A MAN OF UNCONTROLLABLE APPETITE

One evening, after I had given a lecture in New York, a man approached me to ask about seeing me as a patient. He was rotund, with a round, ruddy face, a booming voice, and a gentle manner. Everything about him was large—his appetites, his belly, and his heart. He seemed tentatively curious about my work, and I was surprised when he showed up in my office. Samuel was almost 60 years old, and his love of everything big was waning as he felt the encroachment of death. He described years of feeding his fat, drinking a pint of heavy whipping cream every night before bed to keep his weight up. At times he would have a change of heart and try to lose weight. He tried to lose weight as he gained it—with big attempts and extreme diets, but he always gained back more than he lost. Finally, he realized that the big presence his more than 300-lb corpus gave him was not worth the infirmities he suffered. He was doggedly fatigued and short of breath at nearly every step, his nose was congested, and his legs were swollen. His skin was dry, and yeast grew over his body, fermenting on the sweetness of his skin. He was not aware that he was diabetic, had dangerous cholesterol levels, angina, sleep apnea, and a sluggish thyroid. He did notice that his leg hair was gone and that his face and chest had a feminine appearance. Because of the estrogen produced by his fat cells, his level of female hormones was that of a woman. He did not realize he was rusting inside, that his liver couldn't keep up with his body's detoxification demands, or that his body could not burn fat effectively anymore. At one time, his large appetite for life created his personality, and he controlled it. Now his appetite controlled him and he felt powerless to stop it, no matter how hard he tried to will the cravings away.

His testing showed severe sleep apnea; a thallium stress test with myocardial ischemia; atherogenic small, dense LDL and HDL cholesterol particles; large triglyceride particles; and high fasting insulin and blood glucose levels. His hormones were completely out of balance—his insulin was over 200 µIU/mL (normal <20) after a 75-g glucose load, his estrogen was high, his thyroid-stimulating hormone (TSH) was high and his free T3 low, and his growth hormone was very low. He also had IgG food sensitivities, impaired hepatic detoxification, and fatty liver (nonalcoholic steatohepatitis).

I told him that if he did everything I suggested, he would lose weight, feel better, and his symptoms would go away. Everything he had done, he did to himself and could undo. I prescribed a simple program for him. I had him eat a whole-foods, unrefined diet without any restriction on calories or portion size. I taught him the concept of nutrient density—foods with lots of nutrients and fewer calories such as whole grains, vegetables, fruits, and nuts. I had him start walking and slowly build up his exercise and ultimately include interval training. I gave him supplements to balance his blood glucose (magnesium, chromium, vitamin A); antioxidants such as lipoic acid, which helps reduce blood sugar and improve mitochondrial energy production; and coenzyme Q10 for his heart. I also recommended herbs to heal his fatty liver, fish oil, and extra fiber. I also gave him a small dose of Armour thyroid to balance his thyroid, and treated his sleep apnea with a continuous positive airway pressure (CPAP) machine.

Enthusiastic, though somewhat skeptical, he left my office determined. Three months later I spoke to him. He had lost 30 pounds, had more energy, and was beginning to look forward to exercise. His nasal congestion was gone and his fluid-filled, swollen legs were better. All of his cravings were gone, he never felt hungry, and he found the program easy to follow. Eight months later I saw him again and repeated his blood tests. I was shocked when he weighed in. He had lost 110 pounds without being on a strict deprivation diet. He simply changed his eating habits and lifestyle. His diabetes was cured, his blood sugar had dropped from 130 to 74 (>126 fasting denotes diabetes). His HDL and LDL cholesterol and triglycerides were normal without any medication. His liver function test returned to normal. He was exercising vigorously 3-4 times a week and felt 20 years younger. He had, after a lifetime of uncontrollable appetite, finally found balance and health without suffering, as well as continued pleasure in food.

GOOD COMMUNICATION = HEALTHY METABOLISM

Do our appetites control us, or can we control them? The neuroendocrine-immune signals that influence appetite and metabolism are becoming clearer daily. The signals provide the answer to the greatest health epidemic of our generation—more
than 1 billion people around the planet are overweight or obese. The question, then, is how could the critical systems that regulate our weight go awry?

