MEDICAL GRAND ROUNDS

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TREATMENT OF INSULIN DEPENDENT DIABETES MELLITUS WITH PORTABLE INSULIN INFUSION PUMPS: TWO YEARS LATER

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INTRODUCTION

Since the discovery of insulin in 1921 by Banting and Best there have been few major advances in the treatment of insulin dependent diabetes mellitus. In fact, if anything, treatment of this disease has resulted in enormous argument between experts in this field[1,2] regarding both what represents adequate (or inadequate) treatment as well as the effectiveness of the treatment in terms of the long-term vascular complications of diabetes.

It seems almost unbelievable that in the almost 60 years since insulin treatment has been available that the relationship between long-term diabetic control and the microvascular complications of the disease is not better worked out. Although many experts would perhaps disagree, from my point of view, the answer to the question is far from clear. There is, however, an increasing body of data, especially in animals, that relates the development of vascular complications to the metabolic abnormalties of the diabetes. This is perhaps most clearly shown by the work of Mauer et al[3,4] who showed that both pathological and immunofluorescent changes that are characteristically seen in kidneys from rats made diabetic with streptozotocin (similar but not identical to changes seen in diabetic man) can be reversed within two to ten weeks following the restoration of normal glucose and insulin levels by successful islet cell transplantation. In man evidence is accumulating that the blood glucose levels can be related to the complications. For example, in studies of the Pima Indians there is a clear cut relationship between the incidence of retinopathy and the blood glucose levels. The incidence

of retinopathy increases almost in a linear fashion once the plasma glucose level two hours after a glucose load exceeded 180 mg/dl.[5]

However, in man the question remains unanswered.[6] It has been impossible to clearly show that the development of the vascular complications of diabetes are related in any cause and effect way with the level of diabetic control. One might wonder why this is the case? There are several possible reasons why this important question remains unanswered. First of all, the proper long-term clinical experiment is yet to be done. What is really needed is a prospective study in which patients are randomly assigned to either a "tight' or "loose" control, treatment group. This study would have to continue for decades, as clearly many of the vascular complications may take decades to develop. However, the major reason that this question remains unanswered deals with the fact that it is practically impossible with presently available modes of therapy to completely restore blood glucose levels to normal throughout the day in most insulin dependent diabetics. This fact was first pointed out by Service, et al[7] who showed that there are wide fluctuations in plasma glucose levels throughout the day in diabetic patients receiving two injections of intermediate and short acting insulin daily. While the fluctuations diminished somewhat when four injections of regular insulin were used plasma glucose levels nevertheless still were not completely normal. Figure 1 shows the glucose "profile" in nine non-diabetic subjects studied over a 48 hour period. The plasma-glucose level rarely, if ever, exceeded 150 mg/dl even when blood samples are taken one hour after meals.[8]

This is to be compared with the example shown in Figure 2 of an insulin dependent diabetic patient whose diabetes was eventually brought under what would be considered exceptional control using two injections of intermediate and short acting insulin. Despite the fact that glycosuria was eliminated and fasting plasma glucose levels were well within the normal range, postprandial plasma glucose concentrations often exceeded 200 mg/dl. We have repeated this experiment in more than 20 diabetic patients with similar results.[9] It is a relatively simple task in the controlled environment of a clinical research center to eliminate glycosuria and restore fasting glucose levels to normal, but postprandial hyperglycemia often continues despite large doses of insulin. If one is unable to completely normalize the blood glucose level throughout the day in a clinical research unit, imagine how impossible it must be to do so in a real-life situation.

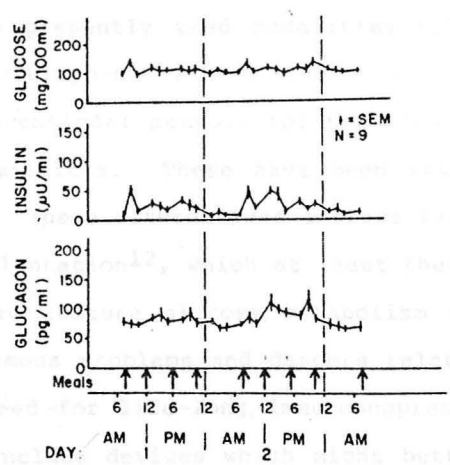

Figure 1. Plasma glucose, insulin and glucagon "profiles" in nondiabetic subjects. Blood samples were obtained at 2 hour intervals. Meals as marked by the arrows. (from Unger et al[18])

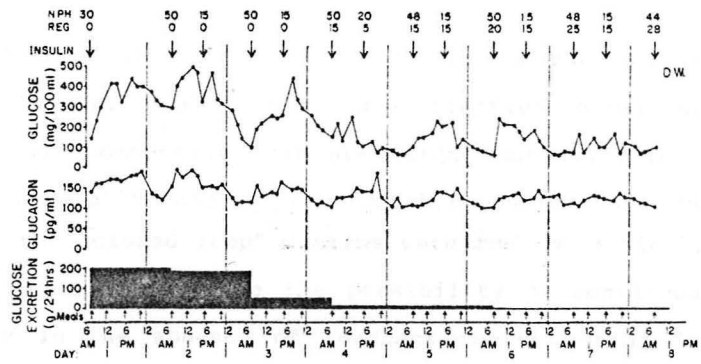

Figure 2. Plasma glucose and glucagon "profile" and the daily 24 hour glucose excretion in a Type I diabetic patient during 8 days of aggressive conventional insulin treatment. Times of meals and insulin administration are marked by the arrows.

Because of the inadequacy of conventional forms of insulin treatment investigators have looked toward the development of alternatives to presently used modalities of treatment. There are several hopeful possibilities with regards to alternatives or adjuncts to conventional methods for treatment of insulin dependent diabetes mellitus. These have been reviewed elsewhere in great detail.[10] These alternatives include islet cell[11] or whole pancreas transplantation[12], which at least theoretically, have the potential to restore glucose metabolism to normal, but are subject to enormous problems and dangers related to graft rejection and the need for life-long immunosuppression.[13] The other possibilities include devices which might better deliver insulin in a more physiological way. The most sophisticated of these devices uses a "closed loop" system which delivers insulin based on a feedback system in which insulin delivery is controlled by

information obtained from the continuous monitoring of plasma glucose levels. These devices are effective in maintaining normal glucose homeostasis but are large, not portable, expensive and can generally only be used for short periods of time.[14,15,16] Because the "closed loop" systems were too impractical, investigators began to evaluate the possibility of continuous insulin delivery in the absence of feedback control using "open loop" systems. Slama, et al[17] first showed the effectiveness of these "open loop" systems which used continuous intravenous infusion in the absence of feedback control. This was shortly followed by several other confirmatory studies.[18,19] Because of the potential hazards related to continuous intravenous infusion that was used in these original studies, investigators looked for other routes of insulin delivery. In 1978 the first article appeared by Pickup and his colleagues[20], in which they reported normalization of plasma glucose levels in nine insulin dependent diabetic patients treated with a continuous 24 hour a day subcutaneous insulin infusion delivered by a small battery powered infusion pump.[21] This pump was portable enough enough to be worn by the patient on a belt or in a harness. Thus began a new era in the treatment of insulin dependent diabetes mellitus. The remainder of this chapter will be devoted to a description of this form of treatment, the equipment used, its effectiveness in terms of the metabolic abnormalities of diabetes, as well as evidence which bears on the question of the long term vascular complications and diabetic control. Finally, I will discuss the problems that have arisen with this form of treatment and what my expectations are for its future use as a therapeutic modality.

