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Medical publishing is so far dismissing the information presented in this paper. Many of you already sense what is said here. You just need scientific confirmation, making it all the more important that it be made available to you, because it could save your life. The synopsis is followed by the complete review article.

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#### REVIEW ARTICLE:

CHRONIC ILLNESS AS AN IMMUNE FUNCTION OF NUTRITION:  
A NEW DISEASE MODEL AND ITS TREATMENT  
From Empiricism to Biochemical System

#### SYNOPSIS

We used to think that that overweight was linked mainly to risk of heart disease and diabetes, and other illnesses were random events. Research shows us otherwise:

Most illnesses are manifestations of the same basic process: Activation of the immune system by environmental stressors resulting in inflammation.

So what stressors activate the immune system to create inflammation? We already know that microbes do, the resulting immune activation is called infection (also an inflammation), so do toxic substances and gases, i.e. lead, alcohol and asbestos, cigarette smoking, we now also recognize that the brain communicates with the immune system, and mental stress is an immunotoxin.

What we don't understand yet, is that certain edibles are immune triggers. There is a plethora of studies showing that sugar and bad fat and their downstream metabolites activate the immune system.

Though we use it as one, sugar is not a food group. It is the mother of all edible immunotoxins, and starts the following biochemical reaction once in our system:

sugar-> insulin-> fat-> activation of the immune system-> inflammation-> illness

The resulting illnesses manifests differently because of our genetic predisposition for certain illnesses, location in the body and the nature of the stressor.

Pathological specimens confirm this by showing the immune system prominently represented in inflammation.

What does this mean to us?

It means that we need to avoid sugar at all cost if we want to stay healthy. The snag here is that it is also very addictive. In other words, we are addicted to illness.

The other snag is that there is no use in blaming soft drinks, fructose or whatever else we come up with. Sugar appears in many guises, and we need to recognize them all or we'll just switch sugar of choice.

Worse yet, the medical treatments for these illnesses do not make us well, in fact, some of them increase our risk of complications, including death. This is the bad news.

The good news is that the immune system can be de-activated by removing the sugar. This reverses the inflammation and heals the body. A plethora of studies confirm that if we can beat sugar, we can and heal you ourselves of most chronic illness

Some 40% of all health care resources in the US spent treating an unnecessary illness, diabetes type 2, and the numbers are projected to bankrupt health care, reform or not.

We know what good nutrition can do, the research is there. The Food Tree or a similar program will restore normal weight and health. I devote my time to helping patients do this. The results are quick and striking.

How long, Lord, how long, before we accept the inevitable facts?

## FULL REVIEW ARTICLE:

### THE PROBLEM

Chronic illness accounts for some 75% of health spending in the US (1). The World Health Organization estimates that 80% of these conditions are preventable by lifestyle. We have established that inflammation related to adipocytes (adipocyte dysfunction) is a common denominator of a growing number of chronic illnesses (2), first recognized and described in clusters as syndrome X and Metabolic Syndrome (MBS) (3, 4, 5).

As an empiric or evidence (experience)-based science, medicine describes and treats these unrelated events.

The collective body of medical research available at this time tells us otherwise: The etiology and pathophysiology of inflammation is a system where disease process, outcomes and interventions can be predicted.

This review shows a new model of the pathophysiology of illness as a predictable system of biochemistry, physiology and immunology. The model demonstrates that nutrition is one of the basic determinants of health. It shows the effects and shortcomings of treating individual symptoms, and how prevention, even reversal is achievable by reversing inflammation through nutrition (6, 7).

### THE BODY AND THE IMMUNE SYSTEM

The human body, in a computer-like fashion, is operated by messenger molecules that are pre-programmed to work through signals such as kinases that again are pre-programmed to effect specific outcomes (8). These messengers are set in motion by a constant bombardment by outside stimuli, and the body must sort out friend from foe. It does so by presenting them to the immune system. The nature of the stimulus vs. the genetic predisposition of the individual (genetic polymorphism) and the strength of the immune system determines the outcome. We are thus subject to a form of biochemical destiny. Helpful stimuli boost the immune system, while harmful ones challenge it. These immune stressors are as diverse as pathogens, damaged cells, irritants, cigarette smoking, UV radiation, mental stress and metabolites, collectively called mitogens or immunogens. They work via signaling systems such as Mitogen Activated Protein (MAP)-kinases that are implicated in cell growth and division, inflammation and tumor gene transcription (9). The first line of defense by the immune system against injurious stimuli comes from monocytes, macrophages, and mast cells. They are lined up at the body's interfaces with the environment poised to attack by producing immune modulating agents called cytokines (immunokines), particularly Tumor Necrotic Factor (TNF) and interleukin 6 (IL-6). The response results in a complex process known as inflammation. The more noxious the stimulus, the more immune cells are recruited, and the second line, the so called acute phase reactants are recruited locally and from the liver. The immune system fights until death or till the intruder is defeated. If the stimulus persists, the inflammatory

