MATHEMATICAL MODELING OF THE UNSTEADY STATE GLUCOSE AND INSULIN CONCENTRATIONS IN BLOOD FOR NORMAL SUBJECTS AND DIABETICS

BY

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FACULTY COMMITTEE

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ABSTRACT

Title of thesis : Mathematical Modeling of The Unsteady State Glucose and Insulin Concentrations in Blood for Normal Subjects and Diabetics

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A mathematical model of the blood-glucose regulatory system has been developed. This model describes an oral glucose tolerance test adequately and simulates the behavior of the real physiological system using computer techniques.

Regression of the rate constants involved have been effected by conforming the theoretical functions to the data from glucose tolerance test in nonobese normal subjects, obese normal subjects, nonobese mild diabetics, obese mild diabetics, nonobese moderate diabetics and obese moderate diabetics measured by continuous sampling after oral ingestion. Most of the data were conformed within the limits of experimental error. The result of optimal parameters lead to a criterion for separating normal subjects from mild diabetics and moderate diabetics.

The significance of the model conformation is discussed in view of the goals of modeling and the extension of knowledge of blood-glucose mechanism in the human body.

ACKNOWLEDGMENTS

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CHAPTER I

INTRODUCTION

Studies of blood glucose dynamics have attracted the interest of persons with a variety of backgounds. Glucose plays a essential role in the intermediary metabolism of many tissues; both extremely high values and extremely low values of blood glucose are associated with severe pathological symptoms. Thus, criterion, regulation, and control of blood glucose levels are an essential function of the organism.

The body's ability to maintain blood glucose at a relatively constant concentration results from the complex interrelationships between carbohydrate, lipid, and protein-metabolism and various hormones. For the past several years, several various simulations of the blood glucose regulatory system have been performed. Mathematical models of such a complex system represents an abstraction and a lumping of many parameters into a relatively small number of empirically determinable ones. The significance of the model conformations to glucose metabolism is discussed in view of kinetic dynamics and process control. In 1961, V. Bolie suggested a one-compartment model to illustrate the mathematical relationship between the kinetics of glucose and of insulin in plasma. In 1964, E. Ackerme et. al. effectively adopted Bolie's model and by the judicious selection of a mathematical

function to simulate gastro-intestinal abosrption endeavoured to apply the model clinically in the interpretation of the oral glucose tolerance test.

Ackerme's model gives a general valuation of the glucose-tolerance curve for diagnostic purpose than the morphological or semiquantitative criteria employed. Current physiologic knowledge about glucose-insulin homeostasis in liver, brain, pancreas, kidney, peripheral tissues, and central vascular organs has been synthesized to form more accurate dynamics. So, we attempt to develop a mathematical model to include all available knowledge as possible and to map this in a fashion which can represent the overall action of the system. The model developed here is a set of simultaneous nonlinear differential equations which cannot be solved analytically.

In our theorectial investigation we had three aims in view,

1. To develop criteria (by the parameters of the model) to distinguish the difference between normal and abnormal responses.

2. To find out how much information could be extracted from the results of the test data as it is often carried out clinically.

3. To model and extend the knowledge of blood glucose dynamics that enable us to understand the physiological mechanism and control system.

Indeed, our initial interest arose from a desire to combine the blood-glucose levels during the oral glucose-

tolerance test in a kinetic model which would lead to a criterion for separating normals from diabetics.

The results support the hypothesis that the natural period measured can be used to distinguish health from disease. The success of our mathematical model to distinguish the losing function of the dynamic mechanism between normals and diabetics through the judgment of parameters leads to determine the physiological sensitivity domination. It is quite possible that such a criterion might have clinical utility.

CHAPTER II

DEVELOPMENT OF THE MATHEMATICAL MODEL

In originally selecting a mathematical model, the criteria used included simplicity and agreement with experimental oral glucose-tolerance data both in magnitude and form. In the oral glucose-tolerance test, the subject eats a large dose of glucose. The fasting concentration of blood glucose is measured before the glucose is administered. Models for glucose and insulin distribution in man were developed. These are referred to as the Ackerman et al., 1964 and Norwich et al., 1969 respectly. In addition these, a book by W. F. Ganong named "Review of Medical Physiology" describ the mechanism of glucose and insulin in chapter 19. Figure 1 depicts in the form of a block diagram the response of the body to added glucose. It is further apparent that these are interlocked in a feedback loop, thereby making oscillations possible. The diagram contain 16 physiological parameters, a few of which are uncertain. However, this number 16 is a minimum quantities since one would like to indicate, for example, a different rate of glucose utilization in each tissue and also the roles of other hormones and of the nervous system. The basic assumptions used in formulating this overall description of the blood-glucose regulatory system are simplifications of known interactions between glucose, insulin, and other regulatory hormones to take explicit

account of the role of the adrenal cortical and medullary function in glucose economy and of the heterogeneity of pancreatic insulin.

In chemicals and in physical mechanics, the technique of lumping parameters has proved very useful. Figure 2 presents a system of our model in which the parameters of Figure 1 have been lumped into two dependent variables, (G) and (I), seven rate constants. The blood-glucose level (G) can be increased either by glucose from the intestines or intravenous source, or by release of glucose from the liver. The blood-glucose level is decreased by removal of glucose by the liver or other tissues of storage or metabolism. The insulin (I) is assumed to promote the effect of accelerating glucose depletion. The simultaneous nonlinear differential equations of which imply the lumped parameters for blood glucose and insulin concentration are

$$\frac{d(G)}{dt} = -K_1(G)(I) - K_2(G) + K_3 + M_1(t) \qquad (1)$$

$$\frac{d(I)}{dt} = -K_4(I) + K_5(I) + M_2(t) \qquad (2)$$

(G) = Glucose concentration

(I) = Insulin concentration

$K_1(G)(I)$ = Mass transfer of glucose to peripheral tissue which is dependent of insulin. This is a non-linear term.

$K_2(G)$ = Average rate of glucose transfer to brain or to red cells which is independent of insulin.

K_3 = A constant of average rate of release of glucose into blood plasma from tissue or liver. (if (G) is much lower than the fasting glucose concentration (G_0), the extra glucose may be added by breaking down of glycogen in liver or tissue)

$M_1(t)$ = Input of glucose from glucose-insulin adsorption (gastro-intertinal), and

$$M_1(t) = \begin{cases} 1.8 & 0 \leq t \leq t_1 \\ 0 & t_1 < t \end{cases}$$

t_1 : The time at which glucose concentration is maximum.

$K_4(I)$ = Mass transfer of insulin removal which is independent of glucose due to breakdown in plasma by enzyme in 7 to 10 minutes.

$K_5(G)$ = Extra secretion of release of insulin due to glucose by a feedbck mechanism coming from pancreas.

$$M_2(t) = \begin{cases} K_6 + K_7 & 0 \leq t \leq t_1 \\ K_6 & t_1 < t \end{cases}$$

Where K_6 represents insulin coming from β-cells of pancreas to maintain constant influe of insulin and K_7 represents a feedback due to step input of $M_1(t)$.

So, we can therefore express equations (1) and (2) as:

(a) During oral glucose input or meal, $0 \leq t \leq t_1$

$$\frac{d(G)}{dt} = -K_1(G)(I) - K_2(G) + K_3 + 1.8 \qquad (3)$$

$$\frac{d(I)}{dt} = -K_4(I) + K_5(G) + K_6 + K_7 \qquad (4)$$

(b) After a step function of glucose input, $t_1 < t$

$$\frac{d(G)}{dt} = -K_1(G)(I) - K_2(G) + K_3 \qquad (5)$$

$$\frac{d(I)}{dt} = -K_4(I) + K_5(I) + K_6 \qquad (6)$$

There are few important notes we should discuss here:

(1) Glucose metabolizes by cycles in tissue (i.e. kerbs, glycolysis, etc.), so we assume that no disappearance due to reaction in plasma.

(2) Assuming $M_1(t)$ as a step function.

(3) Assuming (I) in equal with (I) ads which is adsorbed on the surface of tissue especially on the liver.

There is wide variation in the values assumed by the rate constants. These parameters in general fall into the "physiological" range and are all positive as required. Accordingly, K_1 represents the lumped effect of the change of liver set-point for glucose absorption and of the change of the rate of glucose removal by the other tissues due to change in insulin. Similarly, M_2 represents the tendency of the system to return the blood glucose concentration towards its fasting value. K_3 represents the extra glucose secretion to keep the fasting glucose level. K_4 represents the tendency of the system to return the net insulin towards the fasting value. K_5 represents the lumped effects of the stimulation of the endocrime system protection of insulin from metabolic removal. The constants K_3, K_6, and K_7 are already explained previously.

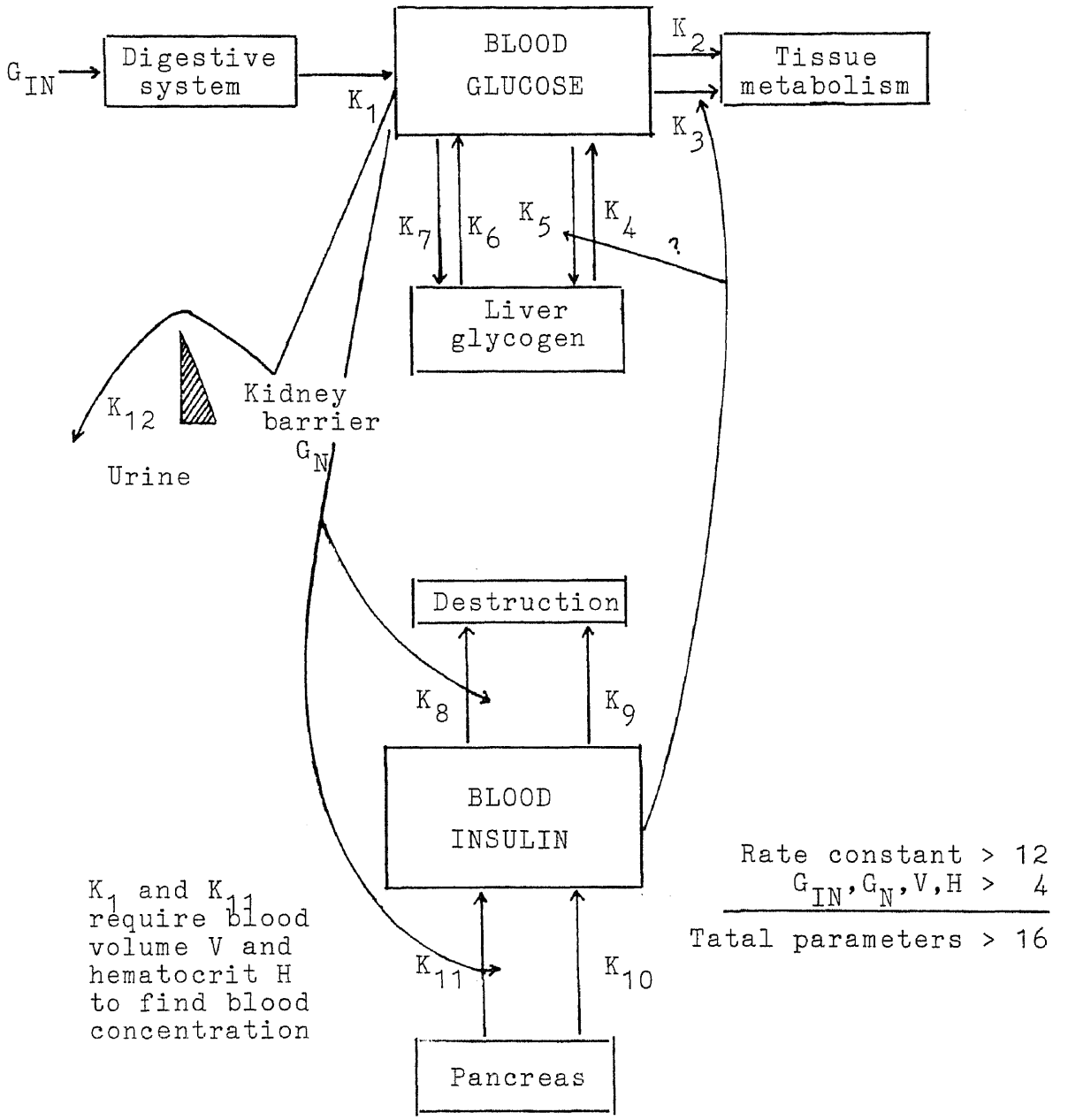

Figure 1. Block-diagram representation of feedback loop involved in glucose tolerance test. Question mark indicate uncertain reactions.

