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Type 2 DIABETES - LIVE NORMAL AGAIN PDF

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EXECUTIVE SUMMARY

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STATEMENT OF PURPOSE & WARNING

THIS IS NOT A PRESCRIPTION OR A SUGGESTION TO USE THIS INFORMATION, THIS IS ONLY INFORMATION AND YOU ARE THE DECIDER OF WHAT TO DO - IT IS YOUR SOVEREIGN RIGHT TO DECIDE WHAT YOU WILL DO FOR YOURSELF. Be forewarned, these

ideas and information are not ever intended for children or pregnant or nursing women, as these are much more constrained by the needs of the child or the embryo or infant. This information is only for mentally competent adults. For competent adults, Doctors or the Law have no constitutional or moral right to force you to continue suffering on to death. YOU ARE THE SOVEREIGN OF YOUR LIFE.

My purpose is to acquaint you with known SCIENTIFICALLY VETTED alternatives that I have carefully studied for low potential problems to ALLEVIATE OR CURE Type 2 DIABETES (T2D). These alternatives require a concerted employment of multiple simple actions to reverse the multiple aspects of T2D. These techniques result in a "SYNERGIC" (results of A+B together far greater than technique A and technique B would separately add) approach to alleviating or "curing" T2D.

A. OVERVIEW

Type 2 Diabetes (T2D) is a worsening with time ("progressive") disease that has proved difficult to reverse. Science has now unlocked the key to the cause of this progression: "inflammatory" mechanisms that began all the way back to Metabolic Syndrome (rising blood pressure, typically increasing intra-abdominal fat (big belly), disturbances of normal lipid profiles). These problems worsen in T2D to massive insulin "insensitivity" of fat cells, muscle, liver and beta cell tissues and problems with maintaining a healthy (low) blood glucose level . T2Ds do not undergo total loss of the insulin producing beta-cells in the pancreas the way Type 1 Diabetics (T1D) usually do. This is because T1Ds have an autoimmune attack on their insulin producing cells. Inflammation is a less extreme disturbance by a process of irritating and causing dysfunction in these tissues. Generally, T2Ds have 50% of a "normal" insulin producing "beta cells" at diagnosis and have some 40% of original

beta cell numbers at death. The insulin producing Beta cells are not lost, nor completely inactive. The Beta cells are not good producers of insulin relative to normals. in T2D. This is because of this inflammatory assault which is not as drastic as autoimmunity, but does disorder the normal scheme. However, beta-cells can return to higher insulin production and even divide and return to nearer normal numbers and activity, but only when they are not subject to the high "inflammatory" stress of T2D. What is occurring in T2D is the insulin resistance (requiring higher insulin production) and elevated blood glucose driven inflammatory caused dysfunction of existing beta-cells and a general whole body inflammatory process. This inflammatory process in the bodyof a T2D promotes the diseases that T2D usually die of (Heart disease, stroke, kidney failure, etc.). Once this inflammatory process is begun, no amount of good glycemic control (good blood sugar management**) will stop the progression of this disease toward PREMATURE and NEEDLESS DEATH (but good glucose control will slow it considerably). The world wide epidemic of T2D is wrecking the financial underpinning of our medical treatment systems. Scientific demonstration of protection from this progression by specific non-drug anti-inflammatories as been accomplished. These non-drug inflammatories are components of foods that have been used by humans for thousands of years. T2D causes a broad range of dysfunction that must be solved by multiple simple voluntary actions of affected individuals. FOR THE FIRST TIME IN HISTORY - we have a clear opportunity to reverse (literally to cure) T2D. This PDF is an explanation of extent of the T2D problem and the recent scientific findings and FINALLY a set of 3 different ways to alleviate or escape this needless deadly condition.**