response becomes systemic and chronic, involving the vascular and other systems. Prolonged unresolved inflammation may cause tissue damage (8, 10). Because defense is critical to its survival, the body operates with a second defense mechanism, the eicosanoid system, which is activated by the same mitogens, and works through fatty acids capable of both anti-inflammatory and inflammatory effects; the latter partly mediated by the pro-inflammatory omega 6 eicosanoids. They act in concert with, and augment the inflammatory response of the cytokine system. (8, 11, 12, 3).

## INSULIN

Insulin is our major anabolic hormone, regulating synthesis, storage and most other cell processes including the regulation of sex hormones and the production of eicosanoids (14, 15). This actually means that insulin regulates part of our immune system. Insulin is produced from two peptides of pro-insulin, yielding one molecule of insulin to one of C-peptide. Mainly released in response to sugar, insulin delivery is intricately designed in order to avoid down regulation of receptors, and the insulin-glucose curve is tightly regulated (16). The amount of insulin required to process sugar varies throughout populations to up to six fold in apparently normal subjects. The high insulin producers are insulin resistant (IR) to varying degree and at risk for inflammatory illness because high insulin is mitogenic, as is high C-peptide (17, 18, 19, 20, 21, 22, 23, 24, 25).

## SUGAR

Carbohydrates are sugar molecules in varying bonding, from single molecules to complex molecular structures known as fiber. The area under the glucose response curve after consumption of 50 g carbohydrate is measured on the Glycemic Index (GI) scale, expressed numerically from 0 to 100 (26). In general, the more manipulated, or refined, the sugar, the higher the GI. Since human beings lack the enzymes to break down certain plant fibers, they are at the lower end of the scale. Glucose tops the scale at 100. Our sources of sugar used to be high fiber plants like fruits and vegetables, which yield low to medium GI, but we have learned to refine grain and other plants to yield high GI products. They constitute a main food group in our culture. When we eat these, we start a complicated biochemical reaction of raising insulin and its byproduct C-peptide. Continued overeating on sugar may lead to exhaustion of insulin production, elevated blood sugar and Advanced Glycation End (AGE) products, which in turn are ligands for AGE-receptors throughout the body (RAGE). High sugar, AGE and RAGE are mitogenic (27, 28, 29, 30, 31, 32). The amount of sugar eaten in one meal may be enough to trigger the mitogenic effect of sugar (33, 34, 35).

The interplay of these metabolites is expressed in the Glucose-Insulin curve (p.4). It also demonstrates the potential of sugar for physical dependency and addiction, mediated by the same pathways as is opiates (36, 37) Here is an interesting correlation between sugar and its fermented form, alcohol: Sugars strong enough (GI 40 and above) to be fermented into alcohol are strong enough to be addictive.

## FAT.

The obvious source of fat is that eaten, but in our glucocentric culture, sugar is our main source of fat because any surplus sugar is converted to fat starting immediately upon its ingestion. The importance of this relationship cannot be overestimated, because sugar metabolism determines that of fat and cholesterol, thereby running the metabolic process that determine our health and weight. Our obsession with low-fat diets only accentuates the problem by inadvertently increasing sugar intake (38). In conditions of insufficient insulin, lipolysis of stored triglycerides (TG) yield glycerol and increased free fatty acids (FFA). TG and FFA are mitogens (14, 39, 40, 41, 42, 43).

