

The Importance of Oxidant Injury as a Cause of Impaired Mitochondrial Oxidation in Diabetes

John P. Cleary, M.D.¹

Introduction

In diabetes, glucose metabolism via the Krebs cycle is impaired, and this leads to reduced cellular energy and elevated blood sugar levels. When a cell is damaged by oxidation injury, cytosol NAD levels fall and ATP levels decrease. If the DNA strand breaks can be repaired, and the cell regains lost NAD, the energy system can function again, but frequently cell death ensues. Experimental diabetes is caused by this same mechanism, except that a chemical alkylating agent is used to cause the DNA strand breaks in the cell nuclei. DNA strand breaks activate the enzyme poly ADP-ribose synthetase which cleaves NAD, and cause NAD levels in the cytosol to fall to zero. Schauffetter (1985) has shown that oxidation injury can act in the same manner with the same resultant low NAD in the cytosol and low ATP.

Antioxidant Defenses Affect Energy Production

The recent work on oxidant injury to cells, by Schauffetter et al (1985), (1986), Spragg (1985), and Wohaieb (1987), has provided us with insight into the potential cause of most cases of diabetes, as well as many other diseases formerly classified as being of unknown etiology. Superoxides and peroxides are produced by the mitochondria in the course of normal oxidation of nutrient molecules. There is an antioxidant defense system which consists of superoxide dismutase and catalase enzymes, ascorbic acid, vitamin E, glutathione, beta carotene and the coenzymes NAD and NADP, that can deal with oxygen radicals and prevent damage to the cell structures. When the oxygen radicals are greater than the ability of the antioxidant

system to deactivate them, then there is oxidation injury.

Experimental oxidation injury was induced by Schauffetter in leukocytes with varying concentrations of peroxide which acted as an oxidizing agent causing DNA strand breaks in the nuclei. This caused activation of the enzyme poly (ADP-ribose) synthetase which cleaves NAD, causing NAD and ATP levels to fall. Schauffetter measured an 80% fall in NAD levels in 20 minutes, in the cells, after a dose of peroxide was 0.1 to 2.5mM. Mitochondrial oxidation is then stopped by the cytosol NAD levels being reduced to zero. Repair of the DNA strand breaks proceeds while the cell is functioning, but using an alternate energy pathway. Specialized cell functions cease during this repair phase due to low ATP levels. If the repair is completed properly the cell must acquire new NAD in the cytosol to return to the mitochondrial oxidation which generates the majority of the ATP in eukaryotic cells. If the NAD in the cytosol cannot be restored or if they are oxidation damaged, the mitochondrial membranes are not repaired, the cell remains in a low energy mode of function that prevents specialized cell function necessary for normal organ function. Thus organ failure is the result of energy failure on a cellular level, because of oxidation damage of the mitochondrial membranes and/or low NAD. In the case of the beta cell in the pancreas this means that pro-insulin production ceases until NAD levels in the cytosol are restored. Giving niacin, vitamin B₃, provides a precursor for NAD. Robbins et al (1980) found superoxide dismutase 105 ug administered 50 minutes prior to 45 mg/kg STZ prevented the diabetogenic effect that is seen when STZ alone is given. Superoxide dismutase is an enzyme known to be part of the antioxidant defense system of the cell, and a scavenger

1. University of Wisconsin, School of Medicine, Dept. of Surgery, 1300 University Ave., Rm. 4635, Madison, WI 53706 USA.

of free radicals, (Oberley 1986). Robbins believes that the mechanism of action is the inactivation of free radicals that are generated by STZ, before damage can be done to DNA. This would prevent activation of poly (ADP-ribose) synthetase and inactivation of mitochondria which prevents decline in ATP and cessation of insulin production by the beta cells.

Membrane Transport of Glucose and Sodium Impaired by Low ATP

When the cell reaches low ATP levels, the sodium pump is impaired (Greene 1987). Boquist (1988) shows that when the Krebs cycle is inhibited, the mitochondria swell up. This has an adverse effect on the membrane transport of glucose, because glucose and sodium are transported into the cell together. Then the sodium ion must be pumped out via the Na^+K^+ ATPase or sodium pump. Sodium transport requires ATP energy, thus membrane transport of glucose indirectly uses ATP.

Early observations by S. Soskin and R. Levine, as discussed by Lehninger (1975) showed that the peripheral tissue of diabetic animals are deficient in removal of hexose, (a 6 carbon sugar) from the blood. This happened when the animals were tested at normal blood sugar levels. If blood sugar is raised to 500 mgm% the hexose uptake by tissues is increased. This indicates that the basic defect in diabetes is membrane transport of glucose into the cell. M. B. Davidson (1986) discusses the pathogenesis of the type II Diabetes Mellitus where there is often normal insulin levels or even an excess of insulin and elevated blood sugar. Insulin deficiency is not the cause of type 2 diabetes mellitus. Diabetes is primarily an impairment of membrane transport of glucose, causing a deficiency of glucose inside the cell and an elevated level of glucose outside the cell.

