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Pulsatile Insulin Delivery – A Common Sense Approach to a Complex Problem

The Food and Drug Administration approved 15 new diabetes drugs between 2013 and 2016[1]. Almost 300 companies are involved in developing drugs for type 2 diabetes alone, and additional companies are working on type 1 diabetes and diabetes complications. Still others are developing new drug delivery devices. The teams dedicated to discovering new molecules should be applauded - diabetes mellitus is a huge public health issue.

The total cost of diagnosed diabetes in 2012 was $245 billion, including $176 billion in direct medical costs and $69 billion in reduced productivity. Medicare spent $11 Billion in 2013 on dialysis alone. Amputations cost between $73,000 to $120,000 for hospital and follow-up care. As the occurrence of diabetes continues to rise along with the ballooning costs of treatments, pharmaceutical companies continue to seek proprietary compounds for development. In recent years, the US FDA has approved several drugs with novel mechanisms of action. These include GLP-1 agonists, DPP-4 inhibitors, and SGLT2 inhibitors. Like their predecessors, these therapies are expected to have rather predictable outcomes of managing hyperglycemia without addressing the root and underlying pathophysiology that leads to the debilitating complications of diabetes and metabolic syndrome.

Ultimately, these treatments and others in development aspire to reduce hyperglycemia by increasing the availability of insulin. However, there is an approach to treating diabetes and other metabolic disorders that produces superior outcomes by mimicking the body's natural method of regulating insulin. The science behind rhythmic or "pulsatile" insulin excretion by the pancreas is not new; the phenomenon has been documented by researchers for decades.

Rather than a continuous flow or stream, the pancreas releases insulin in the same way many other hormones are secreted−in short pulses. The beta-cells in the islets of Langerhans excrete insulin in a slow rhythm. This phenomenon was first observed in 1979 as healthy fasting subjects had their insulin levels monitored every minute for one to two hours[2] (figure 1).

[1] FDA.gov

[2] Normal pulses of insulin, C-peptide, and glucose measured in blood from a peripheral vein. 1979 Lang DA, et al

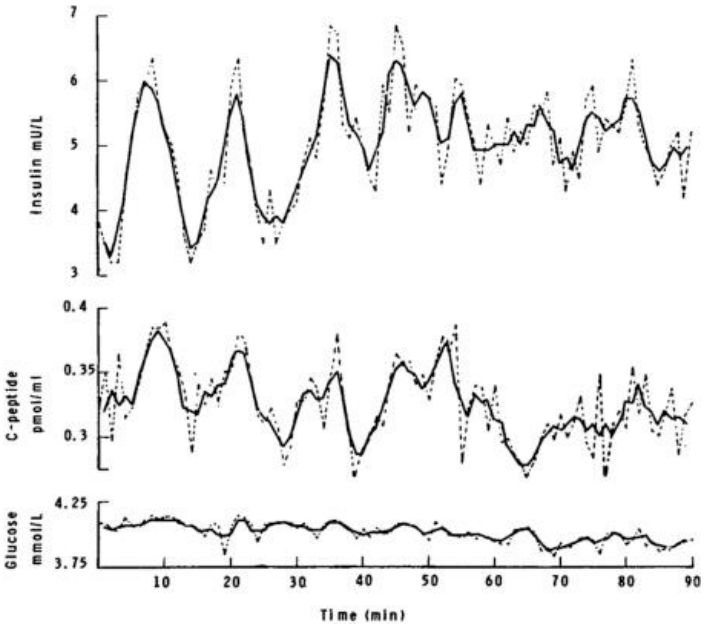

Figure 1

Insulin levels in the blood are not static, but pulse every few minutes. C-peptide, which is secreted along with insulin, follows the same pattern. Corresponding changes in glucose levels are present but less dramatic. After consuming a carbohydrate meal, the height of each peak increases as more insulin is released in each pulse while the pulses continue at the roughly the same frequency. These pulses of insulin are approximately every 5-6 minutes. As well as these fast pulses, an ultradian rhythm made up of slower oscillations of insulin every 80–180 minutes have also been measured. [3]