Body fat increase and metabolic illness are not limited to those who become overweight by conventional measures ( BMI) (44), but is also found in as many as half of normal weight individuals. Because of high body fat relative to their total weight (Normal Weight Obesity) they are at high risk for metabolic illness. Small increases in weight, in fact, in the individual meal composition, can be inflammatory. (45, 46, 47). Enlarged body fat cells produce leptin, which is mitogenic as well (2). Cholesterol is our pool of specialized fat for many important bioactive molecules and maintaining cell membranes. Made during times of plenty from acetyl-coA (activated sugar), its metabolism is ultimately run by insulin (48, 49, 50). Rather than levels, the issue with cholesterol is homeostasis. Mostly bound to protein molecules for transport, LDL brings cholesterol to the cells. HDL returns excess cholesterol to the liver. HDL is also a carrier of excess TG, which may displace LDL, the latter being relegated to the immune system for removal. Under conditions of high sugar, TG-enrichment of HDL increases HDL-clearance to produce an inverse relationship between the two. This leads to a deficit of the anti-atherogenic HDL (51, 52, 53, 54). HDL levels are inversely related to cancer risk (55).

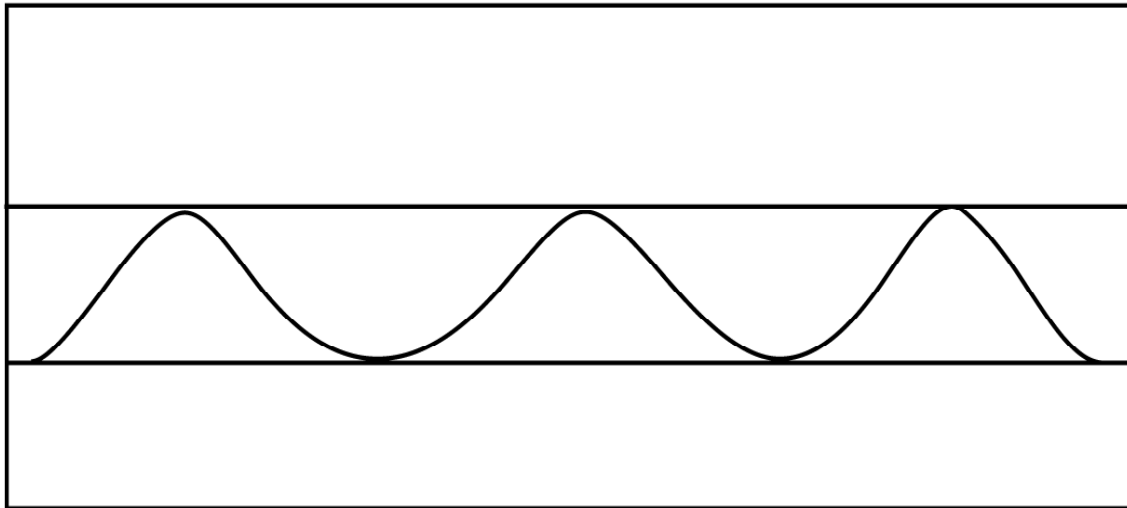
All the metabolic processes described here effect increased production of Reactive Oxygen Species, which of themselves have mitogenic effect. (56, 57, 58).

We have now seen that the body recognizes most sugar and fat related metabolites in excess as mitogens or immunotoxins.

Now let us look at their effects on the body when they activate the immune system

## FOOD, METABOLISM AND THE IMMUNE SYSTEM.

When eating, we write a curve over time of blood sugar combined with the resulting insulin production (59, 36, 60). The conceptual composite (stylized, non- numerical) sugar-insulin curve is represented below:



## Maintenance: Three Balanced Meals Per Day

The horizontal lines represent the upper and lower frame of the Glucose-Insulin window. The upper frame represents the top of the glucose-insulin load that maintains our weight. The lower frame is our blood sugar troughs between meals. The curve is thus our weight thermostat

As long as we eat well balanced meals low in sugar, the glucose curve oscillates gently within this window, writing for normal blood sugar, normal satiety and hunger and stable body weigh.

Upon ingestion of high sugar we raise the curve above the upper frame of the window to create a dumping-type syndrome with high loads entering the cell, overshooting and creating large swings in blood sugar to destabilizing blood sugar, mood, energy and creating extreme hunger at the troughs (60). This makes it a physical dependency curve.

The transformation of ingested sugar to triglyceride starts immediately, and so every time the curve exceeds the G-I window, we increase fat in the body. Moreover, the body registers the increased metabolites as mitogens, activating the immune system.

