Long-term Intraperitoneal Insulin Delivery

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Over the past 5 years, 21 patients with insulin-dependent diabetes mellitus have been managed at the Johns Hopkins Medical Institutions with variable rate, remotely controlled implanted insulin pumps. To date, nearly 70 patient-years of experience has been gained with intraperitoneal delivery of a new U-400 insulin with a surfactant. All 21 patients are alive after a mean of 39.3 months (range, 10 to 65 months) after insulin pump implantation. Nineteen of the 21 patients remain on intraperitoneal insulin, for a 5-year actuarial system survival of 90%. Glucose control was improved, especially during the first 16 months after pump implantation, without an increased incidence of severe hypoglycemia. Catheter blockage has been a significant problem, occurring in nine of the 21 patients (43%). Catheter occlusion has been successfully managed, however, with laparoscopic repair in seven of 10 attempts or with catheter change in four of five patients. Nevertheless, quality of life and patient acceptance remain excellent. Moreover, pre-existing nephropathy, neuropathy, and retinopathy have been surprisingly stable. With an aggressive policy of catheter change or laparoscopic clearance of catheter blockage, long-term intraperitoneal insulin delivery is now a safe and effective treatment for type I diabetics.

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MULTIPLE ALTERNATIVES TO daily insulin injections are becoming available for the management of diabetes mellitus. Newer approaches to patient management include external insulin pumps, whole organ and islet cell transplantation, and a biohybrid artificial pancreas.[1-10] Each of these alternatives, however, has potential disadvantages, including poor quality of life, major postoperative complications with potential risk to life, the need for immunosuppression, and graft or system failure. In the past, implantable insulin pumps also have been limited by fixed infusion rates, insulin precipitation, and intraperitoneal catheter blockage.[11-15] Our initial 18-month follow-up of 10 patients with implanted programmable insulin pumps with intraperitoneal catheter placement and a new U-400 insulin with a surfactant was encouraging, however.[16] This report documents nearly 70 patient-years of experience with intraperitoneal insulin delivery, with the longest over 5 years, in 21 patients with type I diabetes.

Methods

Study Population

Since November 1986, 21 patients with insulin-dependent diabetes mellitus have been managed with intraperitoneal insulin delivery at the Johns Hopkins Hospital. Each patient signed an informed consent form approved by the Johns Hopkins Joint Committee on Clinical Investigation. To be included in the study, patients had (1) insulin-dependent diabetes mellitus for at least 2 years, documented by a history of ketoacidosis, a negative plasma C peptide response to 1 mg of intravenous glucagon, or both; (2) lack of child-bearing potential; (3) the ability to recognize hypoglycemia; (4) absence of serious coexisting disease; (5) use of no medications that could affect glucose regulation; and (6) no life-threatening diabetic complications in the previous 2 years. In addition, patients were required to have monitored their blood glucose levels at regular intervals.

The clinical characteristics of the study population are listed in Table 1. The initial 10 patients (group A) had the Programmable Implantable Medication System (PIMS) implanted between November 1986 and June 1987. These 10 patients had the PIMS electively removed

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TABLE 1. *Clinical Characteristics of the Study Population*

	Group A* (n = 10)	Group B† (n = 11)	Total (n = 21)
Age (yr)			
Mean	33.2	34.7	34.0
Range	19–56	21–54	19–56
Sex (% male)	80	55	67
Diabetes (yr)			
Mean	16.5	18.7	17.7
Range	4–28	3–26	3–28
Complications (%)			
Nephropathy	10	0	5
Neuropathy	40	27	33
Retinopathy	50	55	52

* PIMS inserted November 1986 to June 1987; MIP inserted January 1990 to January 1991.
† MIP inserted February 1990 to June 1991.

and replaced by the MiniMed Implantable Pump (MIP) between January 1990 and January 1991. Eleven additional patients (group B) had the MIP implanted between February 1990 and June 1991. At the time of initial internal pump placement, group A and group B patients were similar with respect to mean age and age range (Table 1). Because of the requirement for lack of child-bearing potential, two thirds of the patients were male. Group A and group B patients were also similar with respect to duration of diabetes and diabetic complications before internal pump insertion (Table 1). Stable azotemia was present at initial pump insertion in only one group A patient. Overall, one third of the patients had peripheral neuropathy when they started on intraperitoneal insulin. Five group A and six group B patients had background diabetic retinopathy at the time of initial pump insertion. Of these 11 patients, two group A patients had proliferative diabetic retinopathy requiring laser photocoagulation before intraperitoneal insulin therapy was begun.

Insulin Pumps

The PIMS was designed at the Johns Hopkins Applied Physics Laboratory and manufactured by MimiMed Technologies (Sylmar, CA). This prototype pump is disc-shaped with a titanium casing and weighs 220 g with a full reservoir. A 5-mm diameter cone-shaped refill port is located on the surface adjacent to the subcutaneous tissue when the pump is inserted in the abdominal wall. Further details of the electronics, power source, and insulin reservoir have been previously published.[16,17] Information on safety features, pumping mechanisms and capabilities, catheter materials and size, dimensions, and alarms are presented in Table 2.

