

The 'Skinny' on Childhood Obesity: How Our Western Environment Starves Kids' Brains

First things first: This article is written to get you motivated enough to do something as a pediatrician, parent, and community leader. The big question: Who's to blame for our current childhood obesity and type 2 diabetes epidemic? Depends on whom you ask. The Institute of Medicine says it's an interaction between genetics and environment. Well, our genetics hasn't changed in 30 years, but our environment has. The body mass index distribution curve shows that all segments of the population are increasing in weight,¹ so whatever's

happening is happening to everybody. The U.S. Government calls it a matter of "personal responsibility." How does the 2-year-old population, who is witnessing the greatest increase in prevalence of obesity,² accept personal responsibility? The Centers for Disease Control and Prevention says obesity results from an energy imbalance, by eating too many calories and not getting enough physical activity. Big Food says it's a lack of activity, the TV industry says it's the diet. The Atkins people say it's too much carbohydrate, the Ornish people say it's too much fat. The juice people say it's the soda, the soda people say it's the juice. The schools say it's the parents, the parents say it's the schools. How are we going to fix this, when no one will accept responsibility? If you want to just blame American apathy and laxity, all you have to do is look at Japan, China, and France, each of which has witnessed a doubling in the prevalence of childhood obesity in the last 10 years, as well as the rise in prevalence in developing countries in which malnutrition used to be rampant.³ In other words, it's not Americans; it's humans.

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So far, it is just “guilt by association.” The not-my-fault two-step has so far succeeded, due to a lack of mechanism, which has allowed each interest group to sidestep their responsibility. So what really has happened in the past 30 years to allow for this? And how did our physiology interact with our environment to create this problem?

HOW WE INTERPRET THE FIRST LAW OF THERMODYNAMICS

The main reason for this conundrum is our casual misinterpretation of the First Law of Thermodynamics, which states: “The energy within a closed system remains constant.” In human terms, the First Law is usually interpreted as follows: “If you eat it (energy intake), you better burn it (energy expenditure), or you’re going to store it (weight gain).” This view is buffeted by studies of increased caloric intake in children,⁴ while other studies document decreased energy expenditure.⁵ This interpretation of the First Law is the source of the notion that obesity is a result of the pathologic behaviors of gluttony and sloth, and allows Government and Big Food to perpetuate the concept of “personal responsibility” for one’s behavior. However, this concept of personal responsibility is not tenable in children. No child chooses to be obese. Children with childhood obesity experience a quality of life commensu-

rate with children on cancer chemotherapy.⁶ Obese children are ostracized by their peers. Furthermore, young children are not responsible for food choices at home or at school, and it can hardly be said that preschool children, in whom obesity is rampant, are in a position to accept personal responsibility.

There is another equally plausible interpretation of the First Law, which is stated thus: “If you store it, and you expect to burn it, then you have to eat it.” In this interpretation, the behaviors of gluttony and sloth become secondary to a pathological process of excess energy storage. Could this instead be what’s happening? What is making energy storage go haywire?

LEPTIN, THE AUTONOMIC NERVOUS SYSTEM, AND ENERGY BALANCE

To understand dysfunctional energy storage, we must first understand how our body normally regulates energy balance⁷ (see Figure 1, page 901). Our energy intake vs. expenditure is normally regulated very tightly (within 0.15% per year) by the hormone leptin. Leptin is a 167 amino acid hormone produced by adipocytes, which transmits the primary long-term signal of energy depletion/repletion to the ventromedial hypothalamus (VMH), which controls energy balance.⁸

On transducing this leptin signal, the VMH does two things. First, the VMH increases the activity of the sympathetic nervous system (SNS).⁹ The SNS increases energy expenditure by: 1) innervating the hypothalamus and appetite centers in the medulla to reduce appetite to decrease further food intake, 2) increasing TSH secretion to increase thyroid hormone release and energy expenditure, 3) innervating skeletal muscles to increase energy expenditure, by stimulating the production of ATP for muscle contractility, and also by increasing uncoupling proteins within mitochondria, which increase heat loss from muscle, and 4) innervating beta₃-adrenergic receptors in white

adipose tissue to increase lipolysis. The magnitude of energy expenditure also has a salutary effect on one’s quality of life; those factors that reduce energy expenditure (eg, hypothyroidism) reduces quality of life, while those factors that increase energy expenditure (eg, caffeine) increase quality of life (at least acutely).

