THE UNIVERSITY OF MICHIGAN

INDUSTRY PROGRAM OF THE COLLEGE OF ENGINEERING

A MATHEMATICAL MODEL DESCRIBING THE INSULIN SECRETORY RESPONSE OF THE PANCREAS IN THE DOG

John A. Campbell

A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy in the
University of Michigan
Bioengineering Program
1967

December, 1967

IP-800

engn
UMR1063

ACKNOWLEDGEMENTS

The helpful guidance and assistance of several faculty members and organizations has made this investigation possible. A sincere thank you is extended to the following:

Assistant Professor Peter H. Abbrecht, Chairman Doctoral Committee, for his helpful suggestions and stimulating discussions throughout this project.

Associate Professor John C. Floyd, Jr., and the Metabolism Research Unit of the Department of Internal Medicine for their assistance in providing equipment, insulin-I-131, and consultation on the insulin immunoassay.

The doctoral committee for their suggestions, directions, and assistance in this investigation.

The Department of Physiology for allowing this investigation to be conducted in its laboratories.

Eli Lilly and Company for a grant-in-aid providing research supplies.

National Institutes of Health for support received through the Bioengineering Training Grant and predoctoral fellowships.

The Industry Program in the College of Engineering for assistance in the preparation of this manuscript.

TABLE OF CONTENTS

TABLE OF CONTENTS (CONT'D)

LIST OF ILLUSTRATIONS

LIST OF TABLES

NOMENCLATURE

Symbol	Meaning	Units
BZERO	Quantity of Trace Insulin bound by the Antibody in the absence of unlabelled insulin	counts/min
CPM	Radioactivity, insulin assay samples	counts/min
ERROR(N)	I(N) - INS(N)	μU/ml
F	F Statistic	
FVI	Plasma Insulin Concentration, Femoral Vein	μU/ml
G	Blood Glucose Concentration, Femoral Artery	mg/100 ml
I	Calculated Insulin Concentration, Pancreatic Vein	μU/ml
INS	Measured Insulin Concentration, Pancreatic Vein	μU/ml
K_1	Coefficient, blood glucose term	$(\mu U/min)(mg/100\ ml)^{-1}$
K_2	Coefficient, derivative term	$(\mu U/min)(mg/100\ ml)^{-1}min$
K_3	Coefficient, peripheral insulin term	$(\mu U/min)(\mu U/ml)_{peripheral}$
K_4	Coefficient, constant term	μU/min
N	Time index	min
N	Number of Experiments (in equation(5.12))	
p	Number of groups into which each experiment is divided	
PBZ	Fraction of Trace Insulin bound by the Antibody in the presence of unlabelled insulin	
t	Time	min
T	Hotelling's T Statistic	
T	Integration Limit (in equation (5.9))	min

Symbol	Meaning	Units
τ	Time Lag	min
V	Pancreatic Venous Catheter Blood Flow Rate	ml/min
X1	Index, Experiment Number	
X2	Index, Model Number	
X1MAX	Total Number of Experiments	
Y	Mean Vector	μU/ml

Subscripts

Cc	Control C
x	Unknown Plasma Sample

I. INTRODUCTION

The objective of this research was to study the dynamic response of the pancreas to regulated changes in arterial blood glucose and to develop a mathematical model describing this response. Knowledge concerning the regulation of insulin secretion is of importance both in obtaining a better understanding of the physiology of the pancreas and in improving the methods used for treating diabetes.

There have been many studies of the factors which effect insulin secretion. In 1937 London and Kotschneff[36] administered glucose orally to dogs and demonstrated increased amounts of substances having a blood sugar lowering property in pancreatic venous blood. In 1947 Anderson and Long[3], using a perfused rat pancreas, demonstrated that the administration of glucose was a stimulus which evoked increased levels of insulin-like activity in blood as detected by an in vivo bioassay using adrenodemedullated, alloxan-diabetic, hypophysectomised rats. Other investigators measured insulin-like activity or immunoreactive insulin in pancreatic venous blood at several intervals following the administration of glucose, but their results were not extensive enough to describe fully the insulin secretory response of the pancreas[10, 14, 32, 39, and 56].

The formulation of a quantitative expression describing the response of the pancreas requires the precise measurement of both the stimuli to, and the response of the organ over a sufficiently long period of time. The development of immunological techniques for the measurement of insulin in small volumes of plasma and the development

of equipment for the monitoring of blood glucose has facilitated the study of the dynamics of insulin secretion.

With time histories of the glucose input and the insulin response obtained by utilizing these techniques it should be possible to apply the methods of engineering systems theory to the analysis of pancreatic endocrine function. Although the pancreas is not a precisely linear system, a linear model can be used to estimate its response over a limited range of operating conditions. In engineering systems theory systematic methods of mathematical analysis have been developed to study the response characteristics of dynamic systems. In this present work these methods have been utilized in the study of the dynamics of insulin secretion by the pancreas in response to the stimulus, glucose.

The development of mathematical models describing biological systems has enabled investigators to state more clearly the relationships between given variables in a particular system. Having postulated certain relationships between experimental variables, it is possible to design experiments which will test the proposed model. Experimenting with the model can often result in new insights into the real system. The information obtained from working with a model for several hours might take months to obtain from the real system. After having studied a mathematical model it should be possible to conduct the most critical experiments on the real system.

In this study mathematical models have been developed to describe the insulin secretory response of the pancreas to stimulation with glucose. The models predict the insulin concentration in the pancreatic vein from the time history of the arterial blood glucose

concentration and the femoral venous insulin concentration. After studying a number of models which have been used to describe similar biological and physical systems, several models have been proposed for the pancreas. Using experimental data the parameters of these models were determined by a least squares procedure. The various models were tested against the experimental data using statistical methods.

The possibility of applying power spectral analysis to obtain a transfer function for the insulin secretory response of the pancreas was also investigated.

II. LITERATURE SURVEY

Mathematical Models

Several investigators have developed mathematical models to describe different endocrine control systems. Models describing the regulation of hormone secretion from the thyroid, parathyroid, and adrenal glands will be reviewed. A more extensive discussion of models describing the relationships between blood glucose and insulin secretion will then be made. These models will be reviewed in the chronological order of their development.

Roston[53] has applied mathematical analysis to a series of endocrine systems. He described the regulation of thyroid function by two simultaneous differential equations. One equation represents the rate of change of the thyroxine concentration outside of the thyroid gland and the other, the rate of change of the thyroid stimulating hormone outside the pituitary gland. Parathyroid function was analyzed using a system of three differential equations to describe the relationships between parathyroid hormone, calcium ion, and phosphate ion concentrations in extracellular fluid. The regulation of water and electrolyte balance was also described mathematically. A system of four differential equations was written to describe the relationships existing between the extracellular fluid volume, antidiuretic hormone, sodium ion, and aldosterone concentrations.

The differential equations describing these endocrine systems were solved by using Laplace transforms. In these models only proportional relationships between the controlling and the controlled variables

were used, the effects of time lags between stimulus and response were not included, and the theoretical equations presented were not tested with experimental data.

Norwich and Reiter[45] developed a mathematical model describing the relationship between the plasma concentrations of the thyroxine and thyroid stimulating hormone, TSH. In their model they assumed that the release of thyroxine from the thyroid is proportional to the plasma TSH concentration, and that thyroxine is degraded at a rate proportional to its own concentration. Other assumptions were that TSH is released by the anterior pituitary at a constant rate, that it is destroyed at a rate proportional to its own concentration, and also the thyroxine concentration. The constants appearing in the solutions of these equations could not be determined, since the necessary data were not available.

Yates and Urquhart[64] studied the control of plasma concentrations of cortisol and corticosterone. They described the regulation of the adrenal cortical system by a closed-loop feedback control system with a variable set point. The set point and feedback effect were observed for corticoids but not for adrenocorticotropic hormone. Adrenal secretion was observed to be independent of adrenal blood flow. The rate of removal of corticoids followed a first order process and was delayed when hepatic blood flow was reduced. The total concentration of plasma corticoids showed diurnal variations within a subject. Different subjects at the same time of day exhibited different plasma corticoid concentrations and the same subject, observed at the same time of day showed day-to-day variations.

The negative feedback system controlling adrenal corticoid secretion was represented by a system equation, (2.1), giving the concentration of corticoids in the plasma, and a controller equation, (2.2), giving the secretion rate.

$$\dot{c}_i - \dot{c}_o = V \frac{dC_p}{dt} \tag{2.1}$$

$$\dot{c}_i = \dot{c}_{max} - K\, C_p \tag{2.2}$$

where: $\dot{c}_i$ = Manipulated variable-inflow rate, corticoid secretion

$\dot{c}_o$ = Load = Corticoid removal rate = $k\, C_p$

$\dot{c}_{max}$ = Maximum secretion rate

C_p = Controlled variable = Plasma corticoid concentration

K = Proportional controller gain constant

k = Rate constant

V = Volume for corticoid distribution

This model of the adrenal cortical system which incorporates the concepts of a load and a variable set point describes diurnal variations and rapid changes in plasma corticoid concentration which have been observed in healthy subjects. Previous models of this system were not adequate to describe diurnal variations and rapid changes in hormone concentration.

Models for the Regulation of Glucose Metabolism and Insulin Secretion

A mathematical model describing the time varying changes in blood insulin and glucose concentrations occurring during intravenous glucose and insulin tolerance tests was presented by Bolie[7] in 1960. The model consisted of four ordinary differential equations representing

changes in the quantities of insulin and glucose in the extracellular and the intracellular spaces. Seventeen independent parameters were required to describe the regulation of blood glucose and insulin. The rate of pancreatic insulin production was described by equation (2.3).

$$\dot{I}_1(G) = \dot{I}_1(G_o) + (G - G_o)\, K_1 \qquad (2.3)$$

where: $\dot{I}_1$ = Rate of pancreatic insulin production

G = Intravascular glucose concentration

G_o = Mean physiological value of G

$$K_1 = \frac{\partial \dot{I}_1(G)}{\partial G} \Big| \; G = G_o$$

An analog computer was used to simulate the results of glucose and insulin tolerance tests on subjects. Numerical values of physiological parameters were determined from the computer potentiometer settings that most closely reproduced the normal response curves.

Seed and co-workers[55] have presented a model describing the changes in glucose concentration occurring during glucose metabolism. Their model consisted of a four compartment system described by four differential equations. The four compartments used in their analysis were: 1) the plasma volume, 2) a "fast" compartment, in which the glucose concentration may change rapidly, 3) a "slow" compartment in which only gradual changes in glucose concentration can occur, and 4) the red blood cells. The model fitted data obtained from the first 65 minutes of a glucose tolerance test. The model has not included the effect of insulin on the transport of glucose, however the model includes an arbitrary substance, Z, which increases and decreases in the "fast" compartment with corresponding changes in glucose concentration.

When the concentration of Z falls below a critical value, Z is defined as having the function of stimulating hepatic glucose release. The authors believed that Z is not the same as insulin, since insulin is released too slowly and has too long a half-life to account for rapid oscillations in the blood glucose concentration. On analyzing several sets of experimental data, the authors found the set of parameters giving the best fit for one experiment did not describe the other experiments adequately and the set of parameters best describing one experiment did not correspond to the physiologically most probable values.

Ackerman and co-workers[1] developed a mathematical model describing the oral glucose tolerance test. The model considers the various sources and fates of glucose and insulin in the subject. The rates of change of the blood insulin and the blood glucose concentrations are given by equations (2.4 and 2.5), respectively.

$$\frac{dI}{dt} = - k_1 I + k_2 + k_3 G \qquad (2.4)$$

$$\frac{dG}{dt} = - k_4 G + k_5 - k_6 I + A \qquad (2.5)$$

where: G = Blood glucose concentration

I = Blood insulin concentration

$A(t)$ = Rate of increase of blood glucose due to absorption from intestines.

k_1 = Rate constant for the degradation of insulin.

k_2 = Rate of secretion of insulin, independent of glucose

k_3 = Rate constant for the secretion of insulin due to glucose

k_4 = Rate constant for the removal of glucose independent of insulin.

k_5 = Average rate of release of glucose into blood.

k_6 = Rate constant for the removal of glucose dependent upon insulin.

In Equation (2.4) the rate of degradation of insulin is proportional to the plasma insulin concentration and the rate of secretion of insulin is controlled by a glucose independent term, k_2, and by a term which is proportional to the blood glucose concentration, k_3G. A similar equation, (2.5), was written to describe the time varying plasma glucose concentration. These two first order differential equations were combined to form one second order equation which was integrated to give equation (2.6).

$$G = G_F + A\, e^{-at} \sin \omega t \qquad (2.6)$$

where: G = Blood glucose concentration

G_F = Fasting blood glucose concentration

A = Undamped amplitude of the glucose curve

a = Damping coefficient = $\frac{1}{2}(k_1 + k_4)$

ω = $(\omega_o^2 - a^2)^{\frac{1}{2}}$ = frequency

ω_o = $(k_1k_4 + k_3k_6)^{\frac{1}{2}}$ = resonant or natural frequency, k's have been defined with equations (2.4) and (2.5)

The natural frequency of this system is related to the rates of glucose removal and insulin release and removal. The damping coefficient is related only to the rates of removal of insulin and glucose. Data from normal and diabetic glucose tolerance curves were fitted with this equation. The following parameters characterize the glucose tolerance test: fasting blood sugar, undamped amplitude of blood

glucose curve, damping factor, damped frequency, and resonant or natural frequency. Of these only the resonant frequency appears to be an adequate criterion for distinguishing diabetic from non-diabetic subjects.

In a later paper Ackerman[2] reported studies on the effects of various oral glucose loads and intestinal absorption rate on simulated glucose tolerance tests. The model could be fitted using five or six points on the glucose and immunoreactive insulin response curves in most cases, but in certain cases many more points on the curves would be needed to fit the models and make satisfactory interpretations.

Janes and Osburn[31] used analog computer techniques to simulate glucose absorption and the blood glucose concentration in the rat and rabbit following oral glucose administration. Their model consisted of two differential equations expressing the time varying glucose and insulin concentrations. The insulin equation stated that the rate of change of the plasma insulin concentration was directly proportional to the blood glucose concentration and that insulin was destroyed at a rate proportional to its concentration. The parameters in the model were adjusted to fit experimental blood glucose data. No insulin measurements were made. The model predicted the maximum glucose concentration in the peripheral blood following the administration of glucose orally. It should be noted that this report assumed values for glucose released by the liver and did not consider glucose uptake by the liver which may occur following a glucose feeding in a fasted animal.

A mathematical description of the peripheral venous blood

glucose concentration during an intravenous infusion of a hypertonic glucose solution was developed by Brodan[9]. Differential equations were written to relate the infusion rate to the plasma glucose concentration, the renal excretion rate and the metabolic rate. The effect of the blood glucose concentration on the pancreas and the subsequent effect of insulin on glucose transport were not included in this model. Methods for obtaining the parameters of the equations were outlined, but values were not given nor was the model tested with experimental data.

Cerasi[13] recently described a mathematical model of the blood glucose and plasma insulin system. He represented the increase in the plasma insulin concentration following an intravenous glucose load as the sum of two terms, one representing preformed insulin that was released immediately upon the intravenous administration of glucose as a function of the blood glucose concentration and another representing insulin that was synthesized and released after a glucose load was given. Using this model it was possible to simulate the peripheral venous blood glucose and plasma immunoreactive insulin responses during intravenous glucose tolerance tests in many subjects.

Insulin Secretion

Recently several investigators have studied the effects of various stimuli on the rate of insulin secretion. The stimuli include glucose, other sugars, metallic ions, sulfonylureas, and hormones. The insulin secretory response of the pancreas has been studied using pancreatic tissue, perfused organs, and intact animals. In most of

the experiments the number of samples of plasma analyzed for insulin was not sufficient to establish a quantitative relationship between the stimulus and the response.

Pancreatic Tissue Experiments

Creutzfeldt and co-workers[18] studied the effect of varying the concentrations of glucose and other monosaccharides in the incubation medium on the release of insulin-like activity (ILA) from rat pancreatic islets incubated in vitro. The ILA of the incubation media was measured by the rat fat pad method[52] after 30 minutes of incubation and then at intervals of one hour for five hours of incubation of the pancreatic tissue. The ILA in the medium increased when the incubation time or the glucose concentration or both were increased. After three hours a maximal level of ILA was attained. Pancreatic tissue was transferred successively between incubation media containing alternately high and low glucose concentrations. The observed secretion rate of insulin was higher when the glucose concentration was higher, and lower when the glucose concentration was lower. Other monosaccharides tested failed to produce an increase in ILA. Since incubation for 120 minutes in 20 mM glucose resulted in the secretion of only five to ten percent of the extractable insulin, the authors felt that only dissolved insulin was released and no true secretion occurred under these conditions.

Coore and Randle[16,17] have studied the regulation of insulin secretion using in vitro preparations of pieces of rabbit pancreas. An immunoassay was used to measure the insulin concentration in the incubation media. The rate of pancreatic insulin output was measured

in the absence of glucose and at glucose concentrations ranging from 0.35 mg/ml to 20.0 mg/ml. There was some insulin output even in the absence of glucose. The rate of insulin release observed at a glucose concentration of 0.70 mg/ml was double that observed in the absence of glucose. The rate of insulin release was observed to increase with increasing glucose concentrations in the media, however the response tended to plateau at the high glucose concentration. The effect of various monosaccharides on the rate of insulin secretion was investigated. Of the sugars tested d-glucose and d-mannose produced the greatest responses. The effects of growth hormone, epinephrine, adrenal cortical trophic hormone, glucagon, and thyroxine were also studied. The only hormones which distinctly affected insulin secretion were glucagon, growth hormone and epinephrine. Addition of glucagon to media containing glucose and pancreatic tissue resulted in augmented insulin secretion. Addition of growth hormone or epinephrine to media containing glucose and pancreatic tissue inhibited insulin secretion. It should be noted that this in vitro effect of growth hormone on pancreatic tissue is different from its systemic effect.

Parry and Taylor[47] have shown that glucose increases the rate of incorporation of leucine into the insulin molecule in slices of ox pancreas. The rate of incorporation of tritiated leucine was considered to be a measure of the rate of insulin synthesis. Increasing the concentration of either glucose or mannose in the media augmented insulin synthesis while galactose had no effect.

Malaisse and co-workers[37] studied the effects of glucose, insulin and anti-insulin serum on insulin secretion using isolated

islets of rat pancreas. An immunological method was used to measure insulin concentrations in the media. Insulin secretion increased with increasing concentrations of glucose in the media. Secretion was not affected by the presence of anti-insulin serum or rat insulin.

Perfused Organ Experiments

Using an isolated perfused rat pancreas Anderson and Long[3] studied the relationship between the glucose concentration in the perfusing solution and the amount of insulin secreted. They measured the insulin concentration in the perfusate by observing the blood sugar lowering effect of the perfusate when it was injected into adrenaldemedulated diabetic hypophysectomized rats. An observation of blood sugar lowering was interpreted as evidence of the presence of insulin in the perfusate. Their results showed that a high glucose concentration (141-569 mg/100 ml) stimulated the secretion of insulin, and that a low glucose concentration (35-84 mg/100 ml) did not result in the secretion of a detectable amount of insulin.

Grodsky and associates[26] studied the insulin secretory response of the isolated perfused rat pancreas to the pulse administration of glucose and glucagon. The stimulating substance was rapidly injected into the arterial cannula and the total effluent from the pancreas was collected at 30 second intervals for the subsequent 4-5 minutes. Immunoassay of the effluent showed that the insulin concentration in the perfusate increased within 30 seconds indicating a prompt response. The insulin levels followed the rise and fall of the glucose concentration in the arterial cannula. Insulin secretion was significantly reduced

30 seconds after terminating the stimulus showing there was no pancreatic memory.

In Vivo Experiments, Intravenous Glucose Administration

Brown and co-workers[10] showed that infusion of glucose into a portion of the pancreas resulted in systemic hypoglycemia and in histologic changes in the islands of Langerhans, including hyperplasia and hydropic degeneration in that portion of the pancreas. In these dogs a 5-17% glucose solution was infused into a pancreatic artery via a hepatic artery at a rate of 4.5 mg/kg/min for up to 18 days. Increased insulin release was infered from the peripheral hypoglycemia that occurred during the glucose infusions. If the same glucose infusion was given through the portal vein, no change in peripheral blood glucose was detected.

One of the first reports of pancreatic insulin secretion estimated from the quantity of insulin present in pancreatic venous blood was presented by Metz[39] in 1960. Pancreatic venous blood was collected from seven dogs during controlled infusions of glucose into a femoral vein. The insulin concentration in the plasma was determined using the rat diaphragm method[50]. The plasma insulin concentration in pancreatic venous blood varied from 100 - 9700 μU/ml with peripheral blood glucose concentrations from 37 - 655 mg/100 ml. Since only one to five insulin measurements were made on each dog, it was not possible to establish whether there was a quantitative relationship between blood glucose concentration and insulin output for a given experiment. When the data from all seven dogs were analyzed together, insulin

output could be related to blood glucose concentration by the following equation (2.8).

$$\log I = -3.14 + 1.64 \log G \qquad (2.8)$$

where: I = Insulin output (mU/min)

G = Blood glucose concentration (mg/100 ml)

These data were not adequate to determine whether there were any time lags in the response of the pancreas to changes in blood glucose or to determine any dependence upon the rate of change of blood glucose. The author believed that this may have accounted for the departure of some of the data points from the curves describing the response. The possibility that the pancreas functioned in a negative feedback loop controlling blood sugar was suggested.

Seltzer[56] investigated the "insulinogenic" effects of glucose and those of several hypoglycemia-inducing substances. The test substance was injected into a femoral vein during a two to five minute period and the entire effluent from the pancreatic vein was collected during three successive ten minute periods beginning at the start of the infusion. A pancreatic sample was collected before starting the infusion to establish a base line. The insulin content of the plasma was measured by determining the glucose uptake of a piece of rat diaphragm incubated with the unknown plasma. Glucose stimulation induced elevations in the plasma insulin level which were greater and more sustained than those induced by sulfonylureas suggesting that glucose is a more potent stimulus for insulin secretion. Salicylate and indole-3-acetic acid did not produce an insulin secretory response. This was one of the first

studies of the comparative insulin secretory effects of various hypoglycemia-inducing substances.

Kanazawa and colleagues[32] used a radio-immunological assay to measure the insulin concentration in femoral, hepatic, and pancreatic venous blood during and after glucose infusions into a femoral vein. Glucose administration produced increased insulin concentrations in femoral, hepatic, and pancreatic venous blood. This implied that the increased peripheral insulin concentrations resulted from pancreatic insulin secretion. Comparison of the peripheral and pancreatic insulin response curves showed a small secondary peak in the insulin concentration in the pancreatic vein only. The authors suggested that the secondary peak may have been caused by surgical stress or changes in the concentrations of epinephrine and growth hormone resulting from stress. The absence of a secondary peak in the peripheral curves may have been due to changes in pancreatic venous blood flow, changes in hepatic insulin clearance, dilution of secreted insulin in the blood volume of the dog, or absorption or release of insulin by some peripheral tissue.

Gjedde[23] studied the effect of glucose on the ILA in the pancreaticoduodenal vein and in the femoral artery of dogs. He found that the ILA measured by the rat fat pad method was significantly greater in the pancreaticoduodenal vein compared to the femoral artery and that the pancreatic vein ILA rose immediately following intravenous glucose administration whereas the femoral arterial ILA required ten to 15 minutes to rise. The fasting insulin output of the dog pancreas was estimated to be 300 μU/kg/min. Insulin was shown to be distributed in 18 $\pm$ 4% of the body weight (mean $\pm$ SEM). The half-life of insulin

was estimated to be 23 ± 5 minutes (mean ± SEM) from femoral arterial blood samples collected immediately following a pancreatectomy. The blood flow rate in the pancreaticoduocenal vein was 1.95 ± 0.068 ml/kg/min (mean ± SD). This flow rate was over five times greater than those reported by Metz[39] and Seltzer[56] and was probably due in part to the method used to catheterize the vessels.

Hausberger and Ramsay[27] studied the effects of glucose alone, and of glucose together with insulin on the degranulation of beta cells in the guinea pig. They found that glucose alone produced considerable or complete degranulation of the beta cells and that glucose with insulin produced no degranulation or at most very little degranulation. Since degranulation of the beta cells usually represents insulin secretion, they concluded that insulin as well as glucose affected the insulin secretory response of the beta cells.

In Vivo Experiments, Oral Glucose Administration

Oral and intravenous routes of glucose administration to humans were studied by Elrick and co-workers[20]. Rate constants for the disappearance of glucose administered by both routes were determined. Peripheral plasma insulin levels were measured using an immunoassay. Oral glucose resulted in greater and more sustained increases in plasma insulin concentration than did the same amount of glucose administered intravenously. The maximum blood glucose concentration in a typical subject in this study was 135 mg/100 ml and the mean blood glucose difference between the two routes of glucose administration was 4.1 mg/100 ml. Glucose administered intravenously resulted in the higher concentration. The rate constant for the disappearance of glucose was

independent of the route of administration. The greater increase in insulin concentration associated with the oral administration of glucose suggested to the authors that ingested glucose stimulated the release of a humoral gastrointestinal factor from the stomach or the upper small intestine or stimulated the release of a factor from the liver, which in some way facilitated insulin secretion.

Effects of Other Stimuli

Factors effecting the synthesis, storage release, transport, and antagonism of insulin were reviewed by Lazarow[34] and by Grodsky and Frosham[25]. In a study of the dynamics of insulin secretion, the effects of hormonal and non-hormonal factors on insulin secretion should be considered. Growth hormone, cortisone, adrenocorticotropic hormone, glucagon, epinephrine, and insulin itself affect insulin secretion. Growth hormone acts as an insulin antagonist. Excessive levels of growth hormone can cause diabetes and in some cases a diabetic can be improved by hypophysectomy. Growth hormone has been shown to increase plasma insulin-like activity by both a direct effect on the pancreas and indirectly by increasing the blood glucose concentration[8]. Cortisone administration produces hyperglycemia and thus results in increased insulin secretion, and beta cell overactivity and proliferation. Adrenocorticotropic hormone can stimulate the secretion of insulin in adrenalectomized animals. Glucagon administration results in increased insulin secretion when it is injected into animals in which the glucose concentration is maintained constant. In vitro studies have shown that glucagon stimulates insulin secretion directly[51]. Unger[61] found

that insulin induced hypoglycemia in dogs resulted in elevated plasma glucagon levels. Campbell and Rastogi[11] studied the effects of glucagon and epinephrine on insulin secretion in dogs. They found that glucagon given intravenously resulted in a three-to-four fold increase in immunoreactive insulin in the pancreatic vein 15-30 minutes following injection. Epinephrine injections resulted in hyperglycemia without any increase in insulin secretion. They believe glucagon caused a transient increase in the rate of insulin secretion. Kris and co-workers [33] studied the effects of epinephrine on insulin secretion in rhesus monkeys. Portal vein insulin levels measured during epinephrine induced hyperglycemia showed no increased insulin secretion. When the epinephrine infusion was accompanied with a glucose infusion, the resulting hyperglycemia did not produce increased insulin secretion either. Epinephrine did not cause any changes in the insulin levels resulting from controlled injections in in vivo or in vitro experiments. Infusion of epinephrine into a carotid artery has shown that its site of action on insulin secretion is not in the brain.

Porte and co-workers[49] studied the effect of epinephrine and glucagon on immunoreactive insulin levels in humans. Intravenous administration of epinephrine resulted in hyperglycemia without any increase in immunoreactive insulin levels during the infusion. Within 15 minutes after the end of an epinephrine infusion the peripheral immunoreactive insulin level increased from 12 μU/ml to 41 μU/ml in a typical subject. Intravenous administration of glucagon resulted in hyperglycemia and increased insulin secretion. The insulin levels attained during glucagon induced hyperglycemia were higher than those

produced during glucose infusions resulting in the same blood glucose level. When glucagon and epinephrine were administered together the insulin secretory response was less than that produced by glucagon alone. One hour after the combined infusion was stopped the insulin level was higher than the level observed one hour after the end of an infusion containing only glucagon. These experiments have shown that epinephrine inhibits insulin secretion and that glucagon administration produces a greater response than would result from hyperglycemia alone. The authors suggested that the mechanism of action of epinephrine on insulin secretion may be due to an effect of epinephrine on the microcirculation of the pancreas, the production of a substance by epinephrine which in turn inhibits insulin secretion, or the accelerated degradation of insulin.

Logothetopoulos and co-workers[35] investigated the effects of hyperglycemia and prolonged treatment with insulin on the pancreatic insulin content in rats. Hyperglycemia was produced in the rats by the infusion of a 20 percent glucose solution into a jugular vein. Three different infusion schedules were followed. The pancreatic insulin content was measured in terms of beta cell granulation, zinc content, and extractable insulin. All three quantities decreased progressively and simultaneously with increasing blood glucose concentrations and increasing periods of hyperglycemia. The effect of prolonged insulin treatment on insulin content of the pancreas was studied by administering increasing doses of insulin to rats until a dose of 7-9 U/day was reached. This dose was then given for 4 - 6 weeks. The amount of extractable insulin measured in two groups of treated rats was 4 percent of that measured in control rats demonstrating that high peripheral

insulin concentrations tend to inhibit insulin production.

Floyd and associates[65] showed that some essential amino acids are stimuli for insulin release. They measured the levels of immunoreactive insulin in peripheral plasma in humans following protein meals, and after oral administration of leucine and intravenous doses of some individual essential amino acids and mixtures of essential amino acids. Of the ten individual amino acids tested L-arginine produced the strongest insulin secretory response and this response was equalled by that of the mixture of the ten essential amino acids. Leucine was intermediate in potency and valine was least potent. Histidine was unique in that it caused modest decreases in the levels of plasma insulin.[48] This effect was accentuated when dexamethasone was administered for three days prior to histidine infusions.

Metallic ions have a significant effect on insulin secretion. Zinc complexes readily with insulin but is not required for insulin to be biologically active. Some workers have suggested that zinc is required for the release of stored insulin. Cobalt also combines with insulin readily, but there is little evidence that it is necessary for insulin synthesis or release. Calcium has been shown to be absolutely necessary for insulin release. Grodsky[24] studied the perfused rat pancreas in a medium free of both calcium and magnesium and found that no insulin was secreted. Addition of 0.2 mM calcium ion restored insulin secretion.

Seltzer and co-workers[57] studied the effects of prolonged sulfonylurea administration on the insulinogenic response of the dog pancreas to intravenous glucose. Pancreaticoduodenal venous blood was

collected during controlled glucose infusions and its insulin concentration was measured using an immunological method. Prolonged sulfonylurea administration did not alter the insulin secretory response of the pancreatic beta cells to infused glucose.

The action of tolbutamide on the pancreas was studied by Colwell and Metz[14]. One gram of tolbutamide was administered to dogs over a period of five minutes. Pancreatic venous blood was collected prior to the start of the infusion and for four ten minute periods following the infusion. The plasma insulin activity was measured by the rat diaphragm method. The results showed the maximum insulin activity to occur during the first ten minutes after the beginning of the tolbutamide infusion. The range of the maximum insulin concentration following the administration of tolbutamide to the test dogs was from 70 to 175% of the base line insulin concentration. Saline infusions given to control dogs elicited no responses. This study showed that tolbutamide stimulates the release of insulin from the pancreas.

Hormones, essential amino acids, sulfonylureas, and metallic ions have been shown to effect insulin secretion. In the work to be described it will not be possible to measure all of these factors. None of the dogs used had been treated with drugs prior to the experiment. Since all dogs were fed the same diet, no significant differences should exist which could be attributed to differences in plasma essential amino acid or metallic ion concentration. Variations in glucagon, growth hormone, and epinephrine levels may vary from dog to dog due in part to stress and individual differences. These variations are not easily measured and may be the cause of some otherwise unexplained

variations in the insulin secretory response of the pancreas.

After studying both the mathematical models and experimental data describing the dynamics of insulin secretion in response to glucose administration, it was apparent that none of the mathematical models gave an adequate description of the response of the pancreas to changes in blood glucose concentration and none of the data published is sufficient to derive a model which would describe this response fully. The model developed by Ackerman[2] provides a good description of the response of the subject to a glucose load but does not describe the action of the pancreas in detail. The model Bolie[7] postulated describes the glucose tolerance test response. Neither of these models includes a term relating the time derivative of the blood glucose concentration to the insulin secretory response of the pancreas. Tepperman[59] suggested that the system may contain such a derivative term and cited experiments by Anderson and Long[3] as support for this suggestion. None of these models considers the existence of lags between glucose stimulation and insulin secretion. Metz[39] in 1960 showed that pancreatic insulin secretion was a function of the arterial blood glucose concentration. His measurements were not made at time intervals short enough to determine the presence of derivative terms or time lags in the system. More recently Seltzer[56], Kanazawa[32], and Colwell and Metz[14] have conducted a variety of experiments, previously discussed, in which pancreatic venous insulin concentrations were measured; but none of these reports contained data adequate to answer questions concerning the existence of derivative terms and time lags in the system. The experimental procedure to be discussed in Chapter III is designed to provide data which should enable these questions to be answered.

III. PHYSIOLOGICAL EXPERIMENTAL PROCEDURES

To verify the proposed mathematical model describing the insulin secretory response of the pancreas a series of acute experiments was conducted in dogs. In this section the experimental procedure will be described. Description of the analytical methods for the determination of blood glucose and plasma insulin concentrations will be given in Chapter IV.

Experiments were designed to measure pancreatic insulin secretion during controlled glucose infusions. Glucose was infused into a jugular vein while blood samples were collected from the pancreaticoduodenal and femoral veins for insulin analysis. Arterial blood glucose was continuously monitored using an on-line analysis system connected to a femoral artery.

Surgical Preparation

Female mongrel dogs, weighing 20 to 30 kilograms were fasted for at least 16 hours prior to the beginning of the experiment. The dogs were anesthetized with nembutal solution containing 60 mg/ml sodium pentobarbital, administered intravenously. The initial dose was 30 mg/kg and additional doses of 60 mg were given as required by observation of the pupillary reflexes. Immediately following the administration of the anesthesia a tracheostomy was performed to facilitate the animal's ventilation during the remainder of the experiment.

The jugular and femoral veins were cannulated using No. 200 polyethylene tubing (ID 1.40 mm, OD 1.90 mm). A midline abdominal incision was made and the pancreas was exposed. A cautery was used in

the surgical procedures to minimize bleeding. The duodenum and the right lobe of the pancreas were brought to the incision. Blunt dissection was used to free a section of the pancreaticoduodenal vein from the pancreas. A silicone rubber catheter, ID 0.75 mm, OD 1.50 mm, was inserted into the vein retrograde to the direction of blood flow. The proximal end of the vein was tied off. Next, the femoral artery was cannulated with a No. 50 polyethylene tube, ID 0.580 mm, OD 0.965 mm, and this was connected to the blood sampling tube of the glucose analysis apparatus.

Collection of Blood Samples

Immediately before cannulation of the pancreaticoduodenal vein the dog was given 750 units of heparin per kilogram intravenously. Pancreatic venous blood was collected by allowing the blood to flow freely from the catheter into heparinized 10 x 75 mm soft glass test tubes held in a beaker of ice water. The pancreatic blood flow varied from 0.15 to 0.50 ml/min.

Femoral venous samples were collected at intervals varying from ten to 15 minutes. Two ml samples were drawn from the femoral venous catheter using a syringe and were transferred to 10 x 75 mm test tubes which were stored in an ice water bath until the end of the experiment. Immediately following the experiment all the blood samples were centrifuged at 1100 g. for 20 minutes in a refrigerated centrifuge at 2° C. Plasma was separated and stored in corked glass test tubes at -20° C.

Glucose Infusion

The glucose infusion contained 100 grams glucose and 4.5 grams

sodium chloride per liter. The infusion was given through a jugular vein using a Sigma Motor kinetic clamp infusion pump. Infusion speeds from 1.0 to 6.0 ml/min were used; this is equivalent to 100-600 mg glucose/minute. For a 20 kg dog this is equivalent to 5-30 mg/kg min or 300-1800 mg/kg hr. An infusion speed of 4 ml/min for one hour introduces 24.0 gm of glucose. If this amount of glucose remained in the blood volume (1.5 liters) a rise of 1600 mg% glucose would occur. If this glucose were distributed in the extracellular space (4 liters) also the rise would be 600 mg%.

Experimental Protocol

Following the surgical preparation of the dog, a ninety minute control period preceded the glucose infusions. During this control period pancreatic venous blood samples were collected for periods of from five to ten minutes depending on the blood flow rate. Femoral venous samples were collected at 15 minute intervals. During this period isotonic saline was infused into a jugular vein at 1-2 ml/min.

A series of ramp changes in the dog's blood glucose concentration, i.e., blood glucose increasing or decreasing linearly with respect to time, was produced by varying the speed of the infusion pump in a step wise fashion. When the maximum desired glucose concentration was attained, as observed on the blood glucose concentration recorder, the infusion was changed from a glucose solution to isotonic saline. The saline infusion was continued until the blood glucose concentration had decreased to a constant level, usually about 100 mg percent. Two or three ramp changes in blood glucose concentration were made during an experiment depending on the condition of the

dog and the time required for each ramp. The rate of increase of blood glucose concentration was varied in order to study the effect of the rate of change of blood glucose concentration on insulin secretion.

During these infusions pancreatic venous blood was collected continuously in 1 - 3 ml samples. The time required to collect each sample varied from two to ten minutes. Shorter collection periods were used when the blood glucose concentration was changing most rapidly. Femoral venous blood samples were obtained at approximately fifteen minute intervals.

A typical experiment is shown in Fig. 1.

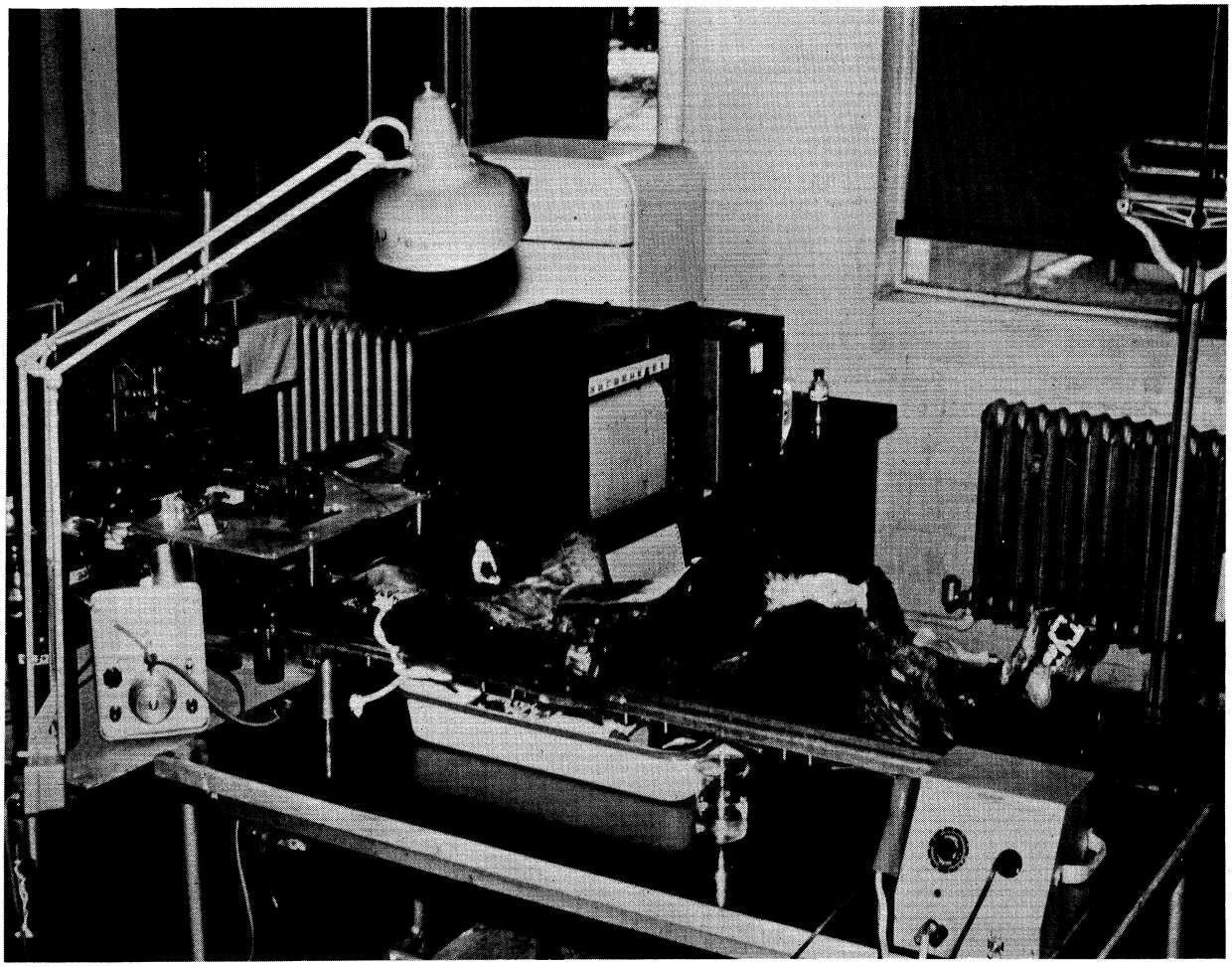


Fig. 1 Experiment in Progress

IV. APPARATUS AND ANALYTICAL PROCEDURES

This section describes the analytical methods and special apparatus used in this investigation. The glucose concentration in the arterial blood of the dog was continuously monitored using a modification of the method developed by Hoffman[28]. Plasma insulin concentrations were determined using the radio-immunological technique developed by Yalow and Berson[63] with the double antibody modification developed by Samols and Bilkus[54]. Morgan and Lazarow have also modified the method developed by Yalow and Berson using a different buffer system[42].