How is weight regulated? Imagine what the effects of eating just 100 extra calories a day does over the course of a year. Every 3,500 calories is equal to one pound of fat. Over the course of a year, the average person eats 900,000 calories. If caloric needs were exceeded by just 2%, or 18,000 calories, 5 pounds would be gained by the end of the year. The average American gains about 20 pounds between the ages of 25 and 55. This accounts for an excess of only 0.3% of calories over 30 years. This incredibly small difference over time leads to significant weight gain.

How do the signals that tell us we are hungry or full automatically regulate our daily, monthly, and yearly energy balance and our consequent weight gain or loss? Why do these signals go awry and lead to obesity?

The Four Parts of the Appetite Control System
There are 4 basic parts to this system:
1) The autonomic nervous system connecting the brain, gut, and fat cells;
2) Metabolic hormones, including the hormones and molecules made by adipocytes;
3) Brain messenger chemicals (neuropeptides),
4) Messenger molecules of the immune system called cytokines, especially those produced in adipocytes (adipocytokines) with wide-ranging effects.

These components work together to communicate between all the organs and tissues responsible for managing weight and survival. Their signals flow between the stomach and intestines, liver and pancreas, to and from adipocytes and the endocrine system, and to the brain and autonomic nervous system (Figure 1). The dance of molecules between these organs and tissues controls appetite and weight gain or loss. Small disturbances in this system can lead to significant changes in weight over time. Because the system was designed in a time of scarce food resources, it is very efficient at increasing appetite and not so efficient at limiting caloric consumption. Eating only 100 extra calories a day leads to a weight gain of 5 pounds in a year.

Why not just count calories? Can calories be counted accurately? Studies of top nutritionists have shown that even they can’t accurately estimate calories consumed in a day. How can the average consumer or patient be expected to count calories when the experts can’t?

MESSAGES AND METABOLISM: OPTIMIZING NEUROENDOCRINE-IMMUNE SIGNALING
The nervous, endocrine, and immune systems all dynamically interact to control appetite, food intake, and metabolism of food. These molecules of intercellular communication act diffusely throughout the body, but the main centers of activity are the brain, the gastrointestinal tract, and the adipocytes. They have many names—hormones, neurotransmitters, and cytokines. Hormones are messengers of the endocrine system, neurotransmitters are the messenger molecules of the nervous system, and cytokines are the messenger molecules of the immune system. They are finely tuned, hopefully harmonious system that determines health and metabolism. Research has clarified which create hunger or satiety and how they are regulated by food intake, eating patterns, meal timing, meal composition, phytonutrient and fiber content, and how this all, in turn, affects eating behavior, metabolism, and weight.

DRUGS DON’T WORK FOR WEIGHT LOSS
For better or worse, human biology is at the mercy of molecules. Willpower has limited control over the limbic regulation of appetite by the complex interplay of neurotransmitters, hormones, and cytokines governing our survival. In the end, drugs or surgery have limited utility due to the multitude of dynamic interactions between all the molecules. Manipulating any one component will have little long-term effect. If drugs modify the activity of one molecule, counter-regulatory signals alter the effects of the drug. The use of appetite suppressants leads to rebound hyperphagia and weight gain when stopped.

The recombinant adipocyte-derived satiety hormone leptin initially held promise for weight loss when used in animal models. Scientists believed that simply injecting the molecule into people would stop them from eating and help them lose weight. There was only one drawback: it didn’t work. Central leptin resistance occurs in obesity. Research focuses on a single drug, binding to a specific receptor for a specific effect that will mimic or block one of the molecules, but that approach is misguided. Attempting to modify the appetite regulatory system balance with a drug results in unpredictable hormonal and neurotransmitter shifts that may promote weight gain through counter-regulatory mechanisms and could have serious side effects. Specific receptor sites in the brain respond to molecules that create the feeling of fullness or satiety, and others create hunger. Researchers have identified marijuana-like molecules in the body that stimulate hunger—the “munchies”—called endocannabinoids, as well as cocaine- and amphetamine-like molecules that bind to receptors in the brain to suppress hunger. Research continues in drug development for molecules that block hunger or speed metabolism. However, long-term success in weight regulation can occur only by normalizing function in the neuroendocrine-immune system through modification of meal timing, composition, nutrient density, phytonutrient content, exercise, and stress management. The effects of modulation of this system can be seen in the article.
The Biology of Obesity

SUGAR IS SUGAR BY ANY NAME

A major problem today is that we are swimming in sugar. The average person eats about 180 pounds of sugar a year, or about a half pound per person per day. Remember that this is the average, which means some are eating more than that. Sugar consumption triggers an unconscious and vicious cycle of sugar cravings, as well as increases in insulin production, appetite, sugar intake, and insulin production, leading to a cycle of cravings, bingeing, and crashing. This leads to weight gain and more rapid aging.