Pulses of insulin are more effective at activating insulin receptors than a constant exposure of insulin in the liver.[4] The pancreas releases insulin into the portal vein, which flows directly into the liver before spreading out through the rest of the body, so the liver experiences the greatest effect of these insulin pulses. In contrast, a continuous exposure to insulin results in downregulation of insulin receptors and results in the phenomenon of insulin resistance.[5]

Diabetes is characterized by a disruption of pulses and rhythmic secretion of insulin by the pancreas. This disruption is believed to be in part a result of inflammation in the pancreas that may result from a variety of causes including obesity, toxins, trauma, etc. and the resulting inflammation ultimately disrupts the neuronal network that coordinates the pulses. The slower, longer ultradian cycles of insulin secretion were found to be disrupted in diabetic patients.[6] In addition to the longer cycles, shorter rhythms are affected in diabetes mellitus as well. Individuals with type 2 diabetes have been found to have shorter and highly irregular pulses in their insulin.[7]

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[3] Abnormal patterns of insulin secretion in non-insulin-dependent diabetes mellitus. 1988 Polonsky KS, et al

[4] Pulsatile insulin secretion dictates systemic insulin delivery by regulating hepatic insulin extraction in humans. 2005 Meier JJ, et al

[5] Disordered insulin secretion in the development of insulin resistance and Type 2 diabetes. 2012 Schofield CJ, Sutherland C

[6] Abnormal patterns of insulin secretion in non-insulin-dependent diabetes mellitus. 1988 Polonsky KS, et al

[7] Association between insulin secretory pulse frequency and peripheral insulin action in NIDDM and normal subjects. 1996 Hunter, et al

The question of causality was explored to determine whether the disruption in pulsatile dispensation of insulin was a sequela of or catalyst for diabetes. First-degree relatives of diabetic patients were studied in 1998 and were found to have abnormal insulin pulses compared to unrelated controls, suggesting that the abnormal oscillations in insulin secretion may be an early phenomenon in the development of type 2 diabetes.[8] Research performed more recently (2012) shed additional light on the role abnormal pulsatile insulin release in the onset of diabetes. The physiologically normal pattern of insulin pulses is important for hepatic insulin signaling and glycemic control, and liver insulin resistance in diabetes is likely, in part, due to impaired pulsatile insulin secretion.[9] Additionally, as disordered insulin secretion may cause intracellular insulin resistance, it may be an initiating factor in the progression to type 2 diabetes. [10]

To summarize the sampling from the research above, the pulsatile secretion of insulin by the pancreas is well established, as is the evidence that impaired pulsatile insulin delivery plays a significant role in the development of diabetes. Even though there are hundreds of teams developing molecules to manage the progression of the disease, the incidence and impact of diabetes continues to grow. It was this challenge that has led to the development of a novel therapeutic regimen that is producing superior outcomes by mimicking the body's own method of regulating insulin. Diabetes Relief's patented treatment improves hepatic glucose process is an effective program that is poised to transform the way diabetes is managed.

Several clinical studies have shown this therapeutic approach to be safe and efficacious. *The Effects of pulsatile intravenous insulin therapy on the progression of diabetic nephropathy* was published in 2000. The purpose of this study was to assess the effects of pulsatile intravenous insulin therapy (PIVIT) on the progression of diabetic nephropathy in patients with type 1 diabetes mellitus (DM). This 18-month multicenter, prospective, controlled study involved 49 type 1 DM patients with nephropathy who were following the Diabetes Control and Complications Trial (DCCT) intensive therapy (IT) regimen. Of these, 26 patients formed the control group (C), which continued on IT, while 23 patients formed the treatment group (T) and underwent, in addition to IT, weekly PIVIT. Blood pressure in all patients was maintained below 140/90 mm Hg on antihypertensive medication, preferentially using angiotensin-converting enzyme (ACE) inhibitors. All study patients were seen in the clinic weekly for 18 months, had monthly HbA1c monitoring, as well as 24-hour urinary protein excretion and creatinine clearance (CrCl) determinations performed every 3 months. The HbA1c levels declined from 8.61% +/- 0.33% to 7.68% +/- 0.31% (P = .0028) in the T group and from 9.13% +/- 0.36% to 8.19% +/- 0.33% (P = .0015) in the C group during the study period. CrCl declined significantly in both groups, as expected, but the rate of CrCl decline in the T group (2.21 +/- 1.62 mL/min/yr) was significantly less than in the C group (7.69 +/- 1.88 mL/min/yr, P = .0343). The authors conclude that when PIVIT is added to IT in type 1 DM patients with overt nephropathy, it appears to markedly reduce the progression of diabetic nephropathy. The effect appears independent of ACE inhibitor therapy, blood pressure, or glycemic control.