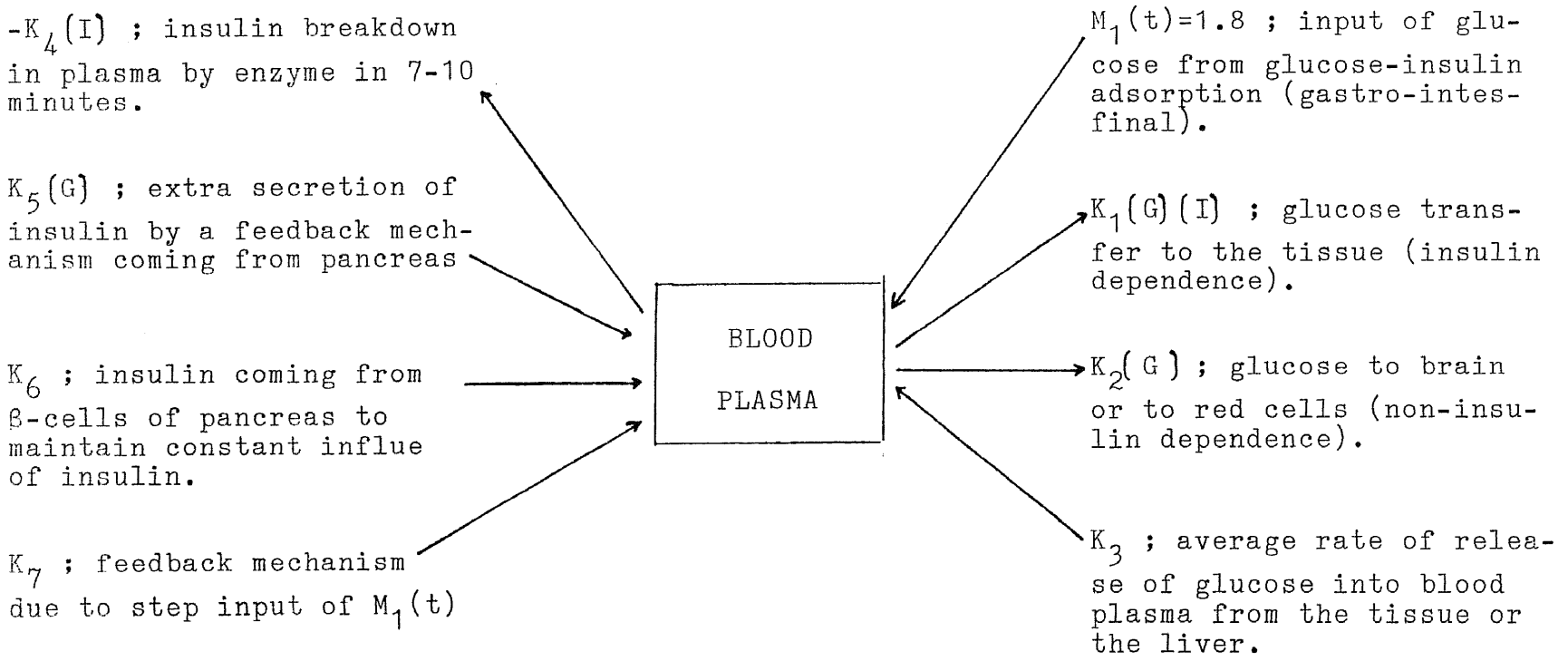

Figure 2. Simplified block diagram representation of the mechanism of glucose tolerance test.

CHAPTER III

EXPERIMENTS AND CURVE FITTING

Glucose tolerance test are a well known example of an experiment designed to classify individuals according to their response to a challenge load of glucose. These tests are also helpful to evaluate the assumptions made in formulating the basic model concerning the regulation of blood. (Gate Wood et. al., 1968)

In the oral glucose test, the subjects eats normal meals for several days, as extreme diets can affect the results. After an overlight fast, a blood sample is drawn. This is the zero time taken as the instant of cessation of loading. The subject then drink a glucose-enriched drink and several intermittent blood samples are obtained at 0, 10, 20, 30, 45, 60, 90, 120, 150, 180, 210, and 240 minutes afterward. The data published by H. S. Seltzer and colleagues who desired quantitative comparison of oral and intravenous glucose administration in different kinds of subjects. The glucose and insulin concentrations were classified in Table 1 and 2. This test reveals the functioning of the overall physiological system, but abnormalities detected may be due to the patterns of intestinal glucose absorption.

After we set up the mathematical model, the first goal is data description. If we use parameters of our model to reduce a mass of data to a small number of constants which

TABLE 1
Blood glucose concentrations during oral glucose tolerance test

		Minutes											
		0	10	20	30	45	60	90	120	150	180	210	240
		mg/100ml											
		Normal subjects											
Nonobese(21)	Mean	75	86	108	113	108	98	88	82	78	77	70	70
	SEM	±1	±2	±3	±4	±6	±6	±3	±2	±3	±3	±4	±4
Obese(11)	Mean	77	89	110	123	126	116	99	90	93	85	76	72
	SEM	±2	±4	±5	±30	±8	±8	±7	±5	±4	±8	±4	±3
		Mild diabetics											
Nonobese(10)	Mean	80	100	135	161	185	201	182	155	127	108	95	77
	SEM	±3	±7	±6	±6	±9	±11	±14	±12	±14	±14	±12	±9
Obese(11)	Mean	82	96	122	145	163	181	179	176	160	144	131	123
	SEM	±3	±3	±4	±4	±6	±6	±10	±12	±9	±10	±12	±13
		Moderata diabetics											
Nonobese(7)	Mean	137	153	172	213	251	284	295	294	274	254	240	211
	SEM	±11	±9	±10	±9	±13	±15	±27	±27	±27	±30	±32	±42
Obese(7)	Mean	142	156	189	223	259	290	313	315	295	280	251	212
	SEM	±12	±11	±13	±12	±18	±21	±22	±29	±34	±34	±28	±25

TABLE 2
Blood insulin concentrations during oral glucose tolerance test

		Minutes											
		0	10	20	30	45	60	90	120	150	180	210	240
		μU/ml											
		Normal subjects											
Nonobese(21)	Mean	11	40	93	111	129	122	103	93	89	70	52	45
	SEM	±1	±7	±8	±7	±10	±11	±16	±14	±16	±15	±8	±8
Obese(11)	Mean	33	68	137	193	269	274	216	199	160	117	72	33
	SEM	±2	±14	±16	±18	±37	±35	±39	±37	±31	±23	±18	±4
		Mild diabetics											
Nonobese(10)	Mean	9	27	67	113	138	195	233	228	178	140	107	61
	SEM	±2	±5	±14	±21	±36	±35	±42	±39	±31	±36	±34	±27
Obese(11)	Mean	22	38	77	116	155	200	200	202	181	167	158	138
	SEM	±2	±5	±8	±15	±20	±30	±16	±27	±23	±20	±19	±28
		Moderate diabetics											
Nonobese(7)	Mean	19	20	27	28	54	59	95	103	89	91	65	49
	SEM	±5	±4	±11	±10	±18	±16	±25	±29	±32	±28	±20	±17
Obese(7)	Mean	19	20	36	47	55	69	102	99	111	94	78	62
	SEM	±7	±4	±11	±13	±17	±16	±33	±30	±27	±27	±17	±15

are more amenable to human discussion, then the application of the model serves a real purpose. This activity, sometimes referred to as curve fitting, was the initial approach of this thesis to models of blood glucose dynamics. For this purpose one asks that the selected model be capable of predicting curves which pass within the limits of experimental error of the observed values. The second goal which we looked for in the studies of our model of the blood glucose regulation is the possibility of using the derived parameters for diagnostic classification. If the derived parameters can separate normal from abnormal, or can help to characterize quantitatively disease states, then the model need not even produce an acceptable description of the empirical data.

Because our model is nonlinear differential equations, we can not solve the equations analytically. So the fourth order Runge-Kutta method is used to integrate our nonlinear differential equations and gets the glucose and insulin concentrations for every minute. Then we use the least square curve fitting procedure with the Rosenbrock Hillclimb regression program to get the optimal parameters of the model.

The computer program used an iterative guessing technique which required initial guesses for K_1 to K_7. These parameters were adjusted by the computer until the cumulative sum of the squares of the derivation between the data points and the calculated points was a minimum.

The regression algorithm of Rosenbrock's theory varied all seven of the parameters in the neighborhood of the first

guess. The best neighboring point was then selected for the second guess, and so forth. When a given point was found to yield a lower cumulative sequare deviation than its neighbors, the step-sizes to the neighboring points were reduced and the entire process reiterated. When the step-size became sufficiently small, the process was terminated.

In this fashion the program always found an estimated set of values for the parameters yielding a least-square fit between the model and the data. It is needed to emphasize here, the initial guess of the parameters and the step-sizes is very important and very sensitive. Because in a case of bad guess, the program might converged to a local minimum with a large cumulative squared deviations, or the program was overflow, but suitable initial guesses enabled the model to be successfully conformed to all the data. On the other hand, a too large value of a step-size will lead to an overflow quickly due to the integration subroutine. We have to choose a suitable step-size in consistency with the size of the parameters which we guessed by trial. The optimization procedures are the most difficult part of this thesis.

The fitted parameters, which could then be used to describe each response qualitatively, and the glucose and insulin concentrations were printed out. Figure 3 to Figure 14 show the calculated curves and the data points. Most of the theoretical values were conformed within the limits of experimental error. The fitting of obese normal and nonobese mild diabetics have some small deviations between the simu-

lated curves and the actual data. These situations can be improved by a modified model.

All the parameters were checked for last twenty regration values to see if the parameters converge on the constant value eventually. The results of checking every parameter on every case show that the parameters do converge on the steady values (Appendix B).

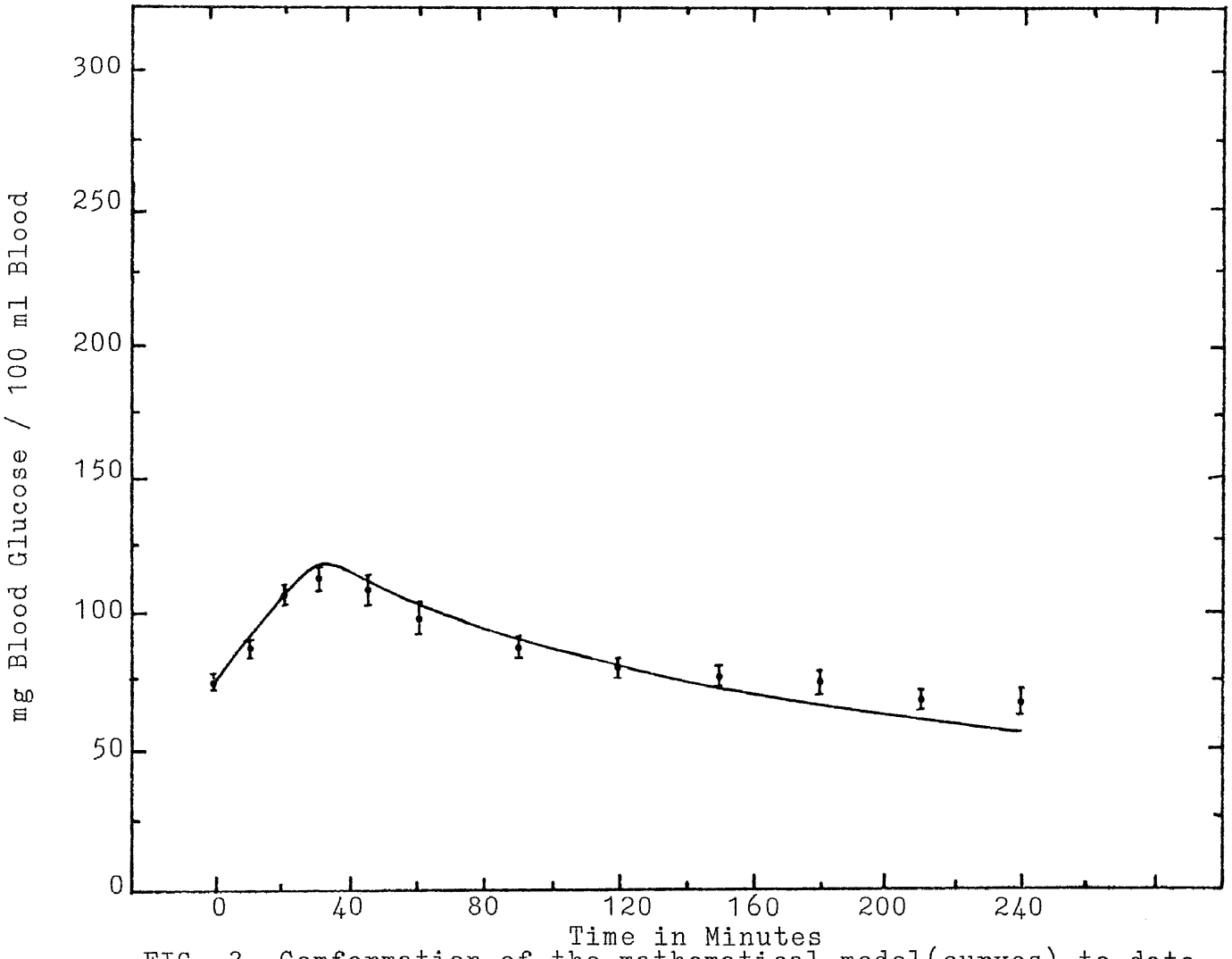

FIG. 3. Comformation of the mathematical model(curves) to data (points) obtained during an oral glucose tolerance test of glucose concentration on nonobese normals.

