CA PUBLIC EMPLOYEES' RETIREMENT SYSTEM (CalPERS)

BOARD OF ADMINISTRATION

In the Matter of the Consolidated Appeals of Denial of Coverage for Hepatic Activation Treatment of: Names Withheld (5)

CASE NO.: 3490-5, 3490-3, 3490-2, 3490-1, 3490-4, and 3490-6

OAH No.: N-2000100209, N-2000100210, N-2000100211, N-2000100212, N-2000100213, and N-2000100214.

DECISION

RESOLVED, that the Board of Administration of the California Public Employees' Retirement System hereby adopts as its own decision the Proposed Decision dated January 17, 2002, concerning the applications of (Name Withheld), (Name Withheld), (Name Withheld), (Name Withheld) and through her Executor, (Name Withheld), with the following minor change: with the exception of the first full sentence ending with the word "evaluation", paragraph 70 on page 25 in its entirety is deleted.

RESOLVED FURTHER, that this Board decision shall be effective 30 days following mailing of the decision.

I hereby certify that on April 17, 2002, the Board of Administration, California Public Employees' Retirement System, made and adopted the foregoing Resolution, and I certify further that the attached copy of the administrative law judge's Proposed Decision is a true copy of the decision adopted by said Board of Administration in said matter.

Dated: APR 30, 2002

James E. Burton
Chief Executive Officer
Board of Administration, California Public Employees' Retirement System

By: Allen Feezor
Assistant Executive Officer, Before the Board of Administration, California Public Employees' Retirement System

PROPOSED DECISION

- Stephen J. Smith, Administrative Law Judge, State of California, Office of Administrative Hearings, heard this matter in Sacramento, California.
- The California Public Employees' Retirement System ("CalPERS") was represented by Julie Weng-Gutierrez, Deputy Attorney General, and Darryl Mansfield, Deputy Attorney General, Department of Justice, State of California.

- Barbara Dittmer, RN., Health Benefits Section, and Ralph Cobb, Chief, Health Benefits Section of Ca1PERS, appeared as representatives of Ca1PERS Self-Funded Health Benefits Progra(Name Withheld)
- (Name Withheld) appeared and was represented by Douglas DeVries, Attorney at Law.
- (Name Withheld) appeared and was represented by Sam Nageley, Attorney at Law.
- (Name Withheld) appeared and was represented by Gregory Gilbert, Attorney at Law and Robert Harris, Attorney at Law.
- (Name Withheld) appeared in propia persona.
- (Name Withheld) is deceased. (Name Withheld), Executor of the Estate of (Name Withheld), is her surviving spouse, appeared and represented the Estate of (Name Withheld).

Evidentiary hearing testimony was taken on June 11, 12, 13, 14, 15, 18 and 19, 2001. The parties submitted a first set of declarations of additional witnesses in July and August, 2001. The matter was convened for additional proceedings in late October 2001. A Post-Hearing Order was issued by the Administrative Law Judge, ruling on motions and objections, and was served on the parties. The parties submitted additional declarations in November 2001, in response to the Order.

The parties then filed additional motions and made objections to the Administrative Law Judge in mid-November 2001. The Administrative Law Judge heard the motions and considered the objections, and issued another Post-Hearing Order, and served the Order on the parties. A short time was permitted for response. The record was closed and the matter was submitted on December 15, 2001.

FACTUAL FINDINGS

This action is the final administrative appeal arising from denial of coverage for hepatic activation treatment for the five living respondents and one deceased respondent. Each respondent was, at all times relevant to this Decision, a member of Ca1PERS and a subscriber to one of Ca1PERS' two self-funded Preferred Provider Organization (hereafter "PPO") health plans, PERSCare and PERSChoice. The respondents are each long-term diabetics. All respondents are insulin dependent, Type I diabetics, except (Name Withheld), who is an insulin dependent Type II, adult onset diabetic.

Type I diabetics are diabetics from birth or early childhood, and typically become diabetic when their pancreas fails to function effectively. A Type II diabetic typically has effective pancreatic function through childhood, but develops diabetes later in adolescence or in adulthood when pancreatic function becomes inadequate or insulin resistance develops.

SECONDARY COMPLICATIONS OF DIABETES

All respondents were suffering in 1987 and later from developing secondary complications of diabetes of varying seriousness, including but not limited to retinopathy

(failing eyesight to blindness caused by diabetes), nephropathy (kidney failure), peripheral neuropathy (loss of sense of touch, particularly in the feet and hands), hypoglycemic unawareness (loss of the ability to sense low blood sugar levels, leading to loss of consciousness without warning), autonomic neuropathy (where organ systems fail to function) hypertension (high blood pressure), postural hypotension (an undetected drop in blood pressure that can cause the patient to become light-headed or lose consciousness when rising from a seated position) and heart problems such as cardiomyopathy.

CONVENTIONAL THERAPY, AKA INTENSIVE INSULIN THERAPY, TIGHT – CONTROL, AND PHYSIOLOGICAL CONTROL

All respondents had been treated for their diabetes and complications by specialists in the field of diabetes treatment. Each respondent was treated by use of widely accepted conventional diabetes therapy, including three to five subcutaneous insulin self-injections or the same number of insulin infusions by an insulin pump, with injection or infusion timed around meals, close blood glucose monitoring, very careful attention to diet, regular exercise, aggressive treatment for cholesterol problems, and regular follow-up treatment with physician, podiatrist or cardiologist to carefully monitor and hopefully control secondary complications. This treatment regimen was referred to throughout these proceedings as conventional intensive insulin therapy, or "tight control", but Dr. Guthrie's testimony that a better reference term is "physiological control" was very persuasive, in that the term incorporates reference to the fact that control of an insulin dependent diabetic's blood glucose is a multi-faceted proposition, including diet and lifestyle controls, disciplines and sacrifices, as well as regular exercise, insulin therapy, regular monitoring and working closely with the diabetic's treating physician to follow, adjust and modify the treatment regimen as need and circumstances change. Physiological control reflects the dynamic character of the treatment needs of the insulin dependent diabetic. The conventional physiological control treatment regimen described above is widely accepted nationwide by specialists and generalists alike in the treatment of diabetes mellitus where the diabetic is insulin dependent.

LIMITATIONS OF CONVENTIONAL THERAPY AND DEVELOPMENT OF SECONDARY COMPLICATIONS

Conventional treatment of diabetes is generally effective in younger, healthy diabetics not yet suffering from the secondary complications of diabetes, as confirmed in 1995 the landmark DCCT study. It still works effectively in many cases in the treatment of diabetics that have manifested some secondary complications, especially if the secondary complications are not serious or debilitating, and are not of long standing. Conventional intensive insulin tight control treatment has sometimes been effective in checking the further progression or development of secondary complications, and has sometimes been effective in causing the reversal of complications, particularly with retinopathy (eye disease leading to blindness), which appears to be quite unpredictable in some diabetics. There was little persuasive evidence however, that even "state of the art" conventional therapy, including the use of hypertension and ACE inhibitor medications, has been routinely successful in reversing or even causing meaningful arrest of the other serious secondary complications of diabetes, particularly nephropathy, hypoglycemic

unawareness, peripheral and autonomic neuropathy, ulcerations of the feet, unawareness, once those complications have developed and begin to progress.

There are some diabetics who develop secondary complications that continue to progress in seriousness, despite the best and most comprehensive physiological control through conventional method, with regular adjustments in injections or infusions, medications, diet, exercise and even weekly follow-up with other specialists. Dr. Nuovo denied this, and believes she can help any diabetic to improve, regardless of complications, and the secret is in continual adjustment and readjustment of the conventional therapy until progress is manifested. Dr. Peters acknowledged that some diabetics still develop progressing complications, in spite of the best efforts in application of the state of the art therapy she offers, and Dr. Axelrod appeared to agree with Dr. Peters.

No one disputed, and Dr. Aoki would be the first to agree, that the state of the art conventional therapy detailed by Dr. Peters in her declaration is the first and best option for insulin dependent diabetics, both Type 1 and Type 2 diabetics, and if satisfactory blood glucose control can be achieved and complications prevented and arrested, this therapy should be continued indefinitely. That *if* is a big one, and the 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. Dr. Peters and Dr. Axelrod offered no advice for what to do with these patients, save keep trying to modify and adjust the conventional therapy, hoping results will follow.

The credible, persuasive evidence in this record is that for some insulin dependent long-term diabetics, no amount of additional conventional physiological control therapy, adjustments or treatment with medications, specialists and the like will contain or arrest the further development of their secondary complications, or reverse complications already developed. 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.

All respondents fall into the sub-population of diabetes patients suffering secondary complications of varying seriousness that had proved unresponsive to very careful conventional physiological control therapy working with their treating endocrinologist or specialist physicians. Respondents were treated by some of the leading diabetic specialists in this region, such as Dr. Stuart Soldener, Dr. William Cushard, Dr. Mahmoud Benbarka, Dr. David Klonoff and Dr. Lorraine Tortosa. These specialists successfully treated respondents employing conventional therapies with physiological control for a number of years.

Nevertheless, over time, all respondents eventually began to develop secondary complications of diabetes of varying seriousness. As detailed in the testimony of Dr. (Name Redacted) and (Name Withheld), considerable and comprehensive efforts to modify treatment regimens, number and frequency of insulin administrations by subcutaneous or pump means, changes in diet, changes or increases in exercise, and the like, all proved unsuccessful in arresting the development of secondary complications, despite the best efforts of both patients and practitioners.

Dr. Nuovo, Dr. Peters, and Dr. Axelrod all expressed or implied in their testimony that the deterioration experienced in respondents' conditions was the product of a failure to make enough effort to find and follow the proper conventional treatment protocol. These opinions are rejected as entirely speculative, lacking in any substantial evidentiary foundation or support. None of these experts had ever seen any of the respondents in a clinical setting, bad only reviewed a very small part of their medical records and histories, and neither had any real idea what respondents did or failed to do within their conventional physiological control regimens over the years. Dr. Peters and Dr. Nuovo acknowledged that the records reviewed of respondents' treatment before hepatic activation were "scant", but neither acknowledged the paucity of the records was a reason for exercise of caution in expressing an opinion regarding the adequacy of respondents' care and treatment before hepatic activation started. Instead, each expert to a greater or lesser degree speculated the "scant" records were evidence that respondents did not receive adequate conventional intensive insulin therapy before being started on hepatic activation.

The same experts alternatively speculated that any positive results experienced by respondents after hepatic activation was commenced must have been due to the conventional therapy that accompanied the hepatic activation. The reasoning process leading to this conclusion is illogical and unpersuasive, as detailed below. These experts' lack of reticence to opine on the adequacy and sufficiency of the conventional therapy followed by respondents before receiving hepatic activation caused significant damage to their respective credibilities.

Time is a factor to be considered as well. (Name Withheld) started to receive hepatic activation in 1988. (Name Withheld) began in 1992. (Name Withheld), the last to start of the respondent group, started in 1996, at a time when the DC (see below) was still news. It appears from the evidence that the "state of the art" in conventional intensive insulin physiological control therapy has experienced advances and progress in this period of time, and it is therefore not reasonable to compare the state of the art in conventional therapy in 1988 or 1992 to what might be expected today in Dr. Peters' practice. The comparison advanced in Dr. Peters' declaration and Dr. Nuovo's testimony between what they consider in late 2001 as state of the art conventional therapy as a basis for concluding what was received by respondents as many as 12 years ago was inadequate is neither fair nor meaningful. It is, however, a very relevant consideration when evaluating any prospective candidate for future commencement of hepatic activation, in that failure to make best efforts to comply with state of the art conventional therapy is a condition precedent to receipt of hepatic activation.

The respondents, particularly the exemplar respondents who testified Dr. (Name Redacted) and (Name Withheld) are very bright, very well educated and exceptionally well informed in the technical details of diabetes and its treatment. They presented as particularly well versed and totally committed to do or refrain from doing whatever is required of them to gain and keep control of their diabetes. The groundless speculation that respondents' 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. No persons connected with this case were more motivated, more interested and totally committed to making every conceivable effort to gain control of their diabetes and arrest the development of secondary complications than were the respondents.

Hepatic activation requires a very substantial financial, emotional and time commitment from the patient, over and above that required for conventional physiological control therapy. Many diabetics are simply not willing to make these exceptional commitments, but that was not the case with respondents. Dr. (Name Redacted) and (Name Withheld) detailed in their testimonies lifetimes of daily extraordinary commitment to diligent pursuit of a very carefully crafted conventional physiological control treatment regimens, with all the lifestyle controls, diligent and regular exercise, together with excellent specialist treatment and monitoring. All experienced long term success and excellent blood glucose control over decades with the conventional treatment regimen. But each respondent, despite the careful and diligent efforts of themselves and their practitioners, began to develop secondary complications after long periods of time of conventional treatment, complications that continued to worsen regardless of a variety of modifications to the conventional treatments. Respondents were quite accustomed to successful control of their diabetes with conventional therapy and their commitments to a careful lifestyle supportive of their treatments, and were very distressed that their considerable efforts to regain control, which had been so effective in the past, were now becoming increasingly unsuccessful.

REFERRALS OF RESPONDENTS FOR HEPATIC ACTIVATION

All respondents were referred to Dr. Aoki and his colleagues at Aoki Diabetes Research Institute (hereafter "ADRI"), between late 1988 and 1993, except (Name Withheld), who was referred to Dr. Aoki by her treating endocrinologist, Dr. Tortosa, in early 1996. All respondents were referred for evaluation to possibly receive hepatic activation, a relatively little known but growing and promising specialized treatment for patients like respondents. ADRI was, at the time, a clinic within the Metabolism and Endocrinology Department of the University of California, Davis University Medical Center (hereafter "UCDUMC"), where Dr. Aoki was the Professor in Chief.

UCDUMC had made considerable and ultimately successful efforts to recruit Dr. Aoki away from the Joslin Diabetes Center, Boston, Massachusetts, the leading diabetes treatment and research center in the world, where Dr. Aoki was the Head of the Metabolism Section of the Research Division, under the headship of Dr. Stuart Soldener, who was Chief of Joslin operations at that time. Dr. Aoki was also serving as a Professor of Medicine at Harvard Medical School at that time. UCDUMC specifically recruited Dr. Aoki to come to UCDUMC to found, operate and offer hepatic activation through UCDUMC. Dr. Aoki equipped, staffed and opened the ADRI clinic at UCDUMC in 1987 and began offering hepatic activation.

HEPATIC ACTIVATION - WHAT IT IS AND HOW IT IS ADMINISTERED

Hepatic activation, which is also known as Chronic Intermittent Insulin Infusion Therapy ("CIIIT"), and more recently as Pulsatile Intravenous Insulin Infusion Therapy ("PIVIT"), is a form of, but a new approach to a relatively old and commonly used

therapy, intravenous insulin administration. Intravenous insulin therapy has been in existence and common use for more than 70 years. Intravenous insulin administration consists of a steady rate infusion of insulin intravenously, using an intravenous drip line or a pump apparatus. Intravenous insulin infusion has been commonly used for decades as a short-term means to get rapid control of widely fluctuating blood glucose levels for diabetics in crisis, where conventional controls have failed. It is most commonly used to assist in a serious health crisis, such as hypoglycemic ketoacidosis (diabetic coma), or other serious uncontrolled blood glucose situation. Intravenous insulin is typically used for a short period, generally a day or two, until the diabetic's blood glucose fluctuations and levels stabilize, and the diabetic's crisis subsides. Then the diabetic is released to conventional treatment again, as continuation of the receipt of insulin via a continuous intravenous administration is not practical for the patient.

Hepatic activation infuses intravenous insulin into one of a patient's peripheral veins by the use of a specially adapted Bionica portable, battery powered pump. Initially, when hepatic activation was still experimental and investigational, in the late 1970's and early 1980's, Dr. Aoki arranged with Miles Laboratories to adapt a beta cell manufactured by Miles to infuse insulin using the algorithm Dr. Aoki developed for pulsatile insulin infusion. A beta cell functions like an artificial pancreas in that it infuses insulin intravenously to offset the failure of the diabetic to produce his or her own. The beta cell is effective, but is very complex, difficult to operate and cumbersome and problematic for the diabetic because it is an intravenous device. But the beta cell work confirmed Dr. Aoki's concept was workable. Later, Dr. Aoki worked with other pump manufacturers and ultimately Bionica to engineer and manufacture an insulin pump specifically designed for hepatic activation. Dr. Aoki obtained a United States Patent for the pump in 1989, and the pump was approved as a medical device by the United States Food and Drug Administration (hereafter "USFDA") in the same year, following a multiday review and inspection of ADRI by FDA inspectors. ADRI and the pump were inspected and reviewed in another multiday inspection again by the FDA in 1994 and reapproved. These specially adapted Bionica pumps are expensive, and both the cost and the existence of the patent are considerable impediments to widespread proliferation of the equipment to clinics where hepatic activation could be performed. The barriers to creating and equipping a clinic for performing hepatic activation are quite high, in large part due to the cost of the pumps. Yet several such clinics have been founded, equipped and are thriving, most notably the ones in Wichita, Kansas, overseen by Dr. Guthrie, and clinics in Midland, Texas, Denver, Colorado, East Dartmouth, Massachusetts and Santa Rosa, California.

The actual therapeutic administration of insulin and the therapy protocol are also unique to hepatic activation. Unlike intravenous insulin administration, which is administered at a steady flow rate, hepatic activation administers insulin intravenously in a specially timed pattern and series of pulses through the pump to the patient in a specific period, usually an hour. The pulses deliver an intense concentration of insulin, designed to mimic as closely as possible the behavior of the pancreas of a nondiabetic person following the ingestion of a meal. The concentration of insulin delivered in hepatic activation pulses is higher than the steady flow concentration of insulin that is administered in ordinary intravenous insulin therapy and significantly higher than the much smaller concentrations

of insulin that can be delivered by a patient to him or herself by self-administering insulin in conventional therapy by subcutaneous injection or through an insulin pump.

Dr. Aoki obtained a United States Patent for the hepatic activation therapy and protocol in 1989. The pattern, intensity, frequency and concentration of the insulin pulses used in hepatic activation are the product of algorithms developed and refined by Dr. Aoki and his colleagues over the many years of research, development and testing of hepatic activation between 1975 and 1985, and constitute the intellectual property protected by the patent. Hepatic activation is presently administered in an outpatient clinic by a specially trained staff consisting of a physician, and usually a nurse or LVN, who also serves as an administrator. Dr. Aoki and his colleagues are conducting trials to investigate the feasibility of self-administered hepatic activation by carefully selected and trained patients at home. Much of the impediment to this extension of the therapy is the engineering problems associated with miniaturization and computer assistance for the pump mechanism, which has evolved from the large and very complex beta cell artificial pancreas used in the late 1970's to a small, battery operated portable unit used now. Dr. Aoki and Dr. Soldener hope to develop a fully automatic, microchip controlled implantable unit.

Hepatic activation treatment begins with two consecutive days of activation. The physician determines whether these days are to be inpatient or outpatient, but since the mid-1990s, most patients begin and continue all in the outpatient clinic. Thereafter, hepatic activation is administered once weekly, or once every two weeks in some cases, on an outpatient basis. The name of the treatment has meaning, as the therapy is directed at the insulin dependent diabetic's liver, and is designed to "activate" it by delivering insulin in a manner that closely resembles that of a nondiabetic. Once activated, the liver continues to function well metabolically and that function is maintained by continuation of tight control conventional therapy. Metabolic function deteriorates in the absence of a: normally functioning pancreas in about a week, and the need for the "tune-up" weekly outpatient visit to the clinic for another activation session arises. Following the weekly "tune-up" activation, the cycle begins again.

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. A total dose of 20 to 100 units of insulin is administered in a full day, consisting of three one hour administration sessions interspersed by three one hour rest periods, for a total of a 6 hour commitment for the patient and the clinic administering the therapy. A number of patients can be activated simultaneously, depending upon the number of pumps available at the clinic. Glucose is administered as needed orally for prevention of hypoglycemia, the only known and documented side-effect of hepatic activation, in the form of a flavored glucose solution similar to that used in glucose tolerance tests. Capillary blood glucose is carefully and frequently monitored during activation to insure that hypoglycemia does not result. 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.

QUALIFYING CRITERIA FOR RECIVING HEPATIC ACTIVATION

Since its arrival and approval at UCDUMC, hepatic activation has only been offered to a very narrow and specifically qualified insulin dependent diabetic patient. The first and foremost prerequisite for receiving hepatic activation is that the diabetic, whether Type I or Type II, must be strictly compliant with a conventional intensive insulin physiological control treatment regimen, including 3 to 5 daily subcutaneous or insulin pump insulin injections, timed around meals, and in strict compliance with all other diet, exercise, lifestyle and medication requirements of that diabetic's individual treatment regimen. The candidate must demonstrate that he or she is in strict compliance with his or her conventional treatment regimen because if adequate blood glucose control can be achieved by modifications or adjustments in the intensive insulin physiological control treatment regimen, hepatic activation is not offered. 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.

There are other limiting factors associated with admission to hepatic activation. Hepatic activation requires considerable discipline and motivation from the patient, and there are a limited number of spaces available for receipt of the treatment. Those not able to prove they are willing, able and actually are in strict compliance with their conventional therapy regimens are not offered the treatment, but are referred back to their specialists for adjustments and modifications to their conventional treatment plans. Upon assurance of best efforts at full compliance with conventional intensive insulin physiological control regimens, the following additional prerequisites must be evident before hepatic activation is offered:

For Type I diabetics:

A. Poor glycemic control with wide blood glucose fluctuations and frequent hypoglycemic events;

B. Hypoglycemic unawareness leading to severe hypoglycemic events;

C. Overt diabetic nephropathy and hypertension;

D. Severe painful peripheral polyneuropathy unresponsive to conventional therapy;

E. Severe autonomic neuropathy unresponsive to conventional therapy, such as postural hypotension or gastroparesis;

F. Proliferative diabetic retinopathy requiring repeated photocoagulation therapy;

G. Diabetic foot ulcers, unresponsive to conventional therapy.

For Type II diabetics:

A. Poor glycemic control despite large doses of insulin-severe insulin resistance;

B. Severe painful peripheral polyneuropathy unresponsive to conventional therapy;

C. Overt diabetic nephropathy and/or proliferative diabetic retinopathy;

D. Diabetic foot ulcers, unresponsive to conventional therapy;

E. Severe cardiac disease, such as CAD or cardiomyopathy, unresponsive to conventional treatment.

All respondents were evaluated and determined to meet the admission criteria for eligibility for hepatic activation, following referrals to ADRI from their endocrinologists or treating specialists. All respondents began receiving hepatic activation between 1988 and 1993, except (Name Withheld) and (Name Withheld) who began in 1996, and all respondents except (Name Withheld) continue to receive it to date. All respondents first receiving hepatic activation started with an overnight hospital admission required, permitting two consecutive days of activation treatments, followed by weekly treatments in an outpatient clinical setting. More recently, the hospital admission is no longer necessary, and all treatments are provided in an outpatient clinical setting.

All hepatic activation treatments received by all respondents occurred at Dr. Aoki's ADRI clinic within UCDUMC through November 1995, at which time Dr. Aoki moved ADRJ out of its physical location within UCDUMC to his own clinic location. ADRI still continued to be closely affiliated with UCDUMC however, even though not located on the premises of UC. All respondents except the deceased (Name Withheld) continue to receive hepatic activation at the relocated ADRI to date.

RESPONDENTS' HEALTH CONDITIONS AND RESULTS

All respondents have experienced improved health outcomes as a result of receiving hepatic activation. Those improved health outcomes range from significant to extraordinary. 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. (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. 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.

Each respondent entered hepatic activation with not only significant development of secondary complications of diabetes but were experiencing poor energy, poor general health and a lack of feeling of well being, despite very careful treatment.

(Name Withheld) had become hypoglycemically unaware and all but housebound because she could not detect low blood sugar incidents coming on and timely respond. She was spilling protein into her urine, and had a very high creatinine clearance, both indicators of developed kidney disease. Her hemoglobin Alc count was very high, over 14. Dr. Soldener testified persuasively hemoglobin Ale is a good measure of blood glucose control, with a measure of 6-7 desirable. She had painful tingling, burning and loss of sensation in her feet and hands, blurry vision and a general feeling of poor health

and a lack of energy. Her progress was followed by Dr. Cushard, who referred her for hepatic activation in 1992, and followed her progress after she began receiving treatment.

(Name Withheld) testified and Dr. Cushard's examination of (Name Withheld) confirmed in August 1999, that after receiving hepatic activation continuously since 1992, (Name Withheld)'s vision impairment was stable and had not further deteriorated, her hemoglobin A1lc was 6.2, well within the desired control level, there was no evidence of any significant protein in her urine and her creatinine clearance was within normal limits. She felt well, had good energy and was able to continue with a productive life. Dr. Cushard expressed his opinion that based upon his evaluation of (Name Withheld) before and after receiving hepatic activation that she was experiencing excellent health outcomes, with the difference attributable to the hepatic activation therapy.

Dr. (Name Redacted), a research scientist, was initially a skeptic. He familiarized himself with the available scientific literature, including most of the scientific materials in evidence in this matter and furnished to the evaluators retained by Blue Shield, Blue Cross and CalPERS. He discussed the therapy with Dr. Aoki and Dr. Grecu at ADRI and studied the procedure and followed it for a year or two before discussing a referral with his treating physician. A significant motivation for Dr. Wright was that he too was developing many of the same complications experienced by the other respondents, including protein in his urine, poor creatinine clearance, fairly significant vision impairment including wooly spots in his vision, poor energy, lower extremity numbness, burning and loss of sensation and a growing impairment in his ability to employment as the State Cancer Registry, where he serves as its head. Dr. (Name Redacted) testified he was "persuaded" after his own research and discussions, that hepatic activation was "scientifically sound, and had strong biological plausibility." He began in December 1992.