Various similarities between the PIMS and the MIP are presented in Table 2. With both the PIMS and the MIP, the basal rate and various bolus options for the patient to use at meal times can be programmed with an external transmitter held over the implanted pump. A two-way confirmation system exists between the implanted pump and the external transmitter. Unique codes are employed to eliminate the chance of interference by extraneous radiofrequency waves. Moreover, the physician may retrieve data from the implanted pump including the complete hourly history of insulin delivery or the total insulin dose delivered over 60 days (PIMS) or 90 days (MIP).

A number of enhancements related to the delivery of insulin, the catheter design, the alarm system, and the physician and patient programmers have been added to the MIP (Table 2). As a result, with the MIP the physician and patient have a broader range of insulin delivery options both for the basal rate and for bolus delivery. The MIP's more flexible, longer intraperitoneal catheter was designed to reduce the incidence of catheter blockage. Moreover, both the physician and patient programmers were enhanced for easier use, more flexibility of programming, and additional memory. Both the PIMS and MIP

TABLE 2. *Comparison of PIMS and MIP*

	PIMS	MIP
Similarities		
Safety features		
Negative pressure	+	+
Passive filling	+	+
Automatic shutdown	+	+
Pumping mechanism		
Solenoid	+	+
Pulsatile	+	+
Catheter materials		
Polyethylene lined	+	+
Silicone rubber	+	+
Dimensions		
Diameter (cm)	8.1	8.1
Thickness (cm)	1.9	1.9
Insulin		
U-400	+	+
Surfactant	+	+
Enhancements		
Stroke volume		
Units/stroke	0.8	0.2
Basal rate		
Units/hr	0–3.2	0–10
Units/day	0–77	0–240
Bolus delivery		
Preprogrammed	+	–
Units/bolus	0–26	0–32
Dose limits		
Programmable	–	+
Catheter		
Flexibility	–	+
Length (cm)	9.0	19.0
Alarms		
Stimulation	+	–
Audio	–	+
Physician programmer		
Hand-held	–	+
Integral printer	–	+
Patient programmer		
Full range	–	+
90-day memory	–	+

have used a U-400 semisynthetic human insulin with 10 μg/mL of a surfactant to prevent insulin aggregation (Hoechst, Frankfurt, Federal Republic of Germany). The surfactant is polyethylene-polypropylene glycol (Genapol), and the mixture also contains TRIS buffer at pH 7.3.[16]

Operative Procedures

All 10 group A patients were treated with continuous subcutaneous insulin infusion with an external insulin pump for a minimum of 3 months before PIMS implantation. In fact, some of these group A patients had been on external insulin pumps for much longer before PIMS implantation (Table 3). The 11 group B patients are part of a multi-institutional, multinational industry-sponsored trial in which patients were randomized to intensive glucose monitoring for either 4 weeks or 4 months before MIP implantation but did not require external pump placement (Table 3). All patients were hospitalized on the General Clinical Research Center at the Johns Hopkins Hospital before and after pump implantation.

All patients received prophylactic antibiotics, usually 1.0 g of a first-generation cephalosporin immediately before and for 24 hours after pump implantation or subsequent manipulations. All initial pump implantations were done under general anesthesia with a temporary nasogastric tube or a Foley catheter in place, depending on the planned pump position. All pumps were placed in a subcutaneous pocket in the abdominal wall superficial to the anterior rectus fascia. All patients were right-handed and, therefore, had their pumps placed on the left side of the abdomen for ease in using the patient programmer. The decision to place the pump above or below the waistline was based on patient preference and the acuteness of the angle of the costal cartilages. Eight of 10 group A patients and five of 11 group B patients had their pumps placed above the waistline. Eleven of 14 men chose to have the pump above the waistline, whereas five of seven women had their pumps placed below the waistline.

TABLE 3. *Duration of Insulin Pump Treatment*

	Group A (n = 10)	Group B (n = 11)	Total (n = 21)
Prestudy external pumps			
Patients (%)	100	36	67
Duration			
Mean (mo)	17.2	27.0	20.0
Range (mo)	3–60	0–42	0–60
Patient-years	14.3	9.0	23.3
PIMS internal pump			
Patients (%)	100	–	48
Duration			
Mean (mo)	39.1	–	39.1
Range (mo)	34–48	–	34–48
Patient-years	32.6	–	32.6
MIP internal pump			
Patients (%)	100	100	100
Duration			
Mean (mo)	20.9	20.6	20.7
Range (mo)	14–26	10–26	10–26
Patient-years	17.4	18.8	36.2
Total internal pumps			
Patients (%)	100	100	100
Duration			
Mean (mo)	60.0	20.6	39.3
Range (mo)	55–65	10–26	10–65
Patient-years	50.0	18.8	68.8