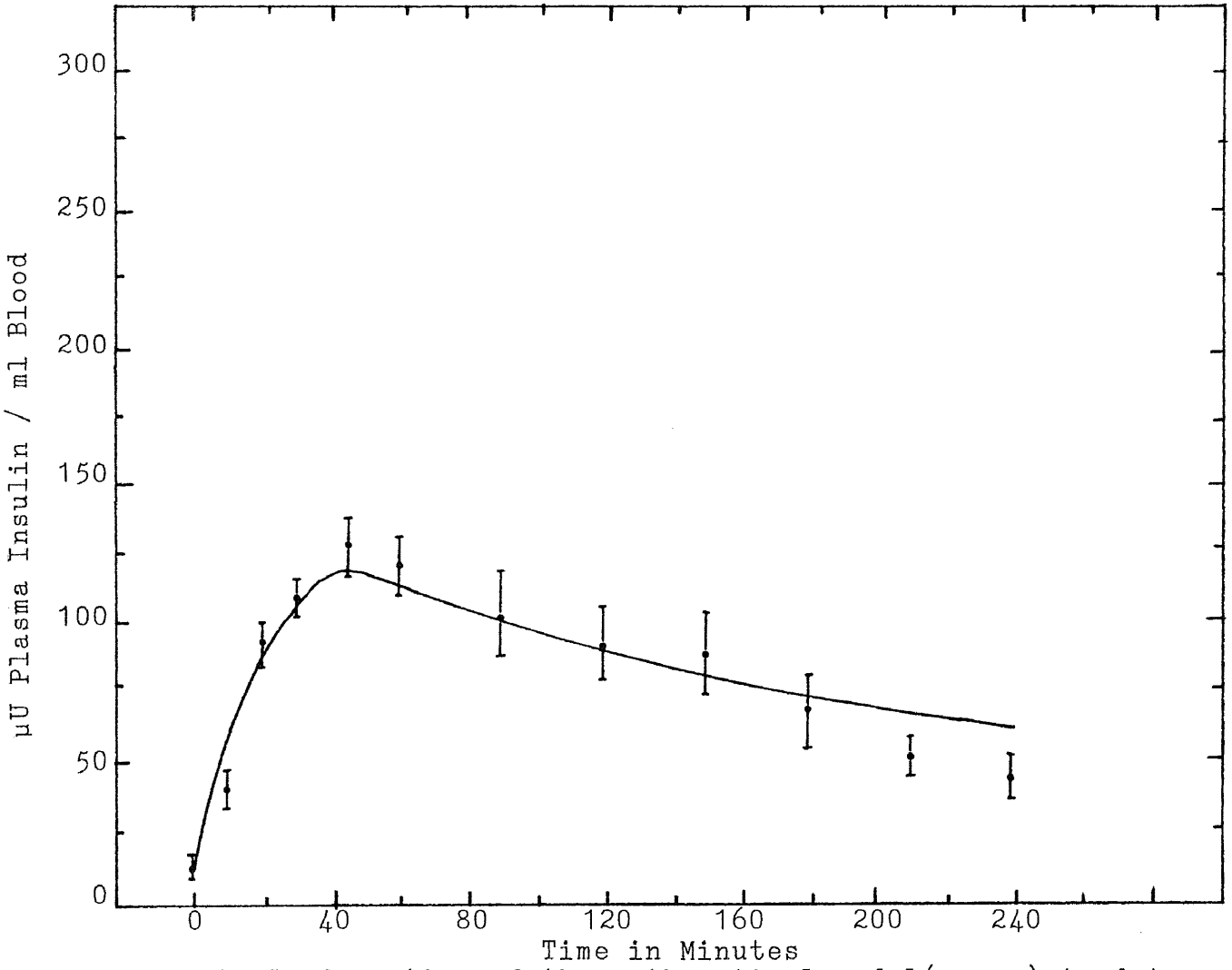

FIG. 4. Comformation of the mathematical model(curve) to data (points) obtained during an oral glucose tolerance test of insulin concentration on nonobese normals

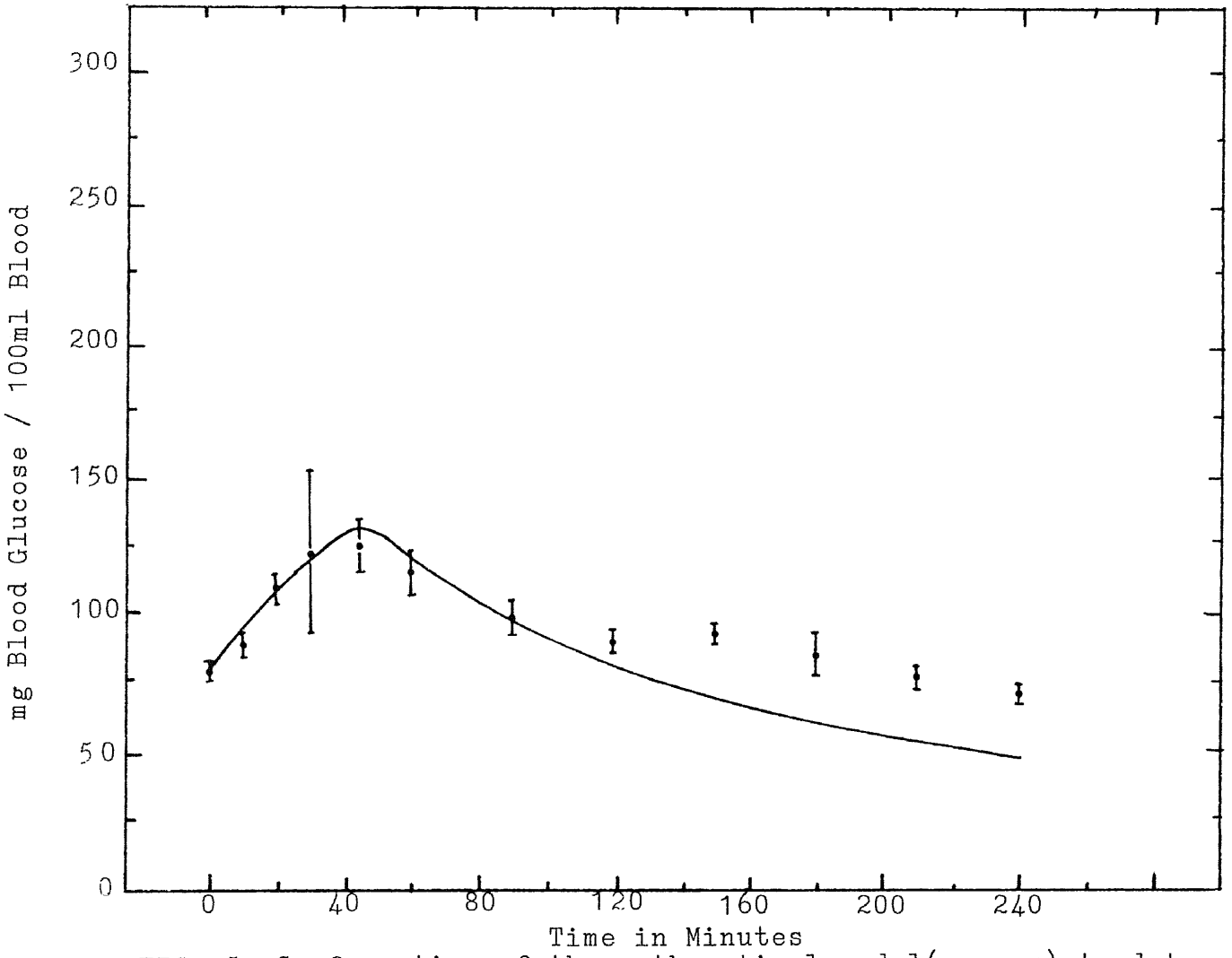

FIG. 5. Comformation of the mathematical model(curves) to data (points) obtained during an oral glucose tolerance test of glucose concentration on obese normals.

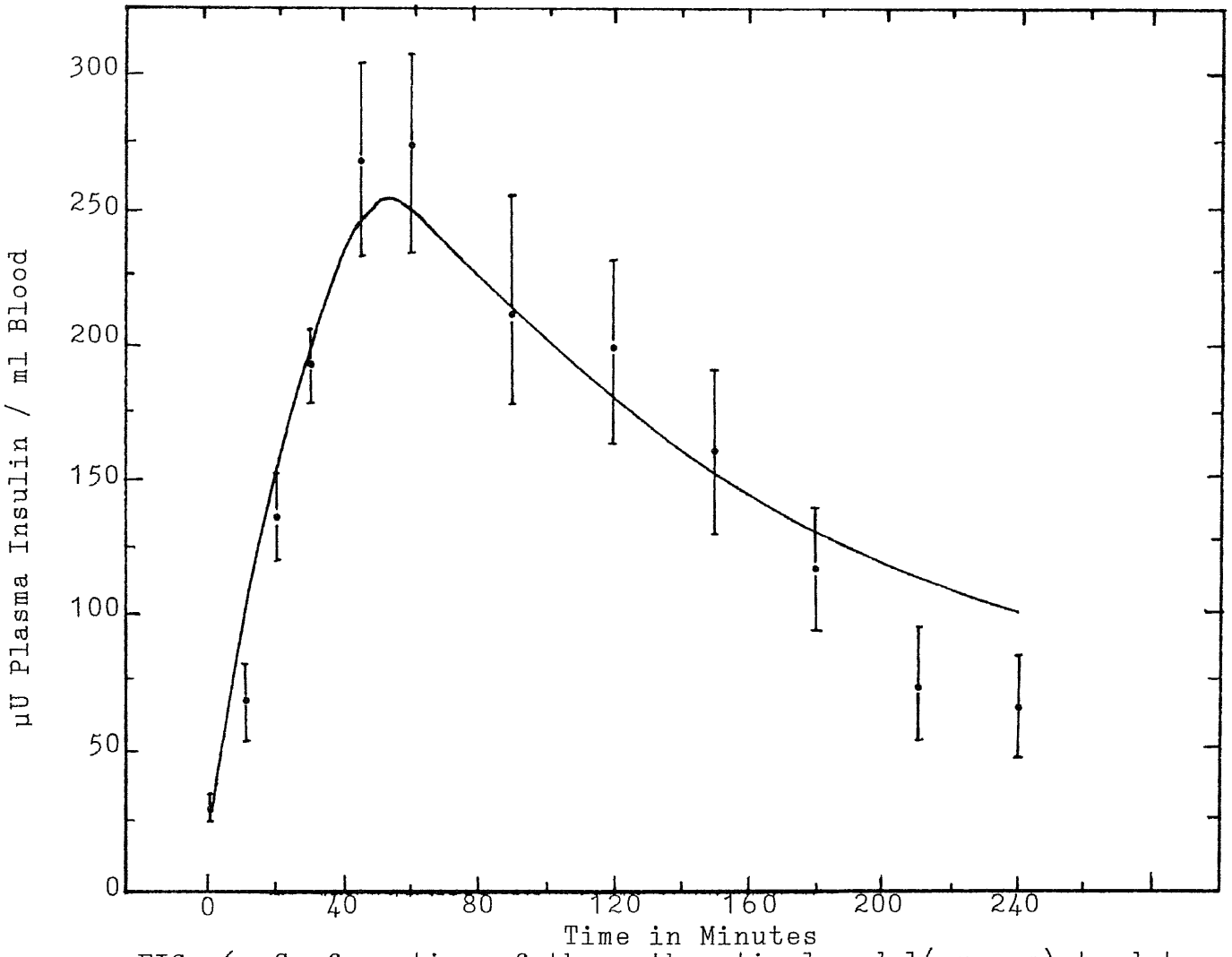

FIG. 6. Comformation of the mathematical model(curves) to data (points) obtianed during an oral glucose tolerance test of insulin concentration on obese normals.

