Clinical Control of Diabetes by the Artificial Pancreas

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SUMMARY

An artificial pancreas capable of maintaining blood sugar homeostasis within the physiological range is described in this paper. The blood sugar is continuously monitored and then interpreted by a minicomputer which in turn controls and implements the delivery of insulin (or glucose). The entire system is automatic and by giving insulin according to a projected blood sugar level the pattern of insulin administration is similar to the biphasic response of the normal pancreas. Five parameters for control can be selected and altered at will so that any level of normoglycemia can be maintained. Hypoglycemia is not encountered, and none of the patients experienced any side effects during or after the trials. The clinical trials involved a two-day study. On the first day the blood sugar profiles were monitored throughout the day. The patients were given their usual doses of subcutaneous insulin and ate measured meals and snacks. On the second day, they received no subcutaneous insulin; insulin was administered intravenously in accordance with the moment-to-moment requirements of the patients who were given meals the same as those of the previous day. Graphs plotted on a common time scale compare the blood sugar patterns on the two successive days and show the significant improvement in blood sugar homeostasis achieved by this artificial pancreas. DIABETES *23*:397-404, May, 1974.

Although insulin was discovered more than fifty years ago, treatment of diabetes has not changed significantly in the interval. Therapy is limited to a daily prescribed dose of insulin and a more or less rigid diet. Also, attempts are made to regulate exercise and discipline the emotions. The success of the regimen is assessed by urinalysis and periodic blood sugar tests. These two methods are extremely coarse and do not provide the actual blood sugar profile that a continuous monitoring technic would record. Only by this latter technic does the daily wide range of changing blood sugars become evident. But even with this continuous information, the clinician is handicapped because at the present time there is no practical way of administering insulin according to physiological demand and thereby of accomplishing consistent normoglycemia. Even the milder diabetic cases controlled by oral hypoglycemic agents or by diet alone are included in this criticism for they too are subject to varying levels of postprandial hyperglycemia. These intervals of hyperglycemia represent intermittent insulin deficit and if the consequences of such deficits are cumulative and provide the basis for degenerative vascular disease, then the present method of clinical control of diabetes is absolutely incapable of preventing the complicating sequelae of that disease.

Also, if insulin could be administered as required, diabetics would be relieved of most of the restrictions to which they are subjected, freed from the embarrassment of insulin reactions and spared the crises brought on by associated illness.

An instrument called the artificial pancreas is described in this paper. It is capable of interpreting the continuously monitored blood sugar and of delivering insulin or dextrose to the diabetic patient as needed and in the amount appropriate to maintain normoglycemia under all conditions regardless of diet or other stress.

EXPERIMENTAL TECHNICS

The artificial pancreas is a closed loop control system configurated about three essential subsystems,

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namely, the subject, the apparatus and the computer algorithm.

A. *Subjects*

Subjects of the clinical trials of the artificial pancreas were ambulant diabetic volunteers who had been under regular medical supervision for not less than three years, who had cooperated faithfully and intelligently with their physician and who were relatively labile.*

Details of their clinical histories are given below.

Case 1. T.P., aged twenty-seven years, weight 69 kg., student, male. Diabetes three years' duration. No degenerative sequelae. Diet 3000 calories. 30 units of Lente insulin daily before breakfast. Blood sugar levels two hours after breakfast range 84 to 285 mg. per 100 ml. with corresponding glycosuria. Fasting urinalysis usually negative. Very hyperglycemic during hay-fever season.

Case 2. S.M., aged twenty, weight 69 kg., male, unemployed, diabetes eight years' duration, no degenerative sequelae. Diet 2100 calories. 55 units of Lente insulin daily before breakfast. Frequent glycosuria with no pattern. Prone to hypoglycemic reactions. Blood sugar levels vary from 70 to 350 mg. per 100 ml. one hour after lunch.

Case 3. T.B., aged forty-two, weight 81 kg., merchant, diabetes thiry-eight years' duration. Bilateral retinopathy without impairment of visual acuity, no other apparent vascular lesions. Blood sugar levels two to three hours after lunch 40 to 300 mg. per 100 ml. Hypoglycemic reactions very infrequent. No pattern of glycosuria. 2200 calorie diet. Daily insulin dosage is 16 units of Protamine Zinc and 56 units of crystalline insulin before breakfast.