Dr. (Name Redacted) has experienced a profound improvement in his vision, with nearly complete resolution of the impairment, good protein in urine and creatinine clearance results, the neuropathy in his lower extremities has stabilized and is not now troublesome, with good feeling in his feet and toes, and a marked improvement in his general health, energy and well being. He has not regained some lost reflexes, but this has not proved to be much of a limitation. He is able to continue to work full time. There was no change in his treatment regimen except the addition of hepatic activation.

Dr. Tortosa referred (Name Withheld) in 1996 following years of careful conventional intensive insulin therapy that had not prevented the development of significant secondary complications. (Name Withheld) has experienced significant bouts with hypoglycemic unawareness, some of which resulted in "life threatening episode and one of which resulted in an unconscious emergency room admission. (Name Withheld)'s glycemic awareness had dropped to the point where she was unable to detect blood glucose readings as low as 30 mg/dl, which is dangerously low and at great risk to lapse unaware into unconsciousness. (Name Withheld) was at risk of losing her job with CalTrans for involuntary disability due to the unawareness episodes. She had developed significant kidney disease, with declining creatinine clearance and protein in her urine, and her blood glucose control was poor, with her hemoglobin A1c in the 9.7 to 9.8 range consistently. Dr. Tortosa was familiar with hepatic activation and urged Ms to give it a try. (Name Withheld) agreed and commenced hepatic activation when approved.

By 1998, (Name Withheld)'s hypoglycemic unawareness had become controlled and she was no longer at risk of losing her job. Her urine showed very little protein and her creatinine clearance had markedly improved. (Name Withheld) hemoglobin A1c had been corrected into the high normal range, measuring 7.2% in October 1998.

(Name Withheld) is the lone Type II diabetic in the respondents' group. Her experiences with hepatic activation provide strong support for the conclusions of Dr. Aoki, Dr. Soldener and Dr. Guthrie that as far as hepatic activation's safety, efficacy and utility is concerned, there is no appreciable difference between Type I and Type II diabetics. However, the Type II diabetic has an additional problem to contend with, that of insulin resistance, and (Name Withheld) was no exception.

(Name Withheld) was showing signs of significant end stage renal disease in 1992, when she was first referred for hepatic activation. She was spilling over 2 grams of protein into her urine and she was expecting to have to undergo dialysis or a kidney transplant in the near future. She began to experience such severe debilitating pain in her legs that she was required to stop work. She was hospitalized for 17 days. She was referred to Dr. Aoki at UCDUMC in September of 1992. Dr. Aoki placed Ms on a conventional intensive insulin tight control regimen. The conventional therapy was ineffective to control the complications, and hepatic activation was commenced in late November 1992.

By January 1993, following consistent hepatic activation, the progression of (Name Withheld) kidney disease had been arrested and her protein and creatinine clearances had markedly improved. For example, (Name Withheld) protein in her urine was over 2200 mg/dl in a 24-hour period in 1992, and had been reduced to about 300 mg/dl in January 1993. (Name Withheld) had more energy, her leg pain markedly subsided and she was able to return to work. She was also able to once more help in her home activities, including being able to actively care for her then three year old. Dr. Benbarka examined (Name Withheld) in September 1998, and confirmed that continuation of consistent hepatic activation had permitted (Name Withheld) to hold and actually modestly improve on her gains. Her protein test showed 225 mg/dl in September 1998, still over the normal range of 50-80, but profoundly improved from where she started.

(Name Withheld) is quite fearful of losing her ability to continue with hepatic activation. She notes in her October 7, 1999 letter, "Insurers must be aware that the exorbitant costs of dialysis, kidney transplant, lifetime antirejection drugs, etc., far exceed the weekly costs of treatment at Aoki Diabetes Center." She notes in the conclusion to her July 9, 1999 letter, "In summary, CIIIT has proven to be safe and effective for me as well as many other diabetic patients. I am most fearful that, without this treatment, my serious complications will return, and the quality of my life will be severely compromised. I will reiterate that I undertook CIIIT because of disease progression; I did not start this therapy for the purpose of glycemic control."

(Name Withheld) was referred to Dr. Benbarka at UCDUMC Department of Endocrinology in August 1996 for management of her diabetes therapy.

Conventional therapy had been adjusted and readjusted, but secondary complications of diabetes had continued to develop, including serious bouts with hypoglycemic unawareness serious enough to interfere with her daily work as the mathematics

coordinator at the Learning Center at California State University, Sacramento, and threatening enough to interfere with her personal life activities. (Name Withheld) also had manifestations of kidney and eye disease, and both autonomic and peripheral neuropathy. Autonomic neuropathy is particularly dangerous because the deadening of sensation and nerve action is in the organs that cannot be controlled by voluntary actions. One such complication is gastroparesis, the failure of the stomach to react to the presence of food and move it along in digestion. Mr. — had poor glycemic control, manifesting hemoglobin A1c readings as high as 12.5%. She was experiencing persistent hypertension, a common complication of long term insulin dependent diabetes. Her general health condition and energy level were poor. Dr. Benbarka pursued conventional intensive insulin therapy with Ms with "tight control" frequent monitoring and physiological controls, to no avai1. The complications persisted and seemed to be worsening. Dr. Benbarka referred (Name Withheld) to ADRI for hepatic activation, which (Name Withheld) was approved for and commenced in October 1996.

(Name Withheld) found hepatic activation time consuming and unpleasant at first and nearly abandoned the therapy. She was encouraged to continue by Mr. Bradley, the LVN who ran the clinic at the time and administered much of the treatment. (Name Withheld) decided to continue, and experienced profoundly positive results by March 1997, when Dr. Klonoff evaluated her for progress, and found her "helped greatly" by hepatic activation. By September 1998, after being on hepatic activation continuously since October 1996, Dr. Benbarka evaluated (Name Withheld) for progress and determined the impact of the receipt of hepatic activation upon her diabetes treatment had been very positive. Dr. Benbarka found (Name Withheld) blood glucose control had markedly stabilized, as evidenced by her hemoglobA1c improvement to 7.5%. There was a marked decrease in frequency and severity hypoglycemic events and "she regained her ability to recognize hypoglycemia." Her neuropathy and retinopathy stabilized, and her past need for laser eye surgery was put on hold. Her blood pressure stabilized without the need for antihypertensive medications. She experienced a significant improvement in general health, feeling of well being and energy, and was able to continue her work as CSUS with "vigor".

(Name Withheld) started hepatic activation the earliest of the respondents and has been receiving hepatic activation for the longest continuous period of all. (Name Withheld) as under the care of Dr. Wreden with the Sutter Medical Group for conventional insulin therapy. She had developed serious hypoglycemia unawareness, protein spilling into her urine and an elevated creatinine clearance indicative of renal disease and failure, and vision problems and problems with loss of sensation in her extremities. Conventional insulin therapy was ineffective to slow the progression of these complications. She was referred to Dr. Aoki at UCDUMC for consideration for hepatic activation.

(Name Withheld) started hepatic activation with Dr. Aoki at UCDUMC in February 1988. She continues to date. Dr. Wreden continued to follow her progress. Dr. Wreden noted in her letter of June 7, 1999 that "hepatic activation had restored her physical sensation of hypoglycemia… and has also reduced her frequent swings in blood sugar value, and this has led to improved eyesight as well." Dr. Wreden also noted that as a result of receiving weekly hepatic activation treatments, (Name Withheld) has experienced minimal neuropathy, has had almost no protein in her urine, has been able to

achieve and maintain a normal creatinine clearance, and has had minimal vision problems, and none requiring treatment. Dr. Wreden concluded by stating, "…I feel that continued activation treatments are likely to minimize or delay further complications of diabetes which, in the long run, are very costly."

SAFETY AND SIDE EFFECTS

There was no evidence anywhere in this record of a single adverse side effect or meaningful incident of threat to the health, safety or welfare of any of the respondents, or any known subject who has received hepatic activation. Mr. experienced a couple of incidents of nausea from too much glucose supplement once or twice, and (Name Withheld) was uncomfortable with the procedure at first. Hypoglycemia is the only known side effect, and that is closely monitored and counteracted quickly when detected. This side effect is common with subcutaneous or pump delivered self-administration in the conventional intensive insulin treatment regimen. There are no reported actual health incidents regarding hepatic activation, and the record reflects that there have been more than 45,000 documented treatments of hepatic activation in the six clinics in the US that offer the treatment Nor were there any documented health or safety incidents in all of the clinical trials, investigations, research and other published materials in the record. Hepatic activation is entirely safe and is effective for the purposes for which it is offered. Hepatic activation appears to be particularly effective in arresting, and actually reversing diabetic nephropathy and hypoglycemic unawareness, as strongly evidenced by the findings of the Dailey, Boden study and confirmed by the clinical results documented and achieved by the respondents.

Dr. Axelrod speculated that hepatic activation could create a health risk to patients by causing a liver inflammation called NASH. He pointed to (Name Withheld) records and commented that there were two unusual liver function test results indicative of NASH, and that could have been caused by hepatic activation. (Name Withheld) has abnormal liver functions test results were produced by mega-doses of niacin. There is no documented occurrence of NASH in more than 45,000 administrations of hepatic activation. The concern that NASH is a potential health risk for patients as a side effect of hepatic activation has no evidence to support it.

All respondents continue to receive hepatic activation, despite Blue Shield and CalPERS decision to deny continued coverage after July 1998. ADRI has refused to cut off the treatment to the respondents. ADRI and Dr. Aoki consider continuation of hepatic activation for the respondents essential to their health, welfare well being and safety, particularly for those respondents who have struggled with serious hypoglycemic unawareness. ADRI has determined to continue to furnish hepatic activation to respondents regardless of the behavior of the insurers.

THE HEALTH INSURANCE CONTRACTS

CalPERS is authorized by statute to create and offer health insurance plans to members of Ca1PERS, including State employees and members by virtue of contract between CalPERS and their employers. Included in this authorization is the authority for Ca1PERS to create, offer and administer its own self-funded health insurance plans, as well as contract with third party providers of health insurance coverage and health

maintenance organizations ("HMOs") for the benefit of members. At all times relevant to this Decision, CalPERS had authorized, created and operated two self-funded health insurance plans, PERS Choice and PERS Care, both of which are preferred provider organizations (hereafter "PPOs"). CalPERS also offered other health plans to its membership during this period, including Kaiser Permanente, and HMOs such as Health Net and Health Plan of the Redwoods.

All respondents were at all times relevant to this Decision, active or retired members of Ca1PERS, or an eligible dependent of a member. All respondents, as members or dependents of CalPERS members, were eligible subscribers to CalPERS health insurance plans.

EVIDENCES OF COVERAGE

The Evidence of Coverage Booklets (hereafter "EOCs") set forth the terms, conditions, limitations and exclusions of the health care insurance contract between CalPERS and the PPO subscriber member. The EOC's for both PERS Care and PERS Choice PPO's, for each of the years relevant to this Decision, were so similar that the parties stipulated that reference to any particular EOC provision relevant 'to this action would be the same, regardless of plan or plan year. The Introduction to the EOC's advises subscribers, "As a Preferred Provider Organization (PPO) plan, PERS Care allows you to manage your own health care through selection of physicians, hospitals and other specialists." The EOC's designated that there were certain procedures and therapies, such as non-emergency in-patient hospitalization and certain surgical procedures that are requiring preapproval by Blue Shield, the third party administrator, before the procedure or therapy would be reimbursed by the CalPERS PPO plans.

It was not disputed that outpatient or inpatient "Physician Services", in office, in hospital and in home, were covered services not requiring prior authorization in any of the EOC's, subject to deductibles applicable to the type of Plan selected. (Page 22, EOC) "Diagnostic, X-ray and Laboratory Services" were also covered without prior authorization. Outpatient prescription pharmaceuticals, with insulin and glucose testing strips specifically named, are covered benefits not requiring prior authorization. Durable medical equipment, such as an insulin pump for rental or purchase, is also covered without prior authorization, subject to deductible (Page 23, EOC). There was no dispute tlfat all equipment, supplies and pharmaceuticals required for subcutaneous self-injection of insulin, or the use of an insulin pump, were covered benefits at all times not requiring prior authorization. Although not specifically named as a covered procedure, it was not disputed that intravenous administration of insulin in a hospital or clinical setting, where deemed medically appropriate by a physician, is a covered procedure by both PPO's at all times relevant to this decision, subject to prior authorization if in an in-patient setting. "Home Infusion Therapy", which includes "intravenously administered pharmaceuticals and medical supplies", are covered when prescribed by a physician, to be administered by self or a nurse, subject to prior authorization.

None of the EOC's specifically name or exclude hepatic activation, under that or its other names, Chronic Intermittent Insulin Infusion Therapy ("CIIIT") of Pulsatile Intravenous Insulin Infusion Therapy ("PIVIT").

Blue Shield of California ("Blue Shield") served as third party administrator for the approval, processing and payment of all health care insurance claims for Ca1PERS' self-funded PPO through a contract that was in place before any respondent received hepatic activation, through December 31, 1998. Blue Shield was replaced as Third Party Administrator by Ca1PERS effective January 1, 1999. There was some overlap of administrative function well into 1999. Blue Cross continues as contract Third Party Administrator for both CalPERS PPO's to date. Through 1999, Blue Shield made determinations on behalf of CalPERS regarding preauthorizations for certain designated treatments, therapies, physician procedures and non-emergency hospitalizations.

PROVIDER AGREEMENT BETWEEN ADRI AND BLUE SHIELD

Blue Shield entered into a Physician Provider Agreement with ADPJ on October 29, 1990. The agreement continued in full force and effect during all times relevant to this Decision. The primary business of ADRI was, at all times relevant to this Decision, the administration of hepatic activation to selected patients, and associated treatment and work required by its business of offering hepatic activation. ADRI sometimes provided respondents conventional intensive insulin therapy as well.

COPAYMENTS AND DEDUCTIBLES

All respondents were fully covered by PERS PPO plans or HMO plans at the time hepatic activation was commenced, and all claims for all hepatic activation treatments were consistently processed and paid for by PERS' third party contract administrator, Blue Shield of California through July 1998. Both CalPERS PPO plans require co-payments by the patient for covered services and therapies, with a larger co-payment for PERS Care than PERS Choice. Each respondent made considerable deductible payments or co-payments for hepatic activation treatments received that were covered by their CalPERS health insurance and processed and paid by Blue Shield. These co-payments or deductible payments were in addition to the costs of coverage to participate in the Ca1PERS health care plans selected by respondents deducted from their salaries or wages, or paid directly. In Mr. Wright's case, that co-payment appeared to average approximately $200-250 per month, in addition to any additional cost he was required to pay in payroll deduction to participate in the PERS PPO he chose. The size of the deductible or co-payment varied with the plan. The CalPERS PPO plans have much higher co-payments than the Ca1PERS contracted HMOs, generally 10-20% of the covered service or therapy in the case of PERS Care and PERS Choice, as opposed to $5 -$25 for HMO co-payments in plans such as Health Net. However, the PPO plans generally offer the member a much wider latitude in choice of physicians and wider range of covered treatments and therapies than do the HMO's, in exchange for the higher member share of cost.

BLUE SHIELD-CalPERS KNOWLEDGE OF HEPATIC ACTIVATION BEFORE JULY 1998

CONTACTS AND PREAUTHORIZATIONS

Some personnel at Blue Shield knew that Blue Shield was paying for hepatic activation as a covered PPO benefit for some or all of the respondents well before July 1998. The

contention Blue Shield did not ever knowingly pay for hepatic activation before that date is not accurate. There was little proof one way or another whether anyone in.Ca1PERS' self-funded health plans unit was aware of hepatic activation before July 1998. But Blue Shield was making the coverage and claims processing decisions for Ca1PERS throughout this period as Ca1PERS' third party administrator, and because of prior authorizations required for the then in-patient commencement of the therapy, and a utilization review of (Name Withheld) entire treatment protocol in 1995, at least some people at Blue Shield, necessary inference, must have known about hepatic activation and were aware that it was being covered.

There were several significant contacts between ADRI and Blue Shield regarding payment for hepatic activation for respondents between the time hepatic activation was started for respondents and Blue Shield's action in July 1998 to deny further coverage. The first contact was the execution of the Physician Provider Agreement in October 1990 between ADRI and Blue Shield. ADRI's primary function and reason for existing was to furnish hepatic activation and related services, almost always upon referral from other physicians. ADRI did furnish conventional intensive insulin physiological control treatment and therapy as well, but that was a distinctly small portion of their activity. It is improbable that the person or persons acting for Blue Shield in entering into the Physician Provider Agreement with ADR1 were not aware of the treatments and therapies, including hepatic activation, that ADRI was offering as a covered benefit in Blue Shield administered health insurances.

In 1988, when (Name Withheld), the first respondent to receive hepatic activation was being proposed to receive hepatic activation, and again in late 1992, when (Name Withheld) was being evaluated for suitability to start treatment, ADRI personnel contacted Blue Shield representatives and inquired whether preauthorization would be required before hepatic activation could commence as a covered and reimbursable treatment under (Name Withheld) and (Name Withheld) health insurance plans. (Name Withheld), (Name Withheld), and Dr. Aoki all assumed preauthorization would be required both because the hepatic activation commencement required a hospital admission and overnight stay, and the weekly hepatic activation treatments afterwards would probably be considered elective procedures. (Name Withheld) commenced hepatic activation in late 1988, and (Name Withheld) began hepatic activation in December 1992. Both have received it continuously to date. By necessary implication, Blue Shield must have approved and issued any required preauthorizations to commence the therapy with the in-patient initial activations. Blue Shield continued to process and pay all claims for reimbursement for all outpatient hepatic activation received by (Name Withheld) and (Name Withheld) at UCDUMC and ADRI from 1988 and 1992 to July 1998.

When ADRI moved its clinic out of UCDUMC in 1995, another call was made by ADRI personnel to Blue Shield to inquire whether prior authorization would be required before hepatic activation could be continued as a covered and reimbursable treatment under (Name Withheld)'s health insurance plan. (Name Withheld) credibly testified that in his telephone conversation with a Blue Shield representative whose name he could not recall, the representative referred to the Physician Provider Agreement and advised (Name Withheld) at ADRI that preauthorization would not be required.

HEALTHMARC 1995-96 UTILIZATION REVIEW

Healthmarc-United Healthcare served as a contract utilization reviewer for Ca1PERS and Blue Shield for its self-funded health plans in at least 1995. Healthmarc advised (Name Withheld) in writing that it was reviewing her utilization of covered health care services in November 1995 for Ca1PERS and Blue Shield, and would report back to them its findings. Specifically, Healthmarc advised (Name Withheld) that it was looking into her utilization of "three or more physician visits in any month", and "three or more outpatient therapy or treatment visits in any month". There were two contact letters from Healthmarc-United Healthcare advising of the utilization reviews4, both of which advised (Name Withheld) that the review was taking place for PERS Care. The United Healthcare letter of November 3, 1995 advised (Name Withheld) that Healthmarc did not make coverage or benefit decisions, that this was Blue Shield's job, and that Healthmarc would send its utilization review findings to PERS Care and presumably Blue Shield as well. United Healthcare additionally advised (Name Withheld) - ii the letter, "When a person's outpatient claims reach a certain level, Healthmarc has been requested by PERS Care to review the services for medical necessity and efficiency. (Name Withheld) was also advised that she should contact a Healthmarc representative to discuss her care. (Name Withheld) did so.

It was not disputed that the utilization review of (Name Withheld) care was completed. The findings were not in evidence, but (Name Withheld) once had a copy that has since been lost. It is inconceivable that the review did not identify hepatic activation as the outpatient therapy (Name Withheld) was attending three times per month or more, and that an analysis of cost, metca1 necessity and efficiency did not take place, just as the letters advised, with the results communicated to PER Care and Blue Shield. Someone at PERS Care and Blue Shield each read those results and, if not already, were familiarized with hepatic activation.

No action to limit or terminate (Name Withheld) receipt of hepatic activation resulted from the completion of the utilization review of her care by Healthmarc. It can only be assumed that as a result, at least in late 1995 and early 1996, Healthmarc confirmed to PERS Care and Blue Shield that hepatic activation was both "medically necessary and efficient" for her.

Similar preauthorization confirmations for in-patient commencement of hepatic activation must have been requested of and made by Blue Shield before hepatic activation commenced for (Name Withheld) and (Name Withheld) even though there was no direct evidence of these contacts. (Name Withheld) and (Name Withheld) started hepatic activation later, and it was not clear whether an in-patient session was still required when she started. There is evidence of other contacts between ADRI personnel and Blue Shield personnel in 1994 and 1995, regarding other patients beginning hepatic activation, other than respondents, in which ADRI personnel were consistently advised that preauthorization was not required for outpatient therapy involving intravenous insulin and coverage was confirmed for covered patients not part of the group of respondents.

Officials at PERS' Self-Funded Health Plans unit received a phone call from (Name Withheld) in the middle of 1998. Open enrollment for her health plan coverage, was in effect, and she had heard Blue Cross was to become the new third party administrator of

PERS self-funded PPO plans. She was concerned about seamless continuation of coverage for her hepatic activation with the switch in third party administrators, and inquired whether other PERS offered plans or HMO's covered the therapy, in case she might need to switch plans during open enrollment. It is a call she deeply regrets making.

CalPERS Self-Funded Health Care Plans unit had some personnel changes in late 1997, and the persons in charge of the unit were not familiar with hepatic activation and commenced an inquiry regarding the therapy. The inquiry was directed to Blue Shield about the therapy and questions were asked regarding under what circumstances Blue Shield had covered hepatic activation as a benefit under PERS self-funded health plans. Blue Shield's Medical Director reviewed the issue, and sought an "outside" review from Dr. Chan, an internist practicing in the San Francisco Bay Area. Information regarding the scientific basis of hepatic activation, and copies of studies and research supporting it were sought and received from ADRI and Dr. Aoki as well. Blue Shield responded to the CalPERS inquiries by deciding hepatic activation was still experimental and investigational and did not meet the medical necessity requirement for coverage under the PPO EOC's, was not demonstrably more effective than conventional intensive insulin therapy, and announced that further coverage for hepatic activation for respondents would be barred under the PPO plans.

CalPERS officials Ms. Dittmer and Mr. Cobb credibly testified they did not know what hepatic activation was when they first heard of it. Clearly they never knowingly approved coverage for a therapy unfamiliar to them. It was apparent from this testimony that someone in Ca1PERS' Self-Funded Health Plans Unit had heard of hepatic activation and was at least distantly aware that Blue Shield was covering it in the past on behalf of the PPOs. It was apparent that most, if not all the Ca1PERS and Blue Shield personnel involved did not fully understand and appreciate the difference between the pulsatile intravenous insulin therapy of hepatic activation and traditional intravenous insulin therapy administered in an outpatient setting. Early contacts between ADRI and Blue Shield personnel regarding the commencement of hepatic activation reveal that someone at Blue Shield generally understood that ADRI and Dr. Aoki were doing something different with their treatment of diabetes complications, but there is little evidence in these contacts one way or another that the Blue Shield personnel actually understood there was a difference between hepatic activation and traditional intravenous insulin administration. The notations of contacts between ADRI and Blue Shield for patients other than respondents receiving hepatic activation6 infer the possibility for this misunderstanding. Whether the differences were understood and appreciated was not much of an issue until the substantial differences in costs between the two therapies, exacerbated by the on-going nature of hepatic activation versus the usual method of administration of traditional intravenous insulin therapy were realized and clearly grasped. This occurred as a result of the inquiry within CalPERS Self-Funded Health Plan unit after (Name Withheld) fateful phone call. However, such an inquiry was probably inevitable, phonll or not, due to the on-going costs issues and a growing number of Ca1PERS PPO plan members who could potentially seek the therapy.

THE BILLING CODES

Ms. Nelson, on behalf of Blue Shield, blamed Blue Shield's alleged lack of knowledge of the fact that it was paying for hepatic activation all along on their computer billing

approval system. She alleged the Blue Shield approval and payment system is set up so that if procedures are billed using codes for services not requiring preapproval, the services are automatically paid, without human involvement. She neglected to acknowledge the several ADRI contacts with Blue Shield to discuss this very issue and the consistent response of Blue Shield personnel that no preapproval was required. If this advice was the result of Blue Shield misunderstanding what ADRI was doing differently than traditional intravenous insulin infusion, that is a different matter than alleging, as she did, that the ADRI billing and misuse of billing codes constituted some sort of fraudulent or deceptive practice. (Name Withheld) Nelson's testimony was disingenuous, lacking in credibility, and was soundly rebutted by other extrinsic evidence. Ms. Nelson herself may not have known about hepatic activation, but others at Blue Shield apparently did and approved coverage and payment for the therapy, particularly when it was commenced for respondents with inpatient hospitalization for activation, which required specific advance preapprovals. It appears neither likely nor even possible that these approvals could have been made without some grasp of what hepatic activation involved, and how it differed from traditional intravenous insulin therapy. Further, the Healthmarc 1995-96 utilization review of (Name Withheld)'s care could not have failed to address hepatic activation, particularly its urgency and cost, as issues in inquiring whether her care was medically necessary and efficient.

The allegation that ADRI and Dr. Aoki deceived or attempted to conceal the true nature of the therapy ADRI and Dr. Aoki were performing, in order to insure coverage and get reimbursed from the health insurers of those receiving hepatic activation, completely lacked merit and had no credible evidentiary support. Blue Shield's payment for the hepatic activation treatments for respondents for years each was, not the product of deception, and was not a reflection of an unknowing decision in favor of coverage by Blue Shield. Blue Shield now seeks to avoid a contention that the exclusions it seeks to enforce should have been known and raised years ago, are not now timely raised and are, after all this time, waived. Blue Shield accused ADRI and Dr. Aoki of deceptive billing practices to deflect the question of why coverage had been provided all these years if the therapy should be excluded, by claiming the billing codes commonly used in the medical industry for billing health insurers were used in a deceptive manner.