B. Extent of World Wide Type 2 Diabetes

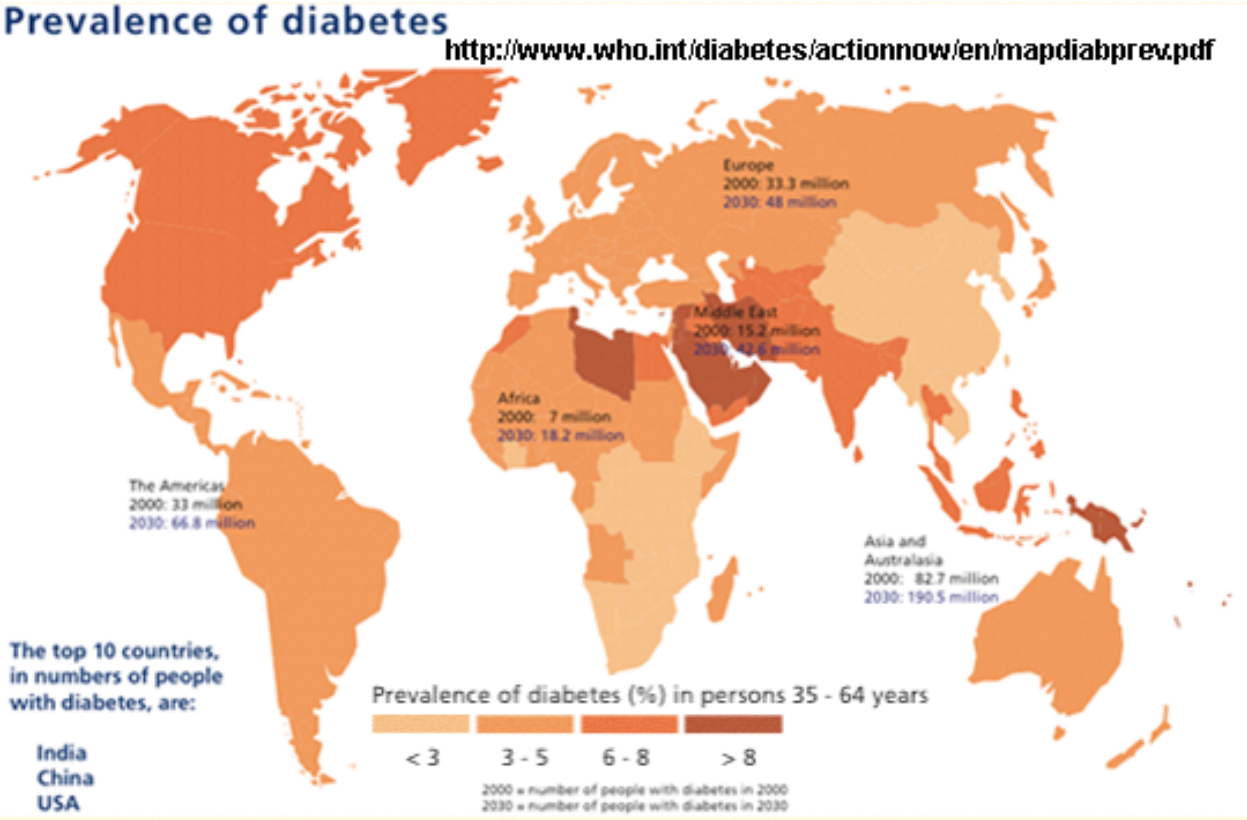
Type 2 Diabetes is becoming an out of control epidemic in the USA and the whole world. Over a third of the population of the USA is now classifiable as diabetic **by the standard criteria in the field (Impaired fasting plasma glucose levels)**. A recent report from Catherine C. Cowie of the **National Institute of Diabetes and Digestive and Kidney Diseases**, in Bethesda based on findings of the National Health and Nutrition Examination Survey (**NHANES**) details the large rise in undiagnosed diabetes in the USA as reported in the **Prevalence of Diabetes and Impaired Fasting Glucose in Adults in the U.S. Population Diabetes Care. 2006 Jun;29(6):1263-8** http://www.ncbi.nlm.nih.gov/pubmed/16732006. A large share of this increase is occurring in minority populations.

Previous data indicated a smaller number and fraction of the US population:

> There are an estimated 23.6 million people in the U.S. (7.8% of the population) with diabetes with 17.9 million being diagnosed,[2] 90% of whom are type 2.[3] With prevalence rates doubling between 1990 and 2005, CDC has characterized the increase as an epidemic.[4] Traditionally considered a disease of adults, type 2 diabetes is increasingly diagnosed in children in parallel to rising obesity rates [5] due to alterations in dietary patterns as well as in life styles during childhood.[6] *Diabetes mellitus type 2* http://en.wikipedia.org/wiki/Diabetes_mellitus_type_2

WHO WORLD MAP OF PREVALENCE OF DIABETES

http://www.who.int/diabetes/actionnow/en/mapdiabprev.pdf



This UN data(2004) is already out of date with the new figures for Mainland China at 1 in 10 people **now diabetic** and **a further 2 in 10 on the path to diabetes** (T2D) (http://news.bbc.co.uk/2/hi/asia-pacific/8587032.stm). This alone would considerably boost the WHO 2000 call of 171 million diabetics in the world (http://en.wikipedia.org/wiki/Diabetes_mellitus). Since world population is highest in Asia, some 70% of the world's diabetics are in Asia (principally India and China). There is also a real higher genetic susceptibility of some humans to T2D than others.