The patients were admitted to a private room the evening prior to starting the trial and introduced to the various members of the team, at which time a detailed description of the bedside apparatus, its function and its modes of operation, was given and the experimental plan outlined in depth. Early the next morning while the apparatus was being calibrated the patient was catheterized at two superficial noncommunicating venous sites usually in the nondominant upper extremity. At one site a dual-lumen catheter was placed for continuous blood withdrawal for glucose analysis while at the other, a slow drip of saline was provided to maintain catheter patency during the first day and to carry insulin and dextrose infusates on the second day when blood sugar was regulated by the artificial pancreas.

On both days of the trial, the subjects were fed identical balanced and carefully measured diets. Each patient was given his usual intramuscular insulin dose on the first day; on the second day insulin was administered as needed by the artificial pancreas. During both days of the clinical trials, the patients were restricted either to a bed or to an armchair for the thirteen hour study periods usually from about 7 a.m. to 8 p.m. They were free to exercise and move about during the intervening evening periods although loosely attached to a portable micro-drip intravenous system which ensured catheter patency overnight.

B. *Apparatus*

A schematic diagram of the apparatus used to monitor and regulate blood sugar is drawn in figure 1. From the arm of the patient venous blood is drawn continuously into the inner lumen of a dual-lumen catheter and is fed to a glucose analyzer (Technicon Instrument Corp., Ardsley, New York) modified to measure glucose in samples of whole blood withdrawn at a rate of approximately 0.05 ml./min. The dual-lumen catheter consists of a small Dual-Lumen Adaptor (Facets, Toronto, Ontario) situated inside the sheath of an 18 to 20 gauge cannula (Aloe Medical, St. Louis, Mo.) and thereby forming an outer lumen and an inner lumen. The former provides a channel for the transportation of a 200 U./ml. solution of Heparin Sodium Injection (Connaught Laboratories, Toronto) in normal saline to the tip of the cannula where it mixes with the aspirated whole blood preventing coagulation in the inner lumen and tubings which conduct the blood to the glucose analyzer. In the analyzer the stream of blood is further diluted with

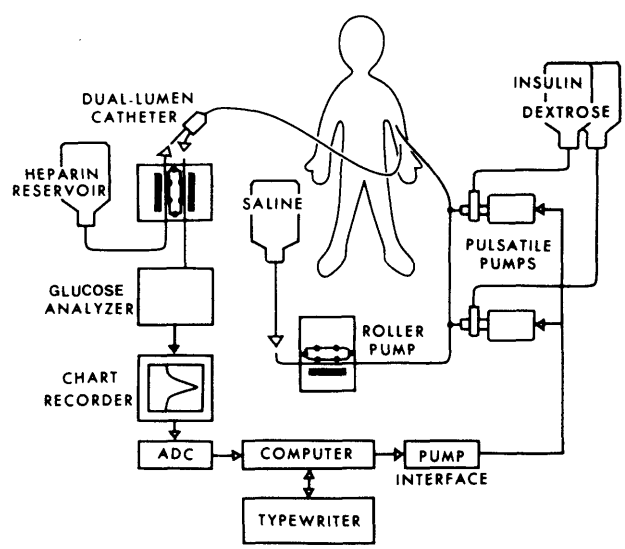

FIG. 1. Schematic diagram of apparatus used for monitoring and automatic regulation of blood sugar.

*In the context of this paper, the labile diabetic is understood to be one whose blood sugar levels vary widely, precipitously and unpredictably.

normal saline, segmented with air and dialyzed against a glucose oxidase color reagent (Boehringer-Mannheim, New York).[1] Blood glucose specifically alters the color of the reagent whose optical density is then measured at 600 nm in a colorimeter and this value is fed to the chart recorder and also by a retransmitting slidewire to the analog to digital converter of a Nova minicomputer (Data General Corporation, Southboro, Mass.). The digital number corresponding to optical density is compared against a semilogarithmic calibration curve defined by previously analyzed standard solutions. Voltage signals from the slidewire are sampled by the computer many times a second, glucose concentration computed and the values averaged for one minute. Elapsed time is printed by the typewriter once every minute along with four variables: measured blood glucose concentration in mg. per 100 ml., insulin infusion rate in mU./min., dextrose infusion rate in mg./min. and total insulin infused in mU. Two pumps controlled by the computer via the pump interface deliver appropriately metered amounts of dextrose and insulin, which are rapidly carried into the patient by a steady infusion of normal saline (0.5 ml./min.).