Refined carbohydrates and sugars are ever present in our diet. White bread, sugar, pasta, white rice, and white potatoes are quickly absorbed starches with a high glycemic load. Consumption of these foods has increased dramatically since the introduction of the original food pyramid that was introduced in 1992 and advised us to eat 6-11 servings of rice, bread, cereal, and pasta a day. Soft drinks or sugar-sweetened beverages and alcohol, consumed in excess, contribute to the problem as well.
Sugars comes in many disguises—high-fructose corn syrup (HFCS), sucrose, glucose, maltose, dextrose, lactose, fructose, corn syrup, white grape juice and other fruit juice concentrate. Sugar is sugar by any other name; this includes honey, barley malt, maple sugar, sucanat, natural cane sugar, and dehydrated cane juice. Food processors do not have to indicate if there is added sugar in their products. Added sugar is any sweetener or sugar put in food other than what’s naturally found in it. For example, HFCS often is added to fruit drinks. The manufacturers are required only to list the total grams of sugar. It is best to avoid or reduce consumption of hidden sugars in foods, including salad dressings, luncheon meats, canned fruits, bread, peanut butter, crackers, soups, sausage, yogurt, relish, cheese dips, chewing gum, and breakfast cereals, and to choose foods with a low glycemic index or meals with a low glycemic load.6

THE EPIDEMIC OF METABOLIC SYNDROME OR PRE-DIABETES

Over time, we can become resistant to the effects of insulin and thus need more and more to do the same job. This is very much like a drug addiction. The more of a drug you take, the more of it you need to do the same job. Hyperinsulinemia increases hunger, systemic inflammation, oxidative stress, hypercoagulability, endothelial dysfunction, and mitochondrial damage. All of these effects alter metabolism to promote weight gain and induce resistance to weight loss. Metabolic syndrome, insulin resistance syndrome, and pre-diabetes are all names for the same thing—a condition that affects to some degree or another almost everyone who is overweight. Sixty-five percent of Americans—193 million people—fit that description.7

THE DANGER OF BELLY FAT

Continued exposure to foods such as refined carbohydrates, white flour, sugar, potatoes, and white rice and unhealthy meal patterns (eg, large, late, or skipped meals) increases insulin production and leads to increased belly fat, or visceral adipose tissue (VAT). This fat cannot be removed with liposuction; it is in and around all organs. These adipocytes produce many hormones and messenger molecules that control weight, overall health, and speak directly to the gut, brain, liver, and pancreas, regulating the complex interplay of messenger molecules involved in metabolism. Unfortunately, all of those signals were designed for times of food scarcity. Exposed to too many calories, particularly those from refined carbohydrates and sugar (along with little physical activity), those signals get stuck in a vicious cycle that promotes weight gain, increases visceral fat storage, increases stress hormones, increases inflammatory molecules or cytokines, depresses thyroid and growth hormone function, and increases levels of estrogen in men and testosterone in women.

Two other important factors control the signals that affect our food intake and appetite: HFCS and fiber.

HFCS: AVOIDING THE SUPER SUGAR

One of the hidden unspoken dangers of our food supply is HFCS, which is found in almost every sweetened or processed food, including sodas, canned foods, cookies, cakes, baked goods, and frozen foods. It is a super sugar. Its consumption increased by more than 1,000% (0.292kg/person/year to 33.4kg/person/year) from 1970 to 1990, and it now represents more than 40% of caloric sweeteners added to foods and beverages.3 The introduction of HFCS into the food supply is associated with the beginning of the obesity epidemic.