All incisions were made vertically in the midline either above or below the umbilicus. Subcutaneous pockets were extended laterally far enough to allow a multilayer closure of subcutaneous tissue in the midline with absorbable sutures. Several group B patients with relatively thick layers of subcutaneous fat underwent a lipectomy as the pocket was fashioned to allow easier access to the pump for refilling and better cosmetic results. The pump, shipped sterile and filled with non–insulin-containing buffer from the manufacturer, was tested and filled with insulin by the endocrinologist in the operating room. All catheters were passed under direct vision through separated rectus muscle fibers and a small opening in the peritoneum. No effort was made to direct the intraperitoneal position of the catheter tip. The flange of the catheter was secured to the anterior rectus fascia with nonabsorbable sutures, as was one of the sewing rings on the pump.

The delivery of insulin through the system was started intraoperatively. Patients were kept NPO (nulla per os; nothing by mouth) on the day of surgery, given clear liquids on the first postoperative day, and usually returned to their preoperative diabetic diet on the second postoperative day. Patient activity was encouraged in the early postoperative period, and most patients went home on the third postoperative day. All patients developed a seroma around the pump, which resolved without aspiration. When re-entered for secondary procedures, the superficial and deep portions of the pocket were surgically separated to allow for pocket expansion. The implanted pumps were refilled by percutaneous injection every 2 months as previously described.[16]

All subsequent procedures on the pump, including elective change from PIMS to MIP and catheter changes for blockage, were done under local anesthesia with intravenous sedation. All laparoscopic procedures for catheter blockage were done under general anesthesia, again, with temporary nasogastric tube or Foley catheter placement as appropriate. In general, two, and sometimes three, access ports were employed for the camera (10-mm port) and catheter manipulations (5-mm port). In recent laparoscopic procedures, the second port was positioned so that the catheter tip could be brought to the external abdominal wall for direct visualization, cleaning, and testing

of the insulin flow rate. Care was taken so that none of the laparoscopic ports violated the pump pocket.

Patient Follow-up

All study patients monitored their blood glucose levels two to four times daily with a Glucometer-M (Miles Laboratory, Elkhart, IN), which has an automatic memory for the blood glucose level, date, and time. These data were transferred electronically to the computer at the Johns Hopkins General Clinical Research Center. All patients were seen as outpatients approximately every 2 to 3 months for pump refills and more frequently for any problems. Patients with unexplained hyperglycemia or increased insulin requirements were admitted to the Johns Hopkins General Clinical Research Center for an insulin challenge test. This test involved pump infusion of 10% of the patient's normal daily insulin dose given to the fasting patient with frequent glucose measurements over the subsequent 4 hours or until hypoglycemic symptoms occurred. If the response to an insulin challenge was blunted, catheter blockage was suspected, and the patient underwent either laparoscopy or catheter change with the latter involving temporary intraoperative explantation and testing of the pump.

Glycohemoglobin levels were measured monthly by gel electrophoresis.[18] The upper limit of normal was 7.9%. Routine physical examinations, ophthalmologic evaluations, serum lipids, blood urea nitrogen, and creatinine levels were monitored every 6 months. Creatinine clearance values were calculated on a yearly basis. Patient acceptance was assessed every 2 to 3 months at the time of pump refills, as well as whenever problems required additional therapy.

Statistical Analysis

The results are expressed as mean ± standard error of the mean. Paired Student's t test was used to compare baseline with subsequent blood glucose, glycohemoglobin, and creatinine clearance values. The actuarial duration of system and catheter function was analyzed by the Kaplan-Meier technique.

Results

System Function

Both the PIMS and MIP have functioned safely for a total of 68.8 patient-years (Table 3) with 100% patient survival. During this time, the 21 patients have undergone a total of 49 surgical procedures, 31 of which were for elective implantation or pump change, with the remaining 18 (0.26 per patient-year) for adverse events. Specifically, 21 procedures were for initial pump implantation (10 PIMS, 11 MIP); 17 were for pump change (12 PIMS: 10 elective, one microchip failure, one air-lock) or catheter change (one PIMS, four MIP); 10 laparoscopies were for catheter blockage (six PIMS, four MIP); and one laparotomy was for small bowel obstruction (PIMS → MIP). Thirty-two of these procedures were done under general anesthesia (21 initial implantations, 10 laparoscopies, and one laparotomy) and 17 under local anesthesia (12 pump and five catheter changes).

None of the patients had complications directly related to the anesthetic or surgical procedures. Specifically, none of the wounds or pockets have required opening or pump removal because of infection. However, several of the MIP patients developed an erythematous, cellulitislike reaction over the pump pocket that usually was not associated with fever or leukocytosis. Nevertheless, these patients were treated with a few extra days of systemic antibiotics and discharged on a short course of oral antibiotics without long-term sequelae. Catheter blockage has been an ongoing problem, the details of which will be outlined below.