The apparatus has a three and one-half minute measurement delay. This means that three and one-half minutes elapse from the time a change in blood sugar enters the dual-lumen catheter to the time a change in optical density is registered on the chart recorder. The computer then reacts within one minute and alters the dextrose or insulin infusion rates.

C. *Computer Algorithms*

The automatic control of blood sugar in diabetic subjects is regulated by a computer which in addition to computing the actual blood sugar concentration from the electrical analog of optical density, also calculates the rate of change of the blood sugar concentration. The computer uses these two important variables to determine the required rates of dextrose and insulin infusion. Such functions as signal filtering, operator controls and other engineering details will not be discussed in this article.

Blood sugar is regulated by the computer in accordance with two control algorithms which relate the respective rates of dextrose infusion R_d and insulin infusion R_i to the measured blood sugar level G and to the combination of measured blood sugar level and its rate of change. The graph in figure 2 illustrates several members of a family of curves described by the following mathematical relationships where subscripts d and i represent dextrose and insulin, M, the maximum infusion rate, S, the slope, and B, the blood sugar

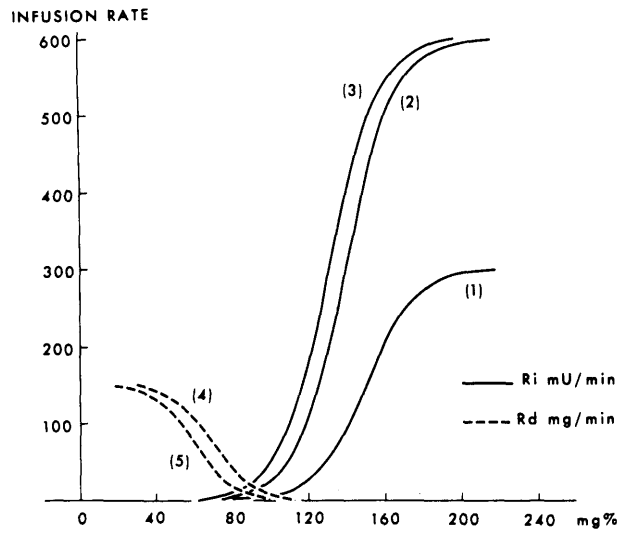

FIG. 2. Control algorithms relating insulin and dextrose infusion rates to projected blood glucose concentration. Curve parameters M, S, B are as follows: (1) 300, 0.04, 150; (2) 600, 0.04, 140; (3) 600, 0.04, 130; (4) 150, 0.05, 70; (5) 150, 0.05, 60.

$$R_d = \tfrac{1}{2}M_d\left[1 - \text{Tanh } S_d\ (G - B_d)\right] \quad (1)$$

$$R_i = \tfrac{1}{2}M_i\left[1 + \text{Tanh } S_i\ (G_p - B_i)\right] \quad (2)$$

level at which half maximum infusion rate is chosen to occur. Parameters M, S, and B are chosen by the operator.

Using the minute-to-minute changes of blood sugar level averaged over the preceding four minutes as an indication of the rate of change A of blood sugar, a projected blood sugar G_p is computed by the addition of a difference factor DF to the current blood sugar level as follows:

$$G_p = G + DF \quad (3)$$

where

$$DF = K_1\left[\text{EXP}\left(A/K_2\right) - 1\right] \quad (4)$$

with K_1 chosen to adjust the magnitude of the difference factor and K_2 selected to establish its sensitivity to changes in A. One member of the family of curves represented by equation (4) is plotted in figure 3. Use of G_p instead of G in equation (2) results in the current insulin infusion rate being set on a projected blood sugar value.