In a study done with Etomoxir (Sandoz) used with and without Nicotinic Acid, FFA levels and triglyceride levels go up in rat plasma when Nicotinic Acid is not included. When Etomoxir is used *with* Nicotinic Acid, glucose levels go down, FFA levels go down and triglyceride levels go down. This study, (Reaven 1988) shows that NAD is needed to reestablish the metabolism. Insulin levels did not change during any stage of the experiment. Reaven's study created an animal

model of adult onset diabetes by using older adult rats and low dose STZ treatment. They were able to lower blood sugar, FFA and triglyceride levels to normal using both Nicotinic Acid and Etomoxir, four hours after administering them both by gastric tube or injection SQ. However, when Etomoxir was administered alone, the FFA and triglyceride levels both went up considerably, although blood sugar levels went down to normal levels. Nicotinic Acid administered alone caused the FFA levels to return to normal, and triglyceride levels to normal, but blood sugar was still somewhat elevated. I feel¹ prolonged use would lower blood sugar to normal, as this has been my experience with Nicotinic Acid. Just lowering blood sugar will not cure diabetes and elevated FFA levels and triglyceride levels, I believe, are symptoms of impaired cell metabolism. In addition there is in the diabetic enhanced gluco-neogenesis, which is the formation of glucose in the liver from amino acids.

The body is metabolizing protein to make glucose. Most of this glucose ends up excreted in the urine and leads to the wasting seen in diabetics. At the same time there is an almost complete cessation of conversion of glucose to fatty acids via acetyl-CoA. Normal animals convert about 1/3 of ingested carbohydrate to fat. The combination of excessive gluconeogenesis with absent fatty acid formation leads to body wasting. Very little metabolism of glucose for energy production occurs in the diabetic. What does occur is mostly in the brain, which can use only glucose and in emergency the ketone body beta hydroxybutyrate can be used to make energy.

Elevated blood glucose is therefore due to impaired membrane transport of glucose into cells and into the mitochondria of the cells where it is metabolized into energy. Impaired transport could lead to further deficient energy levels inside the cell. We know that in artificially induced diabetes, cytosol NAD levels become zero preventing normal metabolism by the oxidative pathways involving the citric acid cycle inside the mitochondria. Then alternate energy pathways are activated including the hexose monophosphate shunt and fermentation

of glucose to lactic acid. These pathways are located in the cytosol of the cell and do not use the mitochondria. The hexose monophosphate shunt requires NADP as a coenzyme and this substance is not split by the poly (ADP-ribose) synthetase enzyme.

The Non-Obese Diabetic Mouse Model

Nakajima, H., and Yamada, K., et al, have documented that when the NOD mice become spontaneously diabetic they also develop antibodies to the beta cells (1986). (Perhaps the body does this in an effort to remove the damaged beta cells from the pancreas.) These researchers also show that this antibody dependent cell-mediated cytotoxicity can be stopped with nicotinamide (1986). Yamada, K., et al, had previously shown (1982) that the nicotinamide inhibits the poly-ADP-ribo-sylation, a reaction which depletes NAD levels, and which in the beta cells can result in no insulin production and even beta cell death.

A Single Metabolic Defect is the Cause of All Complications Seen in Diabetes

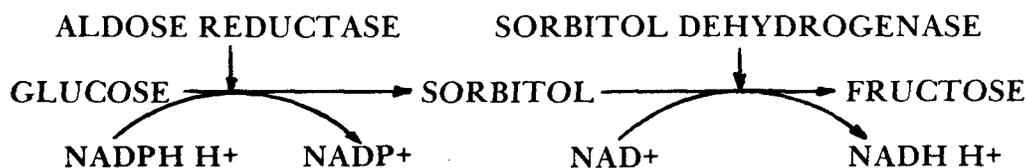
Dr. Albert Winegrad in the 1986 Banting Lecture on diabetes, (*Diabetes*, Vol. 36, March 1986) attempts to show how a single mechanism, the activated Polyol pathway, can cause all the complications seen in all types of diabetes. His whole concept is that a defect in the metabolism leads to activation of this abnormal metabolism, however the low NAD levels in diabetes (Spies 1939) allows a more complete explanation in regard to the Polyol pathway defect, since the pathway depends upon an excess of NADPH being present. This was demonstrated by the Russian researcher Obrosova, (1985). Nicotinamide given in experimental STZ diabetes in rats corrected the sorbitol pathway defect. The nicotinamide induced an increase in

NAD⁺/NADH and NADP⁺/NADPH ratios which was accompanied by a decrease in sorbitol formation. There was inhibition of the aldose reductase which leads to sorbitol formation and an increase in the sorbitol dehydrogenase reaction which metabolizes sorbitol to fructose. Yeh et al (1987) also suggests that sorbinil does not correct the sodium pump defect in diabetic rats by raising the myo-inositol.

It is however interesting to follow the path to the sorbitol buildup. Excess hydrogen ion accumulates in the cytosol causing NAD and NADP to be reduced to NADPH-H⁺ and NADH-H⁺. There would be reduction in ATP production and a fall in pH in the available NAD or NADP. This would keep NAD and NADP at low to non-existent levels. Energy production in the cell then switches to the hexose monophosphate pathway which operates in the cytosol and uses NADPH. I hypothesize that the excess NADPH also drives the Aldose Reductase enzyme to make sorbitol, but does not go on to make fructose because of the NAD deficiency. Sorbitol accumulates in the cells and serves as a means of reducing the excess H⁺ ion.

Dr. Wingrad does not address the problem of the impairment of Na⁺K⁺ATPase which leads to impaired glucose transport. Glucose is transported with Na⁺ ion into the cell, then Na⁺ must be transported back across the membrane by the sodium-potassium ATPase. In a sense the movement of Na⁺ provides the source of energy to move glucose and impairment of sodium transport impairs glucose transport. Insulin alone does not correct impaired membrane transport of glucose, as is seen in adult onset diabetes there is often high or normal insulin levels and still elevated blood glucose from impaired membrane transport of glucose.