ADRI BILLING PRACTICES FOR HEPATIC ACTIVATION

ADRI 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. It was not disputed that there was no code for the bundled services that compose hepatic activation at the time of these billings. It was also not disputed that each and every billed service, once unbundled was unfailingly actually delivered to respondents as part of the administration of hepatic activation. It was additionally undisputed that unbundling and billing separately for compound services sometimes bundled, even where there is a specific code for the bundled service, is a common practice in the world of medicine and health insurance billing, and that there is nothing inherently unethical about the practice.

There was no proof that ADRI's billings for respondents' receipt of hepatic activation was deceptive, concealed any material fact or was adopted to prevent Blue Shield from knowing the true facts about the therapy ADRI was delivering to respondents. Hepatic activation was, is and will continue to be intravenous insulin infusion, uses physician services, insulin, saline and glucose and testing materials, and a pump for infusion. Perhaps the health insurance industry will adopt a specific code for hepatic activation in the future, but that would not prevent the billing agency from unbundling even that specific code and ethically seeking payment for its individual components.

NOTICES THAT COVERAGE TERMINATED AND APPEALS

Blue Shield formally notified respondents that it would no longer pay for hepatic activation effective in July 1998. Blue Shield advised respondents it was refusing to continue to pay for hepatic activation because it had determined the therapy was experimental and investigational and not medically necessary for respondents. It was not disputed that the EOC's exclude from coverage any treatment or therapy that is "experimental or investigational". It was also not disputed that any covered service or therapy must be "medically necessary" for the subscriber member in order to be covered.

The EOC's set forth procedures for subscriber members to dispute adverse coverage determinations made by the plan administrator. The first level of review is internal to Blue Shield. There are two levels of appeal within Blue Shield, administrative review and an "equity" or final review. Dissatisfied subscriber members can appeal an adverse Blue Shield internal review to CalPERS staff, where the opportunity to furnish additional information in support of the members' claims is provided. An adverse determination following Ca1PERS' internal review may be appealed to the CalPERS Board, where the right to an evidentiary hearing in accordance with the Administrative Procedure Act ("APA") exists. All respondents appealed the adverse coverage determinations made by Blue Shield in accordance with all procedures set forth in the EOC's. The adverse coverage determinations were upheld by Ca1PERS' internal review process, and all respondents appealed those decisions to the Board. Fred Steinmetz, Chief, Self-Funded Programs, Board of Administration of Ca1PERS, made the charges and allegations contained in the Statements of Issues in his official capacity, and not otherwise, and caused the Statements of Issues to be filed on December 1, 2000. Each respondent was named in an individual Statement of Issues, and those six Statements of Issues were consolidated for evidentiary hearing before the Administrative Law Judge on the parallel allegations made in each. There is no dispute that the consolidated appeals are properly within the jurisdiction and appropriately before this tribunal for evidentiary hearing and Decision.

BLUE SHIELD AND MCOP REVIEW

Dr. Cederberg testified by declaration. He has been the Medical Director of Blue Shield of California since November 1997. Dr. Cederberg was responsible for reviewing claims submitted for hepatic activation for respondents before Blue Shield was replaced by CalPERS as Third Party Administrator on December 31, 1998. Dr. Cederberg testified that Blue Shield did not knowingly pay claims for hepatic activation on behalf of respondents because ADRI and UCDMC before them submitted claims for hepatic activation using billing codes for unlisted procedures or codes for "intravenous

therapeutic or diagnostic injection", but he had no personal knowledge or information to support his claim, and it has no merit. He also conducted an investigation into the medical necessity and safety of hepatic activation when asked to do so in early 1998. He detailed his efforts to have ADRI submit evidence of medical necessity, safety and efficacy of hepatic activation to him for review.

Dr. Cederberg was dissatisfied with the ADRI information submitted, and sent the matter for review to Dr. Chan, a private practitioner in internal medicine that Blue Shied uses for consultations from time to time. Dr. Chan wrote Dr. Cederberg a letter on November 4, 1998, in which he opined that hepatic activation "is an interesting theory", but he "remains skeptical that this technique actually increases hepatic glucokinase and phosphofructokinase". Dr. Chan continued, "Remember that under his technique, patients are very closely monitored for their sugars and are carefully covered with multiple injections. This could explain his results." Dr. Chan suggested an additional controlled study could be useful, where patients could get infusions of glucose and insulin in pulse form and controls get saline. It was evident that Dr. Chan knew little or nothing about hepatic activation until retained to opine about it. His opinion is largely speculative and lacks much in the way of a persuasive foundation. Dr. Cederberg's declaration, drafted by the Deputies Attorney General, avers that Dr. Chan's opinion is that hepatic activation being provided by ADRI was outside the medical profession's generally accepted professional standards for the treatment for diabetes, and that it is not proved superior to other traditional forms of diabetes therapies. Dr. Chan's letter to Dr. Cederberg in evidence does not make those statements.

Dr. Cederberg sent the issue to the Medical Care Management Corporation's Medical Care Ombudsman Program (hereafter "MCOP") for further review and evaluation. MCOP was presented throughout these proceedings as an "independent group that contracts with medical experts to act as an ombudsman for the review of medical claims" Much was made of the neutrality, independence and confidentiality of evaluations made by experts retained by MCOP for the performance of "independent evaluations" of key medical issues in Dr. Axelrod's testimony. The evidence reveals this neutral and independent sounding title and statement of purpose, and efforts to maintain a panel of disinterested and confidential experts selected for their particular expertise in fields in controversy, was a charade. MCOP's primary purpose appeared to be to lend credibility, expertise and authority to cost containment decisions made by health insurers or their administrators in disputed cases outside the structure of the insurers and their administrators. Regardless of its separate existence, it exists by and for the health insurance industry, and its funding is from the industry and its administrators. To the extent the evidence revealed it, MCOP's structure and the manner in which it contracts with specialists in the matter of inquiry, and the confidentiality of the opinions it produces are all designed to make MCOP evaluations significantly more credible than in-house evaluations by staff physicians and experts employed by the insurers or their administrators. But MCOP is not independent and neutral, as the lay person would define those terms. The experts retained by MCOP do not work for MCOP, but it takes little imagination to figure out where the evaluations solicited by MCOP come from, and what interest the industry has in the outcome issue being presented, particularly if the disputed treatment or therapy is expensive. To call the evaluations from MCOP conservative would be charitable understatement.

Dr. Cederberg did not actually opine in his declaration that he thought hepatic activation is experimental or scientific, or is not medically necessary, safe or effective. He deferred to Dr. Chan's opinions and to the MCOP review. Dr. Cederberg approved the continuation of hepatic activation for two patients, not respondents, after reviewing their cases and histories, after the termination actions the subject of this case. He determined it would be detrimental to those patients' health and welfare to discontinue hepatic activation for them. This was a praiseworthy and ethical decision, in light of the obvious pressure upon him to disapprove of the treatment: Other than respondents, Blue Shield's policy that hepatic activation is experimental and investigational and not medically necessary appears to give way when the facts and circumstances of individual cases are evaluated carefully and compassionately.

"EXPERIMENTAL AND INVESTIGATIONAL"

The EOC's exclude from coverage any treatment or therapy that is "experimental or investigational". Those terms are defined in the EOC's as follows:

"Experimental or Investigational-any treatment, therapy, procedure, drug or drug usage, facility or facility usage, equipment or equipment usage, device or device usage, or supplies which are not recognized in accordance with generally accepted professional medical standards as being safe and effective for use in the treatment of an illness, injury, or condition at issue. Services which require approval by the federal government or any agency thereof, or by any state governmental agency, prior to use, and where such approval has not been granted at the time the services were rendered shall be considered experimental or investigational. Services which themselves are not approved or recognized as being in accord with accepted professional medical standards, but nevertheless are authorized by law or a governmental agency for use in testing, trials or other studies on human patients, shall be considered experimental or investigational. Any issue as to whether a protocol, procedure, practice, medical theory, or treatment is experimental or investigational will be resolved by Blue Shield of California, which will have full discretion to make such determination on behalf of the Plan and its participants."

The only portion to the definition of the exclusion that is open to dispute is the language "not recognized as in accordance with generally accepted professional medical standards as being safe and effective for use in the treatment of an illness, injury, or condition at issue." Government approval is not required for hepatic activation, respondents are not now nor have they ever been enrolled in a clinical trial or research study of hepatic activation. As set forth in more detail below, hepatic 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. There was significant, persuasive, credible proof of this in this record, with respect to respondents, and others as well. This Finding is not based upon a failure of proof that hepatic activation is not in accordance with generally accepted professional medical standards as safe and effective, but the quality and quantum of proof adduced in this record in support of the affirmative.

HEPATIC ACT IVATION- HOW IT WAS DISCOVERED AND DEVELOPED AND ITS SCIENTIFIC BASIS

Dr. Aoki and colleagues discovered the key to hepatic activation when Dr. Aoki was working at the Joslin Institute in the early 1970's on a research project studying the metabolic and endocrine activity of patients who were on extended fasts or had suffered the effects of starvation. Dr. Aoki noted that these patients had no food intake that could be converted to glucose, yet the patients' organs, and particularly brain metabolism, went on functioning as long at the patient had water and electrolytes. Dr. Aoki observed the critical role hepatic glucokinase production by the liver, together with associated other enzymes Such as pyruvate dehydrogenase, and hormones, played in the body's ability to survive by metabolizing fatty acids to produce energy and to stabilize and moderate blood glucose levels, even in a starving person.

Dr. Aoki and his colleague researchers hypothesized that the liver must be the target site in the body for the action of insulin when a meal is ingested as a result of these observations. As a meal is ingested, blood glucose rises quickly to a high concentration, especially when a meal high in sugars or carbohydrates is eaten. Dr. Aoki and his colleagues noted that glucokinase production in the insulin dependent diabetic is almost nil, and studied whether there was a correlation between the absence of glucokinase and other associated enzymes and hormones produced by the liver of a nondiabetic, and the absence of insulin secreted into the portal vein of a diabetic following ingestion of a meal. Dr. Aoki looked at what action was produced in the nondiabetic's liver upon ingestion of a meal, and the action of glucokinase and associated enzymes and hormones. To grossly simplify a very complex process, Dr. Aoki and others found that following ingestion of a meal, the pancreas of a nondiabetic typically secreted a pulse of very concentrated insulin into the portal vein, where it is transported by the blood stream to the liver, "bathing" the liver in a concentration of 200 to 1000 units/milliliter, which triggers the liver to synthesize and secrete hepatic glucokinase, its companion enzymes such as pyruvate dehydrogenase, and hormones. The production and release of these enzymes, among others, are critical to cellular metabolism of glucose and fatty acids as fuel, particularly in organs.

Additional study found a definite correlation between insulin's role in stimulating the liver of the nondiabetic to synthesize and release hepatic glucokinase and its associated other enzymes and hormones and the nondiabetic's ability to metabolize, process and control blood glucose surges following a meal. Dr. Aoki observed that the typical concentration of insulin "bathing" the liver in a nondiabetic was "very high" following ingestion of a meal, much higher that achieved by a diabetic's self-administration of insulin by subcutaneous or pump means just before or just after a meal. He opined that traditional subcutaneous or pump administration of insulin by a diabetic before or after a meal could not produce a high enough concentration of insulin in the diabetic's blood stream to cause much production of these key enzymes and hormones in the liver. Dr. Aoki and colleagues observed that the concentrations of insulin being delivered to the nondiabetic's liver via the portal vein were as much as 10 times the amount of insulin that is delivered in the typical subcutaneous or pump administered dose (20 to 30 units/milliliter) used by insulin diabetics in conventional therapy after a meal.

Dr. Aoki concluded that the liver of the insulin dependent diabetic does not produce hepatic glucokinase and pyruvate dehydroxase and other associated enzymes and hormones due to long periods without adequately intense concentrations of insulin to stimulate synthesis and production of these key substances. He thought there must be a way to replicate the pulsing high concentrations of insulin and cause the liver in a diabetic to react similarly to that which occurs in a nondiabetic's system.

Dr. Aoki first thought an intravenous catheter directly into the portal vein would be a solution, but rejected that due to the significant risks and complications that could develop for the diabetic. He theorized that in some fashion he could use timed pulses of intravenous insulin through a pump into a peripheral vein to 'jolt" the liver, and thus he could cause the liver to begin to produce hepatic glucokinase and associated enzymes and hormones. He sought to design a system where pulses of insulin could be delivered that are designed provoke an approximation of the biochemical and enzymatic activity triggered in the liver by the deposition of insulin from a healthy and properly functioning pancreas into the portal vein connected to the liver that would occur following ingestion of a meal. The pulses could approximate the body's own natural insulin release patterns. Both healthy persons' and diabetics' organs (meaning not insulin dependent diabetic) use fatty acids for 70-80% of their metabolic fuel, as well as glucose. However, the process of using fatty acids as an energy source for cellular metabolism in organs uses more oxygen than the breakdown of glucose for similar energy output. Thus, measurement of a change in metabolic rate, shown by an increased rate of oxidation, would show whether the pulses were working as theorized. Dr. Aoki started to design insulin pulses that he believed would increase hepatic glucokinase, pyruvate dehydrogenase and other enzymatic activity, which in turn permit organs to use an increased percentage of glucose as fuel, decreasing reliance upon fatty acid breakdown as a fuel source and thereby reducing oxygen need in the organs. The pulses would also produce a stabilization of blood glucose levels and a reduction of incidents of hyper and hypoglycemia.

THE PUBLISHED SCIENTIFIC LITERATURE – ONLY PART OF THE PICTURE

Research and clinical trials of hepatic activation was published as early as 1982, with many more following, and even recently, in November 2000. 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:

A. Aoki, Grecu, Gollapudi, Barber, Arcangeli, Benbarka, Prescott and Meisenheimer, "Effect of Intensive Insulin Therapy on Progression of Overt nephropathy inpatients with Type 1 Diabetes mellitus", published July 1999 in Endocrine Practice.8 This is a retrospective, three center longitudinal study to assess the effects of adding hepatic activation to the conventional intensive insulin therapy regimens of insulin dependent Type 1 diabetics manifesting signs of diabetic nephropathy. The results of the study were that when hepatic activation is added to the management of patients with Type 1 diabetes and manifesting overt diabetic nephropathy, the progression of diabetic nephropathy seems to be arrested or considerably slowed. In addition, the study found glycemic control was substantially improved.

B. Dr. Dailey, primary architect and author of the Dailey, Boden study detailed just below, published a critique of the findings in the same journal. He was concerned about making too much of the findings without a control group, which the study did not have, and noted that the therapy is expensive in terms of costs and time required of the patient. He proposed that more evidence of the cost effectiveness financially and in terms of time should be shown before "widespread" use of hepatic activation should be recommended. Dr. Dailey labeled the findings of the study "intriguing", and noted that, "From these and other interventional studies, inevitable progression to renal replacement is no longer the fate awaiting all patients, even those with established diabetic nephropathy." Dr. Dailey cited the other interventional studies he was referring to below his comments. As set forth below, he engineered and constructed his own multi-center study of hepatic activation, addressing and answering in the affirmative the concerns he raised in critiquing this earlier study of the same subject.

C. The Dailey, Boden study, first published preliminarily as "Weekly Pulsatile IV Insulin Treatments Appear to Slow Progression of Diabetic Nephropathy" published as an abstract in the diabetes Abstract Book in June 1995, and fully released in Metabolism, November 2000 as "Effects of Pulsatile Intravenous Insulin Therapy on the Progression of Diabetic Nephropathy". This is a level 1, multi-center, prospective, controlled study that demonstrated that when hepatic activation was added to a conventional intensive insulin therapy regimen in diabetics with developed diabetic nephropathy, significant arrest and even reversal of progression of the nephropathy was attained. The study also noted that blinding of such studies was not ethically possible with patients with advanced diabetic complications because the effects of glucose and Insulin in such patients cannot be disguised. This study was the first really significant study showing the effectiveness of hepatic activation not involving Dr. Aoki.

D. Aoki, Grecu, Prendergast, Arcangeli and Meisenheimer, "Effect of Chronic Intermittent Intravenous Insulin Therapy on Antihypertensive Medication Requirements in 1DDM Subjects with Hypertension and Nephropathy", Published in Diabetes Care in 1995. This is a level 1 prospective, randomized, cross-over clinical trial showing that hepatic activation, when added to a conventional intensive insulin regimen, improves blood pressure control, resulting in less need for blood pressure medications in Type I diabetics with hypertension. This study also pointed out the ethical problem with using placebos in trials populated with diabetics with advancing secondary complications of diabetes.

E. Aoki, Benbarka, Okimura, Arcangeli, Walter, Wilson, Truong, Barber and Kumagi, "Long-Term Intermittent Intravenous Insulin Therapy and Type 1 Diabetes Mellitus", published in The Lancet, August 1993. This study reports the results of a historical control study that demonstrates hepatic activation, added to conventional therapy, assisted in stabilizing the blood glucose levels of subjects and reduced the frequency and severity of major and minor hypoglycemic events in Type 1 diabetic patients.

F. Aoki, Grecu and Arcangeli, "Reversal of Severe Nonschemic Dilated Cardiomyopathy by Intensive Intravenous Insulin Therapy in A Patient with

N1DDM", published January 1996 in "The Journal of Investigative Medicine". This level 5 case report documented the progress achieved in ameliorating the effects of an insulin dependent diabetic patient's cardiomyopathy by using hepatic activation along with intensive insulin conventional therapy, resulting in the patient's restoration of stamina and vigor and removal from a heart transplant list.

G. Aoki, Grecu, Arcangeli and Meisenheimer, "Effect of Intensive Insulin Therapy of Abnormal Circadian Blood Pressure Pattern in Patients with Type 1 Diabetes Mellitus", published December 1995, in the "Online Journal of Clinical Trials". This is a level 3 retrospective, randomized controlled study showing that hepatic activation, when added to conventional intensive insulin therapy improves glycemic control and night/day blood pressures.

H. Aoki, Grecu, Arcangeli, "Chronic Intermittent Intravenous Therapy Corrects Orthostatic Hypotension of Diabetes", published December 1995 in the American Journal of Medicine. This level 5 series of case reports documents dramatic improvement in the patients' postural hypotension with the addition of hepatic activation to their conventional intensive insulin treatments.

I. Aoki, Viachokosta, Foss and Meistas, "Evidence for Restoration of Hepatic Glucose Processing in Type 1 Diabetes Mellitus", published April 1983, in The Journal of Clinical Investigations). This level 3 prospective study demonstrated that use of the artificial beta cell (the precursor to the pump infusion device for hepatic activation) to infuse insulin could reactivate hepatic enzymes and markedly improve glucose processing in the insulin dependent diabetic.

J. Aoki, Grecu, Arcangeli, Benbarka, Prescott and Ahn, "Chronic Intermittent Intravenous Insulin Therapy: A New Frontier in Diabetes Therapy, published in Diabetes Technology and Therapeutics, volume 5, number 1, 2001. This is a review article discussing over 77 studies, trials and other scientific references documenting the extensive clinical experience with hepatic activation and its beneficial effects when used with conventional intensive insulin therapy. "The studies briefly reviewed above indicate that CIIIT improves glycemic control, concomitantly with marked decrease in frequency of both major and minor hypoglycemic events and improved hypoglycemic awareness, improves control of hypertension in diabetes, retards progression of overt nephropathy, reverses the abnormal circadian BP pattern, and corrects postural hypotension in diabetes". Each beneficial effect listed had one or more footnote references to published scientific literature supporting the statements. "Anecdotal clinical experiences suggest that CIIIT also improves diabetic peripheral polyneuropathy, diabetic cardiomyopathy, diabetic retinopathy and diabetic foot ulcer healing." The article concludes with Dr. Aoki's comments that, "Confirmation of these latter observations requires future, larger, prospective clinical studies", and "Furthermore, though we recognize that patients' enthusiasm and enhanced compliance might be a component of any research program's good results, the published results with CIIIT on improving glycemic control, decreased frequency of hypoglycemic events, and on chronic complications of diabetes (e.g. overt nephropathy) have been superior to intensive s.c. insulin therapy (multiple insulin injections or external insulin infusion pumps."

DEFICIENCIES IN THE PUBLISHED SCIENTIFIC LITERATURE

The central support for the Blue Shield-Ca1PERS determination that hepatic activation is experimental and investigational lies in expert opinion offered that the scientific studies are deficient to prove hepatic activation is safe, effective and in accord with generally accepted professional medical standards. There are many more abstracts, paper and published materials regarding the development and use of hepatic activation than those listed above in this record. Some of the results of the studies and clinical trials were published in medical and scientific journals, and some of the results were presented in papers and delivered at symposia and meetings of endocrinologists, where direct, verbal criticism could be made. Some of the journal publications were peer-reviewed, and some were not. Most of the studies and clinical trials consisted of relatively small groups of patients, and some of the studies had a considerable number of dropouts. Some of the published trials and papers were retrospective, reporting on what had already happened in the clinical setting. Some of the studies were more chronicles of clinical observations of treatment of patients with hepatic activation and notations of their progress, rather than findings and conclusions following a prospective, carefully designed, hypothesis testing, controlled investigation. Much of the research is difficult to reproduce, particularly since the therapy requires both a group of highly motivated diabetics with both good adherence to conventional intensive insulin therapy and advanced secondary complications, and the use of a pump and treatment protocol protected by patents issued to Dr. Aoki. Much but not all the published research and clinical trials are the product of Dr. Aoki and colleagues, leading to a charge of bias.

Dr. Axelrod cited these and more deficiencies in his criticism of the paucity and inadequacy of published scientific documentation of the safety and efficacy of hepatic activation in peer reviewed scientific literature. Dr. Axelrod, the primary witness called to testify to criticize the adequacy of the studies supporting hepatic activation, found hepatic activation still experimental and investigational as a result of his opinion that the scientific literature on hepatic activation was not “adequate” clinical trials to demonstrate the safety, efficacy and reliability of hepatic activation. “Adequate” was used in Dr. Axelrod’s testimony, and in the testimony of other experts who agreed with him on this point called by CalPERS, both quantitatively as well as qualitatively. The term “adequate” was only generally defined by categorical reference, to deficiencies in publication in “reputable” scientific and medical publications, number of clinical studies, the small sizes of the study groups, the Construction of studies lacking control groups and failure to use placebos, the interests and biases of the researchers, and the ability to reproduce the results.

The criticisms are legitimate, and the process of critique of scientific presentations, studies and publications advanced in support of hepatic activation, and the scrutiny to which research studies are put plays a very important role in the proving grounds of all new therapies, treatments and medications. The process of running the gauntlet of peer reviewed publication of research results and similar critique is an integral part of the advancement of safe and effective medicine, and, as Dr. Axelrod pointed out, one of the means by which truly safe and effective medical advances are separated from hope, hype and fantasy. 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.

The criticisms of the investigational studies, papers, research projects and clinical trials designed to demonstrate the safety, efficacy and reliability of hepatic activation are not such as to render the therapy still experimental and investigational. None of the criticisms advanced demonstrated the therapy was still in the testing, experimental phase, where anyone receiving the therapy would have to be in a study and provide informed consent. Experimental and investigational therapies are not approved by Institutional Review Boards (IRB) for administration to a general patient populating in a clinical setting, and if the IRB has determined the therapy is still experimental and investigational, it cannot be offered without a filed and approved clinical trial protocol and informed consent from every participant. None of the respondents ever received hepatic activation under those circumstances. IRB approvals did occur at UCDUMC and University of Kansas, for example, without the trial and consent requirements for hepatic activation to be offered through medical centers overseen by those institutions. It is therefore illogical to conclude that these leading University Medical Centers consider hepatic activation still experimental and investigational. It is noteworthy to reflect that there were significant and meritorious criticisms leveled at the DCCT itself and the Daily, Boden study, which experts from both sides generally agreed were reliable studies worthy as references for serious clinicians. All the studies, no matter how widely heralded, have flaws and are targets for a variety of criticism, some casting shadows on the merit and reliability of the conclusions made, and some not. Explanations in response to the criticisms, and correlation to actual clinical observation are important additional factors to consider.

DCCT actually contained ammunition for both views. For Dr. Axelrod and Dr. Nuovo, it confirmed their commitment to intensive insulin therapy as the gold standard for treatment of the insulin dependent diabetic. Dr. Aoki never challenged that proposition for the young, healthy diabetic, and the DCCI was limited to such subjects. For Dr. Aoki and supporters, the DCCT reaffirmed that the overall “success” rate for intensive insulin therapy remains inconsistent to poor, that intensive insulin therapy works pretty well for young, healthy diabetics and does not really prevent the eventual development and progression, much less reverse the secondary complications of diabetes, once those complications have developed, which he believes is inevitable with therapy limited to conventional means.

Critique of the alleged deficiencies in the scientific literature is incomplete without some inquiry into any known reasons for deficiencies alleged. The inadequacies of the inability to locate and enlist enough suitable subjects, create a credible protocol that effectively isolates the desired target, and can be sustained long enough to produce a meaningful conclusion, has controls, yields a reproducible result, is objective and the person can persuade someone reputable to publish is easy to criticize from academia. A good argument could be made from the evidence that no number of studies, with a “large” population of patients, constructed in accordance with the deficiencies cited by the critics, will ever suffice. There could have been more and larger studies, but those that were done were not unreliable, were not biased to the point of destroying their credibility or persuasiveness, and did not fail to offer credible evidence that hepatic activation is a safe therapy, that it offers considerable benefit to those receiving it, and that it is worthy of a

place in the endocrinologist's repertoire of treatment options for patients like respondents who meet the criteria for consideration of the therapy. The studies, investigations, papers and clinical trials have been repeatedly confirmed in clinical findings experienced by those offering the therapy, both at the time of the conduct of the trials, and repeatedly after the therapy began to be administered to patients outside investigational and study populations.

No one disputed there could and should be more clinical trials, research and investigation into the effectiveness of hepatic activation. Dr. Aoki is on record as advocating such. There are many unanswered questions yet to be explored with the therapy, including further discovery of the exact interactions of insulin, blood glucose, enzymes and hormones that produce the results observed in the trials and, more importantly, in the clinical setting. Rather than faults preventing the transition from experimental and investigational to a safe, effective and accepted therapy, these factors identify areas where further work can and should be done.