THE EQUIPMENT

With the hope that continuous subcutaneous insulin infusion (CSII) will become an acceptable and effective means of treatment of insulin dependent diabetes there has been a race by many companies to develop the smallest, most technically advanced system for the delivery of insulin. In the following section I will discuss only those pumps which are already being used or soon to be available for clinical trials on diabetic patients. I will discuss most completely those devices which are available in the United States. However, I suspect that this is only the tip of the iceberg. Many other companies are in various stages of development and testing of pumps, many of which when they are finally ready for use on patients, will make the present equipment appear quite primative. A comparison of the presently available portable insulin infusion pumps is listed in Table 1.

TABLE 1

COMPARISON OF PORTABLE INSULIN INFUSION PUMPS

	AUTO-SYRINGE AS-2C	MILL-HILL INFUSER	PYE DYNAMICS MS16	AUTO-SYRINGE AS-6C	SIEMANS PROMEDOS E1	CARDIAC PACEMAKER INC 9100	DELTA INDUSTRIES IDS-10	PARKER-HANNIFIN MICROMED
DELIVERY PRINCIPLE	SYRINGE	SYRINGE	SYRINGE	SYRINGE	ROLLER PUMP	SYRINGE	ELECTROMAGNETICALLY ACTIVATED, BIVALVULAR RECIPROCATING PUMP	ELECTROMAGNETICALLY ACTIVATED SOLENOID, BI-VALVULAR PISTON PUMP
DIMENSIONS CM	18.3 x 7.3 x 6.4	14.4 x 6.9 x 2.2	16.6 x 8.8 x 3.3	15.3 x 8.3 x 2.5	11.4 x 6.6 x 2.7	14.0 x 8.3 x 3.4	11 x 6.8 x 2.8	6.3 x 4.1 x 1.6
WEIGHT GM	408	300	175	268	190	365	225	100
RESERVOIR CAPACITY	1-2 DAYS	1-2 DAYS	1-2 DAYS	1-2 DAYS	4 WEEKS	1-2 DAYS	5-7 DAYS	10 DAYS
BATTERY LIFE	3-4 DAYS	2 WEEKS	3 MONTHS	24 HOURS	3 MONTHS	30 HOURS	5 DAYS	2-4 MONTHS
ALARM	NO	NO	NO	YES LOW BATTERY RESERVOIR EMPTY PUMP RUNAWAY	YES	YES LOW BATTERY RESERVOIR EMPTY MOTOR FAULT COMPUTER FAULT	YES LOW BATTERY	YES LOW BATTERY RESERVOIR EMPTY OFF MODE
COST	$1150	$1100	235 POUNDS (BRITISH)	$1150	?	$1500*	$1250	$2500*
SPECIAL FEATURES	NONE	NONE	NONE	AUTOMATIC RETURN TO BASAL MODE	SOPHISTICATED NOT AVAILABLE IN UNITED STATES	PROGRAMMABLE AUTOMATIC INSULIN DELIVERY STEP, KEY BOARD LOCKOUT DIGITAL DISPLAY	USES U-100 INSULIN BASAL RATE CHANGED EASILY. AUTOMATIC RETURN TO BASAL MODE	PROVIDES 24 HOUR A DAY PROGRAMMING USES U-100 INSULIN

*Approximate

The pump which has had the most wide spread use in this country is the model AS-2C manufactured by the Auto-Syringe Company, Hooksett, New Hampshire. This is a syringe pump which will accept many different sized syringes. It is fairly large and bulky. It weighs 408 grams and measures 6.4 x 18.3 x 7.3 cm. It is not a continuous infusion pump but delivers the basal infusion by giving an intermittent injection of insulin at time intervals ranging from 1, 2, 3, 4, 8, 16, 32, 64, and 96 minutes. The basal rate is adjusted by either varying the insulin concentration in the reservoir and/or the time interval of administration. The preprandial dosage selection is unlimited, selected by the patient from 99 different insulin doses available on the "dosage selector dial". This injection is activated by the patient depressing the "instant dose" button. The premeal injection is delivered within one minute. The battery is recharged by means of an external charger which needs to be plugged in to an ordinary wall outlet every three or four days. There is no alarm system. The major advantage of this pump lies in the flexibility of insulin delivery so that the basal rate and preprandial doses can be varied independently over an almost limitless range. Major disadvantages include its large size and weight and the lack of an alarm system. Also, because the pump must be turned off to change from the basal rate to the preprandial mode, there is a great tendency for the patients to fail to turn the pump back on. It sells for $1150.

The Mill-Hill Infuser[21] may well be the pump in most widespread use thoughout the world. It was developed at the

National Institute for Medical Research, Mill Hill London, and is manufactured by Muirhead Ltd, Beckenham, Kent, UK. This pump is considerably smaller than the Auto-Syringe AS-2C weighing 300 grams and measuring 14.4 x 6.9 x 2.2 cm in size. It also is a syringe pump which uses a 5.0 cc syringe as the reservoir. It allows for continuous infusion basal rate at 66 ul/h. Thus the amount of insulin delvered per hour as the basal rate is determined by the concentration of insulin in the resevoir. The preprandial injection is given by the patient operating a small hand switch which turns the lead screw and advances the syringe plunger. Each turn of the screw delivers 53 ul of insulin. This allows considerable flexibility allowing an infinite ratio of basal to preprandial insulin delivery. It is powered by a 4 volt mercury battery with a two week continuous operation life. For safety, the battery is usually changed each week. There is no alarm system. The major advantage is its relatively small size and reasonable flexibility in terms of insulin delivery. It's major disadvantage is the lack of an alarm system. It costs approximately $1100 (U.S.).

The Pye Dynamics MS16 Syringe Driver is a British made pump manufactured by Pye Dynamics Ltd, Bushey-Herts, England. It too is a syringe pump which will accept any disposable syringe from 1.0 to 10.0 ml in size. It weighs 175 grams and measures 16.6 x 8.8 x 3.3 cm in overall diameter. It uses a 9 volt alkaline battery (PP3 size) with a 3 month battery life. The pump's delivery rate is given in millimeters per hour of plunger travel. Any rate between 1 and 99 mm/hr can be set. Thus, basal rates of

insulin infusion can be determined either by adjusting the concentration of insulin in the syringe or by changing the rate of delivery. Premeal insulin can be given by increasing the delivery rate. There is no alarm system. The advantage of this pumps is its light weight, but it is fairly inflexible in terms of insulin delivery around meals. It costs 235 pounds (British). It is not available in the United States.

In Europe the Siemens Promedos El pump is presently being clinically tested. It is of a completely different design than the pumps previously discussed. It is quite small and lightweight measuring 11.4 x 6.6 x 2.7 cm and weighing 190 gms. It is a roller pump which uses a 30 ml disposable polyethylene reservoir. The pump is continuous in operation and can deliver a basal rate which ranges from 3 to 30 insulin units per day in steps of 3 insulin units per day or 6 to 60 insulin units per day in steps of 6 insulin units per day. The preprandial insulin administration can be done in two ways. The first uses "amplitude variation" and ranges from 2 to 10 units in steps of two insulin units over a period of one hour, or 1 to 5 insulin units in steps of 1 insulin unit over a period of one hour. The other method uses "time variation" from 20 to 100 units. The insulin dosage ranges from 2 to 10 insulin units in steps of 2 insulin units or in a range of 1 to 5 insulin units in steps of 1 insulin unit. It uses a 5.6 volt mercury battery. It is also waterproof and thus can be worn while bathing. There is both a visual and audio alarm system with an automatic shut off for

pump malfunction. The major advantage is its small size, waterproof housing, and alarm system. It's major disadvantage is its inflexibility in terms of preprandial insulin dosage administration. It is not available in the United States and only elsewhere on an experimental basis.