Glucose Analysis

The basis of the Hoffman method for the determination of glucose is the reduction of potassium ferricyanide to potassium ferrocyanide with the concomitant oxidation of glucose to gluconic acid and other products. This method was adapted for on-line analysis by using a proportioning pump to continuously measure the reagents, a dialyzer to separate glucose from the whole blood, a delay coil immersed in a hot water bath to permit time for the oxidation-reduction reaction, a flow cell in a spectrophotometer to serve as a detector, and a recording potentiometer to make a continuous record of the data. The arrangement of the modules is shown in Fig. 2.

(1) Proportioning Pump

The proportioning pump is a device for delivering measured quantities of solutions to a system continuously. It consists of a

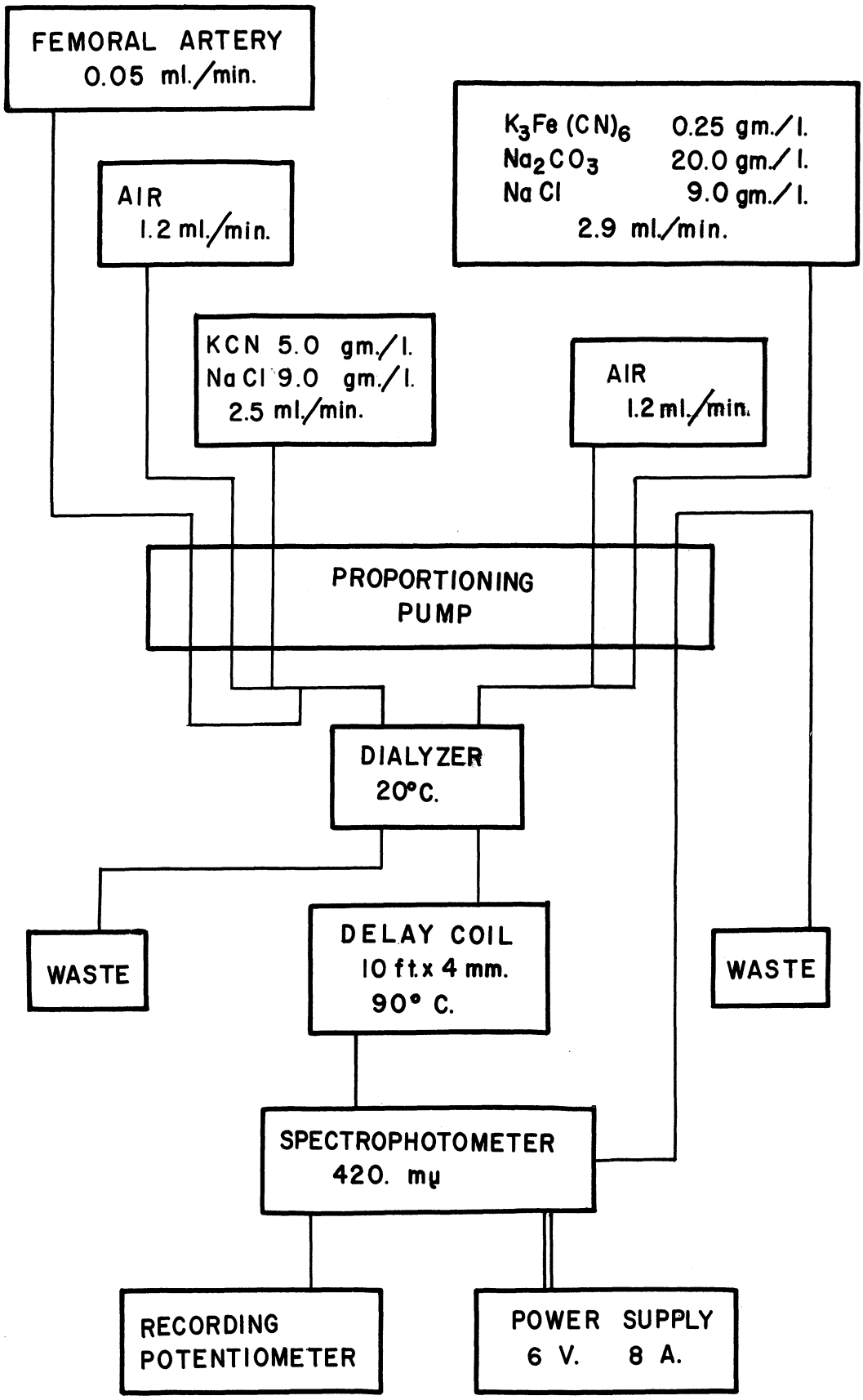


Fig. 2 Flow Chart for On-line Glucose Analysis

manifold of Technicon precision bore Tygon tubes mounted below a roller assembly. Fluid is moved through the tubes by a series of rollers passing over the manifold. Different flow rates may be obtained by varying the tube diameter or the motor speed. The pump is driven by a 1/10 hp motor equipped with a Zero-Max Transmission giving an output shaft speed range from 0-400 rpm. The transmission was adjusted to produce a roller head speed of 13 revolutions per minute. The pump tube sizes used are listed below in Table 1.

TABLE 1

PROPORTIONING PUMP TUBE SIZES

Flow Stream	Inside Diameter inches	Flow Rate ml/min
Blood	0.010	0.05
Potassium Cyanide	0.081	2.50
Air	0.056	1.20
Potassium Ferricyanide	0.090	2.90
Flow Cell	0.073	2.00
Debubbler	0.065	1.60

(2) Dialyzer

The dialyzer was obtained from Technicon, Inc. It consists of two grooved plastic plates separated by a cellophane membrane, and is held in a stainless steel clamp. The total membrane surface area available for mass transfer is 34.5 cm^2. The channel in each dialyzer plate is 2.3 meters long, 1.5 mm wide, and 1.0 mm deep.

Technicon Type C membranes were used in all experiments. The membrane was wetted with water and stretched tightly in a hoop before being placed between the dialyzer plates. The dialyzer was operated in a battery jar filled with distilled water at room temperature.

(3) Hot Water Bath

The hot water bath was constructed from a 12 x 30 inch battery jar, 1000 watt immersion heater, and temperature regulator. The temperature regulator consisted of a mercury thermostat and an on-off relay.

The delay coil consisted of three ten foot, 4 mm ID Pryex coils connected end-to-end with Tygon sleeves.

(4) Spectrophotometer

A Coleman Jr. Model 600 spectrophotometer set at a wavelength of 420 mμ was used to measure the changes in the optical density of the analytical reagent. A flow cell was constructed from a piece of black Lucite with clear Lucite windows. The length of the light path was 1.90 cm and the area of the beam was 9.61 mm^2.

The spectrophotometer power supply was a 6 volt, 8 amp direct current regulated power supply unit. A constant voltage transformer was connected between the laboratory power line and the DC power supply to further stabilize the voltage.

(5) Recorder

A Brown Electronik recording potentiometer was used to record the spectrophotometer output. The full scale voltage of the recorder was 1.0 mv and the response time for a full scale deflection was less

than 0.5 second. The recorder chart speed was 17.5 inches per hour.

(6) Solutions

Blood Diluent. The blood diluting solution contained 9.0 gm sodium chloride and 5.0 gm potassium cyanide per liter. It was prepared in 15 liter quantities.

Alkaline potassium ferricyanide reagent. The alkaline potassium ferricyanide solution or dialyzing solution contained 0.25 gm potassium ferricyanide, 9.0 gm sodium chloride, and 20.0 gm sodium carbonate per liter. It was prepared in 15 liter quantities.

Glucose standards. New standard glucose solutions were prepared at two month intervals and stored at 4°C. First a solution containing 100 mg/ml glucose was prepared by dissolving 10.00 gm glucose in 100 ml saturated benzoic acid solution. Standard solutions were then prepared to contain 50, 100, 150, 200, 250, 300, 350, 400, 450, and 500 mg glucose per 100 ml solution by diluting 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, and 5.1 ml of the initial standard glucose solution to 100 ml with distilled water in a volumeteric flask.

Figure 3 shows a typical standard curve for the on-line glucose analysis. The response, measured in terms of peak height in cm, is plotted against glucose concentration in milligrams percent. The peak height is related to the optical density of the reagent.

Simultaneous measurements were made by the on-line method and by a modification of a manual method[46] on blood samples obtained from one dog to check the accuracy of the procedure. Using the manual procedure glucose determinations were made on samples of whole blood,

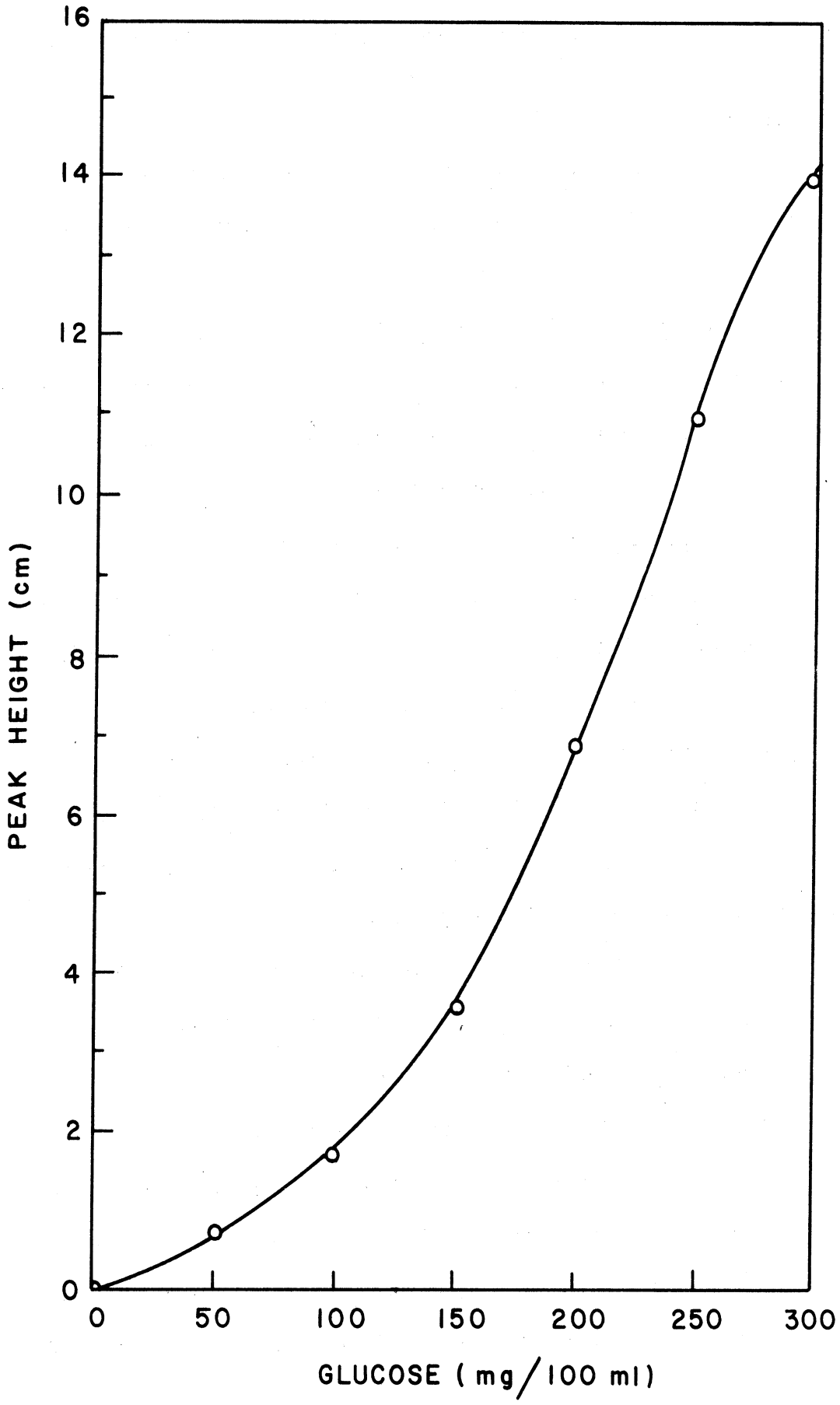


Figure 3. Standard Curve for the On-line Glucose Analysis.

plasma, and red cells. Whole blood, plasma, and red cells were deproteinized using barium hydroxide and zinc sulfate solutions. The barium hydroxide solution was prepared by dissolving 45 grams $Ba(OH)_2 \cdot 8H_2O$ in 1.0 liter distilled water. The zinc sulfate solution was made by dissolving 50 grams $ZnSO_4 \cdot 7H_2O$ in 1.0 liter distilled water. Equal volumes of these solutions must neutralize each other exactly. The neutrality was checked by titration using phenophthalein as the indicator. The protein-free filtrate was prepared by adding 0.4 ml blood, plasma, or red cells to 4.8 ml barium hydroxide solution and mixing, followed by the addition of 4.8 ml zinc sulfate solution. The mixture stood for several minutes and was filtered. One ml of the filtrate was added to five ml alkaline potassium ferricyanide solution. The mixture was heated for five minutes at 90°C and cooled in tap water. The optical density of the sample was measured at 420 mμ. The results are presented in Tables 2 and 3. The on-line method gave a glucose value approximately 10 mg percent lower than the manual determination. This error seemed to be constant throughout the operating range. As long as all data being analyzed are measured by the same method this error should not be serious.

Insulin Analysis

The radio-immunological insulin assay developed by Yalow and Berson[63] and as modified by Samols[54] was used. This method is based on the antigenic nature of insulin. Insulin reacts with specific antibodies to form complexes. In a system in which suitable amounts of anti-insulin antibody and insulin are present some insulin will be

TABLE 2

COMPARISON OF ON-LINE AND MANUAL GLUCOSE MEASUREMENTS FOR WHOLE BLOOD

Sample	Manual Glucose mg/100 ml	On-Line Glucose mg/100 ml
1	117	103
2	116	105
3	126	115
4	144	130
5	149	153
6	164	167
7	198	185
8	222	215
9	249	237
10	274	255

TABLE 3

GLUCOSE CONTENT OF WHOLE BLOOD, PLASMA, AND RED CELLS

Sample	Plasma Glucose Content mg/100 ml	Red Cells Glucose Content mg/100 ml	Hematocrit	Total Plasma and Red Cells mg/100 ml	Whole Blood Glucose Content mg/100 ml
1	172	43	0.48	117	117
5	260	52	0.45	166	149
15	530	94	0.33	384	382

bound to the antibody as an insulin-antibody complex and some insulin will not be bound, that is, it will be free. These complexes are separated from free insulin by addition of a second antibody which combines with the insulin-antibody complex to render it insoluble. The insoluble complex is separated by centrifugation. By adding the appropriate constant amount of insulin labelled with iodine-131 and anti-insulin antibody to a series of samples containing varying known amounts of unlabelled insulin, successively greater amounts of insulin-I-131 are displaced from anti-insulin antibody. Thus a standard response curve is obtained by plotting the percent insulin bound by the antibody vs the amount of unlabelled insulin added. Those standards containing the smallest amount of standard insulin have the highest radioactivity in the bound fraction. The quantity of insulin in unknown plasma samples is measured by comparing the ability of the endogenous insulin in the plasma sample to displace insulin-I-131 from anti-insulin antibody with that of the set of standards.

Reagents for Insulin Analysis

(1) Barbital Buffer

The barbital buffer was prepared by dissolving 3.68 gm barbituric acid and 20.6 gm sodium barbital in 1.0 liter deionized water. The pH of the buffer was 8.6.

(2) Barbital Buffer with 0.25% Human Serum Albumin.

Five ml 12.5% Human Serum Albumin were added to 500 ml of the barbital buffer solution (prepared above).

(3) Trace Insulin (Insulin-I-131)

Pork insulin was iodinated using sodium iodine-131 in sodium hydroxide solution by the method of Hunter and Greenwood[30]. After dialysis to remove unreacted sodium iodide and purification on a Sephadex column the trace insulin was diluted with barbital-albumin buffer solution to make a solution having an activity of 0.45 microcuries/ml on the day following iodination.

(4) Anti-insulin Serum

Anti-pork insulin guinea pig serum solution was prepared from guinea pig anti-insulin serum produced at the University of Michigan. To assay samples of peripheral plasma this serum was diluted 1:25,000 with barbital-albumin before addition to the assay tubes where the final concentration of anti-serum was 1:250,000. For pancreatic venous plasma this serum was diluted 1:2,500 before addition to the assay tubes where the final concentration was 1:25,000.

(5) Carrier Protein

The carrier protein solution was prepared by diluting normal nonimmune guinea pig serum 1:150 with barbital buffer.

(6) Rabbit-anti-guinea Pig Globulin Serum (RAGPS)

RAGPS was obtained from Arnel Products. For use in the insulin assay, RAGPS was diluted with an equal part of barbital buffer. This amount was shown to be 100 percent in excess of the amount needed to precipitate all the bound insulin-I-131 in the presence and absence of plasma at a 1:1 dilution.

(7) Insulin Standards

Crystalline pork insulin was obtained from Eli Lilly and Company, was diluted to 20,000 μU/ml in barbital albumin buffer and used in the preparation of the standard insulin solutions. For peripheral samples the standard insulin was diluted with barbital-albumin to make a standard solution containing 50 μU/ml. For pancreatic samples the standard insulin was diluted to make a solution containing 1000 μU/ml. These solutions were used to prepare the standard curves.

Analytical Procedure

The insulin assay tubes were prepared for the first incubation as shown in Table 4. The reagents were added in the following order: diluent; trace insulin; standard insulin or plasma; and anti-insulin serum. Two control tubes, Cc, were prepared using excess unlabelled insulin to determine the amount of labelled insulin that is precipitated when the antibody is combined with essentially only unlabelled insulin. The same information can be obtained by preparing a control containing no anti-insulin serum.

Each tube was mixed gently on a vortex mixer and stored at 4°C. After 48 hours 100 μl of carrier protein solution and 100 μl of RAGPS solution were added to each assay tube. The second incubation period was 72 hours at 4°C. Following the second incubation the tubes were centrifuged at 1100 g. for 20 minutes at 4°C. in a refrigerated centrifuge. The supernatant was carefully decanted. The tubes were allowed to drain in an inverted position for 20 minutes. They were then counted to measure I^{131} gamma activity using a Nuclear Chicago automatic

TABLE 4

PREPARATION OF THE INSULIN ASSAY TUBES FOR THE FIRST INCUBATION

Tube Number	Volume of Diluent	Volume of Trace Insulin	Volume of Standard Insulin or Plasma	Volume of Anti-insulin Serum
	µl	µl	µl	µl
Tr A	400	50	0	50
Tr B	400	50	0	50
Tr C	400	50	0	50
Tr D	400	50	0	50
1*	390	50	10	50
2	380	50	20	50
3	370	50	30	50
4	360	50	40	50
5	350	50	50	50
6	340	50	60	50
7	320	50	80	50
8	300	50	100	50
9	250	50	150	50
10	200	50	200	50
11	150	50	250	50
12	100	50	300	50
Cc	395	50	5**	50
Standard Plasma	350	50	50	50
Unknowns	350	50	50	50

* All tubes in the standard curve and all unknowns were prepared in duplicate.

**The control, Cc, is prepared using a concentrated insulin solution containing 1 mg/ml.

gamma counter. The samples were counted for five minutes or to obtain 10,000 counts.

The concentration of insulin in each unknown was determined

from the fraction of insulin bound by the antibody, PBZ.

$$PBZ = \frac{CPM_X - CPM_{Cc}}{BZERO}$$

$$BZERO = \frac{(CPM\ Tr\ A + CPM\ Tr\ B + CPM\ Tr\ C + CPM\ Tr\ D)}{4} - CPM\ Cc$$

A standard curve was plotted as PBZ vs amount of insulin, Figure 4. Unknowns were determined by observing the insulin concentration corresponding to a given PBZ.

Diluent was measured using a 5 ml burette equipped with a reservoir. Trace insulin was measured using a 50 µl reservoir pipette. Plasma and standard insulin solutions were measured using the appropriate sized lambda pipettes. Antiserum, carrier protein, and RAGPS solution were measured using 50 µl, 100 µl and, 100 µl reservoir pipettes, respectively. An alternate technique for measuring diluent and plasma is that of using an automatic diluting pipette. Hamilton syringes can be used for measuring carrier protein, RAGPS solution, anti-insulin serum and trace insulin.

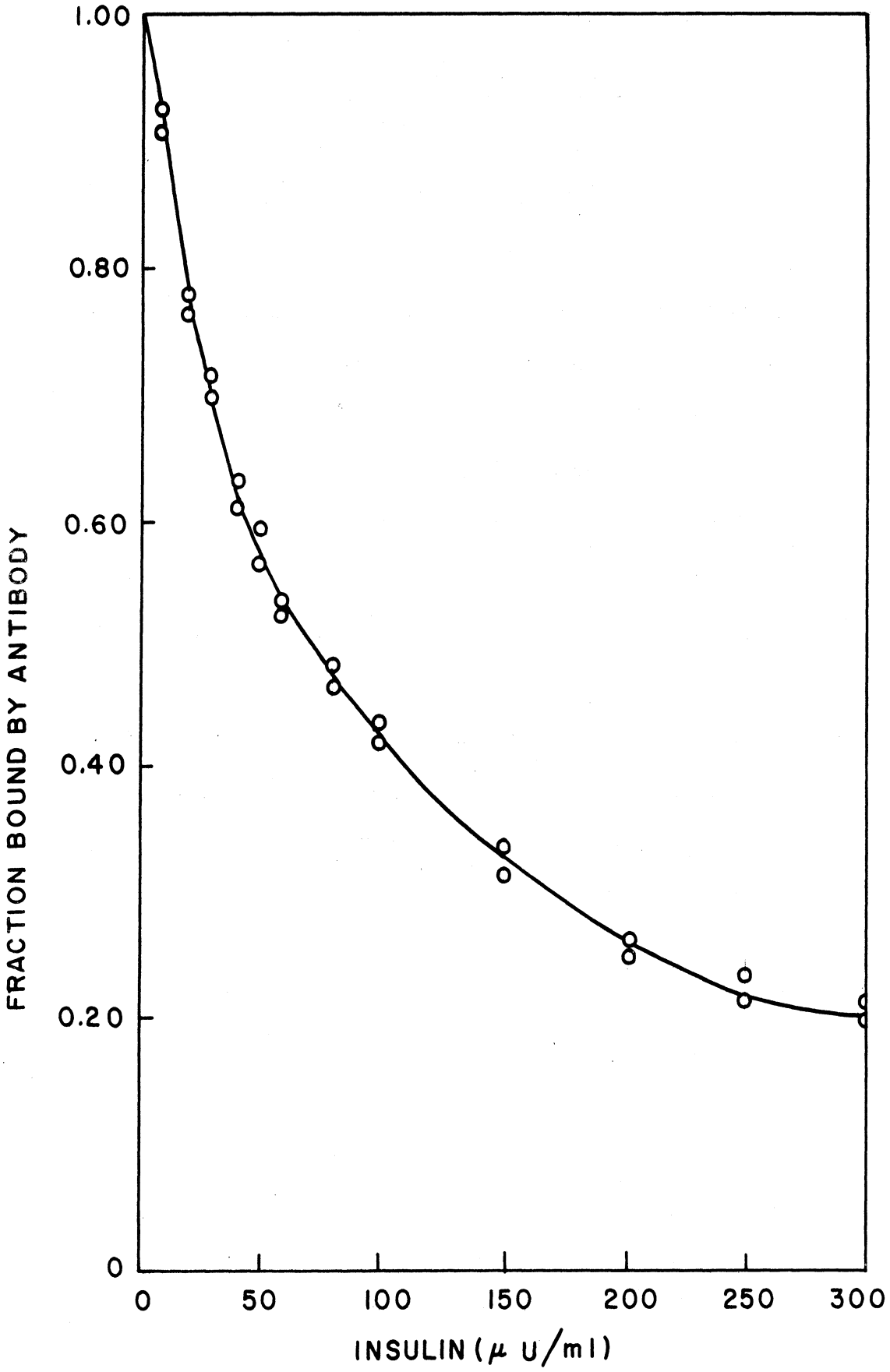


Figure 4. Standard Curve for the Insulin Assay.

V. MATHEMATICAL METHODS

In this chapter the procedure used to develop the mathematical model describing the insulin secretory response of the pancreas will be discussed. Statistical methods used to test the differences between several proposed models will be discussed also.

Development of the Model

After reviewing models describing the insulin secretory response of the pancreas and other biological systems, analyzing the characteristics of physical control systems, and studying the physiology of insulin secretion, the model given in equation (5.1) was postulated.

$$I(t) = \frac{K_1\, G(t - \tau_1) + K_2 \frac{dG}{dt}(t - \tau_2) + K_3\, FVI(t - \tau_3) + K_4}{V(t)(1 - H)} \qquad (5.1)$$

where:

I	=	Plasma insulin concentration, pancreatic vein	$\mu U/ml$
G	=	Blood glucose concentration, femoral artery	mg/100 ml
FVI	=	Plasma insulin concentration, femoral vein	$\mu U/ml$
H	=	Hematocrit	percent
K_1	=	Coefficient, blood glucose term	$(\mu U/min)(mg/100\ ml)^{-1}$
K_2	=	Coefficient, derivative term	$(\mu U/min)(mg/100\ ml)^{-1}$ min
K_3	=	Coefficient, peripheral insulin term	$(\mu U/min)(\mu U/ml)^{-1}$ peripheral
K_4	=	Coefficient, constant term	$\mu U/min$
t	=	Time	min
τ_1	=	Time lag, blood glucose term	min
τ_2	=	Time lag, derivative term	min
τ_3	=	Time lag, peripheral term	min

T_a = Integration limit min

T_b = Integration limit min

Equation (5.1) indicates that the pancreatic venous insulin concentration is proportional to the arterial blood glucose concentration, the first time derivative of the arterial blood glucose concentration, and the femoral venous plasma insulin concentration. The derivatives term provides a more rapid response to large changes in blood glucose concentration and is included because this investigation showed that markedly different plasma insulin concentrations existed in a given dog at the same blood glucose concentration. Further inspection of this data showed that the glucose concentration was rising more rapidly at the time the higher insulin concentration was observed. This observation is explained by the presence of a derivative term in the model. The femoral venous insulin concentration term represents a possible negative feedback effect of insulin on the response of the pancreas. K_3 will be a negative number if this negative feedback can be detected. K_4 represents a base-line insulin secretion independent of changes in blood glucose concentration. A time lag is associated with each of the first three terms. The sum of the four terms on the right side of equation (5.1) is divided by the product of the pancreatic blood flow rate and the hematocrit since the insulin measurements were made on plasma and the flow measurements on whole blood. Thus, if both sides of equation (5.1) are multiplied by the blood flow rate, the equation will represent the rate of insulin secretion into the cannulated vein. The values of the time lags and the constants must now be determined. The lag values are found using an iterative procedure.

For a given set of lag values the four coefficients were determined from the experimental data by applying the least squares method to equation (5.1). The computer program for this procedure is given in Appendix B. The values of the coefficients and the time lags were substituted into equation (5.1) and the insulin concentrations were calculated at given time intervals. The error was defined to be the difference between the measured and the calculated pancreatic venous insulin concentrations at a given time. The criterion used to measure the goodness of the fit of the model to the experimental data was the integral of the square of the error. This is the same criterion that was used in the least squares procedure to determine the coefficients. A model having the smallest integral of the square of the error would be the "best".

An iterative procedure was used to find the combination of lag values providing the "best" fit for the data from each experiment. A grid searching method was used to find the optimum combination of lags.

Having determined the best set of lags for a given experiment, a series of modified models given by equations (5.2-5.7) were applied to the same data to study the effect of omitting various terms.

$$I(t) = \frac{K_1\, G(t - \tau_1) + K_2 \frac{dG}{dt}(t - \tau_2) + K_3\, FVI(t - \tau_3)}{V(t)(1 - H)} \qquad (5.2)$$

$$I(t) = \frac{K_1\, G(t - \tau_1) + K_2 \frac{dG}{dt}(t - \tau_2) + K_4}{V(t)(1 - H)} \qquad (5.3)$$

$$I(t) = \frac{K_1\, G(t - \tau_1) + K_3\, FVI(t - \tau_3) + K_4}{V(t)(1 - H)} \qquad (5.4)$$

$$I(t) = \frac{K_1\, G(t - \tau_1) + K_2 \frac{dG(t - \tau_2)}{dt}}{V(t)(1 - H)} \tag{5.5}$$

$$I(t) = \frac{K_1\, G(t - \tau_1) + K_4}{V(t)(1 - H)} \tag{5.6}$$

$$I(t) = \frac{K_1\, G(t - \tau_1)}{V(t)(1 - H)} \tag{5.7}$$

All the symbols are defined the same as in equation (5.1). The coefficients for each model were determined from the experimental data. Each model was then used to correlate the data and the integral of the square of the error was calculated. The contribution of a particular term to the response estimated by each model was estimated from the change in the integral of the square of the error that occurred when a given term was omitted.

Three other equations were tested. They were models in which the insulin concentration in the pancreatic vein was dependent upon: 1) an integral of the blood glucose concentration, equation (5.8); 2) the logarithm of the blood glucose concentration, equation (5.9); and the reciprocal of the femoral venous insulin concentration, equation (5.10).

$$I(t) = \frac{K_1\, \mathrm{Log}(G(t - \tau_1)) + K_2 \frac{dG(t - \tau_2)}{dt} + K_3\, FVI(t - \tau_3) + K_4}{V(t)(1 - H)} \tag{5.8}$$

$$I(t) = \frac{K_1 \int_{T_b}^{T_a} G(t)dt + K_2 \frac{dG(t - \tau_2)}{dt} + K_3\, FVI(t - \tau_3) + K_4}{V(t)(1 - H)} \tag{5.9}$$

$$I(t) = \frac{K_1\, G(t - \tau_1) + K_2 \frac{dG(t - \tau_2)}{dt} + K_3(1/FVI(t - \tau_3)) + K_4}{V(t)(1 - H)} \quad (5.10)$$

Multivariate Statistics

Multivariate statistical methods were used to test for the existence of significant differences among the different models applied to the experimental data. Hotelling's T^2 test, a multivariate analog of the Student t test, was used to test for significant differences in the mean errors resulting from the use of different models[29,44]. The models given in equations (5.1 - 5.7) were applied to the data obtained from twelve experiments. The record resulting from the application of each model to a given set of experimental data was divided into three sections and the mean error was determined for each section. The means for each section and for each model were then determined for the number of experiments being analyzed. The mean vector and the covariance matrix were determined according to the outline below. Hotelling's T^2 statistic is given by equation (5.11). The T^2 statistic can be related to the F statistic by equation (5.12).

$$T^2 = Y'\, S^{-1}\, Y \quad (5.11)$$

$$F = \frac{(N-p+1)}{pN}\, T^2 \quad (5.12)$$

where: F = F statistic

N = Number of experiments

p = Number of groups into which each experiment was divided

S = Covariance Matrix

T = Hotelling's T statistic

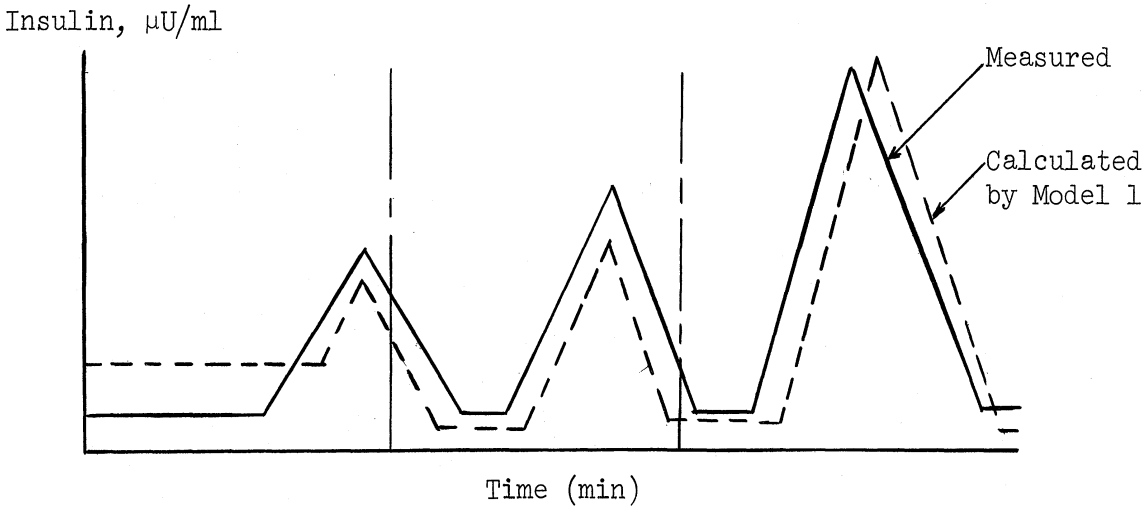
Y = Mean vector

Y' = Transpose of Y

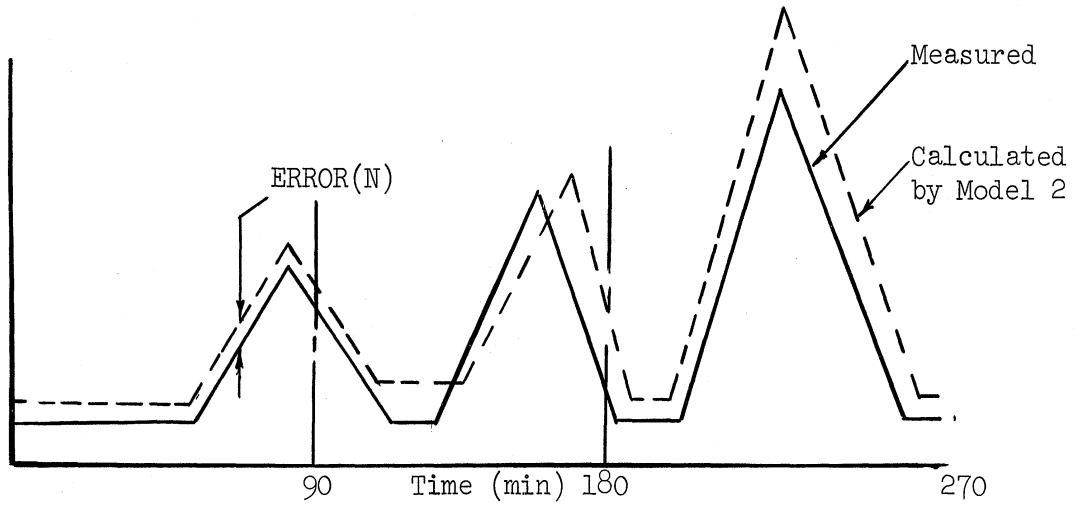
If the calculated value of the F statistic is less than the tabulated α level F percentile, for p and N-p + 1 degrees of freedom, then the probability of being wrong in concluding that the models are significantly different is less than α.

A computer program for determining Hotelling's T^2 statistic and the F statistic is given in Appendix B. The computational procedure is outlined below, and the application to a set of experimental data is shown in Figure 5.

Mathematical Methods for Hotelling's T^2 Test



Experiment 1 correlated with Model 1, X1 = 1, X2 = 1.



Experiment 1 correlated with Model 2, X1 = 1, X2 = 2.

Fig. 5 Intervals used in Hotelling's T^2 Test

Nomenclature:
- X1 - Index, identifies a given experiment
- X2 - Index, identifies a given model
- X1MAX - Total number of experiments being analyzed
- E1 - Mean error in the interval 0-90
- E2 - Mean error in the interval 91-180
- E3 - Mean error in the interval 181-270

Each experiment is divided into a given number of groups, where the number of groups is much less than the total number of experiments, X1MAX. Here the data for each experiment has been divided into three groups. The errors occurring between these groups are considered to have a multivariate normal distribution. The mean errors are determined for each model applied to all the experiments using equations (5.13 - 15).

$$E1(X1,X2) = \frac{1}{90} \sum_{N=0}^{90} ERROR(N) \tag{5.13}$$

$$E2(X1,X2) = \frac{1}{90} \sum_{N=91}^{180} ERROR(N) \tag{5.14}$$

$$E3(X1,X2) = \frac{1}{90} \sum_{N=181}^{270} ERROR(N) \tag{5.15}$$

The mean error for each model was determined in each group using equations (5.16 - 18).

$$Y1(X2) = \frac{1}{X1MAX} \sum_{X1=1}^{X1MAX} E1(X1,X2) \tag{5.16}$$

$$Y2(X2) = \frac{1}{X1MAX} \sum_{X1=1}^{X1MAX} E2(X1,X2) \tag{5.17}$$

$$Y3(X2) = \frac{1}{X1MAX} \sum_{X1=1}^{X1MAX} E3(X1,X2) \tag{5.18}$$

The differences between the errors resulting from the application of two different models to each dog were calculated. For arbitrary values of X2, e.g. X2a and X2b the differences are given by equations (5.19 - 21).

$$DIF1(X1) = E1(X1,X2a) - E1(X1,X2b) \tag{5.19}$$

$$DIF2(X1) = E2(X1,X2a) - E2(X1,X2b) \tag{5.20}$$

$$DIF3(X1) = E3(X1,X2a) - E3(X1,X2b) \tag{5.21}$$

The variance-covariance matrix of the differences in the errors is given by equation (5.22).

$$S = \begin{bmatrix} \hat{\sigma}_{11} & \hat{\sigma}_{12} & \hat{\sigma}_{13} \\ \hat{\sigma}_{21} & \hat{\sigma}_{22} & \hat{\sigma}_{23} \\ \hat{\sigma}_{31} & \hat{\sigma}_{32} & \hat{\sigma}_{33} \end{bmatrix} \tag{5.22}$$

The elements of S are calculated by equation (5.23).

$$\hat{\sigma}_{mn} = \frac{\sum_{X1=1}^{X1MAX} DIFm(X1)\, DIFn(X1) - \left(\sum_{X1=1}^{X1MAX} DIFm(X1) \sum_{X1=1}^{X1MAX} DIFn(X1) \right) \Big/ X1MAX}{X1MAX - 1} \tag{5.23}$$

Hotelling's T^2 statistic can now be determined by using equation (5.11).

VI. RESULTS

In this chapter the experimental results and the results of the mathematical methods are presented.

Experimental Results

The insulin secretory response of the pancreas was studied in 14 dogs. Twelve dogs received glucose infusions and two control dogs received saline infusions. The experimental data and the calculated results from each dog are presented in Appendix A. The measured values for the blood glucose concentration and the pancreatic venous plasma insulin concentration, and the values of the pancreatic venous plasma insulin concentration calculated from equation (5.1) are plotted for the various experiments in Figures 6 - 19. Figures 6 and 7 also show the peripheral venous plasma insulin concentration and the infusion pump speed. The pancreatic and peripheral insulin concentrations increased rapidly when glucose was administered. The pancreatic venous insulin concentration decreased rapidly when the blood glucose concentration decreased. The peripheral insulin concentration decreased more slowly than the pancreatic venous insulin concentration. Variations in the pancreatic venous insulin concentration were in phase with changes in the blood glucose concentration and lagged by less than five minutes in most dogs studied. Changes in the peripheral insulin concentration lagged the blood glucose concentration from 0 - 15 minutes.