Other factors certainly may play a role. These include reduced levels of physical activity; increased portion sizes; eating more than half our meals in restaurants, on the go, and at fast-food restaurants; changes in the types of foods we eat (moving from a whole-food, plant-based, high-fiber unprocessed diet to a sugary, trans fat–rich, low-fiber, low-vitamin and -mineral diet); and the overall “toxic food environment,” with an abundance of low-quality, nutrient-poor, sweetened and trans fat–laden food choices. However, the effect of HFCS consumed in soft drinks and other sweetened beverages merits serious consideration as a cause of the obesity epidemic.8

HOW IS FRUCTOSE DIFFERENT FROM ORDINARY SUGAR?

The digestion, absorption, and metabolism of fructose differ in significant ways from sugar, or table sugar, as we know it, which is a combination of glucose and fructose known as “sucrose.” Glucose is the basic sugar the body uses for energy and metabolism—one of the key building blocks of all carbohydrates, often found as part of other slowly absorbed sugars found in beans and whole grains. Fructose is also one of those building blocks found in nature, mostly in fruit, along with fiber and an abundance of protective nutrients. However, when processed into HFCS, it is absorbed more quickly than regular sugar (glucose + fructose) and enters cells without any help (glucose needs insulin). Once inside the cell, it becomes an uncontrolled source of carbon (acetyl-CoA) that is then made into cholesterol and triglycerides. Eliminating HFCS leads to a dramatic decrease in triglycerides and LDL cholesterol and an increase in HDL.

Fructose does not stimulate insulin secretion and the consequent increase in leptin, which reduces appetite. Foods and beverages containing HFCS trigger none of the normal controls on appetite. Glucose consumption and insulin production produce central feedback inhibition on appetite. Fructose consumption does not. Hunger for more sugar or HFCS increases, which perpetuates this cycle. This has been shown to lead to increased appetite and calorie intake and weight gain, as well as high cholesterol and high blood pressure. It is important to note that the quantities of fructose consumed in fruit are significantly lower than in those in sweetened beverages, and the metabolic effects of fructose in fruit are different because the increased intake of fiber, vitamins, minerals, phytonutrients (healing plant substances), and antioxidants helps slow absorption and improve metabolism.

ARTIFICIAL SWEETENERS

Aspartame, neotame, acesulfame potassium, saccharin,
sucralose, and dihydrochalcones, artificial sweeteners that are consumed by two thirds of US adults, are a significant component of our diets. They are in many packaged foods, artificially sweetened foods, gum, candy, sodas, sweetened drinks, and mints. Questions remain about their safety, including the short- and long-term effects of using them. Known undesirable effects include stimulation of hunger through the cephalic (or brain) phase insulin response. Simply thinking about sugar can cause a spike in insulin, and putting something sweet on the sweet receptors on the tongue signals the brain that something sweet is coming and to prepare by producing hormones like insulin. A number of studies have shown that aspartame ingestion may actually lead to increased food/calorie intake.\(^{11,12}\) Animal and human studies show that aspartame may disrupt brain chemistry\(^ {13}\) and induce neurophysiological changes (altered brain chemistry because the sweeteners mimic normal neurotransmitters) that might increase seizure risk,\(^ {14}\) depression,\(^ {15}\) and headaches.\(^ {16,17}\) Although conclusions have yet to be reached regarding specific outcomes in humans and dosage effects, the existing evidence warrants vigilance. Until better data on long-term risks of non-nutritive sweeteners are available and in light of the conflicting safety data, people should use caution in the use of artificial sweeteners. Sorbitol, maltitol, and xylitol are common non-absorbed sugar alcohol sweeteners found in food and are responsible for increased intestinal gas production, bloating, and abdominal pain.\(^ {18}\)

**MEAL COMPOSITION, MEAL FREQUENCY, AND MEAL TIMING—GETTING IT RIGHT**

There are 3 main factors that control gut-brain-liver-pancreas-fat cell communication. This communication is at the center of metabolism. A dynamic web of molecules interacts moment-to-moment to shift us into health or disease, to weight loss or weight gain, to fat burning or fat storage.\(^ {21}\) The 3 main factors that control this complicated communication are macronutrient composition (or the balance and types of protein, fats and carbohydrates in each meal and the quantity of food at a particular meal), meal frequency, and meal timing.