The Auto-Syringe Co. has just released its "second generation" pump, the model AS-6C. They have attempted in the development of this pump to alleviate the deficiencies of its predecessor. To this end they have been successful. The AS-6C is smaller than the AS-2C weighing 268 grams and measuring 8.3 x 15.8 x 2.54 cm. It is also a syringe pump which uses a 3.0 cc syringe as a reservoir. The basal flow rate is continuous and is adjustable from 20 - 90% of the syringe volume per 24 hour period. The preprandial bolus administration is adjusted from 0.018 to 100% of the syringe volume per delivery. The preprandial insulin dosage is given in less than one minute by a patient initiated procedure. It uses a 9 volt, rechargable nickle cadmium battery with a battery life of 24 hours per charge. It has a digital display which shows either the basal rate as the percent of the syringe volume to be infused in 24 hours or the premeal bolus as the percent of the syringe volume delivered as a single bolus. Finally, it has a visual and audio alarm system which responds to high pressure, reservoir empty, pump runaway, and low battery. Its major advantages are its relatively small size, its flexibility of insulin delivery, the alarm system, and the fact that if left in the "bolus mode" it automatically returns to the basal rate. The cost is $1150.

There are several pumps which have been built but are not yet even available for clinical trials. Delta Medical Industries has built a small (11.9 x 6.8 x 2.8 mm) light weight (225 gms), quite flexible device, the IDS-10. It is an electromagnetically activated bivlvular reciprocating pump. This pump can be worn in the patient's shirt pocket or belt pouch. Unlike the present syringe pumps the IDS-10 uses U-100 insulin in a reservoir large enough to last five to seven days. The electronic control system allows ample range to satisfy virtually any need for insulin without having to change the insulin concentration. The basal rate has 99 choices between 0.18 U/hr and 18 U/hr. The preprandial bolus allows 99 choices between 1.0 and 99 units per bolus. It has an alarm for low battery. Other features include an automatic return to basal mode. The projected cost is $1250.

The Cardiac Pacemakers, Inc. have developed their own infusion device, the CPI-9100. This is a syringe pump that weighs 365 gms and is 14 x 8.3 x 3.4 cm in size. It uses a 2.0 ml syringe as the reservoir giving it a 1-2 day insulin supply with U-100 insulin. The rechargeable nickel-cadmium batteries have a life of 30 hours. It has a liquid crystal digital display. A 17 position keyboard is used to operated the device. It has a sophisticated audio alarm for low battery, motor fault, microcomputer fault, empty reservoir, and illegal computer entry. It has several programmable functions including a very special feature which allows for the automatic delivery of an insulin dose. This supplemental insulin can be either a bolus or square wave infusion and can be programmed to be given with up to a six hour

delay. This pump is about to enter clinical trials. The projected cost to the patient is approximately $1500.

Finally, the Parker-Hannifin Corporation has just released their Micromed device. While this apparatus is not even at the point of clinical trials, it is quite sophisticated. It is the smallest of all the presently available devices, weighing only 100 gms and measuring 6.3 x 4.1 x 1.6 cm (about the size of a pocket cigarette lighter. It uses an electromagnetically activated solenoid bivalvular piston pump which can deliver accurately 2 ul per discharge. The battery life is from two to four months and the reservoir, when filled with U-100 insulin, could last approximately 10 days. It is entirely programmable allowing four preprogrammed changes in the basal rate per day. However, it can also be used as a simple manually activated pump. Its projected cost is approximately $2500.

CSII TREATMENT

Before going into the practicalities of continuous subcutaneous insulin treatment one must clearly point out that this is only another means of insulin delivery. These pumps are "open loop" systems, (i.e.; the amount of insulin given is predetermined in much the same way as doses of conventionally administered insulin are predetermined) and not based on the continuous monitoring of plasma glucose levels as is the case with "closed loop" delivery systems. To put it another way, these pumps are not magical devices that the patients can be attached to that will allow him/her to completely forget about his/her diabetes. In fact, just the opposite is true. This form of

treatment is only effective when used in combination with specific and carefully followed diet and exercise programs. Finally, without the capability to frequently "home monitor" capillary blood glucose levels which permits patient initiated modification of the insulin prescription, based on the data derived from home monitoring, this treatment would be no more effective than other more conventional forms of therapy. Important adjuncts to CSII are diet, exercise and home blood glucose monitoring. It is of the utmost importance to understand that they are as important to the success of this program as is the insulin infusion pump itself.

TABLE 2

Clinical Data On Our Active Patients

Patient	Age	Sex	Occupation	Duration Of Diabetes	Duration Of Pump Treatment
1. (J.A.)	31	M	Salesman	15 years	24 months
2. (P.S.)	20	F	Student	11 years	24 months
3. (J.B.)	40	M	Minister	17 years	23 months
4. (S.S.)	16	F	Student	11 years	23 months
5. (F.H.)	42	F	Lab Tech	30 years	21 months
6. (J.B.)	27	M	Businessman	13 years	20 months
7. (N.L.)	35	F	Housewife	8.5 years	18 months
8. (C.T.)	15	F	Student	5 years	14 months
9. (M.F.)	25	F	Nurse	16 years	16 months
10. (K.C.)	22	F	Housewife	10 years	15 months
11. (L.F.)	37	F	Nurse	19 years	13 months
12. (P.G.)	29	F	Nurse	9 years	14 months
13. (L.D.)	23	F	Medical Student	15 years	11 months
14. (H.V.)	17	M	Student	4 years	10 months
15. (R.H.)	28	M	Office	15 years	8 months
16. (J.C.)	33	F	Teacher	6 years	8 months
17. (K.G.)	23	F	Housewife	14 years	7 months
18. (D.C.)	28	M	Plant Foreman	10 years	3 months
19. (J.G.)	21	F	Student	10 years	3 months

What follows is a description of our rather extensive orientation procedure which allows the physician adequate time to determine the optimum insulin program for each individual patient and the patient adequate time to learn about the pump, its operation, and insulin dosage schedule. We also use this time to educate the patient regarding diet therapy and exercise programs, how to home monitor their blood glucose levels, and how to make appropriate decisions of when and how to modify their insulin dosage schedule. In my experience this period of time averages about two weeks.

In order to be "oriented" to the portable insulin infusion system all patients are hospitalized in our Clinical Research Unit and placed on a weight maintaining diet consisting of 50% carbohydrate, 30% fat, and 20% protein. The meal plan usually consists of three meals and three snacks (1/9 of the total daily calories at breakfast, 1/9 as a mid morning snack, 2/9 at lunch, 1/9 as a midafternoon snack, 3/9 at supper, and 1/9 as a bedtime snack). After hospitalization and equilibration to the diet, a metabolic profile is done on the patient's usual dose of subcutaneous insulin. This is done to acquire baseline information as well as to find a starting place for what the initial total daily dose of insulin to be given with the pump should be. In most instances the initial daily dose of insulin given via the insulin infusion pump approximates the patient's usual total daily dose of conventionally administered insulin. After completion of studies on conventional insulin therapy, treatment with the portable insulin infusion system is begun. Regular insulin

diluted in 0.9% NaCl at concentrations ranging from U-5 to U-15, is infused through a 25 gauge scalp vein needle inserted in the subcutaneous tissue of the abdomen. Each patient receives a constant basal rate of insulin and 30 minutes before each meal (and snack) a predetermined insulin bolus is administered. After the administrations of the preprandial dose, the basal rate is resumed.

