, if you are insulin and leptin resistant, your metabolism is unhealthy and high in what I call "metabolic friction". If you then increase its rate you will likely accelerate your demise. To increase the quality of your metabolism you must be able to properly listen to insulin and especially to leptin.

If your fasting blood serum level of leptin is elevated you are likely leptin resistant and you will not be healthy unless you correct it.

How Do You Become Leptin Resistant?

This is the subject of much research. I believe people become leptin-resistant by the same general mechanism that people become insulin-resistant; by overexposure to high levels of the hormone.

High blood glucose levels cause repeated surges in insulin, and this causes one's cells to become "insulin-resistant" which leads to further high levels of insulin and diabetes. It is much the same as

being in a smelly room for a period of time. Soon, you stop being able to smell it, because the signal no longer gets through.

I believe the same happens with leptin. It has been shown that as sugar gets metabolized in fat cells, fat releases surges in leptin, and I believe that those surges result in leptin-resistance just as it results in insulin-resistance.

The only known way to reestablish proper leptin (and insulin) signaling is to prevent those surges, and the only known way to do that is via diet and supplements.

As such, these can have a more profound effect on your health than any other known modality of medical treatment.

When leptin signaling is restored, your brain can finally hear the message that perhaps should have been delivered decades ago; high leptin levels can now scream to your brain that you have too much fat and that you better start burning some off for your life is in danger.

Your brain will finally allow you access into your pantry that you have been storing your fat in. Your cells will be fed the food from that fat and they will be satisfied. They will not know whether that food came from your belly fat or from your mouth; nor will they care. They will be receiving energy that they need and will not have to ask for more. You will not be hungry.

This also makes counting calories irrelevant, for the calories that you put into your mouth today are not necessarily what your cells will be eating; that will be determined primarily by leptin. Whether or not you put food into your mouth, your cells will be eating, and if they cannot eat fat they must eat sugar.

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A strategic diet that emphasizes good fats and avoids blood sugar spikes coupled with targeted supplements (as recommended in my Rosedale Diet and Dr. Mercola's Take Control of Your Health), will enhance insulin and leptin sensitivity so that you can once again hear their music, allowing your life to be the symphony it was meant to be.

LEPTIN: A PIECE OF THE OBESITY PIE

Source: Minn Liu (August 2004) http://www.scq.ubc.ca/leptin-a-piece-of-the-obesity-pie/

Approximately 23% of Canadians [1] and 200 million [2] people worldwide are considered obese, an increase from 10 years ago. Obesity is usually associated with but not limited to developed nations. In addition to social stigmas, there are significant health risks that come with being overweight. Studies

have shown that having excess weight increases susceptibility to diabetes, cardiovascular disease, high blood pressure and stroke, as well as certain forms of cancer. What causes obesity? The traditional view is that overeating and lack of exercise are responsible for weight gain. Thus, a greater input than output of energy will result in increased fat storage. This explanation is true but incomplete. It is generally thought that only a person's degree of willpower and environment dictate how much one eats and exercises. Recently, however, researchers have found a biological factor which plays a role in weight regulation.

Early Studies

The concept of a biological factor in weight regulation is not new. The hypothalamus is a gland that regulates eating patterns, body temperature, and metabolism. Scientists understood this but were not sure how the hypothalamus received information as to the amount of fat that a person had in store. The lipostatic theory proposed that there was product of fat metabolism that circulated in the blood and acted as a signal to the hypothalamus. The lipostatic theory was supported by an experiment carried out by Hervey in 1959 [3]. In this experiment, the circulatory system of a rat with a lesion in the hypothalamus was surgically joined with the circulatory system of a normal rat. The rat with a damaged hypothalamus overate and grew obese, whereas the normal rat, once it was "hooked up" to the other rat, grew thin. An explanation for this result was that the obese rat was producing some of "satiety factor", which it couldn't respond to but the normal rat could.

What is Leptin?

Leptin is a hormone that is involved in the long term regulation of body weight. The word comes from the Greek word "leptos", meaning thin. It is produced primarily by fat cells, but cells in the gut and placenta also make leptin. It circulates in the blood and acts on different tissue including the hypothalamus, skeletal muscle, and liver. Leptin is a protein that consists of 167 amino acids and has a molecular weight of about 16 kD or 16,000 g/mol. The DNA sequence for the protein was determined by Friedman in 1994 and was found on the obese (ob) gene [4]. The leptin receptor, the molecular structure on the cell surface that binds with leptin, is encoded by the diabetes (db) gene.

