Sugar Toxicity
The Silent Epidemic

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Sugar Toxicity - A Silent Epidemic
A view from the trenches of daily primary integrative medical praxis

Sugar is the generalized name for sweet, short-chained soluble carbohydrates. Carbohydrates are composed of carbon, hydrogen and oxygen (basically carbon + water). The term sugar refers loosely to a number of different types of carbohydrates, including monosaccharides (glucose, fructose), disaccharides (sucrose, lactose), oligosaccharides and polysaccharides (common components of glyco-proteins and glyco-lipids). The most biologically important and well known monosaccharide is glucose. Glucose is the main source of energy fueling aerobic metabolism... a fundamental necessity of living mammalian cells. The most common disaccharide is sucrose (glucose + fructose) or common table sugar. Bio-polymers (oligo and polysaccharides) of sugar are common structural forms of carbohydrates in nature. Plants produce sugar and sugar bio-polymers through the process of photosynthesis. These bio-polymers are converted into structural polysaccharides, such as cellulose and pectin found in plant cell walls. They also may serve as a form of energy storage, such as starch or inulin. In addition, DNA and RNA are polymers of the monosaccharides deoxyribose and ribose respectively and constitute the basis of genetic blueprint and memory for almost all forms of life. The importance of sugar in its various functional and structural forms for life cannot be overstated. However, like Oxygen, which is both essential for most life forms and also extremely toxic to life (physiologic function versus toxic free-radical damage), sugar also has a dark side for living tissue.

Studies in animals and humans have suggested that chronic consumption of added sugar contributes to metabolic and cardiovascular dysfunction. There is also growing evidence that added fructose is more damaging than refined glucose in terms of cardiovascular risk. [1] Cardiac performance has been shown to be impaired by switching from a low carbohydrate diet including fiber to a high carbohydrate diet.[2] Switching from saturated fatty acids to carbohydrates with high glycemic index values shows a statistically significant increase in the risk of myocardial infarction.[3] Other studies have shown the risk of developing coronary heart disease is decreased by adopting a diet high in polyunsaturated fatty acids and low in sugar, but a low fat, high carbohydrate diet showed no reduction.[4] This suggests that consuming a diet with high glycemic load (“high glycemic” = causes a rapid rise in blood sugar) is strongly associated with the development of coronary artery disease.[4] The consumption of added sugars has been positively associated with multiple measures known to increase cardiovascular disease risk in adolescents as well as adults.[5] Multiple studies suggest the impact of refined carbohydrates or high glycemic load carbohydrates is more significant than the impact of saturated fatty acids on cardiovascular disease.[6-26] In addition, a connection between Alzheimer’s disease and fructose has been suggested, but remains the subject of debate.[27,28] Finally, the possible addictive effects of refined sugar simply adds to the scientific concern regarding the toxic effects of sugar in the development of cardiovascular disease.[29]
**Glycocalyx**

One of the lesser known structural/functional physiologic aspects of sugar is the glycocalyx. The glycocalyx is a polysaccharide sugar polymer coating that surrounds all cell membranes.[30-32] This “sugar” coating consists of several carbohydrate moieties of structural membrane glycolipids and glycoproteins which serve as a backbone for support and cell to cell communication. Pischinger’s Matrix Theory of rapid cell to cell communication is centered on the functional aspects of the glycocalyx. (Pischinger A. Matrix and Matrix Regulation Basis for a Holistic Theory in Medicine [English Edition]. Haug International, Brussels. 1991). This carbohydrate (“sugar”) portion of plasma membranes contributes to cell-cell recognition, communication and intracellular adhesion.[30] The slime on the outside of a fish is a common example of a glycocalyx. **It is essentially a functional “bio-film.”** The term glycocalyx was initially applied to the polysaccharide matrix coating epithelial cells, but its functions have been discovered to go well beyond that. The glycocalyx plays a major role in regulation of endothelial vascular tissue, including the modulation of red cell volume in capillaries.[33] It is located on the apical surface of vascular endothelial cells which line the lumen of all blood vessels and may be up to 11um thick [34,35] It is present throughout a diverse range of micro-vascular beds (capillaries) and macro-vessels (arteries and veins). The glycocalyx also consists of a wide range of enzymes (eNOS, ACE, SOD3, etc.) and proteins (growth factors, chemokines, antithrombin, etc.) that regulate and protect the endothelium. They serve to reinforce the glycocalyx barrier against vascular and other diseases. Another function of the glycocalyx within the vascular endothelium is to shield the vascular walls from direct exposure to blood flow while serving as a vascular permeability barrier.[36] Its protective functions are universal throughout the vascular system. In micro-vascular tissue the glycocalyx inhibits coagulation and leukocyte adhesion. It also affects the filtration of interstitial fluid from capillaries into the interstitial space. [37] Research has shown that the glycocalyx is composed of a negatively charged network of proteoglycans, glycoproteins and glycolipids.[36]

The glycocalyx plays a crucial role in cardiovascular system health. Initial dysfunction of the glycocalyx can be caused by hyperglycemia or oxidized LDL cholesterol. In the micro-vessels, dysfunction of the glycocalyx leads to internal fluid imbalance and potentially edema. In arterial vascular tissue glycocalyx disruption causes chronic inflammation ischemic tissue damage, hypoxia, chronic inflammation and atherothrombosis. [37] Fluid shear stress is also a potential problem if the glycocalyx is disrupted for any reason. This type of frictional stress is caused by the movement of viscous fluid (i.e. blood) along the lumen boundary damaging the delicate glycocalyx. **Minimal ischemic damage to the glycocalyx increases capillary hematocrit.** Endothelial (glycocalyx) dysfunction can be tested by a variety of methods. Of all the current tests employed in a research setting, flow mediated dilatation (post-occlusive reactive hyperemia or PORH) is the most widely used non-invasive test for assessing endothelial dysfunction. This technique measures endothelial function by inducing reactive hyperemia via temporary arterial occlusion and measuring the resultant relative increase in blood vessel (capillary) diameter via ultrasound or plethysmography. **Such a reduction of small arteriole/capillary compliance is a marker for endothelial (glycocalyx) dysfunction that is**
associated with both functional and structural changes in the micro-circulation and is predictive of subsequent morbid events. These changes can be distinguished from large artery (Macro-circulation) stiffness and obstruction by the use of pulse volume recording (PVR).

**Endothelium**

Endothelium is mesodermal in embryonic origin. The *endothelium* is a thin layer of squamous cells that line the inner surface of blood and lymphatic vessels, forming an interface between circulating blood or lymph fluid in the lumen and the vessel wall. Endothelial cells in direct contact with blood are called vascular endothelial cells, whereas those in direct contact with lymph fluid are known as lymphatic endothelial cells. Vascular endothelial cells line the entire circulatory system, from the heart (“endocardium”) to the smallest capillaries. These cells have unique functions in vascular biology. Both blood and lymphatic capillaries are composed of a single layer of cells called a monolayer. All endothelial cells are coated with glycocalyx biopolymers. In fact, capillaries are essentially “naked” endothelial cells without any adventitial support forming a pulsating lumen lined by the glycocalyx. Endothelial dysfunction is a hallmark for vascular disease, and is often regarded as a key early event in the development of cardio-vascular disease. Impaired endothelial function has been related to hypertension and vascular thrombosis and is often seen in patients with coronary artery disease, diabetes mellitus and hypercholesterolemia. Endothelial dysfunction is a systemic pathological state of the inner lining of blood vessels and can be broadly defined as an imbalance between vaso-dilating and vaso-constricting forces acting on endothelial cells. Endothelial dysfunction has been shown to be of prognostic significance in independently predicting vascular events including stroke and myocardial infarction. Endothelial dysfunction can result from and contribute to several other disease processes (hypertension, diabetes) and can also result from environmental factors such as smoking and exposure to air pollution. Thus, endothelial dysfunction is a major pathophysiological mechanism of vascular disease. Endothelial dysfunction is synonymous with glycocalyx dysfunction.