Each patient's daily insulin dose and its distribution between basal rate and preprandial dose (Table 3) is determined by the glycemic response to the previous day's insulin dose. After the first week only periodic and minor modifications in insulin dosage are usually required. Although there is considerable variation in the total daily dose given to each patient, the proportion of that dose as basal and preprandial dose is surprisingly consistent. The total daily dose of insulin given via the portable insulin infusion pump in our patients averaged 37 $\pm$ 3 units per day with a range from 15 to 58 units. The basal rate averaged 50 $\pm$ 2% (SEM) of the total daily dose with 17 $\pm$ 1% before breakfast, 3 $\pm$ 0.3% before the midmorning snack, 11 $\pm$ 1% before lunch; 3 $\pm$ 0.5% prior to the midafternoon snack; 14 $\pm$ 1% prior to supper and 4 $\pm$ 0.6% before the bedtime snack. Patients are required to replace the insulin in the infusion system at least daily (often more frequently) and to change the 25 gauge scalp vein needle at least every other day. This avoids the potential problem of needle blockage during CSII. We have treated patients with three different insulin infusion pumps, the Mill Hill Infuser, the Auto-Syringe AS-2C, and AS-6C. We have had equal success with all.

TABLE 3

TOTAL DAILY DOSE OF INSULIN AND IT'S DISTRIBUTION IN TYPE I DIABETICS TREATED WITH CONTINUOUS SUBCUTANEOUS INSULIN INFUSION

	TOTAL DAILY INSULIN (U)	BASAL	BREAKFAST	A.M. SNACK	LUNCH	A.M. SNACK	DINNER	BEDTIME SNACK
		% OF TOTAL DAILY DOSE						
1. J.A.	35	45	19	—	13	—	16	7
2. P.S	58	29	28	—	16	—	19	9
3. J.Be.	46	58	16	—	11	—	11	4
4. S.S.	64	53	16	—	12	—	12	8
5. F.H.	37	65	12	—	10	—	10	3
6. J.Ba.	33	52	12	—	13	6	13	5
7 N.L.	22	40	18	4	18	4	11	4
8. C.T.	48	50	19	2	9	2	17	1
9. M.F.	27	59	13	2	9	2	11	4
10. K.C.	41	58	13	2	8	2	13	2
11. F.F.	15	47	23	3	10	7	13	7
12. P.G.	24	30	21	4	12	4	21	8
13. L.D.	27	66	15	—	7	—	9	2
14. H.V.	52	41	15	3	17	2	16	5
15. W.E.	37	55	18	3	7	1	14	3
16. R.H.	29	46	17	4	11	4	17	1
17. J.C.	28	51	14	2	9	2	21	2
18. K.G.	43	51	16	2	9	2	16	2
MEAN ± SEM	37 ± 3	50 ± 2	17 ± 3	3 ± 0.3	11 ± 1	3 ± 0.5	14 ± 1	4 ± 0.6

All patients were hospitalized for at least an initial two week period. During this time they were instructed on the operation of the insulin infusion system including the filling of the syringe and catheter, loading of the pump and the programming and delivery of basal and preprandial insulin doses. In addition, all patients were instructed on the use of the Ames Eyetone reflectance meter and/or Dextrometer to measure capillary blood glucose on samples obtained by finger pricking. During this initial period the results of glucose measurements made by the patients using this system correlated well with those made on the glucose analyzer (Figure 3). Intensive instruction was also given on diet, meal planning, and exercise.

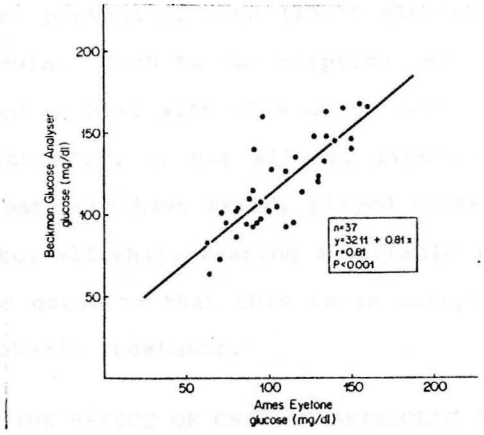

Figure 3. Comparison of glucose determination using either the Beckman Glucose Analyzer or the Ames Eyetone/Dextrometer.

The patients were then discharged and followed as outpatients Initially they were seen at weekly intervals for additional metabolic profiles for the first four weeks. After that they were seen, in most instances, at monthly intervals. All patients continued to perform their usual home, work, or school activities during this period. All are required to follow the rigid diabetic diet and to monitor their capillary blood glucose levels at home from two to six times per day. All patients seem content and wish to continue in the program.

One of our initial concerns was that no patient could tolerate life "attached" to a pump. Patients are required to wear these pumps 24 hours a day, and they are only able to remove it for short periods of time (10-15 minutes) in order to shower, bathe, or swim. Much to our surprise, most if not all, patients have learned to deal with this quite well. They seem quite able to deal with most, if not all of, life's situations with their pump. My patients have skied, played basketball, gone to formal dinners, etc. all while wearing a portable insulin infusion pump. There is no question that this is an acceptable (to the patient) form of diabetic treatment.

THE EFFECT OF CSII ON METABOLIC PARAMETERS

Table 4 lists those metabolic parameters which have been shown to be effected by CSII.

TABLE 4

METABOLIC EFFECTS FROM LONG TERM GLUCOREGULATION WITH PORTABLE INSULIN INFUSION SYSTEMS

1. Normal Plasma Glucose Profiles
2. Normal Levels of Lactate, Pyruvate, Betahydroxybutrate, and Free Fatty Acids
3. Normal Levels of Alanine, Valine, Leucine, and Isoleucine
4. Normalization of Growth Hormone and Catecholamine Response to Exercise
5. Normalization of Glucagon Profile
6. Changes in Plasma Lipids
   a. Fall in total cholesterol and LDL cholesterol
   b. Fall in total triglyceride
   c. Increase in HDL cholesterol

Control of plasma glucose levels: As mentioned in the introduction the major problem with conventional forms of treatment is that are very ineffective in providing 24 hour a day normalization of blood glucose levels. There is little argument that CSII is effective in terms of providing normoglycemia, even for long periods of time. Figures 4 and 5 show plasma glucose profiles (hourly plasma glucose levels from 0700 to 2300 and bihourly from 2300 to 0700) in two of our patients while on conventional insulin treatment and after one, two, four, and six months of CSII, using the Auto-Syringe AS-2C and Mill Hill Infuser respectively. As can be seen CSII is quite effective in

normalizing the glucose profiles. Although these profiles were obtained while the patients were hospitalized, review of records of the patients capillary blood glucose levels done at home show they are normoglycemic at home as well. Table 5 shows the glycosylated hemoglobin data from our patients followed from three months to one year. Glycosylated hemoglobin averaged 9.8 $\pm$ 2.5%* prior to initiation of CSII and after three months of treatment it had fallen to 6.3 $\pm$ 1.5%. Glycosylated hemoglobin remained in the normal range during the period of follow up. Others who have used CSII have all noted the same effectiveness of CSII in terms of glycemic control.[22,23,24]