EXPERIMENTAL PLAN

The clinical trials of the artificial pancreas involved a comparative two-day study. On the first day, the

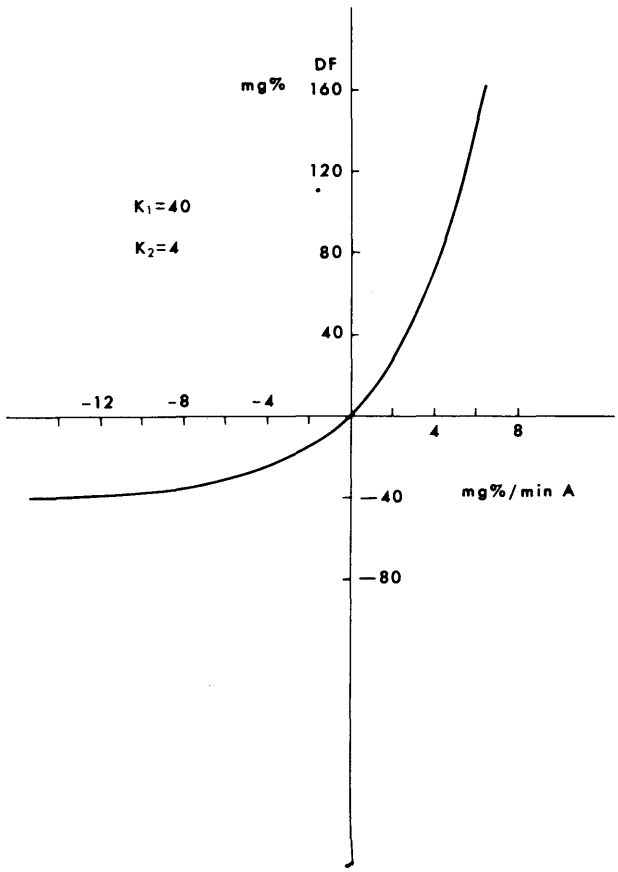

FIG. 3. Control algorithm relating the difference factor DF to the computed rate of change of blood sugar.

patient's blood sugar levels were monitored from early morning before breakfast and throughout the day until evening well after supper. On this first day the patients were given their usual doses of subcutaneous insulin and ate balanced, measured meals and snacks. On the second day, the patient's blood sugar levels were again monitored from early morning until late evening. However, they received no subcutaneous insulin; insulin was administered by the artificial pancreas in accordance with the moment-to-moment requirements of the patient who was given meals the same as those of the previous day. From the data generated during the course of monitoring alone on the first day and then of combined monitoring and controlling on the second day, graphs were plotted on a common time scale to compare the patterns of the blood sugar levels on the two successive days and to demonstrate the changing requirements for intravenous insulin and dextrose as administered by the artificial pancreas.

SELECTION OF CONTROL PARAMETERS

Using as a guide such clinical data as the patient's body weight and daily insulin requirements together with our previous experience in controlling blood sugar in pancreatectomized dogs,[2-4] we selected control parameters M, S, and B in equations (1) and (2) and constants K_1 and K_2 in equation (4). Curves (1) to (3) in figure 2 show the manner in which the infusion rates R_i of insulin vary in relation to the projected blood glucose levels; while curves (4) and (5) show the manner in which the infusion rates R_d of dextrose vary in relation to the measured blood glucose concentrations. Curves (1) and (4) were used for the first patient, curves (2) and (5) for the second and curves (3) and (5) for the third.

Projected blood sugars were calculated by the computer according to equation (4) (see figure 3) and were used either to enhance or retard the rate of insulin infusion depending on whether the recently recorded blood sugar level was rising or falling.

RESULTS

The graphs in figures 4, 5 and 6 show the time course of blood glucose and the rates of insulin and dextrose infusion in each of three patients. In each graph, the uppermost curve is a continuous record of the blood sugar profile in a diabetic patient sustained on his usual daily dose of subcutaneous insulin. The second curve is a continuous record of the blood sugar regulation in the same patient on the following day. Two bar graphs also on the same time scale record the minute-to-minute patterns of insulin and dextrose infusions used by the artificial pancreas to regulate the blood sugar levels on the second day. Increasing dextrose infusion rates are plotted in a direction opposite to that of increasing insulin infusion rates. Annotations on the graphs mark the starting times of meals and snacks.