**Macro v. Micro-circulation**

There are actually two “functionally interrelated” blood circulatory or vascular systems found in the human body: the *Macro-circulation* and the *Micro-circulation*. The *Macro-circulation* consists of the larger “conduit” arteries that conduct blood to the major organs. Included among these arteries are the aorta (chest and abdomen), carotid (neck), femoral (legs), coronary (heart) arteries and others. These are the blood vessels commonly treated with surgery and angioplasty (balloon therapy/stenting). The **acute** treatment of these large conduit “macro” vessels is commonly the focus of cardiologists, vascular surgeons, the news media, internet web sites and television shows. These treatments are routinely used and “sold” by scientific (more properly called statistical) “evidenced-based” medical practitioners. These **Macro-vessels** are the arteries said to be **chronically** “plugged up” (arterial plaque buildup) from the common “statistical” risk factors promoted by “evidence-based” scientific medicine: cholesterol, “bad” genes, high blood pressure, smoking, etc. **Please note that no one that speaks from scientific authority ever said that cholesterol or smoking actually “causes” plaque.** No, that’s not what has been *said*, but
commonly that is what is heard. What is being “said” is these factors are statistically associated with plaque, but science still does NOT know what actually causes arterial plaque to form.

Arterial plaque occurs in localized, “specific” sites within Macro-vessels, but, oddly enough, the statistical risk factors, which occur throughout the entire vascular system, theoretically should affect all Macro-arteries in the same way. Despite this, one commonly sees plaque blocking 90% of one coronary heart artery and no evidence of any blockage in the heart artery right next to the blocked one in the same patient. Isn’t just as much cholesterol going through each artery? Why the difference in presence and/or size of plaque? No one, and certainly no one in “evidence-based” scientific medicine, knows. They simply “know” statistical risk factors that are associated (statistically) with the presence of plaque. Scientific “evidence-based” statistical treatment and/or prevention consists of advising life style changes (weight reduction, exercise, stress control, etc.), and/or prescribing pharmaceutical drugs (statin drugs, ACE inhibitors, ARB blockers, beta-blockers, aspirin, Plavix™, etc.), angioplasty and/or surgery. The typical advice in mild to moderate plaque buildup is to reduce or lower weight, lower cholesterol, lower blood pressure, reduce inflammation, and to increase blood thinning... all things that have been “statistically” (“evidence-based”) demonstrated to reduce the risk and severity of Macro-vascular disease. Interestingly, these statistically based approaches are NOT effective in all patients, simply a “statistically significant” number of patients. Therefore, many patients following the correct “evidence-based” scientific diet and life style and using appropriate “evidence-based” medications or surgery will continue to demonstrate advancing plaque buildup over time. Advanced or high grade plaque buildup (80-90-100%) is mechanically (surgery, angioplasty) repaired as if it is simply defective plumbing, but this mechanical therapy does NOT correct the actual cause!

The Micro-circulation is turning out to be radically “different.” The Micro-circulation is also referred to in scientific medical literature as the “capillary circulation,” “terminal circulation,” “end-circulation,” “endothelial dysfunction” or “endothelium” (dysfunction) These are the tiny blood vessels (capillaries and capillary networks) that actually supply oxygen, nutrients and removes carbon dioxide and other metabolic waste from the vital organs (i.e. heart, brain, kidney, liver, etc.). It now appears, from an “evidence-based” scientific perspective, that Micro-circulatory disease is primarily related to the biological toxicity of Sugar, not fat as in Macro-circulatory theory.[38-48 ] It turns out that substances that are absolutely “essential” to life (oxygen, sugar) also turn out to be extremely toxic to life. Nature has placed a hidden “tax” on aerobic-based (Oxygen-Carbohydrate-Sugar) metabolic energy efficiency. Thus, metabolically utilizing (“burning”) oxygen and sugar for efficient production of energy comes at a potentially high metabolic price... Free Radical Toxicity and protein glycation or Gluco-Toxicity. By way of analogy, oxygen toxicity can be thought of in simple terms as being similar to “rusting” of molecules in the tissue or organ that these molecules make up (Free-Radical pathology). Sugar Toxicity is being discovered to act by causing “glycation,” or “caramelization” of essential structural and functional proteins, including the glyocalyx or endothelium. This process can be thought of in simple terms as causing protein “wrinkling.” Another simple analogy would be that of melting caramel over an apple and the caramel-sugar “coating” then hardens or stiffens, thus slowly, but progressively “caramelizing” the Micro-circulatory endoskeleton of the affected vital
organ (i.e. heart, brain, kidney, etc.). When this process involves living tissue it occurs with subtle, but devastating physiological consequences over time. The “non-enzymatic” (meaning in the absence of the enzyme Insulin) attaching of a sugar to a protein is currently thought to destroy (glycate or caramelize) proteins. **Protein Glycation is currently generally considered to be non-reversible.** This assumption is actually no longer scientifically correct. [48-57]

The most widely scientifically **recognized** clinical condition involving abnormal tissue glycation leading to clinical Micro-circulatory disease is diabetes. This is the biochemical, structural and regulatory basis of the commonly encountered condition of diabetic gangrene. Once a “black toe or foot” develops in diabetes there is no bypass vascular operation, angioplasty or drug that will help. There is only amputation of the dead tissue and usually problems with wound healing due to the subclinical Micro-vascular disease in the remaining “viable” tissue. **Diabetes is a condition that exists in the annals of scientific medicine by definition, and is, “by definition,” irreversible.** Diabetes is defined as a blood sugar that goes “too high...” that exceeds the statistically derived “normal” height or peak of blood sugar seen in an “average” population. The definition includes establishing the “normal” and “abnormal” blood sugar levels during fasting, after eating and/or during a laboratory glucose tolerance test. This definition of diabetes is focused on how **high** the blood sugar goes. It turns out that glycation from gluco-toxicity also occurs from glucose (Sugar) being in **prolonged** contact with tissue. Thus, the newly described “metabolic syndrome” (also called dys-metabolic syndrome, syndrome X or insulin resistance), which also exists **by definition (and is “by definition” reversible),** involves the inability of potentially toxic sugar to exit or, in more technically correct scientific terminology, be “disposed of” from the blood into the cellular metabolism as quickly as possible. Thus, Diabetes, **by definition, is about how high** blood sugar goes and Metabolic Syndrome, **by definition, is about how long sugar remains in the blood (impaired glucose disposal).** [58-64]

The pathological effect of Micro-Circulatory protein glycation is a stiffening of the capillaries throughout the affected organ... actually a **stiffening or caramelization** of the Micro-vascular skeleton within the organ involved. This process involves both abnormal biochemistry (protein glycation) and structural circulatory regulation changes (increased Micro-vascular resistance). The gradual glycation of protein molecules (“endothelium”) lining the small capillary Micro-circulation stiffens those Micro vessels so they cannot pulsate with the heartbeat. In addition, glycation of the proteins on the red blood cell stiffens their external membranes making it more difficult for the stiffened red cells to pass through the caramelized capillary beds one at a time. The resultant structural problem is the inability of the Micro-circulation to pulsate open with the kinetic (pumping) force of the heartbeat, coupled with the red blood cells inability to bend, twist and deform to slip through these stiffened capillaries one at a time. A capillary that is pulsed open during cardiac systole is 10 microns in diameter. During diastole the capillary reduces to 5 microns in diameter. A red blood cell is 8 microns in diameter. Thus, the caramelized capillary cannot dilate effectively and the older caramelized red cell has reduced flexibility. This situation results in small capillary “infracts or strokes” in the affected Micro-circulatory vessel directly involving the affected organ or tissue (i.e. brain, heart, kidney, etc.).