Nineteen of the 21 patients remain on intraperitoneal insulin for a mean of 39.3 months (Table 3). Two original group A PIMS patients had their pumps explanted recently, having had recurrent problems with catheter blockage. Each of these two patients had two laparoscopies and one catheter change before eventually stopping intraperitoneal insulin after 55 and 62 months, respectively. Thus, the actuarial system survival has been 90% at 5 years (Fig. 1A).

A third original Group A PIMS patient recently developed small bowel obstruction due to multiple jejunal adhesions, which required lysis. This patient had no prior abdominal operations but had received intraperitoneal insulin for a total of 64 months before this episode. Interestingly, the catheter had been in the pelvis throughout and at laparotomy was not attached to any of the interloop adhesions in the upper abdomen. Similar adhesions were observed at laparoscopy in the patient whose pump was removed at 55 months, but this patient remains asymptomatic. None of the other nine patients undergoing laparoscopy had such obvious adhesions, nor have any of the other 20 patients had symptoms or signs of bowel obstruction.

No patient has experienced inadvertant overdelivery of insulin, and underdelivery has been easily recognized because of gradual hyperglycemia. Symptomatic hypoglycemia with adrenergic symptoms has occurred at one time or another in most patients. Three patients have had hypoglycemic episodes severe enough to require assistance of another person, but no hypoglycemic episodes with coma or seizures have occurred. No episodes of ketoacidosis or severe hyperglycemia occurred either during the preliminary observation period or after implantation of the internal insulin pumps. Except for one previously reported PIMS microchip failure at 8 months[16] and one

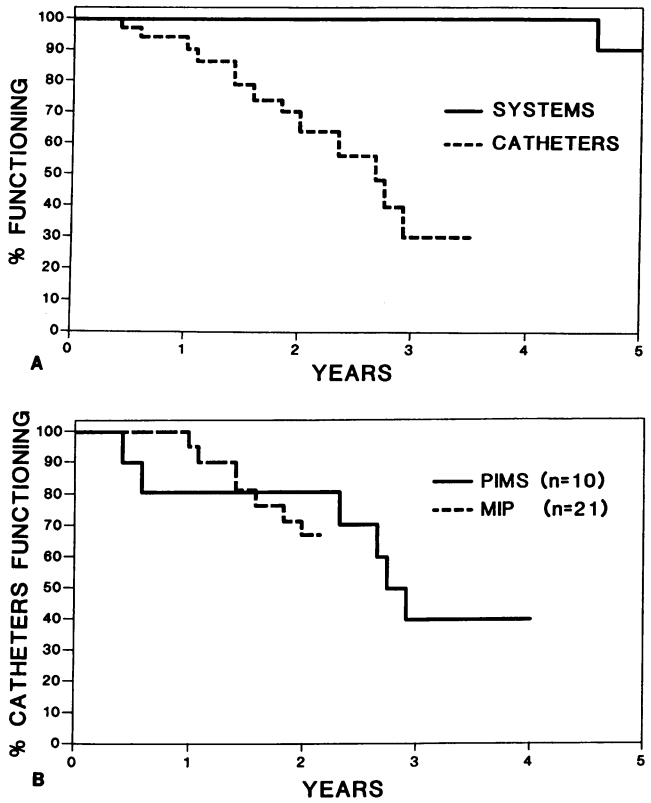

FIG. 1. (A) System and catheter survival by the Kaplan-Meier technique. Both systems and catheters represent 10 PIMS and 21 MIP patients. (B) Individual PIMS and MIP catheter survival by the Kaplan-Meier technique. The curves are not statistically significantly different.

PIMS air-lock at 25 months, the insulin pumps functioned according to specifications. Moreover, no evidence of insulin precipitation, aggregations, or loss of potency was observed.

Catheter Function

Overall, nine of the 21 patients (43%; six group A, three group B) have had problems with catheter blockage. By actuarial techniques, however, only 30% of the catheters will be still functioning at 3 years (Fig. 1A). A comparison of original catheter survival for PIMS and MIP is presented in Figure 1B. Follow-up for PIMS catheters is presently nearly twice as long as for MIP catheters. At 4 years, PIMS catheter survival was 40%, compared with 67% for MIP catheters at 2 years, but this difference in catheter survival was not statistically significant. Six of 10 group A PIMS catheters blocked between 5 and 35 months. Four of these same six group A patients have had their MIP catheters block between 12 and 22 months, whereas none of the four who did not have a block with PIMS blocked a MIP catheter ($p < 0.05$). Three of 11 group B MIP catheters have blocked between 17 and 24 months. With the PIMS catheter, blockage occurred once per 56 patient-months compared with once per 62 patient-months with the MIP catheter and once per 75 patient-months in the 11 group B MIP patients.

