The Omnipresent Medical Necessity of Mimicking Normal Human Burst Insulin via the Bionica Artificial Pancreas Treatment

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CHAPTER 1: Treating Diabetes and Other Diseases of Metabolism:

This document demonstrates the uniform physiological need to reestablish normal carbohydrate metabolism using the Artificial Pancreas Treatment® in order to improve the health of people suffering from one or more of the secondary complications of diabetes and diseases of improper metabolism.

There is an overarching goal regarding medical treatments: Whenever a bodily function can return to normal, it is beneficial to do so. This is particularly true in diseases of metabolism. Abnormal carbohydrate metabolism is never beneficial, and uniformly causes a multitude of disease pathways. Metabolism is basically the force of life. Any disease which adversely affects metabolism causes fundamental defects at the cellular level, resulting in a host of comorbidities.

This paper will demonstrate that the best means to overcome metabolically caused health problems, such as diabetes, is to use the body’s own system of repair through the Bionica Microdose Artificial Pancreas Treatment®. This re-activation of cellular heath is achieved using DNA.

The unstated goal of all medicine is to mimic normal non-disease functionality. There is no known case where restoration of “normal” has been criticized as improper or claimed to be contraindicated. In medicine there exist very few “always” but we should always seek normal.

This is why the Artificial Pancreas Treatment® is so logical, it restores normal carbohydrate metabolism processing through providing burst insulin, as if the human pancreas was secreting insulin in the normal way.

Important realities we cannot ignore:

1. Diabetes is a disease of improper carbohydrate metabolism, not a disease caused by improper blood glucose levels which are merely symptoms. This is not argued, yet most treatments and drugs continue to focus on the blood glucose levels as if achieving euglycemia would be curative. It is not. The core problem of diabetes is abnormal carbohydrate metabolism, and until that core problem is directly addressed there is no logical physiological theory that suggests the degenerative aspects of diabetes would stop. As will be proven herein, the Artificial Pancreas Treatment® (APT) directly addresses this core problem of resting carbohydrate metabolism by mimicking the pancreas.

2. Current modes of treatment, including tight blood glucose control, still allow patients to fail over time. Some succumb to the malaise of diabetes more quickly than others, but the health
of every person with diabetes is adversely impacted. When diabetic complications eventually arise, as they will in well over 70% of diabetic patients, in order to stop and reverse these processes, patients must restore proper carbohydrate processing which is the core problem. The Artificial Pancreas Treatment® is the only known treatment achieving the restoration of proper carbohydrates processing.

3. While not controlling blood glucose exacerbates complications, tight blood glucose control does not stop complications and is actually contraindicated for many patients particularly those who have cardiovascular disease or have hypoglycemia due to depressed storage and release of hepatic glycogen. Thus, current glucose control treatments are better than no glucose control, but a better level of treatment is required to avoid complications or when complications begin. The Artificial Pancreas Treatment® reverses this inability to process carbohydrates and thus treats the core problem. 16 clinical trials and 200,000 treatments prove what is axiomatic, restoring normal processing is remedial because to repair is normal.

4. The natural progression of type 2 diabetes (T2DM) commences with insulin insensitivity and directly causes reduced metabolic integrity. This metabolic dysfunction commonly is associated with weight gain. However, the weight gain is actually caused in part by reduced metabolic integrity and excess uncovered insulin production. This often occurs before the patient is even aware of diabetes, metabolic syndrome, impaired glucose tolerance or any malady as hyperproduction of pancreatic insulin “hides” the high blood glucose. The process is complicated, but metabolic disease increases weight gain. Regaining proper carbohydrate metabolism enhances weight management and provides a new approach where the patient is not abnormally storing fat from hyperproduction of insulin in response to body insensitivity.

5. There is a direct link between improper carbohydrate (glucose) metabolism and the “poor outcomes” of diabetes - disability and death. When carbohydrate metabolism is blunted, the body automatically shifts to lipid, free fatty acid and protein use. Elevated free fatty acids as found in diabetes increases reactive oxidative species (ROS) and cytokine responses to inflammatory processes. This direct link is well understood, and thus complications of diabetes for type 1 and type 2 are very similar; they directly result from lacking proper carbohydrate metabolism and high blood sugar is but one of the symptoms.

6. The Citric Acid cycle is relatively dormant. The dominate pathophysiological defect of both Type 1 and Type 2 Diabetes is caused by a relatively high liver dormancy of non-production and regulation of the enzymes necessary for proper carbohydrate metabolism (reestablishing the tricarboxylic (citric) acid cycle - the Krebs Cycle). These enzyme deficiencies result from the diabetic liver not receiving a unique insulin signal from the pancreas. Oxidative phosphorylation is the metabolic pathway by which the mitochondria in cells use their structure, enzymes, and energy released by the oxidation of nutrients to reform ATP. Although the many forms of life on earth use a range of different nutrients, ATP is the molecule that supplies chemical energy by metabolism. Almost all aerobic organisms carry out oxidative phosphorylation. This pathway is pervasive because it is a highly efficient way of releasing energy, compared to alternative fermentation processes such as anaerobic
glycolysis. Thus, diabetes is occasioned by improper carbohydrate metabolism through reduced mitochondrial carbohydrate oxidative phosphorylation because the mitochondria do not receive the liver activated enzymes for proper carbohydrate oxidative phosphorylation. Without these enzymes, the Krebs cycle does not take place, and these enzymes are produced in the liver, but highly blunted in the diabetic, to the point of near dormancy. This is directly caused by the lack of signal from the pancreas to the liver.

7. It is possible to restore proper carbohydrate metabolism via the Krebs cycle in people with diabetes using the Artificial Pancreas Treatment®, which automatically breaks the causational link between improper metabolism and “poor outcomes.” This restoration is available through the Artificial Pancreas Treatment® using the FDA cleared Bionica Microdose infusion device, as shown by virtually every patient treated. Used in over 200,000 treatments without a single adverse reaction or unintended outcome, this natural approach to mimicking the normal human pancreas burst stimulation of the liver achieves the goal of complication cessation and reversal. It is the only known treatment to achieve documented reversal of multiple diabetes complications. It is uniquely safe, and that safety comes from the fact that all APT does is restore normal by mimicking normal.

8. Bursts of Insulin. It was suggested but unknown until 2002, that all human pancreatic insulin is actually delivered from the pancreas to the liver in “bursts” every 4 to 6 minutes, with these bursts of approximately 660% of base line. It is this burst cyclic insulin via intravenous administration which mimics normal, and which is called the Artificial Pancreas Treatment®.

9. The remedial result of restoring proper metabolism is all-encompassing as it empowers cell repair through DNA encoding. When the core problem of metabolism is directly addressed, and carbohydrate metabolism is restored to patients with metabolic dysfunction, the entire milieu of complications are ameliorated. Every complication which is brought on by improper metabolism, and there are many, can either be stopped, or in the majority reversed by DNA modulated and controlled cellular repair processes. The body knows precisely how to restore these tissues as “repair” is encoded within DNA. With renewed high levels of adenosine triphosphate (ATP) and a reduction of the inflammatory process (by reduction of the inflammatory cytokines and free fatty acids), all metabolically denuded tissues automatically become more healthy through DNA sequenced transcription and repair.

Chapter 2  Diabetes is a disease of improper metabolism, not just blood sugar deregulation. After the disease progresses to the point of diabetic secondary complications, metabolic remediation is required to achieve good health outcomes.

Every medical text book, and paper properly states that diabetes, at its core, is a disease of improper carbohydrate metabolism. However focus on this CORE problem is lost by conventional blood sugar regulation approaches to treat diabetes. People with diabetes, regardless of their blood glucose control or general health, cannot process carbohydrates properly, and this failure causes elevated free fatty acid levels and glucose when they ingest any
significant amount of carbohydrates. Elevated blood glucose levels are merely one of the many symptoms of diabetes and admittedly not the core problem. Yet, all treatments other than the Artificial Pancreas Treatment® continue to have the narrow goal of euglycemia (normal blood glucose levels).

Blood sugar regulation is of course needed, but the relative ease of measuring BG is so seductive, it gives a false sense of achievement and good health. It seduces both the practitioner and patient to believe normality is being achieved, when it obviously is not...good glucose levels do not mean proper metabolism, and abnormal metabolism leads to disability and death.

Medicine has not had an easy way to measure metabolism, so the surrogate measurement of blood glucose, was substituted. But glucose readings are now being widely criticized as either inaccurate or unnecessary. While not controlling blood sugar leads to an immediate (acute) state of poor health, the overall failure to properly metabolize carbohydrates in the extended (chronic) state leads to diabetic disability and death. Blood sugar control is not benefited by the adage “if a little is good, a lot is better” since tight control in the presence of diabetic complications has been shown in several ways to be harmful. This lack of proper metabolism leading to an underlying inability to produce normal levels of adenosine triphosphate in the diabetic cell causes the cells to “slow down” to conserve and survive, and tight control only acts to further starve of ATP the already starving cells. Diabetic cells only have 70% of normal ATP due to the inability to directly oxidize carbohydrates, and require extra oxygen to function.

There is an “Omnipresent Medical Necessity” for metabolic remediation of carbohydrate metabolism after diabetes has caused patients to manifest secondary complications. To fail to do so, condemns the patient to early disability and death with costly disease outcomes affecting the whole family. This paper will provide the means of achieving this remedial goal and proof that the Artificial Pancreas Treatment® using the Bionica Microdose achieves what no other treatment has achieved, proper metabolism. It will also prove that it does this work by means of normalization through burst insulin administration.

Unique effectiveness rates. Metabolic remediation is achieved after a series of treatments in virtually every patient, resulting in normalized bodily functions. The Artificial Pancreas Treatment® provides natural like bursts of insulin which mimics the “normal” way insulin from the non-diabetic pancreas stimulates the liver to produce a cascade of enzymes needed for proper carbohydrate (and thus lipid) metabolism. This return to normal is medically necessary to address the core problem of diabetes with secondary complications. The treatment is uniquely effective because patients cannot live without a functioning liver, and functioning livers are DNA encoded to produce the Kreb cycle enzymes if properly stimulated. By addressing this core problem, diabetic complications of heart, kidney, eye, brain, skin, vascular system, and energy levels, to name the obvious, are all improved. Often asked, why does the APT work to help all complications? The answer is simple, if you effectively address the core problem of diabetes, then all the resulting problems should see improvement …and they do. If there were diabetic complications which were not ameliorated, then we would know that APT was not addressing the core problem. The diverse benefits validate APT, as no other treatment achieves widespread changes, because no other treatment faithfully mimics the pancreas in its bursts of insulin.
Chapter 3  The current mode of treatment, Tight Blood Glucose Control with or without subcutaneous insulin, eventually results in failure by all medical standards.

A medical failure is where a treatment does not cause the patient to return to non-disease functionality, or does not relieve the symptoms and pathophysiological changes from the disease dysfunction(s). Using Webster’s Dictionary: a) a medical failure is a state of inability to perform a normal function; b) a cessation of normal functioning.

The core problem. In the case of diabetes, the core dysfunction is the inability of the patient to properly process both complex and simple carbohydrates (the Krebs Cycle). This results in the mitochondria in every cell failing to properly metabolize carbohydrates, and resulting in the secondary complications of diabetes. Every patient with diabetes who is not treated with the Artificial Pancreas Treatment® suffers from this inherent failure to function normally.

Tight glucose control cannot achieve normal metabolism. Any hope that by controlling blood glucose, one could stop complications has been debased by some of the largest diabetes clinical trials ever conducted, the Diabetes Control and Complications Trial (DCCT), the United Kingdom Prospective Diabetes Study (UKPDS), the Kumamoto Hospital Ohkibo study, and every other major study since. These studies prove two realities: a) not controlling blood glucose levels causes immediate health risks; but b) tight control does not stop the complications, nor is it an effective means to treat certain complications. In fact, tight control is counterindicated for the largest population with diabetes complications, those with cardiovascular disease. This was proven by the Action to Control Cardiovascular Risks in Diabetes (ACCORD) study which showed early death to CVD patients being tightly controlled as opposed allowing higher blood glucose.

This is not suggest that failing to control blood sugar is appropriate. Poor glucose management can cause a number of both temporary and chronic problems. In addition to coma and death, they cause hypoglycemia, ketoacidosis, elevated free fatty acids, elevated cytokines and inflammatory diseases just to name the obvious. However, while necessary, the most careful control of blood sugar still is not enough to stop or reverse the chronic complications of diabetes. There are several major clinical trials which demonstrate this reality.

The DCCT quote quite correctly states that “while not controlling glucose worsens complications, tight control does not prevent 25% to 40% of diabetic patients from developing overt secondary complications within 10 years.”
The large UKPDS likewise shows that all other therapies of diet with exercise, subcutaneous insulin, insulin secretion enhancing drugs, or insulin sensitivity enhancing drugs, which include basically all modes of therapy seeking “intensive treatment” of blood glucose fail to stop the loss of metabolic integrity at almost precisely the same rate. Why? Because tight glucose control does not address the underlying deficiencies of improper carbohydrate metabolism.