Over time (years to decades) the collective effects of this process appears clinically. Interestingly, the clinical syndrome that appears depends on which organ(s) are affected. Thus, if Micro-


circulatory glycation occurs in the heart there will be a development NOT of a major clinical “heart attack” (myocardial infarction), but small areas of tissue damage (i.e. slight elevation of enzymes without ECG changes) or, more importantly, the gradual development of **Diastolic Heart Failure**. [65-82] This process does NOT involve the active process of the heart contracting, but its inability to relax effectively (diastole) after contraction due to Microvascular stiffening of capillaries within the involved heart muscle. Thus, the heart fails to fill effectively and clinical congestive heart failure or CHF (fluid back up into the lungs, legs, etc.) develops. CHF is the now the most common and least curable form of heart disease affecting the American population, with a large proportion being diastolic heart failure. Similarly, if capillary glycation involves primarily the kidney high blood pressure will develop. Interestingly, diastolic dysfunction, diastolic heart failure, high blood pressure and sugar toxicity (“metabolic syndrome”) are now “epidemic” among Americans, old and young.[83,84] If capillary glycation occurs mainly in the brain, a condition called **Leukoaraiosis** or coalescing tiny (lacunar) strokes leading to scaring of the gray matter in the brain occurs, and memory loss/cognitive dysfunction and/or small strokes (lacunar infarcts) will develop.[79-80] **Leukoaraiosis** is still being taught in scientific medical schools as “a result of aging” and of “no medical consequence.” This outdated thinking has been clearly and scientifically dis-proven. The presence of leukoaraiosis on an MRI or CT brain scan should be taken as direct clinical evidence of abnormal Micro-vascular glycation (endothelial dysfunction).[85-128] The connection between heart disease, hypertension and Alzheimer’s syndrome, suggesting a common underlying mechanism (Micro-vascular disease) is now being formally recognized.[129-134]

Figure 1 [86] depicts a diagrammatic representation of this gradual process of capillary cross sectional attrition over time from normal capillary flow through a tissue or organ in the upper diagram to an intermediate reduction in the middle and then finally a significant loss of the illustrated Micro-vascular capillary bed on the bottom. The organ or tissue most affected is where the clinical “syndrome picture” will manifest (heart, kidney, brain, etc.). Figure 2 (86]) is an photomicrograph of a section of brain clearly demonstrating the loss of the Micro-circulatory capillary bed in a histologic section of brain from a patient with dementia.
Figure 1 Brown WR, Thore CR. Review: cerebral microvascular pathology in aging and neurodegeneration. Neropathol Appl Neurobiol 2011 Feb;37(1):64.
Interestingly, in addition to the toxic Micro-circulatory effects of glucose and subsequent endothelial glycation now being described in Alzheimer’s like senile dementia, scientific evidence also shows that the accumulation of abnormal proteins (Beta or β-amyloid and Tau protein) in Alzheimer’s disease also causes reduced Micro-circulation (vaso-constriction) in the brain. Beta (β)-amyloid protein also reduces endothelium-dependent brain vaso-dilation. As if to add insult to injury, any temporary lack of oxygen in the brain can also lead to increased production of β-amyloid protein. Thus, it is apparent that Micro-circulatory compromise plays a very large role in the development of memory loss, cognitive dysfunction and dementia syndromes, regardless of the actual “official name” of the clinical syndrome. In addition to and as further proof of this situation, the microscopic changes in brain tissue that are thought to be “specific” for Alzheimer’s disease (β-amyloid, Tau protein, neurofibrillary tangles) have also been described in patients with heart vascular disease and no evidence of dementia. The increase in body fat that is part of “metabolic syndrome” also contributes to the “bad” situation. Centralized body fat is actually a functioning endocrine organ. Body fat secretes certain pro-inflammatory cytokine hormones (Tumor Necrosis Factor alpha [TNF-α] and Inter-Leukin-6 [IL-6]). Increased body fat leads to increased inflammation (a statistical risk factor for Macro-circulation disease). Inflammation can be measured using the blood test C-reactive protein or CRP. Thus, many previously recognized “independent risk factors” can now be connected through the understanding of the biologically toxic properties of sugar secondary to malfunction
of cellular insulin receptors.

**Insulin Resistance/Metabolic Syndrome**

The underlying metabolic basis of gluco-toxicity is the inability of the enzyme Insulin to activate **Insulin receptors** on cell surfaces (“membranes”) that allow the sugar to move quickly from the blood into the cellular metabolism where it can be used for energy production (and the production of Free Radicals!). Thus, Insulin acts as a “key” that must fit into an **insulin receptor** or “lock” and open that lock so potentially toxic sugar can be transported (“disposed of”) quickly and efficiently from the blood into the cellular metabolism. When sugar is not disposed of quickly several “bad” things begin to happen: 1) glycated Micro-vessels and cellular red corpuscles “stiffen” and lose their ability to pulsate with the heart; 2) the un-disposed of sugar is immediately shunted into centralized body fat production. One of the clinical markers used to define **metabolic syndrome** is centralized body fat (a large waist line); 3) additional pathological events related to poor glucose disposal include excess sorbitol production leading to nerve damage (diabetic neuropathy) and cataracts. The “**defining components**” of metabolic syndrome that have been “suggested” or adopted by various scientific groups and societies are high blood pressure, high cholesterol, high triglycerides, high fasting Insulin levels and/or high fasting blood sugar. Interestingly, all the different criteria put forth by various scientific medical groups (WHO, American College of Cardiology, American Association of Clinical Endocrinology, etc.) do **not** include any evidence of direct tissue sugar-protein glycation as a criteria for diagnosis. Usually, the presence of three or more of these statistical risk factors “qualifies” as a diagnosis of “metabolic syndrome.” In reality, by the time any individual actually qualifies for the formal diagnosis of metabolic syndrome they are already manifesting significant and late stage clinical evidence of severe Micro-vascular glycation (i.e. high blood pressure, obesity, heart disease, dementia, etc.).

The main biochemistry involved in the pathology of gluco-toxicity is known as the Maillard reaction. This common chemical reaction has been known for over 100 years. The main scientific focus of this reaction usually involves food spoilage and industrial applications. Other than in diabetes mellitus (“sugar diabetes”), there was really little medical scientific interest in the Maillard reaction in medical science or practice.[135] However, with the recent and gradually increasing scientific realization that the cholesterol (“fat” toxicity) theory of cardio-vascular disease is, at best, incomplete, or more likely simply wrong, more scientific interest and resources have been re-evaluating the patho-physiological effects of the Maillard (sugar toxicity) reaction.[136-141] There is also scientific evidence rapidly accumulating that in vivo pathological Maillard reactions accumulate both from internal dys-metabolism of sugar and **ingesting Advanced Glycation Age (AGE) products created by excessive heating of food.**[142] In addition to the Maillard reaction, the **Amadori rearrangement and Schiff base reactions** are also part of the complex biochemistry of sugar toxicity.[135]

One major problem faced by clinicians interested in prevention and early intervention of the manifestations of abnormal tissue glycation is that there is no single test that can “diagnose”
metabolic syndrome. Abnormal glycation diseases can be diagnosed using several clinical and laboratory findings, but NOT by a single laboratory test. A simple blood test called the **Hemoglobin A1C** or Glyco-hemoglobin (Hbg A1C) test easily and cheaply provides critical clinical information about the ongoing degree of glycation in the body due to inadequate glucose disposal from blood.[143-146] The “trick” in using this scientific (evidence-based) test as a “new and emerging risk factor for clinical vascular disease” (as it is now being described in scientific medical journals) is to understand that the laboratory statistical “norms” are not related to individual optimal values. A value for **Hbg A1C above 4.6 should be considered “abnormal”** (meaning evidence of accelerated cellular membrane glycation). In most commercial laboratories Diabetes is said to be present, **by definition**, if the value is 6.4 or higher. This is why most diabetics demonstrate severe vascular disease by the time scientific medicine diagnoses it. Membrane receptor resistance to the hormone Insulin is not acknowledged until late in the process (advanced tissue glycation) or a “high” Hbg A1C. Objectively testing using Post Occlusive Reactive Hyperemia (PORH) for disturbed Micro-circulatory function and /or **Pulse Volume Recordings (PVR)** or (Micro-vascular disease of the vasa vasorum in Macro-vessels) can also demonstrate the effects of abnormal vascular glycation (loss of Micro-vascular compliance) in the early stages of occurrence.