Catheter blockage has taken two forms: omental encasement of the catheter and fibrinous tissue buildup on or in the catheter tip. Omental encasement was seen in four of the six group A PIMS catheters that were observed laparoscopically. In comparison, a lesser degree of fibrinous tissue, without omental encasement or a dense fibrous tissue sock, was observed on the MIP catheter tip during all four laparoscopies and four additional catheter changes. Laparoscopic repair of catheters was successful in seven of 10 patients (five of six PIMS and two of four MIP). Temporary pump explantation and catheter change was successful in four of five patients (one PIMS and three of four MIP).

Diabetic Control

The mean of all blood glucose values for the 2 months before and each 2 months after pump implantation are shown in Figure 2A. A "study effect" with relatively lower mean blood glucose levels was observed for the first 12 to 16 months after pump placement for both the PIMS and the MIP patients. However, this effect tended to wear off by 18 months. Interestingly, this "study effect" was observed after MIP implantation in both the group B patients just starting on an internal pump and in the group A patients converted from PIMS to MIP.

The percentage of blood glucose determinations over 200 and under 60 mg/dL for MIP patients is presented in Figure 2B. A similar "study effect" with tighter glucose control for 12 to 16 months followed by a return to baseline levels was again observed for the MIP patients. The percentage of blood glucose values below 60 mg/dL began at 8.8% and increased slightly by 6 months; however, only 6.0% of blood glucose values were below 60 mg/dL at 18 months. Glycohemoglobin levels are presented in Figure 2C. For PIMS patients, these values were also lower after pump placement and remained low for 18 months. This measure of tighter glucose control was not as apparent for the MIP patients.

Diabetic Complications

The pre-existing nephropathy in the one group A patient has remained stable for 65 months. The mean yearly creatinine clearance for the 10 group A PIMS patients who have been maintained on intraperitoneal insulin for a mean of 5 years, and 21 MIP patients, is presented in Figure 3. The PIMS values have decreased from a mean of 117 mL/min to a plateau of approximately 95 mL/min in the last 3 years. Although this reduction was statistically significant at 3 and 4 years, it may reflect a normalization of the glomerular filtration rate. No significant changes in peripheral neuropathy have been observed

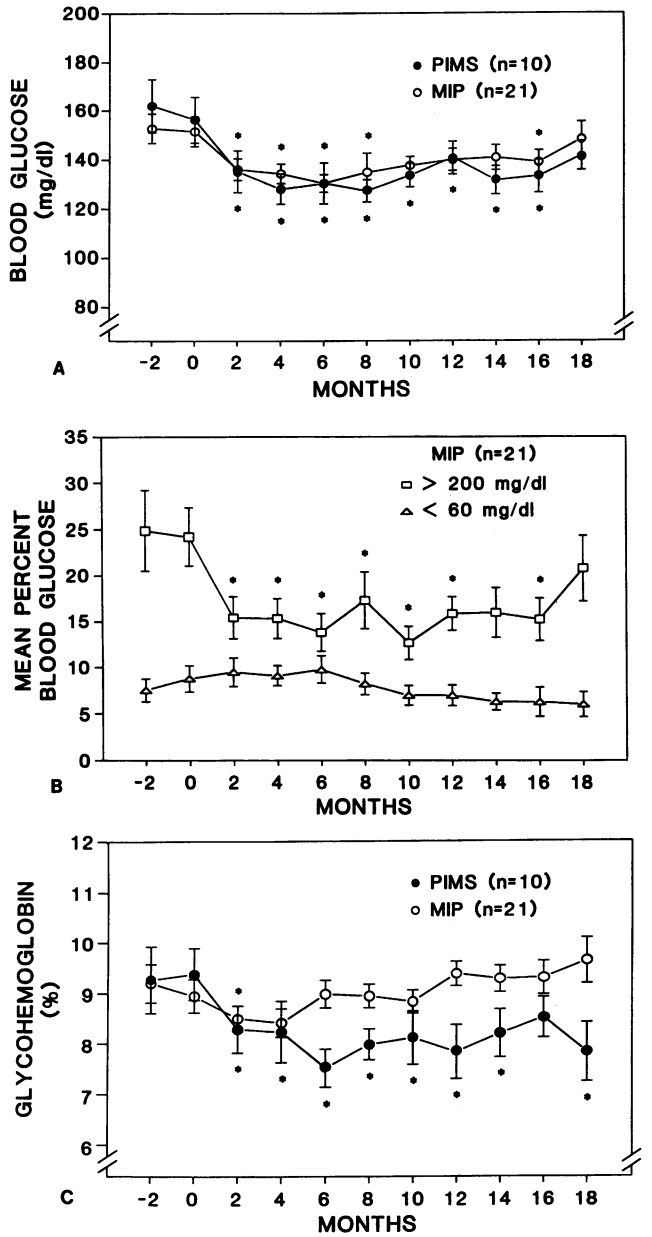

FIG. 2. (A) Mean of all blood glucose values for the 2 months before and each 2 months after pump implantation. *Statistically significant value ($p < 0.05$) compared with the appropriate baseline levels for PIMS or MIP. (B) Mean percentage of blood glucose values either above 200 or below 60 mg/dL. *Statistically significant value ($p < 0.05$) compared with the appropriate baseline for PIMS or MIP. (C) Glycohemoglobin values for the 2 months before and for each 2-month period after pump implantation. *Statistically significant value ($p < 0.05$) compared with the appropriate baseline PIMS or MIP glycohemoglobin level.