"IN ACCORDANCE WITH GENERALLY ACCEPTED PROFESSIONAL MEDICAL STANDARDS AS BEING SAFE AND EFFECTIVE FOR USE IN THE TREATMENT OF. . . TYPE 1 AND TYPE 2 INSULIN DEPENDENT DIABETES"

One of the EOC's requirements is that the procedure or therapy must be "In accordance with generally accepted professional medical standards as being safe and effective for use in the treatment of an illness, injury or condition at issue". This test is materially different than the test of general acceptance in the scientific community, which might be applicable if insulin had never been used in any form to treat diabetes before, or outside the "standard of care", as some of the experts carelessly testified. Insulin in one form and delivery mode or another has been widely used to treat diabetes for many years. Neither general acceptance in the scientific community or within the standard of care is the standard set in the EOC's. The evidence was substantial and persuasive that hepatic activation meets the test of in accordance with generally accepted professional medical standards, now and since the late 1980's, when (Name Withheld) first started to receive the therapy. 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. It is not a "widespread" therapy, defining "widespread" as commonly used or resorted to as a therapeutic option by endocrinologists and physicians with a diabetes treatment practice in all of the United States or around the world. Within the community of practitioners where the therapy is known, such as in Northern California, the Mid-America region (Kansas, Nebraska, Iowa and Missouri, the area covered by Dr. Guthrie's practice), Colorado, Massachusetts and, in Texas, where it is actually available as a therapeutic option for the treatment of diabetes in the circumstances for which it is offered, it is generally accepted and embraced by a significant number of practitioners in those communities as safe and effective for treatment of both Type 1 and Type 2 diabetes, and is generally accepted by a significant number of practitioners as a potential therapeutic option for the treatment of secondary complications of diabetes that have proved unresponsive to conventional intensive insulin therapy and physiological control, and, in Mid-America, for children having extreme hypoglycemia problems and severe

glycemic control problems as well. There was no evidence that hepatic activation has ever been rejected anywhere, or questioned by clinicians familiar with the therapy, as lacking in safety or effectiveness in any place where clinics are equipped and the therapy can actually be offered.

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, as was evident by the research efforts required by specialist practitioners called upon by Ca1PERS and Blue Shield in this action to become familiar with, comment upon and evaluate the nature and medical necessity of hepatic activation. But well known, widely known and practiced or commonly used are not the tests. Costs, health insurer resistance, information and education, and patent and licensing issues have proved considerable impediments to a more widespread proliferation and use of hepatic activation, but have not prevented a reasonable proliferation and acceptance of the therapy in those few areas where it is offered.

Mr. Gilbert, co-counsel for (Name Withheld) correctly pointed out that much of the dispute in this matter revolved around nomenclature and definitions differences. His point was both persuasive and well supported. In many material respects, the parties used similar vocabularies but very different dictionaries. A prime example was the misuse of the term of art "standard of care" as the equivalent of the contractually correct terminology, "generally accepted as in accordance with professional medical standards". Within the standard of care is not equivalent to in accordance with generally accepted medical standards as safe and effective. The two are materially different and represent greatly different concepts. Standard of care is a term of art in assessment of medical negligence" "The courts require only that physicians and surgeons exercise in diagnosis and treatment that reasonable degree of skill, knowledge, and care ordinarily possessed and exercised by members of the medical profession under similar circumstances." "The standard of care in malpractice cases is also well known. With unimportant variations in phrasing, we have consistently held that a physician is required to possess and exercise, in both diagnosis and treatment, that reasonable degree of knowledge and skill which is ordinarily possessed and exercised by other members of his profession in similar circumstances." Analysis of whether hepatic activation is experimental or investigational or medically necessary for respondents has little or nothing to do with the standard of care. Testimony that sought to cast hepatic activation as not in accordance with the standard of care, where those terms were used as the equivalent of in accordance with generally accepted professional medical standards was therefore given little weight.

SAFETY, EFFICACY AND THE VALUE OF ACTUAL CLINCIAL EXPERIENCE

Documented clinical evidence in support of the safety and efficacy of hepatic activation in this case is considerable and spans more than 20 years, hundreds of patients and have occurred in the East, Mid-America and the West. The only known potential adverse effect 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 from concentrated administration during the active period of hepatic activation insulin therapy. The active administration of pulses of insulin in hepatic activation can cause suppression of blood glucose levels. Careful

monitoring of blood glucose levels during therapy and timely administration of the glucose supplement prevents the potential problem with hypoglycemia from occurring.

Dr. Peters' declaration cautions against drawing conclusions regarding the safety and efficacy of hepatic activation from anecdotal experiences with the therapy, and cited a study on the East Coast where such experience proved very disappointing. That study involved efforts to actually try to prevent diabetes from developing in patients thought at risk to become diabetics. The correlation between the disappointing experiences of those participating in that study and respondents or Dr. Guthrie's patients was not evident. Dr. Axelrod sneered at the value of anecdotal clinical experience, and actually confirmed on cross-examination that he would discontinue respondents' receipt of hepatic activation, regardless of how good their documented beneficial health outcomes from receipt of the therapy, because the scientific literature does not support the proposition that respondents could be attaining such good outcomes from the therapy. Commenting the respondents' positive health outcomes results are "too good to be true", Dr. Axelrod revealed his view that documented positive patient clinical outcomes demonstrating beneficial health and welfare improvements are irrelevant when all his questions and concerns have not yet been satisfactorily (to him) answered in scientific studies that meet his criteria for adequacy. This testimony from Dr. Axelrod, and the exchanges of questions and answers that accompanied it, caused considerable harm to the persuasiveness of his testimony.

Dr. Guthrie's testimony regarding his clinical experiences with hepatic activation was compelling, exceptionally credible and very persuasive, and a stark contrast with that of Dr. Axelrod. Raised in Missouri, Dr. Guthrie came to hepatic activation in the early 1990's as very skeptical, and commented that a lengthy review of the procedure, its scientific basis and study of actual clinical experience was required, not because the scientific literature supporting it was deficient, but "because I had to prove it to me." Dr. Guthrie began his own limited use of hepatic activation and cautiously used it for about two years. Now he is an ardent proponent as a valuable therapeutic option for selected patients. To disregard his clinical experiences as "anecdotal" and valueless in determining whether hepatic activation is safe and effective, medically necessary and not experimental and investigational would be absurd. Similarly for Dr. Aoki's experiences, those of Dr. Grecu, Dr. Benbarka and others, their anecdotal clinical experiences are both compelling and persuasive. As Dr. Guthrie put it, "It's not what the articles are trying to say or trying to do, the articles are trying to say here that hepatic activation is a form of therapy that works under certain situations. I don't know that any of the authors were trying to establish a standard of care or care to do so. I certainly don't care to do so. I'm looking for what constitutes good treatment for the patients that I treat that I have been unsuccessful in treating in any other manner. I don't care whether that's standard. I don't know whose standards you are going to go by."

For respondents, Dr. Guthrie's patients, those others receiving hepatic activation and receiving beneficial health outcomes, anecdotal clinical evidence that the therapy works the way it is supposed to is all that matters beyond reasonable assurances of safety. These patients care much more about whether they experience real and measurable improvements after receiving the therapy, and whether they experience any unsafe or unpleasant side effects than academic disputes over the "adequacy" of the scientific literature. Well-documented scientific literature support is important and a necessary part

of scientific and medical advancement, and the absence of any meaningful scientific literature, as that term was defined in this case, is cause for alarm and caution. But to use its adequacy or inadequacy as the exclusive gatekeeper for access to a promising therapy that has an outstanding track record of actually working when used with real patients in real clinical settings suffering from real complications, without any meaningful side effects as revealed by that clinical experience is not reasonable or balanced. Clinical experience is a very important component of this analysis, in combination with a reasonable quantum of scientific literature to validate the therapy is safe and reasonable effective. That quantum is present here, although no one argues it would not be desirable to have more. The debate here over scientific literature was one over its quality, which could be better but is not inadequate. The actual clinical experiences documented in respondents' cases, Dr. Aoki's other patients, others receiving hepatic activation and Dr. Guthrie's patients, confirm the findings in the scientific literature.

THE IMPACT OF COVERAGE DECISIONS BY OTHER INSURERS DECISIONS BY MEDICARE AND CORPORATIONS

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.

Some insurers cover hepatic activation, but have general policies in place to deny coverage and contest claims through an administrative review or hearing, as which time they provide coverage because the findings after hearing have uniformly been favorable to hepatic activation, concluding it is safe and effective for the patient and not an experimental or investigational therapy. There is evidence of several such evidentiary hearings including decisions from Medicare in 1999, two from the Social Security Administration in 1993 and 1996 and two determinations from the Department of Corporations in this record. 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. 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 Ca1PERS PPO EOC’s that govern coverage in this case. The 1996 Social Security Decision contains the following Findings from the AU, “The Administrative Law Judge therefore concludes that, in the case of the beneficiary and of those similarly situated, the treatment of PWIT 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.” The same AU noted, “Until criteria are determined under Medicare for selection of appropriate patients to receive PIVIT therapy, any determination as to whether PIVIT is appropriate and necessary in the treatment of an illness for purposes of Medicare coverage must be made on a case-by-case basis.”

BLUE CROSS – A CONFLICTED POSITION

Blue Cross finds itself in a considerable bind, caught in a conflict between supporting the Blue Shield-CalPERS position that hepatic activation should be excluded from coverage as experimental and investigational and not medically necessary for respondents, and the fact that Blue Cross presently covers the therapy for some patients on a case by case basis, and has covered the therapy in the past, before Blue Cross took over for Blue Shield as Ca1PERS third party administrator. There is considerable evidence that Blue Cross has covered the therapy throughout the mid-to late 1990’s, in California and elsewhere, which is peculiar if the therapy is truly viewed by Blue Cross as still experimental and investigational and not medically necessary.

Dr. Hartman, Blue Cross’ Chief Medical Officer, in his testimony described the policy Blue Cross has drafted and put into place concluding hepatic activation is still experimental and investigational and is not proved medically necessary, safe and effective for patients. He initially confirmed the Blue Cross conclusion that hepatic activation is still experimental and investigational, not medically necessary and not safe and effective, was based primarily upon input and opinion from the MCOP reviewers, primarily the opinions of Dr. Axelrod, as discussed in detail elsewhere.

Dr. Hartman also sought input from ADRI, and expressed mild disappointment at what was furnished. Some of the MCOP reviewers expressed the same problem, and Drs. Robbins and Bran comb, in making their rather equivocal opinions, found the therapy had “promise”, but that they did not feel they had enough material from ADRI to make an adequate evaluation. What was presented to both MCOP, Blue Shield and to Dr. Hartman in defense of hepatic activation’s safety, efficacy, superiority in certain cases to conventional therapy and in defense of the claim that it is not experimental and investigational was spare, and was not really adequate to do the therapy justice. The supporting materials contain much discussion of the scientific bases of hepatic activation and how the therapy was developed and can be measured. The few references to clinical studies, trials and research in the ADRI submission are largely references to how the therapy was developed and how its action can be measured in the clinical setting, and refers only to work of Dr. Aoki and associates. The submission did not reference the Dailey, Boden study (even though it was published formally after these reviews, .preliminary abstract was available), or were just given a passing reference. Almost no reference was made to the very positive clinical experiences documented in Sacramento, Kansas and the other clinics offering hepatic activation over the how many years the

therapy has been successfully employed in these clinics, or delineation of the circumstances in which it has been used effectively. For example, Dr. Guthrie's testimony regarding the safety, effectiveness, therapeutic benefits and substantial cost savings he has achieved in his clinical experiences using hepatic activation, particularly in children manifesting uncontrolled bouts with diabetic ketoacidosis, was powerful and compelling, but was not mentioned in any material advocating hepatic activation to the reviewers raising questions regarding its efficacy and safety.

The evidence marshaled in this record here, in response to these same issues, is substantially different, qualitatively and quantitatively, than that presented to Blue Shield, Blue Cross and MCOP. It is not suggested that the same voluminous record made here should have been assembled and produced to the reviewers, only that the materials that were presented to Blue Shield, MCOP and Blue Cross were sparse and did not include some key evidence in support of the therapy and its role in the treatment of insulin dependent diabetics.

Dr. Hartman testified, quoting Dr. Axelrod primarily, that Blue Shield has concluded, "There is no scientific evidence in the literature to conclude it is superior to standard forms of insulin therapy." "There is no evidence it adds any additional benefit to the quality of life of the diabetic or reduces the complications of diabetes." The record made in this case has credibly and persuasively demonstrated both of those conclusions to be incorrect, and that the conclusions were based upon a good deal less than all the available information, scientific and clinical. Dr. Hartman found himself in a similar position. He conceded that individual reviews of cases coming to him for determination of those same issues are being decided in favor of coverage in many instances, and denied in few, if any, based upon the individual circumstances of each case. It was evident in Dr. Hartman's testimony that he cares a great deal for subscriber patient health, welfare and well-being, that he is not wedded to a particular policy if it interferes with good and safe patient outcomes, and that evidence of good clinical outcomes in the individual circumstances of the cases presented to him for review where approval occurred overrode the policy against the therapy. Those decisions also demonstrated the quoted statements, embodied in the Blue Cross policy, to be inaccurate as applied in those individual cases. Dr. Hartman also placed considerable reliance upon the input of the patient's clinicians' reports of clinical safety and effectiveness of hepatic activation in individual cases in making his individual approvals of medical necessity, a process that was conspicuously absent in the Blue Shield reviews and openly criticized by Dr Axelrod.

The Deputies Attorney General correctly point out that any individual insurer's determination to cover or refuse to cover hepatic activation is not dispositive upon whether the therapy is experimental, investigational, safe or medically necessary. But these other coverage determinations, which often resulted from the application of a review process similar to this, are evidence of strong trend, a widening acceptance of the therapy, as what it entails and the results it achieves in individual patients' cases becomes better and more widely known. The positive coverage decisions are confirmation that hepatic activation is repeatedly being found safe and effective when put to the test, and is well beyond the experimental and investigational stage. 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.

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. The therapy is not experimental or investigational, and was not when it was first offered to respondents.

COSTS AND EFFICACY OF HEPATIC ACTIVATION

Hepatic activation is expensive. In this case, the therapy costs approximately $2,000 every three weeks, less (Name Withheld)'s deductible. Health Net advises in its policy that hepatic activation costs approximately $25,000 per year. The considerable costs associated with hepatic activation, including that of equipment, supplies, medical professional time and patient time, and, galling to many, licensing royalties, is a key fact in these cases. The significant costs of hepatic activation is a central causative factor in producing stout resistance to acceptance of the therapy by health insurers, and is an major impediment to the more widespread proliferation of the therapy. Hepatic activation requires a significant commitment of time, energy and consistency from the patient receiving the treatment Hepatic activation does not replace or supplant conventional therapy. The patient must be willing and able to give up 6 hours of a day per week for life to the therapy. The patient receiving hepatic activation must continue to observe strict compliance with tight control conventional therapy at all times not receiving activation, and failure to observe the tight control conventional therapy can result in discontinuation of hepatic activation for the patient. The clinics must be staffed with specially trained medical personnel, close following of each patient is required by a physician, and the equipment is expensive. Clinics other than ADRI are required to license use of the pump and the therapy from ADRI, and pay a royalty, which adds to the cost.

The Health Net Technology Assessment policy, appended to Dr. Raffin's declaration, is representative of the ascendant role cost plays in these evaluations. The policy statement describes hepatic activation (CIIIT) in very positive terms that appear copied Dr. Aoki's own, explanatory materials and reprinted in the article in the Matrix UCDUMC magazine, which, in its full text, is a very supportive and flattering analysis of hepatic activation. Yet following this very positive description of the therapy and its benefits, the policy contains a note at the bottom, "CIIIT costs $25,000 per year". The "Position Statement" at the bottom, is that hepatic activation is experimental-investigational because, A. The FDA has not approved the procedure for treatment of Type I diabetes; B. The majority of references are from a single investigator; and C. Neither the ADA nor the NTDDK recognizes hepatic activation as a treatment for Type I diabetes. 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 1930's. The FDA has reviewed ADRI and approved the pump after two comprehensive site evaluations in 1989 and 1994. The fact that most of the research and investigation of hepatic activation is from Dr. Aoki and his colleagues is understandable, since the procedure is patented and expensive to replicate. It is cause for further inquiry, but not for concluding the procedure is experimental or investigational, particularly since there are other studies published by other researchers, confirming the conclusions. Dr. Guthrie and Dr. Soldener both persuasively testified that the ADA's role is to make comments and

recommendations regarding therapeutic approaches, not to make binding policy statements, approving or disapproving any particular therapy. Health Net has paid for hepatic activation in the past, and counsel for Ca1PERS suggested in closing argument that respondents failed to mitigate their losses by not switching to a Ca1PERS sponsored HMO (like Health Net), where coverage would have continued after July 1998 and pending this Decision. The prominent note regarding the high cost of hepatic activation makes no sense in the context of this policy unless it has been included as a key reason to apply the policy as negatively and conservatively as possible to contain coverage.

Kaiser is in a similar position to that of Blue Cross, above, and HeathNet. Dr. Fernando's declaration and the references to Dr. Livermore's treatment of Kaiser patients with hepatic activation confirm that Kaiser is approving the therapy in suitable cases on a case-by-case basis, regardless of enactment of a contrary medical policy. Dr. Marc Jaffee's declaration was not persuasive and was given little weight. Dr. Jaffee's conclusion on behalf of the Regional Chiefs of Kaiser that hepatic activation is experimental and investigational was rebutted by actual practice at Kaiser, where at the clinical level, diabetic patients with serious secondary complications not responsive to conventional intensive insulin therapy have been receiving hepatic activation at a Kaiser facility for several years. It is illogical to believe that the local Chief of Endocrinology at Kaiser, Dr. Livermore, and another local endocrinologist, Dr. Fernando, would be authorized by Kaiser to administer a therapy still deemed by Kaiser to be experimental and investigational to Kaiser patients not part of a previously approved and patient-consented trial. These patients, the existence of two of which was acknowledged by Dr. Jaffe in his declaration, were not in a clinical trial when they received their treatments, and were receiving the therapy from Kaiser endocrinologists who had ordered the therapy because it is safe, effective and was determined to be medically necessary for these patients. The treatments were administered at the Kaiser Fair Oaks Endocrine Clinic. The evidence revealed the treatments have been safe and effective and caused no adverse effects to the patients that could be considered evidence of a safety problem with the therapy. These Kaiser patients continue to receive hepatic activation, and the evidence was that Kaiser makes a case-by-case determination whether to authorize hepatic activation for any particular patient. There are not many Kaiser patients who have been authorized to receive hepatic activation, but there are a few.

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, as Dr. Guthrie persuasively pointed out in his testimony. Dr. Guthrie, 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. Guthrie calculated that one hospitalization to treat ketoacidosis costs the same as a year of hepatic activation. Dr. Guthrie's and Dr. Aoki's experiences were similar in that each has found that hepatic 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.

Social cost savings are similar. Dr. Axelrod's comment in his testimony that the social costs of hepatic activation are unacceptably high because patients have to take one day off work per week to receive treatment is unpersuasive. Three of the respondents have been redeemed from significant disability and being housebound by the implementation of the therapy, and even if they have to miss 6 hours of a day per week for treatment, they are still able to work the rest of the week. A fourth, Dr. (Name Redacted), was able to get his progressive complications arrested before the work limitations he was experiencing became actually disabling to the extent that he could not work. Hepatic activation for the patients in the experiences of Dr. Guthrie, Dr. Soldener and Dr. Aoki 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 Song 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, and do not progress to cause disability, and loss of the ability to work and remain self-sustaining.

"MEDICAL NECESSITY"

The EOC's also exclude from coverage any treatment or therapy that is not medically necessary for the patient subscriber. "Except for preventive care services, benefits are provided only for covered services and supplies which are medically necessary and delivered with optimum efficiency".

"Medical necessity means services and supplies as determined through the Plan's review process to be necessary, appropriate and established as safe and effective for treatment of a patient's illness or injury consistent with acceptable treatment patterns in established managed care environments and consistent with Blue Shield of California's Medical Policy on Quality and Technology. The fact that a provider may prescribe, order, recommend, or approve a service, supply, or hospitalization does not in itself make it medically necessary, even though it is not specifically listed as an exclusion or limitation. A service may be determined not to be medically necessary even though it may be considered beneficial to the patient Established medical criteria for medical necessity must be met before that service or procedure is determined to be medically necessary." (Emphasis original)

"Services and supplies that are medically necessary must:

1. Be consistent with the symptoms or diagnosis in treatment of the illness, injury or condition;
2. Be necessary and consistent with generally accepted professional medical standards;
3. Not be furnished primarily for the convenience of the patient, the treating physician, or other provider;
4. Be furnished at the most efficient level of care which provides safe and efficient treatment to the patient;

5. Be consistent with Blue Shield of California Medical Policy on Quality and Technology; and
6. Not be for custodial care.

The parties stipulated that number 6 of the criteria, custodial care, did not apply in this case. It was also not disputed that hepatic activation is not furnished primarily for the convenience of the patient, physician or other provider. The Findings above on experimental and investigational are that hepatic 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. The remaining dispute centers upon whether hepatic is efficient, which translates to whether it provides an equal or better health care outcome for a patient than other available therapies, is furnished at the most efficient level of care which provides efficient treatment to the patient, and whether it is consistent with Blue Shield of California Medical Policy on Quality and Technology.

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. 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. This Finding is not the result of Dr. Aoki or any other physician ordering hepatic activation as medically necessary for any respondent. That fact is evidence of medical necessity and is persuasive on the point, but the EOC's preclude such a Finding on the mere fact that a physician has ordered the therapy and has so stated in the order. The great weight of the evidence in this record that reveals hepatic activation is medically necessary for respondents, as that term is defined in the EOC's.

Blue Shield did not have a Medical Policy on Quality and Technology for hepatic activation until February 2001. The Blue Shield-CalPERS decisions to deny coverage to respondents for hepatic activation as not medically necessary were made in or just before July 1998, and were researched, appealed and reaffirmed before this policy was ever enacted. It is therefore unenforceable as an impediment to the coverage decisions that were made and are at issue here. As Blue Shield is no longer the administrator of record effective January 1, 1999, the policy is inapplicable to any period of time before its enactment, and is inapplicable to any period after Blue Shield's relief as third party administrator of these claims. But the policy is instructive as a post-hoc revelation of Blue Shield's institutional thinking on hepatic activation and the methodology of its efforts to bar coverage.

Even though inapplicable to these claims, application of the Blue Shield Medical Policy on Quality and Technology Assessment Review criteria30 avails Blue Shield-Ca1PERS little. Hepatic activation meets the criteria and the tests set forth in the Policy. Hepatic activation has what little government approval is required. The protocol has been issued a U.S. patent and the FDA has approved the pump and ADRI after two comprehensive visits and evaluations. There was no evidence of any other governmental approval required for the therapy. As set forth in detail in the experimental/investigational portion, the scientific literature is spare but adequate in support of the claims made in support of

hepatic activation, and particularly powerful with respect to containment, of diabetic nephropathy and hypoglycemic unawareness. There are at least four Level 1 studies, nine Level 3 studies, and four more Level 5 studies, as graded by the Policy, and several more abstracts; papers and presentations to professional associations of specialists, including to the American Diabetes Association's ("ADA") West Coast gathering in 1995.

Respondents, others in California and Dr. Guthrie's patients are substantial evidence of significantly improved health outcomes by use of hepatic activation therapy. The little evidence offered that attempted to explain respondents significantly improved health outcomes as the result of other factors was manifestly unpersuasive, as detailed below. Respondents' very positive outcomes with hepatic activation, and those described by Dr. Guthrie 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. Other factors remaining constant, improvements in health outcomes can only be attributed to hepatic activation, and attributing improvements to a therapy that has already failed is illogical. These patients, including respondents, and the scientific literature in this record, are components of a growing body of evidence that conventional intensive insulin physiological control therapy does not prevent or arrest the development of secondary complications of diabetes in many instances. The therapy has become a routine therapeutic option for suitable patients in several locations, in California and in six other clinics in various locations in the United States.

THE IMPACT OF AN ADA POSITION

It was not disputed that the ADA has not issued a guideline regarding hepatic activation, either endorsing or criticizing it. The suggestion there should be such a statement by the ADA on the therapy, if it is not still experimental, was unfounded and misconstrues the purpose of the ADA. Dr. Soldener and Dr. Guthrie's very persuasive testimonies were that the ADA does not set, specify or dictate therapy or methodology. The ADA does issue guidelines for clinical applications of a therapy, often in a frequently asked questions format. The guidelines also contain cautions.

There is an ADA guideline for the DCCT and its implications for conventional "tight control" intensive insulin therapy. That guideline contains a number of cautions, mostly to remind practitioners of the limitations of the findings of the DCCT and the limits upon extrapolation of its conclusions in the "average clinical setting". Both Dr. Soldener and Dr. Guthrie have been high-ranking officers of the ADA nationally and regionally, and have participated in the drafting and publication of many such guidelines. Their persuasive testimony was that the absence of an ADA guideline for any treatment or methodology does not mean that therapy is experimental or investigational, or not safe, effective or medically necessary. They testified the ADA guidelines are advisory, for assistance to the clinician in judging management of patients and therapies, "not standards or rules of management at all." The presence of a guideline is just that, a compilation of material to provide advice and guidance to a clinician in the clinical management of a patient, which may or may not contain advice or information on what is medically necessary for any particular patient. The presence or absence of an ADA

guideline on hepatic activation does not set a standard of care, and does not confirm or refute that hepatic activation is in accord with generally accepted professional medical standards for safe and effective treatment of diabetes, or even general acceptance of a therapy or methodology in the medical community. The absence of an ADA guideline on hepatic activation is therefore not persuasive evidence of whether it is scientific or experimental, or whether it is safe, effective or medically necessary for any of the respondents.