Figure 1



NAD Deficiency is the Other Half of the Story in Diabetes

Because insulin was discovered in 1922 and niacin in 1937, no one realized the importance of NAD deficiency in diabetes, even though a small group headed by Tom Spies in 1939 published their study of low NAD levels in diabetics. Controlling blood sugar will not prevent the progress of the disease diabetes since it is really a subclinical form of pellagra.

Wahlberg (1985) showed that nicotinamide has a protective effect against nephropathy in diabetic rats. If 20% of patients with type 1 diabetes of more than 26 years duration do not develop clinical microangiopathy even though their blood sugar may not have been optimal, it means that long term complications in diabetes are not only related to high blood sugar concentration, but also to other metabolic disturbances. When nicotinamide was given to rats with STZ diabetes of 6 months duration there was a lowering of blood sugar and a decrease in nephropathy as measured IgG immunofluorescence staining of the glomeruli. They found a deficiency of oxidized pyridine nucleotides (NAD+NADP+) which could account for the metabolic impairment of diabetes.

These discoveries should lay to rest any attempts to use aldose reductase inhibitors to block sorbitol synthesis. When a vitamin will correct the metabolic defect, why resort to a drug which can only create more side effects and complications? Any aldose reductase inhibitors now under development must prove they are more effective than nicotinamide or nicotinic acid to warrant their use.

Spies, Sydenstricker (1939), Vilter (1939) found diabetics to suffer from extremely low NAD levels.

Early researchers such as Evans (1939), Sutton (1940) and Spies (1939) had extensive experience with the many subtle symptoms of pellagra. But a lapse of niacin research during and after World War II gave the pharmaceutical companies a voice of unquestioned authority over the new practicing clinicians who had no real experience with niacin deficiency cases and had not lived through events of the Pellagra years in the South, indeed did not

recognize the symptoms of pellagra. I discuss this disease in my recent publication on the NAD Deficiency Diseases, wherein I describe the subclinical pellagras (Cleary 1986), and their response to the administration of niacin.

There was a further study of diabetes niacin therapy done in England in 1943 (Neuwahl) using niacinamide. Incipient cases of diabetes could often be removed from insulin and could actually be cured of diabetes, according to Neuwahl, and some long standing cases had improvement with a lowering of the insulin requirement.

Since niacin could not be patented to make a large profit, I believe the then aggressive marketing of the sulfonylurea compounds by the drug companies also tended to obscure the pursuit of the true cause and treatment of diabetes.

A New Look at the Problem

In 1981 Japanese biochemists studying artificial diabetes in lab animals using the alkylating agents alloxan and streptozotocin found that an enzyme in the cell was activated by single strand breaks of DNA (Yamamoto 1981). This enzyme, poly (ADP-ribose) synthetase split the NAD in the cytosol reducing NAD cytosol to zero and thus inactivating the citric acid cycle energy production of the mitochondria. Pancreatic beta cells, with no NAD and inactive mitochondria stopped functioning, insulin was not produced, and the diabetic condition induced. Further experiments by this group in Japan showed that pretreating the rats with niacinamide, zinc, picolinic acid or benzamide before giving the alkylating agent would prevent the development of diabetes. The outcome depended on whether the pancreatic cells could repair the single strand breaks in the DNA and then obtain new NAD resume insulin production, or whether, the cells were seriously damaged or unable to build up cytosol NAD levels necessary to resume function.

Spies (1939) found that diabetics in ketoacidosis had NAD levels as low as pellagrins, and this leads to impairment of the normal oxidative pathways like the Krebs cycle.

In other words, they had pellagra and this is the real cause of ketoacidosis.

How the Heart and Vascular Complications Result from the Impaired Cellular Energy of Pellagra by Oxygen Injury

Accelerated atherosclerosis is a facet of the diabetic disease progression: it changes the blood vessels of the entire body, and combined with the impairments of the immune system, this vascular restriction leads to tissue breakdown and gangrene.

Jackson (1985) estimates that 80% of diabetic deaths are from vascular disease secondary to the abnormal metabolism found in diabetes.

Hypertension as a cause of some of the pathology of diabetes is also demonstrated by Hommel et al (1986). They show that acute reduction of arterial blood pressure reduces urinary albumin excretion in type 1 diabetic patients with incipient nephropathy. They demonstrate this same result in human insulin dependent diabetic, upon whom Clonidine was used to reduce arterial blood pressure and there was a decrease in urinary albumin excretion.

Roberto Zarz, et al, in discussing the prevention of diabetic glomerulopathy by pharmacological amelioration of glomerular capillary hypertension (1986), also indicate this. Experimental diabetes in rats demonstrate that kidney damage associated with diabetes can be prevented by lowering blood pressure and especially glomerular capillary pressure. Apparently in diabetes there is increased blood pressure to kidney capillaries with increases in blood filtration in the glomerulus. This results in loss of albumin in the urine and destruction of glomeruli. Blood pressure in the rats in this study was lowered by angiotensin I converting enzyme inhibitor called endaprin. Kidney damage is prevented by reducing glomerular hypertension. The albuminuria was also prevented by lowering the glomerular pressure. When niacin is given to hypertensives the blood pressure is gradually reduced, as in my case number 2 discussed below, to normal, and the mechanism of action is believed to involve the improved action of the sodium pump that results from providing adequate ATP levels to the cells. This same mechanism would be involved in correcting the hypertension of diabetics and thus preventing renal damage and albuminuria.

Myocardopathy is Due to Low ATP

In diabetic rats low ATP levels have been found in the myocardium (Jenkins et al 1986), (Jackson 1985) and this could account for the myocardopathy seen in diabetes. The low ATP levels in cardiac tissue provides us with insight into the basic problems in diabetes which is impaired energy production leading to organ failure, including the heart, and death.