Second, the VMH reduces the activity of the vagus nerve, which serves essentially the opposite role of the SNS in the regulation of energy balance, as it promotes energy storage when activated. Vagus nerve activation 1) slows the heart rate, decreasing myocardial oxygen consumption, 2) increases peristalsis and energy substrate absorption in the intestine, 3) increases insulin secretion¹⁰ to increase energy clearance into adipocytes, and 4) increases adipose tissue insulin sensitivity to promote energy accumulation in fat.¹¹ So when leptin levels are high, the VMH senses energy sufficiency, and these vagal energy conserving and storing processes are inhibited.

Every human has a “personal leptin threshold,” above which the brain interprets a state of energy sufficiency. Thus, the leptin-replete state is characterized by high SNS and low vagal tone, leading to low appetite, normal physical activity, and feelings of well-being.

THE STARVATION RESPONSE

Conversely, in conditions of leptin depletion, such as in the “starvation response,” the VMH would of necessity decrease SNS tone (to conserve energy)¹³, with resultant decreases in activity and feelings of well-being, and increase vagal tone to increase appetite and insulin release (to store more energy in adipose tissue). In the energy-replete state, humans burn energy at 50 kcal/kg fat-free mass. However, in the starvation state, this is reduced to 40 to 42 kcal/kg fat-free mass;¹³ in other words, starvation results in a 20% increased efficiency of energy utilization, in an attempt to conserve energy.¹⁴ The result of these autonomic efferents is a rise

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in plasma leptin to restore the periphery and the brain to a state of leptin repletion, energy sufficiency, and improved quality of life.¹⁵

OBESITY IS THE SAME PROCESS IN THE CNS AS STARVATION

On first thought this sounds ludicrous, but in fact, it actually makes a lot of sense. If you examine the constitutional symptoms of obese and starved individuals, they are similar. Both are associated with fatigue, malaise, lack of activity, inability to motivate, and depression. The reason for this is the ability or inability for the VMH to transduce the leptin signal; in starvation because there is inadequacy of leptin, and in obesity because there is resistance to leptin, because it is obviously not doing its job. Furthermore, serum leptin concentrations drop precipitously during periods of short-term fasting (within 12 hours), declining faster than body fat stores,¹⁶ which would account for the recidivism of obesity; the hypothalamus is seeing a declining leptin signal similar to starvation, promoting increased energy intake and decreased energy expenditure. Similarly, giving leptin to obese leptin-resistant individuals is not effective.¹⁷

LEPTIN RESISTANCE AND SENSITIVITY

So what is leptin resistance? And what restores leptin sensitivity? So far, two paradigms for improving leptin sensitivity have been noted.

Forced weight loss

Rosenbaum et al,¹⁸ employed a 10% weight loss paradigm to induce the starvation response. In these individuals, leptin declined and energy expenditure decreased. However, exogenous administration of leptin in physiologic dosing to approximate the prestarvation leptin level resulted in further weight and fat decrease, along with return of energy expenditure to the prestarvation state. In other words, in the baseline state, sub-