As an aside regarding laboratory measurement of Insulin or any other “hormone level,” the clinical reality is that no hormone actually works in the blood (or urine, or saliva)... hormones do their metabolic work by activating a hormone receptor (i.e. the “key in lock” analogy) usually located on the cell membrane (i.e. insulin receptor) or the nuclear membrane (i.e. thyroid receptor). Thus, in many individual (“NOT statistical”) cases the “blood level” (and urine or saliva, for that matter) of a given hormone (i.e. thyroid, insulin, vitamin D, etc.) may be “statistically” normal or even “optimal” and yet the clinical symptoms of the particular hormone “deficiency” may clearly be present. This is a very common clinical phenomenon seen with insulin resistance syndrome. Blood simply acts as a transport medium to get the hormone from where it was made to where it will have its metabolic effect. As stated earlier, the insulin receptor is located on the cell membrane... and some cells have many more insulin receptors than others. This is the functional basis of IPT (Insulin Potentiation Therapy) cancer chemotherapy... to use insulin to activate the insulin receptors on cancer cells. Cancer cells revert to a more primitive cellular metabolism referred to as **anaerobic or “without Oxygen” glycolysis** (fermentation). Because of this cancer cells have significantly more insulin receptors on their cell surface than non-cancer cells. Giving Insulin to activate the insulin receptors on the cancer cells membrane, thus causing a drop in blood sugar and, at the low point of the blood sugar giving very small (15 to 20% of standard) doses of chemotherapy drugs “tricks” the cancer cells into preferentially ingesting the chemotherapy drugs as they are in their insulin activated sugar “feeding frenzy.” An ingenious physiologic “Trojan Horse” approach that significantly minimizes side-effects and yet maximizes therapeutic benefit of chemotherapy to actually target the problem cancer cells, thus sparing drug toxicity to normal cells and tissue. The clinical results in cancer can be quite amazing when appropriately employing IPT therapy.

Returning to the discussion of **Micro-vascular** glycation related stiffening or lack of pulsatile ability of vascular tissue, pulsation of the Micro-circulation turns out to be critical for all major organ health. This is the simple reason that scientific medicine has not yet developed an effective
implantable artificial heart. **Pulsatile flow** is something that is required in normal physiology. Any experimental animal that is put on a heart bypass pump that uses **non-pulsatile or laminar flow** dies within days of progressive, multiple organ (kidney, heart, brain) failure due to progressive Micro-vascular dysfunction... called scientifically **increased peripheral vascular resistance**.[147] Our best technological engineers can make pumps smaller than a dime that can operate in climates as alien as the Martian surface, but they have not yet mastered the essential, life-sustaining properties of biologically imperative pulsatile flow. The main physiologic cause of pathological Micro-vascular stiffness is gluco-toxicity.[139] Clinical counterparts of this “laboratory” phenomenon of increased organ **Micro-circulatory stiffness** are commonly encountered, but just as commonly, the causal underlying mechanism (Micro-vascular stiffening due to glycocalyx/endothelial caramelization) is usually NOT clinically recognized and thus crude, non-curative symptomatic drug or surgical therapy follows. One commonly missed clinical example of this phenomenon may be **heart and peripheral arterial vascular stunning and hibernation**.[148-149] Integrative Medicine employing **Chelation Therapy** has demonstrated clinical effectiveness in reversing stunning and hibernation in both entire organs (heart **Micro-circulation**) and extremities (leg **Macro-circulation/Vasa Vasorum**).[148-149] The actual cause of the phenomenon of stunning and hibernation is “unknown” in evidence-based medicine, but gluco-toxicity of the **Micro-circulation** in the corresponding capillary bed of the heart muscle or the Vasa Vasorum (or **Micro-circulation**) of the **Macro-Vessel** arterial wall may be involved.

Another common and unusual clinical “symptom pattern” manifestation of insulin resistance is **polycystic ovary syndrome (PCOS)**. The currently accepted treatment for PCOS is either using synthetic hormone birth control pharmaceuticals (BCP) or the off-label use of the anti-diabetic drug **Metformin**.[150-151] Interestingly, birth control pills help PCOS symptomatically although they are known to cause weight gain, high blood pressure, high blood sugar and, more importantly, increase vascular resistance.[152] It appears that while improving the clinical picture BCP’s seem to be making the manifestations of insulin resistance and endothelial dysfunction worse. The clinical and laboratory effects of Metformin in PCOS were found to be superior to BCP’s.[153] It is also possible that other chronic degenerative diseases may be related to underlying Micro-vascular pathology. For example, osteoarthritis, which is really osteoarthrosis, since no true inflammation (“itis”) is involved, may be related to reduced Micro-circulation to the associated joint and cartilage tissue. This could explain why the simple clinical methods of heat, massage and/or injecting **Ozone (prolozone therapy)** into the affected joint and/or peri-articular tissue results in reduction and elimination of pain by increasing Micro-circulation. Chronic **unexplained pelvic pain** in both sexes may be related to regional Micro-vascular disease in the pelvis. Localized **“trigger points”** in muscles may also be due to localized Micro-circulatory disturbance. Much like the phenomenon of localized compromise of Micro-circulation in the brain (dementia), heart (diastolic heart failure) and/or kidney (hypertension) lead to different clinical patterns resulting from the same underlying pathology, perhaps other degenerative conditions will be found to be related to reduced Micro-circulation to an affected organ or anatomic/physiologic area.

**Cholesterol**

Since the 1960's cholesterol has been the focus of medical science regarding the major cause of
cardio-vascular disease. This model was based on research demonstrating a statistical connection between elevated blood levels of cholesterol and finding cholesterol products within arterial plaque. While not all patients with sudden vascular accidents (heart attack, stroke) demonstrated elevated levels of blood cholesterol, the cholesterol model was very successful in treating disease in males from the 1960's through the 1990's. The advent of “statin drugs” (HMG-Co A Reductase Inhibitors) seemed to advance the cholesterol theory of vascular disease to the zenith of scientific medicine.[154-158] Initially thought to produce their effects by lowering cholesterol blood levels, further research began to show additional benefits of statin agents, including marked reduction of inflammation among others. This led to the “routine” use of these pharmaceutical agents in all vascular disease patients, whether or not the blood cholesterol level is elevated. Despite this change in approach the decline in the level of vascular disease in males leveled off. Also, during the 1990's despite vascular disease in males showing dramatic declines, heart disease among women correspondingly and dramatically increased in spite of applying the same medical model used in males (bypass surgery, arterial angioplasty and drug cocktails including statins, beta-blockers, ACE inhibitors, ARB blockers and aspirin). This “cook book approach” was far less effective in women which led some to begin questioning the accuracy of the cholesterol model of cardiovascular disease.

Several facts seem to bolster questioning the accuracy of the cholesterol theory of cardio-vascular disease. A major one is the fact that many women having heart attacks had “normal” cholesterol blood levels. In addition, many men and women with high cholesterol never develop cardio-vascular disease. Finally, the erratic way plaque appeared throughout the circulation, with one artery being affected and others seemingly escaping disease (“skip lesions”) strongly suggested that other mechanisms were at play. In the scientific and media frenzy about cholesterol and vascular disease for the past 60 years many overlooked the fact that cholesterol was simply a theory... not a proven fact. Other theories for the cause of vascular disease, including systemic vascular inflammation, occult infection, various immune mechanisms, sugar toxicity, trans fats, free radical damage and others were proposed, but never received the attention (research money, scientific enquiry, etc.) that cholesterol commanded. With the increasing incidence of disease occurring in women beginning in the 1990's these other theories began to take on more significance. The toxicity of sugar and its recognized relationship to obesity, diabetes, Micro and Macro-vascular disease began to challenge and displace the cholesterol theory as a fundamental cause of these common vascular disease syndromes. For example, Micro-circulatory (capillary) disease involving the Micro-circulation of the arterial wall (Vasa Vasorum) can easily explain the phenomenon of atherosclerotic “skip lesions.” In addition, the presence of tissue scaring (wall motion abnormality in the heart and leukoaraiosis of the brain) in the absence of corresponding hemodynamically significant Macro-vascular disease can be explained by local Micro-vascular compromise.