Nomikos et al (1986) conclude that oxygen derived free radicals may be the cause of most diabetes, with a reference to Okamoto's (1981) model for beta cell damage having a common final pathway for toxic agents such as streptozotocin, alloxan, and inflammatory tissue damage. Oxygen injury in the beta cell would indeed cause cessation of specialized cell function producing insulin deficiency. Simultaneous oxygen injury to other cells such as the myocardium would produce the heart disease. Oxidation damage is most severe in mitochondria because mitochondria oxidize the majority of the nutrients, the membranes are therefore most likely to be impaired because the superoxides and peroxides are formed there, leading to peroxidation of the lipids of that mitochondria causing the cell to turn to alternate energy pathways, such as the pentose shunt, as a means of continuing energy production.

Okamoto's model (1981, page 57) shows his concept of a final common pathway for cell injury by alloxan and streptozotocin causing damage to proinsulin synthesis in the beta cell. Additionally there is the superoxide as another cause of free radical formation as per Schaufstetter (1986), vitamin C and E and beta carotene as additional free radical scavengers; and the zinc ion (Zn²⁺) as an additional inhibitor of the poly (ADP-ribose) synthetase.

Measures that also help restore cell energy production because they are also free radical scavengers include Vitamin C in daily doses of 3 to 20 grams (Lehninger 1975), Vitamin E in daily doses of 1200-1600 IU. (Lehninger 1975), Linseed oil 30 to 60 mL daily, fish oil or cod liver oil, and beta carotene and niacin 500 mg daily as a precursor to NAD. Although Okamoto used niacinamide as a free radical scavenger and NAD precursor, there is an advantage

RADICAL SCAVENGERS, GLUCOSE, THIOL, VITAMINS C AND E AND BETA CAROTENE, ETC.

NICOTINAMIDE, PICOLINAMIDE, ZINC ION, AS INHIBITORS OF POLY(ADP)RIBOSE SYNTHETASE

CAUSES OF FREE RADICAL FORMATION

COPPER & IRON
SUPEROXIDE O₂⁻
ALLOXAN
STREPTOZOTOCIN

RADIATION?
VIRUS?