DISCUSSION

All three subjects whose blood sugar levels were regulated by subcutaneous insulin showed both large excursions and persistently elevated levels of blood sugar during the course of the day (upper curves in figures 4, 5, 6). The blood sugar raising effects of meals and snacks are evident as is the continued blood sugar lowering action of the subcutaneous insulin depot. Other reversals in the general downward trend of blood sugar occurred from time to time. These were not related to meals but each one followed an emo-

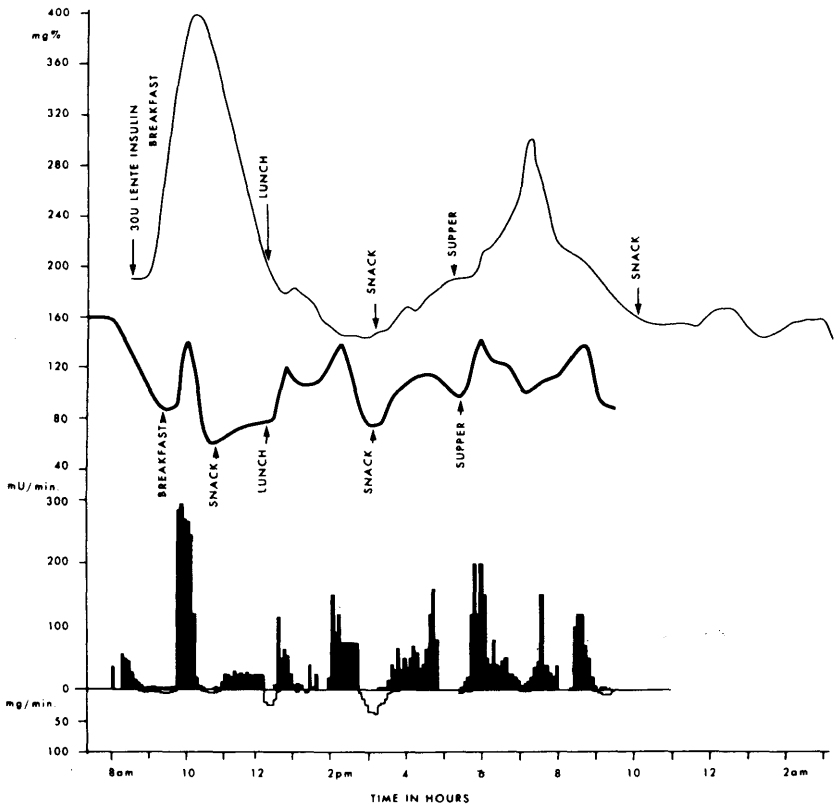

FIGURE 4

Continuous records of blood sugar profiles in subject T. P. sustained by subcutaneous insulin (top curve) and regulated by artificial pancreas (center curve). Minute-by-minute infusion patterns (lower curve) of insulin (black) and dextrose (white). Note dextrose infusion scale is inverted with respect to the insulin infusion scale. Total insulin infused is 27.3 Units.

tional event of some sort, such as, venipunctures for the collection of blood samples for routine biochemistry, the arrival of a visitor such as a relative, fiancée, or friend or the display of arousing or emotional situations on television. Peak variations in blood sugar were as high as 300 mg. per 100 ml. in figure 3. Blood sugars were above accepted normal values all the time in all patients, although this latter result may be biased by the lack of exercise that unavoidably occurred during these clinical trials. However, in this way an accurate blood sugar profile of the postprandial and postabsorptive periods was obtained. This information is the reference or control situation for each patient against which to compare the blood sugar pattern on the following day when the usual dose of insulin was omitted and instead insulin was administered exclusively by the artificial pancreas.