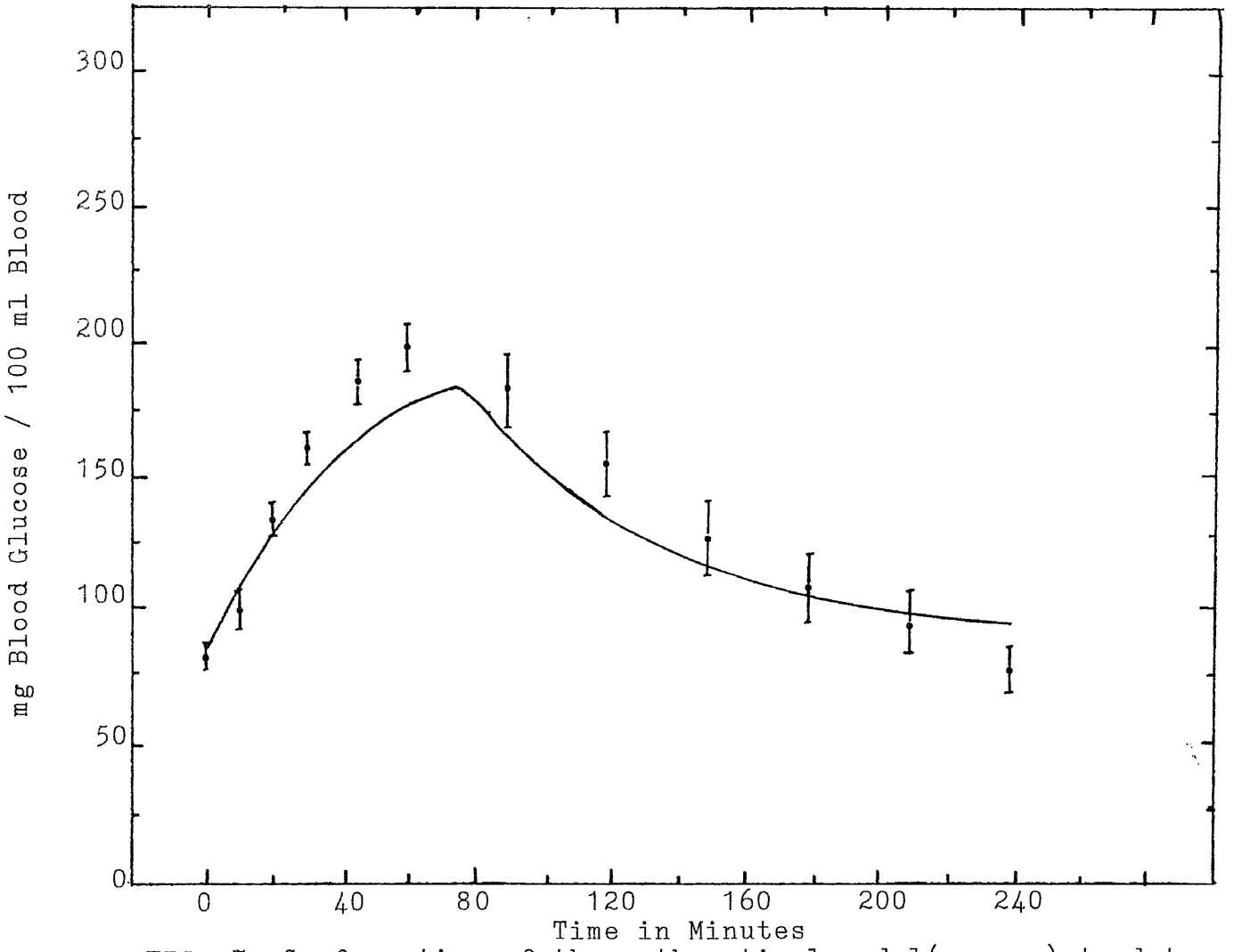

FIG. 7. Comformation of the mathematical model(curves) to data (points) obtained during an oral glucose tolerance test of glucose concentration on nonobese mild diabetics.

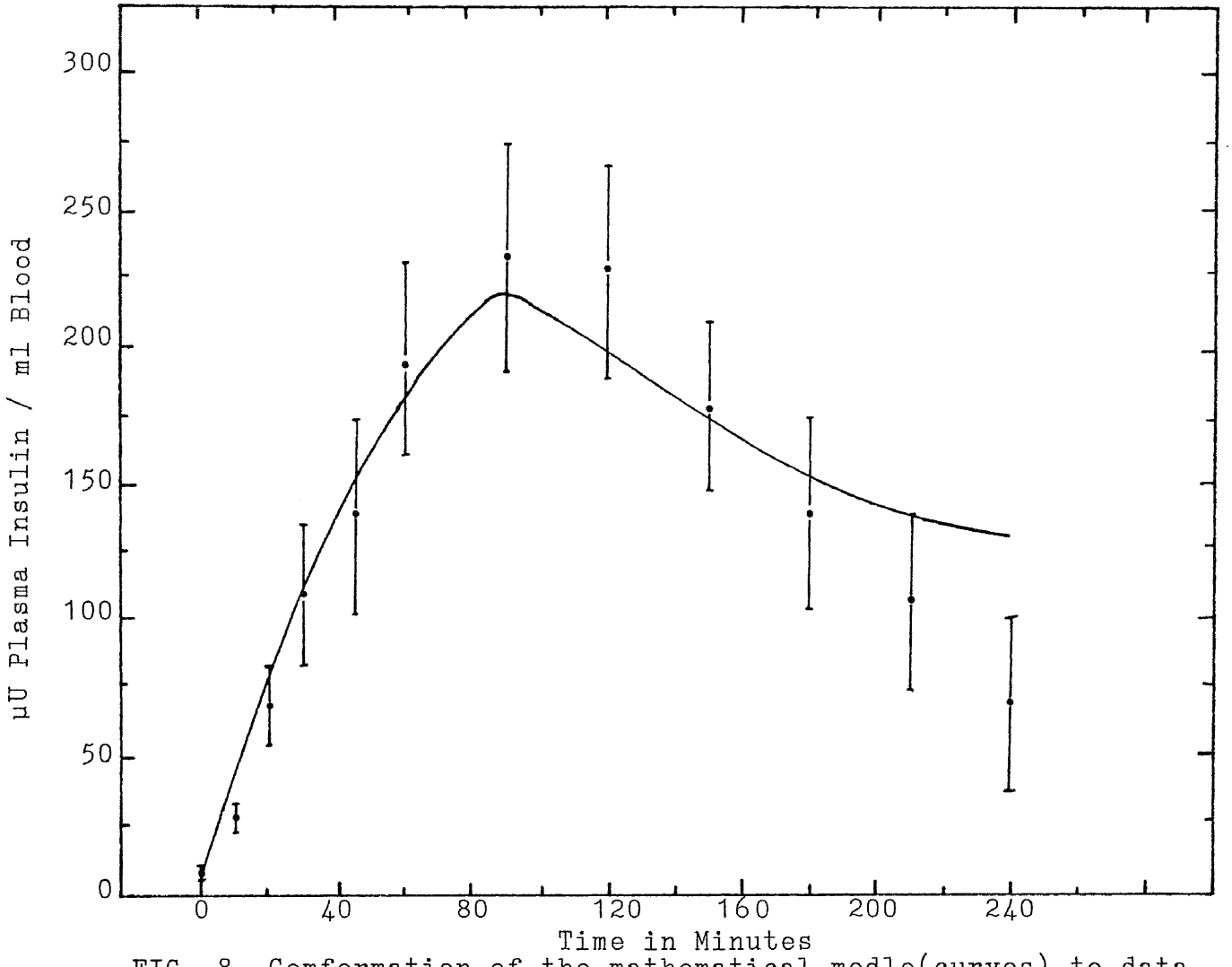

FIG. 8. Comformation of the mathematical modle(curves) to data (points) obtained during an oral glucose tolerance test of insulin concentration on nonobese mild diabetics.

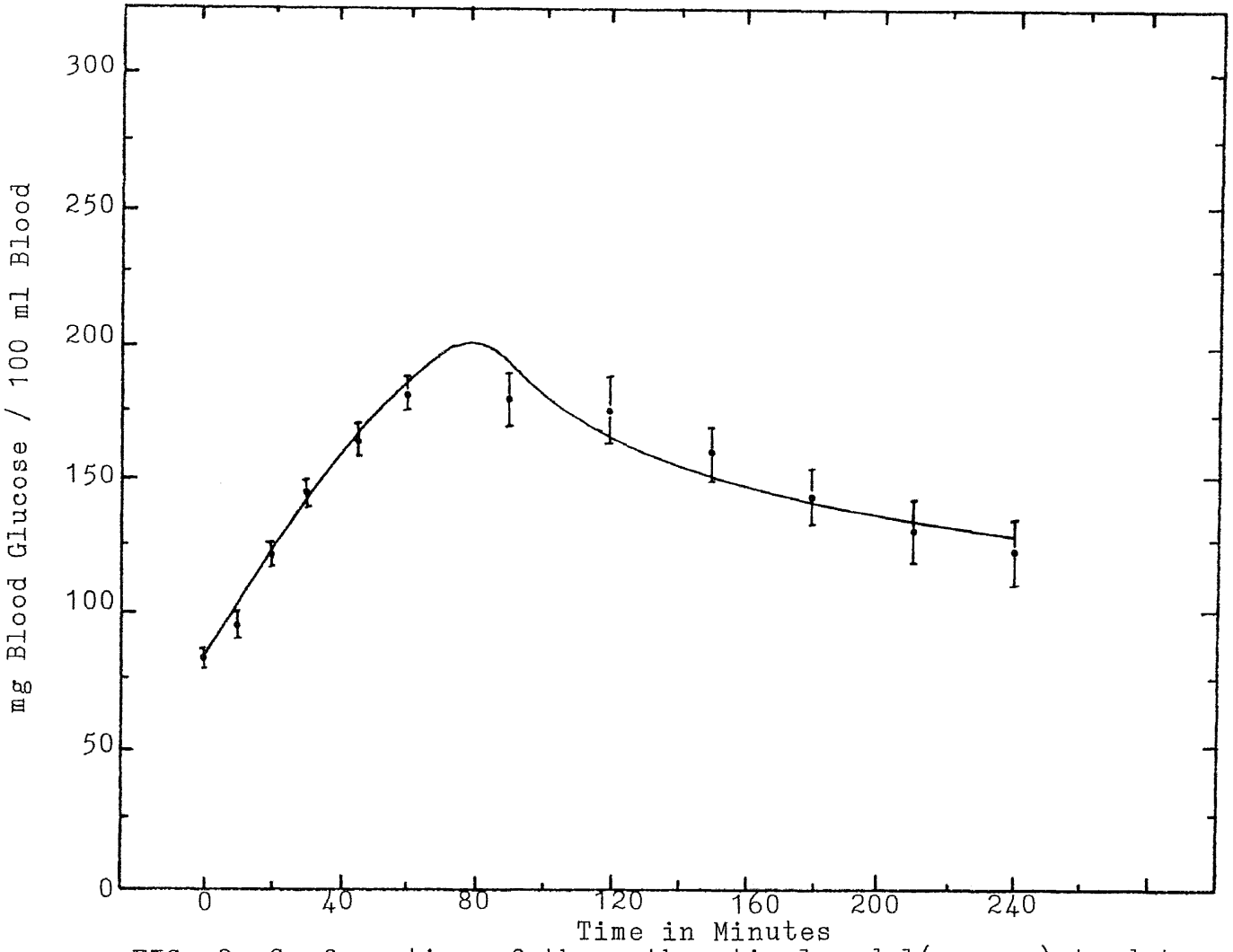

FIG. 9. Comformation of the mathematical model(curves) to data (points) obtained during an oral glucose tolerance test of glucose concentration on obese mild diabetics.