IF DEFICIENCY OF SCAVENGERS HERE THEN

REACTIVE INTERMEDIATES
HO-H₂O₂

LESIONS

POLY(ADP-RIBOSE) SYNTHETASE



REPAIR

NEEDED FOR (ADP-RIBOSE)_n

CLEAVES

B-CELL FUNCTIONS

PROINSULIN SYNTHESIS - INACTIVATED DUE TO LOW NAD AND LOW ATP

MITOCHONDRIA, ATP PRODUCER INACTIVATED DUE TO LOW NAD IN THE CYTOSOL AND THE MITOCHONDRIAL MEMBRANE OXIDATION DAMAGE

NICOTINAMIDE LEAVES THE CELL AND LEADS TO NAD DEFICIENCY

OMEGA 3 ESSENTIAL FATTY ACIDS NECESSARY FOR REPAIR OF OXIDIZED CELL AND MITOCHONDRIA MEMBRANES

BETA CELL MEMBRANE

NUCLEAR MEMBRANE

NICOTINIC ACID PRECURSOR TO NAD

NAD

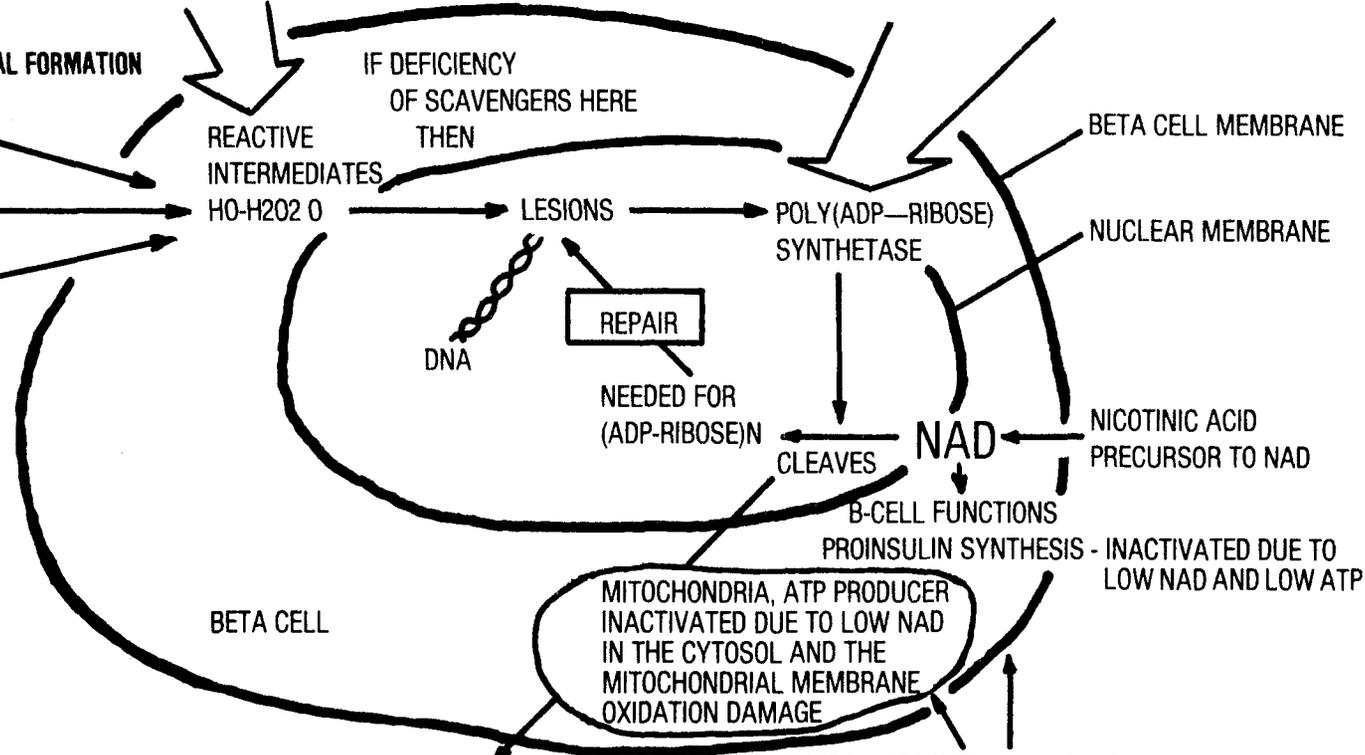


Figure 2

to using niacin instead which is that it doesn't inhibit the DNA repair process, i.e. the poly (ADP-ribose) synthetase reaction. If you use niacinamide you may stop the repair of the DNA strand breaks, by inhibiting the poly (ADP-ribose) synthetase and this would cause abnormal DNA and therefore tumor formation (Yamamoto 1981).

Mitochondrial type oxidation is the Krebs cycle, which relies upon NAD to function. If the cell fails in mitochondrial oxidation and declines to dependence upon the pentose phosphate shunt pathway, the result will be an excessive fatty acid production at the expense of glycogen. Fatty acids are the storage form for the pentose shunt and they tend to be overproduced when mitochondria are impaired, at the same time the burning of these fatty acids is also limited. Overproduction plus limited use leads to a massive accumulation of fat in the blood, cells, arteries, liver, kidney, etc. Fatty degeneration of tissues and arteriosclerosis is therefore caused by mitochondrial membrane damage by oxygen. Alternately, a decrease in the use of the pentose shunt causes a decrease in the fatty acid synthesis and an increase in glycogen as an energy storage molecule.

Smith reports (1981) a case of severe hypertriglyceridemia in an alcoholic with diabetes. The combination of insulin therapy and nicotinic acid 1200 mg daily returned the triglyceride levels to normal. Insulin alone could not do this and Smith demonstrates the effectiveness of including nicotinic acid in diabetes therapy to correct defects not influenced by insulin alone. Niacin releases insulin from the beta cells because it returns them to functioning organs, it generates a coenzyme which restores the mitochondrial Krebs cycle.

The importance of fat metabolism in diabetes is shown by Kamada (1986) who found diabetics to have impaired membrane fluidity due to deficient unsaturated fatty acids. This deficiency in the linolenic 18:3 omega 3 essential fatty acid is the dietary deficiency commonly found in our modern western diet according to Rudin (1981) which complicates the diagnosis and evaluation of diabetes, the deficiency must be corrected also. When sardine oil was given the membranes were restored to

normal. O'Dea (1984) found Australian aborigines who were suffering from diabetes on the Western diet and lifestyle were cured by returning them to their old native lifestyle and diet of fish, kangaroo meat, and vegetation, which included a high amount of omega 3 EFA and niacin, not found in our modern western diet. Membrane fluidity of damaged mitochondrial membranes can be restored by the essential fatty acids, the cellular ATP production is improved, and the cell functions once again. There is improved sodium pumping and improved membrane transport of the nutrient molecules like glucose and amino acids that enter cells and the mitochondria by co-transport with sodium ion. The energy for membrane transport of glucose and amino acids comes from the ATP used to pump sodium back across the membrane in exchange for potassium inside the allows active transport of glucose into the cell by co-transport with sodium. In the cell with low ATP, sodium tends to accumulate inside the cell. The cells are swollen and when niacin is given to diabetics the most dramatic change noticed by patient and doctor alike is the movement of fluid out of the body.

A Biochemical Model for Insulin Resistance

Trishitta (1984) shows ATP inhibits insulin binding to cell receptor sites. It provides a biochemical model to explain "insulin resistance". This concept is applicable to both type I and II diabetes. In type I or insulin dependent diabetes there is often a worsening of the clinical course with the need to raise the amount of insulin injected. Sometimes even a large increase in the amount causes little or no change in hyperglycemia. The reason is that low ATP levels in the cells causes an increase in the need for insulin binding to receptors. Ordinarily this results in an increase in cell membrane transport of nutrient molecules like glucose, amino acids, and fat globules but if the mitochondria of the cell are inactivated due to low NAD in the cytosol or damaged membranes from oxidation injury, or nonfunctioning due to omega 3 EFA deficiency, the increased insulin is not effective in raising ATP levels which then decreases

insulin requirement. Instead the body seems to require more and more insulin as the ATP levels fall in the cells with impaired mitochondrial oxidation.