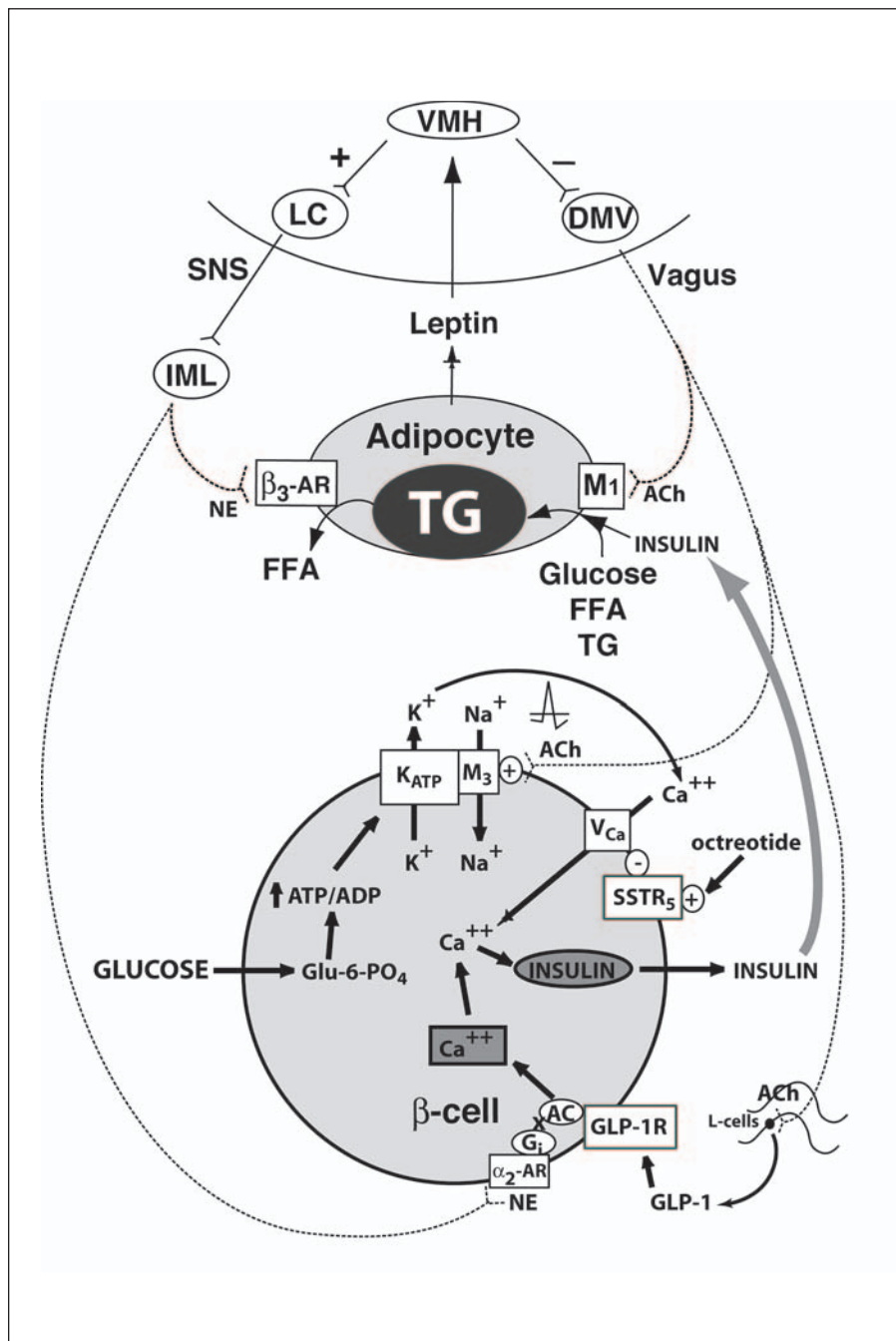


Figure 1. Autonomic innervation of the adipocyte, beta cell, and the starvation response. The ventromedial hypothalamus (VMH) transduces the peripheral leptin signal as one of sufficiency or deficiency. In the state of sufficiency, efferents from the VMH synapse in the locus coeruleus, which stimulate the sympathetic nervous system (SNS). SNS preganglionic motor neurons synapse in the intermediolateral cell column of the spinal cord. From there, postganglionic fibers emanate outward to white adipose tissue. There, norepinephrine (NE) binds to the beta 3-adrenergic receptor, which promotes lipolysis of stored triglyceride into free fatty acids (FFA) that are released. In the state of deficiency, the SNS activation is quiescent, reducing lipolysis. In addition, efferents from the VMH synapse in the dorsal motor nucleus of the vagus. From there, the vagus nerve emanates outward to white adipose tissue. Here, acetylcholine (ACh) binds to the M1 muscarinic receptor, which promotes uptake of FFA for lipogenesis and promotes triglyceride uptake from circulating lipoproteins. Secondly, the vagus innervates L-cells of the small intestine, which secrete glucagon-like peptide-1, stimulate adenyl cyclase, and increase the release of calcium bound inside the cell, contributing to insulin release.

