Clinical evaluation and preliminary studies on the use of an artificial pancreatic beta cell in juvenile diabetes mellitus

A newly developed artificial pancreatic beta cell is described and its use in five children with diabetes mellitus is evaluated. This device can be programmed to bring the blood glucose concentration rapidly to a preselected level and normalize glucose tolerance in juvenile diabetic patients with markedly different insulin requirements. It is portable, can be operated by one person, and has been used to regulate the blood glucose concentration before, during, and after surgery requiring general anesthesia. The potential value of the device as an investigational tool is shown by demonstrating that regulation of the blood glucose concentration with insulin for seven to 24 hours does not alter circulating glucagon concentrations in the juvenile diabetic patients studied.

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Recent research efforts to achieve normoglycemia in insulin requiring diabetes mellitus include two new approaches: pancreatic tissue transplantation and an artificial endocrine pancreas. This report describes the clinical evaluation of a newly developed, artificial pancreatic beta cell as a tool to normalize blood glucose concentrations in children with insulin requiring diabetes mellitus, and preliminary studies of the short-term metabolic consequences of lowering the glucose concentrations in diabetic children.

METHODS
Description of an artificial beta cell. Life Sciences Instruments has developed the Biostator (Miles Laboratories, Elkhart, Ind.) instrument, a system that can be used either as a glucose monitor or a glucose-controlled insulin infusion system. Venous blood is withdrawn continuously through a 20-gauge Medicut cannula with a double-lumen catheter, immediately mixed with a saline EDTA-heparin solution to prevent clotting, further diluted and mixed with a buffered saline solution, and finally pumped to a glucose analyzer. Glucose is measured by an electrical signal generated by the reaction products produced from a membrane with covalently bound glucose oxidase. The signal from this membrane is related linearly to the glucose concentration in the 10 to 1,000 mg/dl range and is continuously recorded graphically while the glucose concentration is displayed visually. The computer module calculates and prints the average glucose concentration each minute. The time lag between blood withdrawal and glucose recording is 90 seconds and the rate of blood withdrawal from the patient is approximately 2 ml/hour. Insulin, glucose, saline, or a fourth solution are infused through a separate 21 gauge scalp vein needle coupled to a three-way adapter. Controlled individually by a novel...
four channel pump, these infusions are delivered independently based upon either the actual glucose concentration (static control) or its rate of change (dynamic control),\(^1\) In addition to blood glucose concentrations, glucose and insulin infusion rates and the cumulative amount of insulin delivered are printed each minute and preserved as a permanent record.

**Control algorithms.** The control algorithms used in the Biostator system were developed by Miles Laboratories\(^1\) on the basis of work performed with an earlier model in collaboration with investigators in Ulm, Germany.\(^1\) The biquadratic equation used to determine insulin infusion rate at a given glucose concentration (static control) is: \[ IR = RI \left( G - BI/QI + 1 \right) \] where \( IR \) is the insulin infusion rate, \( RI \) is the rate of insulin infusion at the predetermined glucose level \( BI \), \( BI \) is the glucose level where \( IR = RI \), \( QI \) is the reciprocal of the static gain, and \( G \) is the average glucose value during the last minute. In order to imitate the biphasic insulin response pattern of perfused rat pancreas described by Grodsky and associates\(^3\) and the similar pattern seen in man after meals,\(^4\) the static control equation is modified so that an additive factor is applied when the glucose concentration is increasing, as occurs after meals. The equation for the static plus dynamic control algorithm is: \[ IR = RI \left( G + GD - BI/QI + 1 \right) \] where \( GD \) is the glucose difference or additive factor described above. The formula for \( GD \) is \( KR \left( or \ KF \right) A_{+}^{10} + 6A \), where \( K_{R} > K_{F} \) and represents constants chosen for a rising or falling glucose concentration respectively; \( A \) is the rate of change of blood glucose concentration over the previous three minutes.

The desired glucose concentration (\( BI \)) and the constants required to shape the insulin response pattern to the absolute and relative change in glucose concentration (\( RI, QI, KR, KF \)) are selected by the operator and can be changed within two minutes. In the studies described in this report, the constants used are given in Table I. With these constants the computer program attempts to stabilize the glucose concentration at 80 mg/dl (\( BI \)) and infuse insulin at a rate of 5 mUnits/minute/25 kg body weight or 7.2 units/25 kg body weight/day. Static plus dynamic control algorithms were used with all Biostator controlled patients in this study. Glucose is infused based on a biquadratic equation similar to the static control algorithm for insulin infusion, except that its infusion rate increases as the glucose concentration falls below a preselected value.