At the present time old recommendations of reducing dietary cholesterol are being challenged as not useful.[159-160] In addition, the actual “beneficial effects” of statin drugs is being seriously questioned.[161] It appears that statistical manipulation and corporate profiteering may have played a large hand in the now questioned widespread acceptance of statin drugs.[161] Interestingly, diabetes, blood sugar elevation, liver and muscle damage and heart failure are known, common and usually limiting side effects of statin drug use. Recent research suggests
that statin drugs may actually cause atherosclerosis ("arteriosclerosis?") and congestive heart failure.[162] While this research needs to be confirmed, it should prompt serious clinical questioning of the widespread use of statin drugs, especially for “primary prevention,” where no vascular event has actually occurred and the drug is being prescribed based exclusively on an elevated level of blood cholesterol in the absence of evidence of significant arterial plaque formation or symptoms. As with the phenomenon of elevated triglycerides, now recognized as a marker of insulin resistance/metabolic syndrome, it appears cholesterol is an effect of the underlying glucose/insulin receptor metabolic dysfunction rather than a cause.

**Vitamin D**

Like all other steroid hormones, Vitamin D (a hormone, not a vitamin or “vital amine”), is made in the body from cholesterol. This unfortunate confusion of terms is the root the new scientific interest in the “sunlight vitamin.”[163-175] The basic concept of “hormone” is a substance made in one area of the body and enters the circulation to have its physiologic effect on another organ or area of the body. Vitamin D3 is naturally made from cholesterol in several steps, beginning with a specific frequency of ultraviolet light from the sun interacting with cholesterol in the skin to form a precursor pro-vitamin D. This pro-vitamin travels through the blood to the liver and is converted into a second pro-vitamin (25-hydroxy Vitamin D3), which is again secreted into blood to be transported to the kidney and converted into the final, metabolically active vitamin D3 (1,25 di-hydroxy Vitamin D3 or Chole-calciferol). In addition to bone and intestine where calcium is absorbed, cellular Vitamin D receptors are found in all neural, endocrine and immune cells, indicating the extreme metabolic and regulatory importance of Vitamin D in the optimal function of the neuro-endocrine-immune system. Due to the past focus on Vitamin D and calcium/bone metabolism, medical science is only recently discovering the widespread effects and physiological disturbances related to low or sub-optimal Vitamin D levels. Inflammation, and symptoms related to chronic inflammation have been shown to be related to Vitamin D function.[176-178] Low Vitamin D has also been implicated in some cases of depression[179], as well as cardio-vascular diseases [180-183], cardio-metabolic disorders [184], cancer[185-188], and more directly related to gluco-toxicity and Micro-vascular disease, cognitive decline [189-193], diabetes/metabolic syndrome and hypertension.[194-197].

There are two active forms of Vitamin D commonly used medically. Vitamin D3 is the bio-identical form of the hormone normally found in humans and other mammals. Given current research results, this is the only form humans should be taking.[192-200] Vitamin D2, which is made by converting Ergosterol into Ergo-calciferol), is found in third kingdom organisms (yeast, algae) and should NOT be taken by humans. While both forms have similar effects on calcium metabolism and bone (D2 is said to be about 40% the “potency” of D3), they have different effects on the immune system.[198] Vitamin D3 activates human immune precursor cells while Vitamin D2 causes these cells to enter a state of hydrogen peroxide induced cellular apoptosis (programed cell death).[199] In addition, low vitamin D levels have been shown to affect delayed hypersensitivity response to skin test antigens.[200], Unfortunately, Vitamin D2 is what the food industry has been “enriching” in processed foods for decades. Most processed
and/or “Vitamin D enriched” foods should be avoided or minimized. A Vitamin D supplement will be labeled as to which type (D2 or D3) is in the product, but if just the term “Vitamin D” is on the label, it is Vitamin D2 (FDA “standard of identity”). The large body of research demonstrating Vitamin D’s effects on inflammation [176-178], blood sugar and blood pressure [194-197] and other manifestations of metabolic syndrome/sugar toxicity suggest that one hormonal effect of Vitamin D3 may involve enhancing the activity of the cellular insulin receptor. Similar to the concept of insulin receptor resistivity (insulin resistance/metabolic syndrome), Vitamin D also works through activating the Vitamin D receptor inside each cell. By optimizing Vitamin D3 blood levels to between 50 and 60 ng/dl many clinical manifestations of insulin resistance commonly improve, indicating Vitamin D is part of the widespread epidemic of metabolic syndrome, insulin resistance, diabetes, hypertension, leukoaraiosis and obesity.[180-184,189-197]

Another interesting concept in the new thinking regarding “low” Vitamin D blood levels and chronic disease involves the Marshall protocol. In some chronic inflammatory diseases, such as “post” (chronic) Lyme syndrome, fibromyalgia, sarcoidosis, multiple chemical sensitivity syndrome, lupus, rheumatoid arthritis and others, the blood levels of the pro-vitamin D (25-hydroxy-Vitamin D) is found to be low while the level of the active 1,25-di-hydroxy-Vitamin D will be found to be high normal to high. Marshall believes that this situation is caused by L-form bacteria and other intracellular infectious agents disrupting the function of the intracellular Vitamin D receptor which interrupts the innate immune system’s ability to find and destroy the infected cells.[201-204] Patients with chronic inflammatory diseases in addition to metabolic syndrome/insulin resistance problems may benefit from having both 25-hydroxy-Vitamin D and 1,25 di-hydroxy Vitamin D blood levels measured together to evaluate for a metabolic disturbance of Vitamin D metabolism. If this situation is found the Marshall protocol advises that Vitamin D not be given or supplemented and the Vitamin D receptor be “reactivated” using the drug Olmesartan (Benicar™) and other specific protocol recommendations.[201-204] Since this information and its clinical application is “anecdotal,” the patient and physician should evaluate the information in light of the underlying clinical reality of each individual patient. Simultaneously evaluating the level of both 25 hydroxy and 1,25 di-hydroxy Vitamin D may serve as a biochemical marker that may distinguish pathologic inflammation or chronic infection from chronic degenerative structural/functional Microvascular disease.

**Diagnosis**

The formal definition of metabolic syndrome requires a patient to manifest a minimum of three of the following criteria: centralized obesity, hypertension, elevated fasting blood sugar, fasting insulin level, and/or blood triglyceride level, low HDL cholesterol level and/or high LDL cholesterol. The clinical difficulty with diagnosing metabolic syndrome/sugar toxicity by definition is that by the time one fulfills the “formal” criteria for academic recognition of sugar toxicity, the process has progressed to a point of clinical disease. The “real world” diagnosis of pre-clinical sugar toxicity depends on a number of factors. There is no single physical finding or test that can accurately “diagnose” sugar toxicity. Pathologic Maillard biochemical/sugar toxicity reactions, like free radical chemistry, are fundamental processes in human
physiology. There is a biological, biochemical, and patho-physiologic continuum from birth through aging, disease and ultimately death (figure 3). Once this fact is acknowledged, it logically follows that the earlier the clinical detection of protein glycation/sugar toxicity, the more effective intervention will be.

Relying on laboratory “normal reference values” and late symptomatic pathological pattern recognition after disease is present is inferior medical practice. The earlier dys-metabolic and Micro-vascular manifestations can be detected, the sooner remedial diet/lifestyle measures can be recommended and/or treatment applied.

**Clinical evaluation** for sugar toxicity can be divided into physical, metabolic, functional and/or structural findings. If diagnosis is suspected in a “pre-clinical” state, before functional or structural metabolic and/or Micro-vascular problems (i.e. hypertension, cognitive decline, cardio-vascular syndromes) are clinically apparent, then evidence of physical and/or biochemical deviations from optimal, rather than statistically derived “normal” values are currently the most accurate diagnostic tools available. Physically, the presence of any degree of centralized body fat accumulation should be considered a harbinger of insulin resistance/metabolic syndrome. In addition, the skin may demonstrate “Liver” or AGE (Advanced Glycosylation End Products) spots on the hands or elsewhere. The presence of Micro-vascular disease can be
determined by several methods. Clinical examination of the feet may reveal delayed capillary filling... a simple bedside test that can detect poor capillary filling reserve after blanching the capillary bed with manual pressure and observing the time taken for color to return to the blanched capillary bed. Normally this should be 3 seconds or less. Ambient temperature should be comfortable, the extremity being examined should be equilibrated to room temperature and pharmaceutical agents that may interfere with the test should be accounted for (beta blockers, etc.).