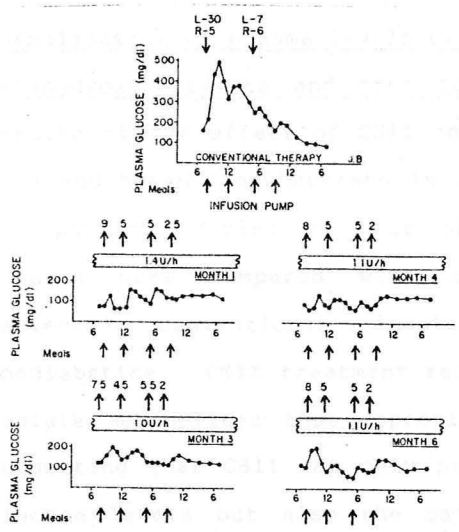

Figure 4. Plamsa glucose "profiles" in a Type I diabetic patient during either conventional insulin treatment or during 6 months of continuous subcutaneous insulin infusion using an Auto-Syringe AS-2C portable insulin infusion pump.

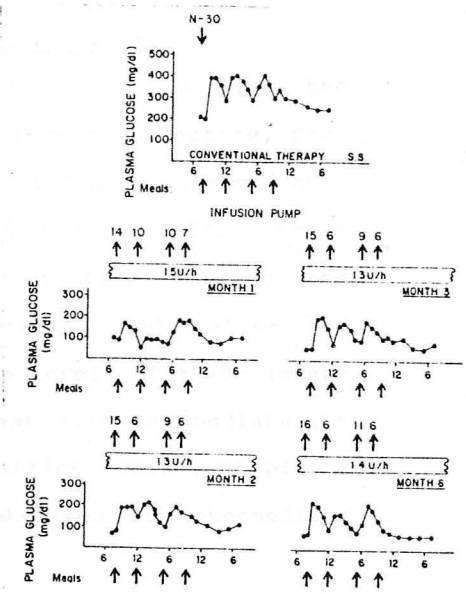

Figure 5. Plasma glucose "profiles" in a Type diabetic patient during either conve tional insulin treatment or during 6 months of continuous subcutaneous insulin infusion using a Mill-Hill insulin infusion pump.

TABLE 5

GLYCOSYLATED HEMOGLOBIN LEVELS AFTER THREE MONTHS TO ONE YEAR OF TREATMENT WITH A PORTABLE INSULIN INFUSION PUMP

	CONVENTIONAL THERAPY	GLYCOSYLATED HEMOGLOBIN %			
		3 mos.	6 mos.	9 mos.	1 yr.
MEAN	9.8	6.3	6.9	6.4	6.6
± SEM	± 2.5	± 1.5	± 1.5	± 0.9	± 0.9
N	17	14	10	6	6

Normalization of plasma levels of lactate, pyruvate, betahydroxy-butyrate and free fatty acids: Table 6 shows the results of the effect of CSII on plasma levels of lactate, pryvate and betahydroxybutyrate in several insulin dependent diabetic patients during 24 hour of treatment with CSII. These results were compared with metabolic profiles during the patients' conventional insulin treatment and those of nondiabetics. CSII treatment resulted in levels of these intermediate metabolites that approximated that seen in nondiabetics suggesting that CSII not only provides strict control of plasma glucose levels but also the major metabolites of intermediary metabolism.[25]

Tamberlane et al[26] also showed that after seven days of CSII treatment, plasma free fatty acid levels, which were elevated on conventional insulin treatment relative to nondiabetic control subjects, fell into the normal range.

TABLE 6

METABOLITE CONCENTRATIONS IN 7 DIABETICS DURING CONVENTIONAL TREATMENT AND DURING C.S.I.I. AND IN 17 NONDIABETICS

MEAN ± S.D. OR RANGE (mmol/l)

METABOLITE	CONVENTIONAL TREATMENT	C.S.I.I.	NON-DIABETICS	P VALUE (C.S.I.I. vs. NORMAL)
Glucose	8.8 ± 2.6	6.0 ± 1.5	5.4 ± 0.8	N.S.
Lactate	1.17± 0.47	0.92± 0.32	0.85± 0.24	N.S.
Lactate/pyruvate	9.8 ± 0.7	9.5 ± 0.4	10.1 ± 1.6	N.S.
3-Hydroxybutyrate	0.16 (0.088-0.95)	0.066 (0.043-0.139)	0.022 (0.006-0.086)	<0.01
Alanine	0.34± 0.8	0.30± 0.04	0.31± 0.07	N.S.

N.S. = Not Significant
*Mean ± S.D. of all measurements made in 24 h or 24 h range of mean values at each time point.
(From Tamborlane et al[25])

Normalization of alanine and the branched chain amino acids:

Table 6 also shows the effectiveness of CSII treatment in returning plasma alanine levels to normal. Tamberlane, et al[25] studied the effect of CSII on plasma levels of the branched chain amino acids (Table 7). Plasma levels of valine, leucine, and isoleucine while the diabetics were on conventional insulin treatment were 50-60% above levels in nondiabetic control subjects. After seven days of CSII all had fallen into the normal range.

TABLE 7

FASTING PLASMA-BRANCHED-CHAIN-AMINOACID LEVELS BEFORE AND AFTER 7 AND 14 DAYS OF TREATMENT WITH THE INSULIN PUMP (MEANS±S.E.M.)

	VALINE (μmol/l)	LEUCINE (μmol/l)	ISOLEUCINE (μmol/l)
PRE-PUMP	328 ± 45	181 ± 22	97 ± 12
DAY 7	208 ± 19*	97 ± 9	54 ± 4†
DAY 14	204 ± 17†	95 ± 11*	56 ± 5†
HEALTHY CONTROLS	218 + 12+	117 + 9+	63 + 5§

*Significantly different from pre-pump value, $p<0.05$, by paired test
†Significantly different from pre-pump value, $p<0.025$, by paired test
+Significantly different from pre-pump value, $p<0.05$, by paired test
§Significantly different from pre-pump value, $p<0.025$, by paired test
(From Tamborlane et al[26])

Normalization of the growth hormone and catecholamine response to excercise: Tamberlane et al[27] also studied the plasma growth hormone, epinephrine and norepinephrine responses to cycle ergometic exercise in Type I diabetics while they were receiving conventional insulin treatment and again after seven to fourteen days of treatment with CSII. The results of the growth hormone study are shown in Table 8. During conventional insulin treatment the plasma growth hormone response to exercise was sevenfold greater than in normal controls. It fell 62% after seven days of CSII and by two weeks it had fallen 83% to value comparable with nondiabetic control subjects. Similar exaggerations in plasma catecholamines were observed in the diabetics while on conven-

tional treatment. They returned to normal after 14 days of CSII. (Table 9)

TABLE 8

PLASMA GROWTH HORMONE RESPONSE TO EXERCISE IN DIABETICS TREATED CONVENTIONALLY AND WITH THE INSULIN INFUSION PUMP AND IN HEALTHY CONTROLS