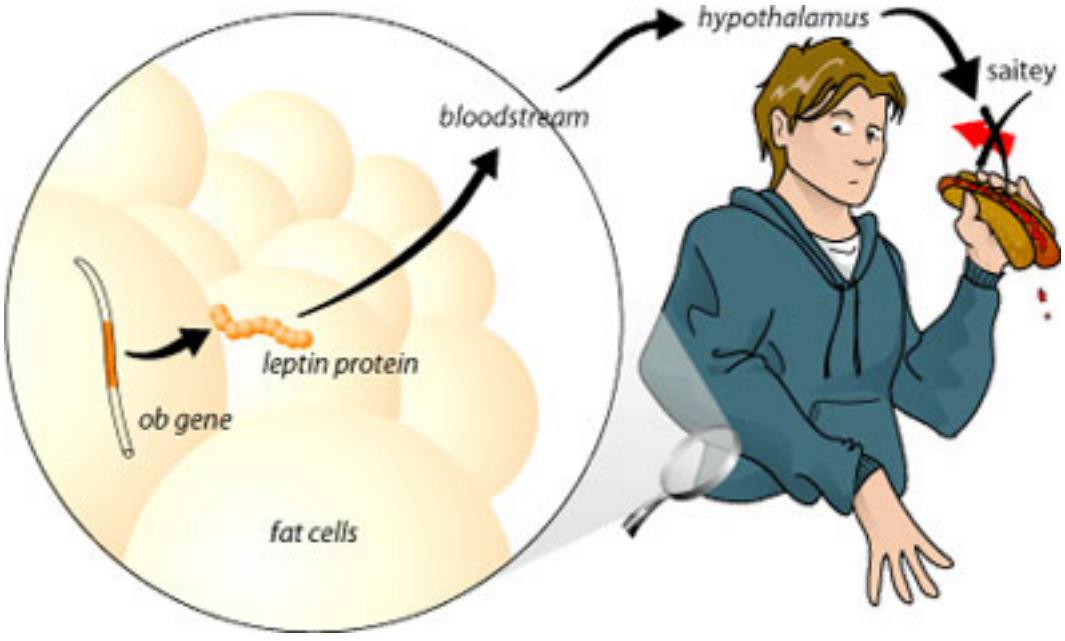

Figure 1: The Leptin feedback loop. the ob gene in fat cells encodes the leptin protein, which triggers the hypothalmus to suppress appetite.

Weight Loss in Mice With Mutations in the Leptin Genes

Mice with mutations on both ob genes (ob/ob mice) cannot produce leptin so they are unaware of when they have sufficient amounts of fat stored. As a result, these mice overeat and become obese. In an experiment it was shown that injection of recombinant leptin into these mutants resulted in reduced appetite and weight loss [4]. Since this discovery, researchers have been trying to understand how leptin works and whether or not it can be used as a treatment for obesity.

It is also possible to have a mutation in the leptin receptor DNA sequence, which is found in the diabetes (db) gene. Conversely, mice with defects in their leptin receptor genes have high (10 times) levels of leptin in their blood. It is believed that this is some type of compensation [5].

A double mutation for the leptin or leptin receptor genes in humans is rare; however, these individuals, like the ob/ob and db/db mice, are obese. Heterozygous mutations result in moderate obesity.

Correlation of Leptin Levels to Weight

The level of circulating leptin in the body is positively correlated with the amount of fat in individuals without any mutations in their ob or db genes (see Figure 2). This means that obese individuals have a higher amount of leptin in their body and that they might have some sort of resistance to leptin. Dieters tend to have low levels of leptin. This indicates that obese individuals may have some sort of resistance to leptin [6]. But it is not clear whether or not obesity causes a resistance to leptin or vice versa.

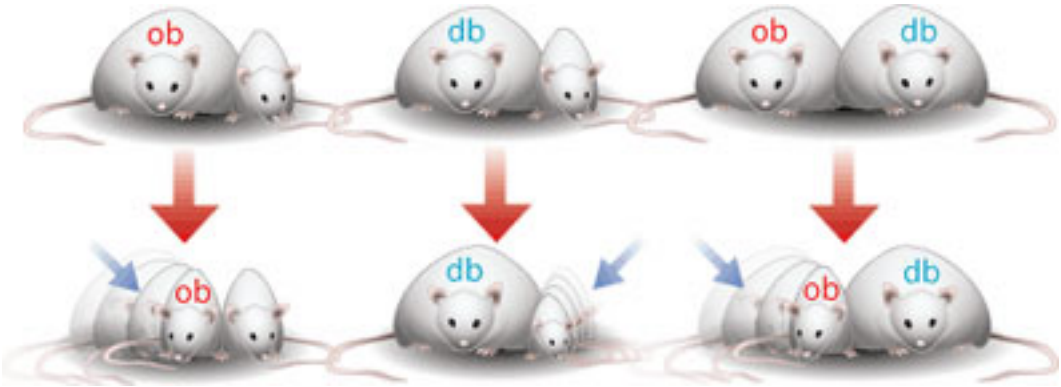

Figure 2: Parabiotic mice. *In this experiment, two mice were sutured together to form a shared circulatory system in the following combinations: a)ob/ob;normal, b)db/db;normal, c)ob/ob;db/db. In a) the obese mouse lost weight (suggesting a circulating ob hormone), in b) the normal mouse lost weight (suggesting that the db component does not circulate, and the ob factor is overexpressed by the db mouse), and in c) the ob mouse lost weight (suggesting that the ob factor was produced by the db mouse and circulates).*