Mathematical Model

The mathematical model given in equation (5.1) was applied to

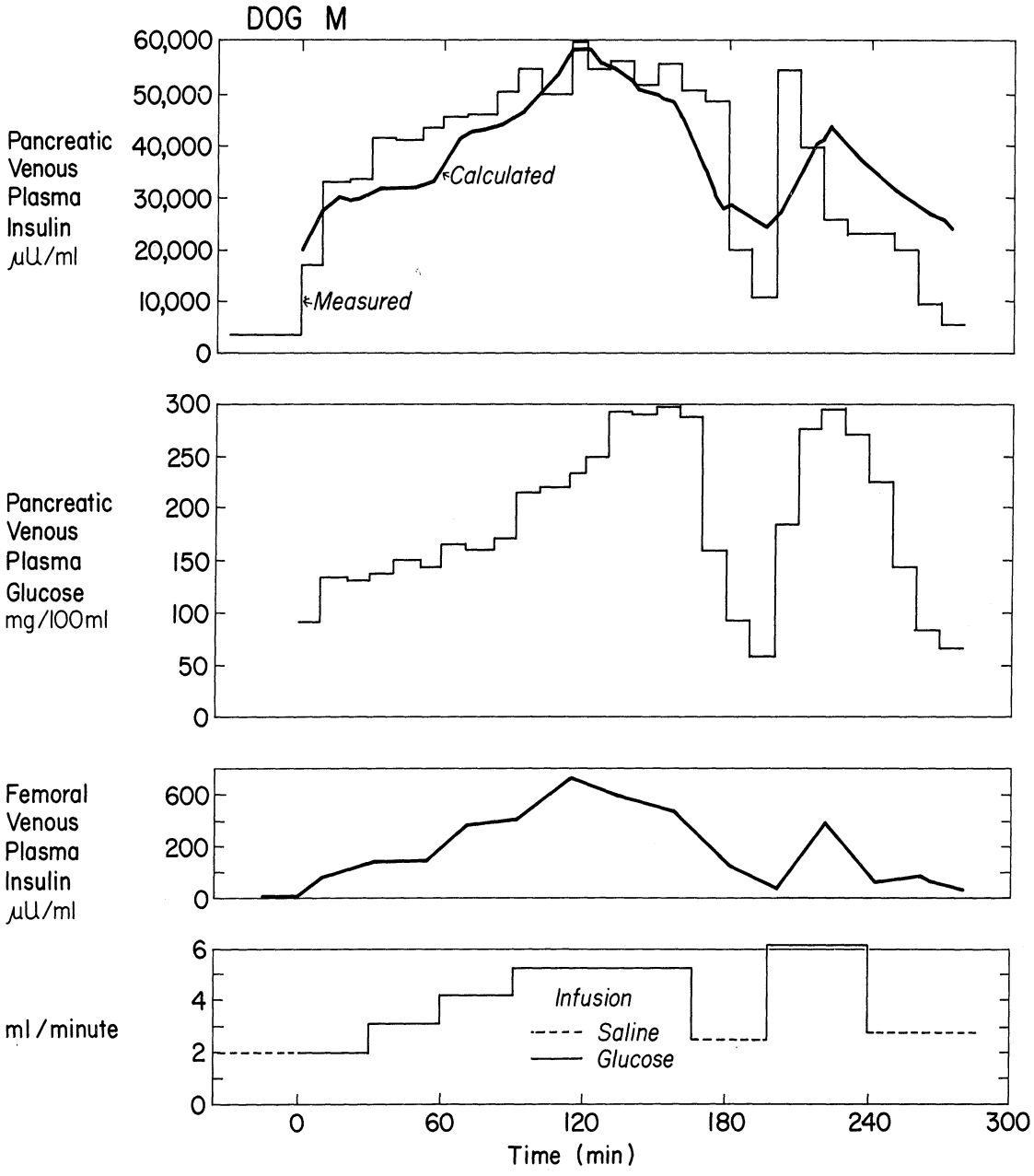

DOG M
Pancreatic Venous Plasma Insulin μU/ml
60,000
50,000
40,000
30,000
20,000
10,000
0
Calculated
Measured
Pancreatic Venous Plasma Glucose mg/100ml
300
250
200
150
100
50
0
Femoral Venous Plasma Insulin μU/ml
600
200
0
ml / minute
6
4
2
0
Infusion
Saline
Glucose
0
60
120
180
240
300
Time (min)

Fig. 6

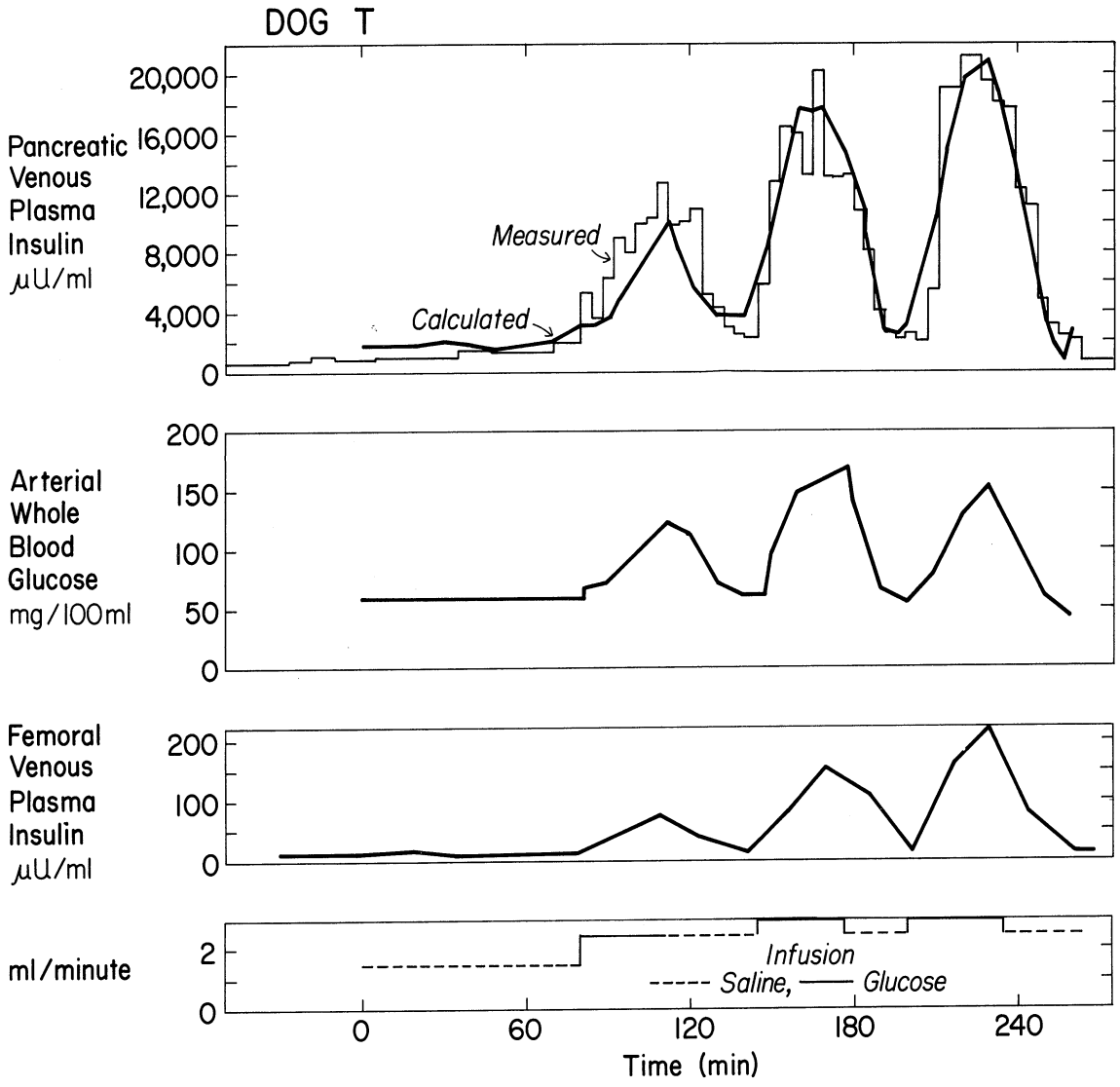

DOG T
Pancreatic Venous Plasma Insulin μU/ml
20,000
16,000
12,000
8,000
4,000
0
Measured
Calculated
Arterial Whole Blood Glucose mg/100ml
200
150
100
50
0
Femoral Venous Plasma Insulin μU/ml
200
100
0
ml/minute
2
0
Infusion
----- Saline, —— Glucose
0
60
120
180
240
Time (min)

Fig. 7

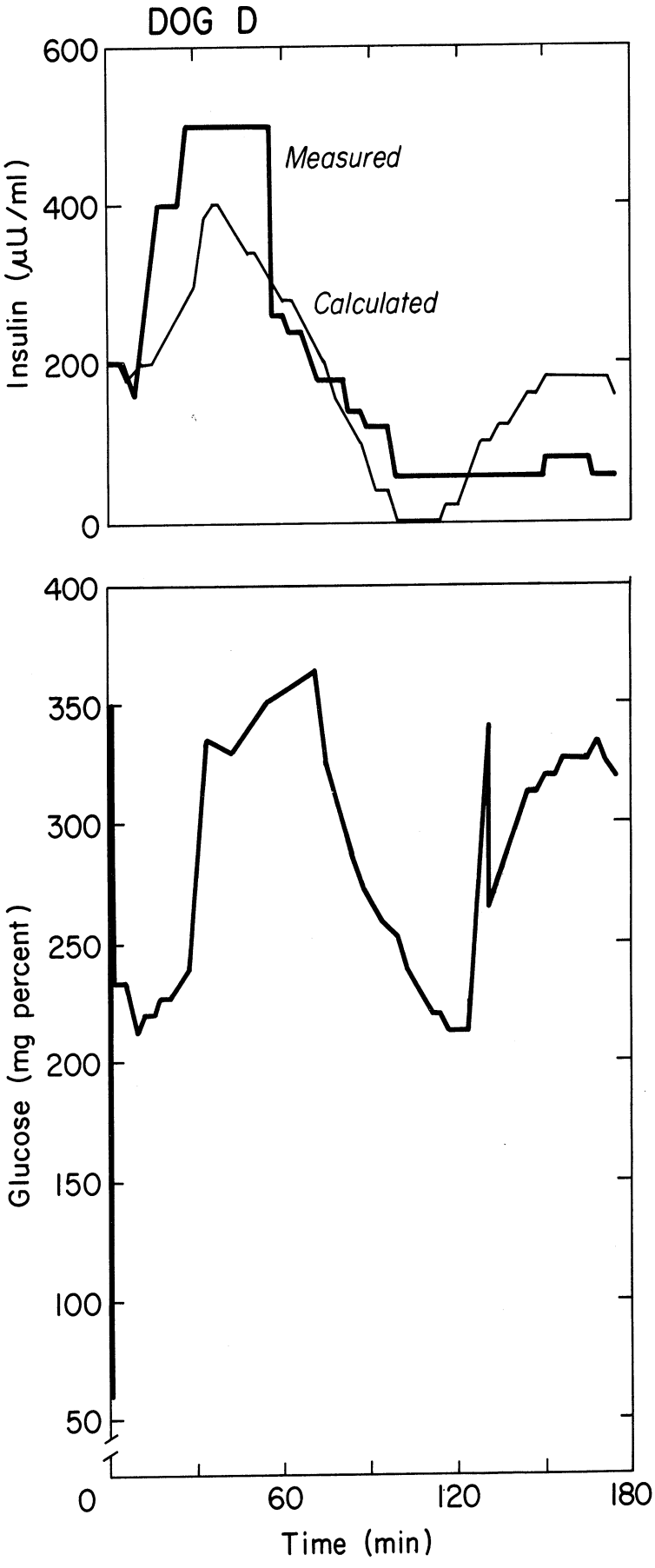

DOG D
600
400
200
0
Insulin (μU/ml)
Measured
Calculated
400
350
300
250
200
150
100
50
0
Glucose (mg percent)
60
120
180
Time (min)

Fig. 8

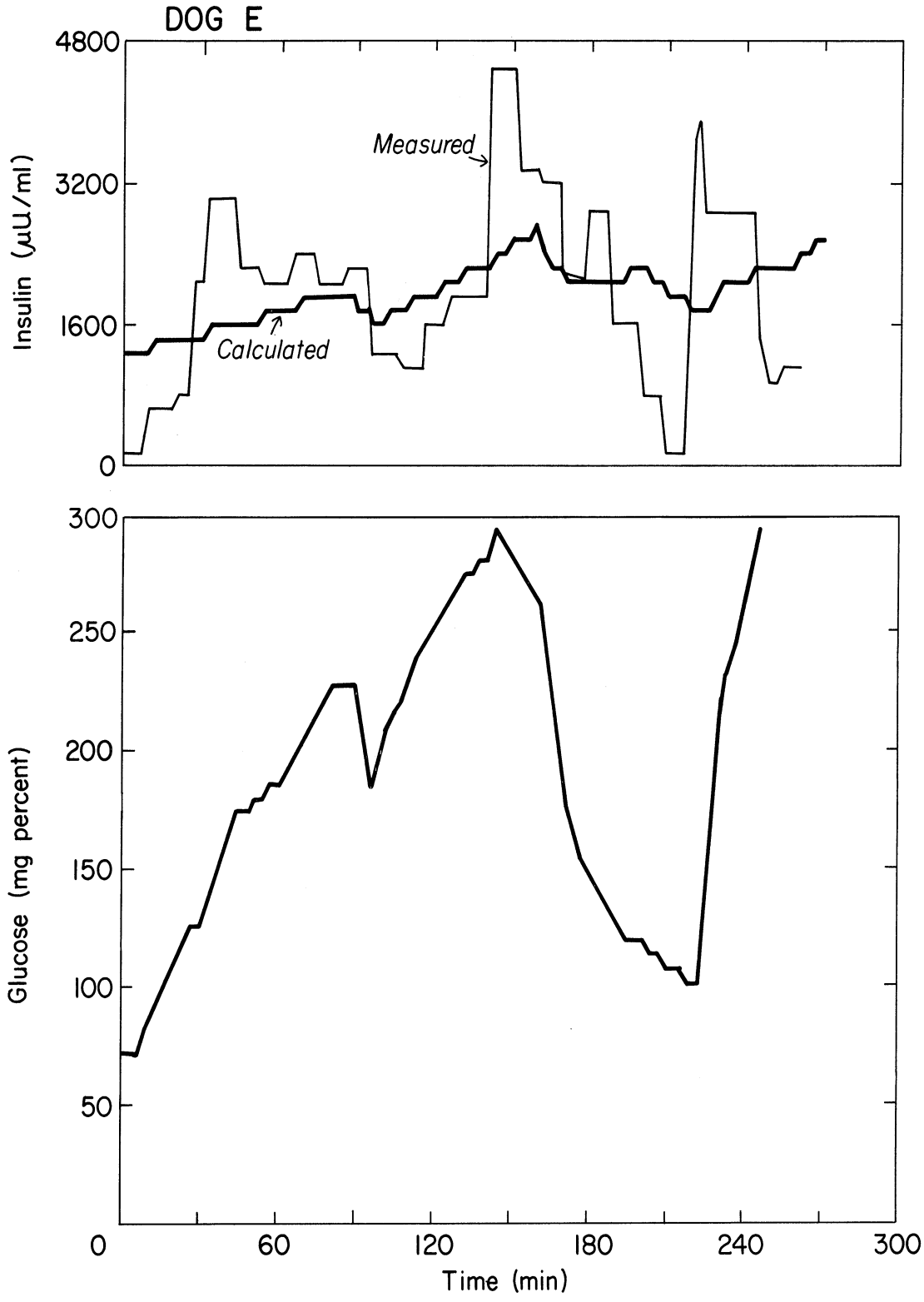

DOG E
4800
3200
1600
0
Insulin (μU/ml)
Measured
Calculated
300
250
200
150
100
50
0
Glucose (mg percent)
0
60
120
180
240
300
Time (min)

Fig. 9

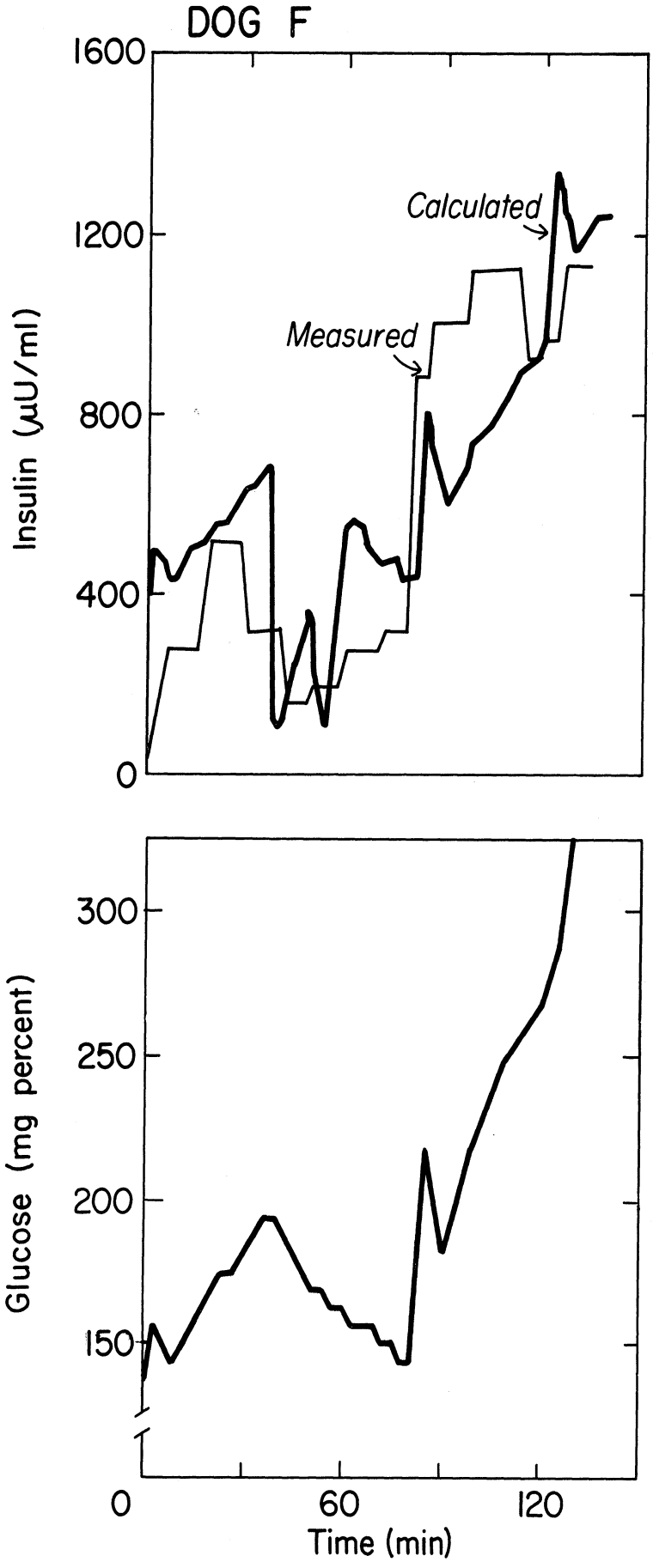

DOG F
1600
1200
800
400
0
Insulin (μU/ml)
Calculated
Measured
300
250
200
150
Glucose (mg percent)
0
60
120
Time (min)

Fig. 10

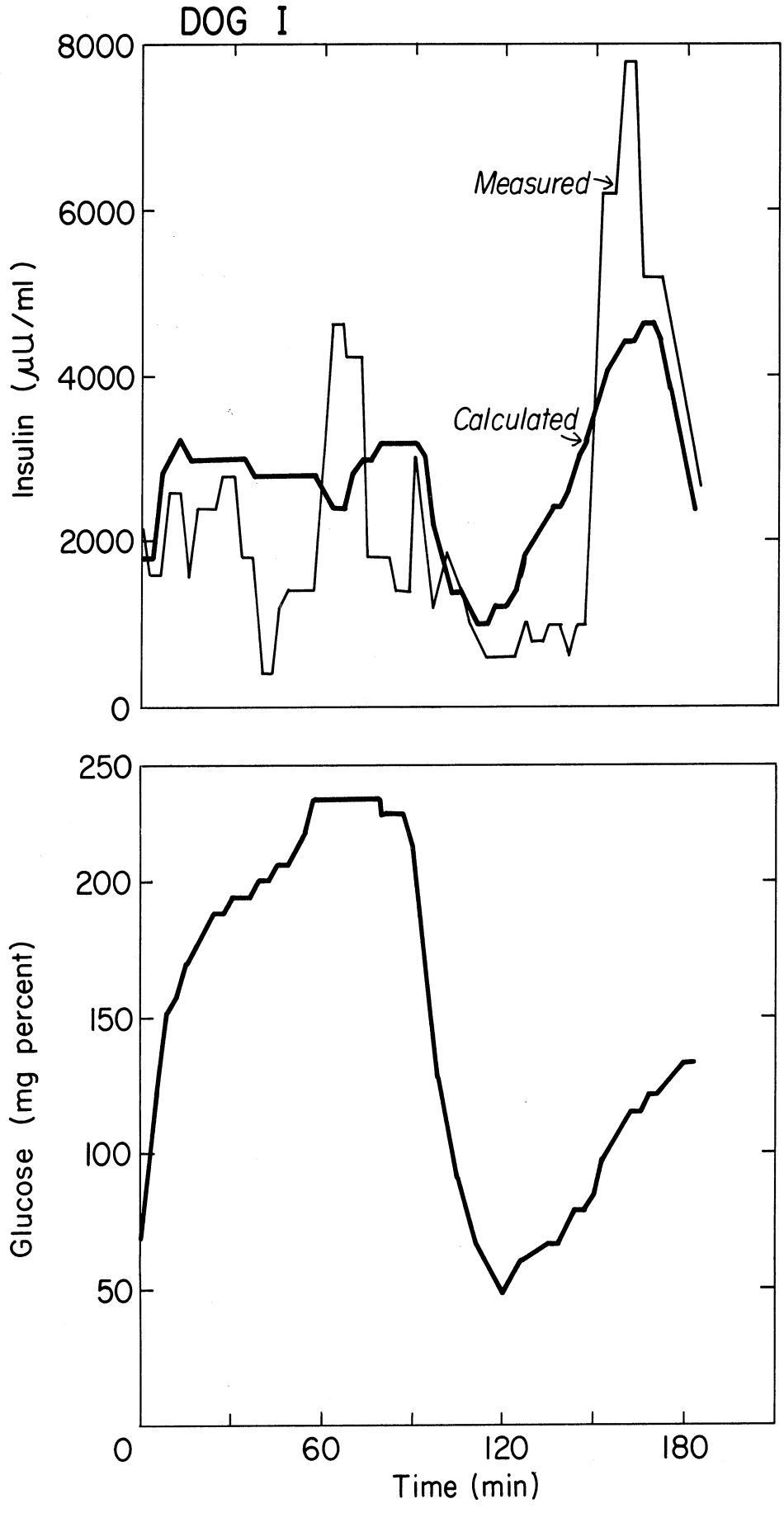

DOG I
8000
6000
4000
2000
0
Insulin (μU/ml)
Measured
Calculated
250
200
150
100
50
0
Glucose (mg percent)
60
120
180
Time (min)

Fig. 11

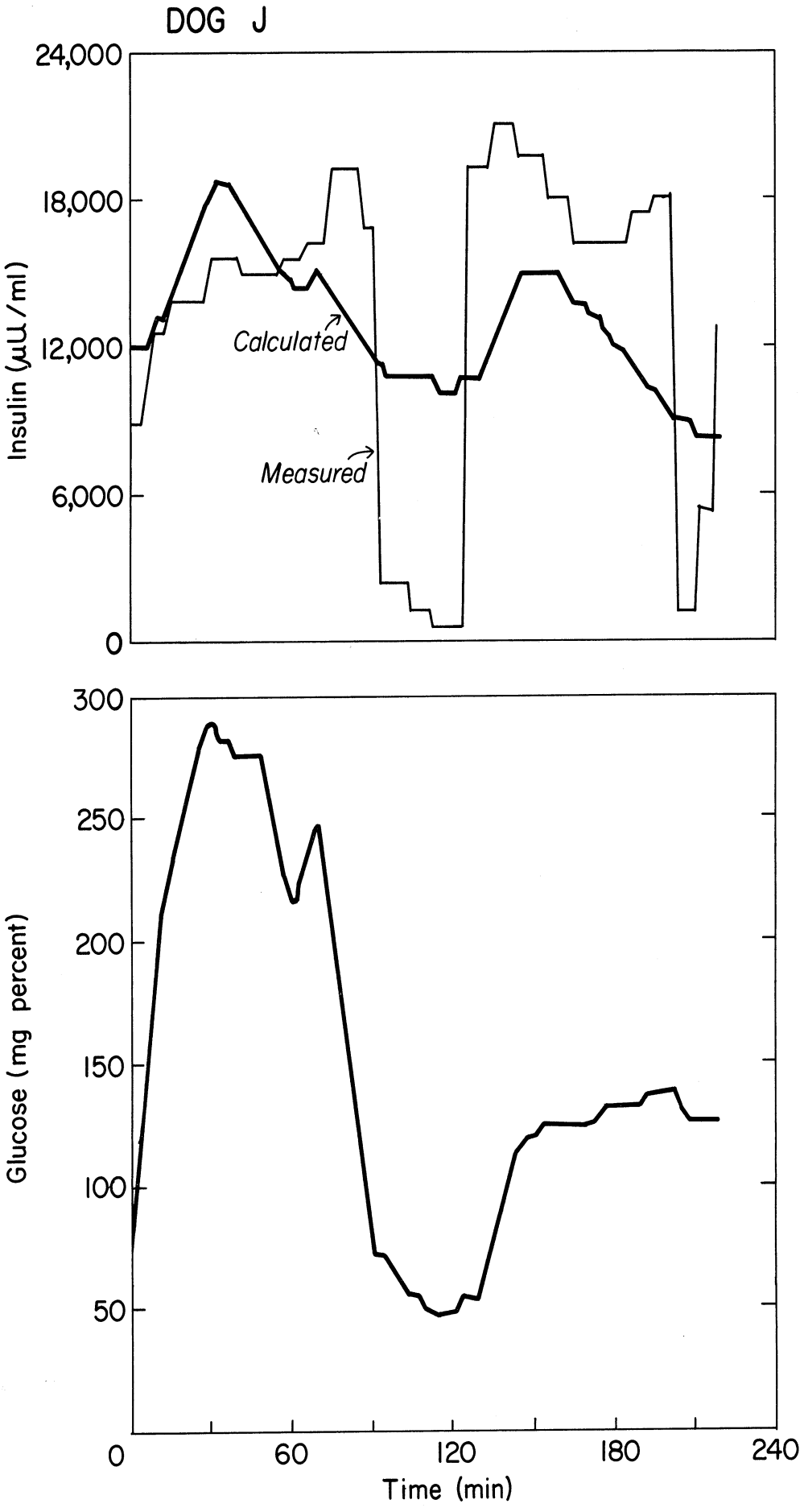

DOG J
24,000
18,000
12,000
6,000
0
Insulin (μU/ml)
Calculated
Measured
300
250
200
150
100
50
0
Glucose (mg percent)
60
120
180
240
Time (min)

Fig. 12

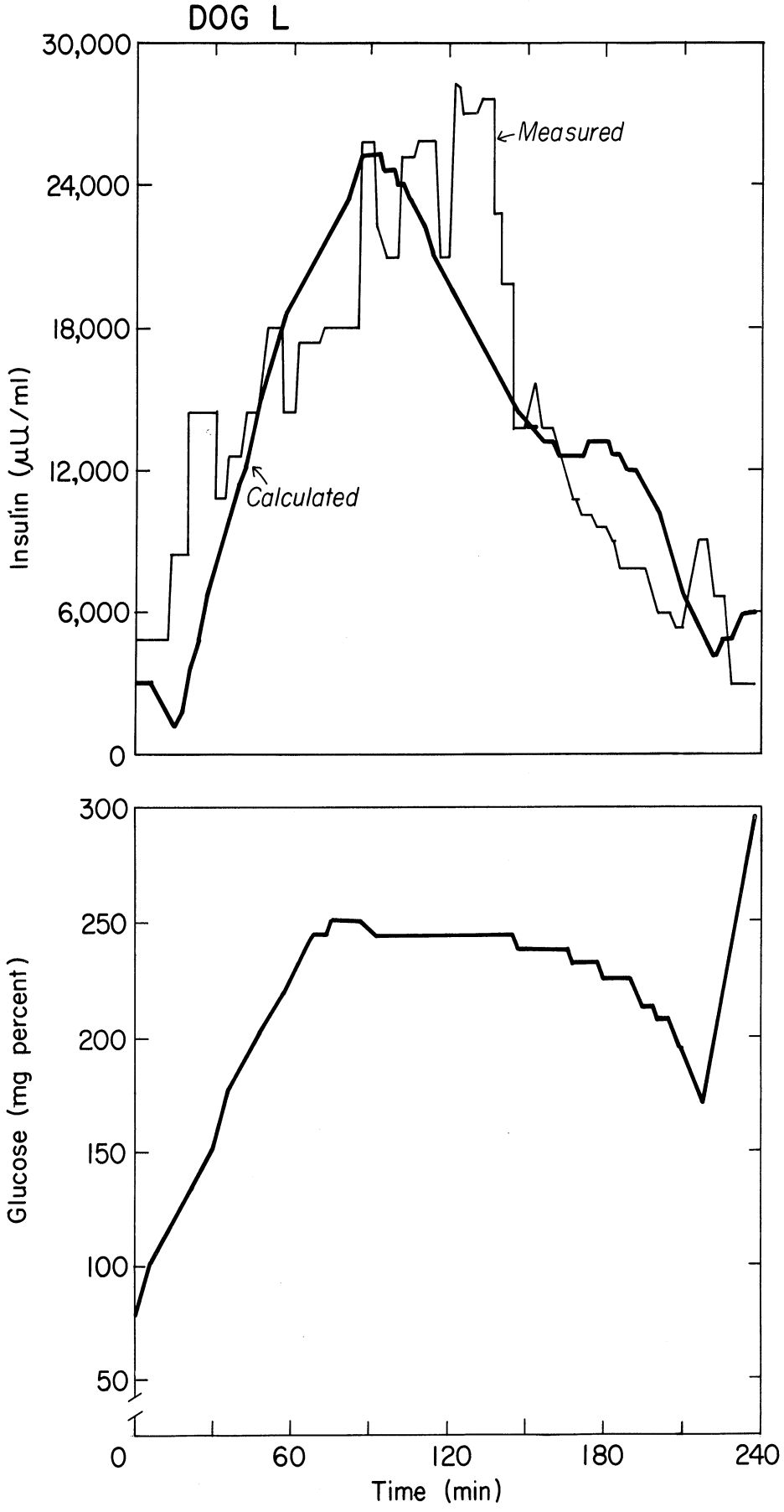

DOG L
30,000
24,000
18,000
12,000
6,000
0
Insulin (μU/ml)
Measured
Calculated
300
250
200
150
100
50
Glucose (mg percent)
0
60
120
180
240
Time (min)

Fig. 13

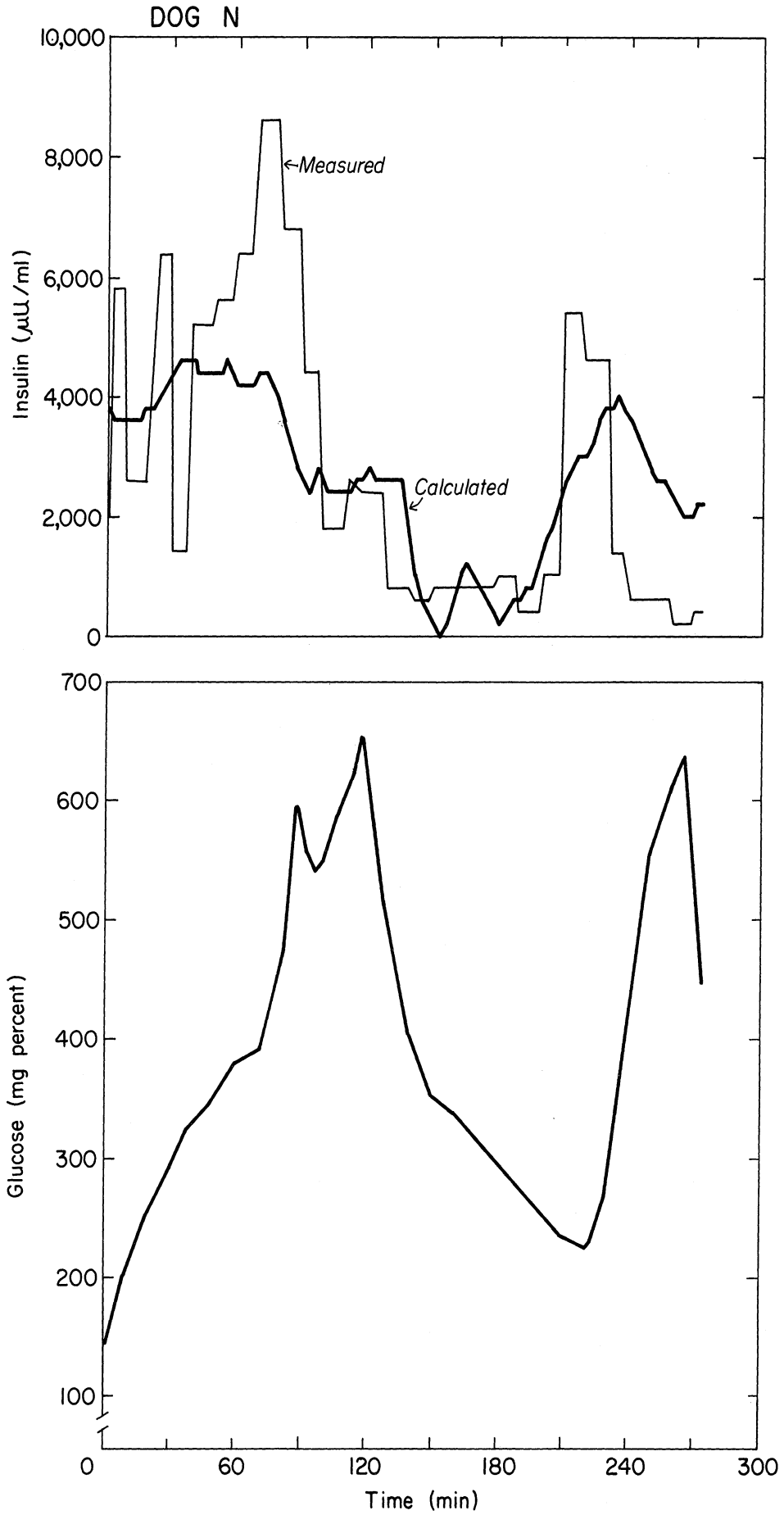

DOG N
10,000
8,000
6,000
4,000
2,000
0
Insulin (μU/ml)
←Measured
Calculated
700
600
500
400
300
200
100
Glucose (mg percent)
0
60
120
180
240
300
Time (min)

Fig. 14

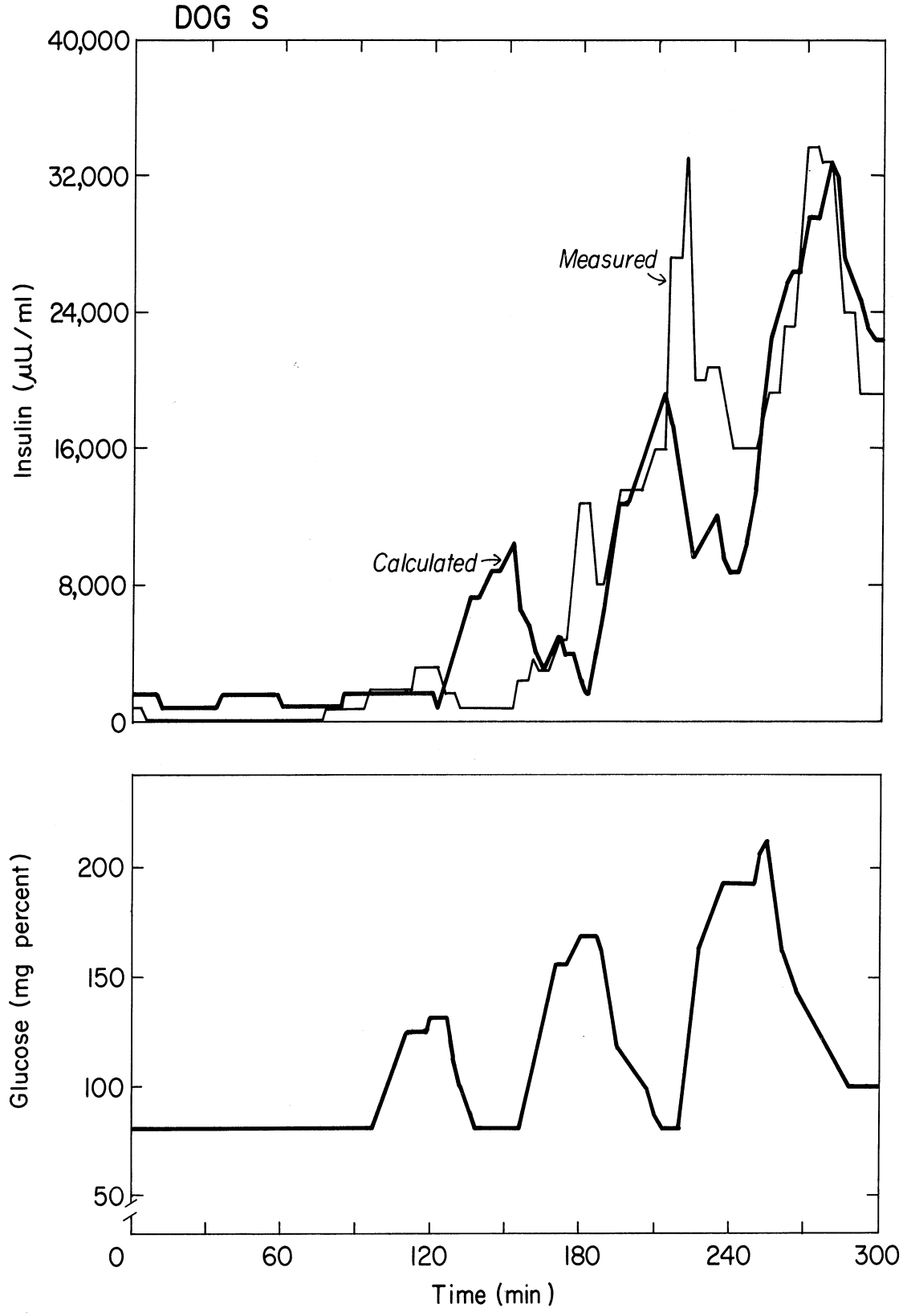

DOG S
40,000
32,000
24,000
16,000
8,000
0
Insulin (μU/ml)
Measured
Calculated
200
150
100
50
Glucose (mg percent)
0
60
120
180
240
300
Time (min)

Fig. 15

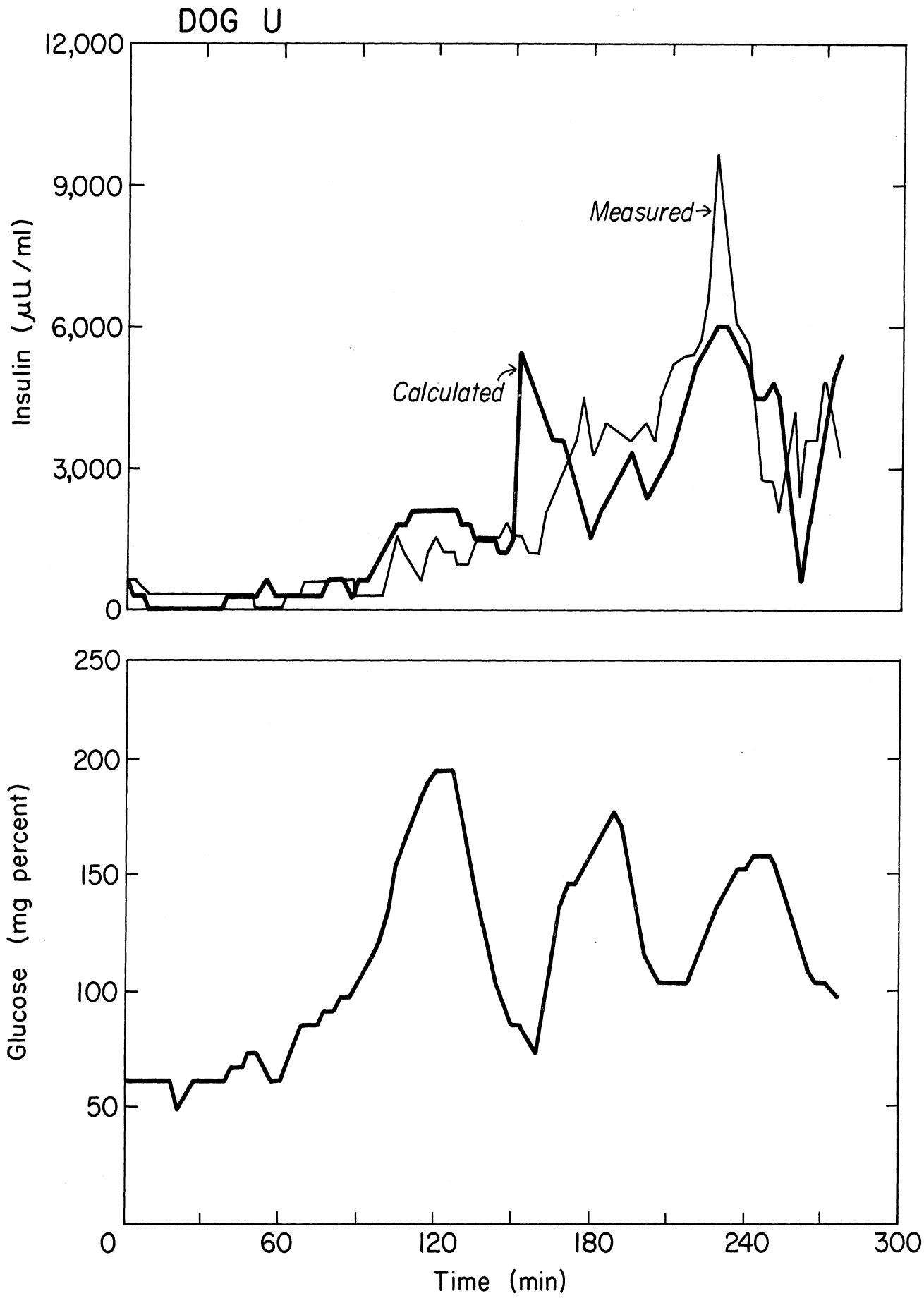

DOG U
12,000
9,000
6,000
3,000
0
Insulin (μU/ml)
Measured
Calculated
250
200
150
100
50
Glucose (mg percent)
0
60
120
180
240
300
Time (min)

Fig. 16

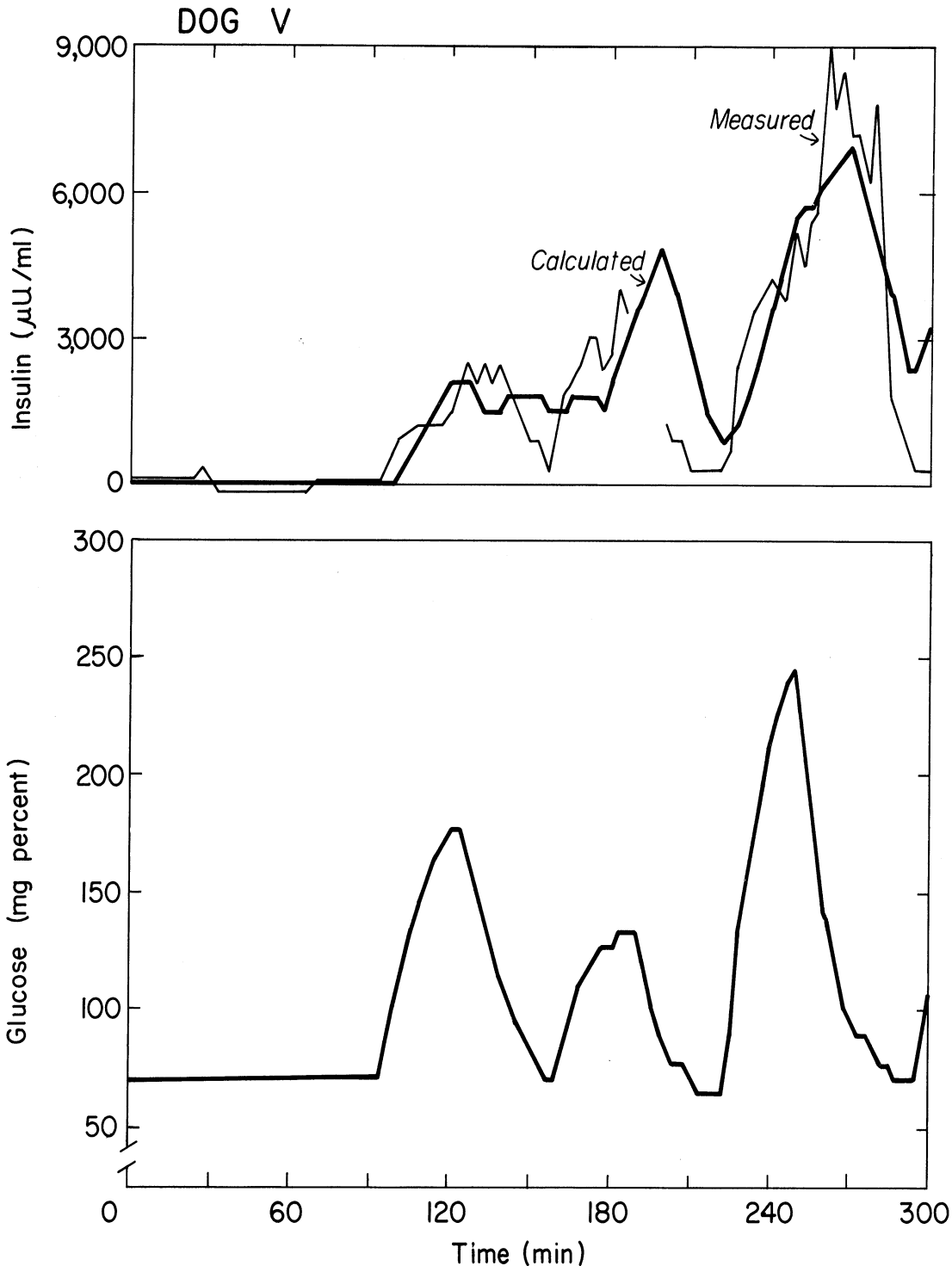

DOG V
9,000
6,000
3,000
0
Insulin (μU/ml)
Measured
Calculated
300
250
200
150
100
50
Glucose (mg percent)
0
60
120
180
240
300
Time (min)