The Kumamoto Hospital Study of NIDDM patients by Y. Ohkubo and colleagues showed that with nearly normal glucose control of HbA1c lower than 6.5%, a fasting glucose of less than 110 and postprandial glucose of less than 180 mg/dl still left a significant population which developed the complications of diabetes during the term of the study. Thus, the best that tight control can even hope to do, is to delay complications, and for many, very tight control will exacerbate their disease.

All known studies combined. Other studies acknowledge the same reality, there has never been a study which showed that tight glucose control will result in diabetes complication avoidance over time. The most that can be said is the obvious…diabetes is a degenerative body wide metabolic disease which can be slowed with tight blood glucose control, but is not a pathway to stopping the disease. You can control blood sugar, but this does little to properly feed the cells.

Even in non-diabetic humans, the pathophysiology of improper carbohydrate metabolism is associated with poor health. Metabolism is life at its most basic, and skewed metabolism, where a disproportionately large substrate is used to sustain life results in poor health. The proof of this is found in the Whitehall II study where just two readings of elevated inflammatory cytokine IL-6 reduced the healthy aging of non-diabetic patients by an incredible 50%. Diabetes is an inflammatory disease with elevated inflammatory cytokines including IL-6, caused directly by elevated free fatty acids, a direct cause of improper carbohydrate metabolism. There is no way to avoid free fatty acid caused inflammatory cytokines without normalizing carbohydrate use (as does the Artificial Pancreas Treatment®).

Thus, when we deal with the core problem of metabolism, by default we deal with the basic wellness of the patient. When we lull diabetic patients into thinking that tight control will stop or treat diabetes complications, we are being simplistic, and now we have a new way to restore their health by correcting the core problem.

Until the advent of the Artificial Pancreas Treatment® there has never been a tool better than tight control with all its limitations. However, with APT, there is now a tool which mimics normal stimulation of the liver and other tissues, and it should not be surprising that by doing so, and treating the core problem, the entire patient is helped through the natural restorative
processes controlled by the ultimate memory of how to do things…DNA.

On a macro level, it is instructive that for the last 23 years, the percentage of diabetes hospital costs have not varied over 1%, yet the use of blood glucose monitors has gone from unavailable to rampant where anyone with an address can get a glucose monitor. The lesson is not that glucose monitoring is unnecessary to avoid acute episodes, but rather that sufficient patients impacted with the secondary complications of diabetes are still being hospitalized at the same rate, whether the population has blood glucose meters or not. The use of blood glucose monitors seeking tighter control is clearly ineffective to stop hospitalizations.

Current treatments which seek to stop diabetic hospitalization by normalizing blood glucose, fail. Why? The answer is found in the fact that conventional diets and treatments limiting carbohydrate intake do not achieve metabolic sufficiency for even marginal health.

**Chapter 4  Improper Carbohydrate Metabolism Directly Causes Diabetes Failure, Which is “Disability and Death.”**

Causation is direct, and relatively simple. The link between metabolic disorders and diabetic complications is well summarized by S. Clement et.al. in Diabetes Care 27:553-91- 2004

This publication summarized pathophysiological reality. It all starts with metabolic dysfunction, glucose and insulin imbalance, and leads to disability and
death outcomes.

This review puts everything into perspective noting the steps of immune dysfunction, increased free fatty acids, and reactive oxidative species, resulting in cellular death, inflammation, altered wound repair and blood flow reductions. This is how the Artificial Pancreas Treatment® directly addresses complications, and why APT outcomes are not disability and death, but rather restored health! This makes sense of the complicated milieu of diabetes, and shows the only pervasive way to treat the disease is to treat it as a disease of metabolism inside the cells.

**Chapter 5  Current Diabetes Treatments have Shortsightedness, Addressing Only Blood Glucose, and Ignoring the Core Problem of Metabolism.**

The relative ease of glucose measurement has channeled most treatments away from the core problem of metabolism and established an invalid end-point… blood glucose levels.

Even though it is undisputed that diabetes is a disease of improper metabolism, treatments have ignored the direct measurement of metabolism using conventional sports medicine equipment, and focused on euglycemia (normal glucose levels) as if achieving euglycemia would result in good health. It does not.

Even perfect glucose does not provide proper metabolism. In fact, treatments today are much the same as the first ever treatment for diabetes of approximately 3,000 BC which focused only on blood sugar control.

The Pharaohs achieved almost perfect blood glucose (euglycemia) in approximately 3 days….they simply starved the patient of all food and no more glucose was seen in their urine. Of course after starvation the patient died or when eating resumed succumbed to ketoacidosis because their bodies could not process carbohydrates and they had no insulin.

Thus, starting with 3,000 BC and continuing to 2015, it has been one of the oldest known medical facts, that normal blood glucose does not mean proper metabolism. We underscore this 5,000 year physical law because it is so illogical to have tight blood glucose as the goal, yet tight glucose control is still the endpoint of success. This paradigm (prejudice) of glucose focus over metabolism is so pervasive it is even found when celebrities ask audiences to “Watch your glucose, I do.” (Bromley). In fact, celebrities say “I'm not diabetic anymore” (Drew Cary) which is, of course, not true, he is just starving his body with extraordinarily low intake of carbohydrates…much like the Pharaohs.
Paradoxically, every known current mode of treatment only seeks to achieve some measure of euglycemia, without any measurement of the core deficiency, carbohydrate metabolism, and without ever even trying to mimic normal bodily functions. It is almost ludicrous to realize that diabetes is defined as a “disease of metabolism” and yet treat it as if it were a “disease of blood glucose.” By measuring only glucose and ignoring the available means to measure metabolism, the true endpoint of proper metabolism is never achieved because it has not been sought. All scientists have needed to do was measure resting metabolism and all would have learned what we now know so well...that treating glucose is not treating metabolism. Metabolism is explained in this paper, and Metabolism is what is achieved by the Bionica Artificial Pancreas Treatment®.

Chapter 6 Why does Diabetic Body Does Not Metabolize Glucose Properly?

The core problem of carbohydrate metabolism is a failed chain, with the beginning failure being the lack of proper pancreas stimulation of the liver to produce enzymes for the Krebs Cycle, and the end being the inability of the mitochondria to process carbohydrates causing disease.

The mitochondria are tiny organelles which reside in every cell except blood cells, and process substrates into chemical energy called adenosine triphosphate (ATP). This is the basic energy molecule used by cells for their energy and processing.

Logically, the mitochondria prefer to metabolize glucose (carbohydrates) because that metabolism provides more cellular energy and does not require extra oxygen. It is anaerobic and very quick.

When the mitochondria cannot burn glucose, it switches to metabolizing free fatty acids, fats and proteins. This is not the type of metabolism that directly leads to the “poor outcomes” above of disability and death.

Here are the problems:

- Metabolizing carbohydrates generate many more molecules of ATP than fat.
- Fat metabolism requires extra oxygen to produce ATP, taking oxygen from other tissues.
- People need 45% - 65% energy from carbohydrates (not just sugars, but also complex)
- Diabetic People have approximately 70% of normal ATP levels in their cells due to this improper metabolism. (Why would anyone be surprised at diabetes disease with this?)
- Proper metabolism resolves all of these issues, which is why treating metabolism using the Artificial Pancreas Treatment® is the next level of care. No other treatment achieves normalized resting metabolism.
The inability to burn carbohydrates is caused by a lack of enzymes processed in the liver. The pancreas signals the liver of the presence of carbohydrates. These enzymes are needed for body-wide metabolism.

Thus, the definition of diabetes should not be a disease of glucose, but rather the failure to provide necessary enzyme levels.

Diabetes is technically a single disease of missing enzymes, causing multiple malaise, and can be properly treated by addressing this fundamental core failure.

Conceptually, these enzymes could be synthesized, but the complicated balance and delivery to mitochondria is all but impossible to date. Thus, it is both necessary and desirable to have the body produce these enzymes endogenously. To stimulate natural production of these enzymes is the only logical way to treat this single need for the foreseeable future.

Thus, restoring the Krebs cycle, not blood glucose control must be the endpoint. The body must be stimulated to restore these enzyme pathways, some of which we do not measure or even fully understand.

Carbohydrate fuel is the basic means of healthy life, and diabetic disabilities and death are directly caused by this missing metabolic pathway. All scientists acknowledge the fundamental need to avoid chronic inflammatory processes. The natural way to achieve that avoidance of inflammation is to avoid the failure of improper carbohydrate metabolism since free fatty acid levels directly increase inflammatory cytokines.

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*The Enzymes Needed by the Mitochondria for Glucose Metabolism are Triggered by Insulin/Glucagon Ratios in the Liver*

<table>
<thead>
<tr>
<th>Enzymes induced</th>
<th>Enzymes activated</th>
</tr>
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<tbody>
<tr>
<td>Glucokinase</td>
<td>6-phosphofructo 2-kinase</td>
</tr>
<tr>
<td>6-phosphofructo 1-kinase</td>
<td>Pyruvate kinase (I-isoenzyme)</td>
</tr>
<tr>
<td>Citrate cleavage enzyme</td>
<td>Pyruvate dehydrogenase complex</td>
</tr>
<tr>
<td>Acetyl - coa carboxylase</td>
<td>Acetyl - coa carboxylase</td>
</tr>
<tr>
<td>Hmg - coa reductase</td>
<td>Glycerol phosphate acyltransferase</td>
</tr>
<tr>
<td>Pyruvate kinase</td>
<td>Hmg - coa reductase</td>
</tr>
</tbody>
</table>

Enzymes repressed ratio:

- Glucose 6-phosphatase
- Fructose 1,6-biophosphatase
- Phosphoenolpyruvate carboxykinase

Enzymes inactivated by a high insulin:glucagon ration:

- Glycogen phosphorylase
- Fructose 2,6 biophosphatase

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*Result of Bionica Pulses Delivery of Insulin Krebs cycle – Enzyme Pathway Restored*

When the Krebs Cycle (Citric Acid Cycle) is restored,

- The body processes carbohydrates.
  - a) avoids high lipid use,
  - b) Provides more energy,
  - c) Reduces Free Fatty Acids
  - d) Reduces Cytokines.

This is why the Artificial Pancreas Treatment® system is simple, it just restores metabolism which provides more ATP and reduces inflammation.

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Starvation of the cells by high lipid utilization is why conventional treatments do not stop diabetes illness. Starvation is the unintended result from treatments that limit carbohydrates in order to limit blood sugars. Current treatments tightly controlling glucose actually result in starvation-like metabolism.

The unfortunate reality is, that by tightly controlling glucose in patients with diabetes, the cells are no longer able to function as well, having an average of only 70% of normal ATP (cellular chemical energy) in each cell. Their inability to withstand background inflammatory process is cause by reduced nitric oxide levels reduce, and high levels of inflammatory cytokines.

Non-diabetic “prolonged fast” of 30 to 40 days, glycogen is depleted, and fats and free fatty acids are converted to provide the energy

Most diabetic people are Starving:

a) cannot burn carbs, so they have 70% of normal ATP levels,

b) Process lipid hepatic glycogen of a Prolonged Fast all the time.

People ask, "Why don't you exercise and lose weight...try exercise when you have less energy and your brain and body know that you are starving!"

Tight Control in Treating Complications
The ACCORD
Action to Control Cardiovascular Risk in Diabetes

The ACCORD study studied Intensive Glucose Control (tight control) in diabetic patients with cardiovascular disease.

Normally, Type 2 patients die from cardiovascular disease at rates 2 to 4 times normal, by increased MI’s (heart attacks) and strokes.

This huge study of 10,251 patients was designed to study the effects of tight blood glucose control on heart disease patients with diabetes.

The glycemia trail showed that tight blood glucose control was actually worse than keeping higher glucose levels!

This caused the glycemia trial to be terminated early due to accelerated deaths.  

_Tight Control does not stop complications, and, Tight Control is not the way to treat these complications either._

Failing to understand starvation and that lower energy is a fundamental loss, investigators were shock by the landmark ACCORD study to learn that tight control actually increased mortality significantly, and the glycemic control trial was halted for patient safety.

The logic is obvious, starving patients who already have cardiovascular inflammatory disease is contraindicated.
The endpoint of normal blood glucose ("tight control") was put to the test in this ubiquitous complication of diabetes, cardiovascular disease. Tight control failed, but few understood why. We know that it failed because tight control does not achieve proper metabolism, and tight control does not address the core causes of cardiovascular disease, inflammation.

Still, some process the same old question. The most recent works expose tight control as not being an answer. The JAMA Internal Medicine most recent clinical study on tight control adds to a growing list of cautions against tight control. In fact, it is counter-indicated for older patients with poor health:

January 12, 2015:

Potential Overtreatment of Diabetes Mellitus in Older Adults With Tight Glycemic Control  Kasia J. Lipska, MD, Joseph S. Ross, MD; Yinghui Miao, MPH; Nilay D. Shah, PhD; Sei J. Lee, MD, MAS; Michael A. Steinman, MD:

"Using a nationally representative sample of US adults, we showed that nearly two-thirds of older adults with diabetes who have complex/intermediate or very complex/poor health attained tight glycemic control. These vulnerable adults are unlikely to experience the benefits of intensive glycemic control and instead are likely to experience harms from treatment, such as hypoglycemia and other adverse effects. Recognition of both the harms and benefits of glycemic control is critical for patients and physicians and other health care professionals to make informed decisions about glucose-lowering treatment." - 1,288 patients, JAMA Jan 2015 emphasis added.