As Applied to Porphyria

Streptozotocin and alloxan have been used extensively to induce experimental diabetes in animals. At one time it was believed that they had action only on the beta cell of the pancreas, but this is not true. The beta cell is just the most sensitive to these agents. Other cells can also be alkylated in the same way with the same outcome; decreased cytosol NAD, low ATP, and cessation of specialized cell function. Porphyria can be induced by STZ, alloxan, and mycotoxins which alkylate hepatocytes and induce the same reaction seen in the cured by returning them to their old native lifestyle and diet of fish, and vegetation, which included a high amount of omega 3 EFA and niacin, not found in our modern western diet. Membrane fluidity of damaged mitochondrial membranes can be restored by the essential fatty acids, the cellular ATP production is improved, and the cell functions once again. There is improved sodium pumping and improved membrane transport of the nutrient molecules like glucose and amino acids that enter cells and the mitochondria by co-transport with sodium ion. The energy for membrane transport of glucose and amino acids comes from the ATP used to pump sodium back across the membrane in exchange for potassium inside the allows active transport of glucose into the cell by co-transport with sodium. In the cell with low ATP, sodium tends to accumulate inside the cell. The cells are swollen and when niacin is given to diabetics the most dramatic change noticed by patient and doctor alike is the movement of fluid out of the body.

beta cell. Massive production of porphyrins is the hepatocytes response to low ATP levels. Gadjos (1969) used glucose to elevate ATP and cure porphyria in rats. Pinelli (1972) reversed STZ-induced porphyria with nicotinic acid, Spies (1938, 1938, 1939) gave a single dose of niacin 500 mg orally to diabetic patients with porphyria and the porphyrinuria cleared for three days. So we have a model in the beta

cell for studying oxidation injury and the resultant organ failure, and the restoration of function with vitamin B₃, which we can apply to porphyria also. Rather, we should probably say porphyria is a stage of diabetes, or the two are a form of pellagra, or substrate pellagra as Rudin (1987) discusses it. Sato (1987) has used STZ to produce hypertension and diabetes in an animal model which confirms our experience in humans that they are both caused by low NAD.

The Case Reports

Case #1. Hypertension brought under control with niacin.

A fifty-four year old Negro man with diabetes, hypertension and early heart failure, was on Tolinase 250 mg daily for diabetes, Lasix 40 mg daily, Aldomet 250 mg qid, Apresaline 50 mg daily. The diabetes was well corrected when measured by blood sugar levels. The patient however, had developed early heart failure and loss of control of the hypertension with the blood pressure at 180/120 with medication. He felt very lethargic and suffered headaches. Niacin 750 mg P.O. daily was given in three doses of 250 mg. Within six days his blood pressure was 140/90 and he felt much better. At four weeks blood pressure was 120/86 and medication remained with Tolinase 250 mg, Lasix 40 mg daily, Aldomet 250 mg daily, and Apresaline 50 mg daily. At eight weeks he had blood pressure 130/90 but he had also eliminated the Apresaline 50 mg daily. The patient had a feeling of increasing well being, and began to walk several miles each day.

Case #2. Diabetes and gout.

A forty-seven year old white man with hypertension who was taking four different drugs for his hypertension, arthritis, and gout. He then was found to have elevated blood sugar and could not accept the idea of going on five different medications so he stopped taking all of them, by himself. A few days later he consulted me about his condition, flatly stating he would not take the usual regime of pharmaceuticals. I started him on niacin 500 mg daily. In addition he took vitamin C, 1000 mg daily,

zinc 50 mg tab daily, as well as one multiple vitamin daily. After four weeks a glucose tolerance test was done which measured as normal. His hypertension was gone also. There was no evidence of gout or arthritis and the patient seemed to feel more energetic and slept better than before. Six months later he continued on just niacin 300 mg with normal blood pressure and blood sugar, no gout or arthritis.

Case #3.

A sixty-four year old white male with an earlier history of alcoholism and now with adult onset diabetes, presenting with emphysema, insomnia, a pre-gangrenous condition on his left middle toe, chronic productive cough and shortness of breath, and edema with abdominal distention (his waist had increased seven inches in size). He had been on Tolinase 250 mg per day for two years and Theodur 600 mg per day for his emphysema for several years. His edema was at this point life-threatening, his enlarged heart was failing. Although he had been treated for hypertension in the past years, his blood pressure appeared normal, because his heart was unable in heart failure to raise the blood pressure. During that time that he was being treated with thiazides he developed diabetes, and in as much as the thiazides do not cure the original problem, and diabetes is but another step of the pellagra and omega 3 EFA deficiency that he actually had, his pellagra was progressing to its terminal stages.

A pharmaceutical diuretic would have improved superficially his edema but niacin is an effective diuretic and as my diagnosis was that of pellagra, I used niacin very successfully on this patient.

He had a pellagra type skin breakdown on his elbows, not very significant alone, but also an unhealing blister on his hand, an area exposed to the sunlight. He was irrational, his urine was noted to be dark at times, both very significant pellagra symptoms. Also classical for pellagra was his insomnia, he slept only a few hours each night. He was unable to eat except for very small amounts, also indicative. I did not have to check for low NAD levels, he had pellagra written all over him.

I put him on 500 mg niacin per day, 2000 mg vitamin C per day, and a multiple vitamin. He quit all of his prior medicines and at first for three months took only the niacin. With only the niacin his pre-gangrenous condition on his middle left toe cleared up in a matter of days. The pressing problem of his edema improved, slowly, the first month he lost 10 pounds and three inches off his waist and the swelling in his ankles was cured. The second month he lost another 10 pounds and two more inches off his waist. At six months he takes no pharmaceutical medicines, only his vitamins. His blood sugar is normal, he is eating well, he is rational, his urine is not dark, he feels in excellent health.

Case #4.

A sixty-two year old white man with a long history of gout and a recently discovered diabetes based on a blood sugar of 1190 mg% and 540 mg%. He usually took Butazolidin for his gout when it flared up but decided to experiment with niacin. He was given 250 mg bid. In four days his gout pain was gone and never returned, which was better than the results he had experienced with Butazolidin treatment. He continued on niacin 500 mg daily for one month, then he began testing his urine with a test tape and noted 0 sugar at 7:00 a.m. and 1+ sugar two hours after meals. This was much better than anticipated based on the blood sugar readings at onset of treatment. That he was improving was obvious to us both. After six weeks of therapy he developed a visual disturbance, inability to focus, which may have been due to decreases in internal pressure in the eye from the diuretic effect of niacin. He had a 5 diopter change in his glasses and then could see well again. At eight weeks the blood sugar fasting was 156 mg%. At ten weeks the two hour postprandial blood sugar was 120 mg%. At sixteen weeks he had a 95 mg% blood sugar, and the blood pressure was 118/78.