The ADA did issue cautions on the implications to the findings of the DCCT in the clinical environment. These cautions contain relevant information to this inquiry. The ADA guidelines advise the DCCT warns of 40%+ failure rate for intensive insulin "tight control" therapy, even in young, healthy subjects free from secondary complications. The guidelines also note the DCCT warns of a documented three fold increase in incidents of hypoglycemia in study subjects, weight gains and hypertension risks, and development of secondary complications in some patients, leading to advice in the guideline that "universal recommendation of "tight control" may not be appropriate, because in patients with advancing complications there was "no evidence that tight control was beneficial". The guideline also advised practitioners that there was no basis for concluding from the DCCT that intensive therapy was effective in such patients (ones with advancing complications). Finally, the ADA guideline advised clinicians that the results of the DCCT were probably not reproducible in the average clinical setting, because the great quantity of clinical support given the subjects of the study could not be offered practically in a "real world" setting.

The ADA guidelines regarding the DCCT results and their applicability to the average clinical setting produced conflict in some of the other evidence. Dr. Nuovo and Dr. Peters testified that they have not had an experience of treating a diabetic, regardless of development of complications that they did not think they could help with conventional intensive insulin physiological control. Dr. Axelrod, although not stating the opinion so directly, seemed to agree. The clinical experiences reported by Dr. Nuovo and Dr. Peters appear to conflict with the ADA guideline, warning intensive insulin "tight control" therapy has a significant failure rate, regardless of strong clinical support and excellent controls, and is not particularly suitable for diabetics with advanced secondary complications. Dr. Nuovo and Dr. Peters' opinion, founded entirely upon their own clinical experiences, are evidently "anecdotal", in the words of Dr. Axelrod.

It was not suggested that Dr. Nuovo, Dr. Peters and perhaps Dr. Axelrod, should abandon their treatment approach based upon their own clinical experiences because the DCCT study's conclusions and the ADA's view of them reflected in its guideline conflicts with their own "anecdotal" clinical experiences. The apparent conflict only serves to showcase the great value of the development of "institutional knowledge" reflected in the collective whole of tried and true "anecdotal" clinical observation and experience, resulting from the crucible of trial and error, and how that collective clinical experience can differ markedly from the "published scientific literature".

POSITIVE HEALTH CARE OUTCOMES

A considerable effort was made to offer plausible alternative explanations for the documented positive health care outcomes experienced by and maintained by respondents

after commencement of hepatic activation. Dr. Nuovo, Dr. Peters, Dr. Chan and Dr. Axelrod opined that the good results attributed to hepatic activation were likely to be the result of the strong clinical support given hepatic activation patients. These opinions are rejected as entirely speculative and wholly lacking in any evidentiary foundation. Respondents are and have been consistently achieving exceptional health outcomes, year in and year out. Any clinical support effect, to the extent it exists at all, will diminish or vanish altogether over a significant period of time. These opinions were soundly and directly refuted by the testimony of Dr. Soldener, Dr. Guthrie, Dr. Aoki and a good deal of the documentary evidence. The source of Dr. Nuovo, Dr. Peters and Dr. Axelrod's opinions appears at least in part to be the DCCT, where the issue of strong clinical support for patients was raised as a possible positive influence skewing outcomes.

The ADA warns directly in its guidelines that the good results observed in the DCCT study subjects might at least partially be the result of similar strong clinical support. This ADA guideline pointedly warned clinicians that similar strong clinical support cannot likely be replicated in a "real world" clinical setting. ADRI is certainly a "real world" setting, as is Dr. Guthrie's clinic. Dr. Soldener persuasively explained in his testimony that the DCCT's results showing improved blood glucose control in some subjects could not have been the result of strong clinical support, as the study's own data refute that conclusion. He pointed out that the average levels of hemoglobin Ale, the key measurement of good blood glucose control, rose gradually over time in the DCCT subjects, despite such strong clinical support that the ADA warned it could not be reproduced in the average clinic. Dr. Soldener thus refuted any explanation that strong clinical support was producing better blood glucose control in the study subjects, because their blood glucose levels were rising over time, even with the support. That is not what is happening in hepatic activation with respondents and others, where measured hemoglobin Ale levels generally drop into the desired or high desired range, and stay fairly stable over time. Nothing of the sort was reported as observed in the DCCT. Strong clinical support, as an explanation for hepatic activation's exceptional positive health outcomes for respondents, year in and year out, as well as for Dr. Guthrie's patients, has no meaningful evidentiary support.

Dr. Axelrod, Dr. Nuovo and Dr. Peters' each also suggested in their testimony that the outstanding results achieved by hepatic activation are entirely attributable to the conventional therapy the respondents continue to receive in addition to their hepatic activation. The contention is barely worthy of any serious consideration. Admission to receive the therapy is an elimination process that precludes the explanation these experts suggest. Best efforts at conventional intensive insulin therapy must have already failed to achieve the results these experts attribute to conventional therapy to begin hepatic activation. These experts had absolutely no meaningful clinical information about respondents upon which to base this opinion. The opinions were sheer speculation and are rejected accordingly.

The expert opinion in this matter was deeply and intensely divided. It would not be accurate to characterize the division in expert opinion regarding hepatic activation as merely differences of medical opinion. 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 debilitating secondary complications, often leading to death. Hepatic activation represents a significant challenge to this widely held body of accepted medical knowledge.

Dr. Axelrod and Dr. Peters' suggestion that anecdotal evidence of treatment success is irrelevant, unreliable and immaterial to these determinations is rejected. Dr. Axelrod dismissed anecdotal evidence of positive clinical experiences with hepatic activation as illusory, hope for relief placed in a therapy making claims "too good to be true". He characterized such hopes as the feeble clinging of desperate folks to any possibility for relief, no matter how potentially harmful, destructive, expensive, unsafe, or even entirely psychological, and condemned the exploitation of such fragile persons by practitioners and advocates of all sorts therapies untried and unproved in the scientific literature. The point is well taken but the proof did not support the contention that hepatic activation is one of those unsupported therapies, nor did it appear that respondents are the sorts of persons referred to in this testimony.

Well educated and impressively well informed regarding all aspects of their own diabetic conditions and treatment options, the evidence will not admit of any conclusion that the respondents were or are willing to try anything in the hopes of improvement. On the contrary, the respondents demonstrated themselves to be very aware of their medical conditions and of their treatment options, and uniformly unwilling to try anything unsafe, unaccepted or unusually risky. All respondents received detailed information and advice before trying hepatic activation, and some performed comprehensive research before trying it. All respondents found hepatic activation to be safe and effective, with markedly superior results than their conventional therapy. All of the respondents have repeatedly demonstrated their willingness and ability to, and did carefully and fully comply with all of the demanding requirements of their own self-care and treatments. Contrary to Dr. Axelrod, Dr. Nuovo's and Dr. Peters' unflattering inferences, there was no evidence any of the respondents ever failed to be fully and completely compliant with the rigors of their respective conventional intensive insulin therapy regimens. There are undoubtedly diabetic patients suffering end stage serious secondary complications that would be willing to try anything, no matter how experimental, unsafe or untried, in the hope of obtaining some relief, regardless of the risk. It is responsible medicine and science to protect these very vulnerable folics from untried, risky and untried treatment methodologies that appear to offer more hope than substance. Hepatic activation is not one of these treatments, and the respondents are not the type of people Dr. Axelrod seeks to protect. The inference in some of the testimony of some of these experts, that Dr. Aoki is the type of physician who would attempt to prey upon these fears in a hope to profit from foisting an illusory treatment upon the unsuspecting and very vulnerable, is absurd. Dr. Aoki consistently demonstrated a high degree of professionalism, ingenuity, scientific and medical expertise and great energy in the application of his considerable skills to develop, test, and bring to the clinic a therapy that holds out real promise for diabetics suffering secondary complications.

The process of innovation, testing and bringing to actual clinical treatment an innovative treatment, therapy or medication is more than arduous, as was evident here. The role of innovator is far more trying and difficult than that of peer reviewer or critic in this process. The gauntlet of criticism of peer review, with the role of critic often taken by those unwilling or unable to advance an innovation themselves, is a considerable barrier to entry, and the "thin skinned" need not apply to try to advance an innovation. This process is not all bad, as a high barrier to entry generally eliminates some unworthy or speculative ideas. The process of review and criticism can and has sometimes become a vehicle for the suppression of promising new therapies or medications due to factors other than legitimate scientific concerns and deficiencies, or for the furtherance of professional envy. As long as the process remains reasonably focused upon legitimate concerns for safety and efficacy, it serves as a very valuable feature for the expansion of the frontiers of medicine.

Dr. Axelrod and Dr. Peters spent little time discussing what to do with the diabetic who has been strictly, faithfully and rigidly compliant with everything he or she could do to follow the DCCT gold standard intensive insulin therapy, and all dietary, exercise, medication and follow up procedures, and still develops uncontrolled secondary complications. These patients exist, regardless of the best and most compliant efforts of patient and physicians. Dr. Aoki, Dr. Benbarka, Dr. Grecu, Dr. Soldener, and Dr. Guthrie, among others, offer these patients realistic hope for improvement. Dr. Axelrod, rather subtly, and Dr. Peters and Dr. Nuovo more directly, were critical of these patients and their physicians for their circumstances. All three experts made clear in their expressions of opinion that diabetics with uncontrolled secondary complications are deficient in some fashion in their intensive insulin therapy programs, to which they imply blame for both the physician overseeing treatment, and the patient, for failure to strictly discipline themselves and make an intensive insulin program work. Dr. Axelrod condemned the use of the word "brittle" to describe diabetics enduring this very unpleasant development in their conditions, because he considered it a term that implies the patient is to blame for his or her condition, but then implied in his testimony that it was his opinion that the development of these uncontrolled secondary complications was a blameworthy combination of physician failure of oversight and therapy design and patient failure to strictly follow all aspects of the program. Dr. Soldener, Dr. Aoki, and Dr. Guthrie all very persuasively pointed out that this opinion is not only inaccurate, but unfair to place the blame for an unresponsive condition on a patient or physician who are doing everything they can do to control the condition and are following an appropriate multifaceted protocol. These opinions caused additional harm to the credibility and persuasiveness of Dr. Axelrod, Dr. Peters and Dr. Nuovo.

HEPATIC ACTIVATION CHALLENGES THE DOMINANT DIABETES TREATMENT PARADIGM

Dr. Aoki's research and conclusions challenge a deeply held paradigm regarding what causes diabetes and how to treat it. Many physicians have embraced it as a significant advance with great promise for improving patient outcomes in an area of medicine notorious for poor long-term results. Some of Dr. Aoki's research conclusions and study findings contain comments that are challenging to the conventional view of what diabetes is and how to competently treat it. "Thus, it is theoretically impossible for an insulin-

dependent diabetic patient, whose sole source of insulin is via subcutaneous injections of regular insulin, to ever achieve normal fed insulin concentrations in the portal vein and liver." "For the past seventy years, clinicians have administered insulin on the basis of the above assumptions, i.e., diabetes mellitus is simply due to insulin deficiency. It is surprising during that this period of time more attention has not been directed to the question of why glucose homeostasis, and even more importantly, why overall metabolic control was not achieved simply by giving diabetic patients insulin. Based upon this analysis, it should be clear that the primary purpose of insulin administration in Type I insulin- dependent diabetes mellitus should be reestablishment of the normal biochemical and physiological relationships between the gastrointestinal tract, liver and muscle." The ability to read between the lines was not required to understand that Dr. Aoki's hepatic activation procedure and, the science that underlies it, implies that, for at least a small minority of insulin-dependent diabetic patients, the conventional intensive insulin therapy approach and the medical and scientific understandings that underpin it, are inadequate, incomplete or simply wrong.

Dr. Nuovo and Dr. Peters, and Dr. Axelrod understandably reacted to such statements defensively. It is not surprising that they have reacted negatively to such comments in published scientific literature supporting hepatic activation, and found fault with the studies and their conclusions. The reservations noted in the American Diabetes Association's guidelines commenting on the DCCT are enlightening, in that they support Dr. Aoki's views more strongly than the approach advanced by Dr. Nuovo, Dr. Peters and Dr. Axelrod. Dr. Aoki's claims of nearly 100% success rates with hepatic activation treatment have not helped reduce criticism from his more skeptical colleagues. Time will tell.

LEGAL CONCLUSIONS

1. CalPERS acts as a health insurer in offering its self-funded health plans, PERS Care and PERS Choice. These are premium plans, offering wider choice of physicians, therapies and treatments than HMO plans offered by CalPERS to members through contracts with the HMO's. Both PPO plans are very comprehensive and broad based, essentially all-risk health insurance policies. Health insurance policies are insurance contracts, subject to specific rules of construction.

2. Any contract is construed against the party who prepared the contract35 An insurance contract imposes an even more stringent duty upon the court to interpret in favor of the insured.36 Health insurance contracts have an even higher level of scrutiny, and a contract term or terms in dispute seeking to enforce an exclusion from coverage is subject to the highest scrutiny of all.37

3. It was not really disputed that respondents' hepatic activation treatments are covered and reimbursable services under the PERS Care and PERS Choice PPO health insurance contracts, unless a specific exclusion from coverage applies. Coverage was provided for the therapy from at least 1988 for the earliest of respondents, through July 1998, when Blue Shield notified all the respondents that it was seeking to exclude the therapy from coverage due to application of two specific exclusions contained in the EOC's, the details of coverage and exclusions

from coverage for each plan. Blue Shield and Ca1PERS have, at all times relevant to this Decision, applied the provisions in the EOC's under "experimental/investigational" and "medical necessity" as limitations of, exceptions to and exclusions from coverage that would otherwise exist, if the treatment, therapy or procedure at issue falls within the language of one of these exclusionary categories.

4. The allegations made by Blue Shield and CalPERS, that hepatic activation is still experimental and investigational, and/or is not medically necessary for respondents effective July 1998 are efforts to enforce exclusions from coverage. Therefore, the presumption in favor of coverage applies, and the effort to exclude the procedure form coverage is subject to the strictest scrutiny. The exclusions must be narrowly construed, construing every reasonable inference and interpretation in favor of coverage in favor of the insured, ensuring that the end result conforms to the insured's objectively reasonable expectations.

5. Preliminary to commencing with the taking of the evidence, the Administrative Law Judge ruled that the burden of proof to demonstrate the exclusions from coverage apply to respondents was upon the insurer, Ca1PERS. The ruling was based upon the authorities cited above, and others. The AU determined that coverage for the therapy was presumptively covered under the terms of the EOC's, unless a specific exclusion applied. The experimental investigational and medical necessity exclusions were advanced as the applicable exclusions that bar coverage. It is Ca1PERS' burden to prove the language of these exclusions bar coverage, otherwise the respondents prevail.

6. CalPERS' effort to enforce a portion of the EOC's entitled "Benefit Limitations, Exceptions and Exclusions" was rejected. The provision is a contractual device that seeks to shift the burden to prove the applicability of the alleged exception to the individual insured. The provision requires the individual insured to prove enforcement of the exclusion would be "prohibited by laws and establish that the service or procedure is medically necessary according to Blue Shield of California's Medical Policy on Quality and Technology". The provision was rejected because it is adhesive, violates the objectively reasonable expectations of the insureds and manifestly unfair to policyholders, because it seeks to shift from the party with far superior bargaining power and resources, Ca1PERS and Blue Shield, to respondents a nearly impossible burden of proof. The provision also seeks to reverse the settled law of this State regarding enforcement of exclusions, limitations and exceptions to coverage in health insurance contracts.

7. Respondents had the opportunity to select other health plans from the offerings made by Ca1PERS, but this does not save the provision or make it enforceable. To participate in a PPO plan, which is trumpeted in the EOC's themselves as superior in flexibility and coverage to a HMO plan, the plan participant must "take it or leave it" with respect to the entire panoply of provisions in the EOC for the PPO selected, including an overreaching provision such as this one. It is indisputable that the language of this provision is far outside the reasonable expectations of the insured, as it constitutes a foregoing of the general provisions of law that protect insureds under similar circumstances. Choice of another plan

without the provision is illusory under these circumstances, because the plans are by no means equivalent. Under these circumstances, the provision was ruled to be unenforceable to the extent it seeks to shift the burden of proof and require respondents to prove Blue Shield-CalPERS' actions to deny coverage and enforce the exclusions are prohibited by laws, and/or that hepatic activation is medically necessary for them.

8. The Blue Shield of California's Medical Policy on Quality and Technology is not enforceable in this action. The policy was not enacted until February 2001, almost three years after the denial actions that compose this action, and was enacted under circumstances that raise at least an inference that it was enacted as a tactic to assist in this litigation.

9. The contention that coverage for hepatic activation was provided unwittingly and unknowingly by Blue Shield on behalf of CalPERS from 1988 through July 1998, despite the exclusionary language, was rejected in the Factual Findings as lacking in merit. The fact that coverage occurred for all respondents during this period of time for hepatic activation confirms that coverage for the therapy is covered unless specifically excluded.

10. The EOC's contain provisions permitting CalPERS and its third party administrator to review coverage at any time for applicability of an exclusion or exception. Respondents did not generally dispute the fact that the EOC's provide the insurer the right to review coverage at any time. The Blue Shield-Ca1PERS review of hepatic activation coverage in July 1998 did not violate the EOCs. It was not disputed that the experimental/investigational and medical necessity exclusions were phrased in clear and understandable language, and are generally enforceable limitations upon and exclusions from general coverage, even if the service or therapy has been provided in the past, if the terms of the provisions apply to the individual circumstances.

11. The great weight of the evidence in this matter, as detailed in the Factual Findings, is that hepatic activation is not and was not experimental and investigational for respondents at the time it was offered forward, and is and has remained medically necessary for each one of them throughout the period under review in this action. The burden of proof was really not much of a factor, as the evidence in support of these propositions was substantial and persuasive, and the evidence in support of the application of the exclusions and limitations was not.

12. Ca1PERS did not dispute the contention from counsel from (Name Withheld) that Ca1PERS has a fiduciary duty to its members, and to its members who subscribe to its PPO self-funded health plans. This duty is dual, and runs toward the individual members and to all members collectively. The duty to the individual requires Ca1PERS to treat each individual fairly and reasonably. The duty does not necessarily correlate to a duty to grant coverage for health care in every disputed case, even where the care is shown to benefit the member. The collective duty generally requires Ca1PERS to manage the self-funded health care plans for the benefit of all the members. Part of that duty is to carefully review coverage decisions and enforce reasonable exclusions and limitations of coverage. In

specific cases, the duty requires CalPERS to balance its obligations, weighing its obligation to act in the best interests of the individual member with the duty to protect the collective whole. The individual duty requires CalPERS to act reasonably and in accordance with the best interests and welfare of the individual member, as long as that action does not significantly prejudice the interests of all the other members in the fund

13. Hepatic activation represents an unquantified potential but unproved cost threat to the financial health of the plans. Yet the "state of the art" conventional intensive insulin therapy alternative proposed by Dr. Peters in her declaration, with weekly or more physician visits combined with multidisciplinary treatments with specialists, appears to be approaching similar costs. Diabetes care in long-term insulin dependent patients is expensive, regardless of therapeutic route followed. 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. Over time, without coverage, some or all respondents will no longer able to afford the therapy on their own. Thus far, ADRI has continued to furnish the therapy pending a coverage decision. ADRI has committed to continue the therapy for respondents as an ethical matter, demonstrative of their commitment that the therapy is medically essential for respondents' continued health and welfare. But if coverage is denied, the financial ability of ADRI to continue to provide the therapy for the co-payment or deductibles respondents have been paying since Blue Shield cut off the therapy in July 1998 is quite uncertain.

14. Balancing the relative fiduciary duties of Ca1PERS to respondents and the membership in general, the balance falls solidly with respondents. This is not to say that CalPERS acted unreasonably in reviewing the coverage of hepatic activation for respondents, and even acting as it did after its internal reviews. Following the reviews, there existed what appeared to be, on the evidence as it existed at that time, a bone fide dispute. The evidence presented in this matter is qualitatively and quantitatively far different than that relied upon to make the decisions to deny further coverage. But, under 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 Ca1PERS' fiduciary duty to respondents to sustain the termination actions or to discontinue the therapy for respondents.

15. For the first time in CalPERS' closing responsive brief, the issue of what should be done if respondents prevail was raised. CalPERS contends respondents should be limited in any recovery resulting from a favorable ruling here because they could have mitigated any damages by transferring their health coverage to one of the health plans offered by Ca1PERS that covers hepatic activation during open enrollment, and/or that any recovery by respondents is capped by the specific provisions of the PPO's. The first contention neglects to recall that this whole action began when (Name Withheld) made an inquiry about doing exactly that, changing plans, a call she now deeply regrets. It also neglects to consider that

Ca1PERS has taken the position throughout the period of review and this action that hepatic activation is experimental and investigational and not medically necessary, and thus presumably not a covered benefit under any CalPERS sponsored health plan. If this were not the case, Ca1PERS should have advised and directed respondents to at least consider an alternative plan where coverage was assured, but there is no evidence this occurred. Respondents were never advised of a reasonable alternative through another plan that would have permitted them to continue covered hepatic activation in the interim and not have to fight with that plan the same coverage battle as here. Respondents were frozen into this dispute within their own plans, and switching plans raises the prospect of having to fight the same battle again under a different plan's review process, which seems, under the circumstances, inconceivable. Respondents did not fail to mitigate their damages. The contention is rejected. 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.

16. The amount of damages resulting from the denial of coverage for respondents cannot be determined on this record, as very little evidence was adduced regarding the amounts and shares of costs that should have been covered and were not. Respondents are not entitled to recover any of the co-payments or deductibles that they paid that would have been applicable, had coverage continued. Claims for payment of services that should have been covered and were not will undoubtedly be filed. Ca1PERS has raised a limitation to recovery that is contained in the EOC's. To the extent that the provision seeks to limit respondents' recovery to the cost of conventional therapy, "the estimated cost of standard treatment", however, the provision, is inapplicable and unenforceable. CalPERS is required to pay for the coverage actually furnished, and that which should have been covered, as it was before July 1998. To conclude otherwise would reward what has been here determined an incorrect action. To cut off and deny coverage in a disputed situation such as this one, and yet only have to pay for the less costly coverage that was unsuccessfully contended should have been required, would permit achievement of the outcome that was attainable only if CalPERS prevailed in. sustaining the termination of coverage.

17. "The problem of retrospective denial of coverage can be reduced through the growing practice of preadmission screening." Rather than continuing to enact internally inconsistent technology utilization policies that acknowledge and accurately describe hepatic activation, and then conclude it is experimental investigational and not medically necessary, a more prudent approach would be to recognize the actual current practice of many insurers, who make decisions for suitability on a case by case basis, requiring preauthorization, applying strictly the criteria set by Dr. Aoki and perhaps requiring review of the conventional therapy or a second opinion that conventional therapy has actually proved ineffective to arrest progression of secondary complications. This could assist greatly in resolving much of the tension between the need to provide promising therapy to those who need it, even if expensive, and containing costs, by making certain that only patients truly suitable for the therapy receive it, but those who prove to be suitable get the therapy they need.

ORDER

The appeals of respondents are all SUSTAINED, and each of them Ca1PERS shall approve, and direct Blue Shield of California, Blue Cross, or any other third party administrator serving in that capacity for Ca1PERS, to provide coverage for hepatic activation from July 1998 forward and to date.

Reimbursement shall be made for all hepatic activation treatments received by respondents from July 1998 to date, for which reimbursement has not already been received.

Respondents, ADRI and any other affected persons or entities shall promptly submit claims to CalPERS or, as directed, to a third party administrator, for reimbursement for coverage furnished from July 1998 forward. CalPERS, Blue Shield, Blue Cross or other representative of Ca1PERS shall timely process and pay the claims for reimbursement.