> Rates of type 2 diabetes, obesity and their associated detrimental cardiovascular effects are rapidly increasing. Despite the availability of several treatment options for type 2 diabetes and the use of intensive regimens combining several antidiabetic drugs, **less than one-half of all patients reach a target glycosylated hemoglobin level of less than 7%. Disease progression due to ongoing deterioration of pancreatic islet cell health and beta-cell function is likely**

responsible.*The incretin system and cardiometabolic disease.* Szmitko PE, Leiter LA, Verma S. Can J Cardiol. 2010 Feb;26(2):87-95. http://www.ncbi.nlm.nih.gov/pubmed/20151054

C. WHY IS TYPE 2 DIABETES A PROGRESSIVE DISEASE ?

As all **T2D**'s know, two problems swamp all others. The **first** is **maintaining normal levels of (blood) plasma glucose** both under **fasting conditions** and **under fed conditions (post-meal = post-parandial)**. The **second** is the **steadily eroding insulin sensitivity** (or rising insulin resistance) that worsens the problems of the first problem. Since insulin is needed to trigger conditions that lower blood plasma glucose levels to normal, an insensitivity to insulin in muscles, fat cells, and the liver is going to worsen the problems of clearing glucose from the blood.

Momentarily excluding longer term pathology consequences, **several other problems arise from this process of T2D**. The **liver acts aberrantly in making more glucose** which would be correct during starvation or a prolonged fast in a normal individual. In a T2D individual struggling with blood plasma glucose levels, it adds more problems **that is the primary reason for the use of metformin** to diminish this. The **fat cells also develop insulin resistance and thus begin adding more free lipid to the blood** rather than a more physiologically appropriate removal of sugar to become fat stored in the fat cell. Even the **kidney functions to increase reabsorption of glucose under high blood plasma glucose load**. When the central nervous system becomes more insulin resistant, one gets various neurotransmitter dysfunction (http://www.ncbi.nlm.nih.gov/pubmed/ 20206731).

> Currently, the management of type 2 diabetes focuses on glucose control via lowering of blood glucose (fasting and postprandial) and hemoglobin A(1c). However, **the goal of therapy should be to delay disease progression and eventual treatment failure**. Treatment should target the known

pathogenic disturbances of the disease (i.e., **reducing the deterioration of beta-cell function and improving insulin sensitivity**). ***Current issues in the treatment of type 2 diabetes. Overview of newer agents: where treatment is going***. DeFronzo RA. Am J Med. 2010 Mar;123(3 Suppl):S38-48. (http://www.ncbi.nlm.nih.gov/pubmed/20206731)

T2D is a progressive disease that just keeps getting worse, albeit at a slower rate for those individuals who maintain excellent glycemic control and try to exercise.

Type 2 diabetes is a progressive disease in which the risks of myocardial infarction, stroke, micro-vascular events, and mortality are all strongly associated with hyperglycemia (1). **The disease course is primarily characterized by a decline in β-cell function and worsening of insulin resistance**. The process is manifested clinically by deteriorations in multiple parameters, including A1C, fasting plasma glucose (FPG), and postprandial glucose levels.

Obesity plays a key role in the pathophysiology of type 2 diabetes (T2DM), and weight loss is a major objective, although difficult to achieve with medical treatments. *Bariatric surgery in patients with type 2 diabetes: benefits, risks, indications and perspectives*. Scheen AJ, De Flines J, De Roover A, Paquot N. Diabetes Metab. 2009 Dec;35(6 Pt 2):537-43. http://www.ncbi.nlm.nih.gov/pubmed/20152741

How much decrease in Pancreatic function occurs before one gets Type 2 Diabetes?

It was found that **islet function < insulin producing beta-cell are called "islets of Langerhans" in the pancreas > was about 50% of normal at the time of diagnosis** and **reduction in beta-cell mass of about 60% at necropsy (accelerated apoptosis) < end stage T2D (death) do not usually go to zero beta-cell, only an average of 10% reduced from the**

typical 50% of normal at diagnosis ! > . ***Clinical Approaches to Preserve beta-Cell Function in Diabetes***. Wajchenberg BL Adv Exp Med Biol. 2010;654:515-35. http://www.ncbi.nlm.nih.gov/pubmed/20217513

According to the most recent data from the Centers for Disease Control, **nearly 24 million Americans have type 2 diabetes mellitus (T2DM)**; **of these, 6 million individuals with T2DM remain undiagnosed**. **At least 57 million more American adults are at high risk for developing T2DM by virtue of having impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or both, which constitute pre-diabetes**. Treating T2DM remains challenging, despite the availability of effective therapies. **Recent data indicate that slightly more than half of the patients (~56%) with T2DM are achieving the American Diabetes Association (ADA) glycosylated hemoglobin (HbA1C) goal of <7%**. **A major contributing factor to the inability to maintain glycemic control in patients with T2DM is its progressive nature < disease continues to worsen on to death, this despite good glycemic control, but accelerates with poor glycemic control >**. **There is a continuum from normoglycemia to IGT/IFG (prediabetes) to diabetes, and from uncomplicated diabetes to more difficult-to-control diabetes and diabetes with complications**. This continuum has implications for treatment strategies and for the need to continually modify these strategies as the disease progresses. Understanding where the patient is on the continuum of disease may help identify mechanisms of action that can be targeted and aid in therapeutic decision-making. For example, early in the disease process, T2DM is characterized by insulin resistance and hyperinsulinemia. As such, agents that target insulin sensitivity and insulin resistance may be especially useful early in the disease process. **Although the 2 main defects of T2DM are insulin resistance and pancreatic beta-cell dysfunction/failure, other aspects of its pathophysiology may be targeted to specific metabolic pathways and effects**.