**Procedure.** In preparation for feedback control, an insulin reservoir is created by adding 300 units of regular pork insulin to a half liter of isotonic saline in a plastic container. In order to minimize insulin adsorption to the tubing during the infusion, 100 ml of the insulin-saline mixture is allowed to wash through the administration set over 5 to 10 minutes.\(^5\) Using this procedure 4% of the theoretical insulin concentration is adsorbed to the tubing. The glucose reservoir is created with a 10% glucose in water solution. The maximum insulin and glucose infusion rates using these reservoirs are approximately 600 mU/minute and 200 mg/minute, respectively. The Biostator system is initially calibrated to a plasma glucose sample analyzed with a Beckman glucose analyzer. This

**Table I.** Constants for the control algorithms chosen to stabilize blood glucose concentrations at 80 mg/dl (\( BI \)); with a blood glucose at this level, insulin is infused at 7.2 units/25 kg body weight/day (\( RI \))

<table>
<thead>
<tr>
<th>( K_{R} )</th>
<th>( K_{F} )</th>
<th>( BI ) (mg/dl)</th>
<th>( QI ) (mg/dl)</th>
<th>( RI ) (mU/min)</th>
<th>( FI ) (mU/min)</th>
<th>BD (mg/dl)</th>
<th>QD (mg/dl)</th>
<th>RD (mg/min)</th>
<th>FD (mg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>125</td>
<td>25</td>
<td>80</td>
<td>85</td>
<td>10</td>
<td>620</td>
<td>80</td>
<td>20</td>
<td>10</td>
<td>200</td>
</tr>
</tbody>
</table>

**Table II.** Description of subjects evaluated in this study

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Duration of JDM</th>
<th>Weight</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>F</td>
<td>2</td>
<td>28.7</td>
<td>Six previous hospitalizations for ketoacidosis and/or over insulinization</td>
</tr>
<tr>
<td>2</td>
<td>14</td>
<td>M</td>
<td>5</td>
<td>33.2</td>
<td>Increasing insulin requirements with persistent glycosuria; three recent hospitalizations for ketoacidosis</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>M</td>
<td>2</td>
<td>59.7</td>
<td>Poor compliance with diabetes management; increasing insulin requirements</td>
</tr>
<tr>
<td>4</td>
<td>16</td>
<td>F</td>
<td>5</td>
<td>53.6</td>
<td>History of hypoglycemic seizures; seven hospitalizations for regulation of insulin dosage</td>
</tr>
<tr>
<td>5</td>
<td>15</td>
<td>F</td>
<td>5</td>
<td>63.2</td>
<td>Admitted for removal of impacted wisdom teeth under general anesthesia</td>
</tr>
</tbody>
</table>

JDM = Juvenile diabetes mellitus.
Subjects. The subjects studied are described in Table II. All had juvenile onset diabetes mellitus of at least two years' duration and all but one (Subject 5) were judged to be in poor control with glycosuria, ketonuria, and/or frequent insulin reactions during the month prior to the study. No patient had ketoacidosis (CO₂ less than 20 mEq/l) during the study. Informed consent was obtained in every case and all subjects were admitted to the Washington University Clinical Research Center where they were maintained on their usual diet for at least 48 hours prior to any investigation.

Subjects 1 and 2 underwent glucose monitoring for 12 hours (Day 1) while receiving the usual dose of subcutaneously administered insulin and then were monitored and controlled for 24 and 12 hours respectively, by the Biostator system (Day 3). Subjects 3 and 4 were each studied for 12 hours with Biostator control. Subject 5 was controlled with the Biostator system throughout the day of a surgical procedure. All patients were confined to bed throughout the investigation. Subcutaneous insulin was withheld on the morning of each Biostator feedback control study.