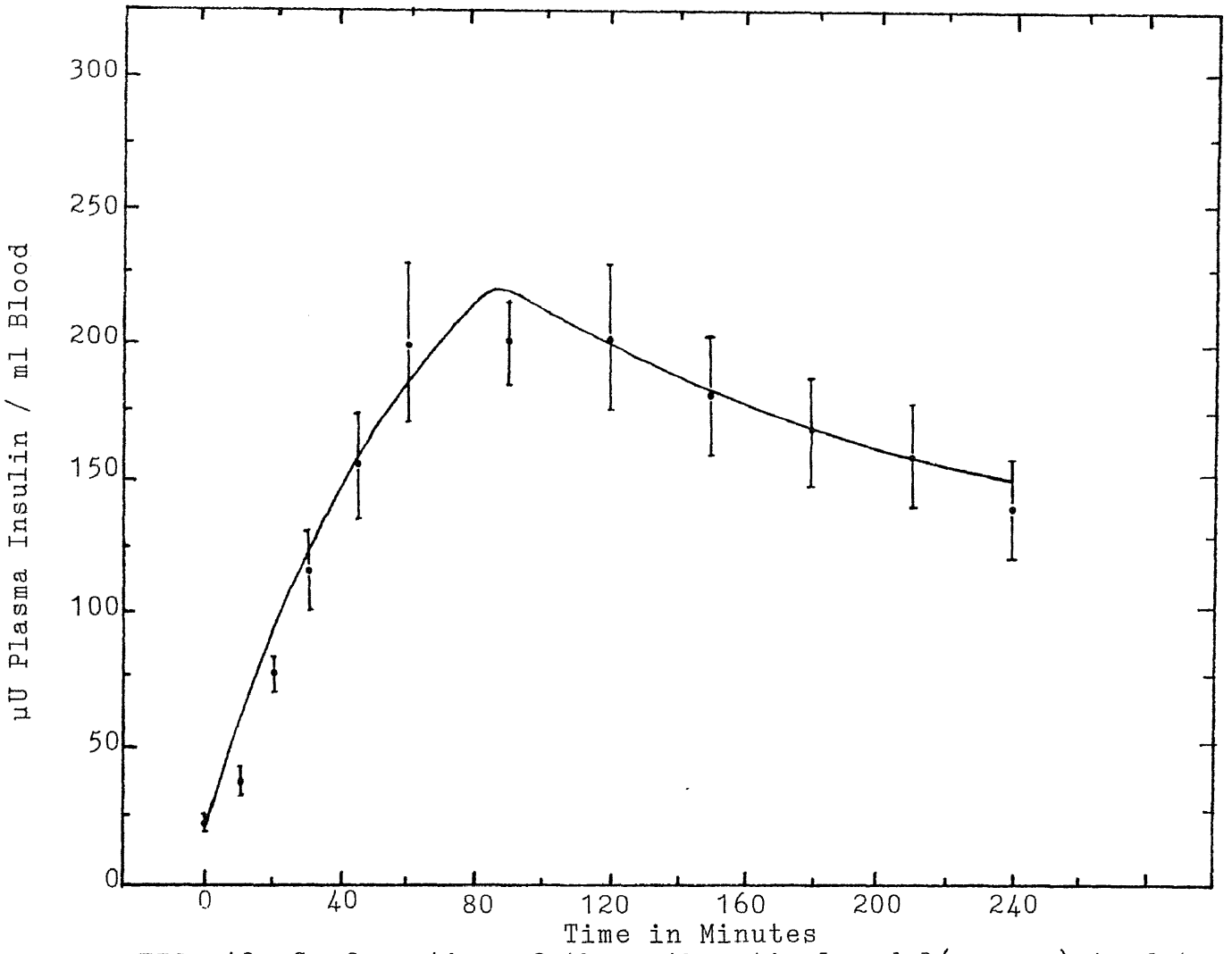

FIG. 10. Comformation of the mathematical model(curves) to data (points) obtained during an oral glucose tolerance test of insulin concentration on obese mild diabetics.

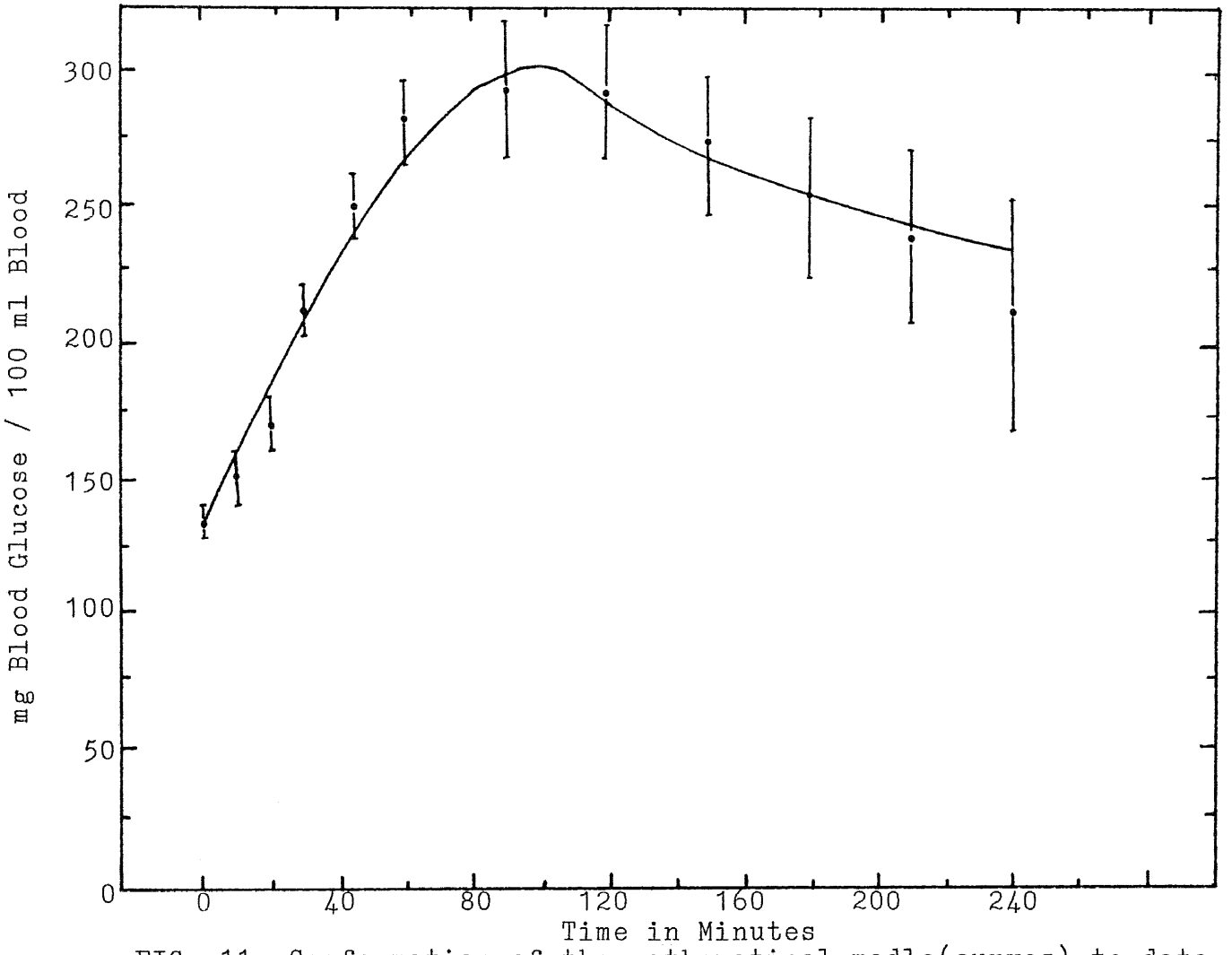

FIG. 11. Comformation of the mathematical modle(curves) to data (points) obtianed during an oral glucose tolerance test of glucose concentration on nonobese moderate diabetics.

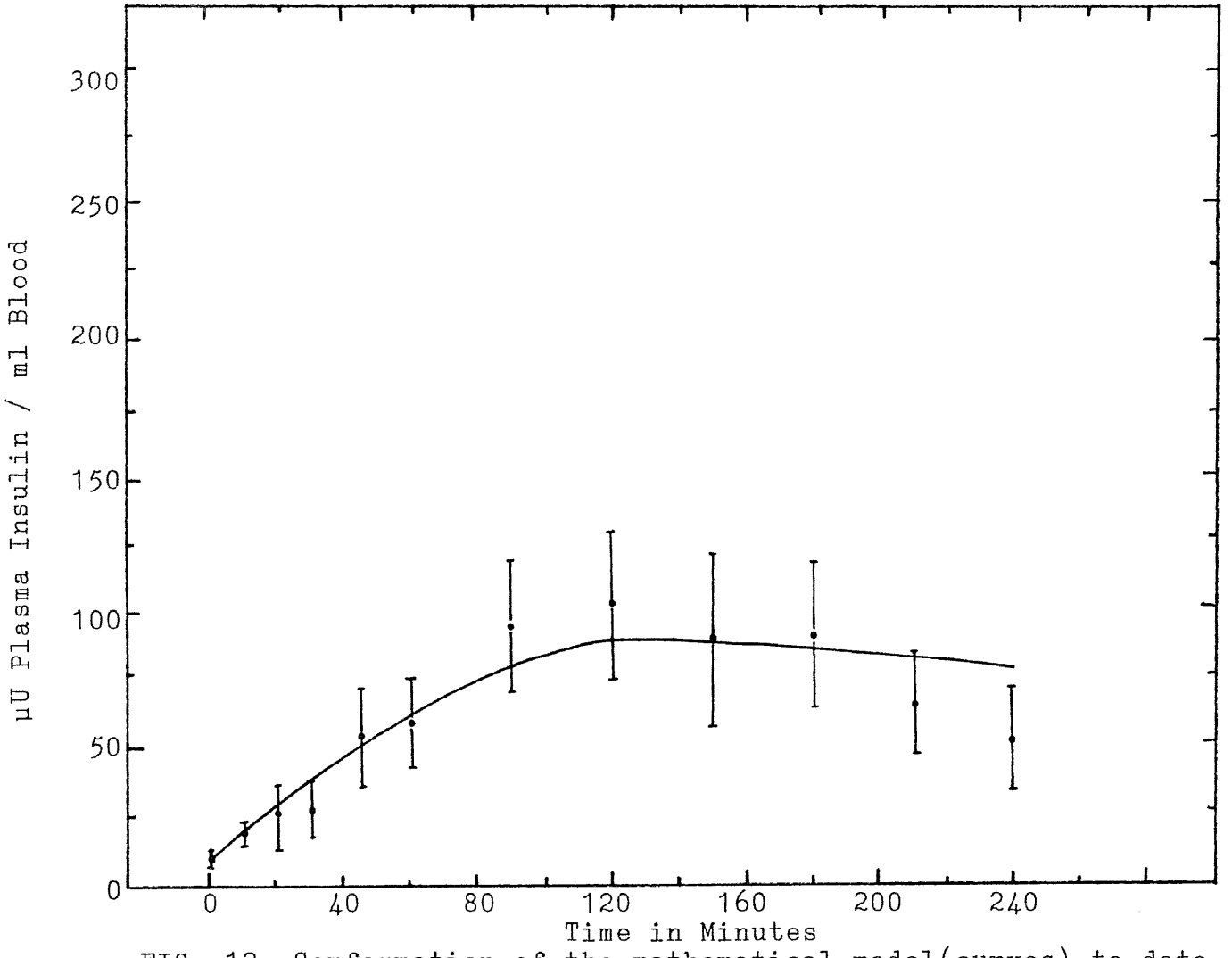

FIG. 12. Comformation of the mathematical model(curves) to data (points) obtained during an oral glucose tolerance test of insulin concentration on nonobese moderate diabetics.

