Devices for Insulin Administration

Jean-Louis Selam, MD
M. Arthur Charles, MD, PhD

There is a significant need for revised, safe, and more effective insulin-delivery methods than subcutaneous injections in the treatment of both type I (insulin-dependent) and type II (non-insulin-dependent) diabetes. The aim of this review is to describe the rationale and methods for better use of injection and infusion devices for intensive insulin therapy and to describe results of animal and human research that will lead to an implantable artificial pancreas. Injection devices, e.g., jet injectors, insulin pens, and access ports, cannot be considered as a major breakthrough in the quest for improved control, although they may improve the patient's comfort. External pumps have benefits over multiple injections and conventional insulin therapy only in specific subgroups of patients, e.g., those with recurrent severe hypoglycemia, but only when used by experienced personnel. The external artificial pancreas (Biostator) is also to be used by experienced personnel for limited clinical and research applications, e.g., surgery of the diabetic patient. The development of an implantable version of the artificial pancreas is linked to progress in the field of reliable long-duration glucose sensors. Finally, programmable implantable insulin pumps, used as an open-loop delivery system, are the most promising alternative to intensive subcutaneous insulin strategies in the short term, although clear evidence of improved safety and efficacy remains to be documented. ***Diabetes Care*** **13:955–79, 1990**

RATIONALE FOR IMPROVED INSULIN DELIVERY

The relationship of improved acute blood glucose control with the amelioration of acute diabetic complications, e.g., ketoacidosis, is established (1). The relationship of more chronic blood glucose control and chronic complications, although firmly established for pregnancy, is not as well established for other specific diabetic complications, e.g., retinopathy, nephropathy, and neuropathy. These results have come about because short-term studies can only be evaluated within a few years after a hypothesis is formulated. Hypotheses related to long-term complications require decades to thoroughly evaluate. With regard to long-term complications, several animal and human studies suggest a direct relationship between poor blood glucose control and an increase in prevalence or incidence of most chronic complications (2–6). In the pregnancy model, not only is the degree of metabolic control linked to the incidence of chronic complications, but also complete resolution of congenital malformations in infants born of diabetic mothers requires that glycosylated hemoglobin levels actually be in the normal range; i.e., blood glucose levels must be nearly normal before conception (7–9). These data suggest a positive curvilinear relationship with worsening metabolic control and fetal malformation rates similar to those described for cholesterol and coronary artery disease. Similar data may be true for nephropathy (10). For pregnancy and probably other complications, prevention and/or early intervention will be the major strategy in the prevention of chronic complications. Of the various interventions that will be used, the most important is likely to be improved chronic blood glucose control.

With these concepts in mind, there is a significant need for revised, safe, and more effective insulin-deliv-

From the Diabetes Research Program, Department of Medicine, University of California at Irvine, Irvine, California.

Address correspondence and reprint requests to J.-L. Selam, MD, Service de Diabétologie, Hotel-Dieu, 1 Place du Parvis Notre-Dame, 75181, Paris, Cedex 04, France.

ery methods in the treatment of both type I (insulin-dependent) and type II (non-insulin-dependent) diabetes. These needs stem from the fact that currently used intensive insulin treatment methods are ineffective in the general population and even in research patients for the long-term normalization of glycosylated hemoglobin values. For example, the Diabetes Control and Complications Trial (DCCT) evaluated ~300 patients cared for by health-care providers in >27 academic institutions. These patients were randomized into intensive- and standard-therapy groups. The standard-therapy group used no more than two insulin injections and less frequent glucose monitoring. Although the intensive-treatment group received multiple insulin injections or continuous subcutaneous insulin infusion (CSII), both associated with multiple daily blood glucose determination at a high health-care provider–patient ratio, this group was unable to achieve a normal mean glycosylated hemoglobin value (11; Fig. 1). Subsequent data show a slow drift upward of glycosylated hemoglobin values in the intensively treated groups, demonstrating the difficulties of chronic blood glucose management. Review of these data illustrates that ~25% of patients achieved normal glycosylated hemoglobin levels, i.e., near-normal blood glucose control, for ~1 yr. Similar studies in 130 nonresearch patients from our clinic at the University of California at Irvine revealed that only 20% of individuals can maintain a normal glycosylated hemoglobin level for a 1-yr period (12). Finally, when data were examined for 261 patients from the general diabetic population cared for by non–diabetes specialists, no improvement was observed in the moderately elevated glycosylated hemoglobin levels over a 5-yr period of observation during which intensive control was becoming more frequently used (13). Thus, intensive metabolic control, as practiced in various United States diabetes clinics, is ineffective for long-term lowering of glycosylated hemoglobin levels into the normal range in large groups of patients.

There are various studies documenting that small groups of research patients can be treated in such a way as to normalize their glycosylated hemoglobin values; however, these studies are short term and do not reflect the clinical or nonresearch setting (14). For these reasons, it appears that intensive insulin treatment (i.e., self-monitoring of blood glucose and intensive use of allied health personnel including the nutritionist, psychologist, exercise physiologist, diabetes teaching nurse, and diabetes nurse practitioner), in addition to strong physician support at the pediatric and adult levels, is not sufficiently successful to normalize glycosylated hemoglobin levels and perhaps eliminate chronic diabetic complications. These intensive methods are also cumbersome and expensive, and over the last 10 yr have only had a positive impact at certain centers. Even then such success is rarely documented. Thus, it should be apparent that innovative treatment plans are needed, as suggested by the U.S. Department of Health and Human Services (15).

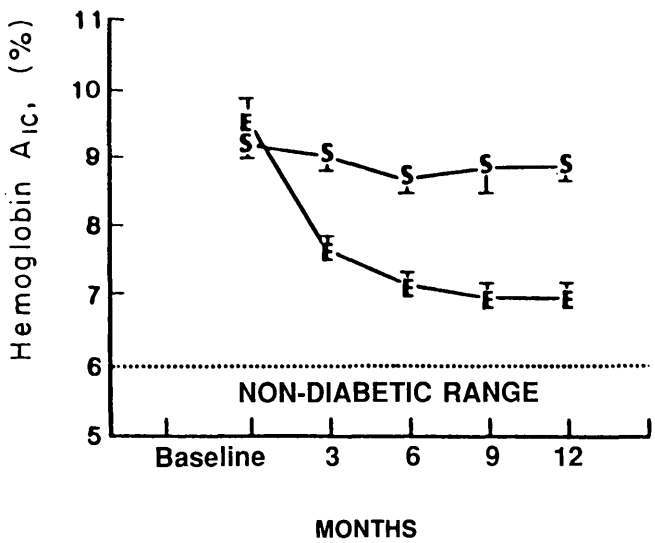

FIG. 1. Mean HbA_{1c} (±2SE) for Diabetes Control and Complications Trial (DCCT) feasibility study. Standard-group subjects (S) compared with experimental-group subjects (E). Differences between treatment groups significant ($P < 0.0001$) for all time points after baseline. From the DCCT Research Group (11). © by the American Diabetes Association.

It must be stressed, however, that intensive insulin treatment is exceedingly more desirable than conventional or nonintensive management. Various studies indicate improvement in acute diabetic complications, e.g., ketoacidosis and infections, and general well-being or life-style after the use of intensive methods of diabetic control (1,16,17). Furthermore, even partial improvement in glycosylated hemoglobin levels may improve some chronic complications, at least in the fetal malformation model (7). If the DCCT confirms these data for other complications, then at least we have started to have a positive effect on diabetic complications. This would be an important milestone in the treatment of this disorder.

The reasons for the lack of success with current metabolic control technologies are unclear, but some investigators believe that the predictability of insulin availability to the patient is extremely variable (18). These observations are derived from the concept that multiple, intermittent, and subcutaneous injections are highly artificial. Available insulins do not permit sufficient similarity to physiologically delivered insulin. Furthermore, the subcutaneous depot site is associated with too many insulin absorption variables to be successful (19–23). Finally, physiological systems require closed-loop feedback control when there is direct positive feedback of blood glucose levels on insulin infusion. Current methods that use open-loop feedback are not effective because the patient and health-care provider attempt to predict the insulin response to a given blood glucose value (11–13). In an attempt to improve these problems,

various alternative subcutaneous insulin-delivery systems were developed in the late 1970s. However, these more advanced systems, e.g., CSII, were equally unsuccessful, indicating that the subcutaneous route of insulin administration, even with intensive patient support, is not successful in normalizing glycosylated hemoglobin levels.

There are other factors that influence and create barriers to effective metabolic control in the diabetic patient, e.g., nutritional, psychosocial, and logistical; however, most of these seem to be unresolvable by physicians and allied health-care providers with the use of the end point of normal glycosylated hemoglobin levels. Thus, there is a strong need to improve insulin management, and it appears that increasing the intensity of personnel is not a realistic answer at this time. It is hoped that improving the predictability of insulin availability to the patient and closing the insulin-glucose feedback control loop could help resolve these issues. These ideas reinforce the need for innovative methods of insulin delivery, preferably avoiding the subcutaneous route.

To approach these problems, a few investigators have used open-loop intravenous and intraperitoneal insulin-delivery systems. Preliminary data, which are described in more detail below, indicate that the predictability of insulin availability to the patient is improved. From these pilot safety trials, it seems that there may be an improvement in glycosylated hemoglobin levels associated with improved and diminished glycemic excursions, although these studies were not designed to answer such questions. Virtually all intravenous or intraperitoneal studies preclude evaluation of the most important end point efficacy (i.e., glycosylated hemoglobin) because of the lack of long-term randomized controlled methods that use sufficient numbers of patients. Economic considerations are also important, especially in relation to the risk-benefit ratio.

Many lessons have been learned during the last 10 yr with intensive insulin management. Several treatment methods have been used with the hope of an improvement in treatment success. Although there has been some impact, there are many subgroups of patients whose care can be improved with some of these newer methods. It is the aim of this review to describe the rationale and methods for more successful use of these methods and to describe the results of animal and human research that will lead to an implantable artificial pancreas. If such devices can be used safely, they would be the next milestone in intensive metabolic control, because the physician and patient are to a major extent removed from the insulin-glucose closed-loop feedback dynamic.

INJECTION DEVICES

In the past few years, several devices have been proposed to avoid or ease the use of needles for insulin injection. In none of these devices was blood glucose improvement the original goal. However, it is suggested that more comfort may indirectly promote improved diabetes control via patient adherence to treatment.

Jet injectors. With jet injection, the needle is replaced by an ultra-thin (0.008-inch-diam) liquid stream of insulin forced through the skin under high pressure. The rationale for jet injections is to decrease the pain of injection as found with needles (24). Devices available in the U.S. are listed in Table 1. The Task Force on Jet Injection of the Youth Council of the American Diabetes Association reviewed the scientific literature available on jet injections and recommended usage guidelines (25). The following is a summary of the Task Force statement. First, jet injections appear mechanically reliable. Second, insulin absorption and activity differ when insulin is administered by jet injection than when syringes are used. Jet injection results in a 10–20% greater decrease in blood glucose, and a 30 min more rapid rise in free-insulin levels (26–32). The latter may result in a shorter overall duration of action, although this has not been clearly measured (26,27,32). Thus, jet-injected short-acting insulin may be a more effective regimen than conventional injections. On the other hand, jet-injected long-acting insulin may be less effective because of the shorter duration of action than conventional injections. Studies specifically designed to address whether these results improve blood glucose levels are needed. Furthermore, the major advantage of decreased pain at injection and better acceptability requires clear documentation, because 2–5 yr of continuous use is necessary to compensate for the expense of purchasing the jet injector (Table 1).