Leptin and the Feedback Loop

Leptin acts within a feedback loop to regulate body weight. In normal metabolism, high leptin levels indicate sufficient energy stores and low levels indicate a starvation mode. Leptin is involved in long-term regulation of weight because levels don't increase immediately after a meal. As previously mentioned, the leptin receptor is expressed in various tissue such as the muscles and the gut, but it is especially expressed in the ventromedial hypothalamus (VHM). In response to leptin level, the VHM will produce varying levels of neurotransmitters and neuropeptides that regulate food intake and body weight. It reduces the effects of neuropeptide Y (NPY), which is a feeding stimulant. It promotes a-melanocyte-stimulating hormone (a-MSH), which acts as an appetite suppressant. Leptin may also suppress other feed stimulating hormones including melanin-concentrating hormone (MCH) and endocannaboids and increase the effects of appetite suppressants like cocaine-amphetamine-regulated transcript (CART), bombesin, and corticotropin-releasing factor (CRF) [6]. In addition to food intake, leptin also moderates the burning of fatty acids in skeletal muscle, i.e. high levels stimulate the metabolism. Depending on food intake and energy expenditure, the size of fat cells will vary. It has been shown that the rate of production of leptin in fat cells depends on cell size [6]. Leptin receptors have also been found on pancreatic b-cells, which produce insulin. It has been shown that leptin enhances the effects of insulin [6] and it is possible that insulin may stimulate the release of leptin in return [3].

Other Roles of Leptin

Leptin also plays a role in reproductive function. It regulates the onset of puberty in women. Individuals deficient in leptin tend to mature sexually at a later stage. This could be related to amount of fat that is stored. For example, many athletes (people with a low percentage of body fat), do not have their periods.

Leptin has also been implicated in immune system functioning and the development of bones.

Leptin as a Treatment of Obesity

The administration of leptin acts differently from food restriction and exercise. Diet and exercise can result in a loss of both fat and muscle, whereas taking leptin results in fat loss. Good news right? Well not exactly: Leptin has been shown to have therapeutic effect in patients with defects in their ob genes. In 1999, an experiment was carried out to determine whether recombinant leptin could be used to treat obesity in a girl who was homozygous for the ob mutation. After receiving daily injections for one year, the girl's appetite and food intake decreased and she lost 36 pounds of which most was fat [7,8]. However, it is uncertain how therapeutic leptin will be in individuals without genetic defects. So far, no definitive studies have shown that leptin will cause weight loss in all individuals [8] indicating that obesity is likely to not only be caused by biological factors. In studies with mice, it was found that some strains became obese after being fed a high-fat diet (diet-induced obese mice or DIO mice), whereas some mice did not. These DIO mice exhibited a partial response to leptin therapy [6]. This suggests that a subset of the population may be predisposed to obesity and environmental factors may alter leptin sensitivity. It is for these individuals that leptin may be beneficial [6].

References

1. Health Canada

2. World Health Organization

3. R and D Systems

4. Halaas JL, Gajiwala KS, Maffei M, et al. Weight reducing effects of the plasma protein encoded by the obese gene. Science (1995) 269:543-546.

5. Rockefeller Institute

6. Freidman, JM. The function of leptin in nutrition, weight and physiology. Nutrition Reviews (2002) 11(Supplement):1-14.

7. Farooqi IS, Jebb SA, Langmack J, et al. Effects of Recombinant Leptin Therapy in a Child with Congenital Leptin Deficiency. New England Journal of Medicine (1999) 341:879-884.

8. Kimball's Biology Pages

(Art by Jen Philpot)

FAT METABOLISM AND LEPTINS

Source: Minn Liu (August 2004) http://www.scq.ubc.ca/leptin-a-piece-of-the-obesity-pie/

Fat metabolism is related to both arteriosclerosis and bone metabolism. Obese patients have higher risk of coronary artery disease and lower risk of osteoporosis. Recent studies by Ricci show that even moderate weight loss due to dieting in obese women leads to bone loss. A study from Denmark by Jensen found a 4.2% decrease in whole body bone mineral and 4.0% decrease in the hip in women after 6 months of a diet which resulted in 5.5% weight loss (average 94 to 89 kg, or 207 to 196 lbs). The loss in bone density was attenuated by calcium supplementation. On the other hand, a study of 130 young women with anorexia showed a high prevalence of fractures and of low bone density. The bone density was related to weight at all skeletal sites. Bone density did not differ by use of estrogen (Grinspoon).

Leptin is a hormone made by adipocytes which acts centrally to control body weight. Leptin appears to interact with CNS factors. Leptin inhibits NPY and AGRP and stimulates proopiomelanocortin (POMC) (Wardlaw, JCEM 01) which then inhibit eating behavior and modify energy utilization. Studies of leptin and its role in the skeletal system are conflicting. Mundy proposed that leptin regulation was responsible for increased body weight as well as increased bone density. Mice who have congenital absence of leptin (ob/ob) are obese and have very high bone density. Leptin makes them lose both fat and bone. Leptin injected into the brain of animals will inhibit bone formation at doses lower than those that cause loss of body weight (see below).