Referring to the second curves in figures 4, 5, 6, it may be seen that all subjects regulated by the artificial pancreas showed both smaller excursions and much lower levels of blood sugar following meals and emotional events. At the start of each graph, the transition from diabetic to nondiabetic is clearly demonstrated along with the minute-by-minute pattern of intravenous insulin that was infused by the artificial pancreas. Successively better control was achieved in succeeding patients, always without any reactive hypoglycemia. The patient in figure 4 was the first to be controlled by the artificial pancreas and the parameters used were very conservatively selected. In the following patients, tighter limits were selected, comparing in figure 3 curves (3) and (5) for the last patient with curves (1) and (4) for the first.

The last patient, who had been diabetic for thirty-eight years, demonstrated some insulin resistance and required 47 units to bring his blood sugar under control. Just after his breakfast, it was decided to alter the parameters in the computer algorithm in order to achieve a lower postabsorptive blood glucose level. This was accomplished readily by interrupting the program and simply typing in the new half-maximum infusion rate of insulin. The half-maximum infusion rate of curve 2 in figure 3 was thus moved from 140 to 130 mg. per 100 ml. Once under the control of the artificial pancreas, a marked reduction occurred in the amount of insulin required to regulate this patient's blood sugar. The reduction is clearly visible in figure 6 by the diminished areas under the insulin infusion bar graph.

The key feature to the good regulation achieved by the artificial pancreas lies in the fact that it bases its minute-by-minute insulin infusion rates on projected

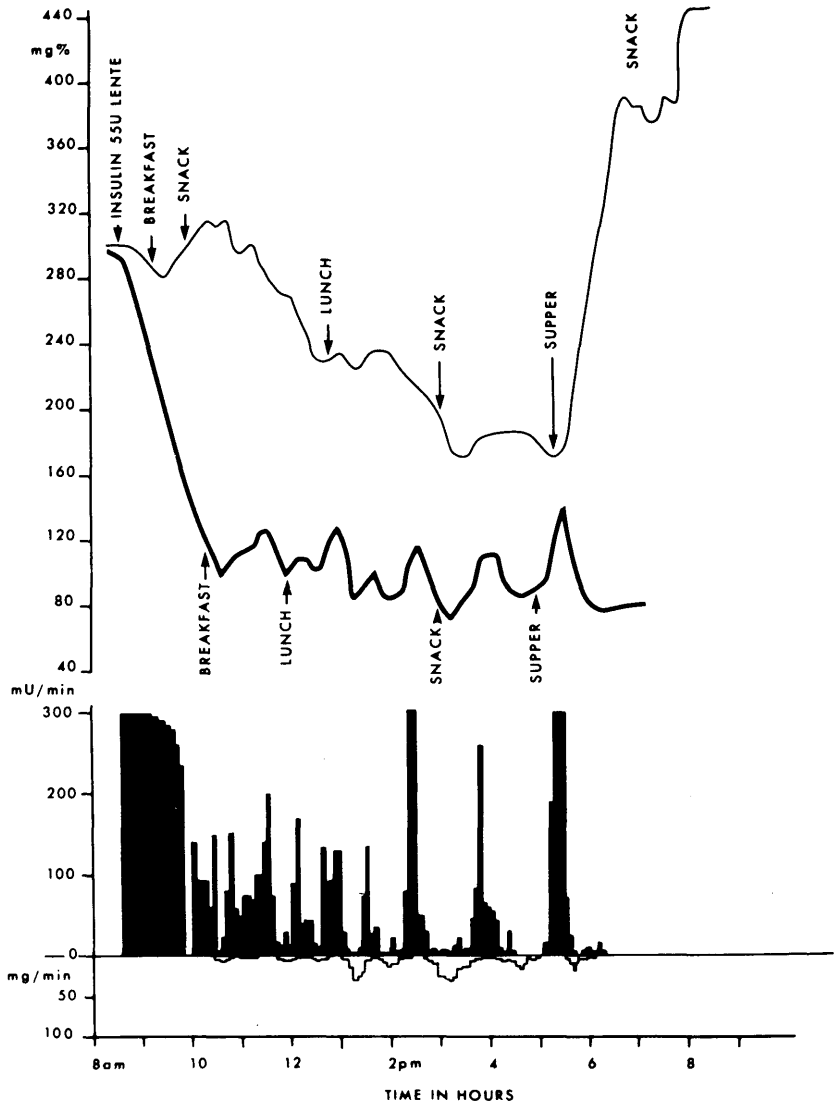

FIGURE 5

Continuous records of blood sugar profiles in subject S. M. sustained by subcutaneous insulin (top curve) and regulated by artificial pancreas (center curve). Minute-by-minute infusion patterns (lower curve) of insulin (black) and dextrose (white). Note dextrose infusion scale is inverted with respect to the insulin infusion scale. Total insulin infused is 53.1 Units.