Fig. 17

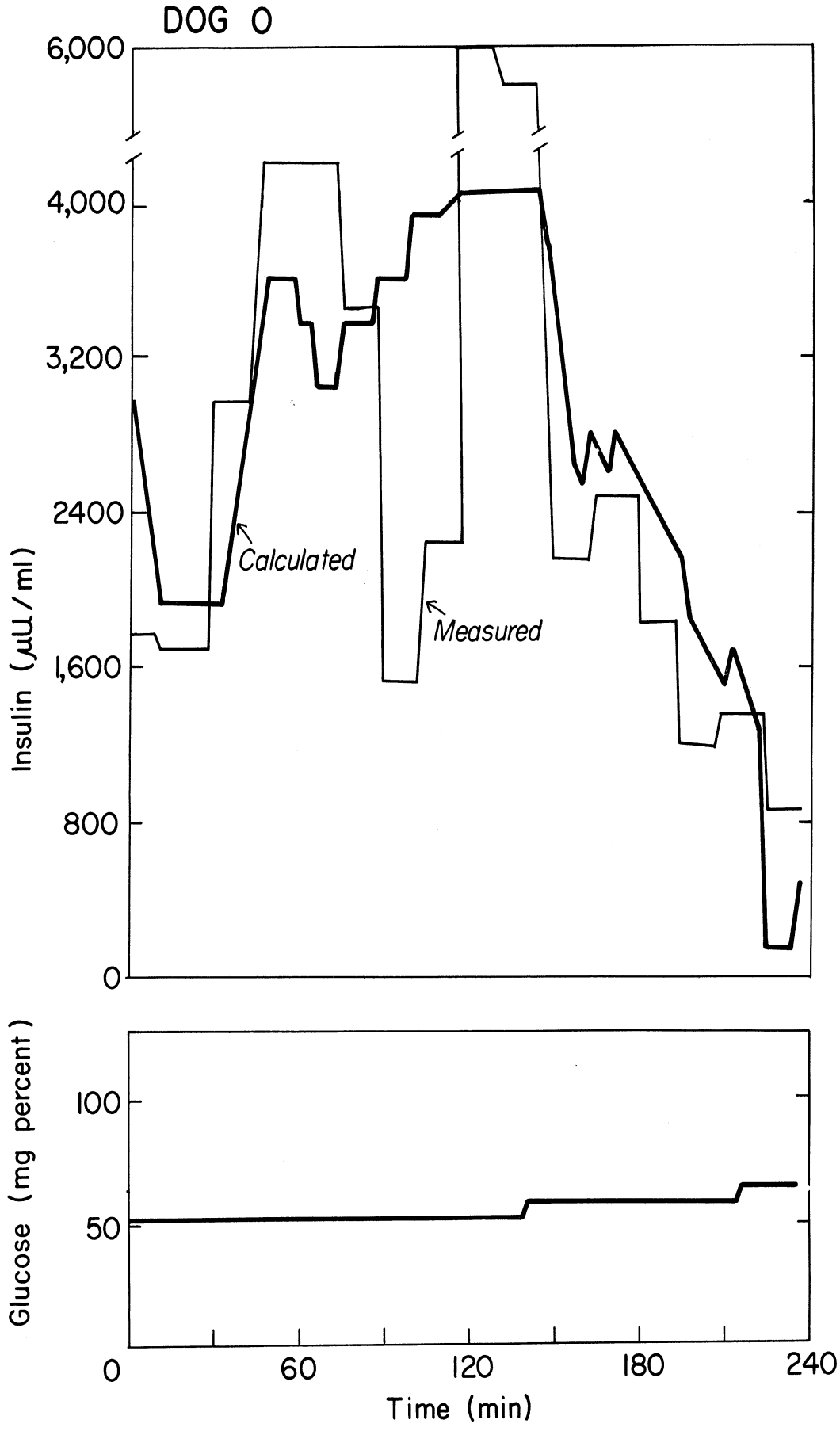

DOG O
6,000
4,000
3,200
2400
1,600
800
0
Insulin (μU/ml)
Calculated
Measured
100
50
0
Glucose (mg percent)
60
120
180
240
Time (min)

Fig. 18

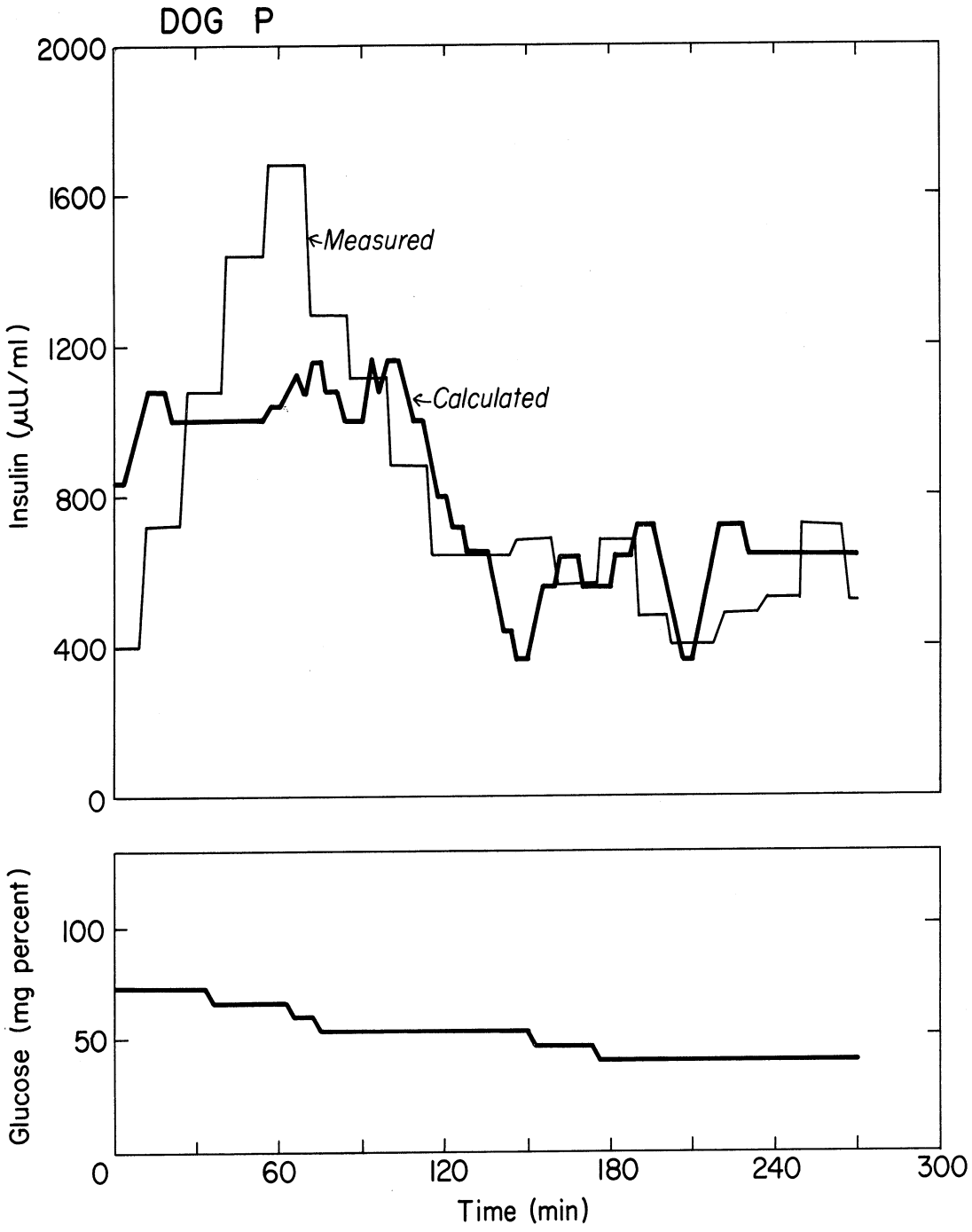

DOG P
2000
1600
1200
800
400
0
Insulin (μU/ml)
←Measured
←Calculated
100
50
0
Glucose (mg percent)
0
60
120
180
240
300
Time (min)

Fig. 19

the data from each experiment to determine the time lags and the values of the coefficients. These results are summarized in Table 5 and are shown in Figures 20 and 21.

TABLE 5

TIME LAGS AND COEFFICIENTS FOR THE MODEL REPRESENTED BY EQUATION (5.1)

Experiment	Lag 1	Lag 2	Lag 3	K1	K2	K3	K4
D	1	18	38	.07	.001	-.70	17.5
E	0	4	45	.41	.74	1.04	83.6
F	0	0	49	.31	.06	-1.5	19.5
I	2	5	65	2.2	16.8	2.58	-281.
J	4	0	35	3.4	-34.2	-4.8	614.
L	18	7	71	13.8	-58.4	-12.6	-612.
M	0	4	0	.34	51.5	2.0	119.
N	4	11	55	-.37	-4.3	-8.9	838.
S	26	9	47	25.8	99.3	7.25	-2276.
T	0	1	50	12.9	16.9	6.0	-717.
U	6	17	52	3.1	21.	85.	-1410.
V	0	6	13	3.3	5.4	34.1	-569.
Control Dogs							
O	8	6	23	-49.2	-41.	-35.1	3002.
P	0	29	47	.04	-15.3	8.9	-94.2

The model describes the phasic nature of the data reasonably well. The correlations of data from dogs D, E, I, J, M, N, S, and U show that the model does not fit the data as well at the maximum and minimum values of the pancreatic venous insulin concentration as it fits at the intermediate values. This result is to be expected since the least squares method was used to determine the coefficients.

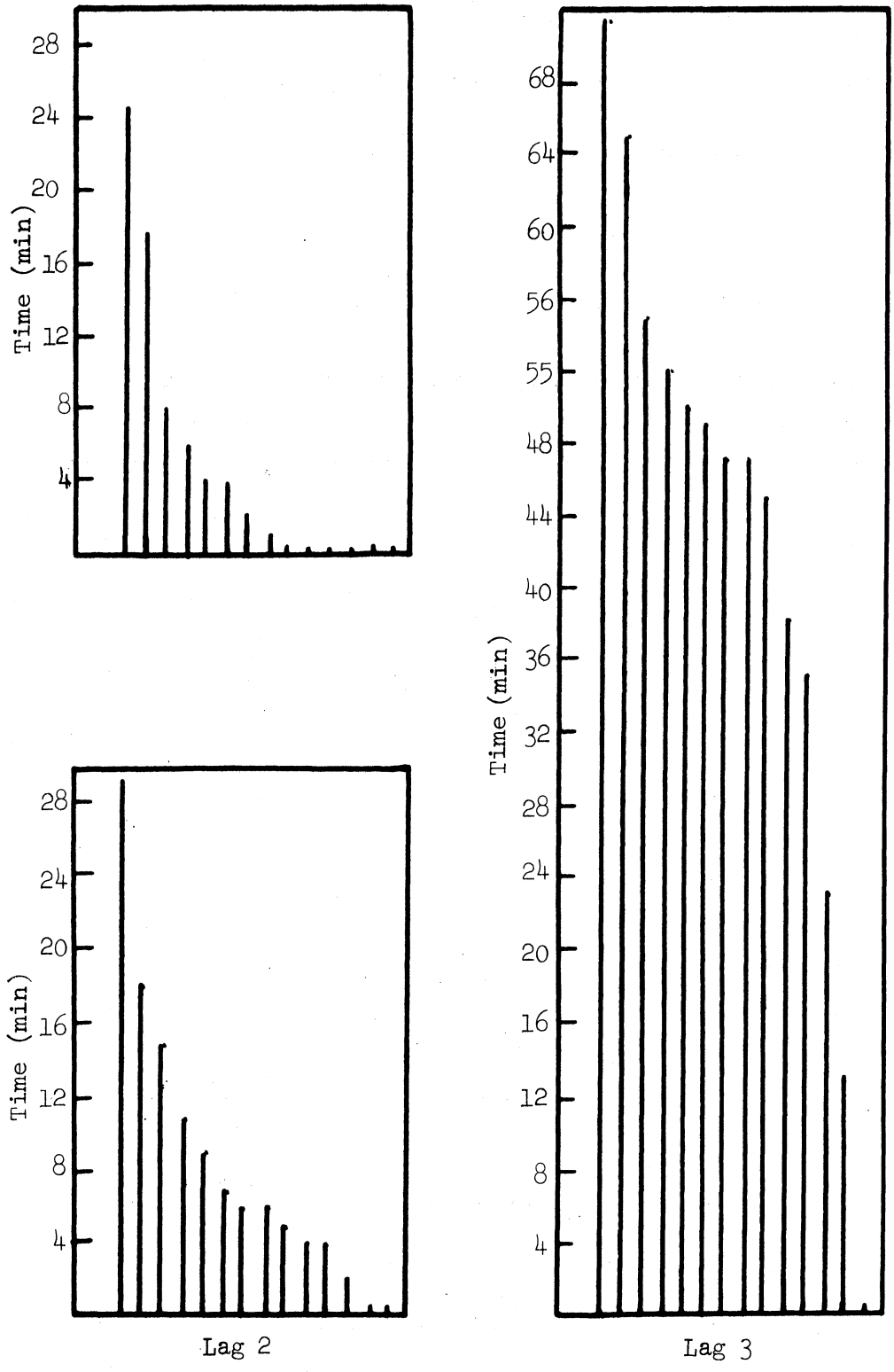


Figure 20 Time Lags for the Model Represented by Equation (5.1) for all the experiments.

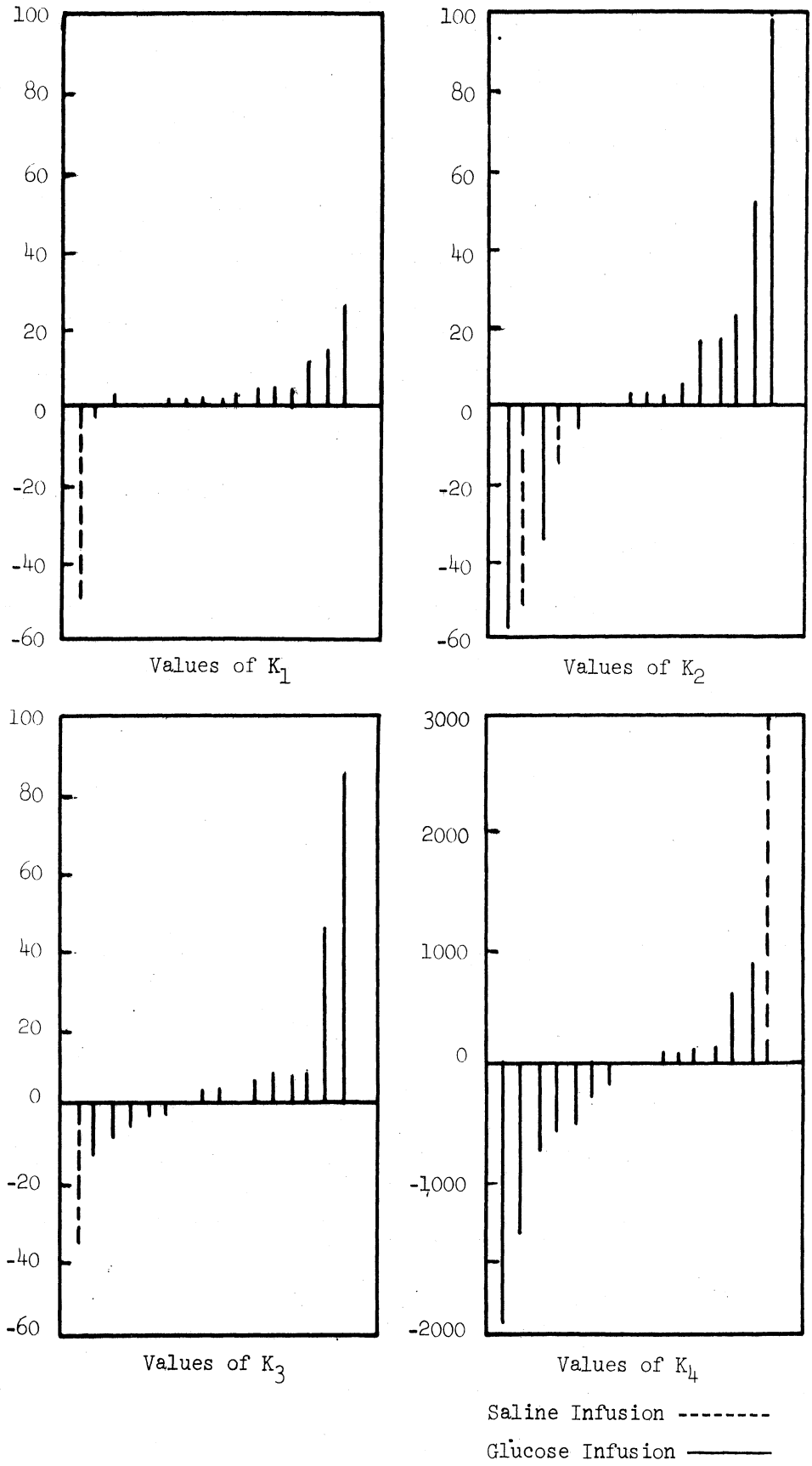


Figure 21 Coefficients for the Model Represented by Equation (5.1) for all the Experiments.

The significance of the different terms in the model was studied by comparing the normalized* integral of the square of the error obtained with different models related to the model of equation (5.1) but lacking certain terms. Table 6 shows the effects of removing various terms from the model given by equation (5.1). Equation (5.1) provided the best correlation of the experimental data in 11 of 12 dogs.

The variation in the pancreatic venous blood flow rate was studied. Using data from nine dogs the predicted insulin concentration was corrected for changes in the pancreatic venous blood flow rate at the time each sample was collected. Equation (5.1) was used to describe the response for the variable blood flow case and for the same experiments assuming the pancreatic venous blood flow rate remained constant throughout the experiment. The normalized integrals of the square of the error for the variable blood flow calculations and for the constant blood flow calculations are given in Table 7. Since the normalized integral of the square of the error is larger for the

---

* The normalized integral of the square of the error is given by:

$$\frac{1}{INS_{ave}} [\Sigma(I(N) - INS(N))^2/N_{max}]^{\frac{1}{2}}$$

where:

$I(N)$	= Predicted pancreatic venous insulin concentration at time N	μU/ml
$INS(N)$	= Measured pancreatic venous insulin concentration at time N	μU/ml
INS_{ave}	= Average measured pancreatic venous insulin concentration	μU/ml
N	= Time	min
N_{max}	= Length of experiment	min

TABLE 6

THE NORMALIZED INTEGRAL OF THE SQUARE OF THE ERROR FOR THE MODEL OF EQUATION:

Experiment	5.1	5.2	5.3	5.4	5.5	5.6	5.7
D	0.484	0.501	0.787	0.484	0.791	0.791	0.988
E	0.540	0.553	0.553	0.540	0.598	0.553	1.10
F	0.347	0.354	0.401	0.348	0.447	0.402	1.11
I	0.568	0.613	0.759	0.583	0.819	0.768	1.23
J	0.442	0.447	0.455	0.443	0.455	0.455	0.578
L	0.274	0.290	0.457	0.276	0.461	0.457	0.831
M	0.281	0.280	0.329	0.291	0.329	0.337	0.692
N	0.687	0.913	0.848	0.687	0.927	0.854	1.09
S	0.530	0.640	0.708	0.531	0.902	0.728	1.47
T	0.336	0.499	0.461	0.338	0.661	0.472	1.37
U	0.532	0.826	0.866	0.535	0.871	0.874	1.20
V	0.510	0.642	0.962	0.511	0.964	0.983	1.46

TABLE 7

EFFECT OF VARIATIONS IN THE PANCREATIC VENOUS BLOOD FLOW RATE

Experiment No.	Normalized Integral of the Square of the Error	
	Variable Blood Flow	Constant Blood Flow
D	0.480	0.484
E	0.536	0.540
F	0.843	0.347
M	0.357	0.281
N	0.781	0.687
S	0.627	0.529
T	0.426	0.336
U	0.548	0.532
V	0.907	0.510

variable blood flow rate calculations in 7 of 9 experiments, variations in the pancreatic venous blood flow rate have not been included in the analysis of any other experiments. All coefficients and lags where calculated from constant blood flow rate data.

Models in which the insulin concentration in the pancreatic vein was dependent upon: 1) an integral of the blood glucose concentration, equation (5.8); 2) the logarithm of the blood glucose concentration, equation (5.9); and 3) the reciprocal of the femoral venous insulin concentration, equation (5.10) were applied to the experimental data. The integral of the square of the error occurring with each of these models was compared to the integral of the square of the error occurring with the model of equation (5.1) in Table 8. Since application of equations (5.8, 5.9, and 5.10) resulted in errors not significantly less than the error associated with equation (5.1), the model of equation (5.1) was used for the determination of the time lags and coefficients.

TABLE 8

THE NORMALIZED INTEGRAL OF THE SQUARE OF THE ERROR FOR THE MODEL REPRESENTED BY EQUATION:

Experiment	5.1	5.8	5.9	5.10
D	0.484	0.474	0.510	0.508
E	0.540	0.521	0.514	0.528
F	0.347	0.325	0.321	0.346
I	0.568	0.535	0.602	0.709
J	0.442	0.421	0.460	0.455
L	0.274	0.289	0.210	0.349
M	0.281	0.273	0.281	0.324
N	0.687	0.694	0.702	0.706
S	0.529	0.542	0.595	0.470
T	0.336	0.307	0.555	0.432
U	0.532	0.523	0.559	0.539
V	0.510	0.500	0.593	0.733

Multivariate Statistical Analysis

Hotelling's T^2 test was used to test for the existence of significant differences in the different models applied to the experimental data from 12 dogs. The significance of the different terms in the model given by equation (5.1) was studied by using Hotelling's T^2 test to determine significant differences in the mean errors occurring when equation (5.1) was applied to the experimental data compared to the mean errors occurring when equations (5.2 - 5.7) were applied. The results are given in Table 9. The F statistic was calculated for $N-p+1=10$ and $p=3$ degrees of freedom. At a 0.90 confidence level F must be greater than 2.73 with $N-p+1=10$

and $p = 3$ for a significant difference to be indicated between the models. Since all the models that were compared to equation (5.1) resulted in a value of F less than 2.73, the probability of being wrong in concluding that the models are significantly different from equation (5.1) is more than 0.10.

TABLE 9

COMPARISON OF DIFFERENT MODELS USING HOTELLING'S T^2 TEST

Models Compared Equation Numbers	F Statistic
5.1 and 5.2	0.10
5.1 5.3	0.53
5.1 5.4	0.07
5.1 5.5	0.14
5.1 5.6	0.40
5.1 5.7	0.27

VII. DISCUSSION

In this chapter the results presented in Chapter VI will be discussed. The experimental results and the results of the mathematical procedures will be considered separately.

Experimental Results

The insulin secretory responses observed during and after glucose infusions were similar to those observed by other investigators (32,39,56). Administration of glucose resulted in increased insulin concentrations in pancreatic venous blood within five minutes. In dogs J, L, M, S, and T the pancreatic venous plasma insulin concentrations reported here are higher than those reported by other investigators (32,39,56). Analytical errors are not likely the cause of these high insulin levels, since several plasma samples were measured using both the double antibody and the paper electrophoresis immunoassays and the results were comparable. These high insulin levels may be related to the location at which the pancreaticoduodenal vein was cannulated or the responsitivity of the pancreas of a given dog.

One inherent problem associated with the determination of a mathematical model of the insulin secretory response of the pancreas is the difficulty in obtaining representative measurements of the input and the output variables. Blood flows into the pancreas from many arteries and blood is drained from the pancreas by many veins making it difficult to obtain an accurate measurement of the pancreatic blood flow rate and the rate of insulin production. The glucose concentration in all the pancreatic arteries can be assumed to be the same without

introducing any significant error. The beta cells, the insulin producing tissue of the pancreas, are not uniformly distributed throughout the organ. Therefore, pancreatic venous blood collected from different veins cannot be expected to have the same insulin concentration. Some investigators have tried to overcome this problem by working with perfused organ or tissue preparations[17,18,24]. These methods introduce many new problems, however.

Inspection of the data in Appendix A showed different pancreatic venous insulin concentrations occurred in the same dog at the same blood glucose concentration at different times during the experiment, indicating the pancreas is responding to some stimulus other than the arterial blood glucose concentration. In some instances this observation could be explained by the derivative term in equation (5.1). Other factors including the effects of growth hormone, adrenal corticoids, epinephrine, glucagon, nembutal, and surgical stress may be causing variations in the response of the pancreas which are not described by the model.

Mathematical Model

Application of equation (5.1) to the data of 14 dogs resulted in the time lags and coefficient values given in Table 5. In 11 of 14 dogs studied Lag 1 was observed to be from 0-7 min and Lag 2 was observed to be from 0-11 min while Lag 3 ranged from 23-65 min. It should be noted that Lag 3 is associated with the response of the pancreas to changes in the peripheral insulin concentration and is not the lag between changes in arterial blood glucose concentration and peripheral

venous insulin concentration. The values determined for Lag 1 are in the same range as those values reported by Seltzer[57], 0-5 min and Gjedde[23], 0-2 min. No values for Lag 2 or Lag 3 have been reported.

The values of the coefficients K1, K2, and K3 represent the responsitivity of the pancreas to changes in the blood glucose and insulin concentrations. In 7 of 12 dogs the values of K2 exceeded K1. Since the magnitude of the time derivative of the blood glucose concentration is generally smaller than the magnitude of the blood glucose concentration, K2 must be larger than K1 if the derivative term is to have a significant effect on the response. K3 was observed to have positive as well as negative values. Positive values of K3 imply high peripheral insulin concentrations result in more insulin secretion. This does not agree with the inhibitory effect of insulin on the pancreas suggested by Logothetopoulos[35] and by Hausberger[27]. Another investigator has reported that insulin secretion was not effected by insulin itself[37]. The large variability in the values of the coefficients may be due to differences in: 1) the responsiveness to glucose of the dogs studied, 2) the location at which the pancreaticoduodenal vein was cannulated and 3) the distribution of beta cells within the pancreas. Variables which were not measured or included in the model, such as changes in the plasma epinephine or growth hormone concentrations, may also be partly responsible for the variations in the coefficients and the errors between the measured and predicted pancreatic venous insulin concentrations.

Inspection of the data in Table 6 shows that in 11 of 12 dogs equation (5.1) is the best representation of the insulin secretory

response of the pancreas. The contributions of the derivative and the negative feedback terms are small but generally reduce the integral of the square of the error. Therefore, for an individual dog the four term equation (5.1) is the "best" model. This model indicates the absolute level of the blood glucose concentration is the greatest factor in determining pancreatic insulin secretion. The derivative term functions to provide more rapid response to fast changes in blood glucose concentration and the peripheral or negative feedback term protects the animal from excess insulin secretion. A model containing the derivative of the input represents a system having infinite gain at high frequencies. Since the frequency range associated with the input to the pancreas is very low and is bounded, this is not a serious problem.

The physiological mechanism for the derivative response is not known at this time. Recently Frohman and associates have shown that vagal stimulation results in augmented insulin secretion and vagotomy in reduced insulin secretion[21]. These effects were reported to be independent of the larger response of the pancreas to blood glucose. Since derivative control mechanisms have been shown to be present in neurological control systems, vagal control of part of the insulin secretory response of the pancreas may explain the mechanism for the derivative term. Additional experimentation will be necessary before any conclusion can be made. It may be noted that biological systems have been shown to respond to the rates of change of stimuli as well as to the absolute magnitude of the stimuli. One example of such a system is the carotid sinus baroreceptor which responds to the rate of change of blood pressure as well as to the absolute magnitude of the blood pressure[19].

Multivariate Statistical Analysis

Utilization of statistical methods to determine significant differences between two models is difficult when the models have been applied to time series data. Univariate statistical tests are based on independence assumptions. Therefore, multivariate statistical procedures must be used to analyze time series.

While it was possible to show that the addition of various terms to the model reduced the integral of the square of the error for a given dog, application of Hotelling's T^2 test to determine significant differences in the mean errors resulting from the application of different models to the data from 12 dogs together showed no differences between the average performance for any of the models. Although large differences in mean errors occurred between the different models, the elements of the covariance matrix were much larger. This produced an inverse covariance matrix composed of very small numbers. Multiplication by this inverse covariance matrix produced small values for the F statistic.

Spectral Analysis

Spectral analysis provides a systematic method for determining the mathematical relationship which exists between the input and the output of a linear system[5,6]. Spectral analysis is applied to a set of experimental data by first determining the autocorrelation function of the input variable and the cross-correlation function between the input and the output variables. Second, the power spectral density function of the input and the cross-spectral density function between the input and the output variables are calculated. The power or cross-spectral

density function is the Fourier transform of the appropriate correlation function. The transfer function can now be determined as the quotient of the cross-spectral density function divided by the power spectral density function of the input.

Application of spectral analysis to the experimental data was inconclusive. The difficulty encountered may be due to the relatively short records available and the low frequency range of the data. The possibility of a computational error could not be totally eliminated.

Conclusions

A model was developed which permitted reasonably accurate prediction of the pancreatic venous insulin concentration as a function of the time history of the arterial blood glucose concentration and the peripheral venous insulin concentration. A record of the pancreatic venous insulin concentration, peripheral venous insulin concentration, and arterial blood glucose concentration was used to determine the parameters of the model. Of the variables studied, the arterial blood glucose concentration is the most important factor in determining pancreatic insulin output. This response is augmented by a response which is proportional to the time derivative of the blood glucose concentration. In some experiments a negative feedback effect of the peripheral insulin concentration on pancreatic venous insulin concentration was observed. In three-quarters of the dogs studied time lags from 0-6 min were associated with the response of the pancreas to changes in the blood glucose concentration, lags from 0-7 min were associated with the response to the derivative of the blood glucose concentration, and lags

from 15-55 min were associated with the response to changes in peripheral insulin. The values of the time lags and the coefficients of equation (5.1) varied greatly in the different experiments, consequently it was not possible to estimate a set of average time lags and coefficients which could be used to predict the response of the pancreas to changes in the blood glucose concentration in any normal dog. These variations may have been caused by the following: 1) differences in the responsiveness of the pancreas in different dogs, 2) variations in the location at which the pancreaticoduodenal vein was cannulated with respect to the distribution of the beta cells in the pancreas, and 3) changes in the levels of other hormones which effect the insulin secretory response of the pancreas.

Multivariate statistics were applied to determine significant differences between different models. The variability of the data was so great that these techniques did not show any difference between the models tested.

Spectral analysis was applied to estimate a transfer function describing the insulin secretory response of the pancreas. It was not possible to obtain a satisfactory transfer function by this method. The relatively short records available and the low frequency range of the data may be preventing an accurate determination of the transfer function.

APPENDIX A

EXPERIMENTAL DATA AND PREDICTED PANCREATIC VENOUS INSULIN CONCENTRATIONS FOR ALL THE EXPERIMENTS

TABLE 10

EXPERIMENTAL DATA AND CORRELATION FOR DOG D

TIME MIN	GLUCOSE MG PCT	DG/DT	FEMORAL INSULIN MU U/ML	BLOOD FLOW ML/MIN	MEASURED PANCREATIC INSULIN ML/ML	ESTIMATED PANCREATIC INSULIN MU U/ML	ERROR MU U/ML	PERCENT ERROR	TERM 1	TERM 2	TERM 3	TERM 4
1	350	.00	8	.23	87	232	145	167	36	0	-42	239
4	230	.00	11	.23	194	391	197	101	194	0	-42	239
7	236	.00	14	.23	194	348	154	79	152	0	-42	239
10	214	.00	17	.25	160	336	176	110	139	0	-42	239
13	217	.00	20	.18	209	332	123	59	135	0	-42	239
16	220	.00	23	.18	209	334	125	60	137	0	-42	239
19	224	136.50	25	.20	404	337	-67	-17	140	0	-42	239
22	225	-30.00	28	.20	396	339	-57	-14	142	-0	-42	239
25	233	-6.00	30	.20	396	342	-54	-14	145	-0	-42	239
28	237	-3.50	33	.20	500	344	-156	-31	148	-0	-42	239
31	280	1.00	36	.20	500	347	-153	-31	150	0	-42	239
34	333	1.50	39	.20	500	409	-91	-18	212	0	-42	239
37	333	1.00	41	.20	500	406	-94	-19	210	0	-42	239
40	330	1.50	44	.20	500	392	-108	-22	207	0	-55	239
43	334	1.50	47	.20	500	375	-125	-25	209	0	-73	239
46	339	1.50	50	.20	500	359	-141	-28	211	0	-91	239
49	344	50.00	52	.20	500	344	-156	-31	214	0	-109	239
52	347	-1.50	55	.20	500	334	-166	-33	217	-0	-121	239
55	349	-1.50	58	.20	500	317	-183	-37	218	-0	-140	239
58	351	.00	60	.26	260	300	40	16	219	0	-158	239
61	353	1.50	63	.26	260	284	24	9	221	0	-176	239
64	356	1.50	65	.21	230	273	43	19	222	0	-188	239
67	358	1.50	66	.21	230	256	26	11	224	0	-206	239
70	360	.50	64	.21	230	239	9	4	225	0	-225	239
73	343	.50	63	.23	181	215	34	19	219	0	-243	239
76	324	1.00	61	.23	181	191	10	6	207	0	-255	239
79	307	1.00	60	.23	181	164	-17	-9	198	0	-273	239
82	294	.50	58	.23	181	134	-47	-26	186	0	-291	239
85	285	.75	57	.20	144	116	-28	-19	180	0	-303	239
88	276	-2.00	55	.20	144	92	-52	-36	175	-0	-322	239
91	268	-6.50	54	.21	116	68	-48	-41	169	-0	-340	239
94	262	-6.00	52	.21	116	46	-70	-60	165	-0	-358	239
97	256	-8.00	51	.21	116	30	-86	-74	162	-0	-370	239
100	250	-3.00	49	.24	67	8	-59	-87	158	-0	-388	239
103	242	-3.00	48	.24	67	-7	-74	-111	154	-0	-401	239
106	235	-3.00	46	.22	59	-7	-66	-112	149	-0	-394	239
109	227	-2.00	45	.21	69	-5	-74	-108	144	-0	-388	239
112	222	-2.00	43	.21	69	2	-67	-97	140	-0	-376	239
115	219	-2.00	43	.21	69	7	-62	-90	138	-0	-370	239
118	216	-2.00	43	.23	61	17	-44	-72	136	-0	-358	239
121	214	-3.00	43	.23	61	21	-40	-66	134	-0	-352	239
124	214	-2.00	43	.23	63	33	-30	-47	134	-0	-340	239
127	340	-3.00	44	.27	79	68	-11	-14	163	-0	-334	239
130	260	-1.00	44	.27	61	105	44	73	188	-0	-322	239
133	271	-1.00	45	.23	66	91	25	37	167	-0	-316	239
136	283	-1.00	46	.20	67	110	43	65	175	-0	-303	239
139	295	.00	46	.22	66	124	58	88	182	0	-297	239
142	303	.00	47	.22	66	142	76	116	189	0	-285	239
145	310	40.00	47	.25	68	153	85	125	193	0	-279	239
148	316	-18.50	48	.25	68	169	101	148	197	-0	-267	239
151	320	4.00	49	.25	83	179	96	115	201	0	-261	239
154	322	4.00	49	.25	83	179	96	116	201	0	-261	239
157	324	4.00	50	.25	81	180	99	123	202	0	-261	239
160	326	2.00	50	.25	81	182	101	124	204	0	-261	239
163	327	2.00	51	.26	80	183	103	128	205	0	-261	239
166	329	2.00	52	.26	80	177	97	122	206	0	-267	239
169	330	.50	52	.26	62	172	110	178	206	0	-273	239
172	326	.50	52	.26	62	172	110	177	206	0	-273	239
175	320	.75	52	.26	62	162	100	161	202	0	-279	239

LAG1 = 1, LAG2 = 18, LAG3 = 38

K1 = .072068, K2 = 1.365341E-03, K3 = -.697925

K4 = 17.472030, SUM = 5.347178E+05, HCT = .500000

NMAX = 176, NORMER = .484175, AVGINS = 198.310734

TABLE 11

EXPERIMENTAL DATA AND CORRELATION FOR DOG E

TIME MIN	GLUCOSE MG PCT	DG/DT	FEMORAL INSULIN MU U/ML	BLOOD FLOW ML/MIN	MEASURED PANCREATIC INSULIN MU/ML	ESTIMATED PANCREATIC INSULIN MU U/ML	ERROR MU U/ML	PERCENT ERROR	TERM 1	TERM 2	TERM 3	TERM 4
1	72	.00	10	.22	100	1225	1125	1125	271	0	94	860
4	72	.00	11	.22	100	1225	1125	1125	271	0	94	860
7	76	.00	13	.22	100	1240	1140	1140	286	0	94	860
10	84	2.00	14	.22	600	1274	674	112	316	3	94	860
13	92	2.00	15	.24	600	1304	704	117	346	3	94	860
16	101	2.50	17	.24	600	1338	738	123	380	4	94	860
19	109	2.50	18	.24	600	1369	769	128	410	4	94	860
22	116	3.00	19	.26	850	1396	546	64	436	5	94	860
25	122	2.00	21	.26	850	1417	567	67	459	3	94	860
28	127	1.50	22	.21	2150	1435	-715	-33	478	3	94	860
31	132	1.50	21	.21	2150	1453	-697	-32	496	3	94	860
34	140	1.50	19	.21	3050	1483	-1567	-51	526	3	94	860
37	151	3.00	17	.22	3050	1527	-1523	-50	568	5	94	860
40	161	4.00	15	.22	3050	1567	-1483	-49	605	7	94	860
43	171	3.50	13	.22	3050	1603	-1447	-47	643	6	94	860
46	176	3.00	11	.24	2300	1621	-679	-30	662	5	94	860
49	180	1.50	9	.24	2300	1643	-657	-29	677	3	104	860
52	184	1.50	7	.24	2300	1677	-623	-27	692	3	122	860
55	186	1.00	5	.24	2150	1693	-457	-21	699	2	132	860
58	188	.50	3	.24	2150	1709	-441	-20	707	1	141	860
61	192	.50	3	.24	2150	1743	-407	-19	722	1	160	860
64	199	1.50	5	.24	2150	1781	-369	-17	748	3	170	860
67	205	2.00	8	.24	2400	1814	-586	-24	771	3	179	860
70	212	2.00	11	.24	2400	1859	-541	-23	797	3	198	860
73	218	2.50	13	.24	2400	1892	-508	-21	820	4	207	860
76	224	2.00	16	.23	2100	1904	-196	-9	842	3	198	860
79	228	2.00	18	.23	2100	1900	-200	-10	857	3	179	860
82	232	1.50	21	.23	2100	1895	-205	-10	872	3	160	860
85	232	1.50	24	.23	2100	1877	-223	-11	872	3	141	860
88	232	.00	27	.23	2200	1855	-345	-16	872	0	122	860
91	232	.00	29	.23	2200	1836	-364	-17	872	0	104	860
94	218	.00	32	.23	2200	1765	-435	-20	820	0	85	860
97	190	-7.00	35	.23	1300	1629	329	25	715	-12	66	860
100	200	-8.00	38	.23	1300	1646	346	27	752	-14	47	860
103	213	4.00	41	.23	1300	1696	396	30	801	7	28	860
106	222	4.50	44	.23	1300	1731	431	33	835	8	28	860
109	230	3.00	47	.24	1100	1777	677	62	865	5	47	860
112	240	2.50	50	.24	1100	1842	742	67	903	4	75	860
115	246	3.50	53	.24	1100	1895	795	72	925	6	104	860
118	252	2.00	56	.16	1550	1934	384	25	948	3	122	860
121	258	2.00	59	.16	1550	1985	435	28	970	3	151	860
124	264	2.00	62	.16	1550	2026	476	31	993	3	170	860
127	270	2.00	65	.16	1950	2077	127	7	1015	3	198	860
130	276	2.00	68	.16	1950	2128	178	9	1038	3	226	860
133	281	2.00	71	.16	1950	2175	225	12	1057	3	254	860
136	284	1.50	74	.16	1950	2204	254	13	1068	3	273	860
139	287	1.00	77	.16	1950	2243	293	15	1079	2	301	860
142	290	1.00	80	.16	4550	2282	-2268	-50	1091	2	330	860
145	300	1.00	83	.16	4550	2348	-2202	-48	1128	2	358	860
148	313	4.00	86	.16	4550	2430	-2120	-47	1177	7	386	860
151	326	4.00	89	.16	4550	2507	-2043	-45	1226	7	414	860
154	333	4.50	92	.25	3400	2563	-837	-25	1252	8	443	860
157	337	1.50	93	.25	3400	2601	-799	-23	1267	3	471	860