Insulin pens. Insulin pens are no more than ready-to-use sophisticated insulin syringes. Insulin pens available in the U.S. are listed in Table 2. Their main advantage is that they decrease the materials a patient has to carry compared with patients who use regular syringes. Pens include an insulin cartridge lasting 3–5 days, a disposable needle, and a trigger button for selecting and injecting the dose. The latest version of the insulin pen (NovolinPen, Squibb-Novo, Princeton, NJ) can be used with regular or intermediate insulins (33). Several clinical trials have been performed, mostly in Europe, where insulin pens were first introduced in the early 1980s. These studies have shown that insulin pens provide a glucose control similar to multiple daily injection regimens, but that they are preferred by 80–90% of the patients according to end-of-study questionnaires (34–

TABLE 1
Jet injectors available in U.S.

Product name (manufacturer)	Size (cm)	Weight (g)	Price ($)
Medi-Jector II (Derata)	15.2 × 3.8	397	825
Medi-Jector EZ (Derata)	15.2 × 2.5	170	695
Preci-Jet 50 (distributor, HDI)	15.2 × 2.5	159	689
Vitajet (distributor, MEC)	17.8 × 1.9	227	549

Adapted from *Diabetes Forecast* (45).

TABLE 2
Insulin pens available in U.S.

Product name (manufacturer)	Features	Price ($)	Comments
Accupen (Ulster)	Cartridge-pen injection device	59.95	
NovoPen (Squibb-Novo)	Penlike injection device	95.00	Use only with Novolin PenFill and PenNeedle
NovolinPen (Squibb-Novo)	Penlike injection device	39.95	PenFill cartridge available in Novolin R, Novolin N, and Novolin 70/30 insulin

Adapted from *Diabetes Forecast* (45).

39). However, questionnaire evaluations carry well-known problems, i.e., patient bias, and therefore these results should be interpreted with caution. The obvious convenience of the insulin pen, combined with its relatively modest price, should be attractive, especially for patients on multiple insulin injection regimens (Table 2). Still, neither insulin pens nor jet injectors represent a major breakthrough in the search for improved glucose control.

Access ports. Subcutaneous external access ports, e.g., the Button Infuser (Markwell), have been developed to avoid multiple daily needle injections. The needle of the infuser remains in the skin for 24–72 h, and the subject injects insulin with a syringe into the button port instead of directly into the skin. Totally implantable access ports are used routinely for chronic intravenous drug administration for nondiabetic indications. The peritoneal route has also been used to administer cytotoxic drugs via access ports (40). However, there are only a few studies of intraperitoneal insulin administration via access ports (41,42). Subcutaneous external access ports and intraperitoneal implantable access ports carry a high risk of infection. This risk is intrinsic to the design of these devices and their use in diabetes, i.e., a chronically implanted (intraperitoneal port) or semi-chronically implanted (subcutaneous port) device being punctured several times daily. In a limited evaluation of the totally implanted subcutaneous peritoneal access device (Motion Control, Salt Lake City, UT), we experienced an unacceptable high frequency of infections and port occlusions (unpublished observations). Fortunately, these infections were limited by the occluding omental capsule that almost invariably forms around the intraperitoneal opening of the device (42). Others have obtained more encouraging results, possibly because of their longer and more important experience and the use of these restricted devices in patients with renal disease (42).

INFUSION DEVICES

Whatever the device mechanism or the route of insulin administration used, insulin injections remain a preprogrammed and irretrievable method of administration of insulin having little to do with continuous and feedback-regulated normal insulin secretion. In the last decade, the growing use of self-monitoring of blood glucose and glycosylated hemoglobin levels and the relationship of chronic complications, e.g., fetal malformations and overall metabolic control, documented the need for more effective methods of administering insulin. It also made possible the use of patient-activated (open-loop) infusion pumps. Although insulin pumps are not closed-loop systems because glucose sensors are not available, these devices represent a significant advance toward more physiological insulin delivery and thus potentially improved glucose control.

EXTERNAL PUMPS

Several excellent reviews have been published related to CSII use (43,44). Some of these reviews focus on buyer's guide information or technical issues (45,46). This review focuses on the medical aspects of CSII use, especially safety, i.e., prevention of pump-related complications.

History. The concept of CSII is admirable. This technique uses physiological principles of continuous insulin delivery coupled with meal-associated increases in pancreatic islet insulin delivery, thus attempting to more closely simulate normal physiology. In 1979, the use of external devices coupled with daily self-monitoring of blood glucose seemed to be an ideal method to restore blood glucose levels to the near-normal range and perhaps normalize glycosylated hemoglobin levels. Such physiological and clinical principles were rapidly evaluated in various research clinics, and a multitude of studies indicated a major success. Unfortunately, most of the above research studies were not performed with appropriate experimental designs, and many subjects were rarely evaluated in randomized or controlled prospective trials. Because most studies used few patients, certain infrequent complications of CSII use were not observed because of the lack of statistical likelihood. These are important concepts for new device studies. After these early studies, clinicians and patients began to purchase CSII devices, and rapid widespread treatment outside of the research setting ensued. It was not until ~8000 devices were being used in the U.S. that information became available, suggesting that these devices were not as effective as originally thought. Studies began to appear in the mid-1980s indicating that, in larger population samples, the devices were not effective in normalizing or perhaps even in improving blood

glucose levels (47,48). During the initial (apparent but not real) success of these devices, the dangers became more obvious and federal agencies became interested in these potential problems. In the U.S., the Centers for Disease Control documented that the frequency of severe side effects associated with CSII needed to be more rigorously examined (49). After this notification, studies suggested that these devices were too unsafe for widespread use (50,51). The rise and fall of CSII therapy in the U.S. was the result of false expectations based on inadequate information, e.g., significant clinical dangers and lack of significant blood glucose improvement.

There are some important messages from the CSII trials of the late 1970s and early 1980s. These messages need to be carefully evaluated before other mechanical insulin-delivery systems achieve widespread clinical acceptance before well-documented studies including prospective, randomized, and controlled trials involving many patients.

Current status. It is clear that CSII safety, when related to clinical efficacy, does not achieve the appropriate risk-benefit ratio for widespread use by clinicians caring for diabetic patients (52). There are, however, uses for these devices in special settings, e.g., when CSII is used by clinicians who have broad experience with such devices associated with low complication rates. When the latter is true, there is also an improved adherence of long-term CSII use (53). The following section reviews the safety and efficacy of these devices in special settings, apropos to subjects who already use or are anticipating the use of CSII.

There are major and minor medical safety issues related to CSII use. Minor complications include skin infections and other rare events. Of the major complications observed, diabetic ketoacidosis and severe hypoglycemia are the most important.

Ketoacidosis. Of the many CSII treatment–related complications, ketoacidosis is the most serious because it is common and dangerous (54–57). Ketoacidosis usually is found to be related to patient and/or provider inexperience, concurrent infection (usually unrelated to CSII use), or accidental cessation of insulin infusion (55–61). The latter is most often caused by infusion-set obstruction or one of several other potential mechanical failures (57,61–64; Table 3).

Treatment with CSII has been associated with a 2- to 17.5-fold increased frequency of ketoacidosis compared with patients treated by other methods (49,55,57–60,62–64). With the use of self-monitoring of blood glucose and intensive treatment with CSII, these ketoacidosis rates are often too high. The incidence of ketoacidosis with CSII use is reported to be from 0.07 to 0.75 patient events/yr (57–59,65–67). Ketoacidosis rates in the diabetic population are not known, but in the DCCT (68) study, 0.03–0.045 patient events/yr were reported before study entry. Ketoacidosis events during the DCCT trial were similar in the control and intensive groups and were not increased over the 1 yr before study entry (68). Fortunately, data reported by the Centers for Disease Control did not reveal increased death rates related to diabetic ketoacidosis.

TABLE 3
Causes of CSII-associated ketoacidosis

	Incidence (%)
CSII mechanical	40
Catheter obstruction	15
Catheter leakage	10
Pump failure	10
Inflammation at needle site	2
Needle displacement	2
Cracked catheter	1
Infections	40
Upper respiratory tract	25
Trauma-cellulitis (non-CSII related)	7
Viremia	7
Urine infection	1
Brittle diabetes	15
Other	5

Table is arranged in order of likelihood. CSII, continuous subcutaneous insulin infusion.

To compare the safety and efficacy of intensive subcutaneous insulin injections (ISII) and CSII and to identify patients most likely to benefit from CSII, referred patients cared for in a university diabetes clinic were studied (69). The ability to normalize glycosylated hemoglobin levels and the occurrence rates of serious complications during CSII treatment were compared with those of a preceding 5-yr period of ISII treatment. Mean glycosylated hemoglobin levels in 45 patients who used ISII and CSII were 8.5 and 8.1%, respectively (normal <7.0%). The frequency rates of ketoacidosis with ISII and CSII were 0.17 and 0.20 patient events/yr, respectively (NS). Ketoacidosis frequency during CSII treatment was within the range reported by others; however, these rates are much higher than those observed in research studies, e.g., the DCCT. These high rates may reflect the selection of difficult-to-manage patients for CSII treatment, because the frequency of ketoacidosis in this study was similar during both ISII and CSII treatment. The reported high rate of CSII-associated ketoacidosis is unacceptable but may be reduced by more intensive education methods. Thus, a follow-up evaluation 16 mo later in our study showed that the 30 patients still available had only 0.10 ketoacidosis events/yr compared to 0.22 events/yr (NS) for the same patients earlier in the study (Fig. 2). Ketoacidosis may also be a reason for discontinuance of CSII treatment (53).

The diagnostic criteria for ketoacidosis are seldom sought in patients with moderate (11–17 mM) elevations of blood glucose levels. In the setting of CSII treatment, however, earlier diagnosis must be sought because of euglycemic diabetic ketoacidosis. Although euglycemic diabetic ketoacidosis is a misnomer because it is not euglycemic, it is an important concept. We observed severe ketoacidosis, e.g., pH <7 in patients with blood