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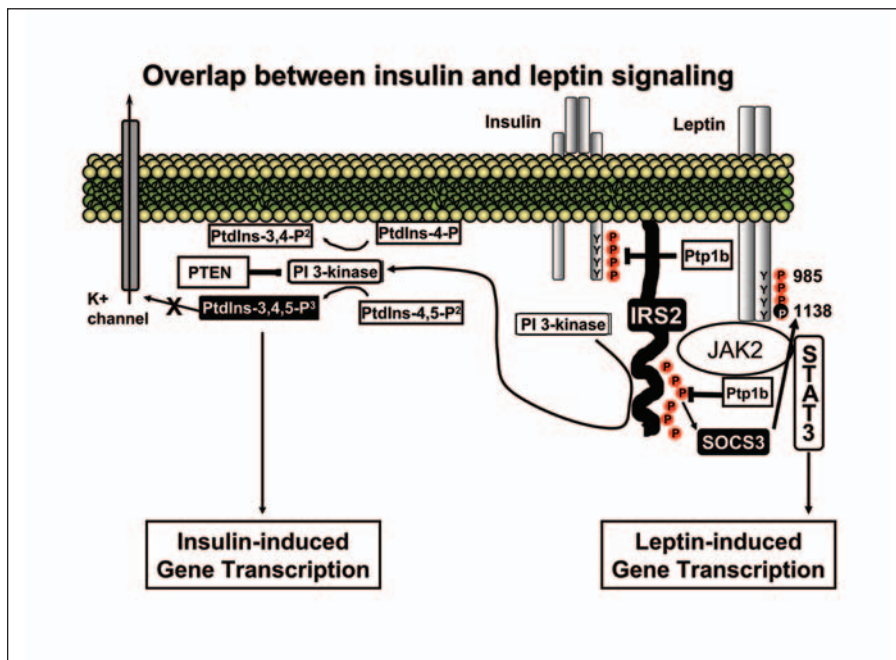


Figure 2. Overlap between insulin and leptin signaling pathways in the VMH neuron (in black). Both the insulin receptor and the leptin receptor recruit the low-abundance message IRS2. Insulin could tie off available IRS2. Lack of available IRS2 for the leptin receptor could result in defective leptin signal transduction. Alternatively, insulin induction of SOCS3 could inactivate the leptin receptor through dephosphorylation of tyrosine 1138 or 985. Finally, chronic insulin stimulation promotes excessive production of phosphatidylinositol triphosphate (PIP3), which prevents closure of the potassium (K⁺) channel and causes the cell to stop firing. (Figure adapted, courtesy of J. Kushner; from the American Heart Association)

jects were resistant to physiologic concentrations of leptin, while in the weight-reduced state, they were responsive to the same concentrations of exogenous leptin; thus, forced weight loss improved their leptin sensitivity.

INSULIN SUPPRESSION

We studied children who became obese after hypothalamic damage from brain tumors, surgery, or radiation, termed “hypothalamic obesity.” Death of these VMH neurons prevents normal leptin signaling, resulting in an “organic leptin resistance,” which manifests as a never-ending starvation response. Decreased SNS tone¹⁹ leads to decreased physical activity,²⁰ decreased energy expenditure, and decreased quality of life.²¹ Conversely, increased vagal tone leads to increased insulin secretion, promoting incessant energy storage into adipose tissue, and intractable obesity. Hypothalamic obesity is classically unresponsive to diet, exercise, and most pharmacologic

manipulations. We treated patients with the somatostatin analog and insulin suppressive agent octreotide.^{22,23} We were able to suppress insulin, stabilize BMI, decrease caloric intake, increase spontaneous physical activity, and improve quality of life commensurate with the degree of insulin suppression. In other words, reduction in insulin reduced hunger, fatigue, malaise, and sloth.

We then treated obese adults (without CNS lesions) with octreotide.^{24,25} We noted significant and progressive BMI loss in about 20% of treated subjects. Recall measurements of caloric intake demonstrated that these responders reduced carbohydrate intake selectively, along with suppression of insulin, while nonresponders did not. In the responders, leptin concentration dropped by 50%, which of necessity should elicit the “starvation response;” despite this, energy expenditure increased in these subjects. We also demonstrated that insulin suppression by octreotide correlated with improved leptin sensitivity.²⁶

WHAT IS THE MECHANISM OF LEPTIN RESISTANCE?