We now have a trigger-sequence or loop:

High sugar - high insulin/C- peptide - high fat - activation of the immune system – inflammation- any inflammatory disorder +/- IR group of illness, the latter may cause high sugar.

This sequence implies that the inflammatory chain can be started at any link since they are all mitogens in their own right, and that they may produce any inflammatory

disease including IR. It also implies that the G-I curve is a determinant of our inflammatory status, and thus of our health.

We see that at normal weight and good nutrition, sugar, fat and their co-metabolites are peaceful co-riders. In excess they become immunotoxins and are pro-inflammatory. The G-I curve depicts this relationship. If the toxins persist, there is an inflammatory stalemate between these immunologic stressors and the two-pronged immune system. This is the basis of nutrition-based chronic illness

## INFLAMMATORY PATHWAYS

If we look at inflammatory illness in purely biochemical terms, we can trace the gluco/lipotoxic activation of the immune system through their cascade of interwoven reactions to produce the final inflammatory pathway of biochemical abnormalities, manifest in a plethora of seemingly unrelated clinical presentations from asthma to cancer (61, 62).

The inflammation is mediated by macrophages through the activation of MAP kinases, such as (ERK), Jun kinases (JNK) and IKK-Beta, which are major mediators of pro-inflammatory immunokines (9, 63, 64, 65, 66, 67, 68). The response is proportional to the stressor (69) and tailored to the mitogen whether it is seen as an attacker (70), a case of mistaken identity (71) or a wayward metabolite (72).

Since the original mitogenic trigger is overfeeding, a common feature of the inflammatory response is to protect the body against more by restricting glucose transportation into the cell, which raises insulin (73, 74, 75). This is Insulin Resistance (IR) and is largely mediated by the pro-inflammatory macrophageal kinases at several levels including blocking GLUT 4 translocation, receptor-mediated signal transduction and substrate sensitivity (76, 77, 78, 79, 80, 81, 82, 83). Aside from being mitogenic, the high insulin causes continued down regulation of receptors. Increased C-peptide, a mitogen as well, co-localizes with macrophages and may accelerate inflammation (84).

In the scenario of unyielding sugar intake, IR may progress to diabetes type 2 (DM2), characterized by rising blood sugar, AGE, triglycerides, free fatty acids, weight gain, rising cholesterol, overload of the cholesterol removal system, lowering of HDL leaving the displaced LDL to bond with AGE. The RAGE-bound LDL is a potent mitogen, activating MAP-kinases and augmenting vascular toxicity. (51, 85, 86, 87, 88). Insulin production wanes. The immune system continues to shut down glucose transport, while seeking to destroy mitogens and anything they are attached to (89, 90). The inflammation becomes chronic and systemic, augmented by liver-based cytokines that contribute to the characteristic process of simultaneous destruction and healing with permanent tissue damage.

In short, inflammatory illness is the immune system gone amok blindly trying to rid the body of intruders.

Considering the cumulative effects of the mitogens unleashed by dysglycemia and carried by the cardiovascular system,, it is not surprising that any elevation of long term blood sugar carries increased risk for inflammation of target cells all through the body including the endothelium of the cardiovascular system itself, and that diabetes is a cardiovascular equivalent. One could argue that cardiovascular disease (CVD) is a circumstance of vascular inflammation fueled by sugar metabolism and cholesterol-removal gone awry (51, 88, 91).

There is an inconstant relationship among the constituents of chronic disease: Some two thirds of Americans are overweight, one third obese and one third is IR, Inflammation is positively correlated with IR but not with weight. TG and insulin concentration are markers for IR. High blood sugar, insulin and triglycerides are all so called independent risk factors for CVD. They are also the links of the inflammatory trigger equation on page 4. The only correlating cholesterol level, low HDL, underscores the interconnectedness of the risk factors.

DM2 and CVD show a linear risk relationship with blood sugar, triglycerides and insulin, but not with weight and other conventional risk factors. (92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103).

Genetic predisposition and polymorphism along with immune of the properties of the mitogens and the host and intensity of exposure may explain the different manifestations of illnesses and their complications (104).