Discussion of Case Studies

If diabetes results from low cell ATP, then attempts to restore the energy production system should improve or cure diabetes. Complete recovery depends on the

number of viable beta cells left in the pancreas that can be restored to insulin production, however the complications of diabetes may be ameliorated by restoring normal energy production to the rest of the body even though insulin must be given in addition.

My clinical trial was limited to four cases of adult onset diabetes and of these, two were old cases treated with oral antidiabetic agents. The reason antidiabetic agents work is that they mimic the action of NAD which is very low in diabetes, causing a release of insulin from the beta cells, but they do not restore function of the mitochondrial Krebs cycle as NAD does, they do not cure this problem. Two of the cases were newly discovered cases not yet treated. All four cases responded to therapy with nicotinic acid (vitamin B₃). The old cases stopped taking their oral agent, and the new cases took no pharmaceutical drugs, only vitamin supplements. Blood sugar levels return to normal and the patients all experienced a water diuresis over a period of several months that resulted in a loss of 20 to 30 pounds. Nicotinic acid was given in oral doses of 500 mg a day for the first month to attempt to restore depleted NAD levels in the cells. It takes 3 or 4 weeks on the 500 mg a day level to do this, and this is the same dose used to treat pellagra, the known NAD deficiency disease. After a month, 250 mg per day is given long term. If the antioxidant system of the body could be totally repaired, it is possible that niacin supplements would not be necessary long term, but persons with diabetes have a lot of oxidation damage that causes a higher niacin intake to be required to prevent relapses.

Infants born to diabetic mothers have long been known to suffer a higher than normal perinatal mortality rate. They are usually heavier than normal as a result of fluid accumulation due to defective membrane transport of sodium and glucose. These infants could be quickly restored to normal metabolism by giving them nicotinic acid and raising the depleted NAD levels of their cells.

Biochemical abnormalities of diabetes include excessive ketone body formation with ketonuria and acidosis or excessive H⁺ ion accumulation. When normal metabolic pathways of the citric acid cycle are disrupted, the oxidation of

hydrogen ion and the combining with oxygen in the cytochrome system of the mitochondria is defective. Niacin corrects this.

Why are the eyes of a diabetic more susceptible to vascular damage? We know that the retina uses only fermentation of glucose to lactate to obtain energy. Is lactate concentration more elevated in the retinal vessels of a diabetic? Are the cell membranes of a diabetic damaged also by excess H⁺ ions? Membrane "fluidity" is dependent upon maintaining unsaturated fatty acids in the membranes. Excess H⁺ ion seen in diabetic acidosis may combine with unsaturated fatty acids to make them more saturated and less fluid. Less fluid membranes are not able to be effective in membrane transport. Since diabetes is the leading cause of blindness, treatment with nicotinic acid and the omega 3 fatty acids may reverse the abnormal metabolism and prevent blindness in diabetes.

Bibliography

1. Boquist L et al: Structural B-Cell Changes and Transient Hyperglycemia in Mice Treated with Compounds Inducing Inhibited Citric Acid Cycle Enzyme Activity. *Diabetes*, Vol. 37, Jan. 1988, pp 89-98.
2. Cleary JP: The NAD Deficiency Diseases. *Orthomol. Med.* Vol. 1,3 149-53 (1986).
3. Davidson MB: Pathogenesis of the type II Diabetes Mellitus, *Amer. J. Med. Sci.* 291(6), 35-39(1986).
4. Evans VL: Pellagra with Psychosis and Minimal Physical Symptoms, *JAMA*, Apr. 1 (1939), pp 1249-50.
5. Gadjos A: Le Role de TATP dans l'effect inhibiteur du glucose sur la biosynthese exageree des porphyrines. *Societe de Biologie*, Seance de 26 April (1969), pp 848-51.
6. Greene DA et al: Sorbital, Phosphoinositides, and Sodium-Potassium-ATPase in the Pathogenesis of Diabetic Complication. *Seminars in Medicine of the Beth Israel Hospital, Boston. N.E.J.M.* Mar. 5, 1987, pp 599-606.
7. Hommel E: Acute Reduction of Arterial Blood Pressure Reduces Urinary Albumin Excretion in Type I (Insulin Dependent) Diabetic Patients with Incipient Nephropathy. *Diabetologia* 29: 211-215 (1986).
8. Jackson CV: A Functional and Ultrastructural Analysis of Experimental Diabetic Rat Myocardium. *Diabetes* 34: 876-883 (1985).