blood glucose values.[4] This anticipatory action, or 'biphasic response' is evident in figures 4, 5, 6 from the rapid manner in which insulin is infused following slight increases in the blood glucose levels, even in the normoglycemic range. The necessity of a biphasic response by the pancreas for fine and precise blood sugar regulation has been implied[5-8] and was demonstrated[2-4] by this group in previous work done on pancreatectomized dogs.

Small dextrose infusions in each patient are recorded in figures 4, 5, 6 concurrent with the minimum excursions of blood glucose in normoglycemia. In the design of this artificial pancreas, a contingency factor was included to automatically counter any episode of reactive hypoglycemia which may occur during the course of computer controlled blood glucose regulation. It proved essential in our earlier experiments on dogs which were not only pancreatectomized, depriving them of alpha cell activity, but also anesthetized and thereby shielded from external stimuli. However, its need in the clinical trials reported here is not significant and the actual amounts of dextrose infused are negligible being governed mainly by the rather high positioning on the glucose scale of the R_d curves in figure 2. In future clinical trials this contingency factor will be moved further to the left so that the half-maximum dextrose infusion rate occurs at a lower level.

Since the patients were restricted to a bed or to an armchair during both days of the clinical trials, exer-

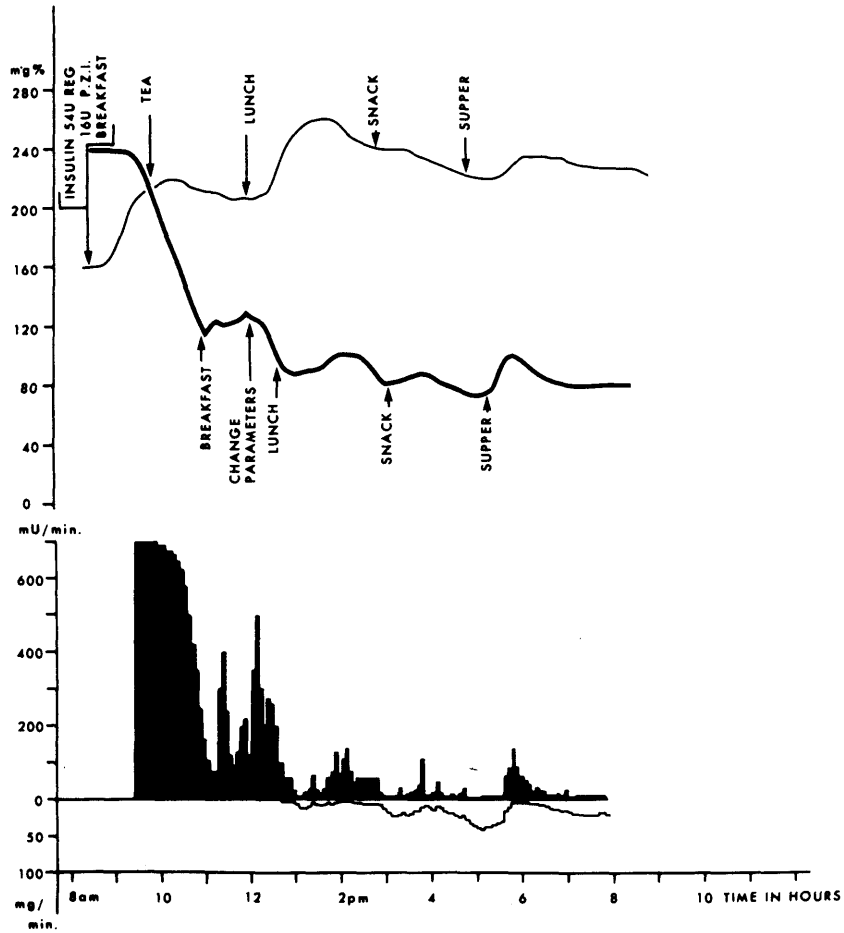

FIGURE 6

Continuous records of blood sugar profiles in subject T. B. sustained by subcutaneous insulin (top curve) and regulated by artificial pancreas (center curve). Minute-by-minute infusion patterns (lower curve) of insulin (black) and dextrose (white). Note dextrose infusion scale is inverted with respect to the insulin infusion scale. Total insulin infused is 87.4 Units.