**Meal Composition: Low-Fat Diets Slow Your Metabolism**

Let’s look at 3 studies that illustrate this. The first is by Dr David Ludwig from Harvard, who has demonstrated in study after study that all calories are not created equal. In a study in JAMA, he demonstrated that low-fat diets slow your metabolism more than low-glycemic load diets.\(^ {22}\) The study provided 1,500 calories a day for each group and was designed to cause a 10% weight loss over a few months. The low-fat group had a diet similar to that recommended by the National Cholesterol Education Program for a heart-healthy diet. The low-glycemic load diet was not low in carbohydrates, just low in refined or rapidly absorbed carbohydrates, such as white bread, and it included whole grains. In fact, 43% of the low-glycemic load diet was from carbohydrates. The results were startling. Even though both groups lost weight, members of the low-fat diet group had a slower metabolism at the end of the study, were hungrier, and were more resistant to further weight loss. They also had more inflammation (higher C-reactive protein) and higher triglyceride, insulin, glucose, and blood pressure levels. The complex signals that regulate our weight and metabolism, therefore, are controlled by meal composition. Foods that are absorbed slowly (meals that have a low glycemic load) and high in fiber, such as whole foods, grains, beans, nuts—even though they are high in carbohydrate—actually keep your metabolism running faster, burning more calories and creating a harmonious balance of metabolic signals, which facilitates long-term weight loss and healthy metabolism.

**Meal Timing and Frequency and Weight Loss**

Not only is the composition of the meal you eat critical, but when you eat it and how often you eat it are essential to regulating your weight. Studies have shown that eating regular meals throughout the day, grazing vs gorging, and not skipping meals, improves weight loss, and reduces many risk factors for heart disease, diabetes, and aging in general.\(^ {23,24}\) Eating in a regular, rhythmic pattern (at roughly the same time every day, and eating more frequent meals, such as 3 meals and 2 snacks) reduces caloric consumption, increases fatty acid oxidation, and lowers cholesterol and insulin levels. This occurs naturally through what is known as thermogenesis (literally “heat creation”), as a series of physiological processes are initiated to digest what you’ve eaten and turn it into usable energy. Eating erratically, on the go, away from home, and at your desk will lead to a certain path of inefficient energy production (thus low energy levels), weight gain, and obesity.

The old proverb, “Eat breakfast like a king, lunch like a prince, and supper like a pauper,” now has scientific verification. Most think skipping breakfast will reduce overall calorie intake for the day and promote weight loss. Unfortunately, the opposite is true. Avoiding breakfast increases total daily caloric consumption. In a study of people who ate breakfast compared to those who skipped breakfast, the ones who skipped breakfast ate more food, had higher levels of cholesterol, and were more insulin-resistant.\(^ {21}\) Over time, this promotes weight gain, heart disease, inflammation, and all age-related diseases. One researcher from the University of Texas evaluated the effect of circadian and diurnal rhythms of food intake.\(^ {25}\) Analysis of 7-day diet diaries of 867 men and women showed that eating more calories earlier in the day is more satiating than eating the same number of calories later in the day and reduces overall calorie consumption. Eating more later in the day is not as satisfying and promotes increased caloric consumption.

Eating breakfast is just that: “breaking” the overnight “fast.” Eating upon waking normalizes glucose, enhances metabolism, and regulates appetite and total food intake for the rest of the day. The study also demonstrated that food with a higher nutrient density and lower energy density (fewer calories), such as vegetables, fruits, whole grain, beans, and nuts, led to a lower intake of overall calories, regardless of the time of day they were eaten.
The Biology of Obesity

How Fiber Promotes Weight Loss
The higher the fiber content of a single food or of a meal in total, the harder and longer your body has to work to digest it. This promotes weight loss in 3 ways:

- increased thermogenesis during digestion;
- longer duration of digestion, which improves satiety; and
- reduction in overall insulin production because of slowed absorption and slowed rise and fall of blood glucose.

The goal of increasing dietary fiber (or lowering dietary glycemic load) is to create a metabolic balance that controls appetite and allows efficient metabolic function.

Can You Eat a Low-Fiber, Low-Carb Diet and Still Lose Weight? No!
One study was done recently to discredit the low-carb craze.25 The study compared a low-fat diet to a low-carb diet. The low-fat diet group did better in every way. But the author never really mentioned what was hidden in the fine print—that he gave the low-fat group a special supplemental fiber shake a few times a day, amounting to over 60 g of fiber. The average American eats 8-12 g of fiber per day, and the American Heart Association recommends 25 g a day. The weight loss in that study had nothing to do with the amount of fat or carbohydrates consumed—the fiber that made all the difference. Why? Because it lowered the glycemic load of the diet.