DATED: January 17, 2002

STEPHEN J. SMITH
Administrative Law Judge
Office of Administrative Hearings

25392992

Request # 25392992 **AUG 08, 2008**

Email (PDF) To: scott.zettlemoyer@stjoe.org

St. Joseph Hospital
Burlew Medical Library ILL
1100 West Stewart Drive
P.O. Box 5600
Orange, CA 92863-5600

DOCLINE: Journal Copy EFTS Participant

Title:	Metabolism: clinical and experimental
Title Abbrev:	Metabolism
Citation:	2007 Nov;56(11):1453-7
Article:	A pilot study to test the effect of pulsatile insu
Author:	Weinrauch L;Burger A;Aepfelbacher F;Lee A;Gleason R;DElia J
NLM Unique ID:	0375267 Verify: PubMed
PubMed UI:	17950093
ISSN:	0026-0495 (Print) 1532-8600 (Electronic)
Publisher:	W.B. Saunders, Philadelphia, PA :
Copyright:	Copyright Compliance Guidelines
Authorization:	Scott Zettlemoyer
Need By:	N/A
Maximum Cost:	**$20.00**
Patron Name:	Dr George Taylor
Referral Reason:	Not owned (title)
Library Groups:	FreeShare,MLGSCA
Phone:	1.714.771-8291
Fax:	1.714.744-8533
Alternate Delivery:	Fax,Web(PDF)
Routing Reason:	Routed to AZUMGP in Serial Routing - cell 2
Received:	Aug 11, 2008 (02:45 PM EST)
Lender:	Maricopa Integrated Health System/ Phoenix/ AZ USA (AZUMGP)

This material may be protected by copyright law (TITLE 17,U.S. CODE)

Bill to: CAUORJ

St. Joseph Hospital
Burlew Medical Library ILL
1100 W.Stewart Drive
P.O. Box 5600
Orange, CA 92863-5600

Available online at www.sciencedirect.com
ScienceDirect
Metabolism Clinical and Experimental 56 (2007) 1453 – 1457
Metabolism
Clinical and Experimental
www.elsevier.com/locate/metabol

A pilot study to test the effect of pulsatile insulin infusion on cardiovascular mechanisms that might contribute to attenuation of renal compromise in type 1 diabetes mellitus patients with proteinuria

Larry A. Weinrauch[a,b,c,d,*], Andrew J. Burger[b,d], Franz Aepfelbacher[b,d], Annette T. Lee[e], Ray E. Gleason[d], John A. D'Elia[a,b,d]

[a]*Joslin Diabetes Center, Boston, MA, USA*
[b]*Beth Israel Deaconess Medical Center, Boston, MA, USA*
[c]*Mt Auburn Hospital, Cambridge, MA, USA*
[d]*Harvard Medical School, Boston, MA, USA*
[e]*North Shore University Hospital, Manhasset, NY, USA*

Received 25 January 2007; accepted 10 May 2007

Abstract

We hypothesized that correction of insulin deficiency by pulsatile intravenous insulin infusion in type 1 diabetes mellitus patients with nephropathy preserves renal function by mechanisms involving cardiac autonomic function, cardiac mass, or efficiency, or by hemostatic mechanisms. The control group (8 patients) received subcutaneous insulin (3-4 injections per day). The intravenous infusion group (10 patients) received three 1-hour courses of pulsed intravenous insulin infusion on a single day per week in addition to subcutaneous insulin. Laboratory measurements included 2-dimensional Doppler echocardiography, 24-hour ambulatory monitoring with heart rate variation analysis, platelet aggregation and adhesion, plasma fibrinogen, factor VII, von Willebrand factor, fibrinolytic activity, plasminogen activator inhibitor, and viscosity measured at baseline and 12 months. Blood pressure control was maintained preferentially with angiotensin-converting enzyme inhibitors. Ratio of carbon dioxide production to oxygen utilization was measured with each infusion and showed rapid increase from 0.8 to 0.9 ($P = .005$) at weekly treatments through 12 months. We observed an annualized decrease in creatinine clearance of 9.6 mL/min for controls vs 3.0 mL/min for infusion patients. Annualized fall in blood hemoglobin was 1.9 vs 0.8 g/dL, respectively ($P = .013$). There were no differences between the control and infusion group with respect to glycohemoglobin, advanced glycated end products, cholesterol, or triglycerides. No differences between the study groups for hemodynamic or hemostatic factors were evident. Blood pressures were not significantly different at baseline or 12 months. We conclude that although preservation of renal function with attenuation of loss of blood hemoglobin during 12 months of intravenous insulin infusion was associated with improvement in the efficiency of fuel oxidation as measured by respiratory quotient, this occurred without differences in metabolic/hemostatic factors, cardiac autonomic function, cardiac wall, or chamber size. Our hypothesis that preservation of renal function in type 1 diabetes mellitus patients with proteinuria by weekly pulsed insulin infusion involves mechanisms from the autonomic nervous system, cardiac size, and function, or elements of hemostasis was not confirmed.
© 2007 Elsevier Inc. All rights reserved.

1. Introduction

Computerized control of glucose/insulin by means of the BioStator GCITS insulin infusion pump (Miles Laboratories, Elkhart, IN) in patients with type 1 diabetes mellitus has been shown to correct hepatic disposal of glucose [1]. Increased efficiency of equimolar amounts of hormones administered in pulsatile fashion when compared with continuous infusion has been demonstrated for insulin [2], glucagon [3], and growth hormone [4,5]. The addition of pulsatile infusion to multiple daily subcutaneous injections has been reported to be of benefit in the prevention of metabolic and microvascular complications in type 1 diabetes mellitus [6,7]. A multicenter, prospective, randomized study has demonstrated preservation of renal function in type 1 diabetes mellitus patients with albuminuria by pulsatile insulin infusion [8]. We hypothesized that correction of insulin deficiency by pulsatile intravenous insulin infusion in patients with type 1 diabetes mellitus preserves renal function by mechanisms

Presented in part at the 40th Scientific Sessions of the American Society of Nephrology, San Francisco, CA, November 2007.

* Corresponding author. 521 Mount Auburn St, Suite 204, Watertown, MA 02472. Tel.: +1 617 923 0800; fax: +1 617 926 5665.
E-mail address: lweinrauch@hms.harvard.edu (L.A. Weinrauch).

0026-0495/$ – see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2007.05.016

Table 1
Effect of 12 months of intensive insulin treatment

Parameter	Control		Infusion	
	Baseline	1 y	Baseline	1 y
Glycohemoglobin A_{1c} (%)	9.8 ± 0.5	8.0 ± 0.3	9.1 ± 0.6	8.5 ± 0.6
AGE products (U)	13.0 ± 1.8 (8)	7.2 ± 1.9 (7)	12.5 ± 3.5 (8)	8.3 ± 1.5 (9)
Insulin dose (U/d)	48.6 ± 4.5	39.5 ± 2.2	40.1 ± 4.2	42.4 ± 4.9
Assisted hypoglycemia (no. per patient/y)	5 (range, 0-32)	0	35 (0-303)	0
Assisted hypoglycemia during study (no. per patient/y)		0		1
Self-treated hypoglycemia (no. per patient/y)	7 (range, 0-14)	17 (2-55)	9 (0-20)	21 (7-109)
Weight (kg)	77.8 ± 4.0	76.7 ± 4.5	73.3 ± 3.7	73.2 ± 4.2
Edema (% present)		83		17*
MAP (mm Hg)	103.8 ± 3.4	104.3 ± 2.6	96.2 ± 2.7	98.0 ± 2.6
24-Hour urine protein (mg)	3754 ± 935	2024 ± 645	3692 ± 998	2203 ± 729
Hemoglobin (g/dL)	13.7 ± 0.5	11.8 ± 0.5	13.5 ± 0.7	12.7 ± 0.7**
Serum creatinine (mg/dL)	1.74 ± 0.14	2.19 ± 0.28	1.78 ± 0.23	1.86 ± 0.25***
Creatinine clearance (mL/min)	55.4 ± 7.0	45.8 ± 7.0	58.4 ± 7.0	55.4 ± 8.7
Loss of clearance (mL/[min y])		9.6		3.0
No decrease in clearance during study (%)		0		55****

AGE indicates advanced glycated end-products.
* $P = .043$, 2-tailed Fisher exact test.
** $P = .013$.
*** $P = .001$.
**** $P = .029$, 2-tailed Fisher exact test.

involving cardiac autonomic function, cardiac mass, or efficiency, or by hemostatic mechanisms.

2. Patients and methods

Patients (n = 71) participated in a 12- to 18-month randomized protocol at 7 centers that demonstrated a slowing of loss of renal function in diabetic individuals with proteinuria treated with a weekly pulsatile insulin infusion. Description of the full protocol was previously published [8]. In brief, the control group received 3 to 4 subcutaneous insulin injections per day; the infusion group received, in addition, three 1-hour infusions in a pulsatile fashion over one 8-hour period each week. Both groups were seen weekly by investigators with the goal of optimizing glycemic and blood pressure (preferentially treated with angiotensin-converting enzyme inhibitors) control. On infusion days, by means of the metabolic cart, oxygen utilization and carbon dioxide production were simultaneously measured at the beginning and at the end of the infusion hour. Mean results for the 3 infusion hours included 9 determinations preinfusion and 9 at the end of infusion.

The group at the Joslin Clinic enrolled 18 patients (8 randomized to control and 10 to insulin infusion) who underwent an extensive cardiovascular evaluation in addition to the multicenter protocol as part of a pilot study attempting to identify intermediate mechanisms that might contribute to the preservation of renal function. This subgroup underwent 2-dimensional Doppler echocardiography at baseline and 12 months, and 24-hour ambulatory monitoring with heart rate variation analysis every 6 months. Study group designation was concealed from readers of the individual tests.

Plasma samples taken at baseline and at 6 and 12 months were analyzed in duplicate for fibrinogen, factor VII, von Willebrand factor, fibrinolytic activity, plasminogen activator inhibitor, and viscosity. Platelet aggregation after stimulation with adenosine diphosphate, collagen, and epinephrine was performed in a platelet aggregometer at baseline and 12 months. Platelet adhesion was also determined using a modified Hele-Shaw flow system at baseline and 12 months.

Because of the risk of hypoglycemia in patients with multiple cardiac risk factors from tight diabetes control, a detailed diary of hypoglycemic reactions was kept and analyzed with respect to total insulin dose.

The study was designed to run for 12 months, with an option for the investigators to extend it to 18 months in the event that the treatment seemed effective but had not yet reached statistical significance at 12 months. Patients were offered the opportunity to extend participation for up to 6 months, at which time the study was terminated.

3. Results

3.1. Glycemic control

For our study group (n = 18), as in the multicenter study, glycemia control as measured by glycohemoglobin ($P = .006$) and advanced glycated end products ($P = .01$) decreased. No significant differences in measures of diabetic

Table 2
Effect of 12 months of intensive insulin treatment on autonomic (24-hour ambulatory electrocardiographic) and standard echocardiographic measurements

Parameter	Control		Infusion	
	Baseline	1 y	Baseline	1 y
Day-night MAP ratio	1.01 ± 0.03 (7)	1.07 ± 0.03	0.98 ± 0.36	1.04 ± 0.03
SDNN (ms)	68.9 ± 7.7 (6)	73.0 ± 7.3	96.2 ± 16.2 (9)	86.7 ± 14.1
PNN50 (%)	0.51 ± 0.22 (6)	0.35 ± 0.25	2.16 ± 1.48 (9)	3.76 ± 2.36
RMSSD (ms)	10.8 ± 0.8 (6)	10.2 ± 1.4	14.0 ± 4.6 (9)	17.1 ± 5.6
CVNN	10.4 ± 1.0 (6)	10.8 ± 1.1	14.0 ± 1.9 (9)	12.8 ± 1.8
HF (ms^2)	33.7 ± 4.34 (7)	35.5 ± 5.3	258.2 ± 181.4 (9)	189.6 ± 146.2
LF (ms^2)	142.2 ± 31.2 (7)	83.9 ± 25.3	901.3 ± 682.6 (9)	637.6 ± 493.1
LV mass (g)	217.7 ± 33.8 (6)	194.8 ± 30.8	207.0 ± 10.9	184.5 ± 15.9
LV septum (mm)	10.3 ± 0.3 (6)	9.8 ± 0.5	10.0 ± 0.5	9.4 ± 0.6
Fiber shortening (%)	36.8 ± 1.7 (6)	39.3 ± 2.4	38.6 ± 1.7	39.4 ± 2.5
Ejection fraction (%)	56.7 ± 5.4 (6)	57.5 ± 5.6	62.0 ± 1.1	61.5 ± 1.1
E/A ratio	1.10 ± 0.08 (6)	1.09 ± 0.12	1.32 ± 0.16	1.42 ± 0.7

SDNN indicates standard deviation of RR intervals; PNN50, percent of NN intervals with variation of greater than 50 months; RMSSD, square root of the mean squared of successive RR intervals; CVNN, coefficient of variation of RR intervals; HF, high frequency; LF, low frequency; LV, left ventricular.

control between the control and infusion groups were demonstrated. As noted in Table 1, in the 2 years before entry into the study, the control patients (n = 8) had 7 episodes of hypoglycemic coma and an additional 57 hypoglycemic episodes that required assistance. Patients in the infusion group (n = 10) had 13 episodes of coma and an additional 347 episodes necessitating assistance.

During the 12-month period studied, control group patients (n = 8) had 132 hypoglycemic events (average, 22 per patient per year), of which none resulted in either coma or required assistance. Mean daily insulin dose decreased significantly from 49 to 40 U ($P = .014$). Infusion patients (n = 10) had 272 hypoglycemic events (average, 30 per patient per year), of which 1 was associated with a minor motor vehicle accident. Mean daily insulin dose increased slightly from 40 to 42 U. The 12-month change in insulin dose was significantly different between the study groups (−13.8 ± 3.7 vs 2.3 ± 3.5, $P = .009$). Both groups had decreases in weight (control, 77.8 to 76.7 kg; infusion, 73.3 to 73.2 kg). Despite a fall in insulin dose by 12 months, the control group had a higher incidence of edema ($P = .043$) than the infusion group, in which the insulin dose rose slightly. Infusion patients demonstrated respiratory quotient (RQ) (V_{CO_2}/V_{O_2}) increase from 0.854 ± 0.003 to 0.954 ± 0.050 ($P = .005$) in the initial few weeks of infusion therapy. At the end of 1 year of weekly treatments, RQ increased from 0.826 ± 0.002 to 0.915 ± 0.001 ($P = .005$).

3.2. Renal function

Creatinine clearance decreased during the study period from 55 to 46 mL/min in the control group and from 58 to 55 mL/min in the infusion group (Table 1). These differences were not significant for either group. The change in serum creatinine over 12 months was 0.45 ± 0.16 in the control group and 0.08 ± 0.06 in the infusion group ($P = .056$). The change in hemoglobin was significantly different between the 2 study groups (control, −1.9 ± 0.32; infusion, −0.77 ± 0.25; $P = .013$). Between the control and weekly infusion groups, there was no difference in mean arterial pressure (MAP) at baseline or at 12 months. The change from baseline to 12 months in MAP was also not significantly different between the control and infusion groups. There was a significant increase in the presence of edema in the control group without significant difference in degree of proteinuria when compared with the insulin infusion group.

3.3. Cardiac autonomic function and echocardiographic measurements

Details of the relationship between time and frequency domain measures of heart rate variation (cardiac autonomic function) and echocardiographic measurements of left

Table 3
Effect of 12 months of intensive insulin treatment on hemostatic parameters

Parameter	Control		Infusion	
	Baseline	1 y	Baseline	1 y
Fibrinogen (mg/dL)	391 ± 31	338 ± 41	428 ± 51	357 ± 41
Factor VII (%)	126.1 ± 5.8	105.9 ± 5.2	139 ± 5.7	100.3 ± 9.8
Von Willebrand factor (%)	163 ± 15	110 ± 22	163 ± 19	157 ± 17
Fibrinolytic activity (mm^2)	173.9 ± 14.6	75.1 ± 12.2	138.6 ± 22.4	90.2 ± 20.0
Plasminogen activator inhibitor 1 (ng/mL)	10.22 ± 3.00	9.41 ± 1.77	5.46 ± 0.76	12.9 ± 1.45
Platelet adhesion (no. of platelets)	135 ± 24	184 ± 27	161 ± 35	
Platelet aggregation				
ADP (mmol/L)	1.73 ± 0.34	2.44 ± 0.42	1.99 ± 0.76	2.50 ± 0.84
Collagen (s)	92.8 ± 8.3	84.4 ± 7.8	105.3 ± 15.0	86.0 ± 12.6
Epinephrine (mmol/L)	0.13 ± 0.08	1.20 ± 0.90	1.47 ± 0.81	1.12 ± 0.37

ADP indicates adenosine diphosphate.

ventricular mass and function in control and insulin therapy study groups are shown in Table 2. There were no significant differences demonstrated between study groups at baseline and 12 months, or in changes over the course of the study period with respect to measures of parasympathetic, sympathetic, or left ventricular function. Likewise, no differences with respect to left ventricular geometry or mass were found.

3.4. Hemostatic function

There were no significant differences between study groups with regard to baseline and 12 months, or in changes in hematocrit, albumin, fibrinogen, factor VII, fibrinolytic activity, plasminogen activator inhibitor, von Willebrand factor, viscosity, and tests of platelet aggregation or adhesion (Table 3).

4. Discussion

4.1. Glycemic control

The study groups experienced similar levels of improvement in glycohemoglobin and advanced glycated end products. Weekly infusion therapy was associated with no change in mean daily insulin dose, in contradistinction to the control group in which mean daily insulin decreased significantly. We could not therefore attribute the high incidence of edema in the control group to insulin excess.

In the 2 years before randomization, our patient population had demonstrated a considerable requirement for assistance to treat hypoglycemia. Because of a protocol that involved careful weekly monitoring of all patients by health care personnel, a marked reduction in episodes of hypoglycemia that required assistance or hospitalization was observed in both groups.

The renal medulla and the retina require an RQ of 1.0, suggesting that energy production is highly dependent upon glucose utilization [9]. An RQ of less than 0.80 is most likely associated with some risk to these vital target tissues [1,10,11]. More important may be the capacity to respond to therapy with an increase to greater than 0.80 [1,10,11]. Patients with type 2 diabetes mellitus treated with sulfonylurea [12] and normal adults have been documented at 0.90 [10,11]. A significant increase in carbohydrate/fat oxidation was routinely noted in each infusion patient throughout the duration of the study. The pulsed infusions in this study increased RQ significantly. Uncontrolled diabetes has been demonstrated to increase energy demands generated from the oxidation of glucose in the renal medulla [9]. Increased efficiency of fuel utilization may result in preservation of function.

Diminished production of advanced glycated end products would be associated with decreased direct deposition in the glomerular mesangium and decreased adherence to the glomerular epithelial podocyte by means of a specific receptor [13]. Mesangial deposition resulting in scarring would account for decreased filtration of nitrogen waste products. Podocyte adherence via the receptor for advanced glycated end product would result in albuminuria [14].

4.2. Renal function

It is possible that partial correction of total body RQ may have been reflected in that part of the kidney most sensitive to increased demand for energy production from glucose oxidation associated with type 1 diabetes mellitus.

In the multicenter study that included a larger group of patients [8], creatinine clearance in the control group decreased by 7.69 mL/(min y) compared with 2.21 mL/(min y) in the infusion group. The duration of that study was only 18 months. If continuation of therapy beyond 12 months were to demonstrate durable and linear effects, the projected time to reach a creatinine clearance of 10 mL/min with a probable need for renal replacement therapy would be 6 years for the control group and 22 years for those on insulin infusion therapy. For the 18 patients in our substudy, rate of loss of creatinine clearance was 9.6 mL/(min y) for the control group and 3 mL/(min y) for the infusion group, which would predict a need for renal replacement therapy in 5 years for the control group and 16 years for the infusion group.

A rise in serum creatinine with a fall in creatinine clearance has been described in patients with type 1 diabetes mellitus followed for 3 years after islet cell transplantation due to the effects of the immunosuppressive drugs [15]. The mean creatinine clearance at baseline was about 92 mL/min, with a fall of about 7 mL/(min y) over 3 years in patients without significant proteinuria. The study population with significant albuminuria and a mean creatinine clearance of 56 mL/min could not safely be offered islet cell transplantation instead of pulsed insulin because of the likelihood of accelerated renal deterioration.

4.3. Cardiac and autonomic function

Improvements in glycemic control have been demonstrated to be associated with improvement of autonomic reflex responses [16,17], cardiac function [18,19], and outcome [20]. In this study, we postulated that weekly pulsatile insulin infusion would also be associated with autonomic functional, cardiac structural, and functional changes. The absence of any significant differences in blood pressure, autonomic, cardiac structural, or functional measurements when the control group was compared with the infusion group led us to conclude that the preservation of renal function was independent of autonomic and hemodynamic causes.

4.4. Hemostatic function

We have previously shown a significant fall in elevated levels of fibrinogen and factor VII in patients with type 1 diabetes mellitus whose glycohemoglobin and advanced glycated product levels simultaneously improved [21,22]. In these same patients, there was evidence of both accelerated platelet adhesion and accelerated fibrinolysis at baseline. There were no significant decreases in platelet aggregation over

12 months, but fibrinolytic activity fell toward the reference range, whereas levels of plasminogen activator inhibitor rose toward the reference range. None of these findings reached statistically significant differences between the study groups in the present report, suggesting that preservation of renal function was independent of hemostatic cause.

5. Limitations

This is a small single-center study of limited duration. If the reduction in the slope of creatinine clearance loss is also associated with a decrease in major adverse cardiac events and an increase in the duration of time to renal replacement therapy, then the benefits that we attribute to weekly insulin infusion therapy may be understated. Instability of renal function is a predictor of major adverse cardiovascular events in patients with diabetes and heart disease. Because renal dysfunction is associated with truncated survival, the excess cost of major adverse cardiovascular events must be incorporated into future studies. A larger study in type 1 or 2 diabetes mellitus patients with any level of renal dysfunction should be undertaken to determine whether metabolic manipulation is associated with a lessening of major adverse cardiovascular events.

6. Conclusions

Our hypothesis that preservation of renal function in type 1 diabetes mellitus patients with proteinuria by weekly pulsed insulin infusion involves mechanisms from the autonomic nervous system, cardiac size, and function, or elements of hemostasis was not confirmed. It seems therefore that the improvements of cardiac structure and function and the changes in hemostatic balance seen with improvement in glycemic control are independent of the method of insulin administration.

Acknowledgment

Supported in part by the Pat Covelli Foundation and the Advanced Diabetes Treatment Centers.

References

[1] Aoki TT, Vlachokosta FV, Foss MC, Meistas MT. Evidence for restoration of hepatic glucose processing in type 1 diabetes mellitus. J Clin Invest 1983;71:837-9.

[2] Paolisso G, Scheen AJ, Giugliano D, Sgambato S, Albert A, Varrichio M, et al. Pulsatile insulin delivery has greater metabolic effects than continuous hormone administration in man: importance of pulse frequency. J Clin Endocrinol Metab 1991;72:607-15.

[3] Paolisso G, Sgambato S, Giunta R, Varrichio M, D'Onofrio F. Pulsatile rather than continuous glucagon infusion leads to greater metabolic derangements in insulin-dependent diabetic subjects. Diabete Metab 1990;16:42-7.

[4] Maiter D, Underwood LE, Maes M, Davenport ML, Ketelslegers JM. Different effects of intermittent and continuous growth hormone administration on serum somatostatin-C/insulin-like growth factor 1 and liver growth hormone receptors in hypophysectomized rats. Endocrinology 1988;123:1053-9.

[5] Pal BR, Phillips PE, Matthews DR, Dunger DB. Contrasting metabolic effects of continuous and pulsatile growth hormone administration in young adults with type 1 (insulin-dependent) diabetes mellitus. Diabetelogia 1992;35:542-9.

[6] Aoki TT, Benbarka MM, Okimura MC, et al. Long-term intermittent intravenous insulin therapy and type 1 diabetes mellitus. Lancet 1993;342:525-8.

[7] Aoki TT, Grecu EO, Arcangeli MA. Chronic intermittent intravenous insulin therapy corrects orthostatic hypotension of diabetes. Am J Med 1995;99:683-4.

[8] Dailey GE, Boden GH, Creech RH, Johnson DG, Gleason RE, Kennedy FP, et al. Effects of pulsatile intravenous insulin therapy on the progression of diabetic nephropathy. Metabolism 2000;49: 1491-5.

[9] Korner A, Eklof AC, Celsi G, Aperia A. Increased renal metabolism in diabetes. Mechanism and functional implications. Diabetes 1994;43: 629-33.

[10] Wohl P, Wohl P, Girman P, Pelikanova T. Inflexibility of energy substrate oxidation in type 1 diabetic patients. Metabolism 2004;53: 655-9.

[11] Perseghin G, Lattuada G, de Cobelli F, Esposito A, Constantino F, Canu T, et al. Reduced intrahepatic fat content is associated with increased whole body lipid oxidation in patients with diabetes. Diabetologia 2005;48:2615-21.

[12] Avignon A, Lapinski H, Rabasa-Lhoret R, Caubel C, Boniface H, Monnier L. Energy metabolism and substrates oxidative patterns in type 2 diabetic patients treated with sulphonylurea alone or in combination with metformin. Diabetes Obes Metab 2000;2:229-35.

[13] Pugliese G, Pricci F, Romeo G, Pugliese F, Mene P, Giannini S, et al. Upregulation of mesangial growth factor and extracellular matrix synthesis by advanced glycation end products via a receptor-mediated mechanism. Diabetes 1997;46:1881-7.

[14] Wendt T, Tanji N, Guo J, Hudson BI, Bierhaus A, Ramasamy R, et al. Glucose, glycation, and RAGE: implications for amplification of cellular dysfunction in diabetic nephropathy. J Am Soc Nephrol 2003; 14:1383-95.

[15] Shapiro AMJ, Ricordi C, Hering BJ, et al. International trial of the Edmonton protocol for islet transplantation. N Engl J Med 2006;355: 1318-30.

[16] Weinrauch LA, Kennedy FJ, Burger AJ, Gleason RE, Keough J, D'Elia JA. Prospective evaluation of autonomic dysfunction in aggressive management of diabetic microangiopathy. Am J Hypertens 1999;12: 1135-9.

[17] Burger AJ, Weinrauch LA, D'Elia JA, Aronson D. Effect of glycemic control on heart rate variability in type 1 diabetic patients with cardiac autonomic neuropathy. Am J Cardiol 1999;84:669-87.

[18] Aepfelbacher F, Yeon SB, Weinrauch LA, D'Elia J, Burger AJ. Effect of improved glycemic control on left ventricular structure and function in patients with type 1 diabetes mellitus. Int J Cardiol 2004;94:47-51.

[19] Weinrauch LA, Burger A, Gleason RE, Lee AT, D'Elia JA. Left ventricular mass reduction in type 1 diabetic patients with nephropathy. J Clin Hypertens 2005;7:159-64.

[20] Weinrauch LA, Burger A, Aronson D, Gleason RE, Lee AT, D'Elia JA. Regression of left ventricular hypertrophy in diabetic nephropathy: loss of parasympathetic function predicts response to treatment. J Clin Hypertens 2006;8:330-5.

[21] D'Elia J, Weinrauch L, Gleason R, Lipinska I, Keough J, Pendse S, et al. Fibrinogen and factor VII levels improve with glycemic control in type 1 diabetic patients with microvascular complications. Arch Int Med 2001;161:98-101.

[22] Roshon B, Tofler G, Weinrauch L, Gleason R, Keough J, Lipinska I, et al. Improved glycemic control and platelet function abnormalities in diabetic patients with microvascular disease. Metabolism 2000;49: 88-91.