Clinical practice in type 2 diabetes: After metformin and lifestyle, then what? Cobble ME, Peters AL. J Fam Pract. 2009 Nov;58(11 Suppl Clinical):S7-14. http://www.ncbi.nlm.nih.gov/pubmed/19891948

Why do things keep getting worse? Why does Pancreatic function continue to decline in Type 2 Diabetes? Even when individuals achieve relatively good glycemic control and show near normal blood glucose levels?

In type 2 diabetes (DM2) **there is progressive deterioration in beta-cell function and mass**. It was found that islet function was about 50% of normal at the time of diagnosis and reduction in beta-cell mass of about 60% at necropsy (accelerated apoptosis). ***Clinical Approaches to Preserve beta-Cell Function in Diabetes***. Wajchenberg BL. Adv Exp Med Biol. 2010;654:515-35. http://www.ncbi.nlm.nih.gov/pubmed/20217513

In type 2 diabetes, **β-cells fail to adapt to impaired glucose tolerance < cannot keep increasing insulin production so blood glucose rises >**. This failure appears to be related to **a reduction in insulin secretion per islet as well as a reduction in the total number of islets**. **Progressive loss of β-cell function** and, to a lesser extent, **reduced β-cell mass** lead to **worsening glycemic control and development of complications**. **Although they lower glucose, current therapies do not completely abolish this progressive loss of β-cell function, and their use is also associated with hypoglycemia and weight gain** (Table 2). Thus, **the need for additional glucose-lowering therapies that can halt β-cell deterioration without contributing to weight gain continues**. *Defining and characterizing the progression of type 2 diabetes*. Fonseca VA. Diabetes Care. 2009 Nov;32 Suppl 2:S151-6. http://www.ncbi.nlm.nih.gov/pubmed/19875543 .

> Rates of type 2 diabetes, obesity and their associated detrimental cardiovascular effects are rapidly increasing. Despite the availability of several treatment options for type 2 diabetes and the use of intensive regimens combining several antidiabetic drugs, **less than one-half of all patients reach a target glycosylated hemoglobin level of less than 7%**. **Disease progression due to ongoing deterioration of pancreatic islet cell health and beta-cell function is likely responsible**.***The incretin system and cardiometabolic disease***. Szmitko PE, Leiter LA, Verma S. Can J Cardiol. 2010 Feb;26(2):87-95. http://www.ncbi.nlm.nih.gov/pubmed/20151054

> ..much interest is focused on the possibility of **preserving the β-cell to prevent the onset of diabetes**, **or impede the progressive deterioration of glycemic control**, observed after diagnosis and developing over the years. ***Goals of treatment for type 2 diabetes: beta-cell preservation for glycemic control.*** Marchetti P, Lupi R, Del Guerra S, Bugliani M, D'Aleo V, Occhipinti M, Boggi U, Marselli L, Masini M. Diabetes Care. 2009 Nov;32 Suppl 2:S178-83. http://www.ncbi.nlm.nih.gov/pubmed/19875548

As the earlier DeFronzo quote about "reducing the deterioration of beta cell function", the underlying problems are regarded as insulin sensitivity and the deterioration of the beta-cell function. However, recent published scientific work indicates that **a major (if not the major) reason for this deterioration process is an ongoing inflammatory damage** to the **beta-cells** that then spreads to **inflammatory damage and dysfunction to the whole body**. **This places T2D as a inflammatory disease like that of heart disease and as some have characterized cancer**.

> Evidence in support of the concept of local pancreatic islet inflammation as a mechanism of beta cell failure in type 2 diabetes is accumulating. Observations in human islets from type 2 diabetic patients and rodent models of the disease **indicate the increased presence of IL-1 driven <**

inflammatory > cytokines and chemokines in pancreatic islets, concomitant with immune cell infiltration. **Inflammation is the body's protective response to harmful stimuli and tissue damage. However, under chronic stress (e.g. metabolic stress in obesity and type 2 diabetes) the body's own defensive response may become deleterious to tissue function.** ***Pancreatic islet inflammation in type 2 diabetes: from alpha and beta cell compensation to dysfunction.*** Ehses JA, Ellingsgaard H, Böni-Schnetzler M, Donath MY. Arch Physiol Biochem. 2009 Oct;115(4):240-7. http://www.ncbi.nlm.nih.gov/pubmed/19645635