throughout the course of the study. Two of the group A patients who had preexisting proliferative retinopathy had vitreous bleeds, but have had stable vision now for 12 and 18 months after vitrectomy. Surprisingly, none of the other nine patients with background retinopathy have had any further progression of their disease, and no new cases of retinopathy have developed in the other 10 patients. None of the patients have developed peripheral microvascular problems.

Patient Acceptance

All 21 of the patients receiving intraperitoneal insulin have been very pleased with their pumps. Patient acceptance remains very good whether or not there has been a need for repeat surgical procedures. Even the two patients with recurrent catheter blockage who eventually had their pumps explanted remain enthusiastic about the therapy. Similarly, the one patient who developed small bowel obstruction, requiring laparotomy for lysis of adhesions after 5 years of intraperitoneal insulin, continues to be strongly in favor of continuing the therapy. These three and the other 18 patients who have had fewer problems agree that the freedom from daily insulin injections, the ease of activity in comparison to external pumps, and the acceptable cosmetic result all contribute to improved quality of life with intraperitoneal insulin delivery.

Discussion

This report documents nearly 70 patient-years of experience with open-loop, variable rate, programmable, implanted pumps that deliver small pulses of U-400 insulin into the peritoneum. All 21 patients with type I insulin-dependent diabetes who have received this therapy are alive after a mean of 39.3 months (range, 10 to 65 months) after implantation. Nineteen of these patients remain on intraperitoneal insulin, and the 5-year actuarial system survival has been 90%. Glucose control was improved, especially during the first 16 months after pump implantation, without an increased incidence of severe hypoglycemia. Catheter blockage has been a significant

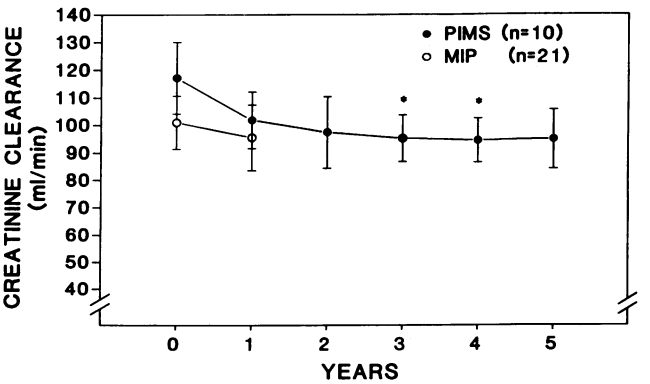

FIG. 3. Creatinine clearance values measured yearly after PIMS or MIP. *Statistically significant value ($p < 0.05$) compared with the appropriate PIMS or MIP baseline level.

problem, occurring in nine of the 21 patients (43%). Catheter occlusion has been successfully managed, however, with laparoscopic repair in seven of 10 attempts or with catheter change in four of five patients. Thus, with an aggressive policy of laparoscopic clearance or catheter change, long-term intraperitoneal insulin delivery is now a feasible and safe alternative for type I diabetics.

Over the past decade, several hundred insulin-infusion pumps have been implanted worldwide.[11–16,19] Until recently, most of these pumps were fixed-rate and not programmable. Nevertheless, freon-driven constant rate pumps with intravenous delivery have been demonstrated to improve glycemic control in non–insulin-dependent diabetics.[12,20] Data from the registry of the International Study Group on Insulin Infusion Devices suggest that the eight variable-rate pumps that were implanted before 1986 become nonfunctional after an average of 13 months.[21] In a more recent European trial of 20 programmable pumps with intraperitoneal insulin delivery, 21 clinical and 11 technical problems occurred in 18 patient-years of experience.[22] Six of these 20 pumps were either difficult to program or stopped working within the first year.

In the authors' initial report of intraperitoneal insulin delivery with PIMS, 18 patients (10 Johns Hopkins Medical Institutions, eight University of California, Irvine) were managed for a mean of 18 months (range, 4 to 25 months) and a total of 28 patient-years.[16] This preliminary trial demonstrated the feasibility of intraperitoneal insulin delivery with good glycemic control without severe hypoglycemia. In this report, the actuarial survival rate of catheter function was 78% at 1.5 years. The University of California, Irvine group has recently updated their experience with three different implantable, programmable insulin pumps in 25 type I diabetic patients managed since 1987.[23] Initial catheter placement was intraperitoneal in 24 cases and intravenous in six cases. Nineteen of the 25 patients (76%) had functioning pumps at the time of the report, but actuarial system function was only 50% at 3 years. In comparison, the current series provides the longest and most successful experience with intraperitoneal insulin delivery, with a 90% actuarial system survival for PIMS and MIP at 5 years.