TABLE 11 (CONT'D)

160	340	1.50	87	.25	3400	2641	-759	-22	1279	3	499	860
163	273	1.00	81	.25	3150	2416	-734	-23	1027	2	528	860
166	243	-14.50	75	.25	3150	2305	-845	-27	914	-24	556	860
169	215	-10.00	69	.25	3150	2236	-914	-29	809	-17	584	860
172	184	-10.00	63	.22	2000	2148	148	7	692	-17	612	860
175	172	-10.50	57	.22	2000	2130	130	6	647	-18	641	860
178	162	-3.00	51	.22	2000	2133	133	7	609	-5	669	860
181	154	-3.50	45	.25	2850	2131	-719	-25	579	-6	697	860
184	146	-3.00	39	.25	2850	2130	-720	-25	549	-5	725	860
187	140	-2.00	36	.25	2850	2137	-713	-25	526	-3	754	860
190	134	-2.00	33	.24	1550	2143	593	38	504	-3	782	860
193	129	-2.00	30	.24	1550	2152	602	39	485	-3	810	860
196	126	-1.50	27	.24	1550	2170	620	40	474	-3	838	860
199	123	-1.00	24	.24	1550	2188	638	41	463	-2	867	860
202	120	-1.00	21	.25	800	2186	1386	173	451	-2	876	860
205	117	-1.00	18	.25	800	2118	1318	165	440	-2	820	860
208	114	-1.00	15	.25	800	2050	1250	156	429	-2	763	860
211	111	-1.00	12	.25	200	1982	1782	891	417	-2	706	860
214	109	-1.00	10	.25	200	1918	1718	859	410	-2	650	860
217	108	-.50	10	.25	200	1858	1658	829	405	-1	593	860
220	107	-.40	12	.20	2300	1797	-503	-22	401	-1	537	860
223	105	-.45	18	.33	3850	1735	-2115	-55	395	-1	480	860
226	136	-.50	24	.24	2900	1795	-1105	-38	511	-1	424	860
229	180	16.00	30	.24	2900	1932	-968	-33	677	27	367	860
232	224	15.00	36	.24	2900	2067	-833	-29	842	25	339	860
235	242	14.50	42	.24	2900	2106	-794	-27	910	24	311	860
238	255	5.00	48	.24	2900	2110	-790	-27	959	8	283	860
241	270	4.50	52	.24	2900	2138	-762	-26	1015	8	254	860
244	285	5.00	55	.24	2900	2167	-733	-25	1072	8	226	860
247	301	5.50	58	.43	1425	2199	774	54	1132	9	198	860
250	317	5.50	61	.28	900	2231	1331	148	1192	9	170	860
253	332	5.50	64	.28	900	2259	1359	151	1249	9	141	860
256	344	5.00	67	.12	1050	2275	1225	117	1294	8	113	860
259	356	4.00	70	.12	1050	2300	1250	119	1339	7	94	860
262	368	4.00	73	.12	1050	2345	1295	123	1384	7	94	860
265	378	4.00	76	.40	50	2402	2352	4703	1422	7	113	860
268	388	3.00	79	.40	50	2494	2444	4888	1459	5	170	860
271	397	3.50	82	.40	50	2585	2535	5070	1493	6	226	860

LAG1 = 0, LAG2 = 4, LAG3 = 45

K1 = .413668, K2 = .743070, K3 = 1.036188

K4 = 83.626175, SUM = 9.982430E+07, HCT = .500000

NMAX = 272, NORMER = .539604, AVGINS = 1951.739914

TABLE 12

EXPERIMENTAL DATA AND CORRELATION FOR DOG F

TIME MIN	GLUCOSE MG PCT	DG/DT	FEMORAL INSULIN MU U/ML	BLOOD FLOW ML/MIN	MEASURED PANCREATIC INSULIN MU/ML	ESTIMATED PANCREATIC INSULIN MU U/ML	ERROR MU U/ML	PERCENT ERROR	TERM 1	TERM 2	TERM 3	TERM 4
1	130	22.50	34	.15	50	216	166	331	524	16	-634	309
4	152	-2.00	40	.15	100	287	187	187	613	-1	-634	309
7	148	-1.50	46	.15	260	271	11	4	597	-1	-634	309
10	143	.50	20	.15	260	252	-8	-3	577	0	-634	309
13	149	2.50	20	.07	260	278	18	7	601	2	-634	309
16	156	2.00	20	.07	260	306	46	18	629	1	-634	309
19	162	2.00	20	.05	520	330	-190	-37	653	1	-634	309
22	166	1.00	21	.05	520	345	-175	-34	670	1	-634	309
25	170	1.50	21	.05	520	362	-158	-30	686	1	-634	309
28	174	1.50	21	.05	520	378	-142	-27	702	1	-634	309
31	178	2.00	22	.07	300	394	94	31	718	1	-634	309
34	184	2.00	22	.07	300	419	119	40	742	1	-634	309
37	190	2.00	22	.07	300	443	143	48	766	1	-634	309
40	196	-1.00	23	.07	300	465	165	55	791	-1	-634	309
43	187	-2.50	23	.09	160	427	267	167	754	-2	-634	309
46	180	-2.50	23	.09	160	399	239	150	726	-2	-634	309
49	172	-2.50	23	.09	160	367	207	129	694	-2	-634	309
52	168	-1.00	23	.09	210	233	23	11	678	-1	-753	309
55	165	-1.00	23	.08	210	102	-108	-51	666	-1	-872	309
58	162	-1.00	23	.08	210	-29	-239	-114	653	-1	-991	309
61	159	-1.00	23	.07	270	554	284	105	641	-1	-397	309
64	156	-1.00	23	.07	270	541	271	101	629	-1	-397	309
67	153	-1.00	23	.07	270	529	259	96	617	-1	-397	309
70	150	-1.00	24	.08	270	497	227	84	605	-1	-416	309
73	147	-1.00	24	.08	320	485	165	52	593	-1	-416	309
76	144	-1.00	24	.08	320	473	153	48	581	-1	-416	309
79	141	-1.00	24	.08	320	441	121	38	569	-1	-436	309
82	140	.00	24	.10	860	438	-422	-49	565	0	-436	309
85	220	40.00	24	.10	860	790	-70	-8	887	29	-436	309
88	200	-10.00	24	.09	980	673	-307	-31	807	-7	-436	309
91	181	3.50	25	.09	980	586	-394	-40	730	3	-456	309
94	194	4.50	23	.09	980	639	-341	-35	783	3	-456	309
97	207	4.00	20	.09	980	691	-289	-29	835	3	-456	309
100	220	3.50	15	.10	1100	743	-357	-32	887	3	-456	309
103	229	3.00	15	.10	1100	779	-321	-29	924	2	-456	309
106	238	3.00	15	.10	1100	816	-284	-26	960	2	-456	309
109	247	3.00	15	.10	1100	852	-248	-23	996	2	-456	309
112	255	2.50	15	.10	1100	884	-216	-20	1029	2	-456	309
115	262	2.50	15	.08	900	912	12	1	1057	2	-456	309
118	269	2.50	15	.08	900	940	40	4	1085	2	-456	309
121	276	2.00	16	.10	940	948	8	1	1113	1	-476	309
124	365	-2.50	16	.10	940	1304	364	39	1472	-2	-476	309
127	350	-7.00	16	.10	1100	1240	140	13	1412	-5	-476	309
130	330	-1.50	16	.10	1100	1164	64	6	1331	-1	-476	309
133	338	2.50	16	.10	1100	1199	99	9	1363	2	-476	309
136	345	2.50	16	.10	1220	1227	7	1	1392	2	-476	309
139	352	2.00	16	.10	1220	1235	15	1	1420	1	-496	309

LAG1 = 0, LAG2 = 0, LAG3 = 49

K1 = .302541, K2 = .218062, K3 = -1.487083

K4 = 19.457024, SUM = 2.046324E+06, HCT = .500000

NMAX = 141, NORMER = .346748, AVGINS = 601.760559

TABLE 13

EXPERIMENTAL DATA AND CORRELATION FOR DOG I

TIME MIN	GLUCOSE MG PCT	DG/DT	FEMORAL INSULIN MU U/ML	BLOOD FLOW ML/MIN	MEASURED PANCREATIC INSULIN MU/ML	ESTIMATED PANCREATIC INSULIN MU U/ML	ERROR MU U/ML	PERCENT ERROR	TERM 1	TERM 2	TERM 3	TERM 4
1	66	.00	18	.25	175	-773	-948	-542	1008	0	289	-2070
4	94	.00	30	.25	1625	-444	-2069	-127	1337	0	289	-2070
7	122	9.30	41	.25	1625	361	-1264	-78	1830	312	289	-2070
10	150	9.30	50	.25	2525	855	-1670	-66	2324	312	289	-2070
13	159	9.30	57	.25	2525	1239	-1286	-51	2707	312	289	-2070
16	169	3.10	60	.25	1595	1195	-400	-25	2872	104	289	-2070
19	178	3.10	63	.25	2462	1359	-1103	-45	3036	104	289	-2070
22	183	3.10	66	.25	2462	1524	-938	-38	3201	104	289	-2070
25	187	2.10	69	.25	2462	1549	-913	-37	3259	70	289	-2070
28	190	1.10	72	.25	2850	1573	-1277	-45	3318	37	289	-2070
31	193	1.10	75	.25	2850	1632	-1218	-43	3376	37	289	-2070
34	194	1.10	78	.25	1838	1669	-169	-9	3413	37	289	-2070
37	196	.50	81	.25	1838	1675	-163	-9	3440	17	289	-2070
40	197	.50	84	.25	400	1702	1302	325	3466	17	289	-2070
43	201	.50	87	.25	400	1742	1342	336	3507	17	289	-2070
46	205	1.30	92	.25	1162	1838	676	58	3576	44	289	-2070
49	209	1.30	101	.25	1425	1907	482	34	3645	44	289	-2070
52	214	1.30	110	.25	1425	1976	551	39	3714	44	289	-2070
55	221	1.75	119	.25	1300	2108	808	62	3830	59	289	-2070
58	228	2.20	128	.25	1300	2240	940	72	3947	74	289	-2070
61	232	2.20	137	.25	2288	2357	69	3	4064	74	289	-2070
64	232	2.20	143	.25	4600	2395	-2205	-48	4103	74	289	-2070
67	232	.00	149	.25	4600	2487	-2113	-46	4103	0	455	-2070
70	232	.00	155	.25	4275	2735	-1540	-36	4103	0	703	-2070
73	231	.00	161	.25	4275	2933	-1342	-31	4094	0	909	-2070
76	229	-.50	167	.25	1788	3076	1288	72	4067	-17	1095	-2070
79	228	-.50	175	.25	1788	3152	1364	76	4041	-17	1199	-2070
82	226	-.50	184	.25	1788	3188	1400	78	4014	-17	1261	-2070
85	224	-.55	196	.25	1437	3216	1779	124	3982	-18	1323	-2070
88	222	-.60	208	.25	1437	3245	1808	126	3951	-20	1385	-2070
91	212	-.60	214	.25	3050	3275	225	7	3919	-20	1447	-2070
94	183	-.60	216	.25	3050	2990	-60	-2	3572	-20	1509	-2070
97	155	-9.50	217	.25	1275	2250	975	76	3068	-319	1571	-2070
100	126	-9.50	219	.25	1737	1808	71	4	2564	-319	1633	-2070
103	110	-9.50	221	.25	1737	1438	-299	-17	2133	-319	1695	-2070
106	94	-5.40	213	.25	1437	1351	-86	-6	1846	-181	1757	-2070
109	77	-5.40	186	.25	1088	1127	39	4	1560	-181	1819	-2070
112	67	-5.40	159	.25	1088	985	-103	-9	1273	-181	1963	-2070
115	60	-3.95	132	.25	600	1087	487	81	1141	-133	2149	-2070
118	52	-2.50	108	.25	600	1189	589	98	1008	-84	2335	-2070
121	49	-2.50	92	.25	637	1242	605	95	875	-84	2521	-2070
124	53	-2.50	94	.25	637	1441	804	126	888	-84	2707	-2070
127	58	1.65	96	.25	950	1830	880	93	973	55	2873	-2070
130	63	1.60	98	.25	863	2038	1175	136	1058	54	2997	-2070
133	64	1.60	100	.25	863	2225	1362	158	1121	54	3121	-2070
136	65	.40	102	.25	938	2330	1392	148	1142	13	3245	-2070
139	67	.40	104	.25	938	2475	1537	164	1164	13	3369	-2070
142	71	.40	107	.25	595	2641	2046	344	1185	13	3514	-2070
145	76	1.10	108	.25	1063	2926	1863	175	1280	37	3679	-2070
148	81	1.80	110	.25	1063	3231	2168	204	1376	60	3865	-2070
151	88	1.80	113	.25	4075	3595	-480	-12	1471	60	4134	-2070
154	95	1.80	140	.25	6125	3963	-2162	-35	1592	60	4382	-2070
157	103	2.50	167	.25	6125	4181	-1944	-32	1724	84	4444	-2070
160	110	2.50	194	.25	7800	4335	-3465	-44	1857	84	4464	-2070
163	113	2.50	221	.25	7800	4482	-3318	-43	1963	84	4506	-2070
166	116	1.00	238	.25	5100	4526	-574	-11	2016	34	4547	-2070
169	119	1.00	238	.25	5100	4620	-480	-9	2069	34	4588	-2070
172	122	1.00	238	.25	5100	4301	-799	-16	2122	34	4216	-2070
175	125	1.00	239	.25	4150	3796	-354	-9	2175	34	3658	-2070
178	128	1.00	239	.25	4150	3292	-858	-21	2228	34	3100	-2070
181	131	1.00	240	.25	2750	2787	37	1	2281	34	2542	-2070
184	135	1.00	240	.25	2750	2373	-377	-14	2343	34	2067	-2070

LAG1 = 2, LAG2 = 5, LAG3 = 65

K1 = 2.210507, K2 = 16.782595, K3 = 2.583465

K4 = -280.676727, SUM = 1.062105E+08, HCT = .500000

NMAX = 184, NORMER = .567604, AVGINS = 2324.735107

TABLE 14

EXPERIMENTAL DATA AND CORRELATION FOR DOG J

TIME MIN	GLUCOSE MG PCT	DG/DT	FEMORAL INSULIN MU U/ML	BLOOD FLOW ML/MIN	MEASURED PANCREATIC INSULIN MU/ML	ESTIMATED PANCREATIC INSULIN MU U/ML	ERROR MU U/ML	PERCENT ERROR	TERM 1	TERM 2	TERM 3	TERM 4
1	73	.00	23	.30	9100	14299	5199	57	1648	-0	-544	13195
4	114	.00	41	.30	9100	15199	6099	67	2548	-0	-544	13195
7	154	13.40	59	.30	11700	15337	3637	31	3450	-764	-544	13195
10	194	13.40	77	.30	12400	16242	3842	31	4355	-764	-544	13195
13	211	13.45	95	.30	12400	16630	4230	34	4746	-767	-544	13195
16	229	5.80	110	.30	13600	17457	3857	28	5136	-331	-544	13195
19	246	5.80	115	.30	13600	17847	4247	31	5527	-331	-544	13195
22	259	5.80	115	.30	13500	18139	4639	34	5819	-331	-544	13195
25	270	3.60	115	.30	13500	18507	5007	37	6061	-205	-544	13195
28	281	3.60	116	.30	13500	18750	5250	39	6304	-205	-544	13195
31	287	3.60	116	.30	15700	18889	3189	20	6443	-205	-544	13195
34	284	1.30	116	.30	15700	18953	3253	21	6376	-74	-544	13195
37	281	-1.00	116	.30	15700	18633	2933	19	6308	57	-928	13195
40	278	-1.00	117	.30	15700	17989	2289	15	6241	57	-1504	13195
43	278	-1.00	117	.30	14800	17413	2613	18	6241	57	-2081	13195
46	278	.00	117	.30	14800	16780	1980	13	6241	-0	-2657	13195
49	278	.00	118	.30	14800	16236	1436	10	6241	-0	-3201	13195
52	265	.00	118	.30	14800	15468	668	5	5954	-0	-3681	13195
55	246	-6.40	118	.30	14800	15402	602	4	5523	365	-3681	13195
58	227	-6.40	119	.30	15700	14971	-729	-5	5092	365	-3681	13195
61	217	-6.40	119	.30	15700	14753	-947	-6	4874	365	-3681	13195
64	226	-1.65	119	.30	15700	14659	-1041	-7	5083	94	-3713	13195
67	236	3.10	120	.30	16400	14597	-1803	-11	5291	-177	-3713	13195
70	245	3.10	120	.30	16400	14806	-1594	-10	5500	-177	-3713	13195
73	224	3.10	120	.30	16400	14302	-2098	-13	5029	-177	-3745	13195
76	203	-7.00	120	.30	18900	14407	-4493	-24	4557	399	-3745	13195
79	182	-7.00	120	.30	18900	13936	-4964	-26	4086	399	-3745	13195
82	155	-7.00	120	.30	18900	13329	-5571	-29	3480	399	-3745	13195
85	125	-10.00	120	.30	18900	12795	-6105	-32	2806	570	-3777	13195
88	95	-10.00	120	.30	17000	12122	-4878	-29	2133	570	-3777	13195
91	74	-10.00	120	.30	17000	11650	-5350	-31	1661	570	-3777	13195
94	71	-5.50	120	.30	2537	11294	8757	345	1594	314	-3809	13195
97	68	-1.00	113	.30	2537	10970	8433	332	1527	57	-3809	13195
100	65	-1.00	92	.30	2537	10903	8366	330	1459	57	-3809	13195
103	61	-1.00	71	.30	2537	10770	8233	325	1358	57	-3841	13195
106	56	-1.50	51	.30	1075	10697	9622	895	1257	86	-3841	13195
109	52	-1.50	33	.30	1075	10596	9521	886	1156	86	-3841	13195
112	50	-1.50	27	.30	1075	10563	9488	883	1122	86	-3841	13195
115	50	.00	27	.30	700	10477	9777	1397	1122	-0	-3841	13195
118	50	.00	27	.30	700	10477	9777	1397	1122	-0	-3841	13195
121	51	.00	27	.30	700	10490	9790	1399	1136	-0	-3841	13195
124	52	.30	34	.30	700	10514	9814	1402	1176	-17	-3841	13195
127	54	.60	46	.30	19100	10537	-8563	-45	1217	-34	-3841	13195
130	56	.60	58	.30	19100	10577	-8523	-45	1257	-34	-3841	13195
133	70	.60	70	.30	19100	11342	-7758	-41	1574	-34	-3393	13195
136	84	4.70	82	.30	21100	12097	-9003	-43	1890	-268	-2721	13195
139	98	4.70	94	.30	21100	13086	-8014	-38	2207	-268	-2048	13195
142	107	4.70	106	.30	21100	13885	-7215	-34	2398	-268	-1440	13195
145	113	1.90	118	.30	19800	14748	-5052	-26	2526	-108	-864	13195
148	118	1.90	130	.30	19800	14876	-4924	-25	2654	-108	-864	13195
151	122	1.90	145	.30	19800	14971	-4829	-24	2748	-108	-864	13195
154	124	1.15	160	.30	19800	15040	-4760	-24	2775	-66	-864	13195
157	125	.40	175	.30	17800	15110	-2690	-15	2802	-23	-864	13195
160	126	.40	190	.30	17800	14785	-3015	-17	2829	-23	-1216	13195
163	126	.40	204	.30	17800	14401	-3399	-19	2829	-23	-1600	13195
166	126	.00	216	.30	16400	14040	-2360	-14	2829	-0	-1984	13195
169	126	.00	222	.30	16400	13655	-2745	-17	2829	-0	-2369	13195
172	128	.00	228	.30	16400	13307	-3093	-19	2865	-0	-2753	13195
175	130	.80	234	.30	16000	12931	-3069	-19	2918	-46	-3137	13195
178	132	.80	238	.30	16000	12601	-3399	-21	2972	-46	-3521	13195
181	134	.80	240	.30	16000	12253	-3747	-23	3008	-46	-3905	13195
184	134	.40	242	.30	16000	11860	-4140	-26	3008	-23	-4321	13195
187	134	.00	244	.30	17100	11402	-5698	-33	3008	-0	-4801	13195
190	134	.00	246	.30	17100	10922	-6178	-36	3008	-0	-5281	13195
193	135	.00	248	.30	17100	10469	-6631	-39	3035	-0	-5761	13195
196	136	.40	249	.30	18200	9993	-8207	-45	3062	-23	-6242	13195
199	138	.40	251	.30	18200	9604	-8596	-47	3089	-23	-6658	13195
202	136	.40	253	.30	18200	9239	-8961	-49	3044	-23	-6978	13195
205	132	-1.20	255	.30	1200	9057	7857	655	2963	68	-7170	13195
208	128	-1.20	257	.30	1200	8785	7585	632	2883	68	-7362	13195
211	126	-1.20	259	.30	1200	8539	7339	612	2829	68	-7554	13195
214	126	-.60	261	.30	5600	8408	2808	50	2829	34	-7650	13195
217	126	.00	263	.30	5600	8310	2710	48	2829	-0	-7714	13195
220	126	.00	264	.30	12600	8246	-4354	-35	2829	-0	-7778	13195

LAG1 = 0, LAG2 = 4, LAG3 = 35

K1 = 3.367422, K2 = -34.227822, K3 = -4.801161

K4 = 614.311539, SUM = 2.531180E+09, HCT = .500000

NMAX = 220, NORMER = .442275, AVGINS = 1.331398E+04

TABLE 15

EXPERIMENTAL DATA AND CORRELATION FOR DOG L

TIME MIN	GLUCOSE MG PCT	DG/DT	FEMORAL INSULIN MU U/ML	BLOOD FLOW ML/MIN	MEASURED PANCREATIC INSULIN MU/ML	ESTIMATED PANCREATIC INSULIN MU U/ML	ERROR MU U/ML	PERCENT ERROR	TERM 1	TERM 2	TERM 3	TERM 4
1	89	.00	20	.25	4910	7528	2618	53	9528	-0	-2017	16
4	98	.00	21	.25	4910	7528	2618	53	9528	-0	-2017	16
7	106	.00	21	.25	4910	7528	2618	53	9528	-0	-2017	16
10	115	2.90	22	.25	4910	7189	2279	46	9528	-338	-2017	16
13	121	2.90	23	.25	4910	7189	2279	46	9528	-338	-2017	16
16	127	2.90	23	.25	8530	7189	-1341	-16	9528	-338	-2017	16
19	133	2.00	24	.25	8530	7616	-914	-11	9850	-233	-2017	16
22	139	2.00	25	.25	14600	8580	-6020	-41	10814	-233	-2017	16
25	145	2.00	30	.25	14600	9544	-5056	-35	11778	-233	-2017	16
28	151	2.00	34	.25	14600	10508	-4092	-28	12742	-233	-2017	16
31	158	2.00	38	.25	10500	11172	672	6	13406	-233	-2017	16
34	168	2.00	42	.25	10500	11837	1337	13	14071	-233	-2017	16
37	178	2.65	48	.25	12800	12426	-374	-3	14736	-309	-2017	16
40	188	3.30	53	.25	12800	13015	215	2	15401	-385	-2017	16
43	193	3.30	59	.25	14600	13680	-920	-6	16065	-385	-2017	16
46	200	3.30	65	.25	14600	14344	-256	-2	16730	-385	-2017	16
49	206	1.50	71	.25	15800	15363	-437	-3	17539	-175	-2017	16
52	211	2.00	77	.25	18200	16402	-1798	-10	18636	-233	-2017	16
55	216	2.00	83	.25	18200	17499	-701	-4	19733	-233	-2017	16
58	220	1.50	89	.25	14400	18654	4254	30	20830	-175	-2017	16
61	226	1.50	95	.25	14400	19208	4808	33	21384	-175	-2017	16
64	233	1.50	101	.25	17200	19984	2784	16	22159	-175	-2017	16
67	241	2.00	107	.25	17200	20590	3390	20	22824	-233	-2017	16
70	248	2.50	113	.25	17200	21086	3886	23	23378	-292	-2017	16
73	249	2.50	119	.25	17800	21584	3784	21	23877	-292	-2017	16
76	249	2.50	125	.25	17800	21982	4182	23	24375	-292	-2117	16
79	250	.20	130	.25	17800	22860	5060	28	24984	-23	-2117	16
82	250	.20	133	.25	17800	23590	5790	33	25815	-23	-2218	16
85	250	.20	136	.25	17800	24320	6520	37	26646	-23	-2319	16
88	250	.00	139	.25	25600	25074	-526	-2	27477	-0	-2420	16
91	250	.00	142	.25	25600	25140	-460	-2	27544	-0	-2420	16
94	248	.00	144	.25	22300	24904	2604	12	27610	-0	-2722	16
97	247	-.20	141	.25	21000	24591	3591	17	27677	23	-3126	16
100	246	-.40	138	.25	21000	24233	3233	15	27699	47	-3529	16
103	246	-.40	136	.25	25000	23829	-1171	-5	27699	47	-3932	16
106	246	-.40	134	.25	25000	23325	-1675	-7	27699	47	-4436	16
109	246	.00	133	.25	25600	22730	-2870	-11	27655	-0	-4941	16
112	246	.00	135	.25	25700	21992	-3708	-14	27522	-0	-5546	16
115	246	.00	136	.25	25700	21254	-4446	-17	27389	-0	-6151	16
118	246	.00	138	.25	20700	20516	-184	-1	27256	-0	-6755	16
121	246	.00	139	.25	20700	19911	-789	-4	27256	-0	-7360	16
124	246	.00	141	.25	28300	19306	-8994	-32	27256	-0	-7965	16
127	246	.00	143	.25	26700	18701	-7999	-30	27256	-0	-8570	16
130	246	.00	148	.25	26700	18096	-8604	-32	27256	-0	-9175	16
133	245	.00	157	.25	27700	17491	-10209	-37	27256	-0	-9780	16
136	245	.00	167	.25	27700	16887	-10813	-39	27256	-0	-10385	16
139	244	-.20	176	.25	22700	16305	-6395	-28	27256	23	-10990	16
142	244	-.20	181	.25	19800	15700	-4100	-21	27256	23	-11595	16
145	243	-.20	184	.25	19800	15095	-4705	-24	27256	23	-12200	16
148	242	-.20	187	.25	13700	14490	790	6	27256	23	-12805	16
151	242	-.20	190	.25	13700	14020	320	2	27189	23	-13208	16
154	241	-.20	185	.25	15700	13651	-2049	-13	27123	23	-13511	16
157	241	-.20	170	.25	13800	13282	-518	-4	27056	23	-13813	16

TABLE 15 (CONT'D)

160	240	-.20	155	.25	13800	12913	-887	-6	26990	23	-14116	16
163	239	-.20	140	.25	12300	12544	244	2	26923	23	-14418	16
166	237	-.20	125	.25	12300	12579	279	2	26857	23	-14318	16
169	236	-.50	122	.25	10900	12749	1849	17	26790	58	-14116	16
172	234	-.50	125	.25	9900	12884	2984	30	26724	58	-13914	16
175	233	-.50	128	.25	9900	13019	3119	32	26658	58	-13713	16
178	231	-.50	131	.25	9800	13154	3354	34	26591	58	-13511	16
181	230	-.50	134	.25	9800	12988	3188	33	26425	58	-13511	16
184	228	-.50	133	.25	8900	12721	3821	43	26259	58	-13612	16
187	227	-.50	127	.25	7700	12353	4653	60	26092	58	-13813	16
190	225	-.50	122	.25	7700	12086	4386	57	25926	58	-13914	16
193	222	-.50	119	.25	7800	11718	3918	50	25760	58	-14116	16
196	218	-.50	115	.25	7800	11451	3651	47	25594	58	-14217	16
199	215	-1.10	111	.25	6600	11053	4453	67	25428	128	-14519	16
202	212	-1.10	107	.25	6000	10181	4181	70	25261	128	-15225	16
205	207	-1.10	103	.25	6000	9006	3006	50	25095	128	-16233	16
208	203	-1.10	99	.25	5400	7933	2533	47	24929	128	-17141	16
211	198	-1.60	94	.25	5400	6819	1419	26	24563	187	-17947	16
214	190	-1.10	90	.25	6800	5991	-809	-12	24198	128	-18351	16
217	183	-2.05	85	.25	9100	5434	-3666	-40	23832	239	-18653	16
220	175	-2.50	81	.25	9100	4819	-4281	-47	23467	292	-18956	16
223	193	-2.50	78	.25	6800	3984	-2816	-41	22935	292	-19258	16
226	211	-2.50	75	.25	6800	4672	-2128	-31	22514	292	-18149	16
229	229	6.00	70	.25	3100	4561	1461	47	21882	-700	-16637	16
232	248	6.00	64	.25	2800	5243	2443	87	21051	-700	-15124	16
235	268	6.00	59	.25	2800	5924	3124	112	20220	-700	-13612	16
238	287	6.50	56	.25	2800	6245	3445	123	19389	-759	-12402	16

LAG1 = 18, LAG2 = 7, LAG3 = 71

K1 = 13.849494, K2 = -58.359324, K3 = -12.603527

K4 = -611.749435, SUM = 1.188603E+09, HCT = .500000

NMAX = 240, NORMER = .274459, AVGINS = 1.404415E+04

TABLE 16

EXPERIMENTAL DATA AND CORRELATION FOR DOG M

TIME MIN	GLUCOSE MG PCT	DG/DT	FEMORAL INSULIN MU U/ML	BLOOD FLOW ML/MIN	MEASURED PANCRE-ATIC INSULIN MU/ML	ESTIMATED PANCRE-ATIC INSULIN MU U/ML	ERROR MU U/ML	PERCENT ERROR	TERM 1	TERM 2	TERM 3	TERM 4
1	74	.00	27	.10	16900	20869	3969	23	495	0	1094	19280
4	86	.00	75	.10	16900	22895	5995	35	575	0	3040	19280
7	98	4.00	123	.10	16900	25951	9051	54	656	1029	4986	19280
10	111	4.10	171	.12	33100	28008	-5092	-15	742	1055	6932	19280
13	124	4.20	194	.12	33100	29050	-4050	-12	826	1081	7864	19280
16	132	4.20	209	.12	33100	29713	-3387	-10	881	1081	8472	19280
19	131	2.00	224	.12	33100	29751	-3349	-10	877	515	9080	19280
22	131	-.20	239	.13	33400	29789	-3611	-11	873	-51	9688	19280
25	130	-.20	252	.13	33400	30312	-3088	-9	869	-51	10215	19280
28	132	-.20	264	.13	33400	30811	-2589	-8	881	-51	10701	19280
31	134	.60	276	.14	41400	31515	-9885	-24	893	154	11188	19280
34	135	.60	281	.14	41400	31730	-9670	-23	905	154	11390	19280
37	139	.60	283	.14	41400	31833	-9567	-23	928	154	11471	19280
40	143	1.40	285	.15	41100	32148	-8952	-22	956	360	11553	19280
43	147	1.40	287	.15	41100	32257	-8843	-22	984	360	11634	19280
46	149	1.40	290	.15	41100	32393	-8707	-21	998	360	11755	19280
49	147	.35	290	.15	41100	32109	-8991	-22	984	90	11755	19280
52	145	-.70	292	.16	43700	31906	-11794	-27	970	-180	11836	19280
55	143	-.70	326	.16	43700	33270	-10430	-24	956	-180	13215	19280
58	150	-.70	377	.16	43700	35381	-8319	-19	1000	-180	15282	19280
61	156	2.20	428	.14	45500	38239	-7261	-16	1044	566	17349	19280
64	163	2.20	475	.14	45500	40188	-5312	-12	1088	566	19254	19280
67	164	2.20	520	.14	45500	42022	-3478	-8	1097	566	21078	19280
70	163	-.40	554	.14	46200	42723	-3477	-8	1089	-103	22457	19280
73	162	-.40	564	.14	46200	43120	-3080	-7	1081	-103	22862	19280
76	160	-.40	563	.14	46200	43068	-3132	-7	1069	-103	22821	19280
79	163	-.60	572	.14	46200	43401	-2799	-6	1089	-154	23186	19280
82	166	1.00	580	.13	50600	44157	-6443	-13	1110	257	23510	19280
85	169	1.00	586	.13	50600	44420	-6180	-12	1130	257	23754	19280
88	179	1.00	596	.13	50600	44891	-5709	-11	1195	257	24159	19280
91	192	4.40	604	.13	55000	46178	-8822	-16	1283	1132	24483	19280
94	205	4.40	625	.13	55000	47118	-7882	-14	1372	1132	25335	19280
97	214	4.40	670	.13	55000	49003	-5997	-11	1432	1132	27159	19280
100	215	2.35	715	.17	55000	50305	-4695	-9	1438	605	28983	19280
103	216	.30	760	.17	50000	51607	1607	3	1444	77	30807	19280
106	217	.25	805	.17	50000	53423	3423	7	1448	64	32631	19280
109	219	.20	850	.17	50000	55247	5247	10	1460	51	34455	19280
112	223	.85	895	.17	50000	57268	7268	15	1491	219	36279	19280
115	228	1.50	936	.21	59700	59127	-573	-1	1521	386	37941	19280
118	232	1.50	928	.21	59700	58833	-867	-1	1551	386	37617	19280
121	239	1.50	904	.18	54800	57906	3106	6	1597	386	36644	19280
124	245	2.30	880	.18	54800	57177	2377	4	1635	592	35671	19280
127	257	2.20	856	.18	54800	56260	1460	3	1716	566	34698	19280
130	270	4.40	832	.19	56500	55942	-558	-1	1805	1132	33725	19280
133	283	4.40	808	.19	56500	55057	-1443	-3	1893	1132	32753	19280
136	292	4.40	784	.19	56500	54142	-2358	-4	1950	1132	31780	19280
139	291	2.10	765	.19	56500	52776	-3724	-7	1946	540	31010	19280
142	291	-.20	750	.19	51900	51572	-328	-1	1942	-51	30401	19280
145	290	-.20	735	.19	51900	50960	-940	-2	1938	-51	29793	19280
148	292	-.20	720	.19	51900	50366	-1534	-3	1952	-51	29185	19280
151	294	.70	705	.21	56300	50004	-6296	-11	1966	180	28577	19280
154	296	.70	690	.21	56300	49410	-6890	-12	1980	180	27969	19280
157	295	.70	675	.21	56300	48794	-7506	-13	1973	180	27361	19280

TABLE 16 (CONT'D)

160	293	-.90	630	.20	50900	46540	-4360	-9	1955	-232	25537	19280
163	290	-.90	560	.20	50900	43685	-7215	-14	1937	-232	22700	19280
166	275	-.90	500	.20	50900	41154	-9746	-19	1838	-232	20268	19280
169	236	-6.95	440	.20	50900	36904	-13996	-27	1577	-1788	17836	19280
172	197	-13.00	380	.15	48800	32655	-16145	-33	1317	-3345	15403	19280
175	158	-13.00	320	.15	48800	29962	-18838	-39	1056	-3345	12971	19280
178	139	-13.00	280	.15	48800	28212	-20588	-42	928	-3345	11350	19280
181	120	-6.40	264	.13	19700	29134	9434	48	799	-1647	10701	19280
184	100	-6.40	240	.13	19700	28033	8333	42	671	-1647	9728	19280
187	86	-6.40	216	.13	19700	26961	7261	37	572	-1647	8756	19280
190	75	-4.20	192	.13	10700	26480	15780	147	498	-1081	7783	19280
193	64	-3.70	169	.13	10700	25609	14909	139	430	-952	6850	19280
196	70	-3.70	147	.13	10700	24752	14052	131	465	-952	5959	19280
199	107	4.45	120	.13	10700	26007	15307	143	718	1145	4864	19280
202	145	12.60	93	.15	54800	27262	-27538	-50	970	3242	3770	19280
205	183	12.60	161	.15	54800	30271	-24529	-45	1223	3242	6526	19280
208	210	12.60	230	.15	54800	33248	-21552	-39	1404	3242	9323	19280
211	239	8.85	299	.16	40000	35273	-4727	-12	1596	2277	12120	19280
214	267	9.40	365	.16	40000	38276	-1724	-4	1783	2419	14795	19280
217	280	9.30	425	.16	40000	40769	769	2	1869	2393	17228	19280
220	285	1.80	485	.19	25700	41307	15607	61	1905	463	19660	19280
223	290	1.80	542	.19	25700	43654	17954	70	1941	463	21970	19280
226	292	1.80	518	.19	25700	42689	16989	66	1949	463	20997	19280
229	284	-.30	494	.19	25700	41128	15428	60	1901	-77	20024	19280
232	272	-2.40	470	.18	22700	39532	16832	74	1818	-618	19052	19280
235	270	-5.00	446	.18	22700	37877	15177	67	1805	-1287	18079	19280
238	256	-2.40	422	.18	22700	37478	14778	65	1710	-618	17106	19280
241	242	-4.70	398	.15	22700	35820	13120	58	1616	-1209	16133	19280
244	228	-4.70	372	.15	22700	34671	11971	53	1522	-1209	15079	19280
247	207	-4.70	345	.15	22700	33436	10736	47	1381	-1209	13985	19280
250	182	-8.20	324	.17	19900	31520	11620	58	1216	-2110	13133	19280
253	157	-8.20	303	.17	19900	30504	10604	53	1052	-2110	12282	19280
256	135	-8.20	282	.17	19900	29502	9602	48	902	-2110	11431	19280
259	117	-7.15	271	.17	19900	29204	9304	47	779	-1840	10985	19280
262	98	-6.10	250	.16	9200	28501	19301	210	657	-1570	10134	19280
265	80	-6.10	220	.16	9200	27163	17963	195	535	-1570	8918	19280
268	75	-6.10	191	.16	9200	25951	16751	182	499	-1570	7742	19280
271	69	-1.80	164	.13	6100	25927	19827	325	463	-463	6648	19280
274	64	-1.80	137	.13	6100	24796	18696	306	426	-463	5553	19280

LAG1 = 0, LAG2 = 4, LAG3 = 0

K1 = .334194, K2 = 51.460585, K3 = 2.026766

K4 = 118.985740, SUM = 1.063288E+10, HCT = .500000

NMAX = 275, NORMER = .281051, AVGINS = 3.846087E+04

TABLE 17

EXPERIMENTAL DATA AND CORRELATION FOR DOG N

TIME MIN	GLUCOSE MG PCT	DG/DT	FEMORAL INSULIN MU U/ML	BLOOD FLOW ML/MIN	MEASURED PANCREATIC INSULIN MU/ML	ESTIMATED PANCREATIC INSULIN MU U/ML	ERROR MU U/ML	PERCENT ERROR	TERM 1	TERM 2	TERM 3	TERM 4
1	152	.00	25	.26	920	5303	4383	476	-422	-0	-1647	7372
4	167	.00	29	.26	5875	5303	-572	-10	-422	-0	-1647	7372
7	183	.00	30	.26	5875	5260	-615	-10	-465	-0	-1647	7372
10	200	.00	29	.26	2670	5215	2545	95	-510	-0	-1647	7372
13	217	5.00	29	.26	2670	5124	2454	92	-559	-42	-1647	7372
16	233	5.35	28	.26	2670	5072	2402	90	-608	-45	-1647	7372
19	243	5.70	28	.26	2670	5020	2350	88	-657	-48	-1647	7372
22	254	5.70	30	.26	4050	4989	939	23	-688	-48	-1647	7372
25	268	5.90	33	.22	6350	4956	-1394	-22	-719	-50	-1647	7372
28	281	3.60	36	.22	6350	4940	-1410	-22	-755	-30	-1647	7372
31	289	3.60	39	.19	1480	4897	3417	231	-798	-30	-1647	7372
34	297	4.40	42	.19	1480	4866	3386	229	-822	-37	-1647	7372
37	308	5.00	44	.19	1480	4837	3357	227	-846	-42	-1647	7372
40	320	2.80	45	.19	5100	4829	-271	-5	-873	-24	-1647	7372
43	332	2.70	47	.19	5100	4795	-305	-6	-907	-23	-1647	7372
46	343	3.35	48	.19	5100	4755	-345	-7	-941	-28	-1647	7372
49	352	4.00	50	.19	5100	4715	-385	-8	-976	-34	-1647	7372
52	361	4.00	49	.20	5500	4690	-810	-15	-1002	-34	-1647	7372
55	370	4.00	47	.20	5500	4664	-836	-15	-1028	-34	-1647	7372
58	374	3.00	45	.20	5500	4372	-1128	-21	-1053	-25	-1922	7372
61	378	3.00	43	.22	6400	4218	-2182	-34	-1070	-25	-2059	7372
64	383	3.00	41	.22	6400	4206	-2194	-34	-1082	-25	-2059	7372
67	385	1.40	41	.22	6400	4276	-2124	-33	-1094	-12	-1991	7372
70	386	1.40	43	.22	8500	4335	-4165	-49	-1103	-12	-1922	7372
73	387	1.40	45	.22	8500	4332	-4168	-49	-1107	-12	-1922	7372
76	409	.90	47	.22	8500	4264	-4236	-50	-1110	-8	-1991	7372
79	472	.40	48	.22	8500	4059	-4441	-52	-1114	-3	-2197	7372
82	535	.40	55	.20	6700	3672	-3028	-45	-1295	-3	-2402	7372
85	596	.40	70	.20	6700	3285	-3415	-51	-1475	-3	-2608	7372
88	575	21.00	79	.20	6700	2728	-3972	-59	-1653	-177	-2814	7372
91	558	21.00	88	.23	4420	2576	-1844	-42	-1668	-177	-2952	7372
94	538	20.50	97	.23	4420	2498	-1922	-43	-1613	-172	-3089	7372
97	544	-7.40	98	.23	4420	2713	-1707	-39	-1564	62	-3158	7372
100	562	-6.40	93	.25	1850	2587	737	40	-1544	54	-3295	7372
103	580	-6.40	88	.25	1850	2467	617	33	-1596	54	-3363	7372
106	598	-.20	84	.25	1850	2363	513	28	-1648	2	-3363	7372
109	616	6.00	78	.25	1850	2397	547	30	-1699	-50	-3226	7372
112	634	6.00	78	.22	2510	2482	-28	-1	-1751	-50	-3089	7372
115	652	6.00	81	.22	2510	2568	58	2	-1803	-50	-2952	7372
118	634	6.00	84	.22	2510	2653	143	6	-1854	-50	-2814	7372
121	616	6.00	87	.26	2360	2739	379	16	-1837	-50	-2746	7372
124	598	6.00	90	.26	2360	2654	294	12	-1785	-50	-2883	7372
127	562	-6.00	90	.26	2360	2669	309	13	-1734	50	-3020	7372
130	516	-6.00	89	.22	800	2609	1809	226	-1656	50	-3158	7372
133	468	-6.00	87	.22	800	2601	1801	225	-1527	50	-3295	7372
136	430	-10.50	86	.22	800	2571	1771	221	-1389	88	-3501	7372
139	411	-15.00	85	.22	800	1785	985	123	-1251	126	-4462	7372
142	393	-16.00	83	.22	610	1092	482	79	-1198	135	-5217	7372
145	374	-16.00	78	.22	610	528	-82	-13	-1145	135	-5835	7372
148	363	-6.20	73	.22	610	-119	-729	-120	-1091	52	-6452	7372
151	352	-6.20	69	.18	750	-424	-1174	-157	-1053	52	-6796	7372
154	342	-6.20	63	.18	750	-50	-800	-107	-1022	52	-6452	7372
157	338	-3.60	59	.18	750	234	-516	-69	-991	30	-6178	7372