Rosenbaum et al,¹⁸ through forced weight loss, improved leptin sensitivity as measured by improved energy expenditure in response to leptin. Insulin suppression using octreotide also improved leptin sensitivity, as measured by declining leptin with improved energy expenditure, allowing for weight loss and improved quality of life. Both paradigms share at their core a reduction in insulin concentrations. The similarity of effect between these two paradigms suggest that insulin may be one cause of leptin resistance.

Insulin Antagonizes Leptin Signaling

Although insulin and leptin bind to separate receptors in the VMH, they share the same signaling cascade, called insulin receptor substrate 2 (IRS2)/phosphatidylinositol-3-kinase (PI3K)²⁷ (see Figure 2). It is thought that when insulin levels at the VMH are high, then leptin cannot turn on its signaling cascade. Experimental evidence in rodents suggest three separate cellular mechanisms that may account for this effect: 1) insulin excess ties up all the IRS2 and does not allow leptin to promote its signaling cascade,²⁸ 2) insulin induces the protein Suppressor of Cytokine Signaling 3 (SOCS3), which dephosphorylates and inactivates the leptin receptor,²⁹ and 3) insulin excess causes the buildup of the metabolite phosphatidylinositol triphosphate (PIP3), which stops the leptin-responsive neuron from firing.³⁰ In any case, chronic insulin blocks leptin signaling both in rodents and in humans.

Adaptive Advantage for Insulin as an Endogenous Leptin Antagonist

Teleologically, what could be the biological advantage of insulin antagonism of leptin action in obesity? Leptin is a necessary signal to the VMH for the initiation of high-energy processes, such as puberty and pregnancy. If leptin signaling

were not modulable, the weight accrual for reproductive competency during puberty and pregnancy would be compromised. Therefore, reversible antagonism of leptin action is in the best interest of our survival. Since insulin causes energy deposition into fat, it makes sense that it should be the central blocker of leptin as well. Indeed, both puberty and pregnancy are hyperinsulinemic and insulin resistant states,³¹ with requisite increases in insulin levels. In both, leptin levels increase slowly, and then when adulthood is reached or post-partum, insulin levels fall, weight stabilizes or is lost, and leptin returns back toward baseline.³² However, in maladaptive conditions when insulin rises chronically, leptin signaling continues to be impeded, the brain sees starvation, and obesity worsens.

WHERE DID THE HYPERINSULINEMIA COME FROM?

At least three separate reasons for hyperinsulinemia in children can be discerned. 1) *Genetics*: children from certain racial and ethnic groups have increased insulin dynamics even prior to the development of obesity, which may predispose them to increased weight gain.³³ 2) *Epigenetics*: the “fetal origins of adult disease” hypothesis states that those born small- and large-for-gestational age at birth are prone to developing obesity³⁴; both birth weight extremes are states of hyperinsulinemia and insulin resistance, which may worsen beyond the neonatal period. 3) Our Western environment through three separate submechanisms. A) Increased stress with increased cortisol secretion may lead to insulin resistance. Indeed, television watching may increase stress levels, increase food intake, foment insulin resistance (as in Cushing’s syndrome) and promote obesity.³⁵ B) The loss of daily physical activity due to lack of sidewalks, automobile transport, and screen time (TV, computers, cell phones) foments insulin resistance.³⁶ C) Finally, and most significantly, our current West-