Metabolic markers include elevated fasting blood sugar (>85 mg/dl), elevated fasting insulin levels and/or a blood hemoglobin A1C of 4.6 or higher. It should be kept in mind that insulin receptor resistivity can be manifested by how long the sugar remains in the blood (impaired glucose disposal), as well as how high the blood sugar goes. HBG A1C is a more accurate measure of protein glycation than fasting blood sugar levels. An elevated C-Reactive Protein (CRP) consistent with low grade cardio-vascular inflammation could also point to sugar toxicity. Elevated Homocysteine levels have been related to cerebral Micro-vascular disease.[205] Insulin receptor dysfunction from chronic toxic metal burdening may also a factor.[206-211] Vitamin insufficiency and/or deficiency [212-215] and hormone deficiency/insufficiency also contribute to the clinical presentation of metabolic syndrome.[216-221] Other diagnostic tests can provide objective evidence of sugar toxicity, depending on the “syndrome” or pattern of organ dysfunction present. Cognitive decline is one clinical “syndrome” related to brain sugar toxicity [222-228]. Memory testing can be done using a number of bedside evaluation methods.[229-235] In addition, brain CT or MRI scans can confirm the presence of leukoaraiosis. Supra-optic Doppler PORH studies can confirm reduced cerebral Micro-vascular flow reserve. Loss of compliance (reduced or absent dicrotic wave) on peripheral PVR reflects intramural Micro-vascular involvement (Vasa Vasorum) of the Macro-vessels. Hypertension is diagnosed by clinically measuring blood pressure.[83,84] Exercise induced diastolic hypertension is a more accurate measure and appears earlier clinically than random, casual measurements. Congestive heart failure can be detected using echocardiography, chest x-ray, and clinical evaluation (gallop rhythm, lung rales, peripheral edema and/or cervical venous engorgement). “Diastolic dysfunction” (impaired ventricular relaxation) on echocardiogram is evidence of loss of ventricular compliance due to myocardial Micro-vascular disease. Abnormal myocardial wall motion on nuclear scanning, ECHO or contrast ventriculogram studies in the absence of hemo-dynamically significant (>80% lumenal obstruction) Macro-vascular coronary artery disease also denotes loss of arterial compliance secondary to Micro-vascular disease.

Autonomic dysfunction (palpitations, anxiety, insomnia, vertigo/balance problems, temperature regulation, etc.) is a common feature of sugar toxicity/insulin resistance.[236-238]. Similar dys-autonomic symptoms may be caused by chronic toxic metal burden, such as Mercury, negatively affecting the sympathetic/parasympathetic homeostasis. The symptoms caused by and diagnosis of dys-autonemia can be difficult to detect or manage. In addition to the presence of subjective physical symptoms (anxiety, palpitations, insomnia, etc.), one simple, useful method of diagnosing autonomic dysfunction is Micro-vascular PORH testing. In addition to demonstrating the presence of Micro-vascular disease, PORH is an accurate measure of neurological autonomic tone. Other useful methods for detecting autonomic imbalance are autonomic response testing (ART) and electro-dermal screening (Electro Acupuncture According
to Voll/EAV or Electro-Dermal Screening/EDS.). Considering that Micro-circulation serves all organs and tissues of the body, perhaps other chronic degenerative diseases may be due to Micro-vascular disease involving a specific body region, tissue or organ. For example, Osteoarthritis/Osteoarthrosis (degenerative joint disease) does not involve any inflammation, simply degeneration. Micro-vascular ischemia developing slowly over years may present as “angina” of the joints, with ischemic/hypoxic degenerative physical changes occurring as the final result. Soft tissue trigger points may be localized areas of Micro-circulatory dysfunction. Chronic pelvic pain and congestion, such as non-specific prostate symptoms, may be regional or localized pelvic ischemia/dys-regulation due to Micro-vascular disease. Without objective clinical testing availability involving these areas there is no way to detect the presence of localized Micro-vascular disease. Thus, early detection of un-physiologic (pathological) glycation using the tools previously presented and having a high index of clinical suspicion are most important for the patient and clinician.

**Treatment**

Treatment of sugar toxicity is directed at the metabolic, functional and/or structural problems of the individual patient. The current situation regarding commercialized diet and food choices is difficult if not impossible to correct due to the large amount of added sugar (sucrose, glucose and fructose) in U.S. food supply. Also, the inability or lack of interest of government regulators to address this epidemic underlies the problem.[239-240] The use of sewer sludge as fertilizer on most farm land has led to widespread low level toxic metal burdening. Toxic metals inhibit insulin receptors and competitively inhibit intestinal absorption of essential nutritional minerals. Essential minerals are required for optimum functional of insulin (zinc) and/or insulin receptors (chromium, vanadium). Avoiding gluten is warranted in some patients.[241] A high protein, low carbohydrate-sugar diet, moderate in plant based fats, should be recommended. The goal is to reduce body fat, blood sugar and blood insulin levels. Fructose in all forms (i.e. Agave), and especially high fructose corn syrup, should be avoided completely. There are several specific diet programs (Paleo, HCG, Sugar Busters, Adkins, etc.) that can serve as a guide to individualizing the diet. Regular exercise (lowers blood sugar and insulin levels), along with other lifestyle changes, such as smoking cessation, moderate use of alcohol, etc. should be advised. The effect of diet and lifestyle treatments can be monitored using weight, blood pressure and laboratory parameters such as daily blood sugar and/or Hemoglobin A1C level every three to four months and CPR if elevated. It should be kept in mind that the Hemoglobin A1C test involves both the rise in blood sugar as well and the impaired sugar disposal from blood to cellular metabolism due to insulin receptor resistivity. In addition, it has been shown that advanced glycosylation end products (AGE) can come from food preparation, depending on how high (>120 degrees) and how long the food is heated. These AGE products add to glycation burden.[142]

Currently, there are few drugs and no medical devices or surgical approaches available to treat metabolic syndrome, with the exception of surgical gastric bypass or lap banding for morbid obesity. After such surgery, the metabolic effects of insulin resistance: excess central fat, high blood pressure, diabetes, and cardio-vascular disease improve and may be eliminated in many individuals. Interestingly, those with a thin or normal body habitus manifesting other signs of
metabolic syndrome/sugar toxicity store “excessive body fat” in their organs, such as fatty liver (non-alcoholic hepatic steatosis). Fructose (high fructose corn syrup) has been specifically implicated as a cause of fatty liver.[15,64] The clinical management of sugar toxicity/insulin resistance consists of diet, lifestyle changes, exercise, supplements and/or medication. Supplements that benefit insulin resistance include Chromium, Vanadium, Magnesium, Cinnamon, alpha Lipoic Acid, Benfotamine, Pyridoxamine, Pyridoxal Phosphate, Methyl-B12 and Methyl-Folate, and others (Appendix 1). There is also growing clinical evidence that sub-optimal (not to be confused with “sub-normal”) levels of Vitamin D have been linked to the clinical state of Insulin Receptor resistance. Providing Vitamin D3 in amounts that result in blood level of 25-Hydroxy (OH) Vitamin D above 50 ug/dl (“optimal” 50 to 60 ug/dl) is helpful clinically.[194-197]. Only Vitamin D3 should be employed. Vitamin D2, which has been reported to cause and aggravate atherosclerosis, should be avoided.[180,189,199] Chronic inflammatory conditions as described in the Marshall protocol should be considered if 25 hydroxy-Vitamin D levels are low or sub-optimal and 1, 25 di-hydroxy-Vitamin D levels are normal or high.[201-204] Certain herbal supplements can also be helpful, such as Gymnema sylvestre, Bitter Melon, Prickly Pear Cactus, Ginseng and Fenugreek.[242-243] Carnosine, a dipeptide of the amino acids beta alanine and histidine, is an antioxidant and anti-glycating agent (reverses the sugar toxic Maillard reactions).[56,244]