Onset of Type 2 diabetes occurs when the pancreatic beta-cell fails to adapt to the increased insulin demand caused by insulin resistance. **Morphological and therapeutic intervention studies have uncovered an inflammatory process in islets of patients with Type 2 diabetes characterized by the presence of cytokines, immune cells, beta-cell apoptosis, amyloid deposits, and fibrosis**. This insulitis is due to a **pathological activation of the innate immune system by metabolic stress** and governed by IL-1 signaling **< IL-1 is an immune system inflammatory signaling molecule >** . We propose that this insulitis **< inflammation of the pancreas > contributes to the decrease in beta-cell mass and the impaired insulin secretion** observed in patients with Type 2 diabetes. *Islet inflammation impairs the pancreatic beta-cell in type 2 diabetes*. Donath MY, Böni-Schnetzler M, Ellingsgaard H, Ehses JA. Physiology (Bethesda). 2009 Dec;24:325-31. http://www.ncbi.nlm.nih.gov/pubmed/19996363

Chronic inflammation is being shown to be increasingly involved in the onset and development of several pathological disturbances such as arteriosclerosis, obesity, diabetes, neurodegenerative diseases and even cancer. Treatment for chronic inflammatory disorders has not been solved, and there is an urgent need to find new and safe anti-inflammatory compounds. Flavonoids belong to a group of natural substances occurring normally in the diet that exhibit a

variety of beneficial effects on health. **The anti-inflammatory properties of flavonoids have been studied recently, in order to establish and characterize their potential utility as therapeutic agents in the treatment of inflammatory diseases.** Several mechanisms of action have been proposed to explain in vivo flavonoid anti-inflammatory actions, such as antioxidant activity, inhibition of eicosanoid generating enzymes or **the modulation of the production of proinflammatory molecules. Recent studies have also shown that some flavonoids are modulators of proinflammatory gene expression, thus leading to the attenuation of the inflammatory response**. *Flavonoids as anti-inflammatory agents: implications in cancer and cardiovascular disease*. García-Lafuente A, Guillamón E, Villares A, Rostagno MA, Martínez JA. Inflamm Res. 2009 Sep;58(9):537-52. Epub 2009 Apr 21. http://www.ncbi.nlm.nih.gov/pubmed/19381780

Islets produce a variety of cytokines and chemokines in response to physiologic and pathologic stimulation by nutrients. The cellular source of these inflammatory mediators includes alpha-, beta-, endothelial-, ductal- and recruited immune cells. Islet-derived cytokines promote alpha- and beta-cell adaptation and repair in the short term. Eventually, chronic metabolic stress can induce a deleterious autoinflammatory process in islets leading to insulin secretion failure and type 2 diabetes. ***Cytokine production by islets in health and diabetes: cellular origin, regulation and function.*** Donath MY, Böni-Schnetzler M, Ellingsgaard H, Halban PA, Ehses JA. Trends Endocrinol Metab. 2010 May;21(5):261-7. Epub 2010 Jan 22. **http://www.ncbi.nlm.nih.gov/pubmed/20096598**

This inflammatory generation of T2D is not only the origin of the hyperglycemia that T2D are understandably desperate to keep under control, is the major driving force underlying the continuation of PROGRESSION toward a premature (and needless) death. As you know, your Beta cells are mostly still there, but are not functioning well enough to keep you glucose levels down. On top of this, other aspects of this inflammatory situation are increasing insulin resistance so that what insulin

is produced and released has less effect. Clearly there is a need for a multipronged attack on this problems that solves most of these multiple problems. Otherwise, even if you maintain near perfect glycemic control, the disease still worsens on to needless premature death.

> **Chronic hyperglycemia** and **inflammatory cytokines < Immune system activation molecular signals >** disrupt and/or **attenuate signal transduction pathways that promote normal beta-cell survival**, **leading to the destruction of endocrine pancreas in type 2 diabetes**. There is convincing evidence that autocrine insulin signaling **< good insulin production that feeds back to a receptor on the beta cell >** exerts protective anti-apoptotic **< anti-self suicide >** effects on beta cells. **Suppressors of cytokine signalling (SOCS) were induced by several cytokines and inhibit insulin-initiated signal transduction**. ***High glucose induces suppression of insulin signalling and apoptosis via upregulation of endogenous IL-1beta and suppressor of cytokine signalling-1 in mouse pancreatic beta cells.*** Venieratos PD, Drossopoulou GI, Kapodistria KD, Tsilibary EC, Kitsiou PV. Cell Signal. 2010 May;22(5):791-800. Epub 2010 Jan 11 http://www.ncbi.nlm.nih.gov/pubmed/20067833

This last quote is important because the insulin secreting cells in the pancreas run at what might be described as **a constant speed**. **They do not increase the amount of insulin they are making when a much higher load of blood glucose is present**. **Instead, they prepare a surplus of inactive insulin in granules stored in the insulin secreting cell and use the signal of blood glucose level to determine how much of this pre-made insulin to release as active insulin**. This prestored supply is what the glucose tolerance test measures when you are given a big amount (usually 75 grams) of glucose and monitored 2 hours later to find out if you had enough stored away "ready to go" insulin to normalize your blood sugar below 200 mg/deciliter. The other major test is to find out how able your body is to handle fasting conditions. In that case, after an overnight fast, if you repeatedly (2 times min) have over 126 mg/deciliter of plasma glucose you are also classified as diabetic.