9. Jenkins R: Purine Nucleotide Levels in the Diabetic Heart, Kidney, Liver and Diaphragm. *Diabetes Conf.* 1986 paper 798.
10. Kamada T: Dietary Sardine Oil Increases Erythrocyte Membrane Fluidity in Diabetic Patients. *Diabetes* 35: 604-610 (1986).
11. Lehninger A: Biochemistry 2nd Ed. Worth & Co. Publ. New York N.Y., 846 (1975).
12. Neuwahl FJ: *Lancet* Sept. 18, page 348-51 (1943).
13. Noikos IN: Combined Treatment with Nicotinamide and Desferrioxamine Prevents Islet Allograft Destruction in NOD Mice, *Diabetes* 35: 1302-1304(1986).
14. Oberley L: *Superoxide Dismutase*, Vol. 3, CRC publishers, 152-81 (1986).
15. Obrosova IG: [Nicotinamide Coenzyme Regulation of Sorbital Pathway of Glucose Metabolism in the Aorta of Rats with Strep-tozotocin Diabetes]. *Vopr. Med. Khim.*, Mar.-Apr. 31(2): 125-8 (1985). Russian language with English abstract.
16. O'Dea K: Diabetes in Australian Aborigines. *Diabetes* 33: 596-603 (1984).
17. Okamoto H: Regulation of Proinsulin Synthesis in Pancreatic Islets in a New Aspect of Diabetes. *Mol. Cell. Biochem.*, 37: 43-61 (1981).
18. Pinelli A, Favalli L: Chemically Induced Porphyria: Protection by Treatment with Nicotinic Acid. *Euro. J. Pharmacol.* 20:136-138(1972).
19. Reaven GM et al: Additive Hypoglycemic Effects of Drugs that Modify Free Fatty Acid Metabolism by Different Mechanisms in Rats with Streptozocin-Induced Diabetes. *Diabetes*, Vol. 37, 28-32, Jan. 1988.
20. Robbins MT: Protection Against STZ Induced Diabetes by Superoxide Dismutase. *Diabetologia* 18: 55-58 (1980).
21. Rudin DO: The Major Psychoses and Neuroses as Omega 3 EFA Deficiency Syndrome Substrate Pellagra. *Biol. Psych.* 16, 837-830 (1981).
22. Rudin DO: The Modernization Disease Syndrome as Substrate Pellagra-Beriberi, /. *Orthomol. Med.* Vol. 2,1, 3-14, 1987.
23. Sato, T: New establishment of hypertensive diabetic animal model: neonatally STZ treated spontaneously hypertensive rats. *Metabolism* Vol. 36: No. 8, 731-37 (1987).
24. Schaufstetter IU: Glutathione Cycle Activity and Pyridine Nucleotide Levels in Oxidant-Induced Injury of Cells. /. *Clin. Invest.* 76(3): 1131-1139(1985).
25. Schaufstetter IU: Oxidant Injury of Cell. /. *Clin. Invest.* 11: 1312-1320 (1986).
26. Smith SR: Severe Hypertriglyceridemia Responding to Insulin and Nicotinic Acid Therapy. *Postgrad. Med. J.* Aug. 57:511-515 (1981).
27. Spies TD, Bean WB: The Role of Nicotinic Acid in the Prevention of Pellagra, Roentgen Sickness and Increased Porphyrinuria. /. *Clin. Invest.* 17(1939).
28. Spies TD, Gross ES, Sasaki Y: Effect of Yeast and Nicotinic Acid on Porphyrinuria. *Proc. Soc. Exper. Biol. Med.* 38: 178-181 (1938).
29. Spies TD: Note on the Relationship of Porphyrinuria to Human Pellagra. *South M.J.* 31: 483-486 May (1938).
30. Spragg RF: Alterations in ATP and Energy Charge in Cultured Endothelial and P388D Cells Following Oxidant Injury. /. *Clin. Invest.* 76: 1471-1476(1985).
31. Sutton DC: Interrelationship between the vitamin B Complex and the Anterior Lobe of the Pituitary Gland. /. *Lab. Clin. Med.* 25(11) 1188-92(1940).
32. Sydenstricker VP et al: Avitaminosis Occurring in Diabetic Patients Under Insulin Therapy. *JAMA* 113(2) 2137-8, Dec. 9 (1939).
33. Trishitta V: ATP and Other Nucleoside Triphosphates Inhibit the Binding of Insulin to its Receptor. *Metabolism* 33(6) 577-81 (1984).
34. Vilter RW, Vilter SP, Spies TS: Relationship Between Nicotinic Acid and Codehydrogenase (Coenzymase) in Blood of Pellagrins and Normal Persons. *JAMA* 112: 420-422. Feb. 4 (1939).
35. Vilter RW: Determination of Codehydrogenases I and II (Coenzymase in the Blood of Diabetics in Severe Acidosis) *Am. J. M. Sci.* 197: 322-326 Mar. (1939).
36. Wahlberg G: Protective Effect of Nicotinamide Against Nephropathy in Diabetic Rats. *Diabetes Res.* 2(6) Nov. 306-12, 1985.
37. Winegrad A: Banting Lecture 1986, "Does a Common Mechanism Induce the Diverse Complications of Diabetes?" *Diabetes* 36, 396-406, Mar. (1987).
38. Wohaieb SA and Godin DV: Alterations in Free Radical Tissue-Defense Mechanisms in Streptozocin-Induced Diabetes in Rats. *Diabetes* Vol. 36, 1014-18, Sept. 1987.
39. Yamamoto H, Uchigata Y and Okamoto H: Streptozotocin and Alloxan Induced DNA Breaks and Poly (ADP-ribose) Synthetases in Pancreatic Islets. *Nature* 294: 284-86 (1981).
40. Yeh L et al: Na+K+ATPase Pumping Activity is Not Directly Linked to Myo-inositol Levels After Sorbinil Treatment in Lenses of Diabetic Rats. *Diabetes* Vol. 36, 1414-19, Dec. 1987.
41. Nakajima H, et al: Elevated Antibody-dependent Cell-mediated Cytotoxicity and its Inhibition by Nicotinamide in the Diabetic NOD Mouse. *Immunology Letters*, 12 p. 91-94. 1986.