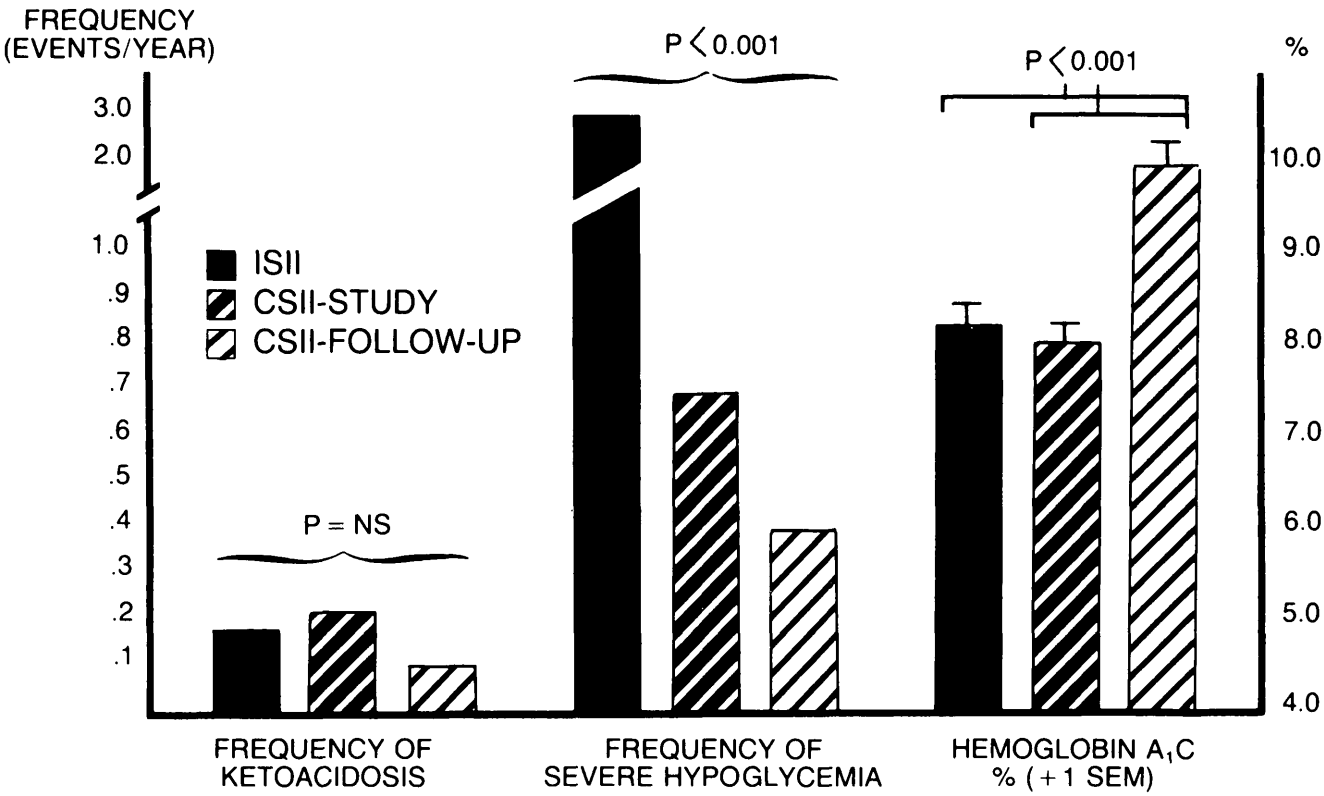

FIG. 2. Frequency of ketoacidosis and hypoglycemic events and level of hemoglobin A_{1c} in 30 patients evaluated during therapy with intensive subcutaneous insulin infusion (ISII), continuous subcutaneous insulin infusion (CSII), and at 15-mo follow-up with CSII.

glucose levels in the 11- to 17-mM range, during CSII treatment. Although no mechanisms are apparent for these observations, the syndrome emphasizes the importance of regular urine ketone testing. This is especially true when an unexpected significant increase in blood glucose levels occurs. This syndrome should also alert providers to avoid phone diagnoses and treatment when ketone levels are elevated or unknown.

As shown in Table 3, infusion-set obstruction is the single leading mechanical cause of ketoacidosis and CSII malfunction, especially in experienced users (57,61–64). It has been reported that buffered insulin is associated with fewer catheter obstructions than nonbuffered insulin (61–63,70). The effect of infusion-set obstruction events is also associated with a deterioration in short-term metabolic control, as shown in Fig. 3 (61). In 19 CSII-treated patients, a 33% lower frequency of infusion-set obstruction was observed after use of a purified pork-buffered insulin when compared with unbuffered purified pork insulin (61). These results confirmed earlier reports that, in 15 CSII-treated patients, insulin crystals were found in 48% of the catheters containing unbuffered insulin versus only 2% of those containing buffered insulin, and 61 episodes of occlusion were reported with unbuffered insulin versus 7 with buffered insulin in 28 CSII-treated patients (62,63). The mechanism of insulin precipitation is unclear but may be the result of a fall in pH toward the insulin isoelectric point at the distal end of the infusion set because of CO_2 permeability of the tubing (70–72). These pH changes may not occur with buffered insulin or with the polyolefin (polyethylene or polypropylene) infusion lines used in some infusion systems (73). Acidic insulin solutions have also been reported to be stable in external pumps, because insulin pH is already below the isoelectric point and thus does not pass the isoelectric precipitating point in case of a further fall in pH (74–76). In our studies, we did not find that the habit of bending the needle or low insulin flow rates increased the chances of occlusion. We also did not find a higher frequency of occlusion in our inexperienced pump patients (61). These data suggest that certain mechanical details are not of major importance in the occurrence of obstruction and ketoacidosis if appropriate instruction is given to patients before CSII use. We use an intensive 1-wk hospitalization for CSII training, although some patients require even more inpatient time. Inpatient education is followed with frequent outpatient visits, the rate determined by the patient's grasp of CSII safety and mechanical concepts. Of course, such training will not be as useful if the health-care providers do not have practical, mechanical, and educational aptitudes.

Previous studies on technical problems with CSII have focused on the causes, e.g., catheter obstruction, and/or the immediate or acute metabolic consequences, e.g., ketoacidosis or temporary hyperglycemia (57,62–64,70–

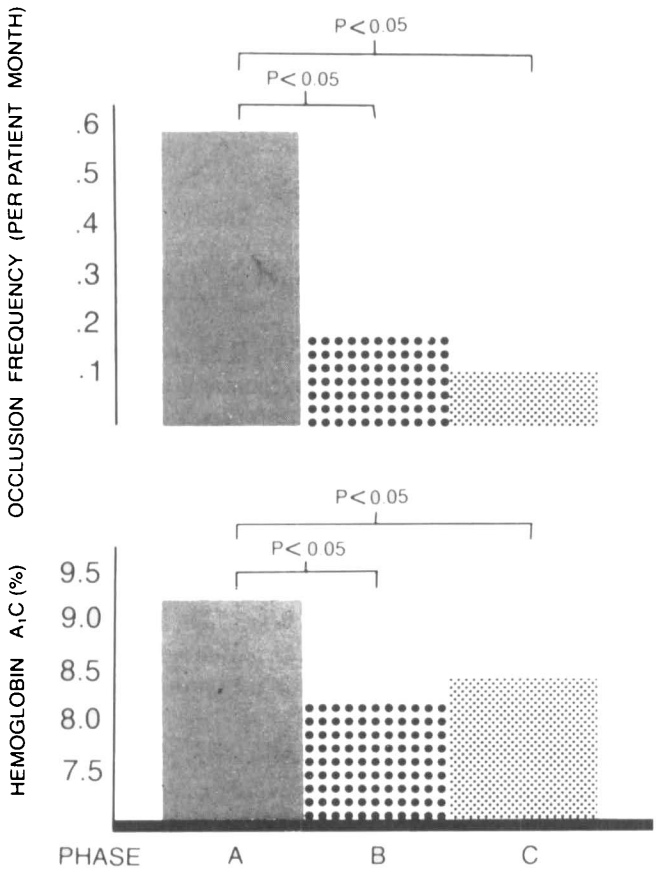

FIG. 3. Occlusion events and metabolic control in 12 patients who completed 3 phases. *A*, usual pump system and insulin; *B*, usual pump system and Nordisk; *C*, Nordisk infuser and Nordisk insulin.

72). Our data expanded these studies by showing that obstruction events are of significant clinical importance for chronic metabolic control, with the use of a randomized crossover design (61). In our studies, the highest glycosylated hemoglobin levels were recorded during the study phase associated with the highest frequency of obstruction events (Fig. 3). On the other hand, our patients experienced only two episodes of ketoacidosis (0.22 events/yr) during the study. Thus, we assume that obstruction events, even if diagnosed and treated before ketoacidosis, can negatively affect overall metabolic control. We conclude that obstruction events in CSII-treated patients are reduced and overall metabolic control is improved with the use of buffered insulins.

We also observed some compliant patients to be unusually sensitive to ketoacidosis with seemingly minor interruptions of insulin flow or with apparently minor illnesses (unpublished observations). We treat such patients with 10% of the total daily CSII insulin dose in one subcutaneous injection of ultralente insulin daily (77). We successfully eliminated the recurrent chronic and mild ketoacidosis events that prevent usual daily activities. Unfortunately, we have not determined the lowest effective dose for each patient. We use the rationale that ambient low insulin levels can be maintained in CSII patients, thus giving the patient and healthcare provider more time to make a diagnosis and begin an effective treatment plan. This technique may also become significant in future implantable pump studies, especially those that use intravenous insulin.

Severe hypoglycemia. The frequency of severe hypoglycemic events during the use of CSII has been reported to be higher, equal to, or lower than ISII (50,54,55,65, 67,69,78,79). In the DCCT, severe hypoglycemia was more frequent in the experimental intensively treated group compared with the control group (68). Unfortunately, the intensively treated group was not randomly selected, because these patients also had more severe hypoglycemia before study entry. Within the DCCT experimental group, CSII was not a factor associated with severe hypoglycemia. The death rates from CSII-associated hypoglycemia are reported to be similar to those in the general diabetes population (49). In our studies, the frequency rate for severe hypoglycemia was 2.73 events/yr for ISII and 0.22 events/yr for CSII ($P < 0.001$) (69; Fig. 2). A frequency of severe hypoglycemia equal to 0.22 events/yr compares with a range of 0.07–1.23 events/yr in other studies (54,55,65,66,79,80). In a subgroup of 23 CSII-treated patients who had frequent severe hypoglycemia with ISII, the frequency of severe hypoglycemia was reduced from 3.72 to 0.32 events/yr ($P < 0.001$). The frequency of severe hypoglycemia continued to decline in 30 patients from 3.0 to 0.7 to 0.4 events/yr ($P < 0.01$) at successive yearly evaluations. We also documented that the frequency of symptomatic mild, moderate, and severe hypoglycemic events can be reduced by CSII treatment without a concomitant rise in the frequency of ketoacidosis events (68). The latter results confirm previously reported findings in 5 patients (81).

Although improved metabolic control could be responsible for a diminished ability to perceive decreases in glucose levels, this does not explain the reduction in severe hypoglycemic episodes reported in the above studies. Probably, the exclusive use of short-acting insulin with CSII is a major reason for the reduction of hypoglycemic events because of its more predictable absorption, especially in the absence of combined depot intermediate-acting subcutaneous insulin. This is especially true when only CSII basal rates are used (81).

Intensive insulin treatment is associated with an increased risk of hypoglycemia because of the inherent risk associated with lower blood glucose level goals, the potential dampening of clinical adrenergic symptoms, and the potential and still controversial abnormalities of posthypoglycemic glucose counterregulation associated with ISII or CSII (50,82,83). Because of these risks for recurrent severe hypoglycemia during intensive insulin treatment, hypoglycemic responsiveness testing has been proposed to detect patients who have defective hypoglycemic counterregulation (79). Stabilized blood glucose levels during the intravenous insulin infusion test reflect adequate and clinically relevant blood glucose

counterregulation. We also used this test to screen candidates for intensive insulin treatment to assess their risk for CSII treatment–associated severe hypoglycemia. During these studies, we observed that counterregulation is also affected by chronic blood glucose control as assessed by comparing blood glucose levels during acute hypoglycemic counterregulation with previous outpatient longer-term metabolic control (84). Blood glucose levels stabilized during insulin infusion in 17 patients. Blood glucose stabilization was 41 ± 2 mg/dl (range 27–58 mg/dl) and was achieved after 109 ± 8 min (Fig. 4). Of these 17 patients, 3 could be classified as having inadequate counterregulation by the White (79) criteria, because blood glucose levels fell to <35 mg/dl within 100 min of the test, although they did not have neurological symptoms. Of the 17 patients who experienced blood glucose stabilization during insulin infusion, and thus exhibited some counterregulation, a positive correlation was found between blood glucose levels at stabilization and glycosylated hemoglobin levels (r = 0.57, $P < 0.02$). In the remaining 5 patients, blood glucose levels continued to fall and the test was discontinued after 106 ± 11 min. This group of patients who experienced blood glucose stabilization had a mean HbA_{1c} of 7.7 vs. 8.0% (NS). We considered these 5 patients to have absent glucose counterregulation.