Edibles are the unrecognized group of environmental immunotoxins. Microbes are triggers of infectious disease, air borne toxins encounter the immune system through the lungs: Mental stress is a well known inducer of illness. Many are of mixed origin: High blood pressure is influenced by salt intake, asthma is exacerbated by cigarette smoke. Whatever the trigger, the final common pathway is inflammation, making most chronic illness inflammatory in nature. Lowering the glucose-insulin curve brings improvement in these conditions.

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## A NEW DISEASE MODEL AND ITS TREATMENT

We now have a multifactorial physiological mechanism engaging the immune system. With respect to edibles, the trigger is sugar or fat, the unifying final common pathway being the activation of macrophages and other immune cells, known as inflammation, again leading to a seemingly bewildering array of clinical presentations. This disease model shows the glucose-insulin curve as a major determinant of weight, health and illness.

These so-called metabolic or chronic illnesses, far from being intrinsic metabolic problems, are the results of our not heeding the laws of the GI curve and our metabolism. Sugar is the mother of all metabolic immuno-toxins, inviting a more descriptive name to these conditions: Sugar Eaters' Syndrome.

Chronic illnesses may be triggered at any link in the inflammatory sequence, and by

small increments in insulin sugar and fat, with MBS being a top of the iceberg. Most recognizable are clusters of IR, diabetes, cardiovascular disease, hypertension, nonalcoholic liver disease, polycystic ovarian, sleep apnea, possibly age-related diseases such as Alzheimer's. However, the inflammatory response may manifest as diversely as acne, asthma, allergies, arthritis, eczema, migraines, depression, gingivitis, inflammatory bowel disease, low testosterone, multiple sclerosis, rheumatoid arthritis, glomerulonephritis, congestive heart failure, dementia and stroke. In short, most chronic illness (61, 89, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118) Over time or for other regulatory reasons the immune system may overreach, resulting in auto-immune disease such as diabetes mellitus type 1, thyroiditis, rheumatoid arthritis sarcoidosis, psoriasis (119, 120, 121, 122, 123) The chronic turnover of an array of inflammatory agents and body cells may leave openings for mutation or other dysregulation including cancer (62, 124, 125, 126, 127, 128, 129, 130).

The body prioritizes its energy according to the task at hand. Any illness diverts energy to the immune system, which might explain the insidious low energy often experienced in chronic illness (131). High insulin secretion is linked to decreased motivation to exercise. (132).

Our sugar-based diet is as low in micronutrients as it is in macro-nutrients, creating a culture of malnourished Americans. Aside from an overweight, ill adult population, we are seeing metabolic illness of the middle aged in toddlers as well as an alarming number of brain-developmental disturbances in young children (133, 134, 135, 136, 137, 138, 139, 140). These conditions parallel the documented lack of Mg, K, CA, vitamin D and omega-3, the latter being crucial for brain development and function. This sets the stage for double-barreled brain inflammation. Their treatment with psychotropic drugs add to the problem. (141, 142).

In terms of studying chronic illness, dysglycemic conditions are most instructive because they show a clear relationship to the intake of sugar. Also, the course and effects of treatment can be observed over time by tracing blood sugar. Furthermore, medicine is grappling to explain the lack of success in treating chronic illness, in particular the deleterious effects of intensive treatment of DM2.

Looking at the biochemistry we can now see why:

DM type 1 is an inflammation-based auto-immune disorder leading to the destruction of the pancreas. In the untreated diabetic type 1 sugar is high while insulin is absent and the G-I curve is destroyed. RAGE dominates. Complications develop slowly. RAGE is thought to be causative in most complications including small vessel disease, neurologic problems and generalized arteriosclerosis (143, 144).

While our current capacity for insulin replacement improves outcome, our attempts to restore the G-I curve by exogenous insulin are crude at best, creating an erratic curve, often outside the window. Intensive insulin-treatment is not precise enough to solve the overproduction of RAGE, causes hyperinsulinemia, receptor down regulation,

increased IR, eicosanoid inflammation, oxidative stress and weight gain (145, 146, 147, 148, 149, 150, 151, 152). Tissue replacement or the perfectly nature-mimicking insulin-delivery system would restore the curve and alleviate the disease.