So, while the doctors pointed out that you have diabetes which is a problem handling glucose levels in your blood, what appears to lie behind diabetes (and heart disease, and numerous other diseases related to aging) is this underlying inflammation. In the case of diabetes (and also heart disease, and others), this appears to be a consequence of over consumption of food !

Obesity, type 2 diabetes, and the associated metabolic syndrome are known as the **aggregate products from nutritional excess**, and have become huge epidemics and represent public health problems in the developed world. **Yet, there exist few successful approaches for the treatment and prevention of these complex diseases, in part because they are not well understood at the molecular levels. Recent research has revealed that many nutrient- and pathogen-sensing systems can be highly integrated, positing the regulatory system of immune response at the mechanistic interface between metabolic regulation and the development of overnutrition-related diseases. The underlying molecular processes have been associated with the basis of how nutritional changes trigger atypical inflammation and how metabolic inflammation affects the signaling and functions of metabolic tissues and cells. In this endeavor, the pro-inflammatory axis consisting of the nuclear transcription factor NFkappaB and its upstream kinase IKKbeta < if prevent NFkB action, will end much (all?) of inflammatory situation > has been identified as one critical mediator that is responsible for nutritionally-induced inflammation, and a large body of research has been documented to support the concept that IKKbeta/NFkappaB represents a general**

cause of various metabolic dysfunctions under overnutrition **< for metabolic dysfunctions read Metabolic Syndrome and Type 2 Diabetes as well as others >**. ***NFkappaB-mediated metabolic inflammation in peripheral tissues versus central nervous system***. Cai D. Cell Cycle. 2009 Aug 15;8(16):2542-8. Epub 2009 Aug 29. http://www.ncbi.nlm.nih.gov/pubmed/19633416

This sets up inflammatory conditions that cause the fat cells inside your gut cavity to release inflammatory molecules that are only now becoming characterized. Thus **T2D** that begins with **Metabolic Syndrome** (hypertension, elevated lipids, rising blood sugar, etc.) and then gets much worse when the alpha cells of the pancreas put out the immune inflammatory messenger called **cytokine IL1b**. The rising glucose levels in blood make this far worse and also jack up the level of inflammation.

Inflammation here is "atypical" or "unusual", and not the immune systems response to a real potential threat (like a bacterial infection or a virus). Here it is acting not against external invaders (bacteria, fungi, etc.) but rather as a response to over eating and its consequences on fat accumulation in the gut and **then the nearby alpha-cells of the pancreas that deliver inflammatory cytokine IL-1b to their next door neighbors the insulin producing beta-cells**.

It gets worse. When the **cytokine IL-1b** that is delivered to the insulin producing beta-cells, it is **a messenger** to **activate an inactive transcription factor called NFkB (Nuclear Factor kappa B)**. This now activated **NFkB** in the beta-cells(NFkB can be activated in almost all cells) builds **yet more inflammatory messengers** (cytokines and others) that make the problem worse for the insulin producing beta-cell. **The poor beta-cells are overwhelmed by inflammatory events and suffer decline in their ability to produce insulin**. **Some beta-cells die** and **the others are just down regulated in insulin production by this inflammatory disaster**.

This is occurring while other inflammatory events are turning down the sensitivity to insulin (or increasing insulin resistance and thus requiring more insulin for the same amount of glucose clearing effect) of your muscles, liver, and fat cells. Is it any surprise that these

organs show dysfunctional behavior when also treated to such a huge inflammatory problem.

Now you understand that even in late T2D, your insulin producing beta-cells are not out of the game. Some or most can recover and may even be able to very slowly divide to repopulate needed levels. This is impossible for the auto-immunity destroyed Type 1 Diabetes (T1D) beta-cell replacements.

Stem cells (not yet committed to tissue type - are literally a reserve of pluripotent cells that can become any one of a limited range of tissues. Uncommitted (to final tissue type) Stem Cell lines in our body that can differentiate to a final adult cell type and function (under the right conditions). Stem cells that can differentiate into particular mature tissues are believed to exist for all somatic tissues, and this would apply to human beta cells as well. In mice, precursor cells that are not active insulin secreting cells have been found that with age or injury to the pancreas, to mature into insulin producing beta cells (http://www.ncbi.nlm.nih.gov/pubmed/20056825). Both of these methods of increasing beta cells (division and maturation of precursor cells) are likely inhibited by the high level of inflammation and its continued increase. Your system is inflaming itself into a dysfunctional state that is in a vicious cycle of getting worse. THIS IS WHAT YOU MUST STOP (along with good glycemic control!)