Serum leptin correlations with bone density: Yamauchi reported that plasma leptin levels were positively correlated with BMD values, and multiple regression analysis revealed that this positive relationship was still observed with BMD values of the femoral neck and of the whole body, even after

%fat and age were taken into account. Moreover, plasma leptin levels but not %fat were significantly lower in women with vertebral fractures than in those without fractures. Thomas found that serum leptin correlated with BMD in women but not in men. Sato found a positive correlation between serum leptina dn calcaneal BMD in men, but the relationship became inverse if adjusted for body weight. Pasco found a signficant positive association between the BMD and serum leptin in women. Golding also found significant correlations between leptin and bone mass, but not between leptin and biochemcial markers. In a small study, Iwamoto found correlations between some skeletal sites and serum leptin, but not at the whole body, and the correlations with biochemical markers were weak. Cauley (ASBMR 2004) reported that men with higher leptin had less bone loss in a longitudinal study of 3075 elderly men and women followed for 5 years. This was not seen in women. There was no significant relation between leptin and risk of fracture, although there was a trend.

Leptin effects on bone cells and adipocyte differentiation: Ducy wrote a great review of osteoblasts, which gives more descriptions of the leptin experiments (which were done by this group). Also, this paper discusses another connection between fat and bone: marrow stromal cells can differentiate into either adipocytes or osteoblasts. One factor that is important in the differentiation of the cells into osteoblasts is the transcription factor Cbfa1 (core binding factor a1). This is further discussed in the article by Nuttall Once differentiated, the mature adipocytes produce a factor which inhibits the osteoblasts (Maurin). Corticosteroid-induced osteoporosis is a serious problem that also involves adipocytes. Wang reviews findings that show how steroids increase the number of adipocytes.

Leptin actions on bone cells: Whereas Ducy found no leptin receptors on osteoblasts, and reported that leptin acted centrally as a very potent inhibitor of bone formation, Iwamoto found that leptin was expressed in and secreted from primary cultures of human osteoblasts and promoted bone mineralization. The cells had leptin receptors, but commercially grown cells did not. Holloway reported another interaction between leptin and bone cells, showing that leptin inhibits osteoclast generation, probably by increasing osteoprotegerin messenger RNA. Consisitent with this is an in vivo study by Burguera, showing that leptin reduced ovariecotmy-induced bone loss in rats, and found significant increases in mRNA for osteoprotegerin. Cornish, J. found that leptin given peripherally increased bone strength in mice and also increased proliferation of osteoblasts in vitro.

Leptin and sympathetic nervous system: Takeda, S. reported that leptin acted via the sympathetic nervous system, and inhibition of beta-adrenergic neurons results in leptin-resistent high bone mass. Schlienger, R. G. and Pasco, J. A. have both reported that the risk of fractures was decreased in patients taking beta-blockers for hypertension. At the 2004 ASBMR, several abstracts discussed beta-adrenergic knock-out mice, but the results were conflicting about whether bone formation was depressed or not in these animals. Ke reported that isoproterenol induced bone loss but the mechanism was increased osteoclast action, not reduced osteoblast activity.

Adiponectin: This is another hormone produded by adipocytes, and levels are lower in obese patients. Cauley (ASBMR 2004) reported that elderly people (age 70-79) with increased adiponectin levels had a trend towards higher fracture risk (p=.07) that was independent of body weight.

References

Schlienger, R. G.(2004). Use of beta-blockers and risk of fractures. Jama 292: 1326-32.

Pasco, J. A.(2004). Beta-adrenergic blockers reduce the risk of fracture partly by increasing bone mineral density: Geelong Osteoporosis Study. J Bone Miner Res 19: 19-24.

Reid, I. R.(2002). Relationships among body mass, its components, and bone1. Bone 31: 547-55.

Cornish, J.(2002). Leptin directly regulates bone cell function in vitro and reduces bone fragility in vivo. J Endocrinol 175: 405-15.

Takeda, S.(2002). Leptin regulates bone formation via the sympathetic nervous system. Cell 111: 305-17.

Simha, V.(2002). Effect of subcutaneous leptin replacement therapy on bone metabolism in patients with generalized lipodystrophy. J Clin Endocrinol Metab 87: 4942-5.

Khosla, S.(2002). Leptin-central or peripheral to the regulation of bone metabolism? Endocrinology 143: 4161-4.

Ruhl, C. E.(2002). Relationship of serum leptin concentration with bone mineral density in the United States population. J Bone Miner Res 17: 1896-903.

Thomas, T.(2002). Is leptin the link between fat and bone mass? J Bone Miner Res 17: 1563-9.

Hoybye, C.(2002). Metabolic profile and body composition in adults with Prader-Willi syndrome and severe obesity. J Clin Endocrinol Metab 87: 3590-7.