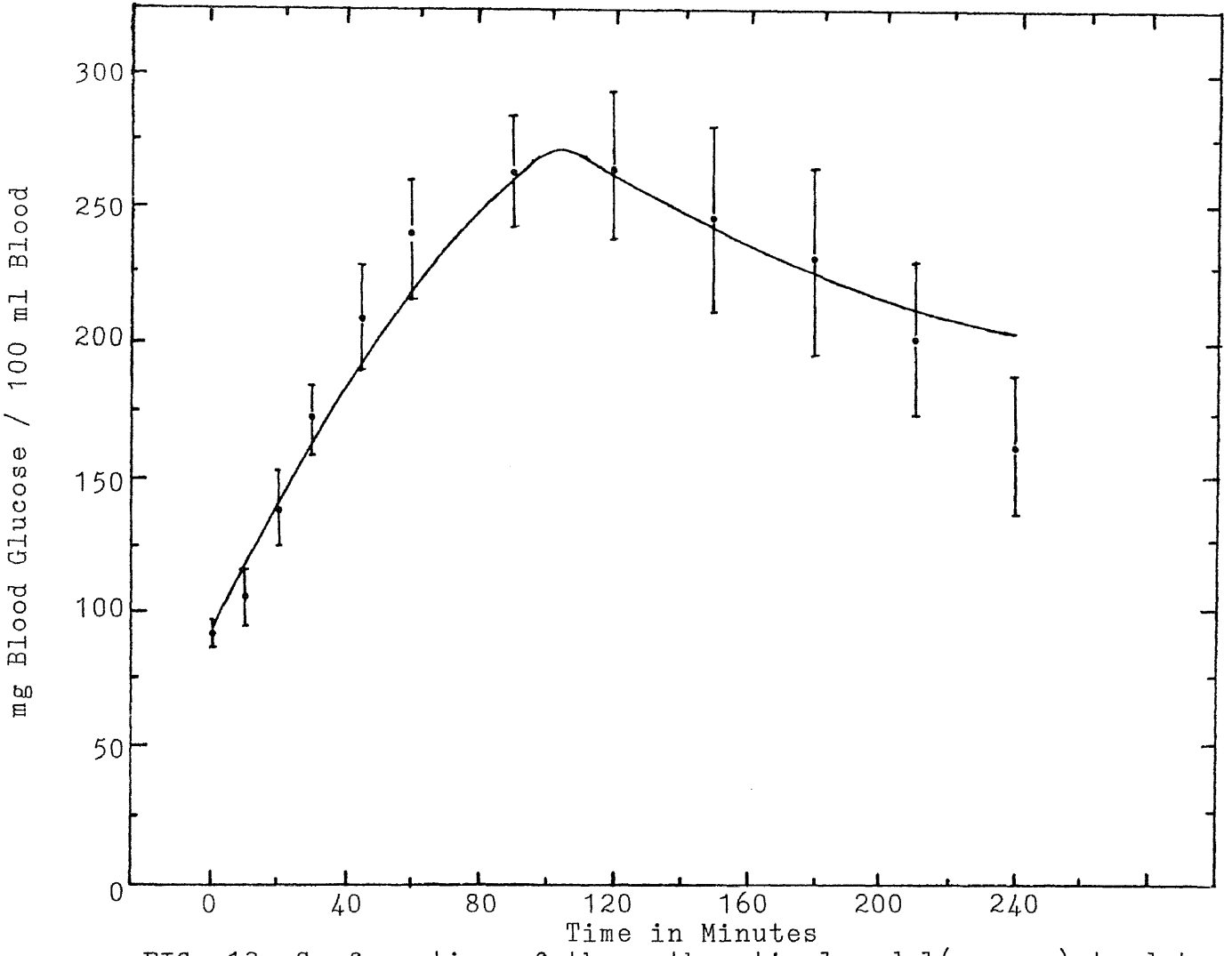

FIG. 13. Comformation of the mathematical model(curves) to data (points) obtained during an oral glucose tolerance test of glucose concentration on the obese moderate diabetics.

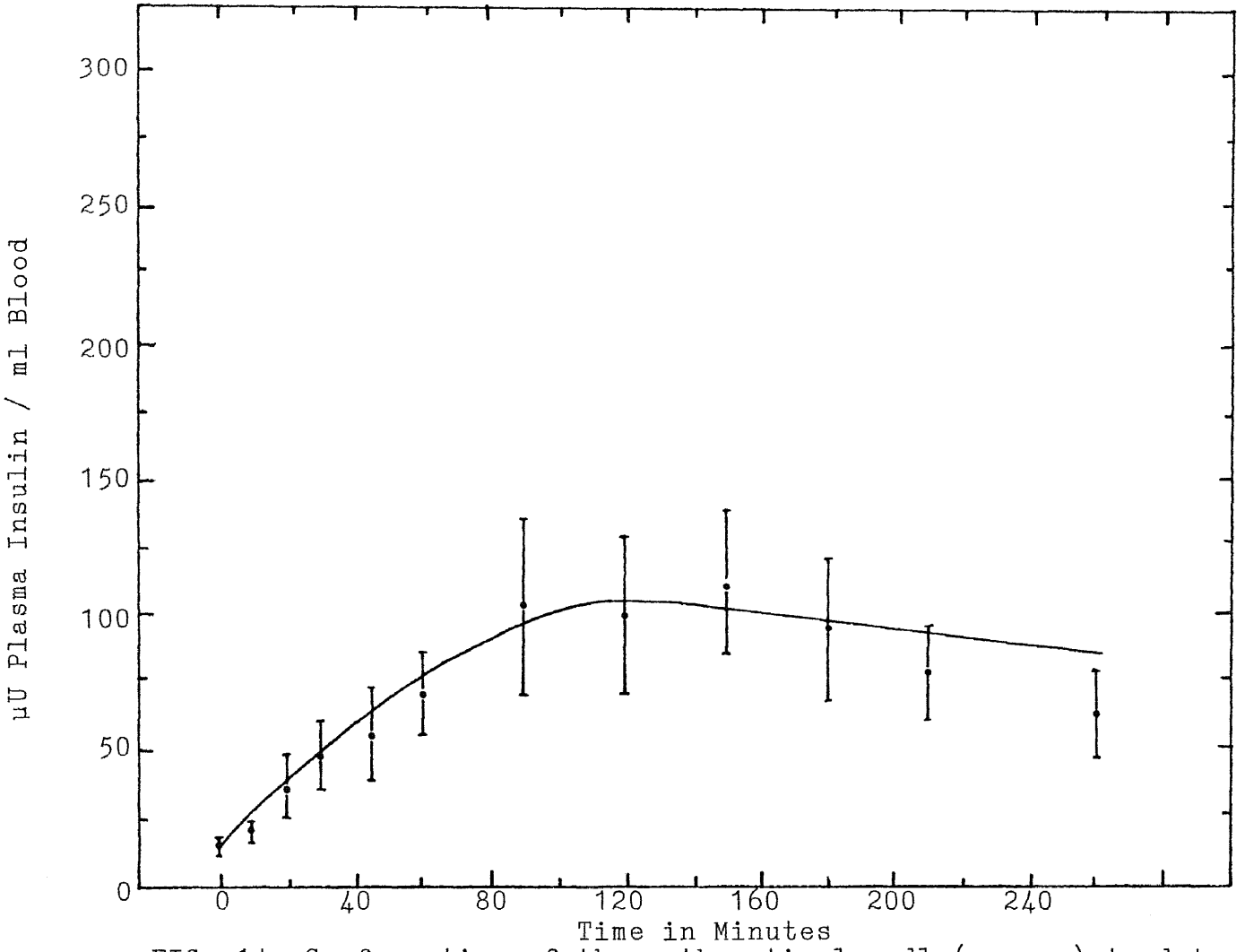

FIG. 14. Comformation of the mathematical modle(curves) to data (points) obtained during an oral glucose tolerance test of insulin concentration on obese moderate diabetics.

CHAPTER IV

RESULTS AND DISCUSSION

The result of the optimal parameters show the change of dynamic mechanisms from normals to diabetics. The final result are discussed as follow:

(I) Case of non-obese normal, non-obese mild diabetics and non-obese moderate diabetics

From Table 3, we can determine that:

(1) K_1 increases for diabetics. This means the glucose mass transfer, which is dependent on insulin, is higher in diabetics than in normals. On the other hand, since the diabetics have an insufficient supply of insulin, the high level glucose concentration thus goes to the tissue. Also, the difference of K_1 in these three cases is not very significant; therefore, it will not effect the mechanism much.

(2) K_2 decreases from normals to moderate diabetics. This is the reason why diabetics tire more easily than normals. Because the smaller the K_2 is the less glucose transfer to the brain or to the red cells, especially for mild diabetics.

(3) K_3 increases as the diabetic condition becomes more serious. From the mechanics, it shows the average rate of release of glucose to blood from liver or tissue was increased. It makes the diabetics have

more glucose in the blood plasma than in the normals due to abnormal release of glucose.

(4) K_4 is decreased from normals to moderate diabetics. This shows the rate of insulin breakdown in plasma by enzyme in diabetics is lower than in normals. If K_4 is small, as compareed with normals, the metabolism of glucose in plasma will be slowed down and causes the concentration of glucose to increase steadily.

(5) K_5 decreased from top to bottom in Table 3 indicates that the diabetics do not get sufficient secretion of insulin by a feedback mechanism coming from the pancreas as normals. Therefore, the diabetics cannot metabolize the glucose in plasma by using the extra secretion from the pancreas.

(6) Table 3 also shows that mild diabetics have the largest value for K_6. This is a very special situation for us, because it show that mild diabetics secrete a lot of insulin from β-cells to maintain constant influe of insulin. This phenomena called hyperinsulinemia is due to the nature response of human body for attempting to keep the glucose concentration at normal level. For normals, they do not need more insulin secretion from β-cell because other mechanisms work in the normal conditions.

(7) K_7 is extremely high in the normal case. We can say that the feedback mechanism which, due to $M_1(t)$

step input, is very sensitive for normals and not for moderate diabetics. Since the feedback mechanism does not work well in diabetics, the diabetics will not be able to metabolize the glucose very effectively.

TABLE 3

Non-obese normal (A), Non-obese mild diabetics (B), and Non-obese moderate diabetics (C)

Subjects	K_1 $\times 10^{-5}$	K_2 $\times 10^{-4}$	K_3 $\times 10^{-1}$	K_4 $\times 10^{-2}$	K_5 $\times 10^{-2}$	K_6 $\times 10^{-3}$	K_7 $\times 10^{-2}$
A	3.59	6.57	0.28	6.18	6.39	0.0096	159.81
B	4.90	2.03	5.40	4.17	5.49	1.01	2.44
C	5.84	3.39	9.35	2.99	0.96	0.16	3.83

(II) Case of Obese normal, Obese mild diabetics, and Obese moderate diabetics

For obese case, the general discussions of the dynamic mechanisms are almost the same as we haved discussed for non-obese case. However, we note that K_2 does not follow the tendency of decrement. K_2 in mild diabetics is higher than in moderate diabetics. This means the transportation rate of glucose to the red cells in mild diabetics is faster than in moderate diabetics. The other significant changes are K_4, K_6, and K_7. On the contrary, the non-obese normals and the obese normals have a lower breakdown rate of insulin by enzyme than

the obese mild diabetics. And, the parameter K_6 shows the obese normals have the highest hyperinsulinemia situation in all cases. Since K_7, the feedback mechanism to secrete the insulin, is much smaller in obese people than in non-obese people, we can say that the obese people have more glucose than the non-obese people in blood. Also, from the value of K_6, it seems that the efficiency of β-cells secretion in moderate diabetics cannot work out well.

TABLE 4

Parameter of Obese normal (D), Obese mild diabetics (E), and Obese moderate diabetics (F)

Subjects	K_1 $\times 10^{-5}$	K_2 $\times 10^{-4}$	K_3 $\times 10^{-1}$	K_4 $\times 10^{-2}$	K_5 $\times 10^{-2}$	K_6 $\times 10^{-3}$	K_7 $\times 10^{-2}$
D	3.07	4.31	0.27	4.10	7.94	6.62	266.85
E	3.52	3.40	6.06	4.27	4.81	5.72	84.86
F	4.74	3.09	7.08	2.94	0.99	0.047	38.37

(III) Case of Non-obese normal and Obese normal

The obese normals transfer less glucose to the tissue or to the red cells than the non-obese normal. The average rate of release of glucose into the blood from the liver are same for both subjects. In regard to the insulin, the insulin breakdown rate by enzyme decreases, and the insulin coming from β-cells or feed-

back mechanism increases for the obese people. The large difference in K_6 and K_7, between non-obese normal and obese normal, proves that large accumulation of insulin which comes from β-cells or feedback mechanism by $M_1(t)$ exists in obese normals. Totally, we might say that the obese normals have more glucose and insulin than the non-obese normals.

TABLE 5

Parameters of Non-obese normal (A) and Obese normal (D)

Subjects	K_1 $\times 10^{-5}$	K_2 $\times 10^{-4}$	K_3 $\times 10^{-1}$	K_4 $\times 10^{-2}$	K_5 $\times 10^{-2}$	K_6 $\times 10^{-3}$	K_7 $\times 10^{-2}$
A	3.59	6.57	0.28	6.18	6.39	0.0096	159.8
D	3.07	4.31	0.27	4.10	7.94	6.62	266.85

(IV) Case of Non-obese mild diabetics and Obese mild diabetics

From Table 6, we see that K_2 in obese mild diabetics is larger than in non-obese diabetics. So, the tranfer of glucose to the red cells will be larger in the obese case than in the non-obese case. K_5 shows that the extra secretion of insulin from pancreas in obese mild diabetics is less than in non-obese mild diabetics. These are different from the normal people. Generally, we may have the following discovery:

(1) Mild diabetics have the hyperinsulinemia phenomena

because of the body response for attempting to lower the glucose concentration.

(2) There are no differences in the rate of insulin breakdown by enzyme between nonobese mild diabetics and obese diabetics.

(3) Mild diabetics have the ability to metabolize the extra glucose which is caused by the abnormal mechanisms of K_3, K_4, K_5, and K_7.