Original Article

EFFECT OF INTENSIVE INSULIN THERAPY ON PROGRESSION OF OVERT NEPHROPATHY IN PATIENTS WITH TYPE 1 DIABETES MELLITUS

Thomas T. Aoki, M.D., F.A.C.E.,[1] Eugen O. Grecu, M.D.,[2] G. M. Gollapudi, M.D., F.A.C.E.,[3] A. Rodman Barber, M.D., F.A.C.E.,[4] Michael A. Arcangeli, M.S.,[2] Mamoud M. Benbarka, M.D.,[1] Pamela Prescott, M.D.,[1] and Ronald Meisenheimer, M.S.[2]

ABSTRACT

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

Methods: We undertook a 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. All study patients had follow-up consultations weekly for at least 12 months (mean duration, 37.0 ± 4.6 months). Each patient had monthly hemoglobin A_{1c} (by high-performance liquid chromatography) and semiannual creatinine clearance determinations.

Results: The hemoglobin A_{1c} levels declined significantly from 8.6 ± 0.6% to 7.6 ± 0.3% ($P = 0.0062$) during the study period. The creatinine clearance remained essentially unchanged (from 46.1 ± 3.0 mL/min per 1.73 m^2 at baseline to 46.0 ± 3.9 mL/min per 1.73 m^2 at the end of the observation period, with an average annualized slope increase of 3.39 ± 1.5 mL/min per year—no significant difference).

Conclusion: 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. **(Endocr Pract. 1999;5:174-178)**

Abbreviations:
ACE = angiotensin-converting enzyme; **BP** = blood pressure; **CIIIT** = chronic intermittent intravenous insulin therapy; **CrCl** = creatinine clearance; **DM** = diabetes mellitus; **ESRD** = end-stage renal disease; **ISIT** = intensive subcutaneous insulin therapy

Submitted for publication December 4, 1998
Accepted for publication April 8, 1999
From the [1]University of California, Davis, [2]Aoki Diabetes Research Institute, Sacramento, California, [3]Diabetes Center of the Southwest, Midland, Texas, and [4]the Endocrine Metabolic Clinic, Santa Rosa, California.
Address correspondence and reprint requests to Dr. T. T. Aoki, Division of Endocrinology, University of California, Davis, 4301 X Street, FOLB II C, Sacramento, CA 95817.
© 1999 AACE.

INTRODUCTION

Diabetic nephropathy develops in 35 to 40% of patients with type 1 diabetes mellitus (DM) (1,2), and it is the most common cause of end-stage renal disease (ESRD) in the United States (3). Experts generally agree that diabetic nephropathy is the result of hyperglycemia, whether alone or in combination with other factors (4-6). Once nephropathy has become clinically overt (that is, macroalbuminuria and decreased glomerular filtration rate are detected), however, the degree of glycemic control is believed to have lost its importance as a risk factor, and other mechanisms have greater influence (4,5,7). Most patients with type 1 DM and proteinuria eventually will have progression to ESRD (4,7) or premature death from cardiovascular complications (8). In such patients, with no medical intervention, the glomerular filtration rate decreases an average of 1 mL/min per month, a deterioration that leads to ESRD in a mean period of 7 years (9). Once overt persistent proteinuria is established, no known strategy exists that can stop or reverse the progression to ESRD (2,10).

For accompany editorial, see page 223

Effective antihypertensive therapy has been suggested to reduce renal- and possibly cardiovascular-related mortality in patients with type 1 DM and proteinuria (11,12), as well as retard the decline of glomerular filtration rate in some patients with impaired renal function (12,13). Although in several studies strict glycemic control has also been shown to be effective in reducing or arresting the progression of microalbuminuria in patients with type 1 DM (14-18), once overt nephropathy has developed, tight glycemic control has been found, albeit not unanimously (19), not to retard progression to renal failure (7,20).

The aim of this pilot retrospective study was to assess the effects of chronic (long-term) intermittent intravenous insulin therapy (CIIIT) on the progression of overt nephropathy in patients with type 1 DM.

PATIENTS AND METHODS

Study Subjects

Thirty-one patients with type 1 DM and overt nephropathy, from three medical centers (Aoki Diabetes

Research Institute, Sacramento, California; Endocrine Metabolic Clinic, Santa Rosa, California; and Diabetes Center of the Southwest, Midland, Texas), who fulfilled the inclusion criteria and had undergone systematic follow-up for at least 12 months, were entered into this retrospective study (Table 1). The inclusion criteria were as follows: (*1*) a classic history of type 1 DM of at least 15 years' duration, with onset before age 41 years, (*2*) persistent albuminuria (>300 mg/24 h), and (*3*) at least two creatinine clearance (CrCl) determinations per year, with values greater than 15 mL/min per 1.73 m^2, performed during the observation period. All patients had been insulin dependent since the time of diagnosis of DM, and all were receiving insulin injections four times a day (intensive subcutaneous insulin therapy [ISIT]). The patients followed their usual American Diabetes Association diet and were instructed in mild restriction of sodium (6 to 8 g of NaCl daily) and protein (0.8 to 0.9 g/kg of body weight). Diabetic nephropathy was diagnosed clinically on the basis of established criteria (21). All participants gave written informed consent.

Table 1
Main Characteristics of 31 Study Patients With Type 1 Diabetes and Overt Nephropathy at Entry Into the Study

Characteristic	Finding*
Sex (M:F)	13:18
Age (yr)	46.8 ± 2.2
Duration of diabetes (yr)	24 ± 1.7
Hypertension (yes:no)	27:4
Hemoglobin A_{1c} (%)	8.6 ± 0.6
Creatinine clearance (mL/min)	46.1 ± 3.0
Diabetic retinopathy (BDR:PDR)†	3:28

*Data are shown as absolute numbers or means ± standard error.
†BDR = background diabetic retinopathy; PDR = proliferative diabetic retinopathy.

Study Procedures

Diabetic control was assessed by monthly monitoring of hemoglobin A_{1c} blood levels, determined by high-performance liquid chromatography [Varian Vista 5560 high-performance liquid chromatographic system equipped with a Waters SP-5PW column (22)]. All patients were instructed to perform self-monitoring of blood glucose with use of an Accu-Chek II meter (Boehringer Mannheim, Indianapolis, IN). Systemic blood pressure (BP) was assessed by monthly 24-hour ambulatory BP monitoring (SpaceLabs, model 90207, Redmond, WA) and by weekly BP measurements, with the patient in the sitting position and using the same ambulatory BP monitoring device. Serum and 24-hour urine specimens were collected for determinations of serum electrolytes, serum creatinine, blood urea nitrogen, CrCl, and urinary protein excretion. These tests were performed at a commercial laboratory (Nichols Institute or Quest). For studies on the progression of renal insufficiency, reliable methods must be used to measure renal function. CrCl determinations, like all renal clearance techniques, have the drawback of possible urine sampling errors unless an indwelling catheter is used. The effects of any sampling errors, however, are reduced by use of multiple collection periods. To decrease methodologic errors, we also used a slope coefficient analysis based on all available CrCl values in addition to the first and last determinations. In this analysis, a total of 163 CrCl determinations were used.

During the entire observation period, all participants were assessed weekly by the investigators, at which time appropriate adjustments were made in their insulin (ISIT) and in their antihypertensive medication dosages, with the goal of maintaining optimal glycemic control and BP below 140/90 mm Hg for each patient. For BP control, low or moderate doses of one or a combination of medications from the following classes were used: (*1*) angiotensin-converting enzyme (ACE) inhibitors (enalapril, lisinopril), (*2*) calcium channel blockers (verapamil), (*3*) loop diuretics (furosemide), and (*4*) centrally acting α_2-adrenergic agonists (clonidine). All subjects with hypertension received ACE inhibitor therapy throughout the observation period. The main characteristics of the 31 study patients with type 1 DM are summarized in Table 1.

For the entire duration of observation, the CIIIT was performed weekly, in addition to ISIT, with use of a Bionica MD-110 infusion pump (Los Angeles, CA). During a 60-minute period, 7 to 10 intravenous pulses (about 2 units of insulin per pulse) were infused while the patient ingested 40 to 100 g of glucose. The insulin pulses were administered during the first hour of a 3-hour treatment, and three treatments were given each treatment day, as described in detail elsewhere (23).

We had no control group in this study. Such a group would receive saline rather than insulin pulses but would otherwise be treated identically to the group receiving insulin pulses. Such control patients, however, would quickly have severe hyperglycemia because large amounts of glucose must also be ingested during CIIIT. Therefore, we judged such a design unethical.

Statistical Analysis

Data are expressed as mean values ± standard error. For statistical evaluation, the two-tailed Student *t* test and the Mann-Whitney *U* test were used. The rate of change of CrCl can be summarized by each subject's slope. A regression model was fit to each subject's data by the standard least squares method, and the estimated slope for the patient was then used as the response variable. The Wilcoxon signed rank test for H_o: $\mu_{slope} \neq 0$ versus H_A: $\mu_{slope} \neq 0$ was performed at the level of 0.05 (two-sided). Differences were considered significant when *P* values were <0.05.

RESULTS

The 31 study patients (who received ISIT + CIIIT) underwent follow-up for a mean of 37.0 ± 4.6 months (range, 12 to 84). Their glycemic control at baseline, as reflected by the mean hemoglobin A_{1c} determination, was 8.6 ± 0.6%. During the observation period, the mean hemoglobin A_{1c} level declined to 7.6 ± 0.3% ($P = 0.0062$) (Table 2). The mean CrCl of the study group remained essentially unchanged: 46.1 ± 3.0 mL/min per 1.73 m^2 at baseline and 46.0 ± 3.9 mL/min per 1.73 m^2 at the end of the observation period (no significant difference). The annualized CrCl slope change was positive (+3.39 ± 1.5 mL/min per year), calculated as the slope coefficient for all available data. The Wilcoxon signed rank test for H_0: $\mu_{slope} \neq 0$ versus H_A: $\mu_{slope} \neq 0$, done at the level of 0.05 (two-sided), yielded a P value of 0.54—an indication of no change in the mean CrCl slope and thus a period of progression-free disease. No significant differential effect of CIIIT on CrCl slope as a function of the initial CrCl level was found; the 10 patients with the highest baseline CrCl had an annualized CrCl slope of +0.53 ± 3.3 mL/min per year, whereas the 10 patients with the lowest baseline CrCl levels had an annualized CrCl slope of +3.59 ± 2.0 mL/min per year ($P = 0.410$). Furthermore, the annualized CrCl slope was negative (−1.24 ± 1.08 mL/min per year) for the 10 patients who had undergone CIIIT for the longest period (60.0 ± 5.6 months) and was positive (+9.7 ± 3.2 mL/min per year) for the 10 patients who had undergone CIIIT for the shortest time (13.2 ± 0.8 months) ($P = 0.002$). No significant change in the 24-hour urinary protein excretion was found in the study subjects during the observation period, although a tendency to decline was evident (Table 2). The reciprocal serum creatinine ($[Cr]^{-1}$) slope also remained stable, showing no statistically significant changes (Table 2).

Throughout the observation period, the mean 24-hour BP values of study subjects were maintained within normal range (132 ± 1 mm Hg systolic and 80 ± 0.7 mm Hg diastolic). No correlation between the mean BP values and the CrCl slope over time was found.

DISCUSSION

Glycemic control, as reflected by hemoglobin A_{1c}, was significantly improved in the study subjects during the observation period ($P = 0.0062$) (Table 2). This finding is consistent with results we previously reported in patients with type 1 DM treated with ISIT and weekly CIIIT (23-26).

The minimal decline in CrCl during the observation period clearly indicates stabilization or arrest of progression of the overt diabetic nephropathy in our study patient cohort. This favorable effect was evident in patients who had undergone CIIIT for the shortest duration (average, 13.2 months) and for the longest duration (60.0 months), albeit the former group showed a significantly better annualized CrCl slope than did the latter group (+9.7 versus −1.24 mL/min per year, respectively) ($P = 0.002$). These data suggest that the CIIIT effect of retarding the progression of overt nephropathy seems to be more pronounced during the first 13 months, and it persists as long

Table 2
Chronic Intermittent Intravenous Insulin Therapy: Effect on Glycemic Control and the Progression of Diabetic Nephropathy*

Variable	Baseline	End observation	*P* value
Hemoglobin A_{1c} (%)			
Mean ± SE	8.6 ± 0.6	7.6 ± 0.3	0.0062
Range	5.8-12.5	4.6-9.3	
CrCl (mL/min/1.73 m^2)			
Mean ± SE	46.1 ± 3.0	46.0 ± 3.9	NS
Range	15-80	12-87	
Proteinuria (mg/24 h)			
Mean ± SE	2,162 ± 518	1,725 ± 399	NS
Range	118-8,280	65-5,947	
$[Cr]^{-1}$			
Mean ± SE	0.636 ± 0.05	0.633 ± 0.06	NS
Range	0.217-1.0	0.222-1.0	
Annualized CrCl slope: +3.39 ± 1.5 mL/min/yr			NS

*$[Cr]^{-1}$ = reciprocal serum creatinine; CrCl = creatinine clearance; NS = no significant difference; SE = standard error.

as the therapy continues. Without medical intervention in patients with overt diabetic nephropathy, CrCl declines an estimated mean of 12 mL/min per year, even though a large (fivefold) variation exists between individuals (2). A mean CrCl decline of 8.15 mL/min per year was reported by Dailey et al. (27) in a recent multicenter prospective controlled study, which included a cohort of 36 patients with type 1 DM and overt nephropathy who received an intensive subcutaneous insulin regimen similar to that used in our study in conjunction with hypertension carefully controlled with use of medications including ACE inhibitors. Furthermore, similar to our results presented herein, the study by Dailey et al. (27) also reported a reduction in the progression of overt nephropathy in their 34 patients with type 1 DM who were given a combination of ISIT and weekly CIIIT and whose hypertension was controlled with medication.

We realize that even sequential CrCl determinations can, at times, yield inaccurate estimates of the progression of chronic renal failure. Nevertheless, the prolonged flattening of CrCl curves against time, as noted in many of our patients who received CIIIT, suggests arrested progression (28), inasmuch as finite limits exist to the disparity between CrCl and glomerular filtration rate (29).

In an attempt to minimize the possible effects of hypertension on the progression of renal disease, we paid close attention to maintaining normal blood pressure in all study subjects, using the antihypertensive medications previously described. Furthermore, all subjects with hypertension received ACE inhibitor therapy throughout the observation period, as did the control group receiving ISIT in the multicenter study by Dailey et al. (27). Thus, a possible ACE inhibitor effect was eliminated as the cause for the arrested progression of overt diabetic nephropathy noted in our study patients. Use of saline pulses instead of insulin pulses in a control group would have allowed unequivocal assessment of the effect of CIIIT on the progression of overt nephropathy, but this design would have been unethical. Nevertheless, the absence of a control group necessitates cautious interpretation of the data reported herein.

The exact mechanism by which CIIIT slows the progression of overt diabetic nephropathy remains to be determined. Improved glycemic control, as reflected by the dramatic decline in hemoglobin A_{1c} levels, may in part be responsible for this effect. In a recent study, McLennan et al. (6) showed that a high glucose concentration inhibits degradation of the mesangium and could promote the mesangial enlargement known to occur in diabetic nephropathy. Enlargement of the mesangium, the most consistent morphologic finding in diabetic nephropathy, can compress the glomerular capillaries and thus alter intraglomerular hemodynamics (30,31). An improvement in glycemic control and metabolic milieu with CIIIT could potentially reverse this process and have favorable effects on the progression of overt diabetic nephropathy. Furthermore, CIIIT has been shown to improve BP control substantially and to reduce by 46% the antihypertensive medication requirements in patients with type 1 DM and nephropathy (24), possibly through improvement in vascular reactivity. This effect could also favorably influence the intraglomerular hemodynamics and delay the progression of diabetes-related renal disease.

Several experiments in animals have demonstrated that glomerular expression of transforming growth factor-β, the key mediator between hyperglycemia and mesangial cell stimulation toward overproduction of extracellular matrix, is stimulated by hyperglycemia, hypoinsulinemia, or both (32). Both hyperglycemia and hypoinsulinemia are favorably influenced through the CIIIT procedure.

CONCLUSION

When CIIIT is added to ISIT in the management of patients with type 1 DM and overt nephropathy, the progression of diabetic nephropathy seems to be arrested or considerably slowed. In addition, glycemic control is substantially improved.

ACKNOWLEDGMENT

We thank Michael Bradley, Sheila Hargrave, and Kristy Jacobs for expert technical assistance. This study was supported in part by Advanced Metabolic Systems Corporation and by Boehringer Mannheim Corporation.

REFERENCES

1. **Andersen AR, Christiansen JS, Andersen JK, Kreiner S, Deckert T.** Diabetic nephropathy in type 1 (insulin-dependent) diabetes: an epidemiological study. *Diabetologia.* 1983;25:496-501.
2. **Viberti GC, Yip-Messent J, Morcutti A.** Diabetic nephropathy: future avenue. *Diabetes Care.* 1992;15: 1216-1225.
3. US Renal Data System: USRDS 1989 Annual Data Report. Bethesda: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 1989 Aug: 15-16.
4. **Hostetter TH.** Diabetic nephropathy. *N Engl J Med.* 1985;312:642-644.
5. **Hasslacher C, Stech W, Wahl P, Ritz E.** Blood pressure and metabolic control as risk factors for nephropathy in type 1 (insulin-dependent) diabetes. *Diabetologia.* 1985;28:6-11.
6. **McLennan SV, Fisher EJ, Yue DK, Turtle JR.** High glucose concentration causes a decrease in mesangium degradation: a factor in the pathogenesis of diabetic nephropathy. *Diabetes.* 1994;43:1041-1045.
7. **Viberti GC, Bilous RW, Mackintosh D, Bending JJ, Keen H.** Long term correction of hyperglycaemia and progression of renal failure in insulin dependent diabetes. *Br Med J (Clin Res Ed).* 1983;286:598-602.
8. **Borch-Johansen K, Andersen PK, Deckert T.** The effect of proteinuria on relative mortality in type 1 (insulin-dependent) diabetes mellitus. *Diabetologia.* 1985;28:590-596.
9. **Viberti GC, Bilous RW, Mackintosh D, Keen H.** Monitoring glomerular function in diabetic nephropathy: a prospective study. *Am J Med.* 1983;74:256-264.

10. **Austin SM, Lieberman JS, Newton LD, Mejia M, Peters WA, Myers BD.** Slope of serial glomerular filtration rate and the progression of diabetic glomerular disease. *J Am Soc Nephrol.* 1993;3:1358-1370.
11. **Mathiesen ER, Borch-Johnsen K, Jensen DV, Deckert T.** Improved survival in patients with diabetic nephropathy. *Diabetologia.* 1989;32:884-886.
12. **Lewis EJ, Hunsicker LG, Bain RP, Rohde RD (The Collaborative Study Group).** The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy [published erratum appears in *N Engl J Med.* 1993;330:152]. *N Engl J Med.* 1993;329:1456-1462.
13. **Parving HH, Andersen AR, Smidt UM, Hommel E, Mathiesen ER, Svendsen PA.** Effect of antihypertensive treatment on kidney function in diabetic nephropathy. *Br Med J (Clin Res Ed).* 1987;294:1443-1447.
14. **Kroc Collaborative Study Group.** Blood glucose control and the evolution of diabetic retinopathy and albuminuria: a preliminary multicenter trial. *N Engl J Med.* 1984;311: 365-372.
15. **Feldt-Rasmussen B, Mathiesen ER, Jensen T, Lauritzen T, Deckert T.** Effect of improved metabolic control on loss of kidney function in type 1 (insulin-dependent) diabetic patients: an update of the Steno studies. *Diabetologia.* 1991;34:164-170.
16. **Diabetes Control and Complications Trial Research Group.** The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med.* 1993;329:977-986.
17. **Reichard P, Nilsson BY, Rosenqvist U.** The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. *N Engl J Med.* 1993;329:304-309.
18. **McCance DR, Hadden DR, Atkinson AB, Johnston H, Kennedy L.** The relationship between long-term glycaemic control and diabetic nephropathy. *Q J Med.* 1992; 297:53-61.
19. **Nyberg G, Blohme G, Norden G.** Impact of metabolic control on progression of clinical diabetic nephropathy. *Diabetologia.* 1987;30:82-86.
20. **Taft JL, Nolan CJ, Yeung SP, Hewitson TD, Martin FI.** Clinical and histological correlations of decline in renal function in diabetic patients with proteinuria. *Diabetes.* 1994;43:1046-1051.
21. **Parving HH, Andersen AR, Smidt UM, Svendsen PA.** Early aggressive antihypertensive treatment reduces rate of decline in kidney function in diabetic nephropathy. *Lancet.* 1983;1:1175-1179.
22. **Ellis G, Diamandis EP, Giesbrecht EE, Daneman D, Allen LC.** An automated "high-pressure" liquid-chromatographic assay for hemoglobin A1c. *Clin Chem.* 1984; 30:1746-1752.
23. **Aoki TT, Benbarka MM, Okimura MC, et al.** Long-term intermittent intravenous insulin therapy and type 1 diabetes mellitus. *Lancet.* 1993;342:515-518.
24. **Aoki TT, Grecu EO, Prendergast JJ, Arcangeli MA, Meisenheimer R.** Effect of chronic intermittent intravenous insulin therapy on antihypertensive medication requirements in IDDM subjects with hypertension and nephropathy. *Diabetes Care.* 1995;18:1260-1265.
25. **Aoki TT, Grecu EO, Arcangeli MA.** Chronic intermittent intravenous insulin therapy corrects orthostatic hypotension of diabetes. *Am J Med.* 1995;99:683-684.
26. **Aoki TT, Grecu EO, Arcangeli MA, Meisenheimer R.** Effect of intensive insulin therapy on abnormal circadian blood pressure pattern in patients with type 1 diabetes mellitus. *Online J Curr Clin Trials.* 1995 Dec 15;Doc No. 199.
27. **Dailey G, Boden G, Creech R, et al.** Weekly pulsatile IV insulin treatments appear to slow progression of diabetic nephropathy [abstract]. *Diabetes.* 1995;44(Suppl 1):83.
28. **Walser M.** Progression of chronic renal failure in man. *Kidney Int.* 1990;37:1195-1210.
29. **Walser M, Drew HH, LaFrance ND.** Reciprocal creatinine slopes often give erroneous estimates of progression of chronic renal failure. *Kidney Int Suppl.* 1989;27:S81-S85.
30. **Steffes MW, Osterby R, Chavers B, Mauer SM.** Mesangial expansion as a central mechanism for loss of kidney function in diabetic patients. *Diabetes.* 1989;38: 1077-1081.
31. **Mauer SM, Steffes MW, Ellis EN, Sutherland DE, Brown DM, Goetz FC.** Structural-functional relationships in diabetic nephropathy. *J Clin Invest.* 1984;97: 1143-1155.
32. **Sharma K, Ziyadeh FN.** Hyperglycemia and diabetic kidney disease: the case for transforming growth factor-β as a key mediator. *Diabetes.* 1995;44:1139-1146.

Effects of Pulsatile Intravenous Insulin Therapy on the Progression of Diabetic Nephropathy

George E. Dailey, Guenther H. Boden, Robert H. Creech, David G. Johnson, Ray E. Gleason, Frank P. Kennedy, Larry A. Weinrauch, Matthew Weir, and John A. D'Elia

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 glycohemoglobin (HbA_{1c}), and every 3 months, 24-hour urinary protein excretion and creatinine clearance (CrCl) determinations. The HbA_{1c} 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). We 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.
Copyright © 2000 by W.B. Saunders Company

DIABETIC NEPHROPATHY, which develops in 35% to 40% of patients with type 1 diabetes mellitus (DM),[1,2] is the most common cause of end-stage renal disease (ESRD) in the United States.[3] It is generally agreed that early diabetic nephropathy is the result of hyperglycemia, whether alone or in combination with other factors.[4-6] Without intervention, type 1 DM patients with proteinuria eventually will progress to ESRD[4,7] or die prematurely of cardiovascular complications.[8] Historically, the glomerular filtration rate (GFR) decreases an average of 1 mL/min/month, ie, 12 mL/min/yr,[9] leading to ESRD in a mean period of 7 years.[10] Once overt persistent proteinuria is established, no special strategy exists to reverse the progression of renal dysfunction.[2,11] Appropriate antihypertensive therapy has been shown to significantly reduce renal and possibly cardiovascular mortality in proteinuric type 1 DM patients,[12,13] as well as retard the rate of decline of GFR in some patients with impaired renal function.[12,14] The Collaborative Study Group showed that angiotensin-converting enzyme (ACE) inhibition significantly diminished the incidence of doubling of serum creatinine in type 1 diabetic patients with both proteinuria and loss of renal function.[12] Thus, at this point the standard of care for patients with diabetic nephropathy is multiple insulin injections with frequent capillary blood glucose monitoring and ACE inhibition with frequent blood pressure monitoring. Over the past 2 decades, a body of literature has described more efficient glucose disposal with pulsatile rather than continuous intravenous (IV) insulin infusion.[15,16] The aim of this prospective, controlled, multicenter parallel group study was to assess the effects of weekly pulsatile intravenous insulin therapy (PIVIT, also known as long-term [or chronic] intensive intravenous insulin therapy) on the progression of overt nephropathy in type 1 DM patients.

PATIENTS AND METHODS

Study Subjects

A total of 90 patients with type 1 DM and clinical nephropathy, recruited from 7 medical centers, were enrolled in this study. Inclusion criteria comprised: (1) a history of type 1 DM of at least 10 years duration, with onset before age 35 years, and negative serum C-peptide after challenge with Sustacal; (2) persistent proteinuria (>300 mg/d) and albuminuria (>100 mg/d); and (3) creatinine clearance (CrCl) with values between 30 and 80 mL/minute. Exclusion criteria included: (1) severe nephropathy (advanced stage III to intermediate stage IV, ESRD); (2) presence of severe underlying chronic disease (eg, cancer, hepatic disease); (3) inability to stabilize blood pressure at 140/90 mm Hg or below using ACE inhibitors, calcium (Ca) channel blockers, alpha-1 blockers, central alpha-2 agonists, or diuretics.