Kaufman, B. A.(2002). Bone density and amenorrhea in ballet dancers are related to a decreased resting metabolic rate and lower leptin levels. J Clin Endocrinol Metab 87: 2777-83.

Older references

Burguera, B.(2001). Leptin reduces ovariectomy-induced bone loss in rats. Endocrinology 142: 3546-53.

Ducy, P.(2000). The osteoblast: a sophisticated fibroblast under central surveillance. Science 289: 1501-4.

Goulding, A.(1998). Plasma leptin values in relation to bone mass and density and to dynamic biochemical markers of bone resorption and formation in postmenopausal women. Calcif Tissue Int 63: 456-8.

Holloway, W. R.(2002). Leptin inhibits osteoclast generation. J Bone Miner Res 17: 200-9.

Iwamoto, I.(2000). Relationships between serum leptin level and regional bone mineral density, bone metabolic markers in healthy women. Acta Obstet Gynecol Scand 79: 1060-4.

Karsenty, G.(2000). The Central Regulation of Bone Remodeling. Trends Endocrinol Metab 11: 437-439.

Pasco, J. A.(2001). Serum leptin levels are associated with bone mass in nonobese women. J Clin Endocrinol Metab 86: 1884-7.

Reseland, J. E.(2001). Leptin is expressed in and secreted from primary cultures of human osteoblasts and promotes bone mineralization. J Bone Miner Res 16: 1426-33.

Ricci, T. A.(2001). Moderate energy restriction increases bone resorption in obese postmenopausal women. Am J Clin Nutr 73: 347-352.

Sato, M.(2001). Association between Serum Leptin Concentrations and Bone Mineral Density, and Biochemical Markers of Bone Turnover in Adult Men. J Clin Endocrinol Metab 86: 5273-6.

Thomas, T.(2001). Role of serum leptin, insulin, and estrogen levels as potential mediators of the relationship between fat mass and bone mineral density in men versus women. Bone 29: 114-20.

Yamauchi, M.(2001). Plasma leptin concentrations are associated with bone mineral density and the presence of vertebral fractures in postmenopausal women. Clin Endocrinol (Oxf) 55: 341-7.

Updated 10/15/04

AN ALTERNATIVE: THE BODY-FAT SET POINT AND SHANGRI-LA

Source: Dr. Seth Roberts in Tim Ferriss' book *The Four Hour Body*

"Hacking is much bigger than clever bits of code in a computer — it's how we create the future."
- Paul Buchheit, creator of Gmail

This chapter was written by Dr. Seth Roberts, professor emeritus of psychology at the University of California–Berkeley and professor of psychology at Tsinghua University. His work has appeared in the New York Times Magazine *and* The Scientist*, and he is on the editorial board of the journal* Nutrition.

In 2000, I spent a week in Paris. To my dismay, I lost my appetite. I almost never felt like eating. There was no obvious reason -- I wasn't sick or upset -- but I thought of a nonobvious reason. Five years earlier, I'd invented a new theory of weight control. The new theory was inspired by what I'd learned from teaching the subject and some rat experiments I'd just learned about (see below). One of its predictions, I realized, was relevant: *unfamiliar food causes loss of appetite*.

I'd been to Paris before without losing my appetite. This visit differed in one big way from earlier visits: It was hot. To cool off, I'd been drinking soft drinks with sugar. I'd chosen unfamiliar brands with unfamiliar flavors. They were sweet, and sweetness was familiar -- but maybe sweetness didn't matter.

When I got home, I tested this explanation. I started drinking fructose water -- water to which only fructose had been added. I used fructose rather than sucrose (ordinary sugar) because fructose is digested more slowly. I added no flavoring because any flavor might become familiar. If my explanation of what happened in Paris was correct, the fructose water should cause loss of appetite. A few years earlier, I'd lost weight eating lots of sushi.

Fructose water might be as potent as sushi, I thought. I'd lost weight eating about 1000 calories of sushi per day. So the first day, I drank about 1000 calories of fructose water. Half an hour after the first glass, my appetite utterly vanished. I was stunned how unhungry I felt. I didn't keep other food intake constant; I ate much less. What stayed constant -- before and after I started the fructose water -- was that I ate as much as I wanted.

I drank no fructose water the next day.

My appetite didn't return. (I'd forgotten that in Paris I'd had about two soft drinks per day -- far less than 1000 calories per day.) I cut the dose in half (500 calories/day) for a few days. I still felt no hunger. I cut the dose in half again (250 calories/day). At this level, which calorically equals two cans of Coke per day, I had a little bit of hunger, but only if I ate one meal every two days.

I lost weight so fast that a colleague asked, "Are you dying?" Over three months I lost about 30 pounds, going from about 180 (BMI 26) to 150 (BMI 21). At 150 pounds I stopped trying to lose weight. It was a nice round number and made the point. The Minnesota Starvation Experiment, done during World War II, shows what usually happens. Its subjects underwent an artificial famine. Their calorie intake was cut in half and they were forced to take long walks. They lost as much weight as me in a similar length of time, but, unlike me, they became very hungry. They thought about food constantly. It was very unpleasant. One subject went crazy and chopped off three fingers.