The overall success of the Johns Hopkins insulin pump program may be attributed to design features of PIMS and MIP, commitment to the peritoneum as the delivery site, and an aggressive management policy for catheter blockage. Multiple safety features of PIMS have previously been reported[16,17] and have been incorporated into and enhanced in MIP. Of the safety features that distinguish PIMS and MIP from other programmable pumps, the insulin reservoir maintained at less than atmospheric pressure, so that insulin is drawn into the pump during refilling, may be the most significant. Delivery of insulin into the peritoneum also may be more physiologic than either continuous subcutaneous or variable intravenous delivery.[23–27] Moreover, intravenous delivery has been associated with a high incidence of catheter blockage.[19]

With PIMS and MIP, at least some of the peritoneally delivered insulin enters the portal venous rather then the systemic circulation. This factor may be important in preventing severe hypoglycemia and defective glucose counter-regulation, which has been reported with other techniques for intensive insulin therapy.[28] Peritoneal delivery also may be important in ameliorating the potentially dangerous peripheral hyperinsulinism that occurs with most insulin delivery approaches, from subcutaneous to organ transplantation.[23,25,27,29] Conversely, long-term intraperitoneal insulin delivery continues to be plagued by catheter blockage. Both laparoscopy and catheter change have been successful in treating this problem. Laparoscopy, however, usually requires general anesthesia; and although catheter change is done under local anesthesia, the pump pocket is re-entered, which increases the risk of infection. Nevertheless, these procedures have been well tolerated by our patients, who have remained enthusiastic about the benefits of the program.

Additional options for the management of type I diabetes include whole organ and islet transplantation and a biohybrid artificial pancreas. In recent years, whole-pancreas transplantation has become more successful, with improved patient and graft survival.[4,5,30] However, whole-pancreas allotransplantation has the disadvantages of the risks of major surgery, the need for chronic immunosuppressive therapy, and limited applicability because of shortage of donor organs. Moreover, although successful pancreas transplantation achieves excellent blood glucose control and insulin dependence, stabilization or reversal of diabetic complications has been difficult to substantiate.[3,30–33] As a result, some have suggested that pancreas transplantation should be done earlier to prevent the development of complications. Whether the risk of surgery and immunosuppression is justified in patients such as those the authors have treated with intraperitoneal insulin remains a matter of debate. With implanted insulin pump therapy the morbidity is far less and is suitable for diabetics with few or no complications.

Islet transplantation has theoretical and practical advantages over whole-organ transplantation.[6–8] With islet transplantation, major surgery is avoided, and islets can be frozen and stored and potentially modified to decrease immunogenicity.[34,35] Conversely, disadvantages of islet transplantation include the large number of donors required, the lack of large-scale isolation procedures, and the need for immunosuppressive therapy.[36–38] As a result, this option is not widely available. An extension of islet transplantation is the use of barrier isolation systems to

immunoexclude the islets with microencapsulation or to create large diffusion chambers composed of semipermeable membranes holding a large number of islets.[8-10] Initial results of this latter technique in pancreatectomized dogs have been encouraging,[9,10] but neither of these methods has yet to be applied in humans.

Two of the long-term goals of all methods of treating insulin-dependent diabetes mellitus are to prevent or stabilize complications and to improve quality of life. Although current data on the effects of pancreas transplantation on diabetic complications are mixed, quality of life with respect to diabetes is improved but is accomplished at a cost of increased hospital admissions due to transplant-related complications.[30,37,38] The current report of long-term intraperitoneal insulin delivery was not designed either as a diabetes complication or quality of life trial. The only diabetic complications that have progressed in the original 10 patients followed over 5 years, however, are in the eyes of the two patients who had proliferative retinopathy at the time of initial pump placement. No other definite progression of existing complications or appearance of new complications has been observed in the 21 patients with nearly 70 patient-years of follow-up. Moreover, freedom from the inconvenience and discomfort of daily insulin injections has clearly improved the quality of life for these patients.

Currently, two multi-institutional trials of the MIP are ongoing. The 21 MIP patients in this report are part of an industry-sponsored trial with more than 250 pumps implanted in type I diabetics in the United States and Europe.[19] In addition, the Department of Veteran Affairs has an ongoing randomized trial of intraperitoneal insulin delivered by MIP *versus* intensive insulin therapy in type II diabetics. These two trials should establish the safety and efficacy of long-term intraperitoneal insulin therapy and begin to look more closely at the relative merits of portal *versus* systemic insulin. With the development of a glucose sensor on the horizon, this experience may be an important step toward a closed-loop system that could consistently normalize blood glucose.