This outcome would have been totally expected when the “starvation model” explained above is superimposed on type 1 and type 2 diabetes. It does not help to starve a starving patient.

Example Heart Metabolism, Cardiac Dysfunction

Diabetic heart muscle is impaired:

1. By 30% less ATP (cellular energy) since lipids provide less ATP.
2. By requiring extra oxygen when carbohydrates cannot be burned
3. By reduced blood flow (ischemia) from elevated free fatty acids
4. By inflammation from increased inflammatory cytokines
5. Neurological stimulation is reduced by neuropathic limitations

Artificial Pancreas Treatment® corrects these impairments:

1. APT provides more ATP (cellular energy), (approx. 30% – 40%)
2. with a reduction of oxygen required, anaerobic functioning,
3. improving blood flow, overcoming ischemia,
4. Reduced inflammatory responses,
5. improved nerve conduction velocity, and
6. anecdotally, the removal of atherosclerotic adhesions,

Uniformly they routinely recover a more normal life.
Their hearts are no longer starved, and begin to heal
Low ejection fractions will increase 200%.

Understanding why starvation is the key is easily demonstrated by a review of cardiac dysfunction. Every heart process is impaired by the starvation improper carbohydrate metabolism and this is causes the CVD “poor outcomes” of diabetes.
Amazingly Seductive Paradigms. Why have not all seen the restoration of the Krebs cycle as the true goal and endpoint for diabetic treatments, and why have so many still cling to blood sugar as the answer for 5,000 years, knowing that diabetes is a fundamentally degenerative disease not stopped by tight blood glucose control? Perhaps the answer in part is that it is financially better to develop a compound which is easy to administer and very profitable to sell.

However, there is another scientific reason for this slow awakening. Looking for a compound, scientist did not focus on the MEANS by which the pancreas secreted insulin to the liver, which turns out to be huge tailored bursts of insulin in the presence of glucose.

The entire historical approach to diabetes has missed the forest for the trees. It is undeniable that diabetes is a disease of metabolism, but glucose regulation approaches are easier and simplistic. Thus, the history that shows tighter and tighter blood glucose still leaves disabilities and death is ignored in the rush for an easy fix.

The Artificial Pancreas Treatment® brings diabetes treatment to the next level of restorative care. It allows the body to heal itself through its own DNA encoded pathways, and avoids common problems of unexpected outcomes by faithfully mimicking normal stimulation of the liver to renew the Krebs cycle for diabetic people of all ages and types.

Chapter 7 Mimicking Normal Pancreatic Bursts with the Artificial Pancreas Treatment®.

The goal of the Artificial Pancreas Treatment® is to restore the ability to properly process carbohydrates. This is done via the most obvious low risk methodology, mimicking normal pancreas actions which stimulate the liver to produce the Krebs Cycle enzymes. In order to learn what was wrong, we had to learn the anatomical basics.

As early as 1973, it was known that the immediate response to a glucose load was a sharp spike in free (plasma) insulin levels in just a few (2-6) minutes. This normal spike is very large. However, type 2 diabetic people do not provide this quick response, and of course, by not making insulin, type 1 diabetics also fail to supply this signal. This failure is common to both type 1 and type 2 diabetes, as are all of the complications of improper metabolism.

It is not surprising that both type 1 and type 2 diabetic patients suffer from the same list of secondary complications, since the genesis of the dysfunction is improper carbohydrate
metabolism leading to inflammatory responses for both. And, since the inability of the pancreas to supply an immediate first phase insulin release is manifested in both, that was the key.

Amazingly, even though this first phase massive outpouring of insulin from the pancreas was known in 1972 to be missing, no treatment has effectively addressed this problem.

Compounds have been unable to regain this uniquely volatile bursts of insulin. Only the Artificial Pancreas Treatment® mimics these functions. Listed hereinafter are the extensive clinical trials showing that insulin stimulation is the key, and is natural. Chemical compounds do not restore this process, and likely never will.

It would be wonderful for a pill to be able to restore the Krebs cycle to patients with metabolic diseases. However, literature and even Pharma announcements have not disclosed any work which would suggest that restorative compounds are in any pipeline. It is this author’s belief that no compound can ever restore bursts of insulin from a pancreas that has been subjected to insulin resistance demands and has lost islet cell integrity.

Until a cure for diabetes is developed, the Artificial Pancreas Treatment® is the next best thing, and the only means by which the Krebs cycle can be restored. This inability by other means is seemingly set in stone as the human body has not shown any other pathway to coordinate the amazingly complicated symphony of hormones other than by inducing it naturally.

Studying the natural progression of type 2 diabetes mellitus (T2DM) is necessary to understand why the pancreas does not react properly with a sudden increase of insulin. As seen here, (brown circle) the patient usually does not know of diabetic onset until insulin resistance has been present and the pancreas is trying valiantly to overcome that resistance with production of insulin of almost 200% of normal. After that, the pancreas begins to fail, and the ability to produce insulin (green line) gradually reduces to zero. If a type 2 diabetic patient lives long enough, he/she should expect to lose all insulin production from beta cell failure. Only when the failure starts do fasting glucose tests show a problem. This is why a fasting blood glucose test is far after diabetes has already started its dire process.
Still more information can be gleaned from reviewing so-called “Pre Diabetes” or impaired glucose tolerance. As seen, even before T2DM is present, the pre-diabetic produces significantly higher levels of insulin than a normal, with the total insulin (area under the curve) being far more than a normal. Thus, the pre-diabetic is already suffering from insulin resistance as the pancreas tries to overcome resistance, and because it is working almost non-stop, it not only begins to fail, it also, most importantly, fails to give a normal signal to the liver.

As seen above, there is a very late and high level of insulin in the blood of a pre-diabetic after eating, causing inappropriate high chemically induced hunger. Almost every pre-diabetic experiences this sensation of hunger after eating, causing snacking and excess calories.

What was not generally known, or at least its importance, is the fact that this first phase of insulin in just 2 to 5 minutes is huge, and is accomplished with a special burst signal from the pancreas. The liver needs to “be told” that there are carbohydrates to burn, for the liver to produce the Krebs cycle regulating enzymes in proper quantities. It is this communication or “language of the pancreas” which causes the liver to produce a cascade of events leading ultimately to the mitochondria being able to convert carbohydrates to ATP in proper amounts.

Without this special communication (signal) the diabetic patient’s liver does not continue to produce and activate the Krebs cycle enzymes which in turn dooms the mitochondria to elevated metabolism of lipids, free fatty acids and proteins.

The Artificial Pancreas Treatment® provides that missing signal of bursts of insulin causing a simple restoration of what is “normal.” Like so many fundamental advancements, it is the simple elegance of replicating the body’s design which proves to be infinitely more valuable and restorative than any combination of starvation and chemically altering secretion drugs.
Our initial goal was to replicate the missing signal to the liver which was the missing stimulation, common to both type 1 and type 2 (and even IGT patients).

However infusions to achieve the same serum level of insulin into the human body at such a rapid rate would drive glucose out of the blood and kill the patient.

Also, it was too dangerous for a catheter to reside in the portal vein to provide this signal to the liver for over a few hours. Thus, wave form experiments finally concluded with the manufacture of an “artificial venous system” made to replicate the natural flows and whirls of blood, with adjustment for various blood pressures and flows. This system used gravity based pressures to mimic normal blood flows in veins and capillaries, and supplied the needed information on pressure and concentrations needed to provide a normal burst-like delivery. This provided a suggested strategy for the Artificial Pancreas Treatment®, as conventional pumps including peristaltic heart pumps would provide the burst infusion.

Final development of the replacement signal started with wave augmentation by frequency adjustments. This required pump determination of pressures and concentrations necessary to obtain a wave form which could be additive, much like bouncing waves in a wave motion pool. The design requirements for the Artificial Pancreas Treatment® Bionica Pump, required specific timing, and pressures which could only be achieved with volume modulation to avoid venus implications. Pressures without risk of infiltration were required and achieved. These burst, modulation pressure and concentration parameters are now built into the Bionica pump delivering the Artificial Pancreas Treatment®.

However, this work actually resulted in an accidental mimicking of the pancreas. Surprisingly, by trying to make a first phase release through adding waive aptitudes, the result was an accidental mimicking of the normal pancreas signal! At the time that the Bionica pump development took place, the importance of wave forms by the normal pancreas was not known, and only after development of the pump, wave forms were recognized as important and then verified. Not recognized at the time of development, independent studies later proved the importance of the wave forms which were developed.
In fact, it was the great debate between cellular studies and organ studies which started in the 1960’s which slowed the discovery of this normal signal of the pancreas. This signal is always present and absolutely necessary for proper metabolism, (thus the term “Absolute” in the title hereof). However, attempting to develop compounds overshadowed the need for a mechanical remedy.

As time progressed from the 80’s to the 90’s to now, the focus is slowly shifting from compounds designed to achieve euglycemia, to methods to achieve proper cellular function. However, most clinicians taught before 2005 have no idea from their anatomy classes that there is a special burst secretion of insulin by the pancreas into the portal vein.

Of course the pancreas secretes insulin into the portal vein, something that every scientist learns early on. Studies have shown that from 50% to 80% of all insulin is retained by the liver as part of that organ’s function.

While the human genome was almost fully mapped by 2002, no one had actually measured the insulin secretion pattern generated by the pancreas. This lack of focus is both logical and yet not.

Who would assume that there was an answer to reversing the complications of diabetes within the study of signals from the pancreas to the liver?

Peter Butler came close. As professor of medicine and chair of the division of endocrinology and diabetes, and research fellow Soon Song, received the Endocrine Society's first prize for best clinical paper published in *The Journal of Clinical Endocrinology and Metabolism* in the year 2002. The paper, "Direct Measurement of Pulsatile Insulin Secretion from the Portal Vein in Human Subjects," reported that insulin is secreted from beta cells in the pancreas almost exclusively in secretory bursts every four to six minutes. The result: very large amplitude oscillations of insulin concentration in the portal vein, which directly perfuses the liver,” Butler said.

“We conclude that insulin release in the human portal vein occurs at a mean periodicity of 4.4 [plus minus] 0.2 min with a high signal-to-noise ratio (pulse amplitude 660% of basal)”. This means that the bursts are very large, approximately 7 times the base levels and six minutes apart.

Dr. Butler and his research fellow Dr. Song were working with significant clues as to the existence of bursts, but did not know of our work being done with the Bionica the Artificial Pancreas Treatment® in developing a “burst wave” pump.

In fact, thirteen (13) years before that award winning paper, the Bionica Pump was published to be achieving very promising results from a burst wave, which actually mimics the bursts measured by Dr. Butler:
The Bionica pump is the product of the fluidic research seeking to augment waves by frequency. 13 years before Dr. Butler measured the insulin bursts generated by a normal pancreas in humans, the published Bionica pump data showed the exact same pattern of equal bursts, both as to frequency and as to amplitude.

As shown on this minute-by-minute measurement of free insulin levels in these human subjects using the Bionica pump, the duration between bursts are directly within normal range, and the amplitude of insulin levels are directly within normal range.

This was achieved with pressure modifications and volumetric changes to avoid any infiltration of an intravenous site. Since this study, there have been approximately 200,000 treatments where the pump and system has performed perfectly, and there have been no recalls, injuries, claims, malpractice suits, settlements, unexpected outcomes, or the likes.

The obvious and necessary goal is to re-establish normal metabolism by recapitulating pulsatile insulin effects to the liver, using the patented US FDA and foreign FDA-cleared pump (Bionica) that re-approximates the periodicity and amplitude of pancreatic insulin secretion bursts to the portal vein as well as the rest of the body. This achieves physiological insulin concentrations needed to re-establish enzymatic pathways needed for the Krebs cycle to begin with the resulting regaining of normal levels of ATP within the cells. This cyclic momentary higher concentrations of insulin in the whole body is also remedial and approximates normal as well.

Normal insulin secretion rates (ISR) show highly dynamic change in just minutes. These changes are the result of the bursts of insulin learned by Butler and colleagues to be normal. These bursts and resulting oscillations occur throughout the entire body, and are likewise achieved by the Artificial Pancreas Treatment®.
Similarly, the dynamicity is found even at night where the amplitudes are approximately 150% of daytime amplitudes.

This clearly demonstrates that a normal person has very “Dynamic Homeostasis” of insulin in response to glucose, which is a concept that should be embraced to overcome the prejudice in favor of mere tight blood glucose regulation.

In fact, there are a multitude of supporting studies showing the need for burst insulin pulsing as by the Artificial Pancreas Treatment® and absolutely NO supporting studies showing that insulin is not highly dynamic (Dynamic Homeostasis) nor studies which suggest that burst insulin signaling is not needed.

**Chapter 8** The following are published papers which conclusively show that it is normal for insulin to be secreted in bursts...and this conclusion has never been contradicted by any other study.

The following papers conclusively, and irrefutably prove that the natural way for insulin to be secreted is in bursts causing the oscillations above. This fact is largely ignored, but is fundamental to homeostasis and the Artificial Pancreas Treatment®.