That is the effect of the total meal on your blood sugar, not just one isolated food. The fiber factor—not the low-fat diet—was the key to that study. In another study, Dr. Ludwig showed that people who ate more fiber lost more weight and reduced insulin, cholesterol and clotting factors, all of which promote heart disease.26 The fiber intake was more significant that the total fat intake.

Super Fibers
Not all fiber is created equal—and 2 types deserve special mention—konjac root and rye.

Konjac, Amorphophallus konjac K Koch, is an Asian tuber or root that is full of a very viscous, water-soluble fiber called glucomannan. It is extracted from the root, dried, and made into rubber jelly and noodles, and has been used for more than 1,000 years in Japan to make noodles. It is 5 times more powerful than psyllium, oat fiber, or guar gum in lowering cholesterol. The magic of this fiber is related to its viscosity. It is like a dry sponge that expands to 10 times its size when put in water.

The root has been studied by researchers at the University of Toronto prepared in pills or powders that can be mixed with water and taken before meals.27 The results have been remarkable. This fiber blocks cholesterol absorption, reduces the production of HMG CoA reductase, the principle regulator of cholesterol in the body, and feeds the healthy bacteria in the gut that then produces short chain fatty acids that reduce the production of cholesterol in the liver. The fiber also makes a gel in...
the intestine that slows the rate of absorption of meals, and thus lowers the all-important glycemic load.

The other fiber worth mentioning is rye fiber. Whole grains—not whole grain flour or whole grain products, but whole grains—are a good source of both soluble and insoluble fibers. A study by Junntunen et al showed that rye fiber has unique properties that lower blood sugar and insulin more than other fiber, such as wheat fiber.10 Rye foods contain lignans, phytonutrients that are chemically similar to human hormones. These compounds have been associated with lowered cancer and cardiovascular disease risk in individuals whose diets contain large amounts of them. Whole grains in general help control blood sugar and insulin and reduce the risk of obesity, metabolic syndrome, and heart disease. Fiber is an important aspect of long-term weight loss. It is found in all unprocessed, unrefined, whole-plant foods, such as beans, whole grains, nuts, seeds, fruits, and vegetables.

SYSTEMS BIOLOGY AND OBESITY: THE PROMISE OF NUTRIGENOMICS

Systems biology provides insight into complex chronic diseases such as obesity and its multiple causes and consequences. The neuroendocrine-immune-gut-adipocyte “system” is a more accurate representation of human function in obesity and disease than current specialties or diagnostic systems. Specific environmental influences regulate this system, including meal timing, stress, activity levels, and consumption of “toxic” foods, such as HFCS and trans fatty acids. The future of medicine lies in breaking down the artificial barriers of thought and practice that impede understanding of complex disorders that require multi-interventional approaches. Obesity and appetite regulation provide a microcosm of systems biology and insight into the modulation of complex cell signaling through lifestyle medicine. In its purest incarnation, systems biology is the clinical application of genomics and understanding how various inputs—diet, thought, toxins, rhythm, and others—modulate gene expression and therefore health and disease. Only a genomic and nutrigenomic approach—that is, finding the optimal pattern of living for each person and the evolutionary nutritional requirements of human life—will solve our epidemic of obesity and chronic lifestyle disease.

References


A Note to Readers

In my editorial, “Refrigerator Rights—The Missing Link in Health, Disease, and Obesity,” which appeared in the July/Aug 2005 issue of Altern Ther Health Med. 2005;11(4):10-12, I intended to cite as the source of inspiration for the article Dr Will Miller’s 2002 book, Refrigerator Rights: Creating Connections and Restoring Relationships, but neglected to do so. I would like to sincerely apologize to Dr Miller, as well as his coauthor, Glenn Sparks, PhD, for the omission. Their important work should not be overlooked.

In fact, page 17 of this issue of ATHM contains a review of Dr Miller’s book, written by Melyn R. Werbach, MD, associate editor of ATHM. Both Dr Werbach and I recommend the book whole-heartedly.

Mark Hyman, MD
Editor-in-Chief