TABLE 6

Parameters of Nonobese mild diabetics (B) and Obese mild diabetics (E)

Subjects	K_1 $\times 10^{-5}$	K_2 $\times 10^{-4}$	K_3 $\times 10^{-1}$	K_4 $\times 10^{-2}$	K_5 $\times 10^{-2}$	K_6 $\times 10^{-3}$	K_7 $\times 10^{-2}$
B	4.90	2.03	5.40	4.17	5.49	1.01	2.44
E	3.52	3.40	6.06	4.27	4.80	5.72	84.86

(V) Cases of Non-obese moderate diabetics and Obese moderate diabetics

Since the moderate diabetics in serious condition, Table 7 shows that there are no differences in K_2, K_3, K_4, and K_5 between the nonobese and the obese. All these mechanisms are under abnormal conditions. K_7 in the nonobese mild diabetics is larger than in the nonobese moderate diabetics. That is due to the total effects from K_2, K_4, K_5, K_6 on K_7. The K_4 in nonobese is larger

than obese. This is different from normal and mild diabetics cases. Thus, it means that non-obese moderate can get more insulin from β-cells than obese moderate diabetics. Therefore, we can conclude that the obese moderate diabetics are in the worst condition.

TABLE 7

Parameters of Non-obese moderate diabetics (C) and Obese moderate diabetics (F)

Subjects	K_1 $\times 10^{-5}$	K_2 $\times 10^{-4}$	K_3 $\times 10^{-1}$	K_4 $\times 10^{-2}$	K_5 $\times 10^{-2}$	K_6 $\times 10^{-3}$	K_7 $\times 10^{-2}$
C	5.84	3.39	9.35	2.99	9.55	1.63	3.83
F	4.74	3.09	9.08	2.94	9.91	0.47	38.36

(VI) The research studies by Drs. Judith and Richard Wurtman shows low-carbohydrate diets are doomed to fail for many overweight people because they upset a chemical regulator in the brain that triggers a craving for sweet, bread and starches. When someone eats carbohydrates, insulin is release into the blood. This raises the body's level of an amino acid called tryptophan. In the brain, tryptophan is used to manufacture a chemical called serotonin. This, in turn, turns off the hunger for carbohydrates.

Referring the research done by Drs. Judith to our model, we find the obese normal subjects have the most

strong appetite for carbohydrates after a diet because they have the highest value of K_5 for extra secretion of insulin by a glucose feedback mechanism.

TABLE 8
Summary of optimal parameters for differents cases

Subjects	K_1 $x10^{-5}$	K_2 $x10^{-4}$	K_3 $x10^{-1}$	K_4 $x10^{-2}$	K_5 $x10^{-2}$	K_6 $x10^{-3}$	K_7 $x10^{-3}$	Max. (G) mg/100ml	Time of (G) Max.	Max. (I) µU/ml	Time of (I) Max.
Nonobese normals (21)	3.59	6.57	0.28	6.18	6.39	0.0096	159.81	118	32	120	44
Obese normals (11)	3.07	4.31	0.27	4.10	7.94	6.62	266.85	130	45	253	52
Nonobese mild diabetics (10)	4.90	2.03	5.40	4.17	5.49	1.01	2.44	188	74	217	88
Obese mild diabetics(11)	3.52	3.40	6.06	4.27	4.81	5.72	84.86	200	80	222	88
Nonobese moderate diabetics (7)	5.84	3.39	9.35	2.99	0.96	0.16	3.83	305	100	90	120
Obese moderate diabetics (7)	4.74	3.09	7.08	2.94	0.99	0.047	38.37	320	104	105	105

CHAPTER V

CONCLUSIONS

The mathematical model presented has been a successful and effective way to average the measure point into several parameters. Through the comparison of parameters, it has enabled diagnostic classification, hypothesis testing, and extension of knowledge of blood glucose dynamics for normals and diabetics.

It is believed that this research can be utilized to determine the effect on the different designed parameters of the glucose dynamics and also can help to characterize quantitatively disease states; the model need not even produce an acceptable description of the empirical data.

CHAPTER VI

RECOMMENDATIONS

Some terms of the mathematical model reprented can be modified as follow:

(1) $K_1(G)(I)$ should be $K_1(G)(I)_{ads}$ which $(I)_{ads}$ is the concentration of insulin adsorped on the surface of tissue.

(2) If (G) is much lower than the fasting glucose concentration (G_0), K_3 will not be a constant. K_3 should increase faster than a constant when $(G)-(G_0)$ is a large negative quantity.

(3) The step function $M_1(t)$ should be modified as a distribution function.

(4) $K_4(I)$ should be modified as $K_4(I)(\text{Enzyme})$. (Enzyme) may be a function of time and follows the Michaelis-Menten kintics.

(5) $K_5(G)$ can be expressed as $K_5((G)-(G_0))$ or a feedback control model.

(6) If (I) is much lower than the fasting insulin concentration (I_0), K_6 should increase faster than a constant.

(7) The same studies can be developed for thyroid gland and iodine balance.