<table>
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<tr>
<th>Insulin, Glucagon and Glucose Exhibit Synchronous Sustained Oscillations in Fasting Monkeys; Science (1977) 195: 177-179</th>
<th>As early as 1923, fluctuations of sugars were found. However, this is the first publication where oscillations of insulin were found. It was so unique, it made Science.</th>
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<tr>
<td>Cyclic oscillations of basal plasma glucose and insulin concentrations in human beings. Lang DA, Matthews DR, Peto, J, Turner RC NEJM (1979) 301:1023-1027</td>
<td>This was the first human trial to measure at one minute intervals the insulin levels (top line) and found them to be “significantly greater than expected”</td>
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<tr>
<td>Brief, Irregular Oscillations of Basal Plasma Insulin and Glucose Concentrations in Diabetic Man Lang DA, Matthews DR, Burnet M, Turner RC Diabetes (1981); 30: 435- 439</td>
<td>This 1981 human study showed that normal insulin oscillations occurred in normal patients, but <strong>blunted in even mild maturity onset diabetes patients.</strong> The first clue that the loss of oscillations was part of diabetes.</td>
</tr>
</tbody>
</table>
| Pulsatile Insulin Has Greater Hypoglycemic Effect than Continuous Delivery  
Matthews DR, Naylor BA, Jones RG  
Ward GM, Turner RC, *Diabetes* (1983) 30:617-621 | This study showed pulsed infused insulin had a greater glucose reducing effect than a steady infusion of insulin. |
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<tr>
<td>Efficacy of Pulsatile Versus Continuous Insulin Administration on Hepatic Glucose Production and Glucose Utilization in Type 1 Diabetic Humans. Bratusch-Marrain PR, Komjati M Waldhausl WK. <em>Diabetes</em> (1986) 35:922-26</td>
<td>This study compared pulse infusion to continuous infusion. “In humans, various hormones e.g. insulin, glucagon, growth hormone, and luteinizing hormone are secreted in pulsatile fashion.” (It is now obvious) “The Cyclic mode of insulin secretion has a biologic advantage in regulating glucose metabolism.”</td>
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<td>Effects of Prolonged Pulsatile Hyperinsulinemia in Humans, Enhancement of Insulin Sensitivity. Ward GM, Walters JM, Aitken PM, Best JD, Alford FP <em>Diabetes</em> 1990 39:501-507</td>
<td>Prolonged IV pulsatile infusion has a greater hypoglycemic effects than continuous insulin infusion, a 55% greater effect.</td>
</tr>
<tr>
<td>Pulsatile insulin delivery has greater metabolic effects than continuous hormone administration in man: importance of pulse frequency. Paolisso G, Scheen A, Giugliano D, et al. <em>JCEM</em> (1991);72:607-615</td>
<td>Perhaps most telling of all, pulse (burst) insulin of the same amount inhibited hepatic endogenous glucose production as compared to 26 minute infusion delivery.</td>
</tr>
<tr>
<td>Glucose-induced amplitude regulation of pulsatile insulin secretion from individual pancreatic islets. Bergsten P and Hellman B. <em>Diabetes</em> (1993); M42: 670-4.</td>
<td>Insulin secretion by single islet cells of animals as glucose increased, resulted in pulses of insulin. Aptitudes increased, but frequency remained the same. This shows frequency of bursts is a signal irrespective of glucose levels.</td>
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<tr>
<td>Title</td>
<td>Abstract</td>
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<td>Oscillatory Insulin Secretion After Pancreas Transplant. O’Meara NM, Sturis J, et al. <em>Diabetes</em> (1993) 42:855-61</td>
<td>After transplant pulse aptitude was not different. Importantly this article confirms that “in many in vivo studies have demonstrated that insulin is released in a pulsatile fashion, and cites 7 papers.</td>
</tr>
<tr>
<td>Pulsatile (burst) insulin secretion accounts for 70% of total insulin secretion during fasting. Porksen N, Munn S, Steers J, et al. <em>Am J Physiol.</em> (1995); 269:E478-88</td>
<td>This Mayo Clinic study simply starts by reciting “Insulin, like the hypothalamopituitary hormones, is secreted in a pulsatile manner” and cites 10 papers.</td>
</tr>
<tr>
<td>Effects of Glucose Ingestion versus Infusion on Pulsatile Insulin Secretion. Porksen N, Munn SR, Steers JL, Veldhuis D, Butler PC. <em>Diabetes</em> (1996) 45:1317-23</td>
<td>“Physiological studies further indicate that insulin is secreted in high frequency, discrete insulin secretory bursts.” Portal vein studies in humans are not practical”…but 8 years later Butler did just that. All studies show the importance of burst (pulses).</td>
</tr>
<tr>
<td><strong>Glucagon-Like Peptide 1 Increases Secretory Burst Mass of Pulsatile Insulin Secretion in Patients with Type 2 Diabetes and Impaired Glucose Tolerance.</strong> Ritzel R, Schulte M, Porksen N, Nauck M, Holst J, Juhl C, Marz W, Schmitz O, Schiegel WH, Nauck M. <em>Diabetes (2001) 50:776-784</em></td>
<td>“GLP-1 increases secretory burst mass and the amplitude of pulsatile insulin secretion in healthy volunteers without affecting burst frequency.” As of this point, every scientist has acknowledged the existence and importance of burst (pulse) insulin!</td>
</tr>
<tr>
<td><strong>Acute and Short-Term Administration of Sulfonylurea Increases Pulsatile Insulin Secretion in Type 2 Diabetes.</strong> Juhl CB, Porkson N, Pincus SM, Hansen AP, Velhuis JD, Schmitz O. <em>Diabetes (2001) 50: 1778-84</em></td>
<td>“High frequency oscillatory patter of insulin release is disturbed in type 2 diabetes…Insulin pulsatility was assessed by 1-min interval. The agent augments insulin secretion by concurrently increasing pulse mass and basal insulin secretion without changing pulse mass and basal insulin secretion frequency or regularity.”</td>
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<td><strong>Do Oscillations of Insulin Secretion Occur in the Absence of Cytoplasmic Ca2+ Oscillations in β-Cells?</strong> Kjems LL, Ravier MA, Jonas JC, Henquin JC. <em>Diabetes (2002), 51 s177-182</em></td>
<td>“Insulin secretion is characterized by a pulsatility that is reflected by oscillation of plasma insulin concentrations”</td>
</tr>
<tr>
<td><strong>Direct Measurement of Pulsatile Insulin Secretion from the Portal Vein in Human Subjects.</strong> Song, SH, McIntyre SS, Shah H, Veldhuis JD, Hayes PC, Butler, PC. <em>JCEM (2002); 85:4491-99</em></td>
<td>“Insulin is secreted in high frequency pulses.” Quantification is complex, In the present study we measured pulsatile insulin release directly into the portal vein. Direct sampling caused the conclusion that insulin is humans has an interval of approximately 5 minutes.</td>
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<tr>
<td><strong>Pulsatile Insulin secretion by human pancreatic islets.</strong> Song, SH, Kjems L, Ritzel R, et al. <em>JCEM (2002); 87: 213-221</em></td>
<td>“Insulin is secreted in discrete bursts. These pulses are also present with islets are perfused.” Perfused single or groups of islet cells exhibited an interval of 6-8 min., comparable to that observed in humans in vivo.</td>
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<tr>
<td>Pulsatile Insulin Release From Islets Isolated From Three Subjects with Type 2 Diabetes. Lin J-M, Fabregat ME, Gomis R, Bergsten P. Diabetes (2002) 51:988-993</td>
<td>“Plasma insulin in healthy subjects shows regular oscillations, which are important for the hypoglycemic action.” It is concluded that islets from the 3 individuals with T2DM release insulin in pulses.</td>
</tr>
<tr>
<td>Pulsatility of Insulin Release- A Clinically Important Phenomenon. Helman, B et. al. Upsala Journal of Medical Sciences (2009) 114:193-205</td>
<td>The islets the β-cells are mutually entrained into a common rhythm by gap junctions and diffusible factors. Synchronization of the different islet in the pancreas is supposed to be due to adjustment of the oscillations to the same phase by output of acetylcholine and ATP. (Thus the “Clinically Important Phenomenon”)</td>
</tr>
<tr>
<td>Pulsatile Portal Vein Insulin Delivery Enhances Hepatic Insulin Action and Signaling. Matveyenko AV, Liuwantara D, Gurlo T, Dirakossian D, Man CD, Cobelli C, et al. Diabetes (2012) 61:2269-2279</td>
<td>“Insulin is secreted as discrete insulin secretory bursts at ~ 5 min intervals into the hepatic portal vein. These pulses being attenuated early in the development of type 1 and type 2 diabetes mellitus.” This is important for hepatic insulin action.</td>
</tr>
<tr>
<td>Loss of Pulsatile Insulin Secretion: A Factor in the Pathogenesis of type 2 Diabetes? Wahren J, Kallas A. Diabetes (2012) 61:2228-2229</td>
<td>Insulin is secreted into the portal vein in a pulsatile fashion with approximately 5-min cycles (Fig. 1) Insulin pulses may account for as much as 70% of the total insulin secretion in the basal state. This pulsatile b-cell secretion pattern is controlled by an intrinsic rhythm of intracellular Ca2+ oscillations.</td>
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The foregoing 25 peer reviewed publications, with new reviews every year conclusively demonstrate the uniform existence and importance of normal burst insulin. And, since there is a total absence of any evidence of showing that bursts are not important or natural, this fundamental reality must now be acknowledged. Not only do all studies show burst insulin resulting in high amplitude pulses, and oscillations, there are no studies which even suggest an alternative to this reality, nor are there any studies which minimize the importance of this basic signal. In fact, the science is so completely one-sided on this issue, there has never even been a mere suggestion that achieving normalized carbohydrate metabolism is possible without burst insulin.

As seen, the bursts cause oscillations which are obviously important to even the most casual observation.

The illogic of ignoring these bursts, and the illogic of delivery of insulin in non-bursts is equally manifest.

**Chapter 9  Burst Insulin and Metabolism**

With the need for burst insulin a fully proven fact, the obvious question is; Why would any other delivery be desired? The complete failure to achieve normal metabolism by conventional Continuous Subcutaneous Insulin Infusion (CSII) pumps (such as Medtronic and others) is known. Therefore, the ONLY reason for not mimicking normal is the prior inability to effectively do so, the lack of the tools needed to achieve this normality. As such Medtronic and others continue to focus on glucose because of business and marketing reasons.
Clearly, putting insulin under the skin, into muscle or into the peritoneum are physiologically incapable of delivering bursts as is needed to achieve these minute-by-minute rhythms of concentrations. In fact, no other pump seeks to achieve the highly accurate, high pressure, low volume insulin bursts delivered by the Bionica for the Artificial Pancreas Treatment®. And whether or not a sensor is tied to that pump (a so-called closed loop system) this physical impossibility will continue to preclude normalization of carbohydrate metabolism. There is simply no way to mimic bursts by infusion under the skin.

It is curious that never, in any of the submitted work, have any of the CSII pump regimens even sought to measure normal metabolism. This lack of desire to address the core problem of diabetes is not likely by accident.

It has been relatively easy to measure metabolism since the 1930’s as shown (picture) of the Elliott P. Joslin Laboratory, where indirect measurement was developed and verified.

As a result of equipment advances this basic metabolic measurement system has become extremely accurate, easy and quick (3-5 minutes). It is almost as easy as laboratory blood glucose, and provides volumes more information. It alone focuses on the core issue.

These metabolic measurement machines accurately measure both carbohydrate metabolism and lipid metabolism volumes, and also develop a ratio of carbohydrate to lipid called the respiratory quotient or R.Q. It is not necessary to record the R.Q. as it only provides the TYPE of metabolism, not the AMOUNT of metabolism, but the amount of carbohydrate metabolism can be accurately followed. (Thus, the Artificial Pancreas Treatment® does not use the R.Q. in its treatment, but does use carbohydrate metabolism volumes.)

The measurement of the amount of carbohydrate metabolism is an important tool for two different reasons.

1. When patients are treated with the Artificial Pancreas Treatment® with the Bionica Microdose, the amount of insulin is calculated to induce proper levels of carbohydrate metabolism. Those levels are checked 3 times per treatment session.

2. When patients have achieved proper carbohydrate metabolism levels, the metabolic cart is also used to determine how long between treatments the patient can maintain proper life.

Thus, the measurement of truly “normal” carbohydrate (and thus lipid) metabolism provides these two functions, and validates that the treatment is properly addressing the core problem of metabolism, not just blood sugars.
The Artificial Pancreas Treatment® method of restoring carbohydrate metabolism is thus easily verified, and is part of the titration and dosing of the treatment.

The range of metabolism in the presence of glucose for diabetic patients is from .70 to .85. Many of the more ill patients are below .75 and can be even .65.

The range of normal patients with an oral glucose load is from .89 to 1.1/1.2. This shows that the patient is able to metabolize carbohydrate with resulting remedial outcomes.

Artificial Pancreas Treatment® patients achieve the “normal” levels of resting carbohydrate metabolism! This prolonged effect is achieved with the current protocols.

This reality is shown in every known patient treated to date. It is a reality that restoring normal is possible for even the most ill and even some near-death patients.

Proof of Concept. In order to prove the theory of normalization, it was necessary to show it was possible to restore carbohydrate metabolism before the initial roll-out work could commence. Anton “Tom” Clemens of Miles Laboratory, developed and held the patents for the “artificial beta cell.” At the Joslin Diabetes center in Boston, clinical work started on the infant theory of the sleeping liver. It was called the “Miles Biostater” and at Clemens’ suggestion, it was modified to allow the first normalization of metabolism clinical trial.