Medication treatment of insulin resistance involves using pharmaceutical agents that improve insulin receptor function, reduce liver sugar production, lower blood sugar, increase sugar excretion and/or inhibit intestinal absorption of sugar. The most effective pharmaceutical agent in common use today is the biguanidine drug Metformin.[245-249] Metformin activates insulin receptors and suppresses endogenous liver production of sugar (gluconeogenesis) to reduce Hemoglobin A1C levels. Side effects and costs of metformin are minimal. The main side effect is gastro-intestinal intolerance (nausea, diarrhea bloating) and is usually self-limited. Current cost for metformin can be as little as $4/month. If side effects persist more than 2-3 weeks a trial of the trade name Glucophage™ should be tried and will commonly eliminate side effects. Another concern with metformin is the rare condition of lactic acidosis, but this effect was found in the now off market biguanidine Phenformin, and may not actually occur with metformin.[250] In addition, if metformin is used for a prolonged period it could possibly lead to Vitamin B12 deficiency.[251] Other pharmaceutical agents that may be helpful in treating insulin resistance include thiazolidinedione drugs (Actos™), SGLT2 inhibitors (Invokana™ etc.), alpha glucosidase inhibitors (Precose™), GLP-1 agonists (Byeta™, Victoza™) and/or DPP-4 inhibitors (Onglyza™, Januvia™ etc.) (See Appendix 2). These additional agents are all still under patent, meaning “expensive.” The side effects can be annoying to life threatening: Actos™ may cause bladder cancer, SGLT2 inhibitor Invokana may cause urinary symptoms and genital yeast infections, Precose™ can cause excessive gas. Insulin receptor sensitizing therapy (Metformin, Chromium, Vanadium etc.) has been shown to improve atherothrombotic and inflammatory parameters in insulin resistance/sugar toxicity.[252] Pharmaceutical agents such as insulin in all its forms and/or sulfonyl urea drugs (glyburibe, glymeperide) should be avoided if possible, since they do not help the resistant receptors and, although they may lower blood sugar and hemoglobin A1C they do so at the expense of increasing body fat (increased inflammation and insulin resistance).
An older pharmaceutical agent with a unique mode of action is Aminoguanidine (Pimagedine). Aminoguanidine acts by reversing the Maillard reaction (Glycation) by removing the sugar molecule from the protein moiety. Originally investigated in the 1980's for its ability to reverse diabetic kidney damage, financial, political and regulatory issues resulted in all research on this agent being terminated in 1999.[253] The drug is still available from England as an “anti-aging” supplement. Another interesting pharmaceutical is Rimonabant. Rimonabant represents a new class of neuro-pharmaceuticals known as endo-cannabinoid 1 (CB1) receptor blockers.[254-255] Developed in Europe as an anti-obesity drug, it was withdrawn from the market due to central neurotoxicity. 

Rimonabant was useful for weight loss, smoking cessation, reducing addictive behavior to cocaine, alcohol, cannabis, opiate agents and sugar, improving short term memory and increasing sperm motility.[256] Based on their profile of activity CB1 receptors appear to be quite widespread in their biologic activity. More importantly, by Rimonabant reducing sugar craving this is additional evidence that sugar is addictive. Interestingly, the use of cannabis (Marijuana) has been shown to reduce blood glucose, insulin levels and the risk for developing diabetes.[257-260] Ironically, an herbal medicinal substance in use dating back to the third millennium BC that is banned by modern legislatures, courts and government bureaucrats turns out to be an effective treatment for the toxicity of an addictive substance (sugar) that is completely unregulated by government[261] and may represent the root cause of almost all chronic degenerative diseases of the modern era.

Beyond the general treatment of metabolic/insulin resistance/sugar toxicity syndrome, specific symptom complexes related to insulin resistance/metabolic syndrome (cardio-vascular disease [CVD], neurologic disease [ALSD], etc.) may require specific additional treatment protocols. Hypertension can be controlled using anti-hypertensive medications. Diabetes is treated with diet, exercise and anti-diabetic medication(s). Coronary artery disease (CAD) is treated with diet, exercise, various “standard” medications (beta blockers, nitroglycerine, ACE inhibitors, ARB blockers, statins, etc.), bypass surgery and/or angioplasty-stenting. Diastolic heart failure is treated with various drug cocktails and/or pacemaker-defibrillator devices, Enhanced External Counter Pulsation (EECP)[262] and/or possible heart transplantation in the extreme. All scientific medical approaches, with the possible exception of EECP, are directed at symptom control and not the actual cause. They do not increase life span and are used to improve quality of life. Additional “clinical anecdotal” approaches that are directed toward the underlying sugar toxicity and Micro-vascular disease have been shown or reported to be beneficial. EDTA Chelation therapy has recently been shown to be effective for coronary disease.[263-265] Interestingly, the reduction in vascular events in patients treated with EDTA Chelation was twice as effective in diabetics then in non-diabetics.[266] The “cholesterol experts”[159-162] are trying to figure out why diabetes responded so well compared to non-diabetics. They are focused on “cholesterol” rather than sugar toxicity. The mechanism(s) of action of EDTA Chelation lowers blood sugar (temporarily), synergizes insulin activity, removes toxic metals and improves Micro-vascular function.[148-149] The mystery is not in how it worked in the trial, but why the findings have yet to be evaluated with consideration that the cholesterol theory of CVD may be incomplete at best and wrong at worst.[161-162]

There are several neurological syndromes related to Micro-vascular disease caused by sugar toxicity. Included are asymptomatic Leukoaraiosis, symptomatic Leukoaraiosis,
stroke/lacunar infarcts, cognitive decline, Alzheimer’s syndrome, lateral temporal sclerosis and/or autonomic dysfunction. Leukoaraiosis in the absence of “symptoms” is generally considered to be related to aging and of no consequence, but recent science now contradicts this “accepted” thinking.[85-128,162-163] The different symptomatic clinical syndromes are generally treated with “standardized” drug therapy, depending on specific clinical pattern (aspirin, anti-platelet agents, anti-seizure drugs, anti-coagulants, memory enhancing drugs, sedative-hypnotics). All drugs only treat symptoms and not the cause of the problem. The underlying “cause” in these clinical syndromes is Micro-vascular disease from sugar toxicity. Symptomatic treatment may be necessary, but treating the underlying causative Micro-vascular disease is more logical, clinically astute and critical. Biological Maillard reactions (sugar toxicity) are fundamentally progressive, degenerative, chronic inflammatory, aging/disease processes that glycate, carameelize and chronically immune activate (“inflames”) specific tissues, organs, and organ systems. The pharmacologic drugs currently used to treat symptoms of Alzheimer’s disease and other labeled “idiopathic” forms of cognitive declines consist of two classes: Cholinesterase inhibitors and NMDA receptor blockers. Cholinesterase inhibitors are basically insecticides.[266]. Their short term effectiveness is marginal and only lasts for months on average.[267-269] Side effects and cost are limiting factors for their use. Additional conventional methods that are helpful include Exercise [270], Melatonin [271], Growth Hormone (hGH) [272] and Testosterone.[273] There is mounting evidence that low level environmental toxic metal accumulation (Aluminum, Mercury, Lead, Cadmium, etc.) contributes to cognitive decline/memory loss. This problem can only be treated medically with the process of Chelation Therapy.[274-278] Certain vitamins, other nutrients [279-282] and herbs [283] have shown effectiveness anecdotally.