Subsequent to these findings, other studies were conducted and published including *Effect of Intensive Insulin Therapy on Progression of Overt nephropathy in Patients with Type 1 Diabetes Mellitus* by researchers at the University of California, Davis. In this clinical trial investigators set out to assess the

[8] Impaired pulsatile secretion of insulin in relatives of patients with non-insulin-dependent diabetes. 1998 O'Rahilly S, et al

[9] Pulsatile portal vein insulin delivery enhances hepatic insulin action and signaling. 2012 Matveyenko AV

[10] Disordered insulin secretion in the development of insulin resistance and Type 2 diabetes. 2012 Schofield CJ, Sutherland C

effects of chronic (long-term) intermittent intravenous insulin therapy (CIIIT) on the progression of overt nephropathy in patients with type 1 diabetes mellitus.

This retrospective longitudinal three-center study of 31 patients with type 1 diabetes mellitus and overt nephropathy who were receiving intensive subcutaneous insulin therapy (four insulin injections daily) and weekly CIIIT. Study patients had follow-up consultations weekly for at least 12 months, monthly hemoglobin A_{1c} (by high-performance liquid chromatography), and semiannual creatinine clearance determinations. The results showed hemoglobin A_{1c} levels declined significantly from 8.6% +/- 0.6% to 7.6 % +/- 0.3% (P = 0.0062) during the study period, while the creatinine clearance remained essentially unchanged. The authors concluded that the addition of CIIIT to intensive subcutaneous insulin therapy in patients with type 1 diabetes mellitus seems to arrest or appreciably reduce the progression of overt diabetic nephropathy, as well as substantially improve their glycemic control.

By leveraging state-of-the-art technology and proprietary algorithms Diabetes Relief has developed and refined a therapeutic process that further improves upon the pioneering work in this field. Diabetes Relief utilizes the administration of insulin via intravenous infusions. These infusions are included as the centerpiece of a customized treatment plan that includes traditional recommendations for diet and exercise along with proprietary nutritional support. While other treatments seek to control the symptom of hyperglycemia, Diabetes Relief reduces insulin resistance by re-sensitizing insulin receptors. The complications of diabetes are not due to a direct toxic effect of hyperglycemia but rather a failure of cells to replicate and replace aging cells. By addressing the impaired pancreatic insulin pulse, Diabetes Relief facilitates carbohydrate metabolism which enhances growth and repair of tissue beds throughout the body and thus dramatically reduces both hyperglycemia and diabetic complications.

Current treatment modalities focus on controlling the symptom of hyperglycemia. The treatments have significant limitations in reversing the devastating complications that occur in progression of this disease. The literature is replete with detailed descriptions of cellular signals between the pancreases and liver which affect carbohydrate metabolism. Armed with this information, Diabetes Relief has developed a program to approximate normal physiologic signaling to restore insulin sensitivity. While others search for more ways to increase the availability of insulin that increases hyperinsulinemia and may ultimately desensitization and downregulate receptors, Diabetes Relief employs an alternate approach to improve the efficiency of insulin by providing a physiologic delivery. With the ever-growing epidemic of this disease, treatments need to go beyond control of hyperglycemia and address the core defects that have propelled this condition into a global health crisis.

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White Paper with Summary of Judicial Opinions

Anyone can understand that it costs more to pay for amputations ($73,000 to $120,000, including initial hospital costs and follow-up care), dialysis (on which Medicare spent $11 BILLION in 2013, according to its own data), and blindness than for a treatment that *avoids* amputations, dialysis, and blindness. It is universally understood that diabetics incur big expenses for medications and equipment, and with some, it is a large portion of their budget. Diabetes Relief's patented treatment consistently helps patients to reduce the number of medications they are taking as well as prevent amputations and dialysis, improve vision, and heal wounds that traditional treatment has failed.