As shown here, published in Lancet, both normal and T1DM diabetic subjects were given 100gms of glucose P.O. and their carbohydrate and lipid metabolism measured by metabolic measurement cart. (Note, it does not matter whether type 1 or type 2, both respond similarly as both have the inability to metabolize carbohydrates.)
As seen, after 4 days of treatment, the patients were able to metabolize carbohydrates and reduce lipid utilization.

Significantly, these diabetic patients had been diabetic for many years, but were able to restore carbohydrate metabolism after just four (4) days. This implies that the ability to metabolize is not lost over time, and is thus a DNA encoded activity which relies on the liver to generate the necessary enzymes (supra).

This clinical study answered the question of whether it was possible to regain the ability to properly metabolize glucose, but what about a mixed meal?

This slide shows the same restoration of carbohydrate metabolism with a mixed meal of carbohydrates, lipids and proteins, and demonstrates it is possible to regain proper metabolism after 3 days, and improve over normal in 4 days.

Restoring metabolism by re-establishing the Krebs cycle with normal food is strong evidence of the fact that no patient is ever so ill that he or she cannot regain proper cellular energy (ATP) within their cells. The restorative implications are obvious.

The above two slides show restoration of metabolism with glucose and a mixed meal, but what about muscle metabolism?

An ergonomic bike was used to determine the “maximum output” of both normal and diabetic test subjects. Their metabolism was then measured after 6 minutes warm up, with the diabetic patients being tested before and after treatment, and compared to normal.

This was designed to fully quantify exercise metabolism, as resting metabolism with both glucose and a mixed meal had shown promising results.

Since “pre-diabetes” is very much like diabetes from a metabolic viewpoint, with the only major difference being the ability of the pancreas to produce so much insulin that it can overcome the insulin resistance and maintain lower blood glucose levels, and;

Since “pre-diabetes” and diabetes are really just two plots on the scale of decreasing metabolic function, such that they approximate the normal aging process; it was important to study high energy output metabolism.

(Note: by merely shifting the threshold of “normal” glucose levels, we can increase the statistical incidence of diabetes to include many people who are just aging. As we get older, we automatically become diabetic from a blood sugar view, but not from a metabolic viewpoint.)
The result of testing before and after 4 days of treatment, and comparing both to normal is as shown.

Note that as to carbohydrate metabolism, diabetics are only marginally impaired, until their individual potential is exposed by treatment for 4 days, whereupon the diabetics outperform normals in both carbohydrate and lipid metabolism.

This led to non-diabetic testing of the treatment which showed increased energy and muscle abilities by normals.

It is well known that professional US Football players commonly inject insulin before a game to allow themselves to pack muscle glycogen storage. However, the Artificial Pancreas Treatment® method of glycogen packing far exceeds simple insulin administration. Currently, every patient, no matter how ill significantly improves their carbohydrate metabolism levels on the Artificial Pancreas Treatment®

These metabolic improvements are impressive, and logically important, but the issue for most diabetic patients is “can I reverse my secondary complications” retain good health and a normal life? The answer thus shifts us to the complications of diabetes.

**Chapter 10 – The mechanisms causing burst insulin delivery to be important.**

As shown above, pulsatile delivery is the only way to achieve normalization of tissue as it upregulates the metabolic enzymes of glycolysis, it has a greater hypoglycemic effect, it enhances peripheral glucose uptake, it increases peripheral insulin receptor sensitivity and it achieves approximately 30% to 40% increases in ATP (cellular chemical energy).

The loss of pulsatile insulin secretion leads to intrahepatic molecular changes and altered gene expression consistent with development of hepatic insulin resistance perhaps by delayed or impaired phosphorylation of intracellular insulin signaling proteins IRS-1, IRS-2, AKT, and Foxo1. Conversely, conventional insulin deliveries, whether by CSII (wearable pump) or by injections have many well-known disadvantages. Absorption is delayed and the variability of absorption is up to 35%. This leads to metabolic liability with ever-changing seemingly unrelated processes of hypo- and hyper-glycaemia. It increases systemic insulin concentrations without correlation to glucose from the gut, and there is significant dosage attrition, (without characterization of cause).
Thus, there have been, and continue to be many attempts at oral, nasal, sublingual, interbuccal, and peritoneal insulin delivery. But all of these systems would, by necessity, fall far short of delivering the bursts of insulin that the Bionica Microdose Artificial Pancreas Treatment® delivers.

Some call a closed loop system that senses sugar and gives subcutaneous insulin an “artificial pancreas.” For the reasons above, this is misleading. Merely attaching a sensor to a CSII pump such as the Medtronic (right) cannot mimic a normal pancreas. Bursts into the liver and body are not possible with under-the-skin delivery.

Without the required burst action no system of insulin delivery has, or can, provide proper metabolism as it fails to stimulate the liver to produce the Krebs cycle enzymes. Without those enzymes the mitochondria cannot process carbohydrates and there is no normalization of metabolism. The FDA Cleared Bionica Microdose pump delivering the Artificial Pancreas Treatment® is the only system that actually mimics a normal pancreas and thus the only “Artificial Pancreas Treatment” worthy of that claim. This ability is not only shown by clinical trials, it is repeated by every treatment as patients watch their metabolism normalize.

Every patient who is treated has their carbohydrate metabolism quantified 3 times to verify and adjust the treatment. With this huge (200,000+) number of treatments, if there were any question as to whether the Artificial Pancreas Treatment® accomplished it metabolic goals, the failures would have been manifested long ago. The predictability, reproducibility and repeatability all remain virtually without any exception, giving clear weight to the assumption that producing the required enzymes for proper carbohydrate metabolism is a DNA function of every liver when presented with the proper signals.

Dna “remembers” how to generate repair to every cell, it just needs cellular energy.

It would be illogical and physiologically naive to think that any process which is absent for YEARS, can be restored in just a few days without that process being encoded in the DNA of patients. The human body almost immediately stops any process which is not “used” to conserve. That is an overarching design of life. Thus, the ability to restore and repair are DNA encoded.
Chapter 11 - The design of the Bionica Microdose Pump and its use, the Artificial Pancreas Treatment® is safe.

There are few examples of medical devices which have not had any unusual or unforeseeable set of circumstances leading to a medical device report. The Bionica device has been in constant use for 24 years, starting with the first clinical trials. It has the unusual distinction of a clear safety record of no recalls, no injuries, no unexpected outcomes, no claims of damage and of course no personal injury claims or settlements of any kind. This clear safety record is easily verified by the FDA where even MUES (telephoned complaints without any backup) are lodged and investigated. The most recent inspection report (right) confirmed that safety record.

Also, Bionica Microdose is ergonomically friendly. The term “mistakes” even include any operator or user error or mistake that results in damage to a person. Error checking software limits mistakes, but the entry design is key. This compact pump is unique in design requirements in order to deliver burst pulse insulin intravenously.

The idea of delivering insulin first came to Banting and Best in the 1920’s and was delivered using a syringe. The same limitations of insulin delivery exist today. While recombinant DNA human insulin is an improvement, as are the protein binders for better uptake, the delivery has not changed much since the 20’s subcutaneous insulin in response to glucose…until the Artificial Pancreas Treatment®.

The difference between subcutaneous insulin delivery (in any of the current forms), and the Artificial Pancreas Treatment® approximates the difference between Pong, the first video game, and a current PS3 video game where 10 million additional independent actions and reactions take place. When all of the additional pathways invoked by ATP increases are added, the complexity and numerical sophistication of the processes of a properly fed body are almost incalculable.

And, while Bionica has very demanding design and performance requirements, the Bionica Microdose pump received a national device design excellence award, and is completely different from other devices due to pressure calculations and its accurate delivery algorithm. It has a 20 year life rating, but many have been in use for over 24 years. It does not need user calibration or any user maintenance. It has no “numbers” to enter which avoids some of the most common mistakes. It is rare in the pump world to have no recalls after so many years.
All applicable approvals have been obtained, including ISO 13485:2009, US FDA as to the device as well as the manufacturing facilities in California, Australian (Therapeutic Goods), South Africa FDA, Mexico COFEPRIS (FDA) and the European CE (re-certifying). Pending are Chinese, CFDA, Taiwan FDA, and India exemptions, UAE applications and others.

The treatment does not need special facilities and is performed in 4 to 5 hours in one sitting where the patient can sit, complete paperwork, work on computer, and walk around (but not out of the clinic).

Shown (right) is all of the equipment needed, which is now incorporated into a turn-key standardized clinic opening system. All training is on-site and support is given via telecommunications.

Glucose per mouth (PO) is given in a calculated amount, and intravenous burst insulin given according to a Trina Health established protocol, with capillary blood glucose measurements every 30 minutes. Metabolic Measurements are taken 3 times a day for dosing and determination of proper duration between treatments (starting weekly and progressing to once per 2 or 3 weeks).

All data is obtained and retained in the system, which complies with all privacy laws including the USA HIPAA, Chinese and German Models.

The Artificial Pancreas Treatment® has been successfully used on virtually all ages to date. This girl, T1DM onset age 2 was first treated at age 6 (left) and is also shown (right) at age 31 with her 5 normal sized children. After 24+ years of treatment, she has no secondary complications of diabetes, and she has lupus but is asymptomatic.
Chapter 12  Patient Outcomes are Consistent, Restoring Metabolism and Good Health

If metabolism is the “core” and fundamental problem, then an effective metabolic treatment should be an effective diabetes treatment and provide health improvement outcomes. The Artificial Pancreas Treatment® does this:

1. Chronic un-healing wounds. Diabetic pressure wounds provide a special problem for clinicians and are “windows” to the overall health and disease fighting abilities of the patient. The next few images are “before and after” of common wounds. Many patients will have chronic “weeping” sores, and they are uniformly resolved with the Artificial Pancreas Treatment®. The images herein are of the more invasive type which have been treated by conventional means and have failed:

   ![Diabetic foot ulcer before and after treatment](image)

Diabetic foot ulcer having failed all conventional treatments including hyperbaric chamber and grafting, 5 ½ months later, healed and patient saved feet and walked.
A typical heel wound after failure on conventional medication. Treated for 4 months, it healed with minimum scaring and no pain.

Necrotic tissue involved to the pad from neurovascular diabetic complications. Patient received treatment for cardiovascular disease and incidentally toe also healed within 4 months. (Patient continued to treat for CVD, and improved so that he did not have the prescribed amputation).
The patient presented with toe (above), already scheduled to have surgery.

After 3.5 months it was obviously responding well (upper right).

After just 4.5 months, this toe which would have been amputated is now fully healed (right).

This curative ability demonstrates the body’s own ability to heal.

This is one of the “poor outcomes” that naturally flows from not modulating the inflammatory process.

This 28mm deep heel wound would require surgery, but with APS treatment alone, it healed and stayed healed, as shown by this picture 10 months later. Wounds respond to routine APT treatment if routine and infection precautions (including staph and strep) are managed.
Chapter 13  Clinical Trials and Outcomes

The Artificial Pancreas Treatment® using the Bionica Microdose has been verified by 20+ years of use with consistent results after Pivotal Clinical Trials and outcome which are supported by a many published papers (see bibliography).

While the treatment has evolved into an easily replicated system, the breadth of the application of normalizing metabolism has not. There appears to be a very broad-based benefit to metabolic normalization, for many diseases, and no apparent physiological disadvantages. The following are reviews of some of the more relevant clinical trials and publications.

1. Restoring Metabolism Possible. It Is Possible and Important to Restore Metabolism. Using the Miles Biostater of Anton Clemens, at the Joslin Diabetes Center, Milton Foss, MD showed that it is possible to restore carbohydrate metabolism in type 1 diabetic patients, and at the same time increase their ability to achieve both active and resting increased ATP while inversely decreasing free fatty acids. [Miles Biostater – Thomas Clemens]


2. Dormant Liver Functions Restored. Certain Functions of the Liver Are Dormant in Diabetes, But Can Be Restored. [Bionica Microdose Pump] It is well known that diabetic patients cannot metabolize carbohydrates properly. In normals, there is a simultaneous arrival of both glucose from the small blood vessels surrounding the stomach and large amounts of insulin which arrive at the liver where over 50% of insulin remains in the liver on first pass. Normal man increases insulin from 5-10 μU/ml to 200-1,000 μU/ml. The hepatocytes begin to synthesize and activate enzymes e.g. Glucokinase and glycogen synthase that are necessary for the metabolic processing of glucose through oxidation, storage, conversion to fat and amino acids. These enzymes are required for the Krebs cycle (citric acid cycle) to process cellular energy within the cells. One of these insulin dependent enzymes is glucokinase which cannot remain in the cell without receiving a phosphate group. The lack of a normal insulin stimulation by the pancreas causes these processes to “sleep” and become dormant. Proper stimulation of the liver can (and does) restore full Krebs cycle functionality.


3. Quality of Life Scale Valid. The Diabetes Impact Measurement Scales (DIMS) are a Valid Measurement of Diabetes Impact. [Bionica Microdose] It is important to measure the diabetes impact reports from the patients as diabetes is virtually ubiquitous, and the 40 of the 44 questions correlated well with subsequent test and laboratory verifications. Results: Patients receiving burst insulin demonstrate a “quality of life” improvement which is easily verified by the Diabetes Impact Measurement Scales.