	PLASMA GROWTH HORMONE (ng/dl)			
	BASAL	PRE-EXERCISE†	POST-EXERCISE	Δ
DIABETICS				
Conventional R_x	5.7 ± 1.3	6.4 ± 1.9	21.3 ± 5.2	14.9 ± 4.1
Pump Day 7	5.0 ± 1.2	4.1 ± 1.5	9.7 ± 2.4+	5.6 ± 1.6+
Pump Day 14	2.5 ± 0.7+	1.6 ± 0.4+	4.1 ± 1.6+	2.6 ± 1.0+
HEALTHY CONTROLS	1.9 ± 0.6§	1.6 ± 0.5§	3.9 ± 0.8§	2.3 ± 0.6§

*Basal samples obtained after an ovenight fast with the patients supine
†Pre-excercise samples obtained with the patients sitting upright on the cycle ergometer immediately before exercise
+Significantly different from corresponding value during conventional treatment, $p<0.001$ (paired t test)
§Significantly different from corresponding value in conventionally treated diabetics, $p<0.01$ (unpaired t test)
(From Tamborlane et al[27])

TABLE 9

PLASMA CATECHOLAMINE RESPONSE TO EXERCISE IN DIABETIC TREATED CONVENTIONALLY WITH THE INSULIN INFUSION PUMPS AND IN HEALTHY CONTROLS

	PLASMA EPINEPHRINE (pg/ml)				PLASMA NOREPINEPHRINE (pg/ml)			
	BASAL	PRE-EXERCISE†	POST-EXERCISE	Δ	BASAL	PRE-EXERCISE	POST-EXERCISE	Δ
DIABETICS								
Conventional Rx	41 ± 8	41 ± 7	139 ± 29	97 ± 26	268 ± 33	280 ± 21	1465 ± 450	1185 ± 438
Pump Day 7	44 ± 6	46 ± 5	71 ± 14+	26 ± 12+	370 ± 73	311 ± 45	529 ± 102+	217 ± 87+
Pump Day 14	55 ± 8	62 ± 9	76 ± 17+	14 ± 10+	304 ± 55	296 ± 45	444 ± 71+	146 ± 57+
NORMAL CONTROLS	43 ± 10	52 ± 9	68 ± 17§	17 ± 14	292 ± 46	317 ± 48	415 ± 50§	98 ± 20

*Basal samples obtained after an overnight fast with the patients supine
†Preexercise samples obtained with the patients sitting upright on the cycle ergometer immediately before exercise
+Significantly different from corresponding value during during conventional treatment. P<0.001 (paired t test)
§Significantly different from corresponding value in conventionally treated diabetics. P<0.05 (unpaired t test)
Significantly different from corresponding value in conventionally treated diabetics. P<0.025 (unpaired t test)
(From Tamborlane et al[27])

Normalization of plasma glucagon: Hyperglucagonemia is a characteristic finding in human diabetes mellitus and its presence contributes to the hyperglycemia and ketonemia present in many patients with the disease.[28] Although the abnormal glucagon responses following the ingestion of oral glucose[29] oral protein[30] and intravenous arginine[31] in Type I diabetes can be restored to normal with large doses of conventionally administered insulin, it has been impossible to completely normalize the 24 hour glucagon profile with aggressive conventional insulin therapy.[9] Figure 6 shows the 24 hour plasma profiles of glucose and immunoreactive glucagon (IRG) in five Type I diabetic

patients during 24 hours of conventional insulin treatment and after four to five weeks of treatment with CSII. The mean of all IRG levels averaged 83 ± 15 pg/ml on CSII which was significantly lower than the value of 105 ± 20 pg/ml obtained while on conventional therapy. Although complete normalization of plasma IRG profiles was impossible during conventional insulin treatment,[32] the use of CSII resulted in a fall of IRG levels to the middle of the nondiabetic range, a result that suggests an additional advantage of this type of insulin delivery over conventional means.

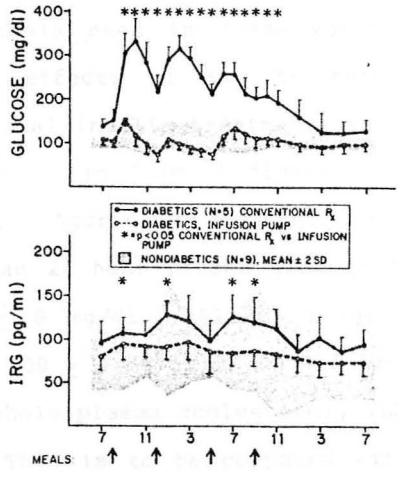

Figure 6. Mean plasma glucose and IRG profiles during 24 hours of conventional insulin treatment (●——●) and after four to five weeks of continuous subcutaneous insulin infusion (o——o) with portable insulin infusion pumps in five Type I diabetics. The shaded area represents the mean ± 2 S.D.'s of values from nine nondiabetics on a similar diet included for comparison. Times of meals are indicated by arrows.[32]

Effects on plasma lipid and lipoprotein levels: One of the first reports on the effectiveness of CSII showed significant decreases in plasma cholesterol and triglyceride levels after one to two weeks of treatment with CSII.[26] However, in this study lipoprotein levels were not measured and there was no attempt to evaluate the effectiveness of aggressive conventional insulin treatment on these parameters. The effect of diabetic control on plasma lipids and lipoprotein levels is an important issue. Diabetes mellitus is associated with an increased incidence of atherosclerosis.[33,34] Hyperlipidemia, which is common in Type I diabetes, appears to contribute to the development of the accelerated atherosclerosis seen in these patients.[35] Pietri, et al[36] compared the effects of two to three weeks of either aggressive conventional insulin treatment or CSII on plasma lipid and lipoprotein levels in Type I diabetics. The results are shown in Table 10. Aggressive conventional insulin treatment resulted in the mean 24 hour plasma glucose levels falling from 260 $\pm$ 18 to 134 $\pm$ 8 mg/dl. Plasma triglyceride levels fell significantly from 100 $\pm$ 9 mg/dl to 84 $\pm$ 6 mg/dl. There were no changes in either whole plasma cholesterol, VLDL, LDL or HDL cholesterol levels. This is to be compared with the patients who were treated with CSII. These patients had a mean 24 hour plasma glucose level of 194 $\pm$ 18 mg/dl while on conventional insulin treatment. This fell to 108 $\pm$ 9 mg/dl after two to three weeks of CSII. This resulted in a significant reduction in whole plasma cholesterol levels (195 $\pm$ 17 to 161 $\pm$ 11 mg/dl) which was

primarily due to a fall in LDL cholesterol levels. (129 ± 13 to 102 ± 9 mg/dl. HDL cholesterol was unchanged. This was the first report showing a significant reduction in LDL cholesterol levels with improved diabetic control, a fact which could have significance in slowing the development of premature atherosclerosis.