The total cost of diagnosed diabetes in 2012 was **$245 billion**, including $176 billion in direct medical costs and $69 billion in **reduced productivity**. People with diagnosed diabetes incur average medical expenditures of about $13,700 per year, of which about $7,900 is attributed to diabetes. People with diagnosed diabetes, on average, have medical expenditures approximately **2.3 times higher** than what expenditures would be in the absence of diabetes. These figures are from a 2012 survey that was updated in 2014, and we can be assured that those costs have only skyrocketed since then. ***Is it not a correct course of action to try to address this problem by helping diabetics to get better? Our treatment does just that, and moreover, it gets to the root cause of diabetes and not simply suppression of symptoms, as is done with conventional treatment***

This type of diabetes treatment has been called many names during the decades since it was first introduced, we believe that the correct term, however, that describes what is happening medically in a human body is **"hepatic activation."**

It is critical to understand the difference. This treatment is not just a different way to administer insulin to the body for sugar control. **Hepatic activation** speaks directly to the therapy's purpose of helping the pancreas and liver communicate effectively, causing the body to function ***normally***. The therapy mimics a healthy liver and pancreas.

In a 2008 California case appealed from the Superior Court of San Francisco County, where an insurance company had denied coverage because hepatic activation treatment

was considered **experimental**, the court ruled against the insurer because a prior court had already ruled that the treatment was not experimental. The appeals court further ordered that the insurer could not deny coverage on a basis of the treatment being experimental.

That court opinion relied on a 2002 California case before a in which the insurer had denied coverage, the judge who heard the case **over seven days of testimony** wrote a lengthy opinion, and his findings are especially worthy to note. Therefore, we have included **quotes directly from his ruling**.

Review of hepatic activation treatment as described in the Opinion of Administrative Law Judge Steven J. Smith of California ordering payment for the treatment and ruling that the treatment is a medical necessity.

Judge Smith, after hearing seven days of testimony, understood that this therapy is not merely an alternative method of delivering insulin to diabetic patients, and stated affirmatively that through hepatic activation patients' health outcomes range from "significant" to "extraordinary."

SUMMARY OF OPINION

> Excerpts from **Opinion issued by Administrative Law Judge Stephen J. Smith**, in the final administrative appeal arising from denial of coverage for hepatic activation treatment, opinion dated January 17, 2002.

Judge Smith SUSTAINED the appeal and **ORDERED reimbursement** for all hepatic activation treatments and that the insurer provide coverage for *past and future* treatments.

Judge Smith heard *evidence over seven days* and reviewed multiple motions, declarations, claims, and responses. **Judge Smith's opinion** was adopted by the Board of

Administration of the California Public Employees' Retirement System on April 17, 2002. Judge Smith's findings and rulings are as **pertinent today** as they were then.

Citations refer to pages in the full opinion, and our emphasis is added.

"[T]he issue of hepatic activation is all about those diabetics who, despite the best efforts of patient and practitioner to follow the state of the art conventional therapy regimen, still develop progressing secondary complications." P. 4, ¶ 2.

"Hepatic activation **offers these patients real hope for improvement** because the great weight of the evidence in this record reveals **hepatic activation works**, is safe and effective, and results, in varying degrees, in arrest and often reversal of the progress of secondary complications." P. 4, ¶ 3.

"The **groundless speculation** that respondents' [the patients] development of serious secondary complications was the product of their failures to diligently and carefully follow a conventional physiological control treatment protocol, or the failure of their specialists to find and make the necessary modifications to their treatment protocols, or a combination of the two, was **demeaning and insulting to both groups, and is rejected as wholly contrary to the evidence**." P. 5, ¶ 4.

"Hepatic activation requires a very substantial financial, emotional and time commitment from the patient . . . . All experienced long term success and excellent blood glucose control over decades with the conventional treatment regimen. But each respondent . . . began to develop **secondary complications** after long periods of time of conventional treatment, complications **that continued to worsen** . . . ." P. 6, ¶ 1.

"Intravenous insulin therapy has been in existence and common use for more than 70 years." P. 7, ¶ 1.