(Note: Diabetes is a chronic disease where patients tend to “cope” with their slow health changes and forget what it is like to feel “normal.” This scale is helpful to overcome the natural process
of forgetting the progressive malaise of diabetes. It is also valid to show overall quality of life improvement from Artificial Pancreas Treatment®.)

4. **Better A1C’s with Long Term Burst Infusion.** [Bionica Microdose] Pluses have a Greater Effect, Long Term IV Insulin Therapy shows HbA1c Decline. The liver of a person with diabetes does not meet its full fuel-processing functions because many of the enzymes depend on proper insulin stimulation. This study involved 20 IDDM patients who were brittle despite a 4 shot regimen and after one year of frequent visits to the physician. Results: Patients receiving Bionica burst insulin treatment for over a 60 month period, the HbA1c levels reduced from 8.5 at entry to 7.0 in 60 months, with the greatest reduction during the first 12 months. This therapy led to improvements in blood glucose control without change in daily insulin, and improved autoregulation of blood glucose, a safe and effective treatment of patients whose diabetes is difficult to control. Long-term intermittent intravenous insulin therapy (burst infusion by Bionica) of once per week was given to type 1 diabetes mellitus patients.

Results: HgbA1c decreased from 8.5% to 7.0% at 41 months (p < 0.0003)
Frequency of major hypoglycemic events decreased from 3.0 events/month to 0.1 events/month (p < 0.0001)
Frequency of minor hypoglycemic events decreased from 13.0 events/month to 2.4 events/month (p < 0.0001)
This phenomenon is not a short-term artifact as it continues for over five years.


5. **Pancreas Transplants Restore Pulse Insulin.** Pancreas transplants continue in a more normal pulse based oscillation of insulin secretion. In normal subjects many in vivo studies have demonstrated that insulin is released from the β-cells in a pulse (burst) fashion. Results: In patients with pancreas transplants the rapid oscillation of burst insulin is restored, although the insulin oscillations occur more frequently and are of a larger amplitude. *Oscillatory Insulin Secretion After Pancreas Transplant. Omeara NM, Sturis J, Blackman JD, Byrne MM, Jaspan JB, Roland DC, Thistlethwaite JR, Polonsky KS, Diabetes (1993) 42:855-861*

6. **High Pregnancy Metabolism Replicated.** [Bionica Microdose] Pregnancy, Restoring Fuel Homeostasis in IDDM with Bionica. Pregnancy represents a particular disturbance of fuel homeostasis. Good diabetic control is important in early pregnancy. Regulation of the metabolic
processes at the cellular level, and avoiding glucose excursions of hyperglycemia and hypoglycemia is important. O₂ and CO₂ levels were monitored while the Bionica pump administered burst pulses of insulin. Normal subjects during early pregnancy have the capacity to increase their whole body carbohydrate oxidation rates while suppressing their lipid oxidation rate after ingestion of glucose meals. Glucose oxidation is significantly increased.

Results: There was no significant difference between normal pregnant metabolic rate and non-Respiratory Quotient oxidation rates (who have increased carbohydrate oxidation rates), and those of the treated diabetic women using the Bionica burst insulin infusion device.


(Note: No other treatment has been able to achieve these increased carbohydrate metabolism results in pregnant women).


Seventy (70) Type 1 nephritic subjects were enrolled and participated for at least 9 months. All patients seen weekly, with randomized treated patient (34), controls (36). All participants were either seen or treated weekly, with good glucose management, and no other changes in treatment. Results: The decline of creatinine clearance is -8.15 in non-treated, and -0.89 (less than 1) in treated. This data also included the initial treatment months when there was little change as the body was restoring carbohydrate processing and allowing for healing, suggesting that there would have been no loss, and some gain in kidney function with continued treatment.


(Note: Following this trial, patients with overt kidney disease are able to restore kidney function. The greatest increase in function appear in patients who have > 33% of their kidney function. Protein in urine reduces and creatinine reduces, even in patients on both hemodialysis and patrilineal dialysis. These outcomes are irrespective of ethnicity.)

8. Improved Metabolism and Glucose Control. Pulse Burst Insulin with Bionica Yields Directly Measurable Benefits on IDDM Patients. [Bionica Microdose] PIVIT enables tight blood glucose control for poorly controlled diabetics on intensive insulin therapy. Results: A) PIVIT improves the efficacy of insulin and a better metabolic effect. B) It will probably find a role in the general treatment of diseases as it improves metabolism. C) PIVIT restores liver glucose metabolism, and yields directly measurable benefits on IDDM endpoints. D) It is effective for routine clinical use for severely out of control diabetes. E) And it is cost effective means to achieve better metabolism, and thus glucose control.


The prevalence of systemic hypertension is increased in patients with diabetes. In this randomized cross-over clinical trial of hypertensive patients with diabetic kidney disease, two groups were selected, one treated with the Bionica burst insulin infusion device and the other followed weekly with conventional therapy. The two groups were crossed over after 3 months. Results: Patients treated with the Bionica burst insulin infusion device (CIIIT) markedly improved Blood Pressure Control and decreased medications by 50% in just 3 months. "Effect of Chronic Intermittent Intravenous Insulin Therapy on Antihypertensive Medication Requirements in IDDM Subjects with Hypertension and Nephropathy." Aoki TT, Grecu EO, Pendergast JJ (1995) Diabetes Care 18 1260-1265

10. Disabling Chronic Hypotension Resolved in 3 Months. [Bionica Microdose] Orthostatic hypotension from diabetes can lead to syncope and is reversed by treatment. Studied patients with disabling orthostatic hypotension from diabetes of 20 years, who failed on conventional intensive treatment and blood pressure drops with changes in posture were enrolled. Patients with severe diabetes often have increased night time blood pressure, a condition that may worsen the complications of diabetes. Patients in randomized, controlled clinical trials comparing two treatments, four subcutaneous insulin injections daily, vs weekly Bionica burst insulin added to the four subcutaneous injections daily, with monthly measures of 24 hour ambulatory blood pressure.

Patients treated with Bionica burst insulin showed a 3% decline in the night/day blood pressure ratio. In contrast, those on only four subcutaneous injections daily had a 3% increase in night/day blood pressure ratio. On the burst therapy, patients reported complete relief from dizziness and fainting when they stood up and blood pressure no longer dropped precipitously with upright posture. In addition, the group on burst insulin had a significant improvement in the average HbA1c levels. This improvement in vasoconstrictor mechanism and correction of circadian blood pressure pattern may be part of it. The improvement was dramatic and unlike any other treatment. "Chronic Intermittent Intravenous Insulin Therapy Correct Orthostatic Hypotension of Diabetes" (1995) Am. Journal of Medicine, 99:683-684.
11. **Intensive Burst Insulin Therapy Normalizes Blood Pressure Patterns.** [Bionica Microdose] Patients on CIIIT burst IV insulin improve glycemic control which reverses or at least prevents further deterioration of abnormal circadian BP patterns. Using 24 hr. BP monitors the normal 25% decline in BP during sleep is not found in patients with diabetes. This is associated with autonomic neuropathy and renal dysfunction, as well as other complications. Patients were treated with a four shot regimen and weekly CIIIT treatments of burst insulin using the Bionica infusion device. Results: After 3 months, the CIIIT patients showed significant glycemic control improvement due to CIIIT. The result was glycemic control improved from HbA1c decreased from 7.9% to 7.2%, while the patients reversed or at least prevented further deterioration of abnormal circadian blood pressure patterns.  

*Effect of Intensive Insulin Therapy on Abnormal Circadian Blood Pressure Patterns in Patients with Type 1 Diabetes Mellitus, Current Clinical Trials, (1995) 199:1-6*

<table>
<thead>
<tr>
<th>Table 1. Main characteristics of IDDM patients.</th>
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<td>Groups</td>
<td>A (CIIIT)</td>
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<td>n</td>
<td>30</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>11/19</td>
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<tr>
<td>Age (years)</td>
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<td>IDDM duration (years)</td>
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<td>BMI (kg/m²)</td>
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<td>HbA1c (%)</td>
<td>7±1/2</td>
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<td>Retinopathy (No/Yes)</td>
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<td>137±1/2</td>
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<tr>
<td>DBP (mm Hg)</td>
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* Data are n or means ±SE. CIIIT = continuous intermittent intravenous insulin therapy, CIIT = chronic intermittent intravenous insulin therapy, BMI = body mass index, HbA1c = glycosylated hemoglobin A1c, AMBP = 24-hour ambulatory blood pressure monitoring, CHF = congestive heart failure, CIIT = continuous intravenous insulin therapy, BDR = background diabetic retinopathy, PC = proliferative diabetic retinopathy

12. **The direct costs of standard vs. intensive insulin are more than saved with the Burst Insulin reduced complications.** The costs of standard care were calculated against the costs of intensive insulin therapy (not the burst insulin by Bionica). There was a slight savings to conventional therapy due to the fact that intensive insulin therapy without burst (Bionica IV) insulin treatment. However, when the very expensive treatment costs of hospitalization are reduced by burst insulin, the cost savings are enormous. This is because Intensive Insulin Therapy has not shown a reduction in Hospitalization costs:

*Annual Healthcare Costs for Diabetes Patients, 1992 ($ Billions)*

- Inpatient hospital $65.2 (63%)
- Outpatient hospital $12.5 (12%)
- DMIE = durable medical equipment

If blood sugar checking helped, hospital percentage would go down.

Hospital costs are the same percentage as 1993, 2002 & 2007, & 2012
The percentage of hospital costs is 63% in 1992 and twenty (20) years later still 63% in 2012. In 1992 glucose monitor use was very low, and by 2012, everyone with diabetes is using them. So the obvious question is…if glucose control were causing better health, why are the percentages the same? The answer is what we now know. Without the Artificial Pancreas Treatment® there is no reduction in complications costs. The financial benefit of the Bionica Microdose Artificial Pancreas Treatment® is a compelling reason for change and a valuable tool for decreasing long term healthcare costs while restoring life to patients.

From both a scientific basis, and a financial basis, there is little support for tight control to save a significant number of patients from developing long term complications. However, even the most skeptical scientists must acknowledge the fact that burst insulin is normal, and when the outcomes of the above clinical trials are reviewed, there is no logical scientific theory or scientific data showing that APT treatment does not work or that it does not stop and reverse the chronic secondary complications.

Therefore applying logic to the studies and cost/benefit approaches to the Artificial Pancreas Treatment® it must be concluded that APT is both costs saving and health saving, a so-called win-win of saving costs and improving the Quality of Life for patients.

13. Type 2 lose their bursts, restoring it is the rationale for proper treatment. The Pathophysiology of Impaired Pulsatile Insulin Release shows that in type 2 diabetic patients, oscillations (and thus the burst pulses) disappear. This rhythm is intrinsic to the islet (β-cell).

The superior efficiency of pulsatile insulin delivery in normalizing glucose swings should be the rational for new principles to “produce a normal oscillatory insulin pattern.”


(Note: The Artificial Pancreas Treatment® does replicate the above body-wide rhythms via the burst-pulse pattern of a normal person. These burst patterns with resulting oscillation normalizes carbohydrate metabolism occur throughout the body.

14. Kidney Disease is arguably the worst complication of diabetes. Burst insulin markedly reduces the progression of diabetic nephropathy. [Bionica Microdose] There is no other treatment which stops and reverses this disease. In this clinical trial in seven prestigious centers of excellence studied 90 patients after 18 months, and the effectiveness of the Bionica Microdose delivered treatment was clear, which was independent of improved glucose control and ACE inhibitors. This multi-center randomized controlled trial in patients with diabetic nephropathy compared outcomes in patients treated with pulsatile intravenous insulin therapy (Bionica Microdose) plus intensive insulin therapy and compared them to patients treated with intensive insulin therapy alone. Blood pressure was controlled in both groups and patients were seen weekly. Results: Hemoglobin A1c levels declined significantly in both groups. However, the rate of decline of the kidney creatinine clearance level was significantly less (2.2 mL/min/yr) in the treatment group (APT plus intensive insulin therapy) as compared to 7.7 mL/min/yr in the
control group (intensive insulin therapy alone.) Conclusion: Pulsatile intravenous insulin therapy [Bionica Microdose] appears to markedly reduce the progression of diabetic nephropathy.


This study end-point was to demonstrate a return of pulse activity by the pancreas of a diabetic person, a move toward normal. Unfortunately the increase is not enough to overcome the blunting effect of abnormally high production of insulin and thus did not achieve normal carbohydrate metabolism (and thus the need for the Artificial Pancreas Treatment®).

16. By 2001, this publication made it General Knowledge that the Bionica Microdose “burst” infusion device was launching “A New Frontier in Diabetes Therapy.” [Bionica Microdose] “Over the last eight decades” only partial success has been achieved in glucose control, and even less in stopping the complications of diabetes. Normal insulin is secreted in bursts, and continuous exposure to the hormone insulin is known to decrease insulin’s metabolic effectiveness.