RESULTS

The continuous glucose concentrations for Subject 1 on the first day (usual subcutaneous insulin) and third day (Biostator feedback control) are shown in Fig. 1. On subcutaneous insulin the glucose concentration remained above 200 mg/dl at all times and above 300 mg/dl for most of the day. During Biostator control the blood glucose concentration declined from 500 to 150 mg/dl within three hours of initiation of feedback control and remained between 75 and 160 mg/dl during the next seven hours despite two meals. Following the evening meal, insulin infusion was stopped for 90 minutes and the glucose concentration increased rapidly from 150 to 325 mg/dl.
After resuming Biostator control the glucose concentration again declined rapidly from 325 to 150 mg/dl within 60 minutes. No glucose was needed to avert hypoglycemia following the rapid correction of hyperglycemia. Throughout the night the glucose concentration was controlled with relatively less insulin (28 mU/minute) than had been needed during the day, and the fasting glucose concentration the following morning was 75 mg/dl. Although the total insulin requirements while on Biostator control were greater than her usual total subcutaneous dosage (112 vs 62 units), the distribution of insulin administration during the day was different, and glucose concentration during Biostator control was much lower. Relatively large amounts of insulin were given during hyperglycemia and when glucose concentrations increased after meals. These results, rather than implying a need for a major increase in total insulin, indicated to us a greater need for insulin during the daytime. Rearrangement of insulin dosage from 18 Reg/28 NPH in the morning and 6 Reg/12 NPH in the evening to 20 Regular in the morning and 12 Regular in the evening has improved her diabetic control by eliminating nocturnal episodes of hypoglycemia, insulin reactions, and persistent glycosuria for the past six months. As in Subject 1, there was no significant difference in glucagon concentrations during the two studies and the glucagon concentrations were not related to the changes in blood glucose.

Subject 3 received a total of 64 units of insulin while on Biostator control and maintained his blood glucose concentration between 60 and 170 mg/dl. This subject had previously been receiving 100 units of insulin per day. Utilizing the information obtained while on Biostator control, the previous insulin given was redistributed and the total amount reduced with significant improvement in the regulation of the blood glucose concentrations.

Biostator control in Subject 4 is shown in Fig. 3. The morning glucose was 435 mg/dl and was reduced to 100 mg/dl in two hours. During the initial hour, insulin was...
infused at near maximal rates (600 mU/minute) producing a fall in the glucose concentration of 2.8 mg/dl/minute. As the glucose concentration declined to 75 mg/dl, glucose infusion was begun. This subject experienced mild hypoglycemic symptoms (dizziness, nervousness, and diaphoresis) as her glucose concentration fell to 72 mg/dl. Glucose was given at a rate of 80 mg/minute for 30 minutes and the symptoms subsided as her blood glucose concentration rose to 100 mg/dl. In this subject a sympathetic reaction was associated with a rapid fall in glucose concentration despite the absence of a glucose nadir in the "hypoglycemic range." Glucagon concentrations remained essentially unchanged throughout the study, even during the sympathetic reaction. This episode was well tolerated by the patient and appropriately handled by the Biostator with a halt in insulin infusion 10 minutes before the episode and an initiation of glucose administration as the glucose concentration fell below 75 mg/dl.

The Biostator system was used in Subject 5 during the day of an operative procedure requiring general anesthesia (extraction of teeth). The fasting glucose concentration was 380 mg/dl at 8 AM and was reduced to 120 mg/dl prior to transfer to the operating room at 10 AM. Control of the blood glucose between 155 and 165 mg/dl in the operating room and recovery room was achieved without interfering with routine anesthetic, or surgical or postsurgical care. This study demonstrates that the Biostator system can function reliably as a portable device even in the relatively confined environment of an operating theatre. As in the previous studies, glucagon concentrations did not change despite marked fluctuations in glucose concentrations.

It is possible that several of these subjects (1, 2, and 3) had extraordinary insulin resistance or were experiencing the Somogyi phenomenon and had been chronically overtreated with insulin prior to this study. However, Subjects 1 and 2 had recently been hospitalized for ketoacidosis shortly after attempts were made to reduce their insulin doses because of suspected Somogyi reactions.

In all of the subjects with a glucose concentration above 300 mg/dl insulin was given initially at the maximum possible rate (600 mU/minute) and the glucose concentration fell rapidly at a rate of approximately 3 mg/dl/minute. Despite this rapid decline in glucose concentrations, glucose infusions were needed to avert hypoglycemia in only two patients, and no subject attained a
blood glucose value below 70 mg/dl during or immediately after Biostator control. Plasma glucagon concentrations remained unchanged in all subjects despite marked fluctuations in glucose concentrations. The studies were well accepted by all of the subjects despite confinement to bed.