Why was my experience so different?

A Body-Fat Set Point

In 1953, a British physiologist named Gordon Kennedy proposed that mammals regulate body fat using a system that tries to keep the amount of body fat at a certain level (the set point). It does so mostly by varying hunger. If your weight is below your set point, you will feel hungry. The further below, the more hunger. If your weight is *above* your set point (which is rare), you will feel less hungry than usual. The system also controls how soon you feel full during a meal. If your weight is far below your set point (which is rare) it will take more food than usual before you feel full. If your weight is above your set point, it will take less food than usual to feel full.

Kennedy's proposal was based on an experimental observation. Rats whose liquid diet was suddenly diluted (half as many calories per unit volume) lost weight for a day or so but then started eating more calories than usual and regained the lost weight. In the following years, similar results were observed many times. The best support for Kennedy's idea came from the discovery of leptin in 1994. Because hunger is controlled by the brain, Kennedy's idea predicted that your brain can tell how much body fat you have. Leptin provides that information. Leptin is made by fat cells and released into the blood. The more fat a cell contains, the more leptin it makes, so leptin concentration in the blood indicates total amount of body fat. Some brain cells have leptin receptors, so they measure leptin concentration in the blood.

The notion of an *adjustable* body-fat set point was introduced by Michel Cabanac, a professor of physiology at Laval University. He believed your set point is not fixed but depends on what you eat.

Some foods produce a lower set point than other foods. This implied there were two quite different

ways to lose weight. If your set point goes down, you will lose weight easily; if your set point does not go down, weight loss will be difficult. In the 1970s, Cabanac and his colleagues did two experiments that showed this. In one experiment, subjects lost weight via calorie restriction (as in the Minnesota experiment). *What* they ate stayed the same; *how much* they ate was now limited. In a second experiment, the subjects drastically changed their diet: They consumed only a liquid Slimfast-like food -- a dietary change meant to lower the set point. They could drink as much as they wanted. *What* they ate changed; *how much* remained unlimited. Both methods produced similar weight loss (10-20 pounds) in similar amounts of time (3-8 weeks) but the experiences were completely different. Losing weight by calorie restriction was "torture," Cabanac said. (He was one of the subjects.) "You dream you are breaking the fast and ruining the experiment." In contrast, while losing weight with the dietary change the subjects didn't suffer at all. Except maybe from boredom.

The Theory Behind the Shangri-La Diet

Cabanac and his colleagues had found one food—their SlimFast®—that lowers the set point. The next step was finding a general rule -- a rule that predicts the effect of any food on the set point. I couldn't imagine how to do this. In 1995, however, I read a paper by Israel Ramirez, a scientist at the Monell Chemical Institute in Philadelphia, that described some rat experiments with surprising results. They suggested that associative learning (the type of learning studied by Pavlov) affected the set point -- a possibility that no one had considered.

But it made perfect sense. Associative learning obviously controlled *what* we eat. Food with an entirely new flavor tastes strange. When a friend of mine tasted his first Coke, he thought: *What's the big deal?* It tasted like medicine. Food with a new flavor tastes strange because the flavor is not yet associated with calories, a type of learning called *flavor-calorie learning*. When we eat a food, we remember its smell for perhaps an hour.

If our digestive system detects calories in the food during that time, a flavor-calorie association is formed. Its effect is to make the food taste better. Anthony Sclafani, a professor of psychology at Brooklyn College, has done many experiments that show the power of this learning.

You can experience it yourself. Buy two new flavors of tea. Have one always with sugar, the other always with artificial sweetener. Cup after cup, the one with sugar will taste better and better; the one with artificial sweetener will not.

Not long after reading Ramirez's paper, I thought of the following theory of weight control:

1. Between meals your set point goes down.

2. Eating raises your set point. The size of the increase depends on how strongly the food's flavor is associated with calories. The stronger the association, the bigger the increase. Flavors not associated with calories don't raise the set point.

The secret to painless and sustainable weight loss, says this theory, is *eat as much as you want while raising your set point as little as possible*. The strength of a food's flavor/calorie association depends on its calorie content, but it also depends on other factors.

You choose foods with those other factors in your favor.

At first I saw four ways to do this:

1. *Avoid eating foods with exactly the same flavor*. Fast food and factory-made foods are the main examples. When a food has exactly the same flavor each time you eat it, a stronger flavor-calorie association can develop than if the flavor is somewhat different each time you eat it.

2. *Eat foods with a weak flavor*. Weak flavor = weak flavor-calorie association. This is why Cabanac's subjects lost weight on a liquid diet: Its weak flavor. I lost weight eating sushi because it was just fish and white rice. No wasabi or soy sauce.

3. *Eat foods that are digested slowly*. If a food is digested more slowly than usual, its calorie signal will reach the brain later than usual. At that point its smell memory will be weaker than usual and the association formed will be weaker than usual. This is why low-carb and low-glycemic-index diets work: They forbid foods that are digested quickly, such as bread and potatoes ()

4. *Eat unfamiliar foods*. New flavors haven't yet developed flavor-calorie associations.