The free insulin levels produced by the high pressure bursts of insulin (left) resulted in:

- A significant decline in HbA1c.
- Near elimination of major hypoglycemia reactions.
- A significant decline in minor hypoglycemia reactions. (even with lowered HbA1c).
- A return of hypoglycemic awareness.
- A marked improvement in blood pressure in diabetic IDDM patients who have hypertension and kidney disease.
- The apparent arresting of predicted progression of diabetic kidney disease.
- The return of circadian blood pressure patterns.
- The correction of postural hypotension in patients with disabling hypotension in 2-2 months.
- The reversal of peripheral polyneuropathy (neuropathy).
- The reversal of diabetic cardiomyopathy.
- The acceleration of foot ulcer healing in patients who have failed on hyperbaric and graph treatment.

This review of the progress achieved using the Bionica burst insulin device concludes that treatment produces all of the above unique outcomes. In practice, these outcomes are routinely seen in the clinics which now provide this therapy.

17. **Pulse (burst) insulin delivery is present in vitro and superior to continuous delivery.**

Insulin release of isolated human pancreas β-cells was pulsatile even in vitro. This study isolated human islet cells from 3 type 2 diabetic patients and perfused them with glucose.

Results: The release of insulin increases with the increase in glucose perfusion. The fact that delivery of insulin in bursts is superior was both observed, and obvious. *Pulsatile Insulin Release from Islets Isolated From Three Subjects with Type 2 Diabetes*. Lin JM, Fabregat ME, Gomis R, Bergsten P (2002) *Diabetes* vol 51: 988-993.

18. **Pulse (burst) insulin delivery preserves renal (kidney) functions.** [Bionica Microdose]

This study examined the cardiovascular mechanisms that might relate to the improved renal function in patients treated with burst insulin in other studies. Results: This study showed that the unique preservation of kidney functions resulting from burst insulin treatment using the Bionica infusion device were not caused by the autonomic system, nervous system, cardiac size or function, nor elements of hemostatic function, elevated levels of fibrinogen, platelet aggregation, or glycolhemoglobin. _A pilot study to test the effects of pulsatile insulin infusion on cardiovascular mechanism that might contribute to attenuation of renal compromise in type 1 diabetes mellitus patients with proteinuria_. Weinrauch LA, Burger AJ, Aepfelbacher F, Lee AT, Gleason RE, D’Elia JA. *Metabolism Clinical and Experimental* (2007) 56:1453-57.

19. **Pulsatile Intravenous Insulin Therapy: The best practice to reverse diabetes complications?** *(Answer is Yes)* [Bionica Microdose]

Although pulsatile insulin is found in normal subjects, currently used methods of insulin administration are not pulsatile. A lesser known therapy, known as PIVIT, CIIIT, HAT and other acronyms all are the same use of the Bionica Microdose burst IV insulin delivery system which mimics normal pancreatic insulin secretion to signal the liver. This paper hypothesizes that the beneficial outcomes from burst IV insulin might be “through several factors and examines mechanisms that may explain the beneficial diabetes outcomes.” They hypothesize that improvements in enhanced expression of insulin receptors and resulting improved hepatic metabolism with amelioration of insulin resistance may be the pathophysiological mechanisms. A review of current therapies is presented, and “the supra-normal insulin signals provided by PIVIT to organs other than the liver (eyes, brain, nerves, kidneys, cardiovascular system) may have beneficial effect through each organ’s insulin receptors, possibly contributing to the clinical improvements observed in patients.”
The paper continues to address the improvements as to why improvement is seen:

- Brittle diabetes
- Nephropathy
- Blood pressure control, possibly through improvement in endothelial function.
- Intra-glomerual hemodynamics and delay of progression of diabetic renal disease.
- Reversal of hyperglycemia and hypoinsulinemia.
- Diabetic neuropathy (factors other than hyperglycemia are responsible). Acute metabolic dysfunction with a host of mechanisms are apparent.
- Abnormal circadian rhythm.
- Orthostatic hypotension.
- Decrease in systolic blood pressure drop and elimination of dizziness and fainting.

Conclusion: Burst IV insulin using Bionica Microdose infusion device has shown several benefits for both T1DM and T2DM patients when added to routine insulin regimens and appears to significantly reduce the progression of diabetic nephropathy and neuropathy. Plausible explanations include sustained improvement of hepatic carbohydrate metabolism and portal vein insulin that mimics normal pancreatic function. It may also be a result of sustained improvement in enzymatic activity within hepatocytes and help with detoxification of waste products from the liver. Mirbolooki MR, Taylor GE, Knutzen VK, Scharp DW, Willcourt R, Lakey JRT (2009) Medical Hypotheses Elsevier mehy 0306-9877.

(Note: This study shows the sweeping benefits of attacking diabetes as a problem of metabolism, not just blood sugar. Why do other therapies only examine blood glucose and continue to try to modulate blood glucose when it is well known that glucose management does not result in diabetic complication reversal? No study shows that glucose control achieves these reversal results. If glucose management addressed the core problems of diabetes, reversal would be expected. They achieve only marginal remediation of diabetes complications, yet the search for glucose control illogically continues! This is nothing short of amazingly short sighted. The answer is obvious to those who study normal physiology, the best way to achieve normal is to mimic normal. Burst insulin mimics normal, thus the need for the Bionica Microdose burst insulin Artificial Pancreas Treatment®.)

20. Retinopathy and Nephropathy. [Bionica Microdose] Burst (Pulsatile) insulin was studied for better understanding of the clinical observations of improvement to both retinopathy and nephropathy. The attenuation of both retinopathy and nephropathy is well reported with pulsatile (burst) insulin administration. Statistically significant preservation of renal function was not matched by statistically significant improvement in Retinopathy within the first 12 months testing time. However, the study allowed for 12 months, and prior vascular studies have required 18 months or more. Renal benefit was matched by improvement in all of the subjective neuropathic components of the Diabetes Impact Measurement Scale. Metabolism Clinical and Experimental Weinrauch LA, Sun J, Gleason RE, Boden GH, Creech RH, Dailey G, Kennedy FP, Weir MR, D’Elia JA, (2010) 59:1429-1434
21. Kidney Disease. Pulsatile Portal Vein Insulin Delivery Enhances Hepatic Insulin Action and Signaling. Insulin is secreted in bursts ~ 5 min. intervals into the portal vein. These pulses are attenuated early in the development of type 1 and type 2 diabetes.

To determine if this is important for regulation of blood glucose and insulin sensitivity this study induced pulses in animals. When pulses were given, the glucose remained in the normal range. When not, diabetes range was observed. Plasma glucose was attenuated for 300+ minutes with pulsed insulin.

This study answered the question of why pulsed insulin administered in bursts by the Bionica Microdose infusion device delivered in a periphery IV was effective when it does not have the same concentrations as bursts into the portal vein. Metabolic pathways triggered by insulin are blunted in the constant presence of insulin, but augmented by burst signaling. Insulin signaling pathways (hepatic insulin receptor) IRS-1 and IRS-2 were delayed with either diabetes or a constant supply of insulin as compared to pulses.

“Given the important role of Foxo1 in regulation of hepatic lipid metabolism, the association between insulin resistance and increase risk of cardiovascular disease in both T1DM and T2DM may be mediated at least in part by impaired pulsatile insulin delivery to the liver.” Impaired Foxo1 from defective pulses (bursts) of insulin is predictive of increased gluconeogenesis and reduced glycolysis, with inappropriate release of glucose from the liver.

The difference between constant insulin and pulsed insulin in hepatic insulin signaling is easily seen. Constant insulin is indistinguishable from type 2 diabetes.

Conclusion: Pulsatile (burst) insulin is necessary for proper insulin signaling receptor pathways and provides better glucose control and regulation of the liver production and release of glycogen. It is important to both insulin signaling and glucose control. Pulsatile Portal Vein Insulin Delivery Enhances Hepatic Insulin Action and Signaling Matveyenko AV, Liuwantara D,
22. **Loss of Burst Insulin is Factor in Diabetes Complications.** Normal insulin secretion five minute cycles of burst insulin accounts for as much as 70% of all insulin, even at fasting. In type 2 diabetes, to compensate for loss of β-cell mass from β-cell failure, the remaining β-cells produce high levels of insulin which markedly attenuates the pulses. The lack of burst stimulation in type 2 diabetes is complete. This is a fundamental signal which is missing in both type 1 and type 2 diabetes. This “**pulsatile secretion of insulin by the β-cells is not a piece of evolutionary whimsy**” yet it has received only limited attention to date. The results of Matveyenko et. al. represent a welcome tour de force of new information in this area. β-cell dysfunction, loss of pulsatile insulin secretion and insulin resistance are frequently observed in relatives of patients with type 2 diabetes. The findings imply that increasing circulating insulin levels by secretagogues or administration of long-acting insulin preparations may contribute to the development of insulin resistance. **Wahren J, Kallas A; Loss of Pulsatile Insulin Secretion: A factor in the pathogenesis of type 2 diabetes?** (2012) Diabetes 61: 2228-2229.

23. **Insulin Therapies, Current and Future Trends.** CSII Continuous Subcutaneous Insulin Infusion (the wearable insulin pump such as Medtronic and others), provides daily insulin to simulate the pathophysiology of daily insulin secretion except bypassing the liver. (This publication demonstrates the lack of physiological stimulation of the liver with CSII). Result: Most people using the (Medtronic) CSII with a “closed loop” glucose sensor do not achieve glycemic goals and continue to have unacceptable rates of hypoglycemia. True minute-by-minute closed loop systems will still have to deal with fast acting insulin lag times of 90-120 minutes. **Yaturu, Subhashini, World Journal of Diabetes. Insulin Therapies: Current and Future Trends at Dawn (2013) 15:1-7**

24. **Burst Insulin [i.e. Bionica Microdose] Must Be Exploited.** The intravascular approach to delivering insulin was abandoned in the 80’s for subcutaneous insulin. However, the performance of subcutaneous insulin has been less than satisfactory. Accordingly, it is now time to reexamine the intravascular approach which has substantial benefits despite its invasiveness. Recent research has demonstrated a convincing body of evidence for the synchronized burst nature of pancreatic beta cells, resulting in oscillatory nature of insulin and blood glucose. Pulsatile insulin activity is lost in type 2 diabetes (and of course does not exist in type 1). Pulsed (burst) insulin has been shown to be more effective in lowering blood glucose levels compared to equal does of continuously infused insulin. And the pulsatile nature of endogenous insulin has been mimicked for therapeutic reasons using the Bionica IV insulin pump. Compared to standard therapy, pulsed therapy has shown better metabolic control, less end-organ damage, and restoration of normal pulsatile pancreatic function in type 2 diabetes. Insulin infused continuously required 2 hours or longer to reach steady state. This means that it would take several hours to adjust any insulin infusion to the correct rate to achieve appropriate and stable blood glucose. Any such infusion will necessarily be running to “catch up” and risks
hypoglycemia. In this study, it was found that the lag time from a bolus (burst) insulin first decrease in blood glucose levels occurs within just 4 to 6 minutes, the maximum rate occurred shortly thereafter, and a nadir was reached in 15 to 20 minutes. This time interval was relatively does independent. Using this, the goal was to achieve blood glucose in the 4.5 to 6.0 mmol: (81-108 mg/dl). Blood Glucose was rapidly and safely brought to this level during the study time with a continuous blood glucose meter (not using capillary blood), which had challenges making the system needing small calibration changes. However, the “The main point of this paper is to illustrate the physiological principle of using nature’s own regulatory system in an artificial control system, without fine tuning the details.” (Note: this is what the Bionica Microdose Artificial Pancreas Treatment® achieves today.)

25. Increased then decreased HbA1c’s on Commencement of Treatment. [Bionica Microdose] It is not uncommon for patients receiving burst insulin, and who have almost normal HbA1c levels of less than 7.0, to experience HbA1c increases of 2-3% for approximately 2 -3 months after commencement. This is due to the following:
   a) HbA1c can actually change in less than two weeks as a result of hypoglycemia. The glycosylation bond at the A1c location is not covalent and this bond can be “ripped off” by a single hypoglycemic reaction, changing the overall percentage.
   b) Diabetic patients with HbA1c < 7.0% have multiple hypoglycemic episodes as they have little or no gluconeogenesis and glycogen release which normally buffer non-diabetic people. Thus, their A1c percentage is averaged out by the hypoglycemic lows where glycosylation is removed, giving them a seemingly normal A1c when in fact they have multiple hypo- and hyper- glycemic episodes.
   c) The Artificial Pancreas Treatment® virtually eliminates all hypoglycemia (and thus all ripping off of glycosylation, by restoring glycogen storage and release and restoring the ability to sense low or dropping.

Accordingly: HbA1c levels will increase at first then decrease to a desired and appropriate level for that patient. Research Gate G Ford Gilbert, PhD, (2015).

Finally, in 2015 this article shows why burst insulin is so necessary:

26. Pulsatile Insulin is More Effective. Insulin secretion occurs in a pulsatile manner in the plasma of both humans and animals, with fast pulses exhibiting a period in the range of 5–15 minutes, and slower ultradian oscillations having periods ranging from 80 to 180 minutes. Insulin pulsatility is disrupted in diabetes, most clearly as reduced pulse amplitude, and this appears to be an early marker of diabetes, as it is observed not only in prediabetics but also in first-degree relatives of patients with diabetes who lack significant metabolic abnormalities. Conversely, pulsatile insulin is more effective at mediating the metabolic effects of insulin, most clearly suppression of hepatic glucose production but possibly also enhanced uptake by peripheral tissues. The pulsatility of insulin secretion is intrinsic to the islet and may involve close coupling between slow metabolic oscillations mediated by glycolysis and faster oscillations involving beta cell ion channels and Ca mediated negative feedback.