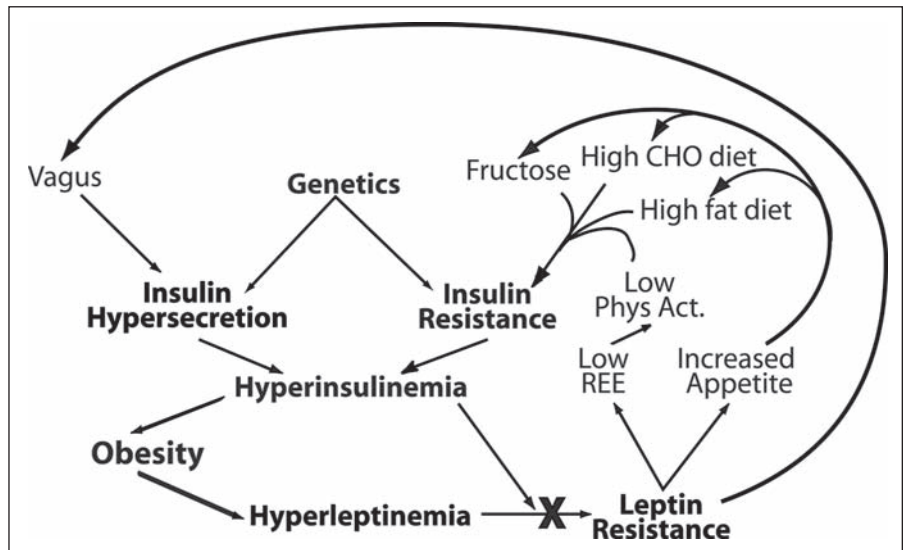


Figure 3. Postulated algorithm describing the role of hyperinsulinemia in the dysfunction of the energy balance pathway, by promoting energy storage in adipocytes, and by interfering with leptin signal transduction in the hypothalamus, which turns a negative feedback pathway into a vicious cycle. (Courtesy of the American Heart Association, with permission)

ern food environment is highly insulino-genic, as demonstrated by its increased energy density, high fat content, high glycemic index, increased fructose composition, decreased fiber, and decreased dairy content.³⁷ In particular, fructose (too much) and fiber (not enough) appear to be cornerstones of the obesity epidemic, through their effects on insulin.

The most commonly used sweetener in the U.S. diet is the disaccharide sucrose (ie, table sugar), which contains 50% fructose and 50% glucose. However, in North America and many other countries, non-diet soft drinks are sweetened with high-fructose corn syrup (HFCS), which contains up to 55% of the monosaccharide fructose. Thanks to its abundance, sweetness, and low price, HFCS has become the most common sweetener used in processed foods. It’s not that HFCS is biologically more ominous than sucrose; it’s that its low cost has made it available to everyone, especially low socioeconomic groups. HFCS is found in processed foods ranging from soft drinks and candy bars to crackers to hot dog buns to ketchup. Average daily fructose consumption has increased by over 25% over the past 30 years. The growing

dependence on fructose in the Western diet may be fueling the obesity and type 2 diabetes mellitus epidemics.³⁸ Animal models demonstrate that high-fructose diets lead to increased energy intake, decreased resting energy expenditure, excess fat deposition, and insulin resistance, which suggest that fructose consumption is playing a role in the epidemics of insulin resistance and obesity and type 2 diabetes mellitus in humans.³⁹ The metabolism of fructose differs significantly from glucose. Fructose is absorbed in the intestine and enters the liver without insulin regulation. There, fructose is converted to fructose-1-phosphate and enters the glycolytic pathway without regulation. This leads to an excess accumulation of acetyl-CoA in the hepatocyte, which cannot be metabolized through the Krebs cycle; therefore it is then reassembled into free fatty acids (which promote insulin resistance), very low-density lipoproteins (VLDL, which promote atherogenesis and serve as a substrate for obesity), and triglycerides (some of which precipitate in the liver and cause non-alcoholic steatohepatitis). Fructose also does not suppress secretion of the so-called “hunger hormone” ghrelin, levels of which cor-

relate with perceived hunger. In sum, fructose consumption has metabolic and hormonal consequences that facilitate development of obesity and its complications. The highest fructose loads are soda (1.7 gm/oz) and juice (1.8 gm/oz).

Our Western diet also tends to be poor in fiber, which may be one of the characteristics that link it to obesity and insulin resistance. Cohort studies of young and middle-aged adults demonstrate that fiber intake is inversely associated with weight gain, fasting insulin levels, and risk of type 2 diabetes mellitus.⁴⁰ Fiber intake may be mechanistically linked to obesity through its effects on glycemic index and energy density. Generally, high fiber foods have low energy density and glycemic index (fiber content accounts for 50% of the variability in glycemic index between foods). But fiber may also influence obesity risk through distinct hormonal and digestive mechanisms. High-fiber meals tend to be more satiating as they induce a greater sensation of fullness than low-fiber meals. Fiber content also tends to add bulk and viscosity to meals, thereby slowing gastric emptying. Fiber-containing foods slow intestinal glucose absorption, which lessens the post-prandial insulin rise and decreases lipogenesis.⁴¹ Why is the Western diet fiber-poor? Because you can't freeze and reheat fiber (try it yourself with a bowl of brown rice). Fast food must be shipped to franchises around the world, thus the fiber must be removed first. Fiber also means food depreciation due to spoilage (economically undesirable), while processing away fiber insures you can freeze it and that it will last forever.