TABLE 17 (CONT'D)

160	338	-3.60	56	.18	730	598	-132	-18	-970	30	-5835	7372
163	338	-3.60	55	.18	730	941	211	29	-970	30	-5491	7372
166	335	-1.80	52	.18	730	1132	402	55	-970	15	-5285	7372
169	325	.00	49	.18	730	911	181	25	-970	-0	-5491	7372
172	315	.00	46	.15	840	733	-107	-13	-942	-0	-5697	7372
175	305	.00	43	.15	840	556	-284	-34	-913	-0	-5903	7372
178	299	-3.30	40	.15	840	406	-434	-52	-885	28	-6109	7372
181	293	-3.30	38	.18	1020	290	-730	-72	-864	28	-6246	7372
184	287	-3.30	37	.18	1020	444	-576	-56	-847	28	-6109	7372
187	280	-2.00	38	.18	1020	519	-501	-49	-830	17	-6040	7372
190	273	-2.00	40	.17	480	675	195	41	-811	17	-5903	7372
193	265	-2.00	41	.17	480	765	285	59	-789	17	-5835	7372
196	258	-2.25	43	.17	480	858	378	79	-768	19	-5766	7372
199	252	-2.50	44	.17	480	1224	744	155	-746	21	-5423	7372
202	246	-2.50	46	.15	1000	1585	585	58	-729	21	-5080	7372
205	240	-2.50	47	.15	1000	1877	877	88	-712	21	-4805	7372
208	239	-2.00	49	.15	1000	2233	1233	123	-695	17	-4462	7372
211	238	-2.00	50	.17	5370	2584	-2786	-52	-687	17	-4119	7372
214	236	-2.00	51	.17	5370	2794	-2576	-48	-683	17	-3913	7372
217	232	-.40	51	.17	5370	2989	-2381	-44	-680	3	-3707	7372
220	226	-.40	53	.16	4590	3066	-1524	-33	-672	3	-3638	7372
223	220	-.40	54	.16	4590	3289	-1301	-28	-654	3	-3432	7372
226	228	-1.20	56	.16	4590	3519	-1071	-23	-637	10	-3226	7372
229	265	-2.00	57	.16	4590	3749	-841	-18	-620	17	-3020	7372
232	301	-2.00	61	.15	1480	3850	2370	160	-725	17	-2814	7372
235	338	-2.00	67	.15	1480	3951	2471	167	-830	17	-2608	7372
238	386	12.20	73	.15	1480	3795	2315	156	-935	-103	-2540	7372
241	434	12.20	79	.15	620	3599	2979	481	-1062	-103	-2608	7372
244	482	12.20	82	.15	620	3393	2773	447	-1200	-103	-2677	7372
247	518	16.00	85	.15	620	3086	2466	398	-1338	-135	-2814	7372
250	548	16.00	88	.19	620	2897	2277	367	-1458	-135	-2883	7372
253	578	16.00	91	.19	650	2673	2023	311	-1544	-135	-3020	7372
256	601	13.00	94	.19	650	2544	1894	291	-1630	-109	-3089	7372
259	612	10.00	97	.19	650	2346	1696	261	-1716	-84	-3226	7372
262	622	10.00	100	.19	210	2248	2038	970	-1746	-84	-3295	7372
265	632	10.00	104	.19	210	2081	1871	891	-1775	-84	-3432	7372
268	569	3.40	109	.19	210	2039	1829	871	-1804	-29	-3501	7372
271	506	3.40	114	.17	435	2150	1715	394	-1693	-29	-3501	7372
274	445	3.40	118	.17	435	2262	1827	420	-1513	-29	-3569	7372

LAG1 = 4, LAG2 = 11, LAG3 = 55

K1 = -.373144, K2 = -4.374039, K3 = -8.923467

K4 = 838.814850, SUM = 3.383696E+08, HCT = .500000

NMAX = 275, NORMER = .686968, AVGINS = 2806.974609

TABLE 18

EXPERIMENTAL DATA AND CORRELATION FOR DOG S

TIME MIN	GLUCOSE MG PCT	DG/DT	FEMORAL INSULIN MU U/ML	BLOOD FLOW ML/MIN	MEASURED PANCREATIC INSULIN MU/ML	ESTIMATED PANCREATIC INSULIN MU U/ML	ERROR MU U/ML	PERCENT ERROR	TERM 1	TERM 2	TERM 3	TERM 4
1	85	.00	31	.30	462	1397	935	202	14610	0	1498	-14711
4	85	.00	30	.30	462	1397	935	202	14610	0	1498	-14711
7	85	.00	29	.30	329	1397	1068	325	14610	0	1498	-14711
10	85	.00	27	.30	329	1397	1068	325	14610	0	1498	-14711
13	85	.00	26	.33	538	1397	859	160	14610	0	1498	-14711
16	85	.00	25	.22	412	1397	985	239	14610	0	1498	-14711
19	85	.00	23	.22	412	1397	985	239	14610	0	1498	-14711
22	85	.00	22	.30	205	1397	1192	582	14610	0	1498	-14711
25	85	.00	23	.30	134	1397	1263	943	14610	0	1498	-14711
28	85	.00	24	.27	134	1397	1263	943	14610	0	1498	-14711
31	85	.00	25	.27	134	1397	1263	943	14610	0	1498	-14711
34	85	.00	26	.30	110	1397	1287	1170	14610	0	1498	-14711
37	85	.00	27	.22	105	1397	1292	1231	14610	0	1498	-14711
40	85	.00	27	.22	105	1397	1292	1231	14610	0	1498	-14711
43	85	.00	27	.22	105	1397	1292	1231	14610	0	1498	-14711
46	85	.00	27	.30	115	1397	1282	1115	14610	0	1498	-14711
49	85	.00	28	.30	115	1397	1282	1115	14610	0	1498	-14711
52	85	.00	28	.22	109	1301	1192	1093	14610	0	1402	-14711
55	85	.00	28	.22	109	1252	1143	1049	14610	0	1353	-14711
58	85	.00	28	.30	173	1204	1031	596	14610	0	1305	-14711
61	85	.00	28	.28	236	1156	920	390	14610	0	1257	-14711
64	85	.00	27	.28	236	1059	823	349	14610	0	1160	-14711
67	85	.00	26	.28	252	1011	759	301	14610	0	1112	-14711
70	85	.00	26	.28	252	962	710	282	14610	0	1063	-14711
73	85	.00	25	.23	346	1059	713	206	14610	0	1160	-14711
76	85	.00	24	.23	346	1107	761	220	14610	0	1208	-14711
79	85	.00	24	.24	404	1156	752	186	14610	0	1257	-14711
82	85	.00	24	.28	548	1156	608	111	14610	0	1257	-14711
85	85	.00	24	.28	548	1204	656	120	14610	0	1305	-14711
88	85	.00	25	.22	543	1204	661	122	14610	0	1305	-14711
91	85	.00	25	.28	808	1204	396	49	14610	0	1305	-14711
94	85	.00	25	.28	808	1252	444	55	14610	0	1353	-14711
97	85	.00	28	.23	1880	1252	-628	-33	14610	0	1353	-14711
100	91	.00	34	.22	1725	1252	-473	-27	14610	0	1353	-14711
103	100	.00	40	.22	1725	1252	-473	-27	14610	0	1353	-14711
106	110	.00	48	.22	1220	1252	32	3	14610	0	1353	-14711
109	119	3.05	54	.22	1220	1757	537	44	14610	505	1353	-14711
112	124	3.10	60	.28	1314	1717	403	31	14610	513	1305	-14711
115	126	3.10	66	.28	3350	1669	-1681	-50	14610	513	1257	-14711
118	128	3.10	72	.28	3350	1620	-1730	-52	14610	513	1208	-14711
121	130	.80	77	.24	2975	1240	-1735	-58	14610	132	1208	-14711
124	130	.80	82	.24	2975	1191	-1784	-60	14610	132	1160	-14711
127	130	.80	81	.30	1525	2755	1230	81	16174	132	1160	-14711
130	112	.00	68	.30	1525	4222	2697	177	17773	0	1160	-14711
133	103	.00	55	.28	718	5868	5150	717	19371	0	1208	-14711
136	95	.00	40	.32	638	7467	6829	1070	20970	0	1208	-14711
139	86	-5.95	40	.32	638	6894	6256	981	21382	-985	1208	-14711
142	83	-2.90	39	.30	608	7812	7204	1185	21795	-480	1208	-14711
145	83	-2.90	38	.30	608	8466	7858	1292	22207	-480	1450	-14711
148	83	-2.90	37	.30	598	8893	8295	1387	22345	-480	1740	-14711
151	83	.00	37	.30	1050	9664	8614	820	22345	0	2030	-14711
154	83	.00	36	.30	1050	10050	9000	857	22345	0	2416	-14711
157	83	.00	42	.30	2580	6748	4168	162	18752	0	2706	-14711

TABLE 18 (CONT'D)

160	88	.00	62	.30	2580	5542	2962	115	17257	0	2996	-14711
163	107	.00	81	.30	3935	4385	450	11	15762	0	3335	-14711
166	125	.00	98	.32	3380	3132	-248	-7	14266	0	3576	-14711
169	144	4.60	116	.32	3380	4135	755	22	14266	761	3818	-14711
172	154	6.20	130	.30	4860	4593	-267	-5	14266	1026	4011	-14711
175	159	6.20	135	.30	4860	4303	-557	-11	14266	1026	3721	-14711
178	164	6.20	140	.35	8040	3675	-4365	-54	14266	1026	3093	-14711
181	168	1.80	145	.36	12620	2270	-10350	-82	14266	298	2416	-14711
184	168	1.80	151	.36	12620	1786	-10834	-86	14266	298	1933	-14711
187	168	1.80	158	.36	8110	3663	-4447	-55	16191	298	1885	-14711
190	160	.00	165	.36	8110	6562	-1548	-19	19388	0	1885	-14711
193	140	.00	174	.34	10590	9711	-879	-8	22585	0	1837	-14711
196	120	.00	175	.32	13800	12860	-940	-7	25782	0	1788	-14711
199	100	-5.15	172	.32	13800	12887	-913	-7	26711	-852	1740	-14711
202	100	-6.70	169	.34	13550	13558	8	0	27639	-1109	1740	-14711
205	100	-6.60	166	.34	13550	15083	1533	11	28567	-1093	2320	-14711
208	100	-3.50	163	.32	15450	16921	1471	10	28876	-579	3335	-14711
211	88	.00	160	.28	15950	18322	2372	15	28876	0	4156	-14711
214	87	.00	156	.28	15950	19191	3241	20	28876	0	5026	-14711
217	86	.00	160	.28	27300	17604	-9696	-36	26418	0	5896	-14711
220	85	-.30	190	.28	27300	14582	-12718	-47	22964	-50	6380	-14711
223	111	-.30	220	.32	32700	11421	-21279	-65	19560	-50	6621	-14711
226	136	-.30	242	.40	20000	9242	-10758	-54	17188	-50	6814	-14711
229	162	4.10	248	.40	20000	10260	-9740	-49	17188	679	7104	-14711
232	175	8.50	254	.30	20550	11327	-9223	-45	17188	1407	7443	-14711
235	182	8.50	260	.30	20550	11665	-8885	-43	17188	1407	7781	-14711
238	191	8.50	266	.36	18050	9838	-8212	-45	15023	1407	8119	-14711
241	194	2.40	272	.34	16200	9157	-7043	-43	14868	397	8603	-14711
244	194	3.40	276	.34	16200	8974	-7226	-45	14713	563	8409	-14711
247	194	2.40	283	.40	16200	10022	-6178	-38	16071	397	8264	-14711
250	194	.00	292	.40	16200	13862	-2338	-14	20454	0	8119	-14711
253	202	.00	298	.40	18350	18100	-250	-1	24837	0	7974	-14711
256	210	.00	301	.33	19250	22338	3088	16	29220	0	7829	-14711
259	180	1.30	304	.33	19250	23646	4396	23	30458	215	7684	-14711
262	164	2.70	316	.40	23400	25218	1818	8	32039	447	7443	-14711
265	155	-3.65	380	.40	23400	26177	2777	12	33276	-604	8216	-14711
268	146	-10.00	460	.26	27450	26645	-805	-3	33345	-1655	9666	-14711
271	138	-3.00	500	.32	33650	29253	-4397	-13	33345	-497	11116	-14711
274	132	-3.00	575	.32	33650	29930	-3720	-11	33345	-497	11792	-14711
277	126	-3.00	650	.34	33050	30667	-2383	-7	33792	-497	12082	-14711
280	120	-2.00	700	.34	33050	32497	-553	-2	35167	-331	12372	-14711
283	114	-2.00	722	.26	29150	31997	2847	10	34377	-331	12662	-14711
286	108	-2.00	741	.34	23900	27130	3230	14	29220	-331	12952	-14711
289	102	-2.00	762	.34	23900	25777	1877	8	27673	-331	13146	-14711
292	100	-2.00	775	.15	19250	24520	5270	27	26126	-331	13436	-14711
295	100	-2.00	775	.15	19250	23359	4109	21	24579	-331	13822	-14711
298	100	-2.00	775	.15	19250	22639	3389	18	23376	-331	14306	-14711
301	99	.00	775	.15	19250	22084	2834	15	22345	0	14451	-14711
304	97	.00	775	.15	15050	21198	6148	41	21313	0	14596	-14711
307	94	.00	775	.15	15050	20457	5407	36	20282	0	14886	-14711
310	92	-.80	775	.15	15050	19873	4823	32	19251	-132	15466	-14711

LAG1 = 26, LAG2 = 9, LAG3 = 47

K1 = 25.782396, K2 = 99.319598, K3 = 7.249457

K4 = -2275.961578, SUM = 2.373112E+09, HCT = .500000

NMAX = 310, NORMER = .529478, AVGINS = 9065.507935

TABLE 19

EXPERIMENTAL DATA AND CORRELATION FOR DOG T

TIME MIN	GLUCOSE MG PCT	DG/DT	FEMORAL INSULIN MU U/ML	BLOOD FLOW ML/MIN	MEASURED PANCREATIC INSULIN MU/ML	ESTIMATED PANCREATIC INSULIN MU U/ML	ERROR MU U/ML	PERCENT ERROR	TERM 1	TERM 2	TERM 3	TERM 4
1	59	.00	9	.20	336	1348	1012	301	7640	0	537	-6829
4	59	.00	10	.20	336	1348	1012	301	7640	0	537	-6829
7	59	.00	10	.20	469	1348	879	187	7640	0	537	-6829
10	59	.00	11	.20	469	1348	879	187	7640	0	537	-6829
13	59	.00	12	.20	469	1348	879	187	7640	0	537	-6829
16	59	.00	13	.19	422	1348	926	219	7640	0	537	-6829
19	59	.00	14	.19	422	1348	926	219	7640	0	537	-6829
22	59	.00	13	.19	422	1348	926	219	7640	0	537	-6829
25	59	.00	12	.25	243	1348	1105	455	7640	0	537	-6829
28	59	.00	10	.25	243	1348	1105	455	7640	0	537	-6829
31	59	.00	9	.25	243	1348	1105	455	7640	0	537	-6829
34	59	.00	7	.25	243	1348	1105	455	7640	0	537	-6829
37	59	.00	7	.20	889	1348	459	52	7640	0	537	-6829
40	59	.00	8	.20	889	1348	459	52	7640	0	537	-6829
43	59	.00	8	.15	918	1348	430	47	7640	0	537	-6829
46	59	.00	9	.20	868	1348	480	55	7640	0	537	-6829
49	59	.00	9	.13	720	1348	628	87	7640	0	537	-6829
52	59	.00	9	.13	720	1348	628	87	7640	0	537	-6829
55	59	.00	9	.13	820	1408	588	72	7640	0	597	-6829
58	59	.00	9	.13	820	1467	647	79	7640	0	657	-6829
61	59	.00	9	.15	930	1467	537	58	7640	0	657	-6829
64	59	.00	10	.15	930	1527	597	64	7640	0	716	-6829
67	59	.00	10	.18	778	1587	809	104	7640	0	776	-6829
70	59	.00	11	.18	1470	1647	177	12	7640	0	836	-6829
73	59	.00	11	.15	1470	1587	117	8	7640	0	776	-6829
76	59	.00	12	.20	1350	1467	117	9	7640	0	657	-6829
79	59	.00	13	.20	1350	1408	58	4	7640	0	597	-6829
82	68	4.50	17	.18	4795	2643	-2152	-45	8805	190	478	-6829
85	70	.50	23	.20	3125	2609	-516	-16	8999	21	418	-6829
88	71	.50	29	.18	5750	2804	-2946	-51	9194	21	418	-6829
91	74	1.40	35	.18	5750	3329	-2421	-42	9621	59	478	-6829
94	81	2.30	41	.18	8405	4247	-4158	-49	10502	97	478	-6829
97	88	2.30	48	.20	7490	5200	-2290	-31	11395	97	537	-6829
100	95	2.35	54	.20	9410	6109	-3301	-35	12301	99	537	-6829
103	102	2.30	60	.18	9410	7000	-2410	-26	13195	97	537	-6829
106	109	2.30	66	.23	10025	7894	-2131	-21	14088	97	537	-6829
109	116	2.30	72	.20	12150	8787	-3363	-28	14982	97	537	-6829
112	122	2.00	70	.20	9290	9650	360	4	15798	84	597	-6829
115	110	-4.00	64	.20	9290	7843	-1447	-16	14244	-169	597	-6829
118	98	-4.00	58	.20	9490	6289	-3201	-34	12690	-169	597	-6829
121	88	-2.90	49	.18	1038	5126	4088	394	11421	-122	657	-6829
124	83	-1.80	40	.18	4750	4533	-217	-5	10722	-76	716	-6829
127	77	-1.80	30	.18	4750	3834	-916	-19	10022	-76	716	-6829
130	72	-1.80	24	.18	3840	3194	-646	-17	9323	-76	776	-6829
133	69	-1.00	20	.20	2300	3198	898	39	8935	-42	1134	-6829
136	66	-1.00	17	.14	2300	3167	867	38	8546	-42	1492	-6829
139	63	-1.00	14	.14	2300	3137	837	36	8158	-42	1850	-6829
142	69	3.30	13	.23	1795	4402	2607	145	8883	139	2209	-6829
145	79	3.30	13	.20	5290	6101	811	15	10165	139	2626	-6829
148	88	3.30	30	.20	5290	7741	2451	46	11447	139	2985	-6829
151	101	4.40	48	.23	12250	9713	-2537	-21	13014	185	3343	-6829
154	117	5.50	66	.23	15950	12254	-3696	-23	15150	232	3701	-6829
157	134	5.50	82	.23	15600	14749	-851	-5	17287	232	4059	-6829

TABLE 19 (CONT'D)

160	150	5.50	97	.23	15600	17243	1643	11	19423	232	4417	-6829
163	153	1.00	112	.23	12600	17084	4484	36	19812	42	4059	-6829
166	156	1.00	127	.23	19600	17114	-2486	-13	20200	42	3701	-6829
169	159	1.00	148	.30	12450	17145	4695	38	20589	42	3343	-6829
172	157	-1.60	147	.23	12400	16153	3753	30	20304	-67	2746	-6829
175	152	-1.60	138	.23	12400	14935	2535	20	19682	-67	2149	-6829
178	147	-1.60	129	.20	12600	13836	1236	10	19061	-67	1671	-6829
181	136	-4.65	120	.20	10250	11938	1688	16	17649	-196	1313	-6829
184	113	-7.70	111	.23	7465	8639	1174	16	14658	-324	1134	-6829
187	90	-7.70	104	.25	3735	5469	1734	46	11667	-324	955	-6829
190	67	-7.70	86	.25	3735	2298	-1437	-38	8676	-324	776	-6829
193	64	-1.10	68	.20	2040	2149	109	5	8248	-46	776	-6829
196	60	-1.10	50	.20	1690	2020	330	20	7821	-46	1074	-6829
199	57	-1.10	33	.25	2015	2667	652	32	7394	-46	2149	-6829
202	61	2.50	15	.25	2015	4398	2383	118	7899	105	3223	-6829
205	69	2.50	14	.20	1540	6444	4904	318	8870	105	4298	-6829
208	76	2.50	43	.25	4910	8311	3401	69	9841	105	5193	-6829
211	86	3.65	89	.25	18400	10523	-7877	-43	11110	154	6088	-6829
214	100	4.80	134	.25	18400	13332	-5068	-28	12975	202	6984	-6829
217	115	4.80	160	.20	18400	16211	-2189	-12	14839	202	7999	-6829
220	129	4.80	175	.25	20600	19210	-1390	-7	16704	202	9133	-6829
223	137	2.50	190	.23	20750	19547	-1203	-6	17675	105	8595	-6829
226	144	2.50	205	.23	20750	19981	-769	-4	18646	105	8058	-6829
229	152	2.50	218	.20	18850	20415	1565	8	19618	105	7521	-6829
232	145	-4.40	223	.20	17500	18771	1271	7	18802	-185	6984	-6829
235	132	-4.40	226	.23	16900	16644	-256	-2	17093	-185	6566	-6829
238	119	-4.40	181	.23	16900	14219	-2681	-16	15383	-185	5850	-6829
241	105	-4.60	136	.23	11600	11375	-225	-2	13622	-194	4775	-6829
244	91	-4.80	91	.23	10500	8427	-2073	-20	11758	-202	3701	-6829
247	76	-4.80	70	.20	4225	5488	1263	30	9893	-202	2626	-6829
250	62	-4.80	58	.20	4225	2609	-1616	-38	8028	-202	1612	-6829
253	56	-2.00	46	.20	2630	1233	-1397	-53	7251	-84	895	-6829
256	50	-2.00	34	.18	1910	337	-1573	-82	6474	-84	776	-6829
259	44	-2.00	22	.18	1660	2246	586	35	5698	-84	3462	-6829

LAG1 = 0, LAG2 = 1, LAG3 = 50

K1 = 12.948901, K2 = 16.856740, K3 = 5.969039

K4 = -716.499863, SUM = 4.024684E+08, HCT = .500000

NMAX = 260, NORMER = .335662, AVGINS = 6444.881226

TABLE 20

EXPERIMENTAL DATA AND CORRELATION FOR DOG U

TIME MIN	GLUCOSE MG PCT	DG/DT	FEMORAL INSULIN MU U/ML	BLOOD FLOW ML/MIN	MEASURED PANCRE-ATIC INSULIN MU/ML	ESTIMATED PANCRE-ATIC INSULIN MU U/ML	ERROR MU U/ML	PERCENT ERROR	TERM 1	TERM 2	TERM 3	TERM 4
1	60	.00	14	.35	517	306	-211	-41	1046	0	6799	-7538
4	60	.00	14	.35	457	306	-151	-33	1046	0	6799	-7538
7	60	.00	14	.35	192	306	114	59	1046	0	6799	-7538
10	60	.00	14	.35	202	306	104	52	1046	0	6799	-7538
13	60	.00	14	.35	275	306	31	11	1046	0	6799	-7538
16	60	.00	14	.35	257	306	49	19	1046	0	6799	-7538
19	60	.00	14	.35	257	306	49	19	1046	0	6799	-7538
22	48	.00	13	.35	257	306	49	19	1046	0	6799	-7538
25	53	.00	13	.35	374	306	-68	-18	1046	0	6799	-7538
28	57	.00	13	.35	374	97	-277	-74	836	0	6799	-7538
31	60	.00	13	.35	299	175	-124	-41	915	0	6799	-7538
34	60	.00	13	.35	226	254	28	12	993	0	6799	-7538
37	60	-6.75	13	.35	226	104	-122	-54	1046	-203	6799	-7538
40	60	1.50	13	.35	226	351	125	55	1046	45	6799	-7538
43	64	1.50	14	.35	226	351	125	55	1046	45	6799	-7538
46	67	1.50	14	.35	226	351	125	55	1046	45	6799	-7538
49	71	.00	14	.35	226	369	143	63	1108	0	6799	-7538
52	70	.00	15	.35	141	432	291	206	1171	0	6799	-7538
55	66	.00	15	.35	141	457	316	224	1234	0	6761	-7538
58	62	1.20	14	.40	141	435	294	208	1213	36	6724	-7538
61	62	1.20	14	.40	234	335	101	43	1150	36	6687	-7538
64	69	1.20	14	.40	234	234	0	0	1087	36	6649	-7538
67	75	.00	13	.40	234	158	-76	-33	1084	0	6612	-7538
70	82	-1.20	13	.40	508	199	-309	-61	1199	-36	6575	-7538
73	84	-1.20	13	.36	508	277	-231	-45	1314	-36	6537	-7538
76	87	-1.20	13	.36	508	355	-153	-30	1429	-36	6500	-7538
79	89	2.20	12	.34	460	461	1	0	1471	66	6463	-7538
82	92	2.20	12	.34	460	466	6	1	1513	66	6425	-7538
85	95	2.20	12	.34	460	470	10	2	1554	66	6388	-7538
88	98	.80	13	.34	460	439	-21	-4	1603	24	6351	-7538
91	102	.80	13	.33	412	454	42	10	1655	24	6313	-7538
94	108	.80	14	.33	412	701	289	70	1708	24	6507	-7538
97	114	.90	15	.33	412	968	556	135	1777	27	6702	-7538
100	120	1.00	24	.34	155	1270	1115	719	1882	30	6896	-7538
103	134	1.00	23	.34	1011	1568	557	55	1987	30	7090	-7538
106	147	1.00	22	.34	1641	1867	226	14	2091	30	7284	-7538
109	161	2.00	22	.35	1326	1938	612	46	2326	60	7090	-7538
112	170	2.00	21	.35	999	1979	980	98	2562	60	6896	-7538
115	179	2.00	20	.35	703	2020	1317	187	2797	60	6702	-7538
118	187	4.50	19	.35	1196	2074	878	73	2969	135	6507	-7538
121	192	4.50	18	.40	1463	2020	557	38	3110	135	6313	-7538
124	192	4.50	16	.40	1105	2064	959	87	3252	135	6216	-7538
127	192	3.60	14	.40	1192	2034	842	71	3346	108	6119	-7538
130	176	2.70	13	.40	999	1910	911	91	3346	81	6022	-7538
133	159	2.70	14	.40	1028	1813	785	76	3346	81	5925	-7538
136	142	2.70	15	.40	1498	1437	-61	-4	3067	81	5828	-7538
139	126	.00	15	.40	1498	1355	-143	-10	2774	0	6119	-7538
142	114	.00	16	.40	1454	1353	-101	-7	2481	0	6410	-7538
145	104	-4.00	16	.40	1454	1232	-222	-15	2189	-120	6702	-7538
148	94	-5.60	15	.40	1724	1268	-456	-26	1981	-168	6993	-7538
151	86	-5.60	16	.40	1554	1390	-164	-11	1812	-168	7284	-7538
154	82	-5.60	17	.40	1554	5338	3784	244	1645	-168	11400	-7538
157	77	-4.35	18	.38	1216	4853	3637	299	1506	-131	11016	-7538

TABLE 20 (CONT'D)

160	72	-3.25	19	.38	1258	4419	3161	251	1422	-98	10633	-7538
163	92	-3.20	21	.35	2013	3953	1940	96	1338	-96	10249	-7538
166	112	-3.20	22	.38	2380	3486	1106	46	1255	-96	9866	-7538
169	131	-1.60	23	.38	3450	3496	46	1	1600	-48	9483	-7538
172	141	-1.60	23	.43	3403	3294	-109	-3	1945	-48	8936	-7538
175	147	-1.60	24	.40	3515	2765	-750	-21	2290	-48	8061	-7538
178	152	6.60	24	.40	4498	2311	-2187	-49	2464	198	7187	-7538
181	157	6.60	23	.40	3291	1526	-1765	-54	2553	198	6313	-7538
184	162	6.60	22	.40	3719	1951	-1768	-48	2642	198	6649	-7538
187	168	4.15	21	.40	3763	2304	-1459	-39	2732	125	6986	-7538
190	173	1.70	20	.40	2665	2661	-4	-0	2826	51	7322	-7538
193	166	1.70	19	.40	2885	3091	206	7	2921	51	7658	-7538
196	145	1.70	19	.40	3642	3159	-483	-13	3015	51	7631	-7538
199	126	1.80	20	.40	2628	2832	204	8	2893	54	7423	-7538
202	116	1.80	18	.40	3989	2521	-1468	-37	2527	54	7479	-7538
205	110	1.30	16	.40	3618	2758	-860	-24	2196	39	8061	-7538
208	104	.00	14	.40	4575	3127	-1448	-32	2021	0	8644	-7538
211	100	-7.00	13	.40	3959	3395	-564	-14	1917	-210	9227	-7538
214	100	-6.50	15	.40	4006	3889	-117	-3	1812	-195	9810	-7538
217	100	-4.00	18	.40	5431	4477	-954	-18	1743	-120	10392	-7538
220	100	-2.00	20	.40	5529	5120	-409	-7	1743	-60	10975	-7538
223	111	-2.00	23	.40	5728	5411	-317	-6	1743	-60	11267	-7538
226	122	-2.00	23	.40	6521	5557	-964	-15	1743	-60	11412	-7538
229	132	.00	23	.40	9564	5950	-3614	-38	1931	0	11558	-7538
232	139	.00	23	.40	9107	6062	-3045	-33	2119	0	11482	-7538
235	143	.00	24	.40	6535	5730	-805	-12	2307	0	10961	-7538
238	147	3.60	28	.40	5982	5429	-553	-9	2419	108	10441	-7538
241	151	3.60	31	.40	5555	4982	-573	-10	2492	108	9921	-7538
244	154	3.60	35	.40	4643	4535	-108	-2	2565	108	9400	-7538
247	154	2.50	28	.40	2849	4534	1685	59	2631	75	9366	-7538
250	154	1.40	22	.40	2650	4761	2111	80	2684	42	9574	-7538
253	150	1.40	18	.40	2207	4511	2304	104	2684	42	9324	-7538
256	137	1.40	21	.40	3028	3346	318	10	2684	42	8159	-7538
259	124	1.00	24	.40	4304	2093	-2211	-51	2609	30	6993	-7538
262	116	.00	23	.40	2463	673	-1790	-73	2384	0	5828	-7538
265	110	.00	20	.40	3636	1686	-1950	-54	2164	0	7060	-7538
268	104	.00	19	.40	3650	2776	-874	-24	2021	0	8293	-7538
271	99	-4.30	20	.40	4833	3775	-1058	-22	1917	-129	9526	-7538
274	98	-4.20	21	.40	4833	4907	74	2	1812	-126	10759	-7538
277	96	-3.10	22	.40	3231	5271	2040	63	1733	-93	11169	-7538

LAG1 = 6, LAG2 = 17, LAG3 = 52

K1 = 3.049453, K2 = 21.002982, K3 = 84.985326

K4 = -1409.673035, SUM = 1.285563E+08, HCT = .500000

NMAX = 279, NORMER = .532178, AVGINS = 2209.267853

TABLE 21

EXPERIMENTAL DATA AND CORRELATION FOR DOG V

TIME MIN	GLUCOSE MG PCT	DG/DT	FEMORAL INSULIN MU U/ML	BLOOD FLOW ML/MIN	MEASURED PANCREATIC INSULIN MU/ML	ESTIMATED PANCREATIC INSULIN MU U/ML	ERROR MU U/ML	PERCENT ERROR	TERM 1	TERM 2	TERM 3	TERM 4
1	80	.00	6	.42	82	-66	-148	-181	1272	0	1290	-2628
4	80	.00	6	.42	82	-66	-148	-181	1272	0	1290	-2628
7	80	.00	6	.42	82	-66	-148	-181	1272	0	1290	-2628
10	80	.00	6	.54	102	-66	-168	-165	1272	0	1290	-2628
13	80	.00	6	.54	102	-66	-168	-165	1272	0	1290	-2628
16	80	.00	6	.52	78	-66	-144	-185	1272	0	1290	-2628
19	80	.00	6	.52	78	-66	-144	-185	1272	0	1290	-2628
22	80	.00	6	.62	117	-66	-183	-156	1272	0	1290	-2628
25	80	.00	6	.62	117	-66	-183	-156	1272	0	1290	-2628
28	80	.00	6	.52	151	-66	-217	-144	1272	0	1290	-2628
31	80	.00	6	.52	76	-69	-145	-191	1269	0	1290	-2628
34	79	.00	6	.62	76	-79	-155	-204	1260	0	1290	-2628
37	79	-.20	6	.48	46	-90	-136	-295	1250	-1	1290	-2628
40	78	-.20	6	.48	46	-99	-145	-315	1241	-1	1290	-2628
43	77	-.20	6	.55	36	-113	-149	-415	1226	-1	1290	-2628
46	76	-.25	6	.55	36	-128	-164	-456	1212	-2	1290	-2628
49	75	-.30	6	.60	19	-143	-162	-851	1198	-2	1290	-2628
52	75	-.30	6	.58	21	-147	-168	-802	1193	-2	1290	-2628
55	75	-.30	6	.06	16	-147	-163	-1022	1193	-2	1290	-2628
58	75	.00	6	.06	16	-146	-162	-1010	1193	0	1290	-2628
61	75	.00	6	.50	20	-146	-166	-828	1193	0	1290	-2628
64	75	.00	5	.50	20	-146	-166	-828	1193	0	1290	-2628
67	75	.00	5	.48	31	-146	-177	-570	1193	0	1290	-2628
70	75	.00	5	.48	31	-174	-205	-662	1193	0	1261	-2628
73	75	.00	5	.57	17	-217	-234	-1378	1193	0	1218	-2628
76	75	.00	5	.55	22	-260	-282	-1283	1193	0	1175	-2628
79	75	.00	5	.55	22	-303	-325	-1478	1193	0	1132	-2628
82	75	.00	4	.50	24	-346	-370	-1542	1193	0	1089	-2628
85	75	.00	4	.38	24	-382	-406	-1692	1193	0	1053	-2628
88	75	.00	4	.38	24	-414	-438	-1826	1193	0	1021	-2628
91	75	.00	4	.38	24	-446	-470	-1960	1193	0	989	-2628
94	75	.00	5	.38	24	-479	-503	-2095	1193	0	956	-2628
97	88	.00	6	.45	295	-301	-596	-202	1403	0	924	-2628
100	108	.00	7	.45	1020	-18	-1038	-102	1718	0	892	-2628
103	122	6.60	7	.45	109	212	103	94	1937	43	860	-2628
106	136	5.60	8	.40	604	586	-18	-3	2157	36	1021	-2628
109	149	4.60	8	.50	1288	960	-328	-25	2376	30	1182	-2628
112	158	4.60	9	.50	1328	1264	-64	-5	2520	30	1343	-2628
115	165	4.60	9	.50	1623	1531	-92	-6	2625	30	1504	-2628
118	172	2.20	9	.50	1136	1749	613	54	2729	14	1633	-2628
121	178	2.20	9	.45	1961	1974	13	1	2826	14	1762	-2628
124	177	2.20	10	.60	1904	2097	193	10	2820	14	1891	-2628
127	166	1.67	11	.65	2358	1960	-398	-17	2643	11	1934	-2628
130	155	-3.71	12	.50	2090	1748	-342	-16	2465	-24	1934	-2628
133	143	-3.71	14	.50	2313	1562	-751	-32	2279	-24	1934	-2628
136	132	-3.81	14	.58	2222	1465	-757	-34	2093	-25	2024	-2628
139	120	-3.90	14	.65	2292	1546	-746	-33	1907	-25	2293	-2628
142	111	-3.90	14	.50	1982	1677	-305	-15	1769	-25	2561	-2628
145	104	-3.90	14	.50	1405	1831	426	30	1654	-25	2830	-2628
148	97	-2.40	14	.50	1184	1905	721	61	1540	-15	3009	-2628
151	90	-2.40	13	.67	990	1795	805	81	1430	-15	3009	-2628
154	84	-2.40	12	.52	864	1694	830	96	1328	-15	3009	-2628
157	77	-2.13	12	.70	303	1594	1291	426	1227	-14	3009	-2628

TABLE 21 (CONT'D)

160	75	-2.13	11	.60	893	1515	622	70	1193	-14	2964	-2628
163	89	-2.13	10	.45	1470	1594	124	8	1408	-14	2828	-2628
166	102	2.25	11	.60	2123	1701	-422	-20	1622	14	2692	-2628
169	116	4.50	12	.50	2381	1795	-586	-25	1837	29	2557	-2628
172	123	4.50	14	.55	2989	1775	-1214	-41	1953	29	2421	-2628
175	127	4.50	16	.60	2878	1706	-1172	-41	2020	29	2285	-2628
178	131	1.40	19	.60	2439	1617	-822	-34	2087	9	2149	-2628
181	135	1.40	22	.50	2676	2056	-620	-23	2139	9	2536	-2628
184	136	1.40	25	.60	3765	2467	-1298	-34	2163	9	2923	-2628
187	138	.50	28	.55	3531	2872	-659	-19	2187	3	3310	-2628
190	139	.50	25	.67	3502	3455	-47	-1	2211	3	3869	-2628
193	125	.50	23	.53	3237	3871	634	20	1982	3	4513	-2628
196	110	-2.15	20	.55	1941	4269	2328	120	1753	-14	5158	-2628
199	96	-4.80	18	.55	1377	4668	3291	239	1524	-31	5803	-2628
202	89	-4.80	15	.60	1163	4403	3240	279	1412	-31	5650	-2628
205	85	-4.80	13	.47	1032	3798	2766	268	1360	-31	5097	-2628
208	82	-1.10	12	.57	1029	3225	2196	213	1307	-7	4553	-2628
211	78	-1.10	10	.56	260	2631	2371	912	1241	-7	4025	-2628
214	72	-1.10	9	.65	352	2008	1656	470	1145	-7	3497	-2628
217	70	-2.00	7	.60	332	1442	1110	334	1113	-13	2970	-2628
220	70	-2.00	8	.45	285	1068	783	275	1113	-13	2596	-2628
223	70	.00	10	.50	207	783	576	278	1113	0	2298	-2628
226	97	.00	12	.35	596	910	314	53	1538	0	2000	-2628
229	137	.00	14	.45	2524	1249	-1275	-51	2174	0	1703	-2628
232	163	13.33	16	.50	2988	1680	-1308	-44	2586	86	1636	-2628
235	181	13.33	17	.45	3721	2375	-1346	-36	2887	86	2030	-2628
238	200	6.30	20	.30	3856	3024	-832	-22	3188	41	2424	-2628
241	217	6.30	23	.45	4129	3676	-453	-11	3446	41	2818	-2628
244	228	6.30	27	.50	4105	4243	138	3	3619	41	3212	-2628
247	238	3.63	30	.65	3907	4793	886	23	3792	23	3606	-2628
250	248	3.63	32	.65	5028	5443	415	8	3945	23	4103	-2628
253	218	3.63	33	.60	4360	5669	1309	30	3468	23	4807	-2628
256	188	-3.50	35	.60	5337	5850	513	10	2990	-23	5510	-2628
259	162	-10.00	37	.45	5768	6090	322	6	2569	-64	6213	-2628
262	145	-10.00	34	.50	8850	6308	-2542	-29	2302	-64	6699	-2628
265	129	-6.50	32	.45	7800	6463	-1337	-17	2058	-42	7075	-2628
268	114	-5.13	29	.40	8300	6603	-1697	-20	1813	-33	7451	-2628
271	101	-5.13	26	.40	7104	6766	-338	-5	1600	-33	7827	-2628
274	96	-5.56	23	.40	7104	6440	-664	-9	1533	-36	7570	-2628
277	93	-1.40	20	.30	6403	5839	-564	-9	1479	-9	6997	-2628
280	88	-1.40	18	.40	7944	5187	-2757	-35	1400	-9	6424	-2628
283	85	-1.00	18	.35	4042	4521	479	12	1352	-6	5803	-2628
286	82	-1.50	18	.45	1853	3825	1972	106	1304	-10	5158	-2628
289	80	-1.00	18	.45	1548	3151	1603	104	1272	-6	4513	-2628
292	77	-1.00	18	.45	1008	2454	1446	143	1219	-6	3869	-2628
295	75	.00	18	.45	323	2434	2111	653	1193	0	3869	-2628
298	87	-1.67	19	.30	274	2606	2332	851	1376	-11	3869	-2628
301	121	.00	19	.30	270	3165	2895	1072	1925	0	3869	-2628
304	156	11.50	19	.50	4157	3822	-335	-8	2473	74	3903	-2628
307	190	11.50	19	.50	5181	4405	-776	-15	3022	74	3937	-2628
310	218	11.50	22	.60	5742	4884	-858	-15	3468	74	3970	-2628
313	300	10.42	25	.60	5418	6215	797	15	4772	67	4004	-2628
316	257	18.33	28	.70	4787	5608	821	17	4080	118	4038	-2628
319	221	6.42	31	.70	4269	4996	727	17	3510	41	4072	-2628
322	202	-14.50	34	.65	4893	5005	112	2	3213	-93	4513	-2628
325	190	-10.67	36	.43	5036	5484	448	9	3022	-69	5158	-2628
328	173	-4.00	39	.65	5101	5906	805	16	2757	-26	5803	-2628
331	151	-4.00	37	.50	7909	6181	-1728	-22	2406	-26	6428	-2628
334	137	-8.67	35	.50	8817	6512	-2305	-26	2181	-56	7014	-2628
337	123	-4.71	34	.42	1154	6899	5745	498	1956	-30	7601	-2628
340	130	-4.71	33	.42	8559	7596	-963	-11	2068	-30	8187	-2628
343	121	-1.19	32	.42	8559	7406	-1153	-13	1918	-8	8124	-2628
346	111	-.40	31	.46	9578	6875	-2703	-28	1768	-3	7737	-2628
349	93	-3.14	31	.46	9578	6187	-3391	-35	1485	-20	7351	-2628
352	86	-3.14	29	.34	7207	5769	-1438	-20	1368	-20	7050	-2628
355	86	-7.33	28	.42	7207	5613	-1594	-22	1368	-47	6921	-2628
358	86	.00	27	.42	7207	5532	-1675	-23	1368	0	6792	-2628
361	86	.00	26	.42	7207	5403	-1804	-25	1368	0	6663	-2628
364	86	.00	25	.42	7207	5145	-2062	-29	1368	0	6405	-2628