The glucose analyzer module functioned reliably during these studies with a coefficient of correlation of 0.989 with the Beckman analyzer for glucose concentrations between 50 and 600 mg/dl. Mean sensor drift was 2 to 5%/hour and the sensor's mean sensitivity was within 10% of the initial sensitivity after 8 to 24 hours of continuous glucose monitoring. Insulin recovery from the infusates averaged 95% of the known concentration in the insulin reservoir.

**DISCUSSION**

The development of a glucose controlled insulin infusion system or a pancreatic beta cell simulator has been brought about by the need to improve carbohydrate homeostasis in patients with juvenile diabetes mellitus. Early work in this field by Albisser and his colleagues led to the development of a system which utilizes a modified Technicon AutoAnalyzer for glucose measurement, a tabletop computer with algorithms different from those used by the Biostator, and a set of Harvard infusion pumps. Normoglycemia following intravenous glucose loading was established in pancreatectomized dogs using this system. However, an eight-minute delay between blood withdrawal and glucose measurement as well as the nature of the algorithms employed, necessitated frequent infusions of glucose to avert postprandial hypoglycemia. Three nonacidotic adult diabetic patients were shown to have substantial decreases in their hyperglycemia during feedback control, though again reactive hypoglycemia was seen.

The delay from withdrawal of blood to measurement of the glucose concentration in previous systems probably contributed to less than optimal control and necessitated significant glucose infusions. The Biostator system and its control algorithms, as used in this study, provide excellent control of hyperglycemia with no glucose concentrations falling below 70 mg/dl. This device is superior to any previously described in that it is portable, can be managed by one operator, and has a markedly reduced lag time between blood withdrawal and measurement of glucose concentration. It utilizes routine tubing such that intravenously administered fluids cannot come in contact with the roller driven infusion pump.

The insulin infusion rate used to control hyperglycemia in these studies is greater than that needed to treat diabetic ketoacidosis by constant intravenous infusion of insulin. This is a consequence of the nature of the algorithms which were designed to deliver large amounts of insulin when a normal basal glucose concentration increases rapidly after meals. Because of the highly unphysiologic nature of the hyperglycemia being monitored in our subjects, larger amounts of insulin were given than would have been necessary to correct marked hyperglycemia in patients ingesting no food. Slama and associates, using continuous insulin infusions without feedback control, found that the insulin infusion rate needed to control hyperglycemia after meals was 15 times greater than that needed during overnight fasting.

The Biostator system, though not yet small enough to be used by ambulatory adults, is easily transported to any area of the hospital. At present, constant attendance by a physician well trained in its operation and capabilities is required. The system incorporates a safety mechanism which sounds an alarm and shuts off all infusion pumps should the machine malfunction or glucose levels change rapidly.

A system that infuses insulin into the peripheral venous circulation by computer controlled pumps may have theoretical disadvantages: Insulin is not delivered directly into the portal circulation and is delivered based on glucose concentrations irrespective of physical activity. Recent studies in dogs, however, indicate that the glycemic responses, insulin infusion patterns, peripheral immunoreactive insulin levels, and total insulin requirements are similar with either portal or peripheral administration of insulin. Thus, the peripheral intravenous route of insulin infusion as used with the Biostator system may be appropriate for the evaluation of diabetic control and its metabolic consequences in diabetic patients. With a constant basal insulin infusion, blood glucose concentrations are not significantly lowered by exercise. The hypoglycemic effect of exercise in patients treated with subcutaneous insulin may be due in part to increased absorption from the injection site. Further studies will be needed to measure the quantitative effect of exercise on insulin requirements in patients with an artificial beta cell.

The studies presented in this report indicate that a glucose controlled insulin infusion system may be a useful adjunct in the management of certain patients with diabetes mellitus, either as a method of evaluating and improving hyperglycemia or of controlling blood glucose concentrations during surgical procedures. Its use in a variety of stressful situations such as surgery and pregnancy and certain medical emergencies such as diabetic ketoacidosis is currently being evaluated.

In addition to these more obvious benefits of the Biostator system, the device can be a helpful research tool.
For example, these studies demonstrate that seven to 24-hour control of blood glucose concentrations with insulin does not appreciably alter the circulating glucagon concentrations in certain nonketoadicotic, hyperglycemic patients with juvenile diabetes. These results are in contrast to previous studies which indicate that glucagon concentrations in fasting adult diabetic patients can be significantly lowered by infusion of insulin. Further studies are needed to explore the potential clinical and experimental applications of the Biostator system.

REFERENCES