The very nature of pulsatile secretion and its biological advantages could have translational
significance for diabetes treatment. Thus, providing insulin in a pulsatile fashion using a device to make pulses of exogenous insulin or by applying insulin secretagogues such as tolbutamide in a pulsatile pattern, would be expected to affect insulin target tissues more effectively by more closely mimicking the changes in plasma insulin observed in normal individuals. As mentioned earlier in the review, this could result in increased peripheral as well as hepatic insulin sensitivity, increased preservation of beta cell function, and increased glucagon suppression by plasma insulin or better liver insulin extraction. While it is difficult to envisage a way in which insulin injected subcutaneously could produce plasma insulin pulses due to the lags inherent in this method of administration, recent simulations suggest that the approach may be feasible (Skjaervold et al., 2013). Alternatively, intravenous insulin injection using an artificial pancreas control system could be used to produce physiological insulin pulse patterns in individuals with diabetes where traditional therapy is insufficient.


Thus, the Bionica Microdose Intravenous Insulin Artificial Pancreas Treatment® is the undeniable best current means to treat diabetes and related diseases of metabolism.

Chapter 14  Metabolism Measurement, the Science and Application.

1. **Use of Metabolic Measurements.** In order to determine the metabolism of someone who is diabetic, resting metabolism must be assessed. Human energy stems from chemical energy, which is released from nutrients through the oxidation of food substrates. Carbon-based nutrients (ie, fuels) are converted into carbon dioxide (CO₂), water (H₂O), and heat in the presence of oxygen (O₂). Indirect calorimetry assesses the amount of heat generated indirectly according to the amount and pattern of substrate use and byproducts production. Specifically, energy expenditure can be calculated by measuring the amount of oxygen used, and carbon dioxide released, by the body. Substrate + O₂ oxidation → CO₂ + H₂O + Heat.

The specific amount of oxygen used can be measured, and is called oxygen consumption (V₀₂), whereas the amount of carbon dioxide gas produced by the cells is carbon dioxide production (VCO₂). The calculation of V₀₂ and VCO₂ can be made through the technique of thermodilution and quantification of hemodynamic parameters (eg, Fick’s equation) or by measuring pulmonary gas exchange, which is the principle of indirect calorimetry. Total average daily energy expenditure in kcal is usually calculated using the modified Weir equation with substitution of the measured V₀₂ and VCO₂ values.

Energy expenditure (kcaVd) = [(V₀₂ x 3.941) + (VCO₂ x 1.11) + (uN₂ x 2.17)] x 1440. (The urinary nitrogen component (uN₂) is often excluded when calculating energy expenditure because it only accounts for < 4% of the true energy).

2. **Respiratory Quotient (RQ)** is defined as the ratio between VCO₂ and V₀₂ (ie, VCO₂ / V₀₂) and reflects the type of substrate being used by the tissues. The complete oxidation of glucose in
a given system yields an RQ value of 1.0, but because this measurement yields only the type of metabolism not the amount of metabolism (because it is a mathematical ratio), the VCO₂ is the measurement which determines the amount of carbohydrates being processed. Thus RQ is an interesting artifact of shifting a diabetic person from abnormal to more normal, but it is not the means to verify that the patient has achieved normality, and able to properly process normal levels of carbohydrates. The Artificial Pancreas Treatment® using the Bionica Microdose is the only current means to achieve normalization of both the type and the amount of carbohydrate metabolism. And, as shown previously, when carbohydrate metabolism is normalized, lipid metabolism is also normalized.

3. The necessary measurement, carbohydrate metabolism. The goal of addressing the milieu of diabetic complications is to restore the ability for mitochondria to produce ATP in each cell from carbohydrates in sufficient amounts. Accordingly restoring resting carbohydrate metabolism is achieved only when there is an increase the amount of carbohydrate metabolism, and not merely determined by the type (carbohydrate-mixed-lipid) of metabolism. This measurement is achieved by respiratory gasses using one of the assay outcomes of indirect calorimetry, the VCO₂. By carefully measuring the amount (volume) of CO₂, and comparing the change in volume between pre- and post- treatment, the percentage becomes validation. When the volume is not sufficient for the size and type of patient, the treatment is increased to the point of achieving normal expressions.

4. Two Days, then Once a Week, then Once every Two Weeks. The treatment is modified by the metabolic response of the patient. Patients on the Artificial Pancreas Treatment® are treated on two successive days and then once weekly. Metabolism measurements are used to determine the duration between treatments, and verify two things: A) the amount (level) of carbohydrate metabolism being achieved by the treatment and B) the duration between treatments that still maintains a minimum healthy level of carbohydrate metabolism.

5. Three (3) metabolic measurements are required for Artificial Pancreas Treatment®. A baseline of the amount of carbohydrate metabolism of the patient is determined by volumetric measurement (liters/min). Pulmonary differences are not significant as the measurement is focused on the differentials between when pre-treatment and post-treatment. The diabetic patient, who is unable to properly metabolize carbohydrates, is treated with burst insulin (Artificial Pancreas Treatment® using the Bionica Microdose) which shifts the patient into metabolizing carbohydrates, something that was not possible without this treatment. The rise in metabolic rates are significant to the point of being dramatic.

   a) A pre-treatment baseline of carbohydrate metabolism level (volume in L/min) is recorded.
   b) The patient is treated weekly for a series of weeks depending on their metabolic recovery, 3 metabolism levels are recorded. 1st value obtained before the first one hour infusion session. 2nd value is obtained before the second one hour infusion, and 3rd value after the third infusion treatment.
c) Glucose administration is adjusted to achieve increases in carbohydrate metabolism volume in accordance with protocol developed and refined over many years.

d) If a patient does not have a significant increase (per treatment protocol) in his or her carbohydrate metabolism level with an increase in volume of CHO2 after the first hour, the patient has not retained carbohydrate metabolic ability and treatments become more frequent or continue weekly. Approximately 3 months is required to achieve this ability, depending upon the patient response.

e) If a patient does not significant increase volume of CHO2 over that day’s baseline after the second treatment, then adjustment of dosing must take place for the 3rd treatment session.

f) If a patient does not respond by the end of the 3rd session, the clinic coordinator will schedule a treatment within 2-3 days until carbohydrate restoration is shown by the end of the 3rd treatment session.

6. The presence of increased carbohydrate metabolism in the presence of glucose and insulin is required to assure that the free fatty acid and ATP normalization functions are resuming. When present, the result is the restoration of the Krebs Cycle (citric acid cycle).

7. The Respiratory Quotient is not used for treatment as it only reports a change in the type of metabolism which is insufficient to determine how long the treatment will sustain the patient. This was misunderstood in prior treatment modalities.

8. **Physiological Concentrations.** Prior protocols approximated the insulin level for a patient and then calculated the amount of insulin for burst therapy. The prior system started with a predicted amount of insulin and provided glucose to “cover” those boluses of insulin. However this is unlike the actions of a normal pancreas. The Artificial Pancreas Treatment® has been further improved by taking the other vantage point, which is more like the normal pancreas. Rather than giving insulin and covering with glucose, the improved Artificial Pancreas Treatment® determines a routine amount of kilocalories (calories) for slightly more than two meals and adjusts the amount of bursts of insulin every 15 minutes. Thus, the set glucose amount is a goal of the therapy, and the insulin must be adjusted to meet the blood sugar which allows for that amount of oral glucose ingestion.

9. **Light Exercise Between Sessions.** Still another change in the treatment protocol that has added to good patient outcomes and extended the time between treatments is a short exercise session between infusion sessions. This exercise must be timed to avoid carryover into the metabolic measurement period, but allows for certain insulin resistant people to avoid mobilizing insulin after leaving. Instead of sitting for 1 hour between sessions, a decision is made as to the level of glucose and other factors to have the patient walk for 5 to 10 minutes.

10. **Conclusion** The now improved Artificial Pancreas Treatment® using the Bionica Microdose is not only physiologically correct in mimicking normal pancreatic insulin bursts with resulting oscillations throughout the body, it is now physiologically correct in the amount of
glucose given which approximates two meals, with interim adjustments of insulin over short periods of time.

**Chapter 15**  
**The Bionica Microdose Artificial Pancreas Treatment® Provides Intravenous Insulin Bursts, and thus Requires Blood Glucose and Potassium Measurements.**

The use of glucometers is sufficient when the glucose level has been verified. Fortunately, since the total amount of insulin being infused is relatively small, and maintained below any hyperinsulinemia (high levels of circulating insulin), a simple glucometer can be sufficient for blood glucose monitoring.

Since the treatment causes the patient to both store hepatic glycogen and muscle glycogen, and since the pancreas of a diabetic person still can release glucagon from the $\alpha$-cells, the treatment results in additional protection from glucose excursions. This is part of the means by which natural blood glucose modulation and buffering are restored in the APT treated patient. Potassium following is necessary for any administration of intravenous insulin, but it appears that potassium reduction which is seen in a constant IV drip of insulin is not seen with burst insulin. To date, no acute hypokalemia has been reported in any of the many patients treated with the Bionica pump and treatment protocols, over many years. Mild cramping is possible with any potassium change, or with low potassium. Thus, medication and medical foods may be needed for patients who present with lower overall levels of potassium. However there is one problem with measurement of serum levels of potassium, they do not automatically correlate with the intra-cellular levels of potassium, and so serum levels may be low due to the effective increase in intra-cellular levels which are beneficial to cell metabolism.

**Chapter 16**  
**Healthy Life Requires Restoration of the Krebs Cycle, Restoration of ATP from Carbohydrates, and thus the Artificial Pancreas Treatment®**

The proper production of ATP (cellular chemical energy) is more basic to mammalian life than any other function. The Krebs cycle is a fundamental requirement of good health in all animals. The lack of the Krebs cycle is a fundamental flaw found in diabetes.

It is thus an Absolutely Medically Necessary, in order to restore natural health, to restore the ability to convert carbohydrates into ATP. **No treatment other than the Artificial Pancreas Treatment®** as it has developed and changed has ever been able to do this.

Every tissue and organ requires proper Krebs cycle metabolism to fully perform its various functions. This is because an abundant and immediate supply of ATP is only available with proper carbohydrate processing.
Normal metabolism is simplistically displayed here. The three major food groups also containing significant amounts of water are needed to provide ATP (which is chemical cellular energy)

The mitochondria require liver produced enzymes to achieve these metabolic normal balance, and the pancreas talks to the liver in bursts.

Conversely, when the liver does not produce the enzymes which are needed for proper carbohydrate metabolism, the body has a very unhealthy level of lipid use which increases the free fatty acids by the fatty acid spiral. This is automatic in the absence of carbohydrate metabolism, and makes the diabetic patient more like that displayed here.
Central Role of Free Fatty Acids

Conclusion:

Artificial Pancreas Treatment® recognizes the core problem of metabolism and mimics the pancreatic stimulation of the liver and other tissues which causes the liver to produce the enzymes related to the Krebs cycle, which causes the mitochondria in every cell to regain the ability to metabolize carbohydrates, which automatically lowers improperly elevated lipid metabolism, causing the tissues to have more cellular energy (ATP) and calming the inflammatory cytokines, while reducing cellular oxygen requirements and helping to normalize blood flow by eliminating excessive free fatty acids, and all together allowing the tissues to heal themselves and remove both toxins and plaque.

This core problem is resolved by an average of only 8 hours treatment per month. The cost/benefit ratio high, and all of the destructive processes are reversed. This is what happens when we undertake to replicate natural.

This is also a reversal of the core problem of diabetes and the reversal of the “medical failure” of diabetes as defined by every scholarly work.

No other treatment has achieved this normalization of basic metabolism, and no other treatment mimics the non-diabetic stimulation of the liver.

More importantly, no treatment that uniformly returns any significant natural process of the human body has been rejected as either experimental or investigational. The argument is compelling. Returning a body to normal processing is always an improvement, and with something so important to wellness as proper metabolism, there can be no argument against necessity.
The development of any new treatment or tool takes time, and on chronic diseases more time than in acute conditions. As to the APT, there is a knee-jerk reaction that “I have not heard of it…it must not be real.” This final argument is illogical and not worthy of science. Why? Because any scientist who opposes a restoration of the Krebs cycle is, by definition saying that normal cellular life is not proper. There is no basis for asserting that burst insulin is anything but natural, and no basis for asserting that the Krebs cycle is not important to good health.

In over 200 scientific interviews, when asked if restoring carbohydrate metabolism would be a fundamental goal of wellness, every single scientist has said “yes.” When asked if clamping carbohydrate metabolism would be healthy, the same total plurality say “no.”

This is uniform agreement. This is an overarching conclusion which leaves no room for informed disagreement.

Thus, when there is absolute unanimity of thought and belief, and no scientific evidence to refute that belief, there can be no argument. Any would be illogical.

The Artificial Pancreas Treatment® must be made available for anyone suffering from significant complications of metabolic dysfunction because it restores normal. To deny treatment unnecessarily operates to condemn patients to poor health.

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