LAG1 = 0, LAG2 = 6, LAG3 = 13

K1 = 3.340288, K2 = 5.412906, K3 = 45.134725

K4 = -569.115639, SUM = 2.040092E+08, HCT = .500000

NMAX = 365, NORMER = .510262, AVGINS = 2544.713104

TABLE 22

EXPERIMENTAL DATA AND CORRELATION FOR DOG O

TIME MIN	GLUCOSE MG PCT	DG/DT	FEMORAL INSULIN MU U/ML	BLOOD FLOW ML/MIN	MEASURED PANCREATIC INSULIN MU/ML	ESTIMATED PANCREATIC INSULIN MU U/ML	ERROR MU U/ML	PERCENT ERROR	TERM 1	TERM 2	TERM 3	TERM 4
1	52	.00	12	.25	1740	1930	190	11	-20461	-0	-3366	25757
4	52	.00	12	.25	1740	1930	190	11	-20461	-0	-3366	25757
7	52	.00	12	.25	1740	1930	190	11	-20461	-0	-3366	25757
10	52	.00	12	.25	1740	1930	190	11	-20461	-0	-3366	25757
13	52	.00	11	.25	1690	1930	240	14	-20461	-0	-3366	25757
16	52	.00	10	.25	1690	1930	240	14	-20461	-0	-3366	25757
19	52	.00	9	.25	1690	1930	240	14	-20461	-0	-3366	25757
22	52	.00	8	.25	1690	1930	240	14	-20461	-0	-3366	25757
25	52	.00	7	.25	1690	1930	240	14	-20461	-0	-3366	25757
28	52	.00	6	.25	1690	1930	240	14	-20461	-0	-3366	25757
31	52	.00	6	.25	2970	1930	-1040	-35	-20461	-0	-3366	25757
34	52	.00	6	.25	2970	1930	-1040	-35	-20461	-0	-3366	25757
37	52	.00	7	.25	2970	2211	-759	-26	-20461	-0	-3086	25757
40	52	.00	7	.25	2970	2491	-479	-16	-20461	-0	-2805	25757
43	52	.00	8	.25	2970	3052	82	3	-20461	-0	-2244	25757
46	52	.00	8	.25	4250	3333	-917	-22	-20461	-0	-1964	25757
49	52	.00	8	.25	4250	3613	-637	-15	-20461	-0	-1683	25757
52	52	.00	8	.25	4250	3613	-637	-15	-20461	-0	-1683	25757
55	52	.00	7	.25	4250	3613	-637	-15	-20461	-0	-1683	25757
58	52	.00	7	.25	4250	3613	-637	-15	-20461	-0	-1683	25757
61	52	.00	7	.25	4250	3333	-917	-22	-20461	-0	-1964	25757
64	52	.00	6	.25	4250	3333	-917	-22	-20461	-0	-1964	25757
67	52	.00	6	.25	4250	3052	-1198	-28	-20461	-0	-2244	25757
70	52	.00	6	.25	4250	3052	-1198	-28	-20461	-0	-2244	25757
73	52	.00	6	.25	4250	3052	-1198	-28	-20461	-0	-2244	25757
76	52	.00	6	.25	3420	3333	-87	-3	-20461	-0	-1964	25757
79	52	.00	5	.25	3420	3333	-87	-3	-20461	-0	-1964	25757
82	52	.00	5	.25	3420	3333	-87	-3	-20461	-0	-1964	25757
85	52	.00	5	.25	3420	3333	-87	-3	-20461	-0	-1964	25757
88	52	.00	4	.25	3420	3613	193	6	-20461	-0	-1683	25757
91	52	.00	4	.25	1550	3613	2063	133	-20461	-0	-1683	25757
94	52	.00	4	.25	1550	3613	2063	133	-20461	-0	-1683	25757
97	52	.00	4	.25	1550	3613	2063	133	-20461	-0	-1683	25757
100	52	.00	4	.25	1550	3894	2344	151	-20461	-0	-1403	25757
103	52	.00	4	.25	1550	3894	2344	151	-20461	-0	-1403	25757
106	52	.00	4	.25	2260	3894	1634	72	-20461	-0	-1403	25757
109	52	.00	4	.25	2260	3894	1634	72	-20461	-0	-1403	25757
112	52	.00	4	.25	2260	4174	1914	85	-20461	-0	-1122	25757
115	52	.00	4	.25	2260	4174	1914	85	-20461	-0	-1122	25757
118	52	.00	4	.25	2260	4174	1914	85	-20461	-0	-1122	25757
121	52	.00	4	.25	6000	4174	-1826	-30	-20461	-0	-1122	25757
124	52	.00	5	.25	6000	4174	-1826	-30	-20461	-0	-1122	25757
127	52	.00	6	.25	6000	4174	-1826	-30	-20461	-0	-1122	25757
130	52	.00	7	.25	6000	4174	-1826	-30	-20461	-0	-1122	25757
133	52	.00	7	.25	6000	4174	-1826	-30	-20461	-0	-1122	25757
136	52	.00	8	.25	5770	4174	-1596	-28	-20461	-0	-1122	25757
139	52	.00	7	.25	5770	4174	-1596	-28	-20461	-0	-1122	25757
142	53	.05	7	.25	5770	4170	-1600	-28	-20461	-4	-1122	25757
145	53	.10	7	.25	5770	3846	-1924	-33	-20500	-8	-1403	25757
148	53	.10	6	.25	5770	3728	-2042	-35	-20618	-8	-1403	25757
151	53	.10	6	.25	2130	3369	1239	58	-20697	-8	-1683	25757
154	53	.10	6	.25	2130	3010	880	41	-20776	-8	-1964	25757
157	54	.10	6	.25	2130	2651	521	24	-20854	-8	-2244	25757
160	54	.10	6	.25	2130	2572	442	21	-20933	-8	-2244	25757
163	54	.10	6	.25	2130	2774	644	30	-21012	-8	-1964	25757
166	54	.10	6	.25	2480	2695	215	9	-21090	-8	-1964	25757
169	54	.10	6	.25	2480	2616	136	5	-21169	-8	-1964	25757
172	55	.10	6	.25	2480	2818	338	14	-21248	-8	-1683	25757
175	55	.10	6	.25	2480	2740	260	10	-21326	-8	-1683	25757
178	55	.10	7	.25	2480	2661	181	7	-21405	-8	-1683	25757
181	55	.10	7	.25	1810	2582	772	43	-21484	-8	-1683	25757
184	55	.10	7	.25	1810	2503	693	38	-21563	-8	-1683	25757
187	56	.10	7	.25	1810	2425	615	34	-21641	-8	-1683	25757
190	56	.10	6	.25	1810	2346	536	30	-21720	-8	-1683	25757
193	56	.10	6	.25	1810	2267	457	25	-21799	-8	-1683	25757
196	56	.10	6	.25	1230	2189	959	78	-21877	-8	-1683	25757
199	56	.10	6	.25	1230	1829	599	49	-21956	-8	-1964	25757
202	57	.10	7	.25	1230	1751	521	42	-22035	-8	-1964	25757
205	57	.10	7	.25	1230	1672	442	36	-22113	-8	-1964	25757
208	57	.10	7	.25	1230	1593	363	30	-22192	-8	-1964	25757
211	57	.10	7	.25	1330	1515	185	14	-22271	-8	-1964	25757
214	58	.10	7	.25	1330	1716	386	29	-22350	-8	-1683	25757
217	60	.10	6	.25	1330	1598	268	20	-22468	-8	-1683	25757
220	60	.20	6	.25	1330	1472	142	11	-22586	-16	-1683	25757
223	60	.00	6	.25	1330	1253	-77	-6	-22822	-0	-1683	25757
226	60	.00	6	.25	845	185	-660	-78	-23609	-0	-1964	25757
229	60	.00	7	.25	845	185	-660	-78	-23609	-0	-1964	25757
232	60	.00	8	.25	845	185	-660	-78	-23609	-0	-1964	25757
235	63	.00	8	.25	845	185	-660	-78	-23609	-0	-1964	25757
238	67	.00	9	.25	845	466	-379	-45	-23609	-0	-1683	25757

LAG1 = 8, LAG2 = 6, LAG3 = 23

K1 = -49.184694, K2 = -41.032647, K3 = -35.067274

K4 = 3002.178925, SUM = 9.372513E+07, HCT = .500000

[illegible] = 239. NUMBER = .399032, AVGINS = 2729.645813

TABLE 23

EXPERIMENTAL DATA AND CORRELATION FOR DOG P

TIME MIN	GLUCOSE MG PCT	DG/DT	FEMORAL INSULIN MU U/ML	BLOOD FLOW ML/MIN	MEASURED PANCREATIC INSULIN MU/ML	ESTIMATED PANCREATIC INSULIN MU U/ML	ERROR MU U/ML	PERCENT ERROR	TERM 1	TERM 2	TERM 3	TERM 4
1	75	.00	15	.20	380	822	442	116	27	-0	1339	-544
4	75	.00	16	.20	380	822	442	116	27	-0	1339	-544
7	75	.00	17	.20	380	911	531	140	27	-0	1429	-544
10	75	.00	18	.20	380	1000	620	163	27	-0	1518	-544
13	75	.00	18	.21	730	1090	360	49	27	-0	1607	-544
16	75	.00	18	.21	730	1090	360	49	27	-0	1607	-544
19	75	.00	18	.21	730	1090	360	49	27	-0	1607	-544
22	75	.00	17	.21	730	1000	270	37	27	-0	1518	-544
25	75	.00	17	.21	730	1000	270	37	27	-0	1518	-544
28	75	.00	17	.21	1060	1000	-60	-6	27	-0	1518	-544
31	73	.00	17	.21	1060	1000	-60	-6	26	-0	1518	-544
34	70	.00	17	.21	1060	998	-62	-6	25	-0	1518	-544
37	65	.00	17	.21	1060	997	-63	-6	23	-0	1518	-544
40	64	.00	17	.21	1060	996	-64	-6	23	-0	1518	-544
43	64	.00	17	.16	1435	996	-439	-31	23	-0	1518	-544
46	64	.00	17	.16	1435	996	-439	-31	23	-0	1518	-544
49	64	.00	17	.16	1435	996	-439	-31	23	-0	1518	-544
52	64	.00	17	.16	1435	996	-439	-31	23	-0	1518	-544
55	64	.00	17	.16	1435	996	-439	-31	23	-0	1518	-544
58	64	-1.00	17	.17	1695	1034	-661	-39	23	38	1518	-544
61	64	-1.50	17	.20	1695	1054	-641	-38	23	57	1518	-544
64	64	-2.00	17	.20	1695	1073	-622	-37	23	76	1518	-544
67	60	-.50	18	.20	1695	1103	-592	-35	21	19	1607	-544
70	60	.00	19	.20	1695	1084	-611	-36	21	-0	1607	-544
73	60	.00	19	.15	1260	1173	-87	-7	21	-0	1697	-544
76	55	.00	18	.15	1260	1172	-88	-7	20	-0	1697	-544
79	55	.00	18	.15	1260	1082	-178	-14	20	-0	1607	-544
82	55	.00	18	.15	1260	1082	-178	-14	19	-0	1607	-544
85	54	.00	17	.15	1260	993	-267	-21	19	-0	1518	-544
88	54	.00	17	.14	1105	993	-112	-10	19	-0	1518	-544
91	54	.00	17	.14	1105	993	-112	-10	19	-0	1518	-544
94	54	-2.00	18	.14	1105	1158	53	5	19	76	1607	-544
97	53	.00	18	.14	1105	1082	-23	-2	19	-0	1607	-544
100	53	.00	19	.14	1105	1171	66	6	19	-0	1697	-544
103	53	.00	19	.13	870	1171	301	35	19	-0	1697	-544
106	52	.00	18	.13	870	1081	211	24	19	-0	1607	-544
109	52	-.10	17	.13	870	996	126	14	18	4	1518	-544
112	52	-.10	16	.13	870	996	126	14	18	4	1518	-544
115	51	-.10	15	.13	870	906	36	4	18	4	1429	-544
118	51	-.10	15	.13	640	817	177	28	18	4	1339	-544
121	51	-.10	14	.13	640	817	177	28	18	4	1339	-544
124	51	-.10	14	.13	640	728	88	14	18	4	1250	-544
127	51	-.10	13	.13	640	728	88	14	18	4	1250	-544
130	51	-.10	13	.13	640	638	-2	-0	18	4	1161	-544
133	51	-.10	13	.15	650	638	-12	-2	18	4	1161	-544
136	51	-.10	12	.15	650	638	-12	-2	18	4	1161	-544
139	51	-.10	11	.15	650	549	-101	-16	18	4	1072	-544
142	51	-.10	11	.15	650	460	-190	-29	18	4	982	-544
145	51	-.10	10	.15	650	460	-190	-29	18	4	982	-544
148	51	-.05	10	.16	660	369	-291	-44	18	2	893	-544
151	51	.00	11	.16	660	367	-293	-44	18	-0	893	-544
154	50	.00	11	.16	660	456	-204	-31	18	-0	982	-544
157	49	.00	12	.16	660	544	-116	-18	17	-0	1072	-544

TABLE 23 (CONT'D)

160	48	.00	13	.16	660	544	-116	-18	17	-0	1072	-544
163	47	.00	13	.18	570	633	63	11	17	-0	1161	-544
166	46	.00	13	.18	570	633	63	11	16	-0	1161	-544
169	45	.00	13	.18	570	633	63	11	16	-0	1161	-544
172	44	.00	12	.18	570	543	-27	-5	16	-0	1072	-544
175	44	.00	12	.18	570	543	-27	-5	15	-0	1072	-544
178	43	.00	12	.21	670	542	-128	-19	15	-0	1072	-544
181	42	-.30	13	.21	670	553	-117	-17	15	11	1072	-544
184	42	-.30	13	.21	670	643	-27	-4	15	11	1161	-544
187	42	-.30	13	.21	670	643	-27	-4	15	11	1161	-544
190	42	-.30	14	.21	670	643	-27	-4	15	11	1161	-544
193	42	-.30	14	.22	475	732	257	54	15	11	1250	-544
196	42	-.30	13	.22	475	732	257	54	15	11	1250	-544
199	42	-.30	12	.21	488	643	155	32	15	11	1161	-544
202	42	-.30	11	.21	488	553	65	13	15	11	1072	-544
205	42	-.30	10	.21	488	464	-24	-5	15	11	982	-544
208	42	-.30	9	.21	395	375	-20	-5	15	11	893	-544
211	42	.00	10	.21	395	363	-32	-8	15	-0	893	-544
214	42	.00	11	.21	395	453	58	15	15	-0	982	-544
217	42	.00	12	.21	395	542	147	37	15	-0	1072	-544
220	42	.00	13	.21	395	631	236	60	15	-0	1161	-544
223	42	.00	14	.23	490	721	231	47	15	-0	1250	-544
226	42	.00	14	.23	490	721	231	47	15	-0	1250	-544
229	42	.00	14	.23	490	721	231	47	15	-0	1250	-544
232	42	.00	13	.24	490	631	141	29	15	-0	1161	-544
235	42	.00	13	.24	490	631	141	29	15	-0	1161	-544
238	42	.00	13	.24	535	631	96	18	15	-0	1161	-544
241	42	.00	13	.24	535	631	96	18	15	-0	1161	-544
244	42	.00	13	.24	535	631	96	18	15	-0	1161	-544
247	42	.00	13	.24	535	631	96	18	15	-0	1161	-544
250	42	.00	13	.24	535	631	96	18	15	-0	1161	-544
253	42	.00	13	.27	725	631	-94	-13	15	-0	1161	-544
256	41	.00	13	.27	725	631	-94	-13	15	-0	1161	-544
259	41	.00	13	.27	725	631	-94	-13	15	-0	1161	-544
262	41	.00	13	.27	725	631	-94	-13	15	-0	1161	-544
265	41	.00	13	.27	725	631	-94	-13	15	-0	1161	-544
268	41	.00	13	.27	535	631	96	18	15	-0	1161	-544
271	41	.00	13	.27	535	631	96	18	15	-0	1161	-544

LAG1 = 0, LAG2 = 29, LAG3 = 2

K1 = .035518, K2 = -15.253547, K3 = 8.929317

K4 = -92.439417, SUM = 5.878529E+06, HCT = .500000

NMAX = 271, NORMER = .320221, AVGINS = 798.110291

**** ALL INPUT DATA HAVE BEEN PROCESSED.
AT LOCATION 17040

APPENDIX B

GLUCOSE AND INSULIN CORRELATION PROGRAM AND MULTIVARIATE STATISTICAL ANALYSIS

This MAD[4] program predicts the insulin concentration in pancreatic venous plasma given continuous records of the arterial blood glucose concentration and the pancreatic venous plasma insulin concentration, and the femoral venous insulin concentration measured periodically. A mathematical model describing the response of the pancreas to changes in the blood glucose and insulin concentrations is given by equation (5.1).

Application of this model to a set of experimental data requires the determination of three time lags and four rate constants. This program determines the rate constants by using the least squares method to fit the model to the experimental data when the time lags are specified. An iterative procedure is used to determine the set of time lags giving the "best" fit of the model to the data. The smallest integral of the square of the error between the measured and the predicted insulin concentrations is the criterion for determining the "best" fit.

Having determined the "best set of time lags the program can be used to study the modified models given by equations (5.2-5.7). For each model the program determines the appropriate rate constants and prints out the arterial glucose concentration, femoral venous plasma insulin concentration, pancreatic venous catheter blood flow rate, measured pancreatic venous insulin concentration, predicted pancreatic venous plasma insulin concentration, error, percent error, and the contribution of each of the four terms of the equation to the total

response at given times during the experiment. The blood glucose concentration, the measured and the predicted pancreatic venous insulin concentrations are plotted as functions of time using the library subroutines[40].

When data from a series of similar experiments are processed together, the program is designed to use multivariate statistical techniques to test for the existance of significant differences between the different models applied to the experimental data. Hotelling's T^2 test is used to test for differences in the mean errors obtained with the different models. This method was described in Chapter V.

Modifications

1. The multivariate statistical analysis section of the program can be deleted by removing all those statements following the statement TRANSFER TO START up to the beginning of the internal function FILLIN.

2. To minimize computer time required for the iterative determination of the time lags, it is desirable to delete the six modified models, the table of results at given times, the plots of the results, and the multivariate statistical analysis, printing only the lags, constants and the integral of the square of the error for each iteration.

TABLE 24

SYMBOLS USED IN THE COMPUTER PROGRAM FOR CORRELATING THE BLOOD GLUCOSE AND THE PANCREATIC VENOUS PLASMA INSULIN CONCENTRATIONS

MAD Name	Mode	Definition	Units
A2	1	Index for plotting INS	
A3	1	Index for plotting I	
AA	1	Index for plotting GLUC	
ADDINS	0	Partial Sum	
AVGINS	0	Average pancreatic venous insulin concentration	μU/ml
BASE	1	Index representing the model used as the references in Hotelling's T^2 test.	
B	1	Index specifying a given model	
D1	0	Number of data points in group 1 for Hotelling's T^2 test	
D2	0	Number of data points in group 2 for Hotelling's T^2 test	
D3	0	Number of data points in group 3 for Hotelling's T^2 test	
DGDT	0	Time derivative of the blood glucose concentration	$\frac{\text{mg/100 ml}}{\text{min}}$
DG	0	Glucose derivative term	
DIF1	0	Difference in mean errors for Hotelling's T^2 test	
DIF2	0	Difference in mean errors for Hotelling's T^2 test	
DIF3	0	Difference in mean errors for Hotelling's T^2 test	
DUMMY	0	Arguement of GJR.	
DY	0	Increment in Y	
E1	0	Mean error in group 1 for Hotelling's T^2 test	
E2	0	Mean error in group 2 for Hotelling's T^2 test	
E3	0	Mean error in group 3 for Hotelling's T^2 test	
ERROR	0	Difference between measured and calculated insulin concentrations	μU/ml

TABLE 24 (CONT'D)

SYMBOLS USED IN THE COMPUTER PROGRAM FOR CORRELATING THE BLOOD GLUCOSE AND THE PANCREATIC VENOUS PLASMA INSULIN CONCENTRATIONS

MAD Name	Mode	Definition	Units
EX	0	Exponent on the peripheral insulin term	
FA2	0	Dummy variable for A2	
FA3	0	Dummy variable for A3	
FA	0	Dummy variable for AA	
FI	1	Integer value of F	
F	0	Scale factor for plotting blood glucose concentration	
FSTAT	0	F statistic	
FVI	0	Femoral venous plasma insulin concentration	μU/ml
GLUC	0	Blood glucose concentration	mg/100 ml
G	0	Blood glucose term	
HCT	0	Hematocrit	
HOTELT	0	Hotelling's T^2 statistic	
II	0	Pancreatic venous insulin term	μU/ml
IMAGE	0	Storage location used to dimension the graph	
INS	0	Measure pancreatic venous plasma insulin concentration	μU/ml
INVSSS	7	Inverse of SSS	
I	0	Calculated pancreatic venous insulin concentration	μU/ml
IX	1	Index	
JJJ	7	Copy of SSS	
J	1	Index	
JX	1	Index	
K11...K44	0	Estimated values of K1, K2, K3, K^4	
K1	0	Coefficient, blood glucose term	$(\mu U/min)(mg/100\ ml)^{-1}$
K2	0	Coefficient, derivative term	$(\mu U/min)(mg/100\ ml)^{-1}min$
K3	0	Coefficient, peripheral term	$(\mu U/min)(\mu U/ml)^{-1}_{peripheral}$

TABLE 24 (CONT'D)

SYMBOLS USED IN THE COMPUTER PROGRAM FOR CORRELATING THE BLOOD GLUCOSE AND THE PANCREATIC VENOUS PLASMA INSULIN CONCENTRATIONS

MAD Name	Mode	Definition	Units
K4	0	Coefficient, constant term	(μU/min)
KK	2	Boolean control symbol	
KX	0	Constant in the peripheral insulin term	
KY	0	Constant in the peripheral insulin term	
L11...L44	0	Estimated time lags	min
LABEL	1	Graph title	
LAG1	1	Time lag on the blood glucose term	min
LAG2	1	Time lag on the derivative term	min
LAG3	1	Time lag on the peripheral insulin term	min
M	0	Argument of SLE.	
N	1	Time	min
N1	1	Time at start of experiment	min
N2	1	Time at end of experiment	min
NAME	0	Identification	
NAME1	0	Identification	
NAME2	0	Identification	
NCHAR	0	Argument of PLOT4., number of characters in LABEL	
NMAX	1	Total number of data points less one	
NMLAG1	1	N - LAG1	min
NMLAG2	1	N - LAG2	min
NMLAG3	1	N - LAG3	
NORMER	0	Normalized Error	μU/ml
PCTERR	0	Percent error	
PR1	2	Printing control	
P	0	Peripheral insulin term	μU/ml
RR	0	Argument of SLE.	
RT	0	Least squares analysis, vector of right side	
SD	0	Standard deviation of the error	
SETS	1	Number of groups into which each experiment is divided in Hotelling's T^2 test	

TABLE 24 (CONT'D)

SYMBOLS USED IN THE COMPUTER PROGRAM FOR CORRELATING THE BLOOD GLUCOSE AND THE PANCREATIC VENOUS PLASMA INSULIN CONCENTRATIONS

MAD Name	Mode	Definition	Units
SIG	0	Element of the covariance matrix	
SKIP	1	Number of data points bypassed in printing results	
SSERR	0	Sum of the error	
SSS	7	Covariance matrix	
SUMERR	0	Sum of the absolute value of the error	μU/ml
SUMSQE	0	Sum of the square of the error	μU/ml
SX...	0	Partial sum	
SY...	0	Sum error for a given group of data	
TA	1	Time required to print summary	
TB	1	Time at given location in program	
TC	1	Time at given location in program	
TERM1	0	Response of pancreas proportional to glucose concentration	
TERM2	0	Response of pancreas proportional to the derivative of glucose concentration	
TERM3	0	Response of pancreas proportional to femoral	
TERM4	0	Response independent of insulin or glucose insulin concentration	
TL	0	Time left	sec
T	0	Storage for least squares calculations	
V1	0	Argument of SLE.	
V	0	Pancreatic venous blood flow rate	ml/min
W1	0	Partial sum of errors	
W2	0	Partial sum	
W3	0	Partial sum	
X1MAX	1	Number of experiments	
X1MAXL1	1	X1MAX - 1	
X1	1	Index, Experiment number	
X2	1	Index, Model number	
XBAR	0	Mean error	
X	1	Index	
XX	0	Index	

TABLE 24 (CONT'D)

SYMBOLS USED IN THE COMPUTER PROGRAM FOR CORRELATING THE BLOOD GLUCOSE AND THE PANCREATIC VENOUS PLASMA INSULIN CONCENTRATIONS

MAD Name	Mode	Definition	Units
Y1	0	Mean error in group 1 for Hotelling's T^2 test	
Y2	0	Mean error in group 2 for Hotelling's T^2 test	
Y3	0	Mean error in group 3 for Hotelling's T^2 test	
YF	0	Floating point equivalent for elements of YY	
YMAX	0	Maximum insulin value to be plotted	
YY	6	Mean error vector	

LIBRARY(40)	SUBROUTINES CALLED BY PROGRAM	MODE NUMBERS
GJR.	DAYTIM.	0 = Floating point
PLOT1.	ZERO.	1 = Integer
PLOT2.	SETERR.	2 = Boolean
PLOT3.	TIMLFT.	6 = Vector
PLOT4.		7 = Matrix
SLE.	INCLUDE MATRIX PACKAGE	

```
$COMPILE MAD, EXECUTE, DUMP, I/O DUMP, PRINT OBJECT
$PUNCH OBJECT
          R    READ INSULIN AND GLUCOSE DATA
           R'N
           INCLUDE MATRIX
           PARAMETER VM(6), MM(7)
           MODE NUMBER MM, JJJ(1*3*3)
           MODE NUMBER MM, SSS(1*3*3)
           MODE NUMBER VM, YY(1*3)
           MODE NUMBER MM, INVSSS(1*3*3)
           EQUIVALENCE (SSS, SIG)
           EQUIVALENCE (YY, YF)
           FTRAP.
           BOOLEAN KK , PR1
           INTEGER AA, A2, A3, B, BASE, E, FI, IX, J, J1, JX, K, LAG1,
          1  LAG2, LAG3, MAX, N, N1, N2, NMAX, NMLAG1, NMLAG2, NMLAG3,
          1  SKIP, X, X1, X1MXL1, X22
           DIMENSION DGDT(400), DIF1(14), DIF2(14), DIF3(14), E1(14*7),
          1  E2(14*7), E3(14*7), ERR(400*7), ERROR(400), FVI(400),
          1  GLUC(400), I(400), INS(400), M(5), PCTERR(400), RT(5),
          1  SIG(3*3), T(4*4), V(400), V1(5), Y1(7), Y2(7), Y3(7), YF,3)
           READ FORMAT FIRST, X1MAX, BASE, SETS
           V'S FIRST = $ 3 I 10 *$
           PRINT RESULTS X1MAX, BASE, SETS
           X1 = 1
START      READ FORMAT PX, EX, KX, KY, TA , PR1
           V'S PX = $ 3F10.0,3I10*$
           READ FORMAT DOG, NMAX, NAME, NAME1, NAME2, SKIP,LAG1,LAG2,
          1    N1, N2, YMAX  , KK, HCT
           VECTOR VALUES DOG = $ I3, S2, 3C6, S2, I3, S2, I3, S2, I3,
          1    S2, I3, S2, I3, S2, F6.0, S5, I1, S5, F5.0*$
           READ FORMAT DOG1, K11, K12, K13, K14, K21, K22, K23, K24
          1    , K31, K32, K33, K34
           READ FORMAT DOG1, L11, L12, L13, L14, L21, L22, L23, L24,
          1    L31, L32, L33, L34
           VECTOR VALUES DOG 1 = $13F6.0*$
           READ FORMAT DATA G, GLUC(0)...GLUC(NMAX)
           FILLIN.(GLUC,NMAX)
           READ FORMAT DATA I, INS(0)...INS(NMAX)
           READ FORMAT DATA F, FVI(0)...FVI(NMAX)
           FILLIN.(FVI,NMAX)
           READ FORMAT DATA V, V(0)...V(NMAX)
           VECTOR VALUES DATA G= $10F6.0*$
           VECTOR VALUES DATA I = $ 10 F 6.0 *$
           V'S DATA F = $10F6.0*$
           V'S DATA V = $20F3.2*$
           T'H AAA , FOR N=1,1, N.G. NMAX
           W'R V(N) .E. 0.0, V(N) = V(N-1)
AAA        W'R I S(N) .E.0.0, INS(N) = INS(N-1)
           ADDINS = 0.0
           T'H AAAA, FOR N = 0,1, N.G. NMAX
AAAA       ADDINS = ADDINS + INS(N)
           AVGINS = ADDINS/(NMAX + 1 )
           PRINT FORMAT TITLE, NAME, NAME1, NAME2, AVGINS
           VECTOR VALUES TITLE = $ 1H1, 40HCORRELATION OF INSULIN AND GL
          1 UCOSE FROM 3C6, F20.0*$
           T'H DONE, FOR B = 1, 1, B .G. 7
          R    SELECT CONSTANTS K1, K2, AND K3
           LAG1 = L11
           LAG2 = L21
```

```
            LAG3 = L31
            W'R KK, T'O B1
            ZERO.(T(1)...T(16), RT(1)...RT(4))
            T'O A(B)
A(1)        THROUGH LOOP1,      FOR N = N1, 1, N.G.N2
            II   =(INS(N) * V(N) - INS(1) * V(1)) * (1.0 - HCT)
            NMLAG1 = N - LAG1
            NMLAG2 = N - LAG2
            NMLAG3 = N - LAG3
            W'R NMLAG1 .L. 0, NMLAG1 = 0
            W'R NMLAG2 .L. 0, NMLAG2 = 0
            W'R NMLAG3 .L. 0, NMLAG3 = 0
            G = GLUC(NMLAG1)
            DG = (GLUC(NMLAG2+1)-GLUC(NMLAG2-1))*0.5
            P = ((KX * (FVI(NMLAG3))).P.EX)*KY
            T(1,1) = T (1,1) + G*G
            T(1,2) = T(1,2) + G*DG
            T(1,3) = T(1,3) + G
            T(2,1) = T(1,2)
            T(2,2) = T(2,2) + DG*DG
            T(2,3) = T(2,3) + DG
            T(3,1) = T(1,3)
            T(3,2) = T(2,3)
            T(3,3) = T(3,3) + 1.0
            RT(2) = RT(2) + II*DG
            RT(1) = RT(1) + G*II
LOOP1       RT(3) = RT(3) + II
            RR = SLE.(3,4,T(1,1),M(1),RT(1),V1(0),0)
            W'R PR1, P'S T(1,1)...T(3,3), M(1)...M(3), RT(1)...RT(3), RR
            K1 = M(1)
            K2 = M(2)
            K3 = 0.0
            K4 = M(3)
            T'O B2
A(2)        THROUGH LOOP2,      FOR N = N1, 1, N.G.N2
            NMLAG1 = N - LAG1
            NMLAG2 = N - LAG2
            NMLAG3 = N - LAG3
            W'R NMLAG1 .L. 0, NMLAG1 = 0
            W'R NMLAG2 .L. 0, NMLAG2 = 0
            W'R NMLAG3 .L. 0, NMLAG3 = 0
            II   =(INS(N) * V(N) - INS(1) * V(1)) * (1.0 - HCT)
            G = GLUC(NMLAG1)
            DG = (GLUC(NMLAG2+1)-GLUC(NMLAG2-1))*0.5
            P = ((KX * (FVI(NMLAG3))).P.EX)*KY
            T(1,1) = T (1,1) + G*G
            T(1,2) = T(1,2) + G*DG
            T(2,1) = T(1,2)
            T(2,2) = T(2,2) + DG * DG
            RT(1) = RT(1) + II * G
LOOP2       RT(2) = RT(2) + II*DG
            RR = SLE. (2,4,T(1,1),M(1),RT(1),V1,0)
            W'R PR1, P'S T(1,1)...T(2,2), M(1)...M(2), RT(1)...RT(2), RR
            K1 = M(1)
            K2 = M(2)
            K3 = 0.0
            K4 = 0.0
            T'O B2
A(3)        THROUGH LOOP3,      FOR N = N1, 1, N.G.N2
            II   =(INS(N) * V(N) - INS(1) * V(1)) * (1.0 - HCT)
```

```
        NMLAG1 = N - LAG1
        NMLAG2 = N - LAG2
        NMLAG3 = N - LAG3
        W'R NMLAG1 .L. 0, NMLAG1 = 0
        W'R NMLAG2 .L. 0, NMLAG2 = 0
        W'R NMLAG3 .L. 0, NMLAG3 = 0
        G = GLUC(NMLAG1)
        DG = (GLUC(NMLAG2+1)-GLUC(NMLAG2-1))*0.5
        P = ((KX * (FVI(NMLAG3))).P.EX)*KY
        T(1,1) = T (1,1) + G*G
        T(1,2) = T(1,2) + G
        T(2,1) = T(1,2)
        T(2,2) = T(2,2) + 1.0
        RT(1) = RT(1) + II*G
LOOP3   RT(2) = RT(2) + II
        RR = SLE. (2,4, T(1,1), M(1), RT(1), V1, 0)
        W'R PR1, P'S T(1,1)...T(2,2), M(1)...M(2), RT(1)...RT(2), RR
        K1 = M(1)
        K2 = 0.0
        K3 = 0.0
        K4 = M(2)
        T'O B2
A(4)    THROUGH LOOP4,      FOR N = N1, 1, N.G.N2
        II    =(INS(N) * V(N) - INS(1) * V(1)) * (1.0 - HCT)
        NMLAG1 = N - LAG1
        NMLAG2 = N - LAG2
        NMLAG3 = N - LAG3
        W'R NMLAG1 .L. 0, NMLAG1 = 0
        W'R NMLAG2 .L. 0, NMLAG2 = 0
        W'R NMLAG3 .L. 0, NMLAG3 = 0
        G = GLUC(NMLAG1)
        DG = (GLUC(NMLAG2+1)-GLUC(NMLAG2-1))*0.5
        P = ((KX * (FVI(NMLAG3))).P.EX)*KY
        T(1,1) = T (1,1) + G*G
LOOP4   RT(1) = RT(1) + II
        K1 = RT(1)/T(1,1)
        K2 = 0.0
        K3 = 0.0
        K4 = 0.0
        T'O B2
A(5)    THROUGH LOOP5,      FOR N = N1, 1, N.G.N2
        II    =(INS(N) * V(N) - INS(1) * V(1)) * (1.0 - HCT)
        NMLAG1 = N - LAG1
        NMLAG2 = N - LAG2
        NMLAG3 = N - LAG3
        W'R NMLAG1 .L. 0, NMLAG1 = 0
        W'R NMLAG2 .L. 0, NMLAG2 = 0
        W'R NMLAG3 .L. 0, NMLAG3 = 0
        G = GLUC(NMLAG1)
        DG = (GLUC(NMLAG2+1)-GLUC(NMLAG2-1))*0.5
        P = ((KX * (FVI(NMLAG3))).P.EX)*KY
        T(1,1) = T(1,1) + G * G
        T(1,2) = T(1,2) + DG* G
        T(1,3) = T(1,3) + P * G
        T(2,1) = T(1,2)
        T(2,2) = T(2,2) + DG*DG
        T(2,3) = T(2,3) + P * DG
        T(3,1) = T(1,3)
        T(3,2) = T(2,3)
        T(3,3) = T(3,3) + P * P
```

```
            RT(1) = RT(1) + II * G
            RT(2) = RT(2) + II * DG
LOOP5       RT (3) = RT(3) + II * P
            RR = SLE. (3,4,T(1,1),M(1),RT(1),V1,0)
            W'R PR1, P'S T(1,1)...T(3,3), M(1)...M(3), RT(1)...RT(3), RR
            K1 = M(1)
            K2 = M(2)
            K3 = M(3)
            K4 = 0.0
            T'O B2
A(6)        T'H LOOP6, FOR N= N1, 1, N.G. N2
            II = (INS(N)*V(N)-INS(1)*V(1))    * (1.0-HCT)
            NMLAG1 = N - LAG1
            NMLAG2 = N - LAG2
            NMLAG3 = N - LAG3
            W'R NMLAG1 .L. 0, NMLAG1 = 0
            W'R NMLAG2 .L. 0, NMLAG2 = 0
            W'R NMLAG3 .L. 0, NMLAG3 = 0
            G = GLUC(NMLAG1)
            DG = (GLUC(NMLAG2+1)-GLUC(NMLAG2-1))*0.5
            P = ((KX * (FVI(NMLAG3))).P.EX)*KY
            T(1,1) = T(1,1) + G*G
            T(1,2) = T(1,2) + G*P
            T(1,3) = T(1,3) + G
            T(2,1) = T(1,2)
            T(2,2) = T(2,2) + P*P
            T(2,3) = T(2,3) + P
            T(3,1) = T(1,3)
            T(3,2) = T(2,3)
            T(3,3) = T(3,3) + 1.0
            RT(1) = RT(1) + G*II
            RT(2) = RT(2) + P*II
LOOP6       RT(3) = RT(3) + II
            RR = SLE.(3,4,T(1,1),M(1),RT(1),V1(0),0)
            W'R PR1, PRINT RESULTS T(1,1)...T(3,3),M(1)...M(3),RT(1)...RT
           1(3), RR
            K1 = M(1)
            K2 = 0.0
            K3 = M(2)
            K4 = M(3)
            T'O B2
A(7)        T'H LOOP7, FOR N = N1, 1, N.G.N2
            II   =(INS(N) * V(N) - INS(1) * V(1)) * (1.0 - HCT)
            NMLAG1 = N - LAG1
            NMLAG2 = N - LAG2
            NMLAG3 = N - LAG3
            W'R NMLAG1 .L. 0, NMLAG1 = 0
            W'R NMLAG2 .L. 0, NMLAG2 = 0
            W'R NMLAG3 .L. 0, NMLAG3 = 0
            G = GLUC(NMLAG1)
            DG = (GLUC(NMLAG2+1)-GLUC(NMLAG2-1))*0.5
            P = ((KX * (FVI(NMLAG3))).P.EX)*KY
            T(1,1) = T(1,1) + G * G
            T(1,2) = T(1,2) + DG* G
            T(1,3)  = T(1,3) + P * G
            T(1,4) = T(1,4) + G
            T(2,1) = T(1,2)
            T(2,2) = T(2,2) + DG* DG
            T(2,3) = T(2,3) + P * DG
            T(2,4) = T(2,4) + DG
```

```
          T(3,1) = T(1,3)
          T(3,2) = T(2,3)
          T(3,3) = T(3,3) +  P * P
          T(3,4) = T (3,4) +  P
          T(4,1) = T(1,4)
          T(4,2) = T(2,4)
          T(4,3) = T(3,4)
          T(4,4) = T(4,4) + 1.0
          RT(1) = RT(1) + II * G
          RT(2) = RT(2) + II * DG
          RT(3) = RT(3) + II * P
LOOP7     RT(4) = RT(4) + II
          RR = SLE.(4,4,T(1,1),M(1),RT(1),V1(0),0)
          W'R PR1, P'S T(1,1)...T(4,4), M(1)...M(4), RT(1)...RT(4), RR
          K1 = M(1)
          K2 = M(2)
          K3 = M (3)
          K4 =  M(4)
          TRANSFER TO B2
B1        THROUGH DONE, FOR VALUES OF K1 = K11, K12, K13, K14
          THROUGH DONE, FOR VALUES OF K2 = K21, K22, K23, K24
          THROUGH DONE, FOR VALUES OF K3 = K31, K32, K33, K34
          THROUGH DONE, FOR VALUES OF K4 = K41, K42, K43, K44
B2        PRINT COMMENT $          CONSTANTS AND PARAMETERS$
          P'S K1, K2, K3, K4, LAG1, LAG2, LAG3, N1, N2, SKIP, EX, KX,KY
          P'S RR
         R         PREDICT INSULIN CONCENTRATIONS
          PRINT FORMAT TOP, X1, NAME, NAME1, NAME2
          X1 = X1 + 1
          PRINT COMMENT $0                                        FEMORAL BLOOD
         1  PANCREATIC      PANCREATIC$
          PRINT COMMENT $        TIME   GLUCOSE  DG/DT  INSULIN  FLOW  M
         1EAS. INSULIN  CALC. INSULIN  ERROR  PERCENT ERROR  TERM1  TER
         1M2  TERM3  TERM4$
          PRINT COMMENT $          MIN  MG/100 ML          MU U/ML ML/MIN
         1     MU U/ML         MU U/ML MU U/ML    $
          SUMSQE = 0.0
          SUMSQE = 0.0
          SSERR= 0.0
          T'H TABLE, FOR N = 1, SKIP, N .G. NMAX
          NMLAG1 = N - LAG1
          NMLAG2 = N - LAG2
          NMLAG3 = N - LAG3
          W'R NMLAG1 .L. 0, NMLAG1 = 0
          W'R NMLAG2 .L. 0, NMLAG2 = 0
          W'R NMLAG3 .L. 0, NMLAG3 = 0
          DGDT(N) = (GLUC(NMLAG2+1)-GLUC(NMLAG2-1))*0.50
          TERM1 = K1*GLUC(NMLAG1)/(V(1)*(1.-HCT))
          TERM2=K2*((GLUC(NMLAG2+1)-GLUC(NMLAG2-1))*0.50)/V(1)*(1.-HCT)
          TERM3 = K3*((KX*(FVI(NMLAG3))).P.EX)*KY/(V(1)*(1.-HCT))
          TERM4 = K4/(V(1)*(1.-HCT)) + INS(1)*V(1)/V(1)
          I(N) =  TERM 1 + TERM 2 + TERM 3 + TERM 4
          ERROR(N) = I(N) - INS(N)
          PCTERR(N) = (I(N) - INS(N))*100./INS(N)
          PRINT FORMAT RESULT, N, GLUC(N), DGDT(N), FVI(N), V(N),
         1INS(N), I(N), ERROR(N), PCTERR(N), TERM1, TERM2, TERM3,
         1TERM4
          SUMERR = SUMERR + .ABS. ERROR(N)
          SSERR = SSERR + ERROR(N)
          SUMSQE = SUMSQE + ERROR(N)*ERROR(N)
```

```
TABLE     CONTINUE
          XBAR = SSERR/(N2-N1)
          SD = ((SUMSQE/(N2-N1))-XBAR*XBAR).P.0.50
          NORMER = (SQRT.(SUMSQE/(NMAX/SKIP)))/AVGINS
          PRINT RESULTS SUMERR, SUMSQE, XBAR, SSERR, SD, AVGINS, NORMER
          W1 = 0.0
          W2 = 0.0
          W3 = 0.0
          T'H ALPHA, FOR N = 1, SKIP, N.G.90 .OR. N .G. NMAX
ALPHA     W1 = W1 + ERROR(N)
          W'R N .GE. NMAX
          D1 = (N-1)/SKIP
          O'E
          D1 = 90./SKIP
          E'L
          E1(X1,X2) = W1/D1
          T'H BETA, FOR N = 91, SKIP, N .G. 180 .OR. N .G. NMAX
BETA      W2 = W2 + ERROR(N)
          W'R N .GE. NMAX
          D2 = (N-91)/SKIP
          O'E
          D2 = 90.0/SKIP
          E'L
          E2(X1,X2) = W2/D2
          W'R E2(X1,X2) .L. 1.0, E2(X1,X2) = E1(X1,X2)
          T'H GAMMA, FOR N = 181, SKIP, N .G. 270 .OR. N .G. NMAX
GAMMA     W3 = W3 + ERROR(N)
          W'R N .GE. NMAX
          D3 = (N-181)/SKIP
          O'E
          D3 = 90.0/SKIP
          E'L
          E3(X1,X2) = W3/D3
          W'R E3(X1,X2) .L. 1.0, E3(X1,X2) = E2(X1,X2)
          P'S E1(X1,X2), E2(X1,X2), E3(X1,X2), D1, D2, D3, N
          PRINT FORMAT T1, NAME, NAME1, NAME2
          PRINT COMMENT $0 * = MEAS. GLUCOSE IN MG PCT.,  + = MEAS. INS
         1ULIN IN MU U/ML,  X = CALC. INSULIN IN MU U/ML$
          F = 10.0 * YMAX/300.0
          FI = F/10
          PRINT RESULTS FI
          PLOT1. (0, 5, 10, 10, 10)
          DIMENSION IMAGE (867)
          PLOT2. (IMAGE, 300., 0.0, YMAX, 0.0)
          T'H P1, FOR AA = 1, SKIP, AA .G. NMAX
          FA = AA
P1        PLOT3. ($*$, FA, FI*GLUC(AA), 1)
          THROUGH P2, FOR A2 = 1, SKIP, A2 .G. NMAX
          FA2 = A2
P2        PLOT3. ($+$, FA2, INS(A2), 1)
          THROUGH P3, FOR A3 = 1, SKIP, A3 .G. NMAX
          FA3 = A3
P3        PLOT3. ($X$, FA3, I(A3), 1)
          NCHAR = 20
DONE      PLOT4. (NCHAR, LABEL)
          W'R X1 .E. X1MAX, T'O OMEGA
          X1 = X1 + 1
          T'O START
OMEGA     T'H SIGMA, FOR X2 = 1, 1, X2 .G. 6
          SY1 = 0.0
```

```
            SY2 = 0.0
            SY3 = 0.0
            T'H CHI, FOR X1 = 1, 1, X1 .G. X1MAX
            SY1 = SY1 + E1(X1,X2)
            SY2 = SY2 + E2(X1,X2)
CHI         SY3 = SY3 + E3(X1,X2)
            Y1 (X2) = SY1/X1MAX
            Y2 (X2) = SY2/X1MAX
SIGMA       Y3 (X2) = SY3/X1MAX
            PRINT RESULTS Y1(1)...Y1(7)
            PRINT RESULTS Y2(1)...Y2(7)
            PRINT RESULTS Y3(1)...Y3(7)
            PRINT RESULTS E1(1,1) ... E1(14,7)
            PRINT RESULTS E2(1,1) ... E2(14,7)
            PRINT RESULTS E3(1,1) ... E3(14,7)
            T'H Z4, FOR X2 = 1, 1, X2 .G. 6
            T'H Z4, FOR X22 = 1, 1, X22 .G. 6
            W'R X22 .E. X2, X22 = X22 + 1
                YF(1)   = Y1(X2) - Y1(X22)
            YF(2)   = Y2(X2) - Y2(X22)
            YF(3)   = Y3(X2) - Y3(X22)
            T'H Z5, FOR X1 = 1, 1, X1 .G. X1MAX
            DIF1(X1) = E1(X1,X2) - E1(X1,X22)
            DIF2(X1) = E2(X1,X2) - E2(X1,X22)
Z5          DIF3(X1) = E3(X1,X2) - E3(X1,X22)
            ZERO.(SX1, SX2, SX3, SX11, SX22, SX33, SX12, SX13, SX23)
            T'H Z6 , FOR X1 = 1, 1, X1 .G. X1MAX
            SX 1 = SX 1 + DIF1(X1)
            SX 2 = SX 2 + DIF2(X1)
            SX 3 = SX 3 + DIF3(X1)
            SX11 = SX 11+ DIF1 (X1)* DIF1(X1)
            SX22 = SX22 + DIF2(X1) * DIF2(X1)
            SX33 = SX33 + DIF3(X1) * DIF3(X1)
            SX12 = SX12 + DIF1(X1) * DIF2(X1)
            SX13 = SX13 + DIF1(X1) * DIF3(X1)
Z6          SX23 = SX23 + DIF2(X1) * DIF3(X1)
            X1MXL1 = X1MAX - 1
            SIG(1,1) =      ((SX11 - (SX1*SX1/X1MAX))/X1MXL1)
            SIG(2,2) =      ((SX22 - (SX2*SX2/X1MAX))/X1MXL1)
            SIG(3,3) =      ((SX33 - (SX3*SX3/X1MAX))/X1MXL1)
            SIG(1,2) =      ((SX12 - (SX1*SX2/X1MAX))/X1MXL1)
            SIG(1,3) =      ((SX13 - (SX1*SX3/X1MAX))/X1MXL1)
            SIG(2,3) =      ((SX23 - (SX2*SX3/X1MAX))/X1MXL1)
            SIG(2,1) = SIG(1,2)
            SIG(3,1) = SIG(1,3)
            SIG(3,2) = SIG(2,3)
            JJJ = SSS
            W'R GJR.(3,3,JJJ(1,1),DUMMY) .NE. 1., T'O INVERR
            PRINT COMMENT $6    $
            P'S X2,  X22, X1MAX, SETS
            HOTELT = YY * (.INVERT. SSS) * YY
            FSTAT = ((1. * X1MAX - SETS + 1)/(SETS * X1MAX)) * HOTELT
            INVSSS = .INVERT. SSS
            P'S SSS(1,1)...SSS(3,3), INVSSS(1,1)...INVSSS(3,3)
            P'S HOTEL T, F STAT
            T'O Z4
INVERR      PRINT COMMENT $ SINGULAR MATRIX $
Z4          CONTINUE
            V'S LABEL = $                    $
            VECTOR VALUES RESULT = $1H , I10, F10.0, F7.2, F9.0, F6.2, 2F
```

```
          115.0, F7.0, F15.0, 4F7.0*$
           V'S TOP = $1H1, 7HTABLE  ,I2,43H     EXPERIMENTAL DATA AND 30
          1RRELATION FOR 3C6*$
           VECTOR VALUES T1=$1H1,40HCORRELATION OF INSULIN AND GLUCOSE F
          1ROM 3C6*$
          R     THIS SUBROUTINE FILLS IN DATA SETS BY LINEAR INTERPOLAT-
          R ION.
           INTERNAL FUNCTION (Y,MAX)
           ENTRY TO FILLIN.
           IX= 0
Z0         T'H Z0, FOR JX=IX+1, 1, Y(JX).NE.0.
           W'R JX-IX .E. 1
           IX= IX+ 1
           T'O Z3
           E'L
           DY = (Y(JX)- Y(IX))/(JX-IX)
           T'H Z1, FOR IX=IX+1, 1, IX.E.JX
Z1         Y(IX) = Y(IX-1) + DY
Z3         W'R IX .L. MAX, T'O Z0
           F'N
           END OF FUNCTION
           E'M

          R
          R     CONTRACTRACTIONS USED IN THIS PROGRAM ARE...
          R     E'L      END OF CONDITIONAL
          R     E'M      END OF PROGRAM
          R     E'N      END OF FUNCTION
          R     P'S      PRINT RESULTS
          R     P'T      PRINT FORMAT
          R     T'H      THROUGH
          R     T'O      TRANSFER TO
          R     V'S      VECTOR VALUES
          R     W'R      WHENEVER
                                                    454 LINES PRINTED
```