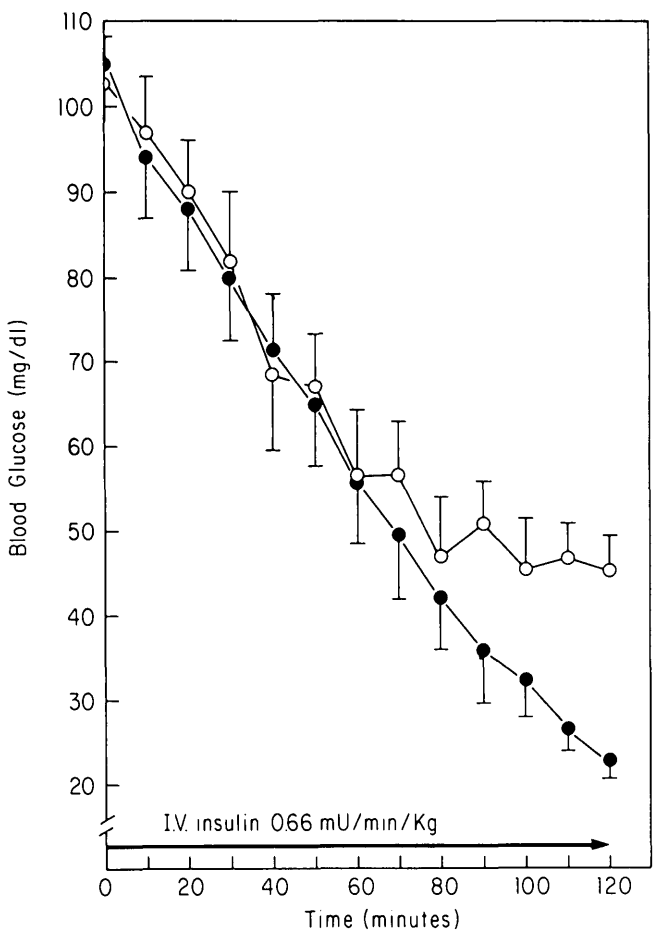

FIG. 4. Hypoglycemia responsiveness testing in 21 individuals documenting blood glucose level stabilization in 16 subjects (○; plateau ≥30 mg/dl) despite continuous intravenous (IV) insulin infusion. Five subjects failed to counterregulate (●), and thus blood glucose levels continued to fall during IV insulin infusion.

The effect of long-term optimization of glycemic control on glucose counterregulation is controversial (83–89). Our data confirm previous studies in which well-controlled diabetic patients showed an exaggerated fall in glucose levels during intravenous insulin infusion when compared with poorly controlled patients (88). We extended these studies by showing that, in 17 of 22 type I diabetic patients of long duration, blood glucose concentration during insulin infusion in patients tested stabilized at different levels that correlated with their respective glycosylated hemoglobin values.

In summary, several studies indicate that in nonresearch type I diabetic patients *1*) ISII and CSII treatments are similar for maintaining similar glycosylated hemoglobin levels, *2*) CSII like ISII is not an effective method for achieving normal glycosylated hemoglobin levels, *3*) CSII and ISII can be associated with similar ketoacidosis rates, and *4*) CSII treatment can significantly reduce the high frequency of severe hypoglycemic events that occur in some patients with ISII treatment. Although the use of CSII is discouraged in routine clinical practice, the use of CSII in certain subgroups of type I diabetic patients, when used by experienced CSII treatment groups, can be helpful.

IMPLANTABLE PUMPS

In addition to the above safety limitations, CSII also has the limitations inherent to the subcutaneous route for insulin administration, i.e., slow and poorly reproducible kinetics of absorption and hyperinsulinemia (90–92). The latter may accelerate the development of atherosclerosis and weight gain, which are often associated with effective subcutaneous insulin treatment (93,94). Attempts to adapt external pumps to other routes for insulin infusion, e.g., intramuscular, intraperitoneal, or intravenous, have been limited by patient discomfort, significant infections, and poor availability of materials adaptable to chronic intraperitoneal or intravenous infusion (74–76,95–100). Implantable infusion devices permit chronic intravenous and intraperitoneal insulin access with minor discomfort and lower risks of infection better than external devices because of fewer interventions required.

History. As early as 1969, the Minnesota group designed and patented the first implantable pump, a relatively simple single-rate pump that was developed further by Infusaid (101). However, it was only in the early 1980s that implantable programmable variable-rate pumps specifically designed for the administration of insulin became available for clinical evaluation both in Europe (Siemens, Karlsruhe, FRG) and the U.S. (Sandia, Albuquerque, NM). Unfortunately, after the initial published studies, follow-ups have only been reported in

abstract form (102–107). From these oral studies, it was obvious that major problems occurred in early implantations, including flow slowdown, insulin aggregation in the pump or in the delivery catheter, hardware problems such as short battery life, and surgical problems such as device-induced skin erosion and catheter traction resulting in catheter leaks, kinks, and displacement. Thus, clinical trials were soon interrupted between 1982 and 1986 to allow insulin and pump manufacturers to improve their materials. The following sections review data from the Human Implantable Pump International Registry, covering all human implantations performed, and the results of the two most recent human trials that began in 1986 (108–111).

Human implantations registry. The International Study Group on Implantable Insulin-Delivery Devices (ISGIID) maintains the international registry. Table 4 lists the status of clinical studies with implantable pumps. As of May 1989, according to the ISGIID registry, 280 implantable pumps have been implanted in 215 diabetic patients (116 women, 99 men) by 15 investigators (10 from Europe, 5 from the U.S.) (38). Seventy-three percent of the patients have type I diabetes, and 70% were between 20 and 50 yr of age. Half of the patients used an external pump before implantation. As expected, the most frequent indications for pump implantations were poor diabetes control and the presence of chronic diabetic complications. The constant-rate pumps were by far the most frequently used pumps. However, since 1986, implantations of constant-rate pumps have represented only 31% of all implantations. Until 1985, the intravenous route was the most frequently used route of infusion. Since then, the intraperitoneal route has become the preferred infusion route, accounting for 72% of recent implantations.

TABLE 4
International Study Group on Implantable Insulin Delivery Devices registry results (May 1989)

	Constant rate	Programmable rate
Patients*	155	57
Pump implants†	212	65
Route of administration‡		
Intravenous	122	8
Intraperitoneal	85	55
Pumps explanted§	117	22
Duration of implantation (mo)	31	13
Reasons for pump explantation		
Flow slowdown	37	0
Catheter obstruction	45	7
Other pump malfunction	2	5
Other catheter problem	17	6
Late infection	14	1
Pump migration	6	3
Patient request	13	2
Other reason	18	4

*With at least 1 pump of specified type.
†Plus 3 pumps when pump type was missing.
‡Plus 2 pumps (1 constant rate, 1 programmable) when route of administration was missing, one programmable pump with subcutaneous route, and one from intramuscular route.
§Plus 1 of 4 pumps when pump type was missing.

A total of 135 pumps have been explanted, representing 59% of the implanted constant-rate pumps and 34% of the programmable pumps. The most common reasons reported for pump explantation were insulin flow slowdown and catheter obstruction, resulting in gradual insulin deficiency and loss of glucose control. Late pump-site infections, i.e., not directly related to implantation surgery, were the second most common cause of pump explantations. Infections were always limited to the subcutaneous pocket and were usually successfully treated only by pump explantation. The above data should be interpreted with caution because more than one problem may lead to explantation, and only one of these may have been identified or reported. Also, some problems may have been incorrectly identified or not recognized at all. For example, discrimination between catheter malfunction and pump failure requires surgical or other invasive identification procedures, such as laparoscopy, which are not always performed. Furthermore, systematic technical review of explanted pumps is usually performed by the manufacturer, potentially resulting in undisclosed data for reasons of confidentiality.

A total of 14 patients died while pumps were still in place, raising the question of whether there was any possible role of the pump in this outcome. From information reported to the ISGIID registry, only one death could be potentially related to pump use because the death was associated with severe hypoglycemia. In all other cases, deaths were attributed to problems apparently unrelated to pump use including cardiovascular (n = 4), cerebrovascular (n = 2), and miscellaneous courses (4 cancer, 1 sepsis, 1 cirrhosis, and 1 senility). As in the CSII Diabetic Report (3), the number of deaths reported in implantable pump users did not exceed that expected in a population of the same age.

Unfortunately, no efficacy data have been recorded by the ISGIID registry. More detailed information, including some efficacy data, may be gained from the two most recent programmable pump trials (110–112). These studies are described below, and their main features are shown in Table 5.

European clinical trial (POINT study). Four centers participated in this 1-yr open-label noncomparative pilot study. The goals of the study were to assess the feasibility of the infusion system, the reliability of the device, and the stability of insulin. The pump (model ID1, Siemens) is an improved version of the earlier one tested in 1981. The major technical features of this pump are shown in Table 6. The pumps were refilled with human U-100 insulin (Hoechst-Roussel, Somerville, NJ) stabilized by a mixture of genapol and polygeline (Table 7; see SUMMARY AND CONCLUSIONS). Twenty type I diabetic patients previously treated with CSII were implanted with an intravenous (5 patients) or intraperitoneal (15 patients)

TABLE 5
Design and results of 1986–1989 implantable programmable pump clinical trials

	POINT study (Europe)	PIMS study (U.S.)
Pump	Siemens (ID1)	Minimed Technologies (PIMS)
Insulin	GH21 Hoechst	PH21 Hoechst
Design	1-yr open-label noncomparative	3-yr open-label comparative to subcutaneous
Patients (M/F)	9/11	14/4
Route of infusion	5 IV, 15 IP	18 IP
Age range (yr)	24–56	19–56
Duration of diabetes (yr)	6–38	3–30
Severe retinopathy	3	3
Severe nephropathy	1	1
Patients on CSII before implantation	20	15
Total experience (patient-yr)	18.2	34.3
Major local problems	2 skin necrosis 2 local infections 3 local pain	1 local infection
Catheter obstructions	3 IV, 2 IP	All IP
Pump failures	1	1
Severe hypoglycemia	0	0
Ketoacidosis	1	0
Mean HbA_{1c} (%)	7.0 ± 0.3 (normal <5.9)	8.0 ± 0.3 (normal <7.3)

CSII, continuous subcutaneous insulin infusion; IV, intravenous; IP, intraperitoneal. Four centers (Munich [2], Milan, Vienna) participated in the POINT study, and 2 centers (Irvine, CA; Baltimore, MD) participated in the PIMS study.

catheter between February and November 1986. The results were reported after 18.2 patient-yr of experience (110). Insulin dosages, mean blood glucose levels, and glycosylated hemoglobin levels remained identical to immediate preimplantation values during the 1-yr follow-up. There were no differences in insulin, blood glucose levels, and glycosylated hemoglobin values between intravenous and intraperitoneal infusion routes. Strict metabolic control was not one of the aims of the study design.