A common problem with understanding the academic, scientific classification of memory loss/cognitive dysfunction syndromes is language. True Alzheimer’s “disease” (cognitive decline and autopsy evidence of amyloid/tau protein with neurofibrillary tangles) as originally described and defined by Alois Alzheimer always occurred, by definition, before 55 years of age. Because of this relatively young age it was also sometimes also referred to as “pre-senile dementia” or “dementia praecox” (psychiatric label). If the patient was 56 years old or older the problem was called “senile” dementia or chronic organic brain syndrome. The two conditions and terms are now commonly mixed and referred to as Alzheimer’s-like Senile Dementia (ALSD) or Alzheimer’s “syndrome.” In addition, there are other “syndromic” variations of memory loss problems (Pick’s disease, Parkinson’s disease, age related cognitive decline, Huntington’s disease and others). To add to this taxonomic confusion, Micro-vascular ischemic cognitive dysfunction, the underlying cause of most “Alzheimer’s-like Senile Dementia (ALSD, Alzheimer’s “syndrome,” Leukoaraiosis or Neurological Micro-vascular sugar toxicity) is much more common than true Alzheimer’s “Disease” (genetics, abnormal amyloid or tau proteins, and anatomic neurofibrillary tangles). There are many theories about how Alzheimer's disease develops.[284] Alzheimer’s syndrome and other forms of Leukoaraiosis are caused or aggravated by Micro-vascular sugar toxicity.[79-80] The similarities and overlap between the two conditions (Alzheimer’s syndrome / Vascular Dementia) is clinically difficult to discern.[285] Despite the clinical and scientific name differences they are all conventionally treated with the same four pharmaceutical drugs, on label or off label.[267-269]
Additional non-standard treatments for cognitive decline related to brain Micro-vascular disease are intravenous EDTA Chelation (Ethylene Diamine Tetra-acetic Acid) therapy [263-266], Intravenous Orthomolecular therapy (Glutathione/Meyer’s cocktail) and/or Enhanced External Counterpulsation therapy (EECP).[262,286-292] Although these approaches are currently considered “off-label” (i.e. not FDA approved for this clinical use), there is mounting evidence for their effectiveness in reversing cognitive dysfunction.[262, 286-292] In addition, ongoing research has demonstrated that modifying standard EDTA Chelation (a modification called Metabolic or Meta-Chelation) to reverse Micro-vascular glycation can lead to further clinical improvement in memory loss/cognitive decline.[293] Capillary Micro – vessels are essentially naked, functional endothelium without the additional connective and muscular tissue normally found in Macro-vessels. Micro-vascular capillary endothelial networks perfuse through all tissues and organs providing the biophysical, biomechanical and biochemical matrix for normal physiologic function. When capillary Micro – vessels maximally dilate during cardiac systole (“contraction”) they are 10 microns in diameter. During cardiac relaxation diastole they collapse to 5 microns. A red cell is 8 microns in diameter. Red cells must pass through these pulsating capillary networks in single file. Caramelized/glycated capillaries (endothelium) and/or red blood cells (HbA1C) gradually become rigid (loss of compliance/abnormal PORH/PVR) leading to small areas of ischemia (lack of oxygen) or cellular/tissue damage (i.e. heart “infract”, brain lacunar “stroke”, kidney “nephrosclerosis”, muscle “trigger point”, joint “degenerative arthrosis”). Standard EDTA chelation therapy acts biochemically to provide therapeutic effects involving free radical toxicity (toxic metals), blood viscosity (anti-coagulant), metabolism (lowers blood sugar), tissue de-calcification and other probable unspecified mechanisms. Meta-Chelation incorporates additional intravenous nutrients, minerals and supplements to reverse protein glycation. Orthomolecular therapy acts biochemically to support metabolism. Enhanced External Counterpulsation (EECP) therapy works by biomechanically disrupting (“fracturing”) the sugar stiffened endothelial glycocalyx via increasing diastolic blood pressure (“augmentation”) and biophysically re-entraining physiologic cardiac pulsation in the endothelial Micro-vascular matrix.

In an interesting study Diabetic patients with cognitive decline due to Micro-vascular ischemic brain atrophy treated in a clinical trial with “intensive” glucose control failed to show improved cognitive function.[294] However, patients in the intensive treatment group had significantly greater brain volume at 40 months of treatment [294] Brain atrophy is common as we age and considered to be “normal aging” in conventional medicine, but it really is not “normal” in healthy aged.[295] The cause is the gradual (years to decades) development of global Micro-vascular ischemic atrophy of the brain. The study [294] demonstrated that while late application of intensive sugar control for a defined period of time did not benefit functional decline it had a positive and dramatically beneficial effect structurally. Function may be preserved if the process is treated much earlier. By slowing glycation, the preservation of brain volume strongly suggests improved Micro-circulation function (fluid balance, oxygenation, nutrients, waste removal, end circulation pulsatile waves). This strongly suggests the earlier clinical evidence of sugar toxicity is detected the more likely the process can be treated and potentially reversed.[98-99,101-106]

Autonomic dysfunction diagnosed by clinical symptoms (palpitations, anxiety, insomnia,
dizziness, etc.) or testing (abnormal PORH, EAV testing, etc.) can be treated and improved or eliminated by improving the underlying metabolic syndrome and/or removing toxic minerals with chelation therapy.[236-238] In addition, following homeopathic-isopathic concepts, dysautonomia is commonly associated with the homeopathic-isopathic nosodes Coxsackie/Enterovirus. Interestingly, scientific evidence that Enteroviruses, such as Coxsackie and other neurotropic Enteroviruses (EV 68-71), cause dysautonomic syndromes by attacking the brain stem and spinal cord has been documented.[296-300] Interestingly, Coxsackie virus has also been implicated as a cause of Type 1 Diabetes.[301] Additional therapy directed at viral issues include intravenous Ozone therapy (major Auto-Hemo Therapy), intravenous Hydrogen Peroxide therapy, Ultra-Violet Blood Irradiation (UVBI) intestinal anti-biofilm therapy and/or, Coxsackie/Enterovirus Isopathic Nosode therapy.

Figure 4: depicts the logical clinical approach to the prevention and treatment of sugar toxicity, beginning with diet and lifestyle changes and progressing to meta-chelation and EECP. The first 3 stages are patient centered and very cost effective ($). Stages 4 and 5 are physician centered and more expensive ($$$). Thus, early detection and treatment of sugar toxicity should be the goal of patient and physician.

Figure 4.

Conclusion:

Free radical chemistry is both necessary for life, but also toxic to life. Sugar interactions
with biological molecules is likewise essential for life (Glycosylation), but also toxic to life (Glycation). The important difference between the two processes is that physiologic Glycosylation is regulated and controlled by enzymes while pathological Glycation is not. Glycation is hazardous in its deactivation and caramelization of structural and functional proteins.[302] With the clinical realization that sugar driven Micro-vascular disease is the fundamental patho-physiologic and pathological process underlying most chronic degenerative syndromes [108-115,117-129] and diseases, sugar excess has become the main dietary element that should be identified and avoided before and after symptomatic disease appears.[303] Perhaps modern society should revisit the ancient Greek Delphic Oracular admonition of “Nothing in excess (‘Meden agan’).” When one considers the extreme amounts of sucrose, glucose and fructose now found in the American diet and the underlying pathology caused by such dietary excess, the clinical implications for treatment and, more importantly, prevention become apparent. Treatment to reverse such Micro-vascular and protein glyco-toxic pathology is time consuming, expensive and could become almost unnecessary if the process is recognized early and effective preventive measures are adopted by government, politicians and medical science. Unfortunately, the politics, economics and rampant scientism currently shaping scientific nutritional and medical thought seem incapable of addressing this problem. One bright glimmer of science on the horizon, however, is the new science of the “Microbiome.” This new science is beginning to relate the microbes that live in and on the human body to overall health and disease patterns, including glyco-toxicity syndromes.[304-305] Perhaps, one day, treating chronic glyco-toxic degenerative diseases may be as simple as fecal transplant or providing an encapsulated freeze dried sample of fecal micro-organisms from those who are healthy to those unfortunate enough to be plagued by these chronic diseases. Until that time, however, patients and practicing physicians will have to make do with the current state of praxis in dealing with sugar toxicity.
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