cise is not a factor in the comparison of results. However, under the circumstances a certain amount of emotional stimulation was unavoidably experienced by the patients although there was no evidence that this was markedly different on each of the two days. None of the patients had any untoward symptoms throughout the clinical trials or thereafter. They remained in good spirits without discomfort. All blood clotting times were normal indicating that heparin did not escape into the circulation from the dual-lumen catheter.

Comparing the regulation achieved in each patient, it is apparent that the third (figure 6) was better than the others (figures 4, 5). This was due to three factors. The first two involved parameter changes in the computer algorithm to increase the rate of insulin infusion and to move the curve of R_i in figure 2 to the left. In effect, these changes increase the sensitivity of the artificial pancreas to changes in blood sugar in the normal range and also raise the level of basal insulin infusion so that the steady state or fasting blood sugar level moves to a lower value. The third factor involved a modification to the glucose analyzer which essentially eliminated a great deal of troublesome base line drift and a persistent slow loss of sensitivity which had theretofore hampered the precision and accuracy of prolonged blood sugar monitoring and control.

The amount of insulin required to sustain the diabetic individuals in normoglycemia was significantly less than that administered subcutaneously each day. Exclusive of the amounts of insulin required to initially bring the blood sugar into the normal range, the artificial pancreas administered less than half the daily subcutaneous requirements of insulin and simultaneously achieved far better regulation.

CONCLUSIONS

The clinical regulation of blood glucose levels by an artificial pancreas has been demonstrated. The results show the success of the application of an artificial pancreas in lean, excitable and kinetic young adults

whose labile diabetes had for many years defied all clinical efforts for good biochemical control. Also, the results are definitive and for purposes of this publication a larger selection of patients was deemed unnecessary.

The blood sugar profile of three patients was recorded during one day while each was sustained on the usual clinical insulin dosage and on the following day while on the artificial pancreas which administered insulin automatically and without any other supportive therapy. In less than two hours the blood sugar was uniformly returned to the normal range and maintained within physiologic limits in both the postprandial and postabsorptive periods.

Better clinical control was achieved with increasing "on-line" experience to guide in the selection of parameter values for the computer algorithms. Better control is here defined to mean smaller excursions from and more rapid recovery of the fasting blood sugar values.

The rate of insulin infusion R_i depends on five parameters, M_i, S_i, B_i, K_1 and K_2. In these trials we varied only B_i and M_i respectively, the blood glucose value at which half-maximum insulin infusion occurs and the maximum rate at which insulin may be infused. Changes in the slope S_i of the control algorithms, the exponent K_2 or the sensitivity K_1 in equation (4) were not made, although the effects of such changes can now be estimated in the light of experience gained. With this system the blood sugar can be set at any desired level in the normoglycemic range and this level can be readjusted momentarily during the experiment by merely informing the computer via the typewriter.

In its present configuration, the artificial pancreas as it relates to diabetes is appropriately termed since it is capable of both lowering and raising blood glucose, in the latter role by infusing dextrose rather than glucagon. It is speculated that the facility for raising blood glucose will not be necessary for most if not all diabetics and the deletion of this feature will thereby constrain its clinical function to that of an artificial beta cell.

As a new research tool for the study of carbohydrate metabolism, this type of system exposes many new avenues of investigation. The ability to externalize and control at will the function of the endocrine pancreas has already provided new insights into the biologic processes involved in carbohydrate homeostasis.

The miniaturization of this apparatus into a prosthesis that is implantable[9,10] into a diabetic patient is necessary before the routine clinical application of the artificial pancreas becomes possible. In the meantime, the present apparatus should prove useful for physiologic research and clinical investigation.

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