Numerous problems were encountered during the study. Local tolerance of the pump was poor, with pain in the area of the pump in three cases leading to skin ulceration in two cases, infection in two cases, and consequently two pump explants. This may have been caused by the rectangular edges of the Siemens pump. A third pump was explanted because of pump failure. Five catheters became nonfunctional after a mean of 7 mo. The clinical assumption was that the catheters were obstructed by fibrous products, because no insulin aggregates were observed in the catheters examined by electron microscopy. However, anatomical exploration of the malfunctioning catheters, such as laparoscopy for intraperitoneal catheters, was not performed before catheter withdrawal; therefore, a definitive diagnosis of catheter malfunction is uncertain. Although not fully

TABLE 6
Operational and near operational implantable insulin pumps

Model	Pumping principle	Battery duration (yr)	Reservoir volume (ml)	Weight with full reservoir	Dimensions (mm)	Stroke volume (ml)	Programmable	Basal rate range (U/h^{-1})	Bolus range (U)	Pressure inside reservoir (psi)*	Side port
Infusaid											
100	Vapor pressure	NA	50	237	87 × 28	NA	No	Fixed/constant	NA	+8.5	No
420	Vapor pressure	NA	50	280	87 × 28†	NA	No	Fixed/constant	NA	+8.5	Yes
1000	Valve accumulator	>3	25	300	90 × 27†	1	Yes	0.1–50	0–99.9	+8.5	Yes
Minimed											
PIMS	Diaphragm	>3	10	215	81 × 23	2	Yes	0–3.2	1–31	−4	No
MIP 2001‡	Piston	>3	10	162	81 × 20	0.5	Yes	0.13–30	0.2–32	−4	No
Siemens ID1	Peristaltic	3	10	180	85 × 60 × 22	NA	Yes	0.3–1.5	0–14	Negative	No
Medtronic 8610H‡	Peristaltic	3	18	203	70 × 28	NA	Yes	§	§	Negative	No

NA, not applicable.
*1 atm = 760 mmHg = 14.7 psi.
†Excluding side ports.
‡Models have not been tested in diabetic patients as of 1 June 1989.
§Minimum rate 0.6 ml/day, maximum 0.9 ml/h.

TABLE 7
Stable insulin solutions for implantable pumps

Name	Manufacturer	Stabilizing additive	Limitations	Status
Glycerol bicarbonate	Novo	Viscous agent (glycerol)	Increased viscosity, formation of oligomers	Used in Infusaid constant-rate pumps
PH21	Hoechst-Roussel	Surface active agent (genapol)	None	Used in Minimed and Infusaid programmable pumps
GH21	Hoechst-Roussel	Surface active agent (genapol) and viscous agent (polygeline)	None	Used in Siemens pumps

successful from a clinical perspective, this trial has revived scientific interest for implantable insulin-delivery systems and stimulated device manufacturers to develop a commercially and clinically acceptable product.

U.S. clinical trial (PIMS study). Two centers, University of California at Irvine and Johns Hopkins University, Baltimore, are participating in this continuing 3-yr longitudinal study, which is summarized in Table 5 (111–112). The goals of this pilot trial are to assess the feasibility, safety, and efficacy of the PIMS system by comparison to a 3-mo preimplantation period in which patients used ISII therapy. Characteristics of the PIMS pump are shown in Table 6. Human U-400 insulin (Hoechst-Roussel) stabilized with genapol was used in the PIMS pump (Table 7). Eighteen type I diabetic patients were implanted with the PIMS pump with the use of the intraperitoneal route between August 1986 and April 1987. Currently, we have 34.3 patient-yr of experience. Local tolerance of the pump was excellent because no pain or skin atrophy and only one pocket infection were experienced. This improved local tolerance of the PIMS pump compared with the Siemens pump is possibly due to the rounded geometry of the PIMS pump; metabolic results are shown in Fig. 5. Mean blood glucose levels, mean glycosylated hemoglobin levels, and mean blood glucose level fluctuations all improved significantly when compared with preimplant values, and no severe hypoglycemia or ketoacidosis was

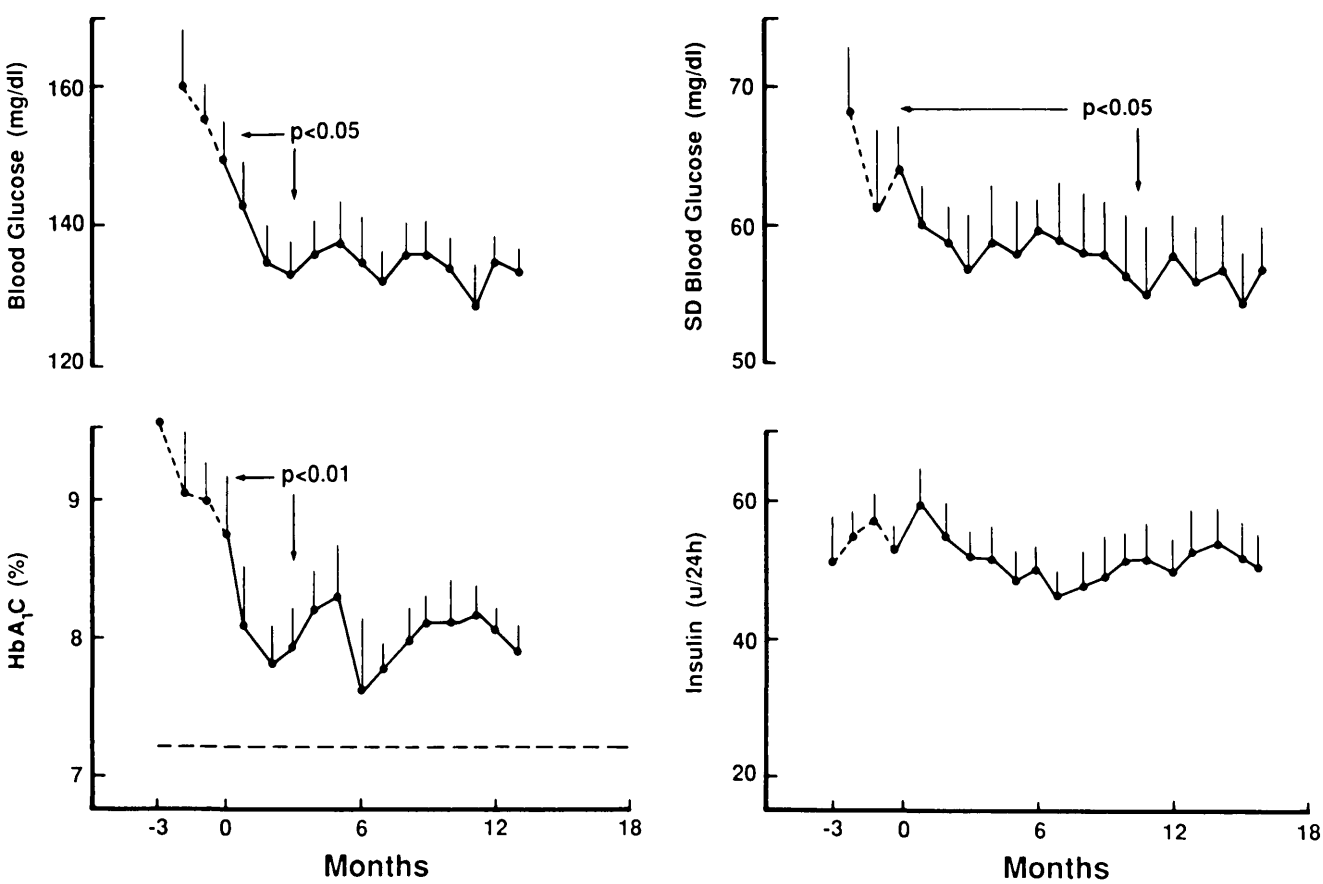

FIG. 5. PIMS study, metabolic results.

observed. Five (28%) catheters failed after a mean of 8.2 mo. Combined laparoscopy and pocket exploration revealed full catheter encapsulation by omentum. Seventy-two percent of the initial catheters have now reached 2 yr of successful function (Fig. 6). As in the POINT trial, no insulin problem was experienced. Inner lumen catheter deposition has been found to be minimal or absent with immunofluorescence techniques to detect insulin and fibrin and microscopic analysis of explanted catheters. Chromatographic analysis of residual insulin obtained from reservoirs at refills revealed that 92% of the insulin remained intact. Fourteen (78%) of the initial 18 patients are still continuing successfully in the study, after an average implantation time of 2.3 yr (Fig. 6). The remaining patients dropped out because of catheter failure (n = 3) or pump-site infection (n = 1).

In summary, the two trials are comparable in terms of patient number, study design, and patient selection. Thus, although the PIMS experience is twice as long as the POINT experience, the two studies can be interpreted jointly. No severe accident has been reported in either study, thus confirming the safety data reported in the ISGIID registry. Pumps and insulins have functioned satisfactorily, demonstrating that there has been progress in the development of biological and mechanical materials. Local tolerance of the pump was undoubtedly better in the PIMS trial. Catheter problems were encountered in both studies and were identified as non-insulin related. Catheter problems were most likely secondary to extraluminal or intraluminal tissue depositions. As a result of previous studies and the most recent trials, crucial issues have been identified that will direct future development of implantable insulin pumps. These issues are discussed in detail below.

Issues and prospects. The three components of the system, i.e., the pump, insulin, and catheter, have not attained the same level of development. Insulin solutions are now stable, but the delivery system, especially the catheter, needs further improvement.

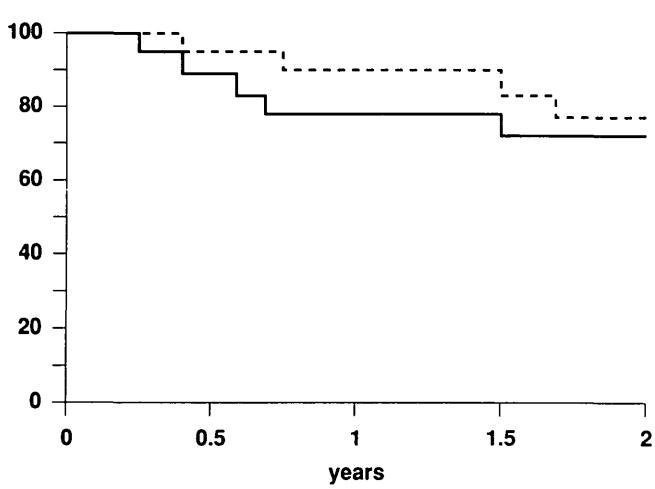

FIG. 6. PIMS study. Life table of percentage of patients still implanted (*solid line*) and percentage of catheters still operating (*dashed lines*).

Insulin. Insulin is the most advanced component of the implantable system primarily because of early and intensive involvement of certain manufacturers, e.g., Hoechst-Roussel (113). One basic problem with an implantable delivery device is the potential to alter the physical properties and/or chemical structure of insulin as a result of motion, continuous contact with pump materials, and prolonged body temperature exposure. The mechanisms involved in physical changes are still unclear and may include polymerization and molecular deformation (113). These mechanisms contribute to form macromolecular, stable, and biologically inactive insulin aggregates that are reported to coat catheter walls and precipitate causing catheter obstruction (113). Of the many proposals to stabilize implantable pump insulin, only a few have been effective both in vitro and in vivo (113). Effectively stable insulins are shown in Table 7. Insulin for implantable pumps has been recommended to be buffered, neutral, and human. However, acidic nonhuman insulin solutions have been proven perfectly stable in external pumps (see CSII SAFETY and CSII EFFICACY) (93,94,96). Insulin additives, e.g., surface active agents and agents to increase viscosity, greatly improve physical stability. For mechanical reasons, viscous agents may not be used in all pumps. Viscous agents increase the formation of oligomers, which are less biologically active than the native insulin molecule (114). Improved insulin-glycerol formulations have been used to limit this problem (115). Insulin stability also depends on the type of pumping mechanism and materials with which insulin is in contact. Genapol-stabilized insulin (PH 21, Hoechst-Roussel) has been shown to be less stable in peristaltic pumps, possibly because the roller mechanism may be more damaging to insulin than the pulsatile system used in the PIMS or other implantable programmable models (116,117).