Beginning at least 4 weeks before enrollment in the study, all patients were placed on an intensive therapy (IT) regimen of multiple daily insulin injections and blood glucose monitoring plus dietary education as developed by the Diabetes Control and Complications Trial Research Group (DCCT).[17] At the time of enrollment, the patients were randomly assigned to either an attention control (C) or a treatment (T) group using a blocked stratified random sampling program. The T group underwent IT plus weekly PIVIT treatments.

Study Procedures

PIVIT consists of administering insulin IV in 7 to 10 pulses over 1 hour to approximate normal portal insulin concentrations, concomitantly with oral glucose as needed, to prevent hypoglycemia. This is repeated 3 times over an 8-hour period once a week. Enhanced glucose oxidation is assessed via measurement of respiratory quotient with a metabolic cart. PIVIT has been described in detail elsewhere.[18] After considering various possibilities for "sham" PIVIT treatments for C group patients, we determined that the effects of glucose and insulin administration in DM patients could not be disguised, and therefore that this study could not be shielded. Instead, we adopted an "attention

From the Scripps Clinic, San Diego, CA; Temple University Hospital, Philadelphia, PA; Summit Medical Center, Nashville, TN; University of Arizona Medical Center, Tucson, AZ; Joslin Clinic, Boston, MA; Mayo Clinic, Rochester, MN; Mt. Auburn Hospital, Cambridge, MA; and the University of Maryland, Baltimore, MD.

Submitted February 4, 2000; accepted April 26, 2000.

Sponsored by Advanced Metabolic Systems and by Boehringer Mannheim Corp.

Address reprint requests to George Dailey, MD, Division of Endocrinology, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla, CA 92037.

Copyright © 2000 by W.B. Saunders Company

0026-0495/00/4911-0010$10.00/0

doi:10.1053/meta.2000.17700

control" design in which the C group underwent IT plus weekly clinic visits and education throughout the study. All patients followed a DCCT-type diet and were instructed in mild sodium (<3 g sodium/d) and moderate protein (<0.8 g/kg body weight/d) restriction. Diabetic nephropathy was diagnosed clinically according to established criteria.[19] All participants gave written informed consent under appropriate institutional approval policies.

During the entire observation period, all participants were seen weekly by the investigators, at which time appropriate adjustments were made in their insulin (IT) and in their antihypertensive medication dosages, with the goal of maintaining optimal glycemic control and blood pressures (BP) below 140/90 mm Hg for each individual patient. Throughout the observation period, the average 24-hour BP values of study subjects were maintained within the target range. For BP control, patients were preferentially treated with ACE inhibitors (enalapril, lisinopril, captopril, or quinipril), and, as needed, other drug categories were added: Ca channel blockers, loop diuretics (Lasix), and centrally acting alpha-2 agonists (clonidine).

Glycemic control was assessed monthly by monitoring glycohemoglobin (HbA_{1c}) blood levels, determined by high performance liquid chromatography (Nichols Institute, Van Nuys, CA). All patients were instructed to perform self-monitoring of blood glucose using a standard glucose meter. Systemic BP was assessed by monthly 24-hour ambulatory BP monitoring (SpaceLabs, model 90207, Redmond, WA), and by weekly BP measurements in the sitting position, using the same ambulatory BP monitoring device. Serum and 24-hour urine were collected at baseline and at 3-month intervals thereafter for determinations of serum electrolytes, serum creatinine and blood urea nitrogen, serum protein levels, CrCl, and urinary protein excretion. These tests were performed at a commercial laboratory (Nichols Institute). For studies on the progression of renal insufficiency, CrCl was the primary method for determining GFR, backed up in some centers by radionucleotide assays. CrCl determinations, like all renal clearance techniques, have the drawback of possible urine sampling errors. The effects of any sampling errors are, however, reduced by the use of multiple collection periods throughout the study (9 to 15 measurements per patient).

The study was designed to run a minimum of 12 months, with an option for the investigators to extend it to 18 months in the event the treatment appeared effective, but had not yet reached statistical significance at 12 months. In case the study was extended to 18 months, patients would be asked to decide whether they wanted to extend their participation for the additional 6 months.

Statistical Analysis

Data are expressed as means ± SEM and were evaluated statistically by 1-way repeated measures analysis of variance (ANOVA) followed by post hoc comparisons among time means using the Student-Newman-Keuls test. Because of the lack of significant differences between the patients completing 18 months and the patients completing only 12 months, only the data for the group that continued to 78 weeks will be presented here. The rate of change of CrCl was determined by first using least-squares regression of each subject's CrCl measurements versus time to determine an individual slope. The slopes were then averaged within each group and the mean slope for C patients versus T patients compared using an unpaired *t* test. The reciprocal serum creatinine, which tends to mirror CrCl, but generally has a narrower error of measurement, was also calculated. Differences were considered significant when $P < .05$. Changes in HbA1c, mean arterial pressure, and proteinuria were also analyzed and *P* values calculated. Correlations and covariances between CrCl slopes and HbA1c were also determined.

RESULTS

At the end of the first 12 months, a highly significant difference in the change of serum creatinine between the control (from 1.60 ± 0.27 to 1.87 ± 0.32 mg/dL) and treated (from 1.60 ± 0.26 to 1.71 ± 0.28) was noted ($P = .015$). CrCl also tended to decline more rapidly in the control group (−6.88 ± 2.17 mL/min/yr) than in the treated group (−2.33 ± 2.08), but at 12 months, the difference in the rate of decline of CrCl was not statistically significant ($P = .13$). Because the difference in the change of serum creatinine was highly significant and because the difference in the decline in CrCl was approaching significance, the option to extend the study to 18 months was exercised, as envisioned in the original protocol.

Seventy-one patients completed the initial 12 months, of which 49 continued to 18 months (group T, n = 23 [10 females and 13 males]; group C, n = 26 [8 females and 18 males]). Among the 22 patients who left the study after 12 months, the predominant reason for not continuing in the extended study was the significant inconvenience imposed by the weekly clinic visit schedule. One patient (group T) was lost to the study because of starting renal dialysis (patient developed gangrenous cholecystitis with complications leading to the necessity of dialysis). The only significant difference between those patients who discontinued after 12 months and those who continued to 18 months was that the treated patients who continued to 18 months had a higher mean baseline serum creatinine (1.73 mg/dL, 23 of 37) than did the treated patients who discontinued after 12 months (1.60 mg/dL, 14 of 37), $P = .043$. Because the treatment group patients who remained in the study group beyond 12 months had more advanced renal disease than those who declined to continue in the study, it is possible that the deletion of the subgroup that could have been expected to have more stable renal function causes an understatement of any benefit conferred by PIVIT. Importantly, there was no significant difference between the continuing versus the discontinuing patients in the rate of change of CrCl in either the C group or the T group. Figure 1 shows that the diminution of CrCl of the patients completing only 12 months was superimposable on that of the patients continuing to 18 months. Table 1 gives the main characteristics of these patients. There were no significant differences in baseline characteristics of age, onset of diabetes, duration of diabetes, BP, HbA1c, CrCl, protein excretion, or serum creatinine between the C and T groups.

During the observation period, the mean annualized CrCl declined by 2.21 ± 1.62 mL/min/yr in the T group and by 7.69 ± 1.88 mL/min/yr in the C group, and this difference in the mean rate of decline between the groups was significant ($P = .0343$, Fig 1). In addition, there was a highly significant difference in the mean rate of change of reciprocal serum creatinine between the C group (−0.088 ± 0.026 $[mg/dL)^{-1}/yr]$) and the T group (−0.005 ± 0.010), $P = .0047$. No significant correlation between the average CrCl slope and BP, age of onset, or duration of diabetes was found.

The mean HbA_{1c} level declined in the T group from 8.61% ± 0.33% to 7.68% ± 0.31% ($P = .0028$) and in the C group from 9.13% ± 0.36% to 8.19% ± 0.33% ($P = .0015$) (Table 2). No significant difference in HbA_{1c} was found between the T and C groups at baseline ($P = .3046$) or at the end of the study HbA1c ($P = .9887$). There was no significant correlation between HbA1c and the slope of CrCl change over the course of the

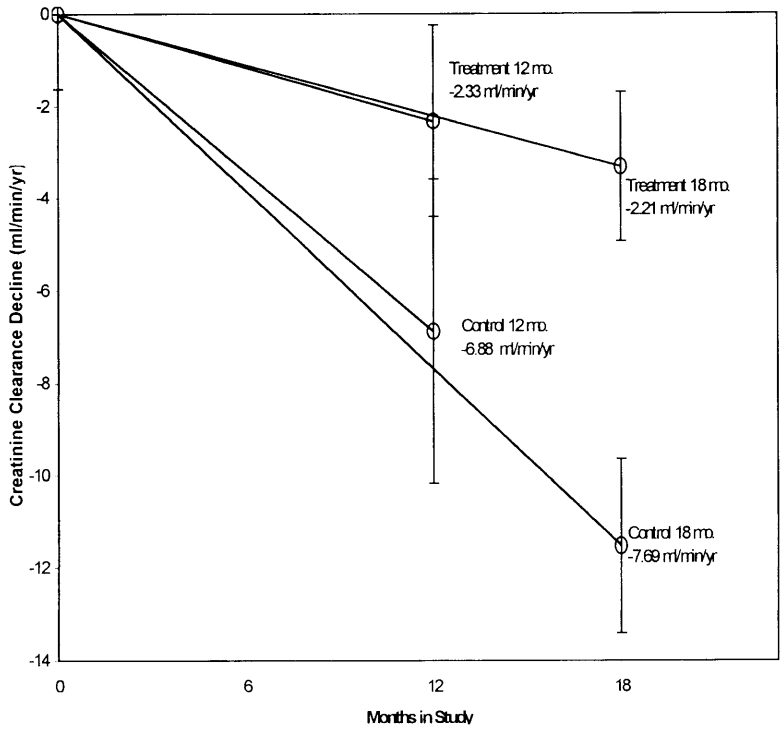

Fig 1. Mean rate of CrCl decline in treatment and control groups.

study ($P = .065$), suggesting that glycohemoglobin in this range did not influence the CrCl slopes. Mean arterial BP, serum cholesterol, triglycerides, high-density lipoprotein (HDL), and 24-hour urinary protein excretion did not change significantly within either study group, and no significant differences in the rate of change of these variables were noted between the groups during the study period. The absence of a reduction in urinary protein excretion in both the T and C groups is in contrast to other studies in which the use of ACE inhibitors in similar populations was associated with reduced protein excretion.[12] There was no significant difference between the T and C groups in the use of ACE inhibitors over the course of the study (Table 3). No significant difference in clinic attendance was found between the T and C groups.

DISCUSSION

To assess PIVIT's effectiveness as an element of best-practices clinical therapy, all patients in the study underwent concurrent IT with weekly patient education and follow-up as per the design of the DCCT,[17] plus preferential treatment of hypertension with ACE inhibitors. As at the time the present study was designed, the standard of care in diabetic nephropathy called for preferential treatment of hypertension by ACE inhibitors, but did not call for the use of ACE inhibitors in normotensive patients; in this study only hypertensive patients received ACE inhibitors. The patients who could not tolerate the latter medications were given diltiazem. ACE inhibitors were not continued in those patients who developed severe hyperkalemia (27%).

On average, group T patients showed significantly less decline in CrCl during the study than did group C patients (2.21 mL/min/yr *v* 7.69 mL/min/yr). Similar reduction in the progression of overt nephropathy in 31 patients with type 1 DM on PIVIT, followed for an average of 37 months, have recently been reported in a multicenter retrospective study.[20] It has been estimated that without intensive medical intervention, CrCl

Table 1. Characteristics of Study Patients at Baseline (mean ± SEM)

	Patients Completing 18 Months		Patients Completing 12 Months	
	Control (C)	Treatment (T)	Control (C)	Treatment (T)
No. (female/male)	26 (8/18)	23 (10/13)	34 (11/23)	37 (17/20)
Age (yr)	40.6 ± 1.8	43.9 ± 1.7	40.2 ± 1.5	42.1 ± 1.6
Age at onset (yr)	14.0 ± 1.6	15.6 ± 2.0	13.6 ± 1.3	14.2 ± 1.5
Duration of DM (yr)	26.2 ± 1.4	27.7 ± 1.6	26.2 ± 1.3	27.4 ± 1.4
Mean arterial pressure	97.1 ± 1.8	96.7 ± 1.6	96.9 ± 1.6	96.4 ± 1.6
Systolic BP (mm Hg)	133.0 ± 2.4	133.6 ± 2.4	133.0 ± 2.1	133.3 ± 2.2
Diastolic pressure (mm Hg)	79.2 ± 1.4	76.9 ± 1.9	79.0 ± 1.3	77.5 ± 1.5
Hemoglobin A_{1C} (%)	9.13 ± 0.36	8.61 ± 0.33	9.00 ± 0.31	8.74 ± 0.25
CrCl (mL/min)	59.6 ± 3.8	55.3 ± 3.7	63.0 ± 3.6	59.2 ± 3.6
Proteinuria (mg/d)	2,107 ± 326	2,057 ± 438	1,959 ± 257	2,042 ± 334
Serum creatinine (mg/dL)	1.66 ± 0.10	1.73 ± 0.12	1.60 ± 0.09	1.60 ± 0.08

Table 2. Changes in Key Variables During Study (mean ± SEM) for Patients Completing 18 Months (N = 49)

	Control Group (C)		Treatment Group (T)	
	Baseline	End of Study	Baseline	End of Study
Hemoglobin A_{1c} (%)	9.13 ± 3.06	8.19 ± 0.33*	8.61 ± 0.33	7.68 ± 0.31*
Mean arterial pressure (mm Hg)	97.1 ± 1.8	98.6 ± 2.6	96.7 ± 1.6	95.3 ± 1.8
Proteinuria (mg/d)	2,107 ± 326	2,609 ± 612	2,057 ± 438	2,362 ± 682

*$P < .05$. N.B., analysis of p(ΔC *v* ΔT) is only appropriate if p(ΔC) and p(ΔT) are individually significant.

decreases at an average of 12 mL/min/yr[9,10] in patients with overt diabetic nephropathy, although a 5-fold variation exists between individuals.[2] The difference in CrCl decline between T and C patients is attributed to the effects of PIVIT treatment in the T group because there was no significant difference between the groups with regard to other potential renal-sparing factors, namely HbA1c, BP, ACE inhibitor use, and frequency of clinic visits. Also, due to randomization by a shielded process, baseline characteristics that might affect progression of nephropathy, namely age, duration of diabetes, serum creatinine, and proteinuria also were not different between treatment groups. Except for the addition of the weekly PIVIT procedure in the group T patients, the 2 patient groups were treated virtually identically.

We recognize that CrCl determinations can, at times, yield inaccurate estimates of the progression of chronic renal failure. Nevertheless, the significant and sustained reduction of CrCl determined by multiple sequential measurements suggests that progression of nephropathy was truly diminished.[21] In addition, the highly significant difference in the rate of change of reciprocal serum creatinine (−0.0047) strongly confirms the hypothesis that PIVIT contributed to a significant reduction in the rate of renal decline in insulin-dependent diabetes mellitus (IDDM) patients with moderate to advanced renal disease. If we postulate a linear deterioration in renal function at a rate of 7 to 15 mL/min/yr for patients not receiving PIVIT, a considerable number could be expected to reach dialysis in 3 to 5 years. Reduction of the deterioration rate to less than 3 mL/min/yr, as in the T group in this study, could be expected to reduce the percentage of patients reaching end stage each year and prolong the time until dialysis therapy or transplantation is required.

Glycemic control was significantly improved during the observation period in the study subjects of both groups T and C. However, there were no significant differences between the degree of improvement in the HbA1c levels of the 2 patient groups over the study period. HbA_{1c} or its changes was not significantly correlated with CrCl or its changes. Therefore, the improvement in glycemic control does not explain the significant reduction in the rate of CrCl decline in group T as compared with group C. Although strict glycemic control has also been shown in several studies to be effective in reducing or arresting the progression of microalbuminuria in type 1 DM patients,[17,22-24] once overt nephropathy had developed, tight glycemic control was found, with some exception,[25] not to retard progression to renal failure.[7,26] Nevertheless, tight glycemic control was a clinical goal for both treatment and control patients in this study.

Because the majority of the patients in this study used ACE inhibitors and because there was no significant difference in ACE inhibitor use between the T and C groups, the antinephropathic effects of PIVIT measured in this study appear to be incremental to the effects of ACE inhibitors.

The exact mechanism by which PIVIT slows the progression of overt diabetic nephropathy remains to be determined. PIVIT has shown positive effects on glycemic control[18] in DM, as well as on BP control in type 1 DM with nephropathy,[27] possibly through improvement in endothelial function. This effect could also favorably influence the intraglomerular hemodynamics and delay the progression of diabetic renal disease. However, the lack of significant difference in HbA_{1c} and in BP between the T and C groups in this study strongly suggests that PIVIT's antinephropathic effects do not arise directly from glycemic or BP control. One hypothesis is that the restoration of nondiabetic physiologic insulin concentrations in the portal system may directly trigger unknown mechanisms that protect renal function to a significant degree. Another possibility is that various mechanisms crucial to protecting the glomerulus may have a higher sensitivity to pulsatile, as opposed to continuous, administration of exogenous insulin. Finally, experiments in animals have indicated that glomerular expression of transforming growth factor β, the key mediator between hyperglycemic and mesangial cell stimulation toward overproduction of extracellular matrix, is stimulated by hyperglycemia, hypoinsulinemia, or both.[28] PIVIT tends to reverse both hyperglycemia and hypoinsulinemia.

CONCLUSION

We conclude that when added to DCCT-style IT in type 1 DM patients with overt nephropathy, PIVIT appears to markedly reduce the progression of diabetic nephropathy. PIVIT's antinephropathic effects appear to accrue independently of, and incrementally to, the benefits afforded by improved glycemic control and by the use of ACE inhibitors.

Table 3. Potentially Confounding Clinical Variables

	Patients Completing 18 Months		Patients Completing 12 Months	
	Control (C)	Treatment (T)	Control (C)	Treatment (T)
Patients using ACE inhibitors	77%	70%	74%	59%
Mean no. of clinic visits/patient	68.7 ± 1.8	70.0 ± 1.3	59.6 ± 3.2	60.7 ± 2.2

REFERENCES

1. Andersen AR, Christiansen JS, Andersen JK, et al: Diabetic nephropathy in type 1 (insulin-dependent) diabetes: An epidemiological study. Diabetologia 25:496-501, 1983

2. Viberti GC, Yip-Messent J, Morcutti A: Diabetic nephropathy. Diabetes Care 15:1216-1225, 1992

3. US Renal Data System: USRDS 1989 Annual Data Report. Bethesda, MD, National Institute of Health, National Institute of Diabetes and Digestive and Kidney Diseases, p 15-16, August 1989

4. Hostetter TH: Diabetic nephropathy. N Engl J Med 312:642-643, 1985

5. Hasslacher C, Stech W, Wahl P, et al: Blood pressure and metabolic control as risk factors for nephropathy in type 1 (insulin-dependent) diabetes. Diabetologia 28:6-11, 1985

6. McLennan SV, Fisher EJ, Yue DK, et al: High glucose concentration causes a decrease in mesangium degradation. Diabetes 43:1041-1045, 1994

7. Viberti GC, Bilous RW, Mackintosh D, et al: Long term correction of hyperglycemia and progression of renal failure in insulin-dependent diabetes. BMJ 286:598-602, 1983

8. Borch-Johansen K, Andersen PK, Deckert T: The effect of proteinuria on relative mortality in type 1 (insulin-dependent) diabetes mellitus. Diabetologia 28:590-596, 1985

9. Jacobsen P, Rossing K, Tarnow L, et al: Progression of diabetic nephropathy in normotensive type 1 diabetic patients. Kid Int 56:101-105, 1999 (suppl 71)

10. Viberti GC, Bilous RW, Mackintosh D, et al: Monitoring glomerular function in diabetic nephropathy. Am J Med 74:256-264, 1983

11. Austin SM, Lieberman JS, Newton LD, et al: Slope of serial glomerular filtration rate and the progression of diabetic glomerular disease. J Am Soc Nephrol 3:1358-1370, 1993

12. Lewis EJ, Hunsicker LG, Bain RP, et al: The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. N Engl J Med 329:1456-1462, 1993

13. Mathiesen ER, Borch-Johnsen K, Jensen DV, et al: Improved survival in patients with diabetic nephropathy. Diabetologia 32:884-886, 1989

14. Parving H-H, Andersen AR, Smidt UM, et al: Effect of antihypertensive treatment on kidney function in diabetic nephropathy. BMJ 294:144-157, 1987

15. Bratusch-Marrain PR, Komjati M, Waldhausl WK: Efficacy of pulsatile versus continuous insulin administration on hepatic glucose production and glucose utilization in type 1 diabetic humans. Diabetes 35:922-926, 1986

16. Paolisso G, Sgambato S, Passariello N, et al: Greater efficacy of pulsatile insulin in type 1 diabetics critically depends on plasma glucagon levels. Diabetes 36:566-570, 1987

17. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 329:977-986, 1993

18. Aoki TT, Benbarka MM, Okimura MC, et al: Long-term intermittent intravenous insulin therapy and type I diabetes mellitus. Lancet 342:515-518, 1993

19. Parving H-H, Andersen AR, Smidt UM, et al: Early aggressive antihypertensive treatment reduces rate of decline in kidney function in diabetic nephropathy. Lancet 1:1175-1179, 1983

20. Aoki TT, Grecu EO, Gollapudi GM, et al: Effect of intensive insulin therapy on progression of overt nephropathy in patients with type 1 diabetes mellitus. Endocr Pract 5:174-178, 1999

21. Walser M: Progression of chronic renal failure in man. Kidney Int 37:1195-1210, 1990

22. Feldt-Rasmussen B, Mathiesen ER, Jensen T, et al: Effect of improved metabolic control on loss kidney function in type 1 (insulin-dependent) diabetic patients: An update of the Steno studies. Diabetologia 34:164-170, 1991

23. Reichard P, Nilsson B-Y, Resenqvist U: The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. N Engl J Med 329:304-309, 1993

24. McCance DR, Hadden DR, Atkinson AB, et al: The relationship between long-term glycemic control and diabetic nephropathy. Q J Med 297:53-61, 1992

25. Nyberg G, Blohme G, Norden G: Impact of metabolic control on progression of clinical diabetic nephropathy. Diabetologia 30:82-86, 1987

26. Taft JL, Nolan CJ, Yeung SP, et al: Clinical and histological correlations of decline in renal function in diabetic patients with proteinuria. Diabetes 43:1046-1051, 1994

27. Aoki TT, Grecu EO, Prendergast JJ, et al: Effect of chronic intermittent intravenous insulin therapy on antihypertensive medication requirements in IDDM subjects with hypertension and nephropathy. Diabetes Care 18:1260-1265, 1995

28. Sharma K, Ziyadeh FN: Hyperglycemia and diabetic kidney disease: The case for transforming growth factor β as a key mediator. Diabetes 44:1139-1146, 1995

: Am J Kidney Dis. 2002 Apr;39(4):721-9. Related Articles, Links

Slowing the progression of chronic renal failure: economic benefits and patients' perspectives.

Trivedi HS, **Pang MM**, **Campbell A**, **Saab P**.

Harry S. Truman Memorial Veterans' Hospital, Columbia, MO 65201, USA. trivedi8@hotmail.com

Because of the predicted increase in end-stage renal disease (ESRD) incidence (projected increase from 1998 to 2010; 86,825 to 172,667), prevalence (projected increase from 1998 to 2010; 326,217 to 661,330), and cost (total cost based on 1998 ratio of Medicare versus non-Medicare cost; $16.74 billion in 1998 to $39.35 billion in 2010), a cohesive national effort is needed to develop strategies to slow the progression of chronic renal failure (CRF). The question arises to how much reduction in the progression of CRF would lead to a meaningful decrease in the prevalence and cost of ESRD. There are no objective data that show the economic impact of slowing the progression of CRF. We developed a mathematical model to assess the economic impact of decreasing the progression of CRF by 10%, 20%, and 30%. US Renal Data System (USRDS) projections were used to model the rate of increase in ESRD incidence and prevalence. Glomerular filtration rate (GFR) at the initiation of ESRD therapy and cost per patient-year were based on USRDS data. The average decline in GFR in subjects with CRF was estimated to be 7.56 mL/min/y. All dollar savings reflect 1998 costs, discounted for the future at 3% per annum. We also determined how much slowing of the progression of CRF is important from patients' perspectives by means of a written questionnaire (which inquired about willingness to go on a restricted diet, take six extra medications per day, and make six extra office visits per year) and calculation of the pre-ESRD time gained for different degrees of reduction in the progression of CRF. If the rate of decline in GFR decreased by 10%, 20%, and 30% after December 31, 1999, in all patients with GFRs of 60 mL/min or less, cumulative direct healthcare savings through 2010 would equal approximately $18.56, $39.02, and $60.61 billion, respectively. For a 10%, 20%, and 30% decrease in the rate of decline in GFR in all patients with a GFR of 30 mL/min or less, estimated cumulative savings through 2010 equal $9.06, $19.98, and $33.37 billion, respectively. Responses to the questionnaire showed that approximately 79% of subjects with CRF (n = 113) perceived a few weeks' dialysis-free period significant (P < or = 0.0001), a period corresponding to a 10% reduction in the rate of decline in GFR. Our data suggest that the cumulative economic impact of slowing the progression of CRF, even by as little as 10%, would be staggering. They provide strong support for the development and implementation of intensive reno-protective efforts beginning at the early stages of chronic renal disease and continued throughout its course. Copyright 2002 by the National Kidney Foundation, Inc.