"Unlike intravenous insulin administration . . . , hepatic activation administered insulin intravenously in a specially timed pattern and series of pulses through the pump to the patient . . . . The pulses deliver an intense concentration of insulin, designed to mimic . . . the behavior of the pancreas of a nondiabetic person . . . ." P. 7, ¶ 3.

"Hepatic activation treatment begins with two consecutive days of activation. . . . Thereafter, hepatic activation is administered once weekly, or once every two weeks in some cases, on an outpatient basis." P. 8, ¶ 2.

"Activation consists of four components. **Insulin is infused** according to the treatment protocol intravenously via the specially designed proprietary pump in discrete pulses of specific dosage, duration and frequency. . . . **Glucose is administered** as needed orally for prevention of hypoglycemia . . . . Capillary **blood glucose is carefully and frequently monitored** during activation . . . . The **patient's respiratory quotient ("RQ") is measured and determined**, using a metabolic measurement device during activation to monitor and confirm the establishment of normal carbohydrate metabolism throughout the procedure." P. 8, ¶ 3.

"Hepatic activation **does not supplant** conventional intensive insulin physiological control therapy, but **is offered as a supplement** to it, when the conventional therapy regimen fails to achieve its goals, and secondary complications continue to develop, despite best efforts at effective conventional therapy." P. 9, ¶ 1.

"**All respondents have experienced improved health outcomes** as a result of receiving hepatic activation. Those improved health outcomes range from **significant to extraordinary**." P. 10, ¶ 3.

"Despite the expense of significant co-payments, burdensome self-discipline and extraordinary commitments of time required of them, **all respondents are intensely motivated to continue hepatic activation**. All respondents see hepatic activation as the only thing separating them from a return to the debilitating progression of secondary complications each was experiencing to a greater or lesser degree, when they started on hepatic activation." *Id.*

"(Name Withheld) persuasively testified that a patient can miss one weekly hepatic activation session without too much negative impact, **but two or more misses results in a noticeable decline in general health** and a return of the development of secondary complications arrested when hepatic activation is continued." *Id.*

"Respondents see continuation of their hepatic activation treatments as the difference for them between active, productive lives and disability, deterioration and **eventual death from diabetic complications**. ***There is considerable evidence in this record to support respondents' views and concerns***."

[Pages 10 through 13 describe details of the patients' experiences, all of which are similar or identical to those of our patients' testimonials.]

"Hepatic activation is entirely safe and is effective for the purposes for which it is offered." P. 14, ¶ 1.

"[Name Withheld] typically billed respondents' hepatic activation treatment by 'unbundling' the procedures that compose hepatic activation, and billed separately for intravenous insulin infusion, insulin, use of a pump for infusion, physician visit, saline, testing equipment and so forth. The persuasive evidence was that this practice was and remains **common in the industry**, particularly where there is no specific code for the bundled therapy." P. 20, ¶ 3.

[In response to claims that the treatment is "experimental and investigational"]: "[H]epatic activation is now, and has been since at least 1987, in accordance with generally accepted medical professional standards as being **safe and effective for use in the treatment of Type 1 and Type 2 diabetes and its complications**." P. 23, ¶ 4.

"Research and clinical trials of hepatic activation was published as early as 1982, with many more following . . . . Because this was such a central foundation of the opinion that hepatic activation is ***still experimental and investigational and not medically necessary***, several of the more important studies published in the scientific literature and their findings are described as follows: [Judge Smith goes on to summarize ten studies from 1983 through 2001]." Pp. 25-27.

"The process of running the gauntlet of peer reviewed publication of research results and similar critique is an integral part fo the advancement of safe and effective medicine, ... But is easy to see how the review and critique process can become an end in itself, ***particularly when clinical experience is given no weight at all and is actually viewed with suspicion***." P. 28, ¶ 3, completed on p. 29.

"Hepatic activation is a form of intravenous insulin therapy, a widely accepted form of diabetic treatment that can be found in most every hospital and clinic in the U.S. Hepatic activation has been in use in clinics in California, Texas, Colorado, Massachusetts and Kansas for more than **13 years, with more than 45,000 documented administrations**." P. 30, ¶ 2-3.

"The places where hepatic activation is not yet offered, and even in places like California, where it is, the therapy is still not well known by a considerable number of practitioners . . . . " P. 31, ¶ 2.