Devices. Contrary to external pumps, only a few companies have been involved in the design of an implantable pump, because of the greater technical complexity and uncertainties about a successful future market (118). The pumps that were clinically evaluated are listed in Table 6.

Although not initially designed for insulin infusion, the constant-rate Infusaid pumps (models 100 and 420) have been used by several investigators in diabetic patients (103,106,119–121). The principle of these pumps is physicomechanical. At body temperature, the vapor pressure of a charging fluid (Freon) contained in one chamber of the pump exerts a constant positive pressure on the bellows of the insulin chamber of the pump. Therefore, the infusion rate is constant and can only be adjusted by varying the viscosity of the insulin or the diameter of the outlet reservoir orifice. Factors such as altitude and body temperature also affect the flow rate. Refills are performed under positive pressure, and precautionary measures must be taken when filling the pump to ensure that insulin is correctly injected into the pump

reservoir. Several investigators used this pump in type I and type II diabetic patients, with the latter requiring supplemental subcutaneous regular insulin injections (103,106,119–121).

The programmable pumps are based on different pumping principles. Siemens and Medtronic pumps are peristaltic pumps, i.e., the fluid is driven by the pressure of rollerheads on the tubing (122). The advantages of the peristaltic system include extreme accuracy, even at low rates, and continuous flow. The disadvantages are significant power consumption, damage to insulin by the shear forces of the rollers on tubings, risk of tubing deterioration and perforation after long-term use, and exposure of mechanical parts, such as rollerheads, to corrosion.

The Minimed models (PIMS and MIP models) and the programmable Infusaid model 1000 pump use a pulsatile rather than a roller-pump mechanism (110–112). Advantages of a pulsatile over peristaltic pumping mechanism include minimal physical trauma to insulin, less power consumption, and, possibly, less insulin requirements because of the intermittent rather than continuous delivery (123). In the Minimed models, insulin is driven by the aspiration/compression cycles of the ejection chamber (Fig. 7). The aspiration/compression cycles are partial in PIMS (a diaphragm pump) and full in the MIP (a piston pump). Diaphragm pumps carry the risk of irreversible insulin flow stoppage if an air bubble is trapped in the diaphragm chamber. In such an instance, pressure would only exert on compressible air instead of pushing fluid out of the chamber (124). This problem has been solved during the PIMS trial by thorough degassing of insulin immediately before reservoir refills.

The Infusaid model 1000 pump is a modification of the nonprogrammable constant-rate model 400 Infusaid pump. Insulin is driven by the high positive pressure in the reservoir and permitted to flow by a programmable solenoid-activated valve system (Fig. 8). The positive pressure principle reduces the potential of air bubble trapping in the pumping mechanism but theoretically increases the risk of insulin leakage out of the reservoir.

Regardless of the pumping principle, features such as telemetry, adjustable insulin flow rates, safety systems for inadvertent overprogramming or system runaway, and a reliable battery life span >3 yr are in our opinion mandatory components of an implantable insulin pump. Although present in some models, e.g., the Minimed and Infusaid pumps, data memory and computer/modem access are of less importance. Furthermore, future pumps should be smaller in size and weight, thinner for improved cosmetic results, and round with smooth edges to avoid pressure and subsequent skin ulcerations. Unfortunately, some parts of the pump, such as the pump reservoir, are difficult to miniaturize. Smaller reservoirs would require more concentrated insulin and thus a more accurate pumping mechanism. Finally, the reservoir refilling septum should be made more accessible to make the refilling procedures safer and easier, especially for use with more deeply implanted pump units.

Catheters. Catheters are undoubtedly the weakest link of the implantable insulin pump system. The ISGIID registry reports that 56% of the problems encountered with pump use are catheter related (109). From experience with 113 catheters, the Vienna group at Lainz Hospital reported a 69 and 51% 2-yr survival rate of intraperitoneal and intravenous catheters, respectively (125). In the U.S. PIMS trial, the 2-yr intraperitoneal catheter survival rate is 72% (111,112). In a survey of pump investigators, a catheter failure rate of 59% was reported, with 90% associated with gradually decreased flow rates (112). According to the ISGIID registry, catheter problems occurred with the same frequency with intraperitoneal and intravenous catheters. The 50% survival rate of intravenous and intraperitoneal catheters was identical, averaging 30 mo (109).

The anatomical findings in cases of catheter failure differed depending on the route of infusion. Nonfunctional intravenous catheters invariably had an organized blood clot at the tip of the catheter. Intravenous cathe-

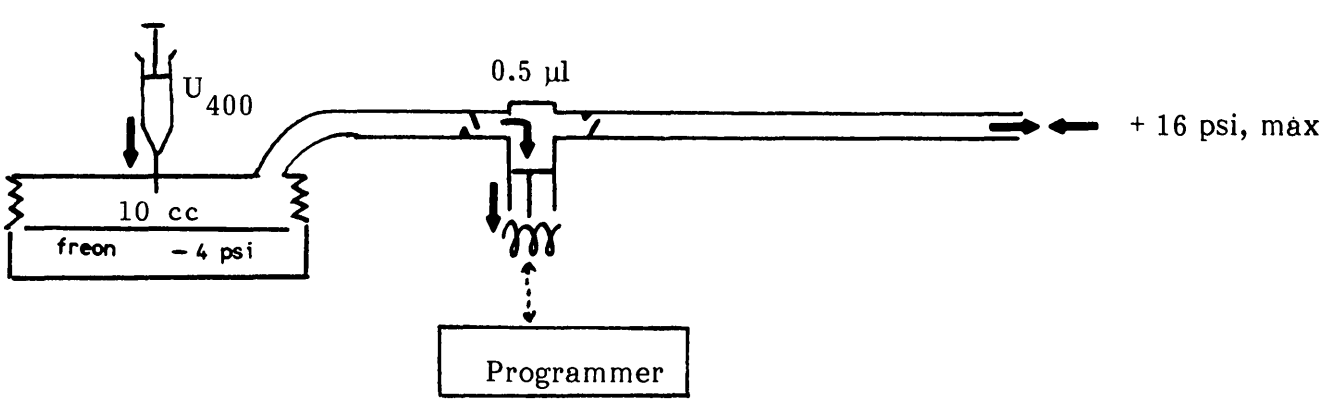

FIG. 7. Diagram of Minimed MIP mechanism. Each pulse sequence is as follows. At inflow cycle, insulin is aspirated from negative pressure reservoir by expansion of ejection chamber through 1-way passive inlet valves. Inlet valve closes passively when pressures equilibrate. At outflow cycle, chamber compresses partially (PIMS model) or fully (MIP model). Positive pressure forces insulin through 1-way passive outlet valve.

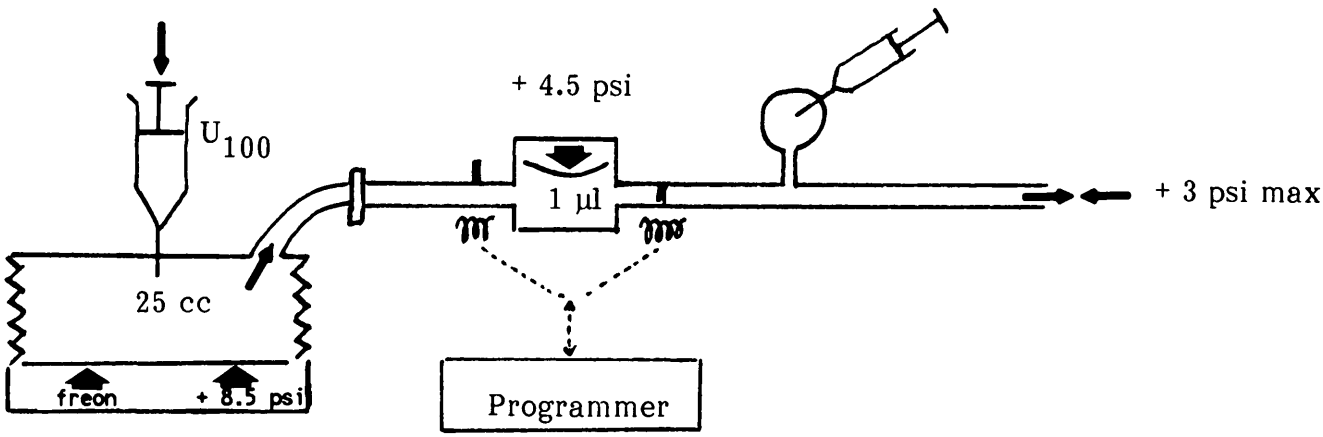

FIG. 8. Diagram of Infusaid programmable pump. Each pulse sequence includes 2 cycles. At inflow cycle, solenoid-activated inlet valve of ejection chamber opens, and insulin is driven under positive pressure from reservoir to ejection chamber. Inlet valve closes electronically. At outflow cycle, solenoid-activated outlet valve opens and lets insulin volume, driven by positive pressure created by separate Freon chamber above accumulator chamber, exit.

ters explored angiographically before removal had tissue formation dividing the vessel lumen and encapsulating the catheter. Nonfunctional intraperitoneal catheters when explored by laparoscopy had three lesions: *1*) intraluminal fibrinous and cellular deposition, *2*) dense fibrous deposition around the tip of the catheter, and *3*) full or partial catheter encapsulation by omentum (74,97,111,112). However, for various reasons, e.g., different insulin, catheter and pump principle, only the latter lesion, i.e., full omental encapsulation, was encountered in the PIMS study (111,112).

In contrast to intravenous catheters, intraperitoneal catheters can be repaired with laparoscopic access. However, after intraperitoneal catheter repair, the relapse rate has been reported to be 50% (111,112). These data raise doubts regarding the rationale for multiple catheter repairs. Clinical or biological markers for identifying patients prone to obstructions before implantation would be of major interest and are under investigation (126). Several technical improvements are or have been under intensive investigation to prevent or limit catheter obstructions. Factors such as the design of the pump and catheter, and catheter chemical composition do not seem to be of major importance, because obstructions have been seen with all types of materials used (127). Biological obstructions are less frequent when intravenous catheters are placed with their tip in the distal superior vena cava or into the right atrium, or when intraperitoneal catheters are placed with their tip in the lower parts of peritoneal cavity (97,126). These improvements may in part be the result of longer and more flexible and mobile catheters that access deeper sites of placement, i.e., right atrium for intravenous or low peritoneum for intraperitoneal infusion.

Of available pharmacological additives aimed at blocking fibrin and/or tissue depositions, only heparin has been studied because *1*) both blood (intravenous catheters) and fibrin (intravenous and intraperitoneal catheters) depositions may theoretically be arrested by heparin, *2*) high-molecular-weight heparins do not cross the peritoneal membrane barrier and are used safely in large quantities during peritoneal dialysis (128–130), *3*) heparin may limit postoperative abdominal adhesions (131), and *4*) we have shown that heparin and insulin are miscible (132,133). Mixed heparin and insulin retained biological and structural properties in pump reservoirs exposed to prolonged (90 days) shaking at 37°C. Alternatively, heparin or other antifibrin products could be coated to the catheter rather than mixed with insulin. Catheter flushing either at the time of obstruction, or intermittently to prevent obstruction can also be used if the pump has a side-injection port and/or high infusion rates, such as with the Infusaid models. Various rinsing solutions have been tried, including highly basic and fibrinolytic mixtures, although the main action of such flushes may be mechanical (125,134).