TABLE 10

CHANGES IN MEAN PLASMA GLUCOSE, LIPID, AND LIPOPROTEIN LEVELS DURING PERIODS OF POOR CONTROL AND AFTER TWO TO THREE WEEKS OF IMPROVED CONTROL IN TYPE I DIABETICS TREATED WITH EITHER CONVENTIONAL INSULIN THERAPY OR CONTINUOUS SUBCUTANEOUS INSULIN INFUSION

Treatment	Glucose	Total Cholesterol	VLDL Cholesterol	LDL Cholesterol	HDL Cholesterol	Total Triglyceride
	mg/dl					
CSII						
Poor Control	194 ± 18[a]	195 ± 17	21 ± 11	129 ± 13	40 ± 2	134 ± 23
Improved Control	108 ± 8*[b]	161 ± 11*	11 ± 1**	102 ± 9*	42 ± 2	84 ± 8**
CONVENTIONAL THERAPY						
Poor Control	260 ± 18	195 ± 8	14 ± 2	128 ± 9	42 ± 4	100 ± 9
Improved Control	134 ± 8*	189 ± 8	10 ± 2*	127 ± 8	44 ± 5	84 ± 6**

* = $p < 0.01$ vs "poor control" phase
** = $p < 0.02$ vs "poor control" phase
a = $p < 0.01$ "poor control" conventional therapy vs "poor control" CSII
b = $p < 0.05$ "good control" conventional therapy vs "good control" CSII
(From Pietri et al[36])

It is interesting to speculate about the reason changes in plasma cholesterol and LDL cholesterol were observed in the CSII treated patients and not in the conventionally treated patients. Was it related in any way to the level of "good control"? In the conventionally treated group, aggressive insulin therapy resulted in a mean plasma glucose level of 134 $\pm$ 8 mg/dl, only 26 mg/dl higher than the group on CSII and certainly respectable control by conventional standards. The fact that plasma cholesterol levels did not fall suggests that exquisite metabolic control is required to produce substantial changes in total cholesterol and LDL cholesterol levels. This same group has followed CSII treated patients for periods up to 10 months.[37] They found that the changes in plasma lipids and lipoprotein continue to improve despite the fact that all patients were followed at home as outpatients. They show a progressive fall in plasma triglyceride, cholesterol and LDL cholesterol levels over the 10 month periods of observations. After two to three months of CSII HDL cholesterol begin to rise and continue to do so over the remaining period of observation. (Figure 7)

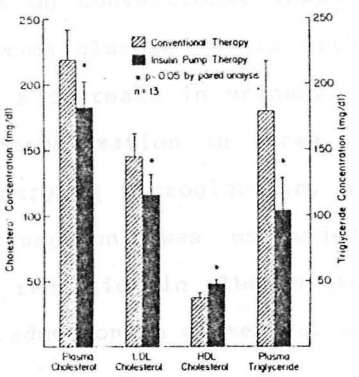

Figure 7. Plasma lipid and lipoprotein levels in Type I diabetes during conventional insulin treatment and following one to ten months of therapy with portable insulin infusion pumps.

These are important observations because of the relationship between atherosclerosis and diabetes mellitus. The long term changes produced in plasma lipid and lipoprotein levels in patients treated with CSII may favorably alter the predicted risk for the development of atherosclerosis in these people.

THE EFFECTS OF CSII ON THE LONG TERM COMPLICATIONS OF DIABETES

Continuous subcutaneous insulin infusion has only been used for the treatment of Type I diabetes mellitus for less than two years, thus it is unlikely that there would be any definitive data available on its effect on the long term complications of the disease in such a short period of time. However, there is some information available that, although far from the final story, is interesting.

Effects on nephropathy: Viverti et al[37] have studied seven patients with long standing diabetes mellitus who were chosen because they had elevated albumin excretion (microalbuminuria, as measured by a sensitive radioimmunoassay procedure) but not gross proteinuria while on conventional insulin treatment. The normalization of plasma glucose levels with CSII for one to three days resulted in a decrease in urinary albumin excretion in all pateints and a normalization in three. Simulataneous radioimmunoassay of urinary B_2 macroglobulin, which serves as a marker for tubular dysfunction, was unchanged, suggesting to these authors that the reduction in albumin excretion produced by CSII resulted from a reduction in glomerular capillary permeability

and not from a change in the tubular reabsorption capacity for proteins. There are of course other possible explanations for this data such as changes in either renal blood flow or glomerular filtration rate, produced by CSII neither of which were measured in this study. Tamborlane et al[38] treated four Type I diabetics with gross proteinuria but without azotemia for three to eleven months with CSII. They found that pump treatment failed to reduce proteinuria in any of these patients. I have treated four Type I diabetic patients, each of whom had a 24 hour protein excretion in excess of 300 mg per 24 hours while on conventional treatment, for 12 months with CSII. In three of four patients protein excretion was diminished (Table 11) with long term normoglycemia, although one patient continued to excrete more than 4.0 gm of protein per day. The final patient is a 20 year old college student who had diabetes for 11 years prior to her entrance in our program. In her case the massive proteinuria has continued unabated and in fact her renal function has continued to deteriorate during the 24 months she has been treated with CSII. This patient is somewhat different than the other three in that she already had decreased renal function prior to the initiation of CSII (creatinine clearance was 39 ml/min and serum creatinine was 1.7 mg/dl). The others did not. It thus appears that there may be some component of diabetic nephropathy which is reversible by long term CSII. However, it appears that once renal function is severely impaired the damage may be irreversible.

TABLE 11

EFFECT OF CSII ON DIABETIC NEPHROPATHY

	CONVENTIONAL TREATMENT			CSII 6 months			CSII 12 months		
	Cr_S mg/dl	CrCl ml/min	Protein Excretion gm/24h	Cr_S mg/dl	CrCl ml/min	Protein Excretion gm/24h	Cr_S mg/dl	CrCl ml/min	Protein Excretion gm/24h
1. J.A.	1.4	109	9.0	1.5	99	6.2	1.3	111	4.6
2. J.B.	1.0	136	0.9	1.1	138	0.6	1.3	114	0.3
3. F.H.	1.1	89	0.3	0.8	127	0.3	0.9	97	0.1
4. P.S.	1.7	39	14.8	3.2	25	16.7	3.1	23	14.1

Effect of retinopathy: Unfortunately data in this area are quite sparse. However, Pickup et al[22] reported two patients in whom three months of CSII treatment resulted in a marked improvement in the diabetic retinopathy. They showed improvement in visual acuity and a reduction of retinovascular permeability to fluorscien dye as well as revascularization by normal appearing blood vessels of previously nonperfused areas. Irsigler[39] reported similar improvement in proliferative retinopathy in a patient treated for 150 days with an "open loop" system using the intravenous route of insulin delivery. Others have not had the same success. Tamberlane et al[38] reported two patients with proliferative retinopathy who developed a vitreous hemorrhage, one and three months after beginning CSII. We have had a similar experience in one patient who showed a marked acceleration in

retinopathy during six months of CSII treatment. Others have reported rapid acceleration of proliferative retinopathy in three patients whose diabetic control was improved with aggressive conventional treatment.[40] These reports of the worsening of retinopathy with improved diabetic control are of great concern and emphasize the importance of caution and careful followup of patients treated with CSII.

Effects of Neuropathy: Perhaps the most exciting data regarding the effects of CSII on the complication of diabetes comes from studies done on neuropathy. Pietri et al[41] studied 10 patients with Type I diabetes mellitus in whom near normal glucoregulation was maintained for six weeks using CSII. This form of therapy resulted in a normalization of mean 24 hour plasma glucose levels and a fall of glycosylated hemoglobin into the normal range. There was a significant increase in motor nerve conduction velocity in the peroneal and medial nerves as compared to values obtained while the patients were on conventional insulin treatment. (Table 12) There was no significant increase in the motor nerve conduction velocity, in the ulnar nerve or in the sensory nerve conduction studies. No changes occured in five additional patients studied in similar fashion with persistent elevation of glycosolated hemoglobin while on conventional insulin therapy. Four of the patients treated with CSII had clinically evident diabetic neuropathy, all noted a marked decrease in their symptoms. Tamborlane et al[38] reported improvement in sensory nerve conduction in diabetics treated with CSII. Action potential latency was reduced and amplitude increased following

3-11 months of treatment. Unlike Pietri, et al[41] they found no change in motor nerve conduction velocity.