HOW DO YOU GET THE INSULIN DOWN?

This is a difficult proposition, especially given the current "toxic environment." The UCSF Weight Assessment for Teen and Child Health (WATCH) Program advocates four simple rules for treating obesity by bringing the insulin down. 1) Get

rid of every sugared liquid in the house.⁴² This means soda, juice, Kool-Aid, sports drinks, etc. Look at the bottle: five calories per serving or less is OK; six or more, leave at the store. 2) Eat your carbohydrates with fiber. White food (bread, rice, pasta, potatoes) is fiberless food. Brown food (brown rice, beans, lentils, peanuts, other legumes) is high-fiber food.⁴³ Alternatively, look at the dietary fiber content: 3 g or more per serving is adequate. 3) Wait 20 minutes for second portions. This takes advantage of another hormone called peptide YY located in the distal intestine, which acts as the satiety signal, preventing that second portion, and further insulin rise.⁴⁴ 4) Get the TV out of the kid's room. And kids should buy their TV time minute-for-minute with activity. Since when did TV watching become a child's right?⁴⁵

SUMMARY

In this review, the mechanism of our "toxic environment's" effects on insulin and weight gain in the genesis of obesity is elaborated. The composition of our diet is highly insulinogenic. The insulin drives energy into fat, and interferes with leptin signaling in the VMH. This results in weight gain and the sense of starvation, which results in decreased SNS activity, reducing energy expenditure and physical activity; and increased vagal activity, which promotes yet further insulin release and energy storage. Thus, hyperinsulinemia turns the leptin negative feedback system into a "vicious cycle" of obesity (see Figure 3, page 905). Externally, this appears as "gluttony and sloth," but it is biochemically driven.

How does this work? A thin, insulin-sensitive, 13-year-old boy might consume a daily allotment of 2,000 kcal, and burn 2,000 kcal daily (or 50 kcal/kg fat-free mass) in order to remain weight-stable, with a stable leptin level. However, if that same 13-year-old became hyperinsulinemic and/or insulin resistant, perhaps as many as 250 kcal of the daily

allotment would be shunted to storage in adipose tissue, promoting a persistent obligate weight gain. Due to the obligate energy storage, he now only has 1,750 kcal per day to burn. The hyperinsulinemia also results in a lower level of leptin signal transduction, conveying a CNS signal of energy insufficiency. The remaining calories available are lower than his energy expenditure; the CNS would sense starvation. Through decreased SNS tone, he would reduce his physical activity, resulting in decreased quality of life; and through increased vagal tone, he would increase caloric intake and insulin secretion, but now at a much higher level. Thus, the vicious cycle of gluttony, sloth, and obesity is promulgated.

Is this personal responsibility, when a kid's brain thinks it's starving? Is it personal responsibility when the American Academy of Pediatrics still recommends juice for toddlers? Is it personal responsibility when the Women, Infant and Children program subsidizes fruit juice but not fruit? Is it personal responsibility when the first ingredient in the barbecue sauce is high-fructose corn syrup? Is it personal responsibility when high-fiber fresh produce is unavailable in poor neighborhoods? Is it personal responsibility when the local fast food restaurant is the only neighborhood venue that is clean and air-conditioned? Is it personal responsibility when in order to meet the criteria for No Child Left Behind, the school does away with physical education class? Is it personal responsibility when children are not allowed out of the house to play for fear of crime? We must get the insulin down. Fixing the "toxic environment" by altering the food supply and promoting physical activity for all children can't be done by government, and won't be done by Big Food. This will require a grassroots, bottom-up effort on the part of parents and community leaders. We as pediatricians must lead the way.

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