"Documented clinical evidence in support of the safety and efficacy of hepatic activation in this case is considerable and spans more than 20 years . . . . The only known potential adverse effecrt of hepatic activation in the thousands of administrations documented is the potential for hypoglycemia in some patients. A glucose supplement is used to moderate any possible hypoglycemia that might result . . . . Careful monitoring of blood glucose levels during therapy and timely administration of the glucose supplement prevents the potential problem with hypoglycemia from occurring." P. 31, ¶ 3. ***[NOTE: THUS THE REASON FOR MULTIPLE FINGER STICKS TO CHECK BLOOD GLUCOSE LEVELS DURING THE PROCEDURE.]***

"**Many health insurers cover hepatic activation** and a few do not. Among others, HealthNet Select, Aetna US Healthcare, Cigna, Kaiser Permanente (now on a case by case basis), Blue Cross (on a case by case basis after review against an internal policy to initially deny coverage), Blue Cross Federal, Blue Cross of South Carolina, Associated Administrators, Blue Cross Prudent Buyer, Medicare, Blue Shield from December 1992 to July 1998, Sutter and Delta Healthcare **all have covered hepatic activation as a medically necessary treatment** for appropriate subscriber patients. Some of these insurers cover the treatment outright, and some cover it only after preapproval, internal review, or initial denial and later review. In Kansas and Mid-America, including Missouri, Iowa, Nebraska, according to Dr. Guthrie, 'all insurers cover it', including 'all PPOs', Coventry Healthcare, Boeing Blue Shield/Blue Cross, PHS Hospital Plan, Cigna and Aetna. Prudential and Health Plan of the Redwoods **cover the therapy after having been ordered to do so** following a determination by the Department of Corporations that hepatic activation is not experimental and investigational, and was safe, effective and **medically necessary** for those subject patients." P.33, ¶ 2.

"Medicare apparently covers some and denies other claims for hepatic activation using a process that was not disclosed in the evidence, and denies claims periodically, about one every five months or so. Administrative law Judges reviewing the Medicare denials have **uniformly concluded that in each individual case, hepatic activation was safe and effective for the patient,** not subject to exclusion upon the claim that the less expensive intensive insulin conventional therapy is just as effective, nor experimental or investigational." P. 33, ¶ 3.

"The Medicare decisions are of particular interest. The 1999 Medicare Decision finds hepatic activation **medically necessary** for the patient, and the definition cited for 'Medical Necessity' is almost verbatim the definition found for 'Medical Necessity' in the CalPERS PPO EOC's that govern coverage in this case." ***Id***. cont'g thru 34.

"'The Administrative Law Judge therefore concludes that . . . the treatment . . . is appropriate, not experimental or investigational, and is a service which **is reasonable and necessary** for the purposes of coverage under the Medicare part B of Title XVIII of the Social Security Act.'" P. 34, ¶ 1.

"The evident trend toward wider acceptance of hepatic activation as a **medically necessary treatment** in certain cases has met considerable resistance in some cases, but the actual results have been like Blue Cross and Medicare's experiences, above, where a negative policy is **overridden when the merits of hepatic activation in individual cases are considered**." P. 35, ¶ 3.

"The trend is clear, and despite the efforts of insurers to enact policies denying coverage for a variety of reasons, on a case-by-case analysis, where *truly independent review* occurs, the **denials are uniformly failing to be sustained**." P. 36, ¶ 1.

"The FDA neither approves nor disapproves procedures like hepatic activation, a form of intravenous insulin, **a therapy that has been almost universally used since the l930's**." P. 36, ¶ 3.

"The **long term care costs** and social costs for a deteriorating diabetic with secondary complications can be **huge and multidimensional**, including dialysis or kidney transplants, cardiological care, neurological care, care of ulcers of extremities, repeated in-patient hospital stays and so forth . . . ."P. 37, ¶ 2.

"Dr. [Name withheld], as an example of **social and medical cost savings** attained by hepatic activation in his own practice, described in his testimony a female adolescent patient of his with uncontrolled hypoglycemic ketoacidosis who had experienced over **220 hospital admissions**, was unable to attend school, had failed to begin puberty and grow properly. Yet **after receiving hepatic activation, her hospitalizations were reduced to one or zero**, her spells of ketoacidosis vanished and she commenced and continued normal growth patterns. She is able to go to school and carry on a relatively normal late teen life. Dr. [Name withheld] calculated that ***one hospitalization to treat ketoacidosis costs the same as a year of hepatic activation***. " P. 37, ¶ 2.