TABLE 12

NERVE CONDUCTION TESTS IN TYPE I DIABETICS FOLLOWING EITHER SIX WEEKS OF CONTINUOUS SUBCUTANEOUS INSULIN INFUSION OR CONVENTIONAL THERAPY

	Motor Nerve Conduction Velocity (meters/second)			Median Nerve Sensory	
	Ulnar	Median	Peroneal	Latency (milliseconds)	Amplitude (μvolts)
CSII (N=10)					
Baseline	52.9 ± 1.6+	50.7 ± 1.2	39.5 ± 1.6	3.5 ± 0.3	7.6 ± 1.7
2 weeks	53.9 ± 1.3	51.4 ± 0.8	41.7 ± 2.0*	3.5 ± 0.2	6.7 ± 1.1
6 weeks	54.2 ± 1.3	53.5 ± 0.8*	44.1 ± 1.8**	3.4 ± 0.2	7.5 ± 1.6
Conventional Therapy (N=5)					
Baseline	55.8 ± 2.2	53.0 ± 0.9	41.6 ± 2.7	3.4 ± 0.1	9.0 ± 2.0
2 Weeks	51.0 ± 1.4	51.7 ± 1.1	36.1 ± 5.8	3.5 ± 0.2	7.2 ± 2.1
6 Weeks	53.4 ± 2.3	52.0 ± 1.5	39.6 ± 3.2	3.4 ± 0.2	7.6 ± 2.0

\+ = Mean + SEM
* = $p<0.05$ by paired analysis
** = $p<0.01$ by paired analysis
(From Pietri et al[41])

These studies although exciting must be viewed with caution. While the methods used to study nerve conduction are well established they provide only a limited evaluation of the overall function of peripheral nerves. Furthermore, it is very difficult to relate clinical neuropathy with changes in nerve conduction velocity.

PROBLEMS WITH CSII TREATMENT

As with any new treatment modality the initial reports are always filled with praise with little mention of potential problems. CSII is of course no exception in that most of the reports published to date mention only its positive features. There are problems with this form of treatment, both real and theoretical. We are dealing with a mechanical device which is always a potential hazard. There is potential for "pump runaway" in which mechanical failure could result in the rapid injection of potentially large doses of insulin. Some investigators have reported such occurances but personally, I have never had such a problem. In fact, I have yet to personally see one instance of "pump failure". We have had a reasonable number of "charger failures" however. This is especially true for the Autosyringe AS-2C. The charger system for the Autosyringe (AS-2C) pump is not very substantial and it is not unusual for the main wire to become broken. Unfortunately, charger failure is usually only recognized when it produces "pump failure", that is to say the pump stops running because its battery has worn down. The remedy for this frequent and potentially important problem is to always have an additional charger on hand. Mechanical failure is especially concerning because most of the insulin delivery devices presently being used do not have alarm systems to warn the patients of impending danger. The "second generation" devices will most likely have very sophisticated alarm systems so that this should be less of a problem.

The major problem related to use of a portable insulin infusion system relates to "operator error". Many of our patients have mistakenly left their pump either off or in the preprandial mode. Because of its design, the Autosyringe AS-2C is quite prone to both. The new model AS-6C is designed in such a way that this should become less frequent.

Other minor problems include rare skin infections at the site of needle implantation. Most of these have been minor responding to local heat treatment and removal of the needle. We have had two major abscesses form which were very painful and required incision and drainage. Patients have either pulled out their needle or had the needle hub become disconnected from the insulin syringe. Both of these problems unfortunately often go unrecognized by the patients. Thus, in my experience, there have been few problems with CSII. Certainly none significant enough to preclude its use. However, it is important to realize that any occurance that results in the cessation of insulin delivery to the patient (pump off, catheter disconnected, etc.) are very serious. Champion et al[42] clearly showed abrupt cessation of insulin administration resulted in the development of moderated ketoacidosis within a 12 hour period. Although we have not systematically studied the problem, our patients report rapid increases in capillary blood glucose concentrations in just a few hours following any interuption of insulin delivery. The rapid deterioration of the metabolic profile in these patients results from the fact that they have no depot insulin within their

tissues as do patients treated by conventional means. Thus even short interruption in insulin administration results in the rapid appearance of hyperglycemia (especially if the patients are eating) and there is the potential for the development of acidosis.

Finally we come to the problem of hypoglycemia. Surprisingly, hypoglycemia has been very infrequent in patients treated with CSII. Certainly it has been much less of a problem than is seen with aggressive conventional insulin treatment. It is interesting that despite continuation of basal infusion rates that hypoglycemia does not occur even when the patient exercises.[27,42] It is this feature of CSII which offers that patient considerable flexibility with regards to meals. When patients are treated by conventional means meals are planned to cover insulin which has been given often hours before. The patient is thus obliged to eat at specific times or run the risk of developing hypoglycemia. With CSII the patient can eat when they wish since hypoglycemia usually does not occur when meals are postponed (or even missed) despite the continuing basal infusion of insulin.[42] All the patient needs to do is postpone the administration of the preprandial insulin dose until a short time prior to beginning the meal.

UNANSWERED QUESTIONS

There are several unanswered questions regarding the long term use and effectiveness of CSII. The first of these deals

with the psychological aspect of the treatment. Will patients be able to deal with "life long" attachment to a mechanical device? This may be more of a problem now than in the future as the pumps being used now are for the most part large and heavy, difficult to hide and in general unpleasant for the patients to carry around. I am certain that with advancing technology they will become smaller, lighter, and more esthetically acceptable to the patient. However, it remains to be seen how patients will deal with dependence on a machine. Can the patients deal with the life long requirement to adhere to rigid diabetic diets and be willing to persist in frequent capillary blood glucose monitoring? It is a difficult life we ask our patients to lead, whether all will be able to continue to be so regimented for many years remains to be seen.

Aside from the practical questions discussed above, there are some important, and as yet, unanswered theoretical questions. The first deals with the question of the appropriate route of insulin administration. Although this discussion covered only subcutaneous insulin administration there are others who feel insulin should be given continuously by either the intraperitoneal[43] or intravenous route.[44] It appears that in studies using the artificial endocrine pancreas with insulin delivered via the peripheral intravenous route results in systemic hyperinsulinemia.[45,46] This supposedly does not occur with subcutaneous administration.[42] Whether or not hyperinsulinism is present or not or what the effects of chronic hyperinsulinemia will be

remains to be seen.

Finally, we must conclude with the question with which we began. Will this form of therapy, with its potential for providing long term normoglycemia effect the development of the vascular complications of diabetes? Although only time will tell, my hope and prejudice is that it will.

CONCLUSION

Treatment of Type I diabetics with long term portable insulin infusion systems appears to be safe, practical, and effective in maintaining normoglycemia in well motivated patients. However, because of the as yet unresolved problems it continues to be a research procedure, and further study will be required before a widespread application can be recommended.

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