DM2 is a condition of overfeeding starting with IR, defined by high insulin and high C-peptide. This raises the G-I curve effecting fat/weight gain and eicosanoid inflammation. The increased C-peptide of IR, may contribute to accelerated CVD (153). Progression to diabetes type 2 is fueled by high sugar intake, inflammation and worsening IR. Blood sugar rises, insulin wanes, high RAGE, TG, low HDL and RAGE-bonded LDL aggravate inflammation and CVD. The course of DM2-related CVD might be more protracted than previously thought due to the positive correlation between IR and CVD and their silent, chronic nature.

The unique combination of hyperglycemia and catabolic state of diabetes suggest a dominant glucagon-like effect, but insulin trumps that. The fasting insulin state of DM2 is never complete and lipogenesis/lysis at fat cell level (normally marked by a high degree of futile cycling) is ongoing, resulting in enough FFA being re-deposited to preserve or to increase weight (48,154,155).

The ROS created in these processes adds to the inflammation.

Looking at the biochemistry involved we can now deduce why the medical treatment is problematic: IR and DM2 are the growing self-defensive resistance to sugar and insulin, and so ever more is needed to literally force feed the resisting body.

Treatment with insulin sensitizers will produce increased sugar uptake, weight gain and increased inflammation, depending on the strength of the agent.

Treatment with insulin secretagogues will lead to increased insulin and C-peptide production, weight gain, inflammation and accelerated CV-complications. (24, 153)

Early insulin will delay the exhaustion of the pancreas, but there will be mismatch with down regulation of receptors, weight gain and inevitable deterioration.

Exogenous insulin treatment will slow endogenous insulin and C-peptide production, but the insulin whatever source is mitogenic. It will cause further insulin receptor down regulation, increase insulin requirements, aggravating IR, overweight, inflammation and CVD. We already know that intensive medical treatment of DM2 increases mortality. (156, 157, 158, 159, 160, 161, 162, 163, 164).

Numerous studies have confirmed the linear relationship between HbA1C and risk of adverse outcome. The course of DM2 is progressive regardless of medical therapy (165). Selecting for late stage disease and intensive therapy we see a U-shaped risk curve peaking at high HbA1C, and then at low HbA1C, suggesting that insulin needed to bring advanced disease under tighter control in the setting of longstanding inflammation and high IR imposes an added inflammatory burden as deleterious as that of chronic high glucose/RAGE.

Our current evidence based approach to all chronic illness is long on cost and short on results. No one gets well. We are caught in a spiral of slow deterioration and the need for ever more medication and treatments including pills, diets, liquid fasts, surgery and other stop-gap measures.

Meanwhile the complex nature of inflammatory process eludes treatment of end-organ manifestations (i.e. an inhaler for asthma) because it will not address the cause.

The mechanisms as outlined here are so diverse, complex and so profoundly tied to our very biochemical makeup that the idea of any “blocking-action”- cure at the level of any particular metabolic stage, i.e. anti-JNK-kinase, anti-TNF, resveratrol etc. is an expression of having missed that point. We are already able to block mitogenic effects, but alternate metabolic pathway renders the block incomplete, and there is often a price to pay for the effect achieved (166, 167).

Chronic illness account for some 75% of the 2.5 trillion dollars spent per year on healthcare in this country. The results of this effort are sadly disproportionate to the effort (168, 169) and the US is behind most industrialized countries in overall health status. We are implementing health care reform, but our current approach is not sustainable because it misses this point (170).

Rather than interventions that increase tolerance of a toxin, the remedy for a toxin is its removal. Removal of excess sugar and fat avoids activating the immune system and reverses the inflammation, thereby its manifestations. There is a plethora of studies confirm the swift reversal of inflammation on the clinical as well as molecular level by this approach The list of diseases ameliorated by nutrition is impressive and probably justifies the 80% estimate of reversible illness made by the WHO (170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182,183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195).

In summary, we can now see that illnesses are caused by environmental toxins overwhelming the immune system, our most prevalent toxins being sugar and bad fat because we call them foods. We also understand that medical treatments are not curative, and may increase risk of morbidity and mortality. We also understand that chronic illnesses respond to removing the toxins, i.e. sugar and fat. That leaves us with the moral and financial imperative to inform ourselves and our patients accordingly, and respond to this epidemic by undertaking a paradigm and resource shift from our ever burgeoning model of fostering chronic disease to result-based interventions. That means finding ways to implement the healing changes to our food culture as a whole.

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