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Discussion

DR. CLYDE F. BARKER (Philadelphia, Pennsylvania): These are really very impressive results, and I was happy to review the manuscript because it is excellent work.

I think that some people might be surprised to see this paper on the program of a surgical meeting, but it is worth remembering that diabetes is in a sense "a surgical disease." Not only as surgeons do we take care of its complications, but I think it is fair to say that many of the important contributions to the understanding and treatment of this disease have been made by surgeons.

It was only a hundred years ago that an experimental surgeon in Europe first made the association of the pancreas with diabetes. Even though this disease had been recognized since ancient times, it was not known until then that it had anything to do with the pancreas. Seventy years ago another young surgeon, a young Canadian surgeon, discovered how to isolate insulin, a story every medical student knows. Probably only our president and other Canadians would know that when Fred Banting went to Toronto to ask for 10 dogs to experiment on during a summer vacation, that he was told by the expert in diabetes, Professor Mcloud, that he was wasting his time and should instead, because he was a surgeon, try to transplant the pancreas. Fortunately, Banting did not take the expert's advice and within a couple of months, of course, he had isolated insulin and shown that he could keep pancreatectomized dogs alive.

Although our efforts in transplantation began a long time ago, they have not really been very successful so far. Back in the 1930s, Jonathan Rhoads, among other surgeons, tried to transplant isolated pieces of pancreas into diabetic patients. Our new vice president, Keith Reemtsma, was probably the first to do a bona fide isolated islet transplantation (in fish). Other members of our group such as Walt Ballinger and Rich Lillihei, John Najarian, and Dave Sutherland, have made major contributions in the transplant field.

I personally believe that pancreatic and islet transplantation will not be the ultimate treatment of this disease. I think that instead we will discover how to prevent it. I had the privilege of presenting a paper to this Society 11 years ago that was the first to show that diabetes in experimental animals could be influenced by manipulation of the immune system. Investigators who work with experimental models of diabetes, such as our president's wife Elenor, I think are going to find the clues to tell us how to prevent the autoimmune process that causes diabetes.

Meanwhile, transplantation and better methods of delivering insulin will be competing treatments. Particularly at European meetings, these modalities frequently share the same program. Transplantation has until recently had an edge, but I am not so sure after hearing Dr. Pitts' paper this morning that this dominance will continue.

I think it is hard to believe in this age of computers that we are not going to be smart enough to figure out how to normalize the blood sugar by improving methods of delivering insulin. Improvements in this technology such as Dr. Pitts uses are likely to allow normalization of the blood sugar. As far as we know, pancreatic transplantation offers nothing beyond that in terms of preventing the complications of diabetes, which in all probability are the result of the wide swings in hyperglycemia that conventional insulin therapy allows. The paper we have heard this morning is in my opinion the description of an excellent new and evolving technology.

I was particularly interested in the choice of the intraperitoneal route, because this is the first one that our group used in our islet transplantation experiments. It did not prove to be very good for transplantation because the dose of islets needed for reversal of diabetes was much larger in the peritoneal cavity than if transplanted to other sites such as the liver. But this may not be true for insulin therapy and, in fact, as Dr. Pitts and his colleagues have suggested, the intraperitoneal route may have the advantage of being more physiologic than subcutaneous or other routes because part of the insulin absorbed reaches the portal circulation. I wonder if he has data on the fraction of insulin that does directly reach the portal circulation and the liver.

The data on complications, as he indicated, are very early, and although they seem encouraging I predict it will be many years before we will see with this or any form of therapy convincing evidence that the complications actually can be prevented by tight control of the blood sugar. This is an important aspect of this evolving therapy, because tight control of the blood sugar, as Dr. Pitts has indicated, also has dangers. In the European experience, a number of patients, using more primitive insulin pumps than the one he's described, have suffered bad hypoglycemic episodes. It is very important to be able to prevent those.

In the European experience with insulin pumps, there were also some patients who had sudden unexplained loss of eyesight. It is encouraging that Dr. Pitts has not encountered this complication.

This approach is quite promising, possibly more so than encapsulation of islet tissue to prevent rejection; perhaps better than any form of transplantation. But it is not as good as prevention.

DR. DAVID E. R. SUTHERLAND (Minneapolis, Minnesota): Dr. Pitt is making a concerted effort to improve the management of diabetic patients and to improve their quality of life, a goal similar to that of pancreas transplantation.

I look on diabetic patients as hovering between purgatory and hell, and the physician's role is to figure out which of the alternative treatments tips the balance more toward purgatory than toward hell for an individual patient. Dr. Pitt needs to inform us as to how the patients are selected for his alternative modality.

None of the current options available will get diabetic patients to heaven, and we continue to search for the Holy Grail. A pump coupled to a glucose sensor might be that grail. Dr. Pitt, please comment on the current status of closed-loop pumps with a servo-type feedback system *versus* the open-loop pump that you used.