> Whereas it is believed that the pancreatic duct contains endocrine precursors, **the presence of insulin progenitor cells residing in islets remain controversial.** We tested whether pancreatic islets of adult mice contain precursor beta-cells that initiate insulin synthesis during aging and after islet injury**,.. Our studies also demonstrate that the percentage of PLAP(+)IN(+) cells in islets increased after islet injury and identified putative precursors in islets. We postulate that PLAP(+)IN(-) precursors differentiate into insulin-positive cells that participate in a slow renewal of the beta-cell mass during aging and replenish beta-cells eliminated by injury. *Precursor cells in mouse islets generate new beta-cells in vivo during aging and after islet injury*.** Liu H, Guz Y, Kedees MH, Winkler J, Teitelman G. Endocrinology. 2010 Feb;151(2):520-8. Epub 2010 Jan 7. **http://www.ncbi.nlm.nih.gov/pubmed/20056825**

Since this **inflammation** (but **not auto-immunity** as in **T1D**) is the driving force behind the progression from **Metabolic Syndrome** (Hypertension, elevated lipid profiles, intra-abdominal obesity, etc.) **to overt diabetes** (and heart disease and yet others with genetic differences important in what we get), what should we do to prevent this? Should we attempt to block the immune messenger IL-1beta that is indicated in **T2D** ?

> **IL-1beta < IL-1b >** is **a regulator of the body's inflammatory response** and is produced after infection, injury, and antigenic challenge **< also plays same role in creating and progressing inflammatory diseases in an otherwise uninfected body >**. It plays a role in various diseases, including autoimmune diseases such as rheumatoid arthritis, inflammatory bowel diseases and type 1 diabetes, as well as in diseases associated with metabolic syndrome such as atherosclerosis, chronic heart failure and **type 2 diabetes**. Macrophage are the primary source of IL-1, but epidermal, epithelial, lymphoid and vascular tissues also synthesize IL-1. IL-1beta production and **secretion have also been reported from pancreatic islets < hyperglycemia causes the glucogon secreting alpha cells in the pancrease to secrete IL1beta which injures the insulin secreting beta cells of the pancreas >**. Insulin-producing beta-cells within pancreatic islets are specifically prone to IL-beta-induced destruction and loss of function. **Macrophage-derived IL-1beta production in insulin-sensitive organs, leads to progression of inflammation and induction of insulin resistance in obesity < and it maintenance in the progression process that kills Type 2 Diabetics >**. ***Interleukin-1 beta targeted therapy for type 2 diabetes.*** Maedler K, Dharmadhikari G, Schumann DM, Størling J. Expert Opin Biol Ther. 2009 Sep;9(9):1177-88. http://www.ncbi.nlm.nih.gov/pubmed/19604125

A likely problem with this is that it will not be effective enough. Why? The immune system is a very complicated - interacting and not fully understood but very complex system. If we decide to approach the problem by just trying to stop one cytokine (immune messenger), **we are likely to fail** - because of the extensive interactions. On the other hand, we can use **well known natural products that have been long consumed in human**

culture that massively inhibit the initial starting of an inflammatory process.

> **Chronic inflammation is being shown to be increasingly involved in the onset and development of several pathological disturbances such as arteriosclerosis, obesity, diabetes, neurodegenerative diseases and even cancer. Treatment for chronic inflammatory disorders has not been solved, and there is an urgent need to find new and safe anti-inflammatory compounds. Flavonoids belong to a group of natural substances occurring normally in the diet that exhibit a variety of beneficial effects on health. The anti-inflammatory properties of flavonoids have been studied recently, in order to establish and characterize their potential utility as therapeutic agents in the treatment of inflammatory diseases.** Several mechanisms of action have been proposed to explain **in vivo flavonoid anti-inflammatory actions**, such as antioxidant activity, inhibition of eicosanoid generating enzymes or **the modulation of the production of proinflammatory molecules. Recent studies have also shown that some flavonoids are modulators of proinflammatory gene expression, thus leading to the attenuation of the inflammatory response**. ***Flavonoids as anti-inflammatory agents: implications in cancer and cardiovascular disease***. García-Lafuente A, Guillamón E, Villares A, Rostagno MA, Martínez JA. Inflamm Res. 2009 Sep;58(9):537-52. Epub 2009 Apr 21. http://www.ncbi.nlm.nih.gov/pubmed/19381780

If chronic stress via **inflammation** is what is behind the progression of **T2D** (as well as many other age related diseases), what is the best target to take out this problem **in a big way** - **rather than a endless piece-meal shooting at everything**? **We go after the modulators of the overall inflammation process !**