"[H]epatic activation for most qualifying patients **substantially lowers long term health care costs** for many patients, but requires some near term expenditures for weekly treatments, which can be a significant cost." *Id.*

"Hepatic activation for the patients . . . **prolongs and improves the quality of life of diabetics receiving the treatment**, at the expense of some near term health care costs for these patients, but exhibits **significant long term potential costs savings** that result when secondary complications are arrested and do not result in expensive complications treatment such as dialysis, kidney transplant, hospital admissions for ketoacidosis and other hypoglycemic events . . . ." P. 38, ¶ 1.

"[H]epatic activation is consistent with generally accepted professional medical standards, and is **safe**. Hepatic activation is manifestly 'consistent with the symptoms or diagnosis in treatment of Type 1 and Type 2 diabetes mellitus." P. 39, ¶ 1.

"Hepatic activation is **manifestly medically necessary** for each one of the respondents. The corollary of this is also true, that **discontinuation of the therapy would have material and significant adverse health condition outcomes** for each of the respondents." P. 39, ¶ 2.

"None of the respondents achieved satisfactory medical condition, health care and general quality of life outcomes as a result of conventional therapies that were consistent with the best available practices. . . . The **great weight of the evidence in this record reveals activation is medically necessary for respondents** . . . ." P. 39, ¶ 2.

"Respondents' **very positive outcomes with hepatic activation**, and those described by Dr. [Name withheld] for his patients, as well as in the numerous other documents discussing patients other than respondents **with excellent improvements as the result of hepatic activation, were all outcomes that could not and were not achieved with use of conventional therapies**. Failure of conventional intensive insulin physiological control therapy to arrest the progression of secondary complications was the condition precedent for receipt of hepatic activation." P. 40, ¶ 1.

"[C]onventional intensive insulin physiological control therapy does not prevent or arrest the development of secondary complications of diabetes in many instances." *Id*.

"The undercurrent of this dispute cuts at the heart of traditional notions of the understanding and treatment of diabetes, developed over many years and pursued by thousands and thousands of practitioners in hundreds of clinics. Unlike many disease mechanisms that are well understood, with a treatment protocol that works well when applied to address the known mechanisms, **diabetes is markedly different**. Widely held understandings of how diabetes develops and operates in the human body are

held by practitioners, clinicians and academicians. But application of that widely held knowledge to treatment of diabetics yields containment at best, and **often fails**, too frequently resulting in the development of terrible and debilitations secondary complications, often leading to death. **Hepatic activation represents a significant challenge to this widely held body of accepted medical knowledge**." P. 42, ¶ 3, through top of 43.

"Actual costs for hepatic activation for respondents were not proved to constitute a meaningful threat to the fiscal integrity of the plans, but the **proof was compelling that removal of coverage for hepatic activation for respondents will have significant adverse and even catastrophic health and social consequences** for respondents." P. 48, ¶ 13.

"[U]nder the circumstances proved in this case, it would constitute a **significant prejudice to the health, safety and welfare of respondents to terminate coverage for hepatic activation for respondents**, and would therefore become a violation of [Name withheld] fiduciary duty to respondents to sustain the termination actions or to discontinue the therapy for respondents." P. 48, ¶ 14.

"Respondents are **entitled to coverage** for the period July 1998 forward, and are **entitled to continue to receive the coverage, as long as the therapy remains medically necessary** for them." P. 49, ¶ 15.

"[P]rudent approach would be to recognize the actual current practice of many insurers, who make decisions for suitability on a **case by case basis** . . . ." P. 49, ¶ 17.

ORDER: "The appeals of respondents are all SUSTAINED . . . . **to provide coverage for hepatic activation** from July 1998 forward and to date." P. 50, ¶ 1.

Judge Smith's thoughtful and carefully considered ruling describes it well.
The treatment works.
Patients are helped more than with traditional therapy.
Insurers should cover the treatment.