APPENDIX C

DOUBLE ANTIBODY INSULIN ASSAY PROGRAM

This MAD program calculates the insulin concentration in plasma which has been assayed using the double antibody method. The fraction of insulin bound is calculated for each sample of standard insulin representing a point on a standard curve. The least squares method is used to determine the coefficients in a polynomial equation which represents the standard curve. The program is written to fit the standard curve using two equations of the same general form:

$$I = x\, q_1 + \frac{1}{x} q_2 + \frac{1}{x^2} q_3 + \frac{1}{x^3} q_4 + q_5 \qquad (C.1)$$

where: I = Plasma insulin concentration

x = Percent of labelled insulin bound by the antibody

q = An array of constants determined by least squares

One array of constants is determined for samples having from 0-50 μU/ml insulin and another array for samples having from 50-300 μU/ml insulin. After the constants are determined, the points on the standard curve are calculated and compared with the experimentally determined values. The standard curve is plotted including both the computed and the experimentally determined points.

The insulin concentration of plasma samples is calculated using the equation given above with the appropriate set of constants. A provision is made to multiply the results by a dilution factor if the samples have been diluted.

TABLE 25

SYMBOLS USED IN THE COMPUTER PROGRAM FOR THE INSULIN ASSAY CALCULATIONS

MAD Name	Mode	Definition	Units
ADD	0	Partial sum	
A	0	Coefficient matrix	
B1	0	B1(I-11) = INS(I)	μU/ml
BKGD	0	Background radioactivity	counts/min
BKPT	0	Breakpoint between the 1 st and 2 nd branches of the standard curve	
BR	1	Break switch	
B	0	B(J) = INS(J-1)	μU/ml
BZERO	0	Average specific activity of Tr A, Tr B, Tr C, and Tr D	counts/min
CCC	0	Counts, control C	counts
CMAX	0	Maximum number of counts	counts
C	0	Counts in period TMAX	counts
D1	0	Storage array	
DIL	0	Plasma dilution factor, DIL = 1.0 means no dilution	
D	0	Storage array	
ENDSC	2	Control - Indicates last test to be run with a given standard curve	
ENDT	2	Control - Indicates last data card of a given experiment	
FTY	0	The value of PCTBZ for standard samples containing 50 μU/ml insulin	
GRAPH	0	Storage location for plotting sub-routines	
H	0	Storage array	
IDENT	1	Sample identification symbol	
IN	0	Insulin concentration in unknown plasma	μU/ml
INS	0	Insulin concentration in standard curve	μU/ml
I	1	Index, 2 nd branch of standard curve	
J	1	Index, 1 st branch of standard curve	
K	1	Index used in plotting	

TABLE 25 (CONT'D)

SYMBOLS USED IN THE COMPUTER PROGRAM FOR THE INSULIN ASSAY CALCULATIONS

MAD Name	Mode	Definition	Units
LABEL	1	Vector name - Graph title	
M	1	Counting index, data cards	
N1	1	Number of points on the first branch of the standard curve	
N2	1	Number of points on the second branch of the standard curve	
NAME	1	Experiment identification - up to 30 characters	
NC	2	Control for reading data cards	
NN	1	Counting index	
N	1	Card number, standard curve	
P1	0	Format variable	
PBZ	0	Percent labelled insulin bound for unknown plasma	
PCTBZ	0	Percent labelled insulin bound for standard curve	
PR1	2	Printing control for table title	
PR2	2	Printing control for deviations	
PR3	2	Printing control for checking program	
Q	0	Coefficient matrix, X or X1	
RRR	0	Result of SLE.	
RR	0	Result of SLE.	
R	1	Index for reading data cards	
RT	0	Vector of the right side of least squares equations	
TCC	0	Time, control C	min
TMAX	0	Maximum time a sample is counted	min
T	0	Time a given sample is counted	min
U1	0	Deviation, below BKPT	μU/ml
U	0	Deviation, above BKPT	μU/ml
U2	0	Arguement of CALC., U2 = PBZ	
V1	0	Arguement of SLE.	
V2	0	Arguement of SLE.	
W1	0	1.0/U2	
W	1	Index	

TABLE 25 (CONT'D)

SYMBOLS USED IN THE COMPUTER PROGRAM FOR THE INSULIN ASSAY CALCUATIONS

MAD Name	Mode	Definition	Units
WT	1	Vector name - weights, here equal-1	
X1	0	Array of constants for CALC.	
X	0	Array of constants for CALC.	
Y	1	Index	
Z	1	Index	

LIBRARY(40) SUBROUTINES CALLED BY PROGRAM

PLOT1.
PLOT2.
PLOT3.
PLOT4.
SLE.
ZERO.

MODE

0 Floating point
1 Integer
2 Boolean

INTERNAL FUNCTION

CALC.

```
$COMPILE MAD, PRINT OBJECT, EXECUTE, I/O DUMP, DUMP
          R......PROGRAM FOR CALCULATION OF PLASMA INSULIN CONCENTRATION
          R       USING THE DOUBLE ANTIBODY ASSAY.
           FTRAP.
           BOOLEAN ENDSC, ENDT, NC, PR1, PR2, PR3
           FORMAT VARIABLE I, J, P1
           INTEGER BR, I, IDENT, J, K, M, N, NAME, NN, R, TO
           INTEGER W, Y, Z, N1, N2
           DIMENSION A(5*)., B(20), B1(30), BB(20), BB1(20), C(30),
          1  D(100,DIM1), D1(100,DIM1), H(5*5), IDENT(30), NAME(9),
          1  PCTBZ(30), RT(5), T(30), U(20), U1(20), V1(5), V2(5),
          1  X(30,DIM2), X1(30,DIM2), W(30,DIM2)
          R......READ, TRANSFORM, AND STORE DATA FOR THE STANDARD CURVE.
           READ FORMAT R1, CMAX, TMAX, PR1, PR3, N1, N2
A1         READ FORMAT R2, NAME(0)...NAME(4), BR, BKPT, DIL
           PRINT COMMENT $1       $
           P'S       CMAX, TMAX, PR1, PR3, BR, BKPT, N1, N2
           PRINT FORMAT P4; NAME(0)...NAME(4), DIL
           W'R BR .E. 1, BKPT = 1.0E04
           FTY = 0.0
           PRINT FORMAT P2
           NC = 0B
           T'H A2, FOR NN= 0,1, NC
           READ FORMAT R3, NC, N, IDENT(N), C(N), T(N), INS(N), BKGD
           W'R C(N)  .E. 0.0, C(N) = CMAX
A2         W'R T(N) .E. 0.0, T(N) = TMAX
           CCC = ( C(28) + C(29))/2.0
           TCC = ( T(28) + T(29))/2.0
           BKGD = (C(28)/T(28) + C(29)/T(29))/2.0
           BZERO = ((C(0)/T(0) + C(1)/T(1) + C(2)/T(2) + C(3)/T(3))/4.0)
          1     -- BKGD
           T'H A3, FOR N = 0, 1, N .G. 29
           PCTBZ(N) = ((C(N)/T(N)) - BKGD)/BZERO
A3         PRINT FORMAT P3, N, IDENT(N), C(N), T(N), C(N)/T(N),
          1     BKGD,PCTBZ(N), INS(N)
           PRINT RESULTS BZERO
           NC = 0B
           T'H A51, FOR I = 12, 1, I .G. 27
           D1(1,I-11) = PCTBZ(I)
           D1(2,I-11) = 1.0/PCTBZ(I)
           D1(3,I-11) = D1(2,I-11)*D1(2,I-11)
           D1(4,I-11) = D1(2,I-11)*D1(3,I-11)
A51        B1(I-11) = INS(I)
           THROUGH A52, FOR J = 1, 1, J .G. N1
           PCTBZ(0) = 1.00
           PCTBZ(1) = 1.00
           PCTBZ(2) = 1.00
           PCTBZ(3) = 1.00
           D(1,J) = PCTBZ(J-1)
           D(2,J) = 1.0/PCTBZ(J-1)
           D(3,J) = D(2,J) * D(2,J)
           D(4,J) = D(2,J) * D(3,J)
A52        B(J) = INS(J-1)
           FTY = (PCTBZ(12) + PCTBZ(13))/2.0
           I = I -1
           J = J - 1
           W'R PR3,
          1P'S D(1,1)...D(4,J), B(0)...B(J), WT, J
           W'R PR3,
          1 P'S D1(1,1)...D1(4,I),B1(1)...B1(16),WT, I
```

```
      R....FIND LEAST SQUARES ESTIMATES.
      ZERO. (A(1)...A(25))
      T'H SUM1B, FOR Y = 1, 1, Y .E. 5
      T'H SUM1B, FOR Z = 1, 1, Z .E. 5
      ADD = 0.0
      T'H SUM1B,FORW = 1,1, W .G. N1
      ADD = ADD + D(Y,W) * D(Z,W)
SUM1B A(Y,Z) = ADD
      THROUGH SUM1A,FOR I = 1,1, I .G. N1
      A(1,5) = A(1,5) + D (1,I)
      A(2,5) = A(2,5) + D (2,I)
      A(3,5) = A(3,5) + D (3,I)
      A(4,5) = A(4,5) + D (4,I)
SUM1A A(5,5) = A(5,5) + 1.0
      A(5,1) = A(1,5)
      A(5,2) = A(2,5)
      A(5,3) = A(3,5)
      A(5,4) = A(4,5)
      ZERO.(RT(1)...RT(5))
      T'H SUM 2, FOR W = 1,1, W .G. N1
      RT(1) =  RT(1) + D(1,W) * B(W)
      RT(2) =  RT(2) + D(2,W) * B(W)
      RT(3) =  RT(3) + D(3,W) * B(W)
      RT(4) =  RT(4) + D(4,W) * B(W)
SUM2  RT(5) =  RT(5) + B(W)
      W'R PR3,
     1P'S A(1,1)...A(5,5), RT(1)...RT(5)
      RR = SLE. (5,5, A(1,1),X(1),RT(1),V1(1), 0)
      W'R PR3,
     1PRINT RESULTS RR, X(1)...X(5)
      ZERO. (H(1)...H(25))
      ZERO. (RT(1)...RT(5))
      T'H SUM3,FOR Y = 1,1, Y .E. 5
      T'H SUM3,FOR Z = 1,1, Z .E. 5
      ADD = 0.0
      T'H SUM3,FOR W = 1,1, W .G. N2
      ADD = ADD +D1(Y,W) *D1(Z,W)
SUM3  H(Y,Z) = ADD
      THROUGH SUM4, FOR I = 1,1, I .G. N2
      H(1,5) = H(1,5) + D1(1,I)
      H(2,5) = H(2,5) + D1(2,I)
      H(3,5) = H(3,5) + D1(3,I)
      H(4,5) = H(4,5) + D1(4,I)
SUM4  H(5,5) = H(5,5) + 1.0
      H(5,1) = H(1,5)
      H(5,2) = H(2,5)
      H(5,3) = H(3,5)
      H(5,4) = H(4,5)
      T'H SUM 5, FOR W = 1,1, W .G. N2
      RT(1) =  RT(1) +D1(1,W) *B1(W)
      RT(2) =  RT(2) +D1(2,W) *B1(W)
      RT(3) =  RT(3) +D1(3,W) *B1(W)
      RT(4) =  RT(4) +D1(4,W) *B1(W)
SUM5  RT(5) =  RT(5) +B1(W)
      W'R PR3,
     1P'S H(1,1)...H(5,5), RT(1)...RT(5)
      RRR = SLE. (5,5, H(1,1),X1(1), RT(1), V2(1), 0 )
      W'R PR3,
     1P'S A(1,1)...A(5,5), RT(1)...RT(5)
      W'R PR3,
```

```
          1P'S H(1,1)...H(5,5), RT(1)...RT(5)
          W'R PR3,
          1P'S V1(1)...V1(5), V2(1)...V2(5)
          W'R PR3,
          1PRINT RESULTS RRR,X1(1)...X1(5)
          R     PRINT OUT LEAST SQUARES ESTIMATES AND DEVIATIONS FROM THE
          R     STANDARD CURVE, AND THE LEAST SQUARES COEFFICIENTS.
          P1 =(1-BR)*6
          P'T T31, $BELOW$,BKPT
          SUM = 0.0
          T'H A23, FOR K = 1, 1, K.G.J
          BB(K) = CALC.(X,D(1,K))
          U(K) = B(K) - BB(K)
A23       SUM = SUM + U(K) * U(K)
          PRINT FORMAT T3, (K=1,1,K.G.J,D(1,K),B(K),BB(K),U(K))
          W'R .NOT. PR2,T'O A9
          P'T T4, X(1)...X(5)
          P'S RR, RRR
A9        P'T  T7, SUM
          T'O A21(BR)
A21(0)    P'T T31, $ABOVE$,BKPT
          SUM1 = 0.0
          THROUGH A24, FOR K = 1, 1, K.G. N2
          BB1(K) = CALC.(X1,D1(1,K))
          U1(K) = B1(K) - BB1(K)
A24       SUM1 = SUM1 + U1(K) * U1(K)
          PRINT FORMAT T3, (K=1,1,K.G.N2,D1(1,K),B1(K),BB1(K),U1(K))
          W'R .NOT. PR2, T'O A22
          P'T T4, X1(1)...X1(5)
A22       P'T T7, SUM1
A21(1)    CONTINUE
          DIMENSION GRAPH (867)
          PLOT2.(GRAPH,300.,0,1.,0)
          T'H A91, FOR B=0.02,0.02, B.G.1.0
A91       PLOT3.($*$,CALC.(X,B),B,1)
          T'O    A95(BR)
A95(0)    T'H A92, FOR B=0.02,0.02, B.G.1.0
A92       PLOT3.($+$,CALC.(X1,B),B,1)
A95(1)    T'H A93, FOR K=1,1,K.G.N1
A93(0)    PLOT3.($O$,B(K),D(1,K),1)
          T'O A96(BR)
A96(0)    T'H A94, FOR K=1,1,K.G.N2
A94       PLOT3.($X$,B1(K),D1(1,K),1)
A96(1)    CONTINUE
          PRINT COMMENT$1 * - CALC. CURVE, 1ST BRANCH  + - CALC. CURVE
          12ND BRANCH  O - OBS. CURVE, 1ST BRANCH ETC.$
          K = 1
          PLOT4.(K,LABEL)
          PRINT COMMENT $                                    TOTAL$
          VECTOR VALUES LABEL = $          PERCENT BZERO$
          R     CALCULATE AND PRINT RESULTS FOR UNKNOWN SAMPLES
          ENDSC = OB
          T'H B2, FOR M = 1, 1, ENDSC
          READ FORMAT R4, NAME(0)...NAME(4), ENDSC,      DIL
          PRINT FORMAT  P4, NAME(0)...NAME(4), DIL
          PRINT FORMAT P6
          ENDT = OB
          T'H B2, FOR R = 0, 1, ENDT
B11       READ FORMAT R3, ENDT, 0.0, IDENT, C, T, 0.0, BKGD
          W'R C .E. 0.0, C = CMAX
```

```
          W'R T .E. 0.0, T = TMAX
          W'R BKGD .E. 0.0, BKGD = CCC/TCC
          PBZ = ((C/T) -BKGD)/(BZERO)
          W'R PBZ .L. FTY
          IN = CALC. (X1, PBZ)
          OTHERWISE
          IN = CALC. (X, PBZ)
          END OF CONDITIONAL
          W'R DIL .E. 0.0, DIL = 1.0
          W'R .ABS.(IN*DIL) .G. 1.0E05
          PRINT COMMENT $ ERROR$
          PRINT RESULTS IDENT, PBZ, IN*DIL
          T'O B11
          O'E
B2        PRINT FORMAT P5, IDENT, C, T, C/T, BZERO, BKGD, PBZ, IN*DIL
          E'L
          TRANSFER TO A1
          INTERNAL FUNCTION (Q,U2)
          ENTRY TO CALC.
          W1= 1.0/U2
          FUNCTION RETURN U2 * Q(1) + Q(2) * W1+ Q(3) * W1*W1+ Q(4) *
         1    W1.P.3 + Q(5)
          E'N
          V'S R1 = $S5, F5.0, S5, F5.0, S5, I1, S5, 4I5*$
          V'S R2 = $ S5, 5C6, S5, I1, S5, F3.0, S5, F5.0*$
          V'S R3 = $ S1, I1, S1, I2, S2, C4, S2, F5.0, S2, F5.2, S2,
         1    F5.0, S2, F5.2, 5F5.0*$
          V'S R4= $ S5, 5C6, S5, I1, S10,      F10.0*$
          V'S P2 = $1HO,H+                    NO.      IDENT.     COUN
         1TS          TIME     COUNTS/TIME      BKG.  PERCENT BZERO
         1  INSULIN+/
         1       H+
         1      MIN.      CTS./MIN.    CTS./MIN.                    MU U
         1/ML.+*$
          V'S P3=$S20,I3,S8,C5,S5,F6.0,S9,F6.2,S6,F6.0,S6,F7.2,S3,F9.4,
         1    S5, F 10.2*$
          V'S P4=$1H1,1H 5C6, H*THE DILUTION FACTOR FOR THE PLASMA IS
         1*F3.0*$
          V'S P5 = $S15, C6, F13.0, F13.2, 3F13.0, F13.4, F13.2*$
          V'S P6 = $1HO,H+              IDENT.        COUNTS        TIM
         1E      COUNTS/TIME     BZERO          BKGD.  PERCENT BZERO   I
         1NSULIN+/
         1      H+                                              MIN.
         1CTS./MIN.     CTS./MIN.     CTS./MIN.                  MU U/ML.
         1+*$
          VECTOR VALUES T3 = $S5, F5.3, S11, F6.2, S11,F6.2,S13,F7.2*$
          VECTOR VALUES T31=$ 1H2,S10,C'P1',S10,F'P1',1/1HO,S5,3HB/F,S1
         12,7HT(OBS.),S10,8HT(CALC.),S10,9HDEVIATION*$
          VECTOR VALUES  T4= $7HOCOEFF.,S8,5E18.4*$
          VECTOR VALUES T6= $H/O****** THERE ARE NO POINTS ON THE STAN
         1DARD CURVE WITH T VALUES EXACTLY EQUAL TO/E18.4,/S5,H/THE PRO
         1GRAM WILL USE FOR THE UNKNOWN SAMPLES THE COEFFICIENTS CALCUL
         1ATED FOR T VALUES LESS THAN THE BREAKPOINT./*$
          VECTOR VALUES T7= $25HORESIDUAL SUM OF SQUARES= ,S2,E18.4*$
          V'S DIM1 = 2,1,20
          V'S DIM2 = 2,1,5
          VECTOR VALUES WT = -1
          VECTOR VALUES DATA (81 )=1.0,1.0,1.0,1.0,1.0,1.0,1.0,1.0,1.0,
         11.0,1.0,1.0,1.0,1.0,1.0,1.0,1.0,1.0,1.0,1.0,1.0,1.0,1.0,1.0
          VECTOR VALUES DATA1(81 )=1.0,1.0,1.0,1.0,1.0,1.0,1.0,1.0,1.0,
         11.0,1.0,1.0,1.0,1.0,1.0,1.0,1.0,1.0,1.0,1.0,1.0,1.0,1.0,1.0
          E'M
         R
         R    CONTRACTRACTIONS USED IN THIS PROGRAM ARE...
         R    E'L      END OF CONDITIONAL
         R    E'M      END OF PROGRAM
         R    E'N      END OF FUNCTION
         R    P'S      PRINT RESULTS
         R    P'T      PRINT FORMAT
         R    T'H      THROUGH
         R    T'O      TRANSFER TO
         R    V'S      VECTOR VALUES
         R    W'R      WHENEVER
```

253 LINES PRINTED

BIBLIOGRAPHY

1. Ackerman, E., Rosevear, J. M., McGuckin, W. F., "A Model of the Glucose Tolerance Test," Physics in Medicine and Biology 9:203 (1964).

2. Ackerman, E., "Blood Glucose Regulation - Model Studies," Bull. Math. Biophysics 27:21 (Special Issue) (1965).

3. Anderson, E., Long, J. A., "The Effect of Hyperglycemia on Insulin Secretion as Determined with the Isolated Rat Pancreas in a Perfusion Apparatus," Endocrinology 40:92 (1947).

4. Arden, B., Galler, B., Graham, R., Michigan Algorithm Decorder, Computing Center University of Michigan, (1964).

5. Bendat, J. S., Piersol, A. G., Measurement and Analysis of Random Data, John Wiley, New York, (1966).

6. Blackman, R. B., Tukey, J. W., The Measurement of Power Spectra, Dover, New York, (1958).

7. Bolie, V. W., "An Analog Computer Model of the Glucose and Insulin Tolerance Tests," Proc. 3rd. International Conference on Medical Electronics P. 39 (1960).

8. Bouman, P. R., Bosboom, R. S., "Effects of Growth Hormone and of Hypophysectomy on the Release of Insulin from Rat Pancreas in Vitro," Acta Endocrinologia 50:202 (1965).

9. Brodan, V., "A Mathematical Expression of the Glucose Curve During Infusion of an Hypertonic Glucose Solution," Physiologia Bohemoslovaca 15:487 (1966).

10. Brown, E. M. et al., "The Effects of Prolonged Infusion of the Dog's Pancreas with Glucose," Endocrinology 50:644 (1952).

11. Campbell, James A., Rastogi, K. S., "Effects of Glucagon and Epinephrine on Serum Insulin and Insulin Secretion in Dogs," Endocrinology 79:830 (1966).

12. Campbell, J., Bower, E., Dwyer, S. J., Lago, G. V., "On The Sufficiency of Autocorrelation Functions as EEG Descriptors," IEEE Transactions of Bio-Medical Engineering 14:49 (1967).

13. Cerasi, E., "An Analogue Computer Model for the Insulin Response to Glucose Infusion," Acta Endocrinology 55:163 (1967).

14. Colwell, A. R., Jr., Metz, R., "Secretion of an Insulin-Like Substance into the Pancreatic Vein," Diabetes 11:504 (1962).

15. Cole, J. W. L., Grizzle, J. E., "Application of Multivariate Analysis of Variance to Repeated Measurements Experiments," Biometrics 22:810 (1966).

16. Coore, H.G., Randle, P. J., "Insulin Secretion from Rabbit Pancreas in Vitro," In Brolin, S. E., Hellman, B., Knutson, H., The Structure and Metabolism of the Pancreatic Islets, MacMillan, New York, 1964, p. 295.

17. Coore, H. G., Randle, P. J., "Regulation of Insulin Secretion Studied with Pieces of Rabbit Pancreas Incubated in Vitro," Biochem. J. 93:66 (1964).

18. Creutzfeldt, W., Frerichs, H., Reich, U., "In Vitro Studies on Rat Islets," In Brolin, S. E., Hellman, B., Knutson, H., The Structure and Metabolism of the Pancreatic Islets, MacMillan, New York, 1964, p. 323.

19. Ead, H. W., Green, J. H., Neil, E., "A Comparison of the Effects of Pulsatile and Non-Pulsatile Blood Flow through the Carotid Sinus on the Reflexogenic Activity of the Sinus Baroceptors in the Cat," J. Physiol. 118:509 (1952).

20. Elrick, H., et al., "Plasma Insulin Response to Oral and I. V. Glucose Administration," J. Clin. Endocrin. 24:1076 (1964).

21. Frohman, L. A., Ezdinli, E. Z., Javid, R., "Effect of Vagotomy and Vagal Stimulation on Insulin Secretion," Diabetes 16:443 (1967).

22. Frohman, L. A., Mac Gillivray, M. H., Aceto, T., "Acute Effects of Human Growth Hormone on Insulin Secretion and Glucose Utilization in Normal and Growth Hormone Deficient Subjects," J. Clin. Endocr. 27:561 (1967).

23. Gjedde, F., "Effect of Glucose on the Insulin-Like Activity of Serum from V. Pancreatico-Duodenalis and from A. Femoralis in Dogs," In Brolin, S. E., Hellman, B., Knutson, H., The Structure and Metabolism of the Pancreatic Islets, MacMillan, New York, 1964, p. 469.

24. Grodsky, G. M., Bennett, "Insulin Secretion from the Isolated Pancreas in the Absence of Insulinogenesis, Effect of Glucose," Proc. Soc. Experimental Biology and Medicine 114:769 (1963).

25. Grodsky, G. M., Forsham, P. H., "Insulin and the Pancreas," Annual Review of Physiology P. 347 (1966).

26. Grodsky, G. M., Bennett, L. L., Smith, D. F., Schmid, F. G., "Effect of Pulse Administration of Glucose or Glucagon on Insulin Secretion in Vitro," Metabolism 16:222 (1967).

27. Hausberger, F. X., Ramsay, A. J., "The Influences of the Administration of Glucose, and of Glucose Together with Insulin on the Granulation of Beta Cells in Guinea Pigs," Anat. Record 112:341 (1952).

28. Hoffman, W. S., "A Rapid Photoelectric Method for the Determination of Glucose in Blood and Urine," J.Biol. Chem. 120:51 (1937).

29. Hotelling, H., "The Generalization of Student's Ration," Annals of Mathematical Statistics 2:360 (1931).

30. Hunter, W. M., Greenwood, C. F., "Preparation of Iodine-131-Labelled Human Growth Hormone of High Specific Activity," Nature 194:495 (1962).

31. Janes, R. G., Osburn, J. O., "The Analysis of Glucose Measurements by Computer Simulation," J. Physiology 181:59 (1965).

32. Kanazawa, Y., Kuzuua, T., Ide, T., Kosaka, K., "Plasma Insulin Responses to Glucose in Femoral, Hepatic, and Pancreatic Veins in Dogs," Amer. Journal of Physiology 211:442 (1966).

33. Kris, A. O., Miller, R. E., Wherry, F. E., Mason, J. W., "Inhibition of Insulin Secretion by Infused Epinphrine in Rhesus Monkeys," Endocrinology 78:87 (1966).

34. Lazarrow, A., "Insulin Synthesis, Storage, Release, Transport and Antagonism," Diabetes 15:281 (1966).

35. Logothetopoulos, J., Kaneko, M., Wrenshall, G., A., Best, C., H., "Zinc, Granulation and Extractable Insulin of Islet Cells Following Hyperglycemia or Prolonged Treatment with Insulin," In Brolin, S. E., Hellman, B., Knutson, H., The Structure and Metabolism of the Pancreatic Islets, MacMillan, New York, 1964, p. 333.

36. London, E. S., Kotschneff, "Measurement of Insulin-Like Substance in the Pancreatic Vein Following Glucose," Ztschr. F. D. Ges. Exper. Med. 101:767 (1937).

37. Malaisse, W. J., Malaisse-Lagae, F., Lacy, P. E., Wright, P. H., "Insulin Secretion by Isolated Islets in Presence of Glucose, Insulin and Anti-insulin Serum," Proc. Soc. Experimental Biology and Medicine 124:497 (1967).

38. Merimee, T. J., Burgess, J. A., Rabinowitz, D., "Influence of Growth Hormone on Insulin Secretion," Diabetes 16:478 (1967).

39. Metz, R., "The Effect of Blood Glucose Concentration on Insulin Output," Diabetes 9:89 (1960).

40. Michigan, University of, University of Michigan Executive System for the IBM 7090 Computer, 1966.

41. Morgan, C. R., Lazarow, A., "Immunoassay of Insulin Using a Two-Antibody System," Proc. Expt. Biology and Medicine, 110:92 (1962).

42. Morgan, C. R., Lazarow, A., "Immunoassay of Insulin-Two Antibody System, Diabetes 12:115 (1963).

43. Morgan, C. R., et al., "Further Studies of an Inhibitor of the Two Antibody Immunoassay System," Diabetes 13:579 (1964).

44. Morrison, D. F., Multivariate Statistical Methods, McGraw-Hill, New York, 1967.

45. Norwich, K. N., Reiter, R., "The Homeostatic Control of Thyroxin Concentration Expressed by a Set of Linear Differential Equations," Bull. Math. Biophysics 27:133 (1965).

46. Oser, B. L., Hawk's Physiological Chemistry, McGraw-Hill, New York, 1965, p. 1054.

47. Parry, D. G., Taylor, K. W., "The Effects of Sugars on Incorporation of Leucine-H3 into Insulin," Biochem. J. 100:2C (1966).

48. Pek, S., Fajans, S. S., Floyd, J. C., Jr., Thiffault, C. A., Knopf, R. F., Conn, J.W., "Effect of Dexamethasone on Amino Acid Induced Changes in Insulin Release in Man," Clinical Research 15:430 (1967).

49. Porte, D., Graber, A. L., Kuzuya, T., Williams, R. H., "The Effect of Epinephrine on Immunoreative Insulin Levels in Man," J. Clin. Invest. 45:228 (1966).

50. Randle, P. J., "Assay of Plasma Insulin Activity by the Rat Diaphragm Method," Brit. Med. J., 1:1237 (1954).

51. R-Canswla, J. L., R-Candela, R., et al., In Perspectives in Biology, Cori, C. F., et al., Eds., Elsevier, Amsterdam (1965).

52. Renold, A. E., Martin, D. B., Dagenais, Y. M., Steinke, J., Nickerson, R. J., Sheps, M. C., "Measurement of Small Quantities of Insulin-Like Activity Using Rat Adipose Tissue. I. A. Proposed Procedure," J. Clin. Invest. 39:1487 (1960).

53. Roston, S., "Mathematical Representation of Some Endocrinological Systems," Bull. Math. Biophysics 21:271 (1959).

54. Samols, E., Bilkus, D., "A Comparison of Insulin Immunoassays," Proc. Soc. Experimental Biology and Medicine 115:79 (1964).

55. Seed, J., Acton, F. S., Stunkard, A. J., "A Model for the Appraisal of Glucose Metabolism," Clin. Pharm. Ther. 3:191 (1962).

56. Seltzer, H. S., "Quantitative Effects of Glucose, Sulfonylureas, Salicylate, and Indole-3-Acetic Acid on the Secretion of Insulin Activity into Pancreatic Venous Blood," J. Clin. Invest. 41:289, (1962).

57. Seltzer, H. S., et al., "Failure of Prolonged Sulfonylurea Administration to Enhance the Insulogenic Response to Glycemic Stimuli," Diabetes 14:392 (1965).

58. Soeldner, J. S., Slone, D., "Critical Variables in the Radioimmunoassay of Serum Insulin using the Double Antibody Technique," Diabetes 14:771 (1965).

59. Tepperman, J., Metabolic and Endocrine Physiology, Year Book Medical Publishers, New York, 1962.

60. Unger, R. H., Eisentraut, A. M., McCall, M. S., Madison, L. L., "Measurements of Endogenous Glucagon in Plasma and the Influence of Blood Glucose Concentration upon its Secretion," J. Clin. Invest. 41:682 (1962).

61. Unger, R. H., Eisentraut, A. M., "Studies of the Physiologic Role of Glucagon," Excerpta Medica International Congress No. 84, Fifth Congress of the International Diabetes Federation 1965.

62. Unger, R. H., Ketterer, H., Dupre, J., Eisentraut, A. M., "The Effects of Secretion, Pancreozymin, and Gastrin on Insulin and Glucagon Secretion in Anesthetized Dogs," J. Clin. Invest. 46:630 (1967).

63. Yalow, R. S., Berson, S. A., "Immunoassay of Endogenous Plasma Insulin in Man," J. Clin. Invest. 39:1157 (1960).

64. Yates, F. E., Urquart, J., "Control of Plasma Concentrations of Adrenalcortical Hormones," Physiological Reviews 42:359 (1962).

65. Floyd, J. C., Jr., Fajans, S. S., Conn, J. W., Knopf, R. F., Rull, J., "Stimulation of Insulin Secretion by Amino Acids," J. Clin. Invest. 45:1487 (1966).

UNIVERSITY OF MICHIGAN
3 9015 02652 8003