Many studies suggest that **NF-kB** should be considered as an important mechanisms of inflammatory processes and autoimmune diseases. Many important anti-inflammatory drugs and immunosuppressants inhibit **NF-kB**. **Several observations have suggested a role of the inappropriate activation of NF-kB in cell proliferation, transformation, and tumor development, mainly lymphomas**. Conversely, it has been proposed that the activation of NF-kB in immune cells may contribute to anti-tumor immunity... **NF-kB is an optimal target of anti-inflammatory and immunosuppresant therapies**. Molecular studies on NF-kB are very important to understand the **pathogenesis of inflammatory, autoimmune and neoplastic diseases**, and to identify new drugs that inhibit NF-kB activation. ***Nf-kB transcription factor: role in the pathogenesis of inflammatory, autoimmune, and neoplastic diseases and therapy implications*** Giuliani C, Napolitano G, Bucci I, Montani V, Monaco F. Clin Ter. 2001 Jul-Aug;152(4):249-53. http://www.ncbi.nlm.nih.gov/pubmed/11725618

NFkB is a protein in cells that has to be activated to move into the nucleus and begin transcription of a huge number of genes **that are chosen by the influence of some other modulatory controllers** (AP1 and others). **Many of these genes are inflammatory cytokines (immune messengers)** that are causing our problem in a variety of age associated diseases. What is important for **T2D** is that when **NFkB** activity is blocked, this cascade of immune activation (and other more protective action like activations like increased endogenous antioxidants) is **blocked**. **The WHOLE CASCADE, NOT A SINGLE PLAYER**. This good (endogenous antioxidants and bad (inflammatory cytokines) is part of the reason you want to have **a generous supply of supplemental antioxidants when you block NFkB**. You don't want to hurt any sickly but needed good cells.

Curcumin (diferuloylmethane **< a flavonoid >**) is an **orange-yellow component of turmeric** (Curcuma longa), a spice often found in curry powder. **Traditionally known for its an**

antiinflammatory effects, curcumin has been shown in the last two decades to be a potent immunomodulatory agent that can modulate the activation of T cells, B cells, macrophages, neutrophils, natural killer cells, and dendritic cells. **Curcumin can also downregulate the expression of various proinflammatory cytokines < immune messengers for inflammation > including TNF, IL-1, IL-2, IL-6, IL-8, IL-12, and chemokines, most likely through inactivation of the transcription factor NF-kappaB.** Interestingly, however, **curcumin** at low doses can also enhance antibody responses. **This suggests that curcumin's reported beneficial effects in arthritis, allergy, asthma, atherosclerosis, heart disease, Alzheimer's disease, diabetes, and cancer might be due in part to its ability to modulate the immune system.** Together, these findings warrant further consideration of **curcumin as a therapy for immune disorders**. "Spicing up" of the immune system by curcumin. Jagetia GC, Aggarwal BB. J Clin Immunol. 2007 Jan;27(1):19-35. Epub 2007 Jan 9. http://www.ncbi.nlm.nih.gov/pubmed/17211725

Curry powder is made with turmeric that contains (@3%) curcumin. This has been used for thousands of years without noticeable danger to humans.

What sorts of anti-inflammatories have been found to be "curative" in T2D?

Oxidative stress caused by cytokine exposure is a major cause of pancreatic islet death in vitro and of diabetogenesis. Antioxidant compounds may prevent cytokine-induced damage to islet cells. Hence, we studied the potential of curcumin, an **antioxidant** and **anti-inflammatory compound**, in vitro to protect islets against pro-inflammatory cytokines... **< not all even potent antioxidants are anti-inflammatories > Curcumin protected islets from cytokine-induced islet death in vitro by scavenging ROS and normalized cytokine-induced NF-**

kappaB translocation by inhibiting phosphorylation of inhibitor of kappa B alpha (IkappaBalpha)... **In vivo**, curcumin also prevented MLD-STZ, as revealed **by sustained normoglycaemia**, **normal glucose clearance and maintained pancreatic GLUT2 levels**. **Pro-inflammatory cytokine concentrations in the serum and pancreas were raised in STZ-treated animals, but not in animals pretreated with curcumin before STZ... Here, we have demonstrated for the first time that curcumin in vitro protects pancreatic islets against cytokine-induced death and dysfunction and in vivo prevents STZ-induced diabetes**. ***Novel role of curcumin in the prevention of cytokine-induced islet death in vitro and diabetogenesis in vivo*.** Kanitkar M, Gokhale K, Galande S, Bhonde RR. Br J Pharmacol. 2008 Nov;155(5):702-13. Epub 2008 Aug 11. http://www.ncbi.nlm.nih.gov/pubmed/18695642

This treatment of rats scaled up to a 140 lb. (65 kg) Human requires only about 500 mg of curcumin per day at 7.5 mg/kg. **This level is easily tolerated by humans**. **Many fold higher levels** have **and are being** used to kill cancer cells that often use the NFkB activity as a self stimulus for growth and cell division.

Sections **D (Details - what to do)** and the rest are reserved for those who purchase of this PDF or **SUBSCRIBERS** to Longer Healthy Life (**LHL.net**). Please do not attempt to do this without the additional information in the **D (Details - what to do) section**. There is considerably more you must know about timing, quantity and preparation of the mixtures, and much more. Failure to know this will compromise the synergy you need to "***achieve your goals***".