The Shangri-La Diet

After my Paris experience, I realized that food without smell is the ultimate way to consume calories without raising the set point. Sugar water has no smell.

For three years I kept my weight down by drinking sugar water -- about 200 calories per day. Then a friend pointed out that some oils have no smell; if my theory was right they should have the same effect. I replaced the sugar water with the same number of calories of extra-light olive oil, which has no smell. My weight stayed the same. The extra-light olive oil seemed be as powerful per calorie as the sugar water and had benefits the sugar water did not: softer skin and hair, no worries about blood sugar.

By then my friends' experiences and a small experiment had shown that sugar water had the same effect on most people as it had on me. Soon after this I wrote *The Shangri-La Diet*. The diet can be summed up very simply:

> ***Eat twice your weight (in pounds) in flavorless calories per day. Eat them at least an hour away from other food.***

If you weigh 200 pounds, for example, eat 400 flavorless calories per day. Avoiding other food means avoiding other food with smell. You can't eat the flavorless calories around the time you have coffee or tea or a diet soda, for example. *I consume them shortly before bedtime.*

The usual sources of flavorless calories have been sugar water and extra-light olive oil.

Since the Book

Since publication of *The Shangri-La Diet* (SLD), many people have posted their experiences, ideas, and

questions at forums.shangriladiet.com. Their posts teach three lessons:

First, *there's something to it*. The diet sounds exceedingly strange, but the vast number of forum success stories leave no doubt it often works. According to conventional weightloss advice (restrict calories, don't eat fat, don't eat carbs), the diet should cause weight *gain*.

The most impressive feature of the success stories is the uniqueness of the experience. Many diets cause weight loss. SLD weight loss is different. For example:

> *It's amazing not to feel my hunger increasing as I lose weight. Usually [dieting] is like holding your breath underwater -- the longer you go without air, the more massively you need air. Usually the longer you are on a diet the more hungry you are. This is so strikingly different.*

SLD makes you feel full much sooner:

> *First time I ever did it I could not finish my bowl of oatmeal. Before SLD I had never, not ever, been able to not finish anything.*

It reduces thinking about food:

> *You're not craving foods. Food is in the background - your other life is in the forefront.*

All this supports Cabanac's idea that there are two quite different ways to lose weight: easy (via set-point reduction) and hard (without set-point reduction). Unlike other diets, or far more powerfully, SLD reduces your set point.

Second, *better ways to do it*. The diet has been improved three ways:

1. *Nose-clipping*. Gary Skaleski pointed out that if you close your nose (using a swimmer's nose clip, for example), you no longer smell your food. Without smell, *every* food has no flavor-calorie association. *Anything* eaten this way should lower your set point. Many reports on the SLD forums suggest this is true:

   > *I was experiencing a driving hunger at night that overwhelmed my efforts to be modest in my eating. Then last Friday, I tried nose clipping. The relief was immediate. The hunger subsided and I even lost a couple of pounds. On Saturday I decided to try clipping every time I ate anything. By evening I could not eat my entire dinner.*

   A less conspicuous way to block smell is to put small pieces of pantyhose in your nose.

2. *The benefits of flaxseed oil*. After some people wondered if they could use flaxseed oil as the calorie source, I discovered that it improves my balance and other mental abilities and reduces inflammation, no doubt due to its high omega-3 content. This was wonderful. I now use flaxseed oil as my SLD calories by drinking it nose-clipped.

3. *Easier ways to drink the oil*. Some people have trouble drinking oil. One solution is to mix it with water. Another solution is to put the oil on toast and eat it nose-clipped. It tastes just like toast

with butter.

Third, *better expectations*. To read the forums is to see that the diet is a tool, not a magic bullet. "Don't expect the wrench to fix the bike by itself," one person said. Data posted by about a hundred dieters showed that the average rate of weight loss was about 1 pound/week. It takes anywhere from six months to a year to get the full weight loss from whatever dose you've chosen. The forums show that, like a wrench, SLD sometimes is and sometimes isn't the only tool you need.

The story of SLD teaches three lessons: 1. Your weight is controlled by a set point. 2. Your set point isn't fixed. It depends on what you eat. 3. Flavorless calories are an easy way to lower your set point, but not the only way.

Less obvious uses of the theory behind SLD may turn out to be more important. For example, why are kids getting fat? The theory says it's because they're eating lots of food with exactly the same flavor every time. It isn't just junk food; it's also frozen juice, vitamin-enriched breakfast cereals, Hamburger Helper, and microwave entrees.

When Cabanac and his colleagues showed that drinking a liquid diet produced much easier weight loss than calorie restriction, they weren't saying: *To lose weight, drink a liquid diet*. They were saying: *Here's a new empirical effect. You should take seriously the idea behind it*. The Shangri-La Diet works, yes, but because it works, it says something far more broad and important: *Take seriously the idea that flavor-calorie associations control your set point.*

References

Roberts's weight-loss self-experimentation: http://escholarship.org/uc/item/2xc2h866 on 2009-10-18.
Minnesota Starvation Experiment:
http://www.possibility.com/wiki/index.php?title=EffectsOfSemiStarvation on 2009-09- 28.