In conclusion, more biocompatible catheters are needed, ideally to increase catheter function time up to those of the pump, i.e., 3–5 yr. A potentially aggravating problem may be insulin, because it is well known that insulin inhibits fibrinolysis and stimulates cell growth locally (90). Therefore, in the short term it might be appropriate to learn how to limit and manage catheter obstruction with improved patient selection and simplification of surgical catheter repair techniques. Also, innovative procedures for early detection of catheter malfunction should be developed. Dynamic technetium scanning of catheter function has only been tested sporadically (H. Kritz, K. Irsigler, unpublished observations). Other methods, e.g., plasma insulin response after a standardized pump bolus or measurement of the pressure in the catheter via the side port, are under investigation (J.-L.S., M.A.C, unpublished observations).

Medical indications. The ISGIID registry reports that ~70% of implanted patients had type I diabetes (109). Thus, the first question is whether type II diabetic patients should also be considered for chronic insulin infusion with a programmable implantable pump. Be-

cause type II diabetes is much more prevalent than type I, this question is of major medical and socioeconomic importance. Several investigators have used constant-rate pumps in type II diabetic patients, based on earlier indications that one of the basic deficiencies in such patients is insufficient basal insulin secretion (119–121,135). More recently, obese type II patients have also been shown to improve considerably over a 3-mo period with subcutaneous long-acting insulin administration (136,137). This improvement was further enhanced by regular insulin boluses (136). However, as expected, circulating free-insulin levels increased in both studies, and weight gain was reported in one study (137). These data nevertheless indicate the potential usefulness of implantable programmable insulin infusion systems, even in obese type II patients.

Regardless of diabetes type, ISGIID registry data show that the most frequent indications for patient selection were poor metabolic control (58%), chronic complications (58%), glycemic instability (36%), and subcutaneous insulin resistance (8%). With the exception of the last, all these indications may be debatable (138). For example, poor metabolic control and glycemic instability indications require thorough documentation before these abnormalities can be attributed solely to subcutaneous insulin therapy and thus be expected to improve with the use of an implantable pump. Furthermore, some forms of retinopathy may temporarily worsen with rapid blood glucose improvement associated with frequent hypoglycemic reactions (139). Thus, we believe that a 3- to 6-mo preimplantation time should be allowed to improve general diabetic management, i.e., to gradually improve control of blood glucose values, to review patient skills, and to treat certain chronic diabetic complications, such as areas with significant retinal ischemia (140). Finally, clear delineation of implantable pump indications needs further evaluation, because most patients have had implants for the purpose of safety or feasibility studies rather than for metabolic evaluation.

Routes of infusion. Because subcutaneous and intramuscular routes are not suitable for continuous infusion with chronically implanted needles or catheters, investigators have used the intravenous or intraperitoneal route. The intravenous route has been chosen for ~50% of pump implantations because of rapid insulin kinetics, which is a major advantage in maintaining insulin-glucose physiological dynamics (141–144; see CSII SAFETY and CSII EFFICACY). In patients with increased insulin antibodies, the intravenous route has been suggested to reduce the antigenic stimulus by bypassing the injection sites, e.g., subcutaneous or intraperitoneal, although in our experience, intraperitoneal insulin delivery did not significantly increase insulin antibodies (144,145). On the other hand, direct entry in the blood circulation has two potentially dangerous effects: higher plasma insulin levels, which may accelerate atherogenesis, and rapid glycemic decompensation after insulin flow discontinuation (59,93). With intraperitoneal catheters, a few studies have suggested that a significant proportion of insulin is directed primarily to the liver via the portal circulation, thus recreating a more physiological portal-systemic plasma insulin gradient (146–148). However, other investigators have found that most of the intraperitoneal insulin was absorbed by lymphatic circulation (149). The route of intraperitoneal insulin absorption is of major importance for deciding whether the intraperitoneal or intravenous route is to be chosen for insulin-delivery systems.

For these reasons, we used a novel noninvasive nonisotopic method to determine the fraction of insulin absorbed by the portal circulation after intraperitoneal insulin administration (150). Conscious fasting diabetic dogs were studied at normoglycemia with the euglycemic insulin clamp. Posthepatic appearance of insulin and C-peptide were measured in peripheral blood during separate equimolar intraperitoneal or intravenous infusions of insulin and C-peptide performed at 2- to 4-wk intervals in random order. Forty to 70% of portal insulin is extracted during the first pass through the liver, whereas C-peptide passes the hepatic bed without uptake, moving directly into the systemic circulation (151). Thus, the fraction of intraperitoneal insulin not extracted by the liver during the first pass, and, consequently, portal absorption of insulin, can be derived from insulin and C-peptide plasma concentrations at steady state with monocompartmental equations (152). Preliminary results show an average value first pass liver extraction of insulin of 50%, indicating that 100% of intraperitoneal insulin was extracted by the liver. These data suggest almost complete intraperitoneal insulin absorption by the portal circulation. The rate of steady-state glucose infusion required to maintain euglycemia during intraperitoneal insulin infusion, however, was threefold lower compared with the rates required during an identically dosed intravenous insulin infusion. These data suggest that the action of an ~70% hepatic insulin extraction by intraperitoneal insulin on overall glucose metabolism is less effective than the action induced during intravenous insulin infusion associated with higher peripheral insulin levels. Similarly, hepatic glucose production has previously been shown to be suppressed to a similar degree by intraportally or peripherally administered insulin, despite intraportal hyperinsulinemia in the former (153). Both of the above studies are consistent with the concept that intraperitoneal insulin is less effective than intravenous insulin on overall glucose metabolism. One possible mechanism is that the hepatocytes nearer the portal triad may be less important for glucose output than hepatocytes closer to the control vein. In our study, a major mechanism may be the lower peripheral circulating insulin levels and, thus, lower peripheral glucose uptake with intraperitoneal insulin compared with intravenous insulin infusion.

There may be other biological differences of portal over subcutaneous or intravenous insulin entry, e.g., on lipids and other fuel metabolites (154,155). In a recent study, we compared the effects of intraperitoneal insulin

administration with those of subcutaneous insulin administration on circulating fuel metabolites, hormones, and lipoproteins in well-controlled type I diabetic patients. We found that when comparing intraperitoneal to subcutaneous insulin, both routes had similar effects on lipoprotein and other intermediary metabolites. Intraperitoneal insulin, however, was associated with a modest but significant reduction of cholesterol content of high-density lipoprotein and with normalized intermediary metabolite levels, suggesting a more appropriate action of insulin at the liver site (155). We also confirmed that the kinetics of plasma insulin appearance after an intraperitoneal insulin bolus more closely resembles normal appearance rates compared with subcutaneous insulin administration (155). The latter, in addition to allowing for potential better glucose control, may minimize the risk of chronic peripheral hyperinsulinemia. From a mechanical point of view, the risk of catheter obstruction is approximately the same with intravenous and intraperitoneal routes. However, surgical access and catheter repair may be easier with intraperitoneal catheters (see CATHETERS).

In summary, although the intraperitoneal route has been suggested to be more physiological, some investigators prefer the intravenous route for pump implantations because of satisfactory experience and clinical results (103,114,115,138). Further data from randomized, controlled, and prospective studies are still needed to identify which of the two routes, intraperitoneal or intravenous, is more advantageous to the patient.

Pump implantation site. As with pacemakers, most implantable pumps have been implanted subcutaneously, usually under the subcutaneous fat layers but above the muscular fascia. With currently available pumps, final cosmetic results may not be acceptable for some younger and more lean patients. With deeper implantations, i.e., underneath a muscular fascia, pump protuberance may be reduced (111,112). However, pump refilling is more difficult in the submuscular site, thus increasing risks of pump pocket hematoma and infection. We recommend the left inferior abdominal quadrant with deep subcutaneous insertion as an area for implantation. This strategy combines *1*) better comfort because the pump is placed under the belt line; *2*) lower position of the catheter, to possibly diminish obstructions (77); *3*) less visible scar because the incision is below the belt line; and *4*) better protection and less bulging because the pump is deeply inserted.

In conclusion, to represent a potential alternative to subcutaneous , ISII, or CSII treatments, implantable pumps require further technical improvements and clear efficacy assessment. The only randomized relatively long-term (3-mo) and comparative studies between the subcutaneous, intravenous, and intraperitoneal routes have been performed on small groups of research patients, and with external pumps (141). With the exception of one clinical trial in which we compared the metabolic control efficacy of programmable implantable systems versus subcutaneous intensive insulin therapy with a randomized crossover and controlled design (unpublished observations), all the ongoing implantable pump trials are pilot, uncontrolled, safety, and feasibility studies. Well-designed safety and efficacy studies that used enough subjects are critical for health authorities and the general medical community to assess the usefulness of implantable pumps over subcutaneous insulin therapies. When catheter longevity is improved and the superiority of glycemic control clearly proven, implantable infusion pumps will represent a safe and effective option for most patients unsatisfactorily controlled with conventional therapies. However, strict normoglycemia may never be attained with such open-loop systems, and for this important milestone, closing the insulin-glucose loop may be required.

FEEDBACK-CONTROLLED SYSTEMS

This section describes the extracorporeal and implantable versions of feedback-controlled insulin infusion systems. The major limitation with available insulin-delivery systems is the absence of automatic and continuous feedback control, i.e., internal pump regulation of insulin infusion by ambient blood glucose levels. In its simplest form, such a closed-loop system, called the *artificial pancreas,* consists of a glucose sensor, insulin and glucose infusion pump, and a computer controller that regulates the administration of insulin based on specific glucose-insulin algorithms.

EXTERNAL ARTIFICIAL PANCREAS

Currently, only large extracorporeal versions of the artificial pancreas are available, due to difficulties of developing a long-duration miniaturized reliable implantable glucose sensor. In the early 1970s, the concept of a bedside closed-loop infusion system as the logical extension of bedside continuous glucose monitoring was revived by Mirouze et al. (156,159), Albisser et al. (157), and Pfeiffer et al. (158) from original earlier work by Kadish (160).

Materials. Miles (Elkhart, IN) has developed the only widespread bedside artificial pancreas called GCIIS (glucose-controlled insulin infusion system) or Biostator (161). The machine, the size of an artificial respirator, includes a special dual-lumen catheter for continuous blood withdrawal; a glucose oxidase electrode; infusion pumps for insulin and glucose; a computer with a specific program of algorithms relating blood glucose levels to corresponding variations of insulin rates; and a printer for times, insulin, and blood glucose minute-to-minute recordings. The machine is permanently connected to the patient by two intravenous lines for glucose analysis and insulin delivery.

The dual-lumen catheter avoids having to use systemic heparin and is designed to prevent blood clotting inside the artificial pancreas tubings. Blood withdrawn from the vein is immediately mixed with heparin inside the catheter, and the mixture is directed into the artificial

pancreas. In practice, this catheter is one of the major weaknesses of the artificial pancreas. Tubings clot frequently. Partial clottings may change the heparin-insulin mixing ratio and thus generate erroneous blood glucose results. Fortunately, it seems that only some patients, possibly because of poor veins or high blood viscosity, are prone to such clotting problems.

The glucose sensor in the Biostator is a glucose oxidase electrode specifically developed by Miles for this application. The enzyme-coated membrane needs to be changed every 1–3 days. Although generally satisfactory and accurate, the electrode requires frequent (every 3–12 h) recalibration.