Kennedy: Kennedy, GC. The role of depot fat in the hypothalamic control of food intake in the rat. Proceedings of the Royal Society of London B 1953; 140: 579-592.

Cabanac calorie restriction: Cabanac M, Duclaux R, Spector NH. Sensory feedback in regulation of body weight: Is there a ponderostat? Nature 1971; 229: 125-7.

Cabanac liquid diet: Cabanac M, Rabe EF. Influence of a monotonous food on body weight regulation in humans. Physiol Behav 1976; 17; 675-8.

Cabanac quotes: Interview, October 28, 2005.

Ramirez: Ramirez I. Stimulation of energy intake and growth by saccharin in rats. J Nutr 1990; 120: 123-33.

Sclafani: Sclafani A. Learned controls of ingestive behaviour. Appetite 1997; 29: 153-8.

Roberts's theory: Chapter 3 of *The Shangri-La Diet*. A more technical description:
http://www.sethroberts.net/about/whatmakesfoodfattening.pdf on 2009-10-18.

"It's amazing not to": http://boards.sethroberts.net/index.php?topic=785.msg5259-msg52 on 2009-10-13.

"first time I ever": http://boards.sethroberts.net/index.php?topic=7133.msg87040-msg87040 on 2009-10-18.

"You're not craving": http://boards.sethroberts.net/index.php?topic=6972.msg83326-msg83326 on 2009-10-18.

"I was experiencing": http://boards.sethroberts.net/index.php?topic=7243.msg90096-msg90096 on 2009-10-18.

"benefits of flaxseed oil": http://www.blog.sethroberts.net/category/nutrition/omega-3/omega-3-directory/ on 2009-10-18.

HOW TO REVERSE LEPTIN RESISTANCE

Source: Evander Blimpington, eHow Contributor,
http://www.ehow.com/how_7877982_reverse-leptin-resistance.html

Leptin is a hormone that is closely related to insulin and is responsible for relaying signals that tell you when you're full, make your body burn fat for fuel and reduce or eliminate stored body fats. But according to Dr. Ron Rosedale, M.D., when you eat excessive carbohydrate-rich foods, especially high fructose corn syrup and refined (white) grains and bread, your body releases too much leptin into the blood stream. This overexposure inhibits the body's ability to understand leptin's messages and leads to obesity as well as diabetes. The only known way to reverse leptin resistance, according to Rosedale, is through proper diet.

Instructions

1. **Eliminate processed sugars and refined grain products from the diet** and replace them with some fruit, unheated honey and minimal amounts of whole grain products (if any at all). Processed sugars including high fructose corn syrup, as well as white, refined grain products, according to Dr. Joseph Mercola, M.D., are most responsible for the modern epidemic of leptin and insulin resistance. These foods trigger surges of leptin and other hormones in the blood due to their refined nature, and these surges cause the body to become desensitized to leptin over the course of time. Some raw fruit, unheated honey and whole grain products won't behave this way and do not contribute to leptin resistance.

2. **Minimize starches in your diet.** Even whole grain products, potatoes and other seemingly healthy starches aren't necessarily ideal for the body, which according to the Weston A. Price Foundation runs best when fat is its fuel source. Starches and fruits should be consumed according to how active a person is over the course of a day. For instance, Dr. Thomas Cowan, M.D., says that your average person only needs 30 to 70 grams of carbohydrates per day, while

an endurance athlete might need up to 300 grams of carbohydrates per day. One banana provides about 20 to 24 grams of carbohydrates, one piece of typical bread provides 12 to 20 grams and one medium potato provides 37 grams.

3. **Eat plenty of protein from the right sources.** Eat meat, as well as some eggs and milk, especially from organic sources. The best kind of protein to consume for weight loss is raw protein (such as unpasteurized milk, steak tartare and sushi). If eating cooked protein, don't eat too much.

4. **Eat all the healthy fats you desire.** According to nutritionist Dr. Aajonus Vonderplanitz, vegetable oils are also partially responsible for the current obesity epidemic. And according to Cowan, all hydrogenated fats (which include soybean oil, canola oil and seed oils), when used as building blocks for constructing and maintaining the body, and more specifically the pancreas, can result in leptin- and insulin-related health issues (including diabetes). The ideal fats to eat are butter, cream, lard, meat fats, cod liver oil, coconut products, avocados and olive oil. Organic and raw fats are always best.

5. **Eat more frequently, and eat until satiated each time.** According to Matt Stone of 180 Degree Health, overfeeding the right foods actually balances insulin and related hormones, while eating less food and less often actually results in the unstable hormone levels that you are trying to avoid. Many individuals under Stone's guidance have balanced their blood sugar within just one month simply by overfeeding the right foods.