The artificial pancreas uses a roller pump for insulin infusion. The traumatic effect of the rollers on the insulin used in the Biostator has been found to induce gradual degradation of insulin during Biostator use (see IMPLANTABLE PUMPS). In one study, only 50% of initial insulin activity was detected after 6 h of Biostator use (162). This problem has been solved by the use of buffered insulin further stabilized with albumin. If these studies are confirmed, insulin data derived before the use of stabilized insulin solutions should be considered with caution.

Earlier studies showed that a 5- to 10-min delay between blood withdrawal and glucose measurement introduced an inherent error in closed-loop control (157,159). Algorithms were developed so that insulin administration was based on extrapolated or predicted glucose concentrations. This prediction was a function of the actual glucose concentration and its rate of change over the previous few minutes. When blood glucose concentrations are declining rapidly, these algorithms blunt insulin delivery well before the onset of hypoglycemia. An alternate approach is to combine the algorithm with the activation of a counterregulatory system, i.e., a glucose or glucagon infusion, when blood glucose concentrations fall below a given value. Both approaches were studied by the Toronto group, and the combined projected algorithms-counter infusion technique was advocated (159–161). Our experience with an artificial pancreas built at the University of Montpellier showed that activation of glucose or glucagon infusion is seldom needed to avoid hypoglycemia after meals when appropriate insulin-glucose algorithms are used (159). The Miles algorithms used in the Biostator only minimally differed from those of the Toronto algorithms but have the advantage that the new control constants could be selected in physiologically meaningful terms, e.g., the desired basal blood glucose level and desired basal insulin infusion rate (161).

Logistics. When properly programmed and used, the Biostator is able to clamp blood glucose values at any desired level for several hours. However, the technique has several drawbacks. The machine is costly and requires specialized maintenance. The blood loss, although modest (<50 ml/24 h), limits the use of the Biostator to short-term (few days) studies. The sessions may require frequent sensor recalibrations and replacements and catheter occlusion repairs. A trained person is required at the bedside always during use. In practice, full coverage also includes an experienced physician and hospital staff.

Clinical applications. Much practical and educational knowledge on individual glycemic fluctuations and insulin efficacy may be gained during Biostator sessions. However, only the specific and more widely accepted clinical and research applications of the Biostator are detailed below.

Patient health-care applications. The bedside artificial pancreas has been proposed for use in many clinical situations when acute blood glucose normalization is required and difficult to obtain (159,163,164). However, bedside intravenous insulin infusions when properly used may successfully replace the artificial pancreas machine (165). All that is needed is frequent (1–4/h) rate adjustments according to fingerstick glucose values performed by experienced nurses with a calibrated standard glucose meter. However, in some instances the artificial pancreas may be of real interest, e.g., during pancreas transplantation, insulinoma removal, or pancreatectomy, or in diabetes-related surgical and obstetrical situations or suicide attempts with the use of insulin overdose when blood glucose levels can vary rapidly and unpredictably (164–167).

Another potential application of the Biostator is when rapid and prolonged near hypoglycemia is required. The artificial pancreas has been used successfully for inducing more frequent remissions in newly diagnosed type I diabetic patients or for preserving C-peptide levels (168,169). In one study, 2-day Biostator sessions were repeated up to three times at 1- to 2-day intervals (168). Sustained insulin-free remissions with improved insulin secretion were induced in 75% of patients after these sessions (168). In another study, newly diagnosed patients were continuously maintained at strict euglycemia for 2 wk with the Biostator. When compared with a conventionally treated group, residual insulin secretion was more completely suppressed during the 2-wk Biostator intervention and significantly higher during the 1-yr follow-up, although no insulin-free remission was attempted. In another study that used ISII for inducing remissions, we confirmed that the mechanism of the remission may involve early and rigorous diabetes control (170).

Another application of the Biostator, or at least of its glucose monitoring component, is the hypoglycemia responsiveness test. Hypoglycemia is induced by a constant intravenous insulin infusion, and hypoglycemic counterregulation is evaluated. Blood glucose values are continuously monitored by the Biostator electrode. These moment-to-moment glucose readouts are especially important at the low blood glucose levels required by the test. This test has been proposed to identify patients at risk of severe hypoglycemia before intensive insulin therapy (see CSII SAFETY and CSII EFFICACY).

Clinical research applications. In reality, the major application of the bedside artificial pancreas is during

clinical investigations requiring accurate blood glucose steady-state and rapid-readout values.

The glucose clamp is a classic procedure for evaluating in vivo hepatic and peripheral insulin sensitivity. Because glucose uptake is dependent on peripheral insulin and plasma glucose levels, accurate and precise steady-state glucose levels must be obtained. Insulin is infused continuously at a single or at sequential rates to generate steady-state insulin plateau(s). Glucose is infused continuously at variable rates that have to be adjusted frequently based on blood glucose values. The amount of glucose required to maintain normoglycemia is equal to tissue glucose uptake and reflects tissue sensitivity to exogenous insulin. The amounts of glucose infused are directly related to the moment-to-moment changes in clamped blood glucose levels, thus the constant glucose readout provided by the Biostator is a major advantage for the glucose-clamp procedure. However, most experienced investigators prefer to use more precisely calibrated insulin and glucose pumps, and some also use frequent blood glucose measurements, simple algorithms, and a small computer rather than the more complex and costly artificial pancreas.

Another application of the artificial pancreas in clinical research was the discovery and understanding of the dawn phenomenon. The modest increase of early morning blood glucose values and insulin requirements was documented with overnight artificial pancreas sessions (171). The dawn phenomenon was further identified and studied with the artificial pancreas (172). However, the increase in insulin requirements (2–3 times the nightly dosages) may have have been overestimated in some patients because of the gradual insulin degradation in the Biostator (see PATIENT HEALTH-CARE APPLICATIONS).

PROGRESS TOWARD IMPLANTABLE ARTIFICIAL PANCREAS

An implantable artificial pancreas would represent a major milestone in insulin-delivery device development. Although the concept emerged >15 yr ago, the major breakthrough, i.e., a chronic implantable glucose sensor, remains to be realized.

The drug-delivery component of the future implantable artificial pancreas (i.e., pump, insulin, and catheter), although still undergoing development, can be considered as operational (see IMPLANTABLE PUMPS). The counterinsulin infusion system, i.e., glucose or glucagon infusion pump, has not been investigated in the context of implantable pumps, but it may not be necessary if proper algorithms are used. However, glucose and glucagon solutions are shown to be stable during external artificial pancreas use (157,161).

Research on glucose sensors has been hampered for many years by the problem of biocompatibility, leading to short sensor life spans (hours to 1–2 days). However, intensive research efforts are currently in progress to improve sensor longevity at several sensor implantations sites, e.g., skin and vascular.

Among the innovative techniques are polarography and infrared sensors, but electrochemical sensors (glucose electrodes) are the most advanced sensors (173–186). Catalytic electrodes carry major specificity and regeneration problems (184). Enzymatic electrodes have oxygen supply and stability problems (178,183,184). Needle-type sensors that may overcome the oxygen and stability problems have been developed (182,183,185). However, in all sensor types, tissue coating may seriously shorten in vivo sensor life.

Another significant issue is the site for sensor implantation. The subcutaneous route seems the most practical site, especially if sensors need to be changed/rejuvenated frequently (187). However, there are uncertainties regarding the true interstitial glucose concentrations and their geographical homogeneity (180,187,188). Minor variations in body temperature, via subcutaneous tissue hyperemia, and oxygen changes may also influence sensor readouts (180). The response time of subcutaneous systems, a critical factor in feedback-controlled insulin delivery, is longer when compared with intravenous systems: 15–40 vs. <10 min, respectively (182,187,188). Therefore, subcutaneous sensors may only be used intermittently as alarm sensors rather than as part of a closed-loop insulin system. Recently, however, longer-term subcutaneous sensors lasting 10 days have been reported, and glucose readout delay times of 15 and 5 min were observed (189,190). These preliminary data indicate that replaceable subcutaneous sensors could be feasible in a closed-loop setting.

The intravenous route solves some problems but creates new issues, including access difficulties, risks of long-term thrombosis, and risk of gradual device isolation by blood products deposition. However, we believe that sensor research should include high priorities for chronic intravenous sensors, because it is the only method that will easily close the loop and permit the algorithms to perform ideally.

Algorithms for intravenous insulin have been reviewed in the external artificial pancreas section. Although these algorithms have been proven effective when used in the Biostator setting, application to different pump mechanisms (e.g., pulsatile instead of roller pump), and to different glucose monitoring (e.g., subcutaneous instead of intravenous, or intermittent instead of continuous) remains to be evaluated.

Algorithms for subcutaneous insulin infusion have been proposed, but the subcutaneous route is technically unsuitable for chronic implantable insulin infusions; chronic subcutaneous catheters invariably become nonfunctional after a few days or weeks due to tissue encapsulation (74,141,191). Algorithms for intraperitoneal insulin infusion have also been described (192). Because of slower insulin absorption with the intraperitoneal route rather than intravenous route, the onset of hypoglycemic effect is delayed (15–20 min) and the action is pro-

longed (4–6 h), which makes feedback control more difficult (142). A hybrid control, including a preprogrammed early bolus infusion followed by a feedback-controlled infusion, has been proposed and shown to be more effective than a pure feedback control algorithm (192). In some ways, the preprogrammed infusion simulates the cephalic phase and the feedback-controlled infusion simulates the second phase of the biphasic response to a glucose stimulus seen with a normal pancreas. In six type I diabetic patients, the combination of an insulin dose corresponding to ~66% the total insulin requirement administered 18 min before a meal and regular Biostator intravenous algorithms was able to significantly reduce postprandial blood glucose rise from 108 to 44 mg/dl and insulin doses from 13 to 8 U (192).

In conclusion, a totally implantable artificial pancreas may be envisaged in the future but requires a major breakthrough in the field of long-term (i.e., years) in vivo glucose sensor life. An interim compromise for the near future may consist of an implantable intravenous or intraperitoneal insulin pump with rates intermittently adjusted according to subcutaneous glucose readings from a disposable needle-type subcutaneous glucose sensor.

SUMMARY AND CONCLUSIONS

In summary, this study indicates that *1*) injection devices, e.g., jet injectors, pens, and access ports, cannot be regarded as a major breakthrough in the quest for improved control, although they may improve the patient's comfort; *2*) despite the quick interest then disinterest in CSII, we believe that CSII still has benefits over ISII and conventional subcutaneous therapy in specific subgroups of patients, e.g., with recurrent severe hypoglycemia, but only when used by experienced personnel; *3*) the external artificial pancreas, e.g., the Biostator, is a useful but costly tool for limited clinical or research indications, e.g., surgery of the diabetic patient and insulin-clamp studies, and its use requires experienced personnel; *4*) the implantable artificial pancreas may represent the ultimate goal for insulin-delivery devices, with research in progress hopefully resulting in reliable long-duration glucose sensors; and *5*) implantable insulin pumps are the most promising alternative to conventional ISII and CSII therapy for the next few years, although clear evidence of improved safety and efficacy remains to be documented.

We conclude that the most important issues this article has raised are the need for the design of properly randomized controlled large-scale academic studies to assess the benefits of the above devices and evaluation of the risk-benefit ratio of improved metabolic control at various glycemic levels, including near normoglycemia and strict normoglycemia, thus permitting the ascertainment of reasonable limits in the constant search for more sophisticated and effective insulin-delivery devices.

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