APPENDIX A

```
C
C       OPTIMIZATION PROGRAM FOR NONLINEAR
C       SIMULTANEOUS EQUATIONS
C
C
      REAL LC
      INTEGER PR
      INTEGER P
      INTEGER R
      INTEGER C
      DIMENSION XX(10,10),XCEN(10,10),XREF(10,10),
     1Z(10),XCON(10,10),XEX(10,10)
      DIMENSION X(10),E(8),V(8,8),SA(8),D(8),G(8),
     1H(8),AL(8),PH(8),A(8,8),B(8,8),BX(8),DA(8),
     1VV(8,8),EINT(8),VM(8),Y(10)
      COMMON EXP(50,50),TR(50)
      DATA ITMAX,IPRINT,L,ALFA,BETA,GAM,ACC,A
     1/40,10,7,1.0,0.5,2.0,0.01,0.0001/
      DATA M,P,LOOPY,PR,ND,NDATA,NSTEP/-1,7,7,1,
     11,0,0,0/
      READ (5,35) (E(J),J=1,L)
      READ (5,35) (XX(1,J),J=1,L)
   35 FORMAT (7F10.2)
      DATA NVAR,NDAT/2,24/
      READ (5,45) (Y(J),J=1,NVAR)
   45 FORMAT (2F10.1)
      READ (5,43) (EXP(IL,1),IL=1,NDAT)
      READ (5,47) (EXP(IL,2),IL=1,NDAT)
   43 FORMAT (8F10.1/8F10.1/8F10.1)
   47 FORMAT (8F10.1/8F10.1/8F10.1)
      NP1=L+1
      Q=(AA/(L*(2.**.5)))*((L+1.)**.5-1.)
      P1=(AA/(L*(2.**.5)))*((L+1)**.5+L-1.)
      MM=L+1
      DO 139 I=2,MM
      AP=1.0
      DO 121 J=1,L
      AP=AP+1
      IF (I .EQ. AP) GO TO 135
      XX(I,J)=XX(1,J)+Q
      GO TO 121
  135 XX(I,J)=XX(1,J)+P1
  121 CONTINUE
  139 CONTINUE
      IF (ALFA .EQ. 0.) ALFA=1.
      IF (BETA .EQ. 0.) BETA=.5
      IF (GAM .EQ. 0.) GAM=2.
      IF (ACC .EQ. 0.) ACC=0.1
      WRITE (6,23)
   23 FORMAT(1H1,10X,28HNELDER AND MEAD OPTIMIZATION)
```

```
      WRITE (6,24)
 24   FORMAT(/,2X,10HPARAMETERS)
      WRITE (6,25) L,ACC,ALFA,BETA,GAM
 25   FORMAT (/,2X,25HNUM OF COEFF OPTIMIZED = ,I2,
     14X,11HACCURACY = ,E10.4,/,2X,8HALPHA = ,
     1E10.4,4X,7HBETA = ,E10.4,4X,8HGAMMA = ,E10.4)
      WRITE (6,29)
 29   FORMAT (//,10X,16HSTARTING SIMPLEX)
      DO 141 I=1,NP1
      WRITE (6,28) (I,J,XX(I,J),J=1,L)
 28   FORMAT(/,4(2X,2HX(,I2,1H,I2,4H) = ,
     11PE12.5))
141   CONTINUE
      ITR=0
150   DO 155 I=1,NP1
      CALL FUNC (I,XX,Z,Y,FNC)
155   CONTINUE
      ITR=ITR+1
      IF (ITR .GE. ITMAX) GOTO 145
      IF (IPRINT) 158,162,158
158   WRITE (6,37) ITR
 37   FORMAT (//,2X,17HITERATION NUMBER, I3)
      DO 161 J=1,NP1
161   WRITE (6,28) (J,I,XX(J,I),I=1,L)
      GO TO 162
162   ZHI=AMAX1(Z(1),Z(2),Z(3),Z(4),Z(5),Z(6),Z(7),Z(8))
      ZLO=AMIN1(Z(1),Z(2),Z(3),Z(4),Z(5),Z(6),Z(7),Z(8))
      DO 165 I=1,NP1
      IF (ZHI .EQ. Z(I)) GOTO 171
165   CONTINUE
171   K=I
      EN=L
      DO 181 J=1,L
      SUM=0.
      DO 175 I=1,NP1
      IF (K .EQ. I) GOTO 175
      SUM=SUM+XX(I,J)
175   CONTINUE
181   XCEN(K,J)=SUM/EN
      I=K
      CALL FUNC (I,XCEN,Z,Y,FNC)
      ZCEN=Z(I)
      SUM=0.
      DO 185 I=1,NP1
      IF (K .EQ. I) GOTO 185
      SUM=SUM+(Z(I)-ZCEN)*(Z(I)-ZCEN)/EN
185   CONTINUE
      EJ=SQRT(SUM)
      IF (EJ .LT. ACC) GOTO 998
      DO 191 J=1,L
```

```
      XREF(K,J)=XCEN(K,J )+ALFA*(XCEN(K,J)-XX(K,J))
191   CONTINUE
      I=K
      CALL FUNC (I,XREF,Z,Y,FNC)
      ZREF=Z(I)
      DO 200 I=1,NP1
      IF (ZLO .EQ. Z(I)) GOTO 205
200   CONTINUE
205   LL=I
      IF (ZREF .LE. Z(LL)) GOTO 241
      DO 207 I=1,NP1
      IF (ZREF .LT. Z(I)) GOTO 208
207   CONTINUE
      GO TO 215
208   DO 211 J=1,L
211   XX(K,J)=XREF(K,J)
      GO TO 150
215   DO 221 J=1,L
221   XCON(K,J)=XCEN(K,J)+BETA*(XX(K,J)-XCEN(K,J))
      I=K
      CALL FUNC (I,XCON,Z,Y,FNC)
      ZCON=Z(I)
      IF (ZCON .LT. Z(K)) GOTO 231
      DO 225 J=1,L
      DO 225 I=1,NP1
225   XX(I,J)=(XX(I,J)+XX(LL,J))/2.
      GO TO 150
231   DO 235 J=1,L
235   XX(K,J)=XCON(K,J)
      GO TO 150
241   DO 245 J=1,L
245   XEX(K,J)=XCEN(K,J)+GAM*(XREF(K,J)-XCEN(K,J))
      I=K
      CALL FUNC (I,XEX,Z,Y,FNC)
      ZEX=Z(I)
      IF (ZEX .LT. Z(LL)) GOTO 255
      DO 251 J=1,L
251   XX(K,J)=XREF(K,J)
      GO TO 150
255   DO 261 J=1,L
261   XX(K,J)=XEX(K,J)
      GO TO 150
145   WRITE (6,10) ITMAX
 10   FORMAT (///,10X,20HDID NOT CONVERGE IN,
     1I5,11HITERATIONS.)
998   WRITE (6,39) ZLO
 39   FORMAT (//,2X,21HOPTIMUM VALUE OF F = ,E16.8)
      WRITE (6,19)
 19   FORMAT (//,2X,'OPTIMUM VALUE OF VARIABLE')
      DO 301 I=1,L
```

```
 301  WRITE (6,26) I,XX(NP1,I)
  26  FORMAT (/,2X,2HX(,I2,4H) = ,1PE16.8)
      WRITE (6,21) EJ
  21  FORMAT (/,2X,'EJ = ',F10.5)
      DO 610 J=1,L
 610  X(J)=XX(NP1,J)
      WRITE (6,13)
  13  FORMAT (1H1,10X,'ROSENBROCK HILLCLIMB PROCEDURE')
C
C
      IF (ND-1) 30,20,30
  20  DO 300 KA=1,NDATA
      READ (NI,2) DA(KA)
   2  FORMAT (1E10.4)
 300  CONTINUE
C
  30  LAP=PR-1
      LOOP=0
      ISW=0
      INIT=0
      KOUNT=0
      TERM=0.0
      DELY=0.001
      F1=0.0
      NPAR=NDATA
      N=L
      DO 40 K=1,L
  40  AL(K)=(CH(X,DA,N,NPAR,K)-CG(X,DA,N,NPAR,
     1K))*0.0001
      DO 60 I=1,P
      DO 60 J=1,P
      V(I,J)=0.0
      IF (I-J) 60,61,60
  61  V(I,J)=0.0005
  60  CONTINUE
      DO 65 KK=1,P
      EINT(KK)=E(KK)
  65  CONTINUE
C
C
1000  DO 70 J=1,P
      IF (NSTEP .EQ. 0) E(J)=EINT(J)
      SA(J)=2.0
  70  D(J)=0.0
      FBEST=F1
  80  I=1
      IF (INIT .EQ. 0) GOTO 120
  90  DO 110 K=1,P
 110  X(K)=X(K)+E(I)*V(I,K)
      DO 50 K=1,L
```

```
  50  H(K)=F0
C
C
 120  F1=F(X,N,Y,FNC)
      F1=M*F1
      IF (ISW .EQ. 0) F0=F1
      ISW=1
      IF (ABS(FBEST-F1)-DELY) 122,122,125
 122  TERM=1.0
      GO TO 450
 125  CONTINUE
C
C
      J=1
C
 130  XC=CX(X,DA,N,NPAR,J)
      LC=CG(X,DA,N,NPAR,J)
      UC=CH(X,DA,N,NPAR,J)
      IF (XC .LE. LC) GOTO 420
      IF (XC .GE. UC) GOTO 420
      IF (F1 .LT. F0) GOTO 420
      IF (XC .LT. LC+AL(J)) GOTO 140
      IF (XC .GT. UC-AL(J)) GOTO 140
      H(J)=F0
      GO TO 210
C
C
 140  CONTINUE
C
      BW=AL(J)
C
      IF (XC .LE. LC .OR. UC .LE. XC)
     1GOTO 159
      IF (LC .LT. XC .AND. XC .LT. LC+BW)
     1GOTO 160
      IF (UC-BW .LT. XC .AND. XC .LT. UC)
     1GOTO 170
      PH(J)=1.0
      GO TO 210
C
C
 159  PH(J)=0.0
      GO TO 190
 160  PW=(LC+BW-XC)/BW
      GO TO 180
 170  PW=(XC-UC+BW)/BW
 180  PH(J)=1.0-(3.0*PW)+(4.0*PW*PW)-
     1(2.0*PW*PW*PW)
C
 190  F1=H(J)+(F1-H(J))*PH(J)
```

```
C
 210  CONTINUE
      IF (J .EQ. L) GOTO 220
      J=J+1
      GO TO 130
C
 220  INIT=1
      IF (F1 .LT. F0) GOTO 420
      D(I)=D(I)+E(I)
      E(I)=3.0*E(I)
      F0=F1
      IF (SA(I) .GE. 1.5) SA(I)=1.0
C
 230  DO 240 JJ=1,P
      IF (SA(JJ) .GE. 0.5) GOTO 440
 240  CONTINUE
C
C     AXES ROTATION
C
      DO 250 R=1,P
      DO 250 C=1,P
 250  VV(C,R)=0.0
      DO 260 R=1,P
      KR=R
      DO 260 C=1,P
      DO 265 K=KR,P
 265  VV(R,C)=D(K)*V(K,C)+VV(R,C)
 260  B(R,C)=VV(R,C)
      BMAG=0.0
      DO 280 C=1,P
      BMAG=BMAG+(B(1,C)*B(1,C))
 280  CONTINUE
      BMAG=SQRT(BMAG)
      BX(1)=BMAG
      DO 310 C=1,P
 310  V(1,C)=B(1,C)/BMAG
C
      DO 390 R=2,P
C
      IR=R-1
      DO 390 C=1,P
      SUMVM=0.0
      DO 320 KK=1,IR
      SUMAV=0.0
      DO 330 KJ=1,P
 330  SUMAV=SUMAV+VV(R,KJ)*V(KK,KJ)
 320  SUMVM=SUMAV*V(KK,C)+SUMVM
 390  B(R,C)=VV(R,C)-SUMVM
      DO 340 R=2,P
      BBMAG=0.0
```

```
      DO 350 K=1,P
 350  BBMAG=BBMAG+B(R,K)*B(R,K)
      BBMAG=SQRT(BBMAG)
      DO 340 C=1,P
 340  V(R,C)=B(R,C)/BBMAG
      LOOP=LOOP+1
      LAP=LAP+1
      IF (LAP .EQ. PR) GO TO 450
      GO TO 1000
C
 420  IF (INIT .EQ. 0) GOTO 450
      DO 430 IX=1,P
 430  X(IX)=X(IX)-E(I)*V(I,IX)
      E(I)=-0.5*E(I)
      IF (SA(I) .LT. 1.5) SA(I)=0.0
      GO TO 230
C
 440  CONTINUE
      IF (I .EQ. P) GOTO 80
      I=I+1
      GO TO 90
C
 450  WRITE (6,3)
   3  FORMAT (//,2X,5HSTAGE,8X,8HFUNCTION,12X,
     18HPROGRESS,9X,16HLATERAL PROGRESS)
      WRITE (6,4) LOOP,FO,BMAG,BBMAG
   4  FORMAT (1H,I5,3E20.8)
      WRITE (6,14) KOUNT
  14  FORMAT (/,2X,'NUMBER OF FUNCTION EVALUATIONS = ',I8)
      WRITE (6,5)
   5  FORMAT (/,2X,25HVALUES OF X AT THIS STAGE)
C
C     PRINT CURRENT VALUES OF X
C
      WRITE (6,6) (JM,X(JM),JM=1,P)
   6  FORMAT (/,2(2X,2HX(,I2,4H) = ,1PE14.6,4X))
C
      LAP=0
      IF (INIT .EQ. 0) GOTO 470
      IF (TERM .EQ. 1.0) GOTO 480
      IF (LOOP .GE. LOOPY) GOTO 480
      GO TO 1000
C
 470  WRITE (6,7)
   7  FORMAT (///,2X,'THE START POINT MUST NOT VIOLATE')
 480  CONTINUE
 490  WRITE (6,8)
   8  FORMAT (///,2X,'FINAL DIRECTION VECTOR MATRIX')
      DO 500 J=1,P
 500  WRITE (6,9) (J,I,V(J,I),I=1,P)
```

```
   9  FORMAT (/,2(2X,2HV(,I2,1H, ,I2,4H) = ,
     1F10.8,4X))
      WRITE (6,11)
  11  FORMAT (//,2X,16HFINAL STEP SIZES)
      WRITE (6,12) (J,E(J),J=1,F)
  12  FORMAT (/,2(2X,2HS(,I1,4H) = ,F10.8,
     14X))
      F7=F(X,N,Y,FNC)
      DO 540 I=1,NDAT
 540  WRITE (6,17) TR(I),FNC(I,1),FNC(I,2)
  17  FORMAT (/,2X,'T = ',F6.2,8X,
     1'G = ',F7.2,8X,'I = ',F7.2)
      STOP
      END
      FUNCTION F(XE,IA,Y,FNC)
      DIMENSION XE(10),Y(10),G(10),FNC(50,50)
      COMMON EXP(50,50),TR(50)
      DATA NDAT,TMAX,H,KOUNT,NVAR,CMAX/24,240.,1.,0,2,75./
      INTEGER RUNGE
      T=0.
      J=0.
      SUM=0.
      T1=0.
C     CALL ON THE FOURTH-ORDER RUNGE-KUTTA NUMERICAL METHOD
  15  CALL RUNKU(RUNGE,2,Y,G,T,H)
C     WHENEVER RUNGE=1 COMPUTE DERIVATIVE
      IF (RUNGE .NE. 1) GOTO 82
      IF (T-CMAX) 45,45,46
  45  G(1)=-(XE(1)*Y(1)*Y(2))-(XE(2)*Y(1))+XE(3)+1.8
      G(2)=-(XE(4)*Y(2))+(XE(5)*Y(1))+XE(6)+XE(7)
      GO TO 15
  46  G(1)=-(XE(1)*Y(1)*Y(2))-(XE(2)*Y(1))+XE(3)
      G(2)=-(XE(4)*Y(2))+(XE(5)*Y(1))+XE(6)
      GO TO 15
  82  IF (T-TMAX) 90,90,95
  90  DO 106 M=1,241,10
      T1=M-1.
      IF (T-T1) 15,53,106
 106  CONTINUE
  53  J=J+1
      TR(J)=T
      FNC(J,1)=Y(1)
      FNC(J,2)=Y(2)
      GO TO 15
  95  DO 100 IL=1,NDAT
      A1=EXP(IL,1)
      B1=FNC(IL,1)
      C1=(A1-B1)**2
      A2=EXP(IL,2)
      B2=FNC(IL,2)
```

```
      C2=(A2-B2)**2
      SUM=SUM+(C1+C2)
  100 CONTINUE
      F=SUM
      IF (KOUNT-25.) 120,140,140
  140 WRITE (6,10) KOUNT
   10 FORMAT (/,2X,'ITERATION NUMBER = ',I8)
      WRITE (6,19) F
   19 FORMAT (/,2X,'FUNCTION = ',F12.1)
      WRITE (6,11) (J,XE(J),J=1,IA)
   11 FORMAT (/,4(4X,2HX(,I1,4H) = ,1PE14.6))
  120 KOUNT=KOUNT+1
      RETURN
      END
      FUNCTION CX (X,DA,N,NPAR,K)
      DIMENSION X(N),DA(NPAR)
C
      CX=X(K)
C
      RETURN
      END
      FUNCTION CG (X,DA,N,NPAR,K)
      DIMENSION X(N),DA(NPAR)
C
      CG=0.0
C
      RETURN
      END
      FUNCTION CH (X,DA,N,NPAR,K)
C
      DIMENSION X(N),DA(NPAR)
C
      GO TO (1,2,3,4,5,6,7),K
    1 CH=X(1)*10.
      GO TO 9
    2 CH=X(2)*10.
      GO TO 9
    3 CH=X(3)*10.
      GO TO 9
    4 CH=X(4)*10.
      GO TO 9
    5 CH=X(5)*10.
      GO TO 9
    6 CH=X(6)*10.
      GO TO 9
    7 CH=X(7)*10.
    9 RETURN
      END
      SUBROUTINE RUNKU(RUNGE,N1,Y,G,W,H2)
      INTEGER RUNGE
```

```
      DIMENSION PHI(50),SAVEY(50),Y(10),G(10)
      DATA M1/0/
      M1=M1+1
      GO TO (1,2,3,4,5),M1
    1 RUNGE=1
      RETURN
    2 DO 22 J=1,N1
      SAVEY(J)=Y(J)
      PHI(J)=G(J)
   22 Y(J)=SAVEY(J)+0.5*H2*G(J)
      W=W+0.5*H2
      RUNGE=1
      RETURN
    3 DO 33 J=1,N1
      PHI(J)=PHI(J)+2.0*G(J)
   33 Y(J)=SAVEY(J)+0.5*H2*G(J)
      RUNGE=1
      RETURN
    4 DO 44 J=1,N1
      PHI(J)=PHI(J)+2.0*G(J)
   44 Y(J)=SAVEY(J)+H2*G(J)
      W=W+0.5*H2
      RUNGE=1
      RETURN
    5 DO 55 J=1,N1
   55 Y(J)=SAVEY(J)+(PHI(J)+G(J))*H2/6.
      M1=0
      RUNGE=0
      RETURN
      END
      SUBROUTINE FUNC (I,XX,Z,Y,FNC)
      DIMENSION XX(10,10),Z(10),F(10),Y(10),FNC(50,50)
      COMMON EXP(50,50),TR(50)
      DATA NDAT,TMAX,H,NVAR,CMAX/24,240.,1.,2,75./
      INTEGER RUNGE
      X1=XX(I,1)
      X2=XX(I,2)
      X3=XX(I,3)
      X4=XX(I,4)
      X5=XX(I,5)
      X6=XX(I,6)
      X7=XX(I,7)
      T=0.
      J=0
      SUM=0.
      T1=0.
C      CALL ON THE FOURTH-ORDER RUNGE-KUTTA NUMERICAL METHOD
   15 CALL RUNKU(RUNGE,2,Y,F,T,H)
C      WHENEVER RUNGE=1 COMPUTE DERIVATIVE VALUE
      IF (RUNGE .NE. 1) GOTO 82
```

```
      IF (T-CMAX) 45,45,46
 45   F(1)=-(X1*Y(1)*Y(2))-(X2*Y(1))+X3+1.80
      F(2)=-(X4*Y(2))+(X5*Y(1))+X6+X7
      GO TO 15
 46   F(1)=-(X1*Y(1)*Y(2))-(X2*Y(1))+X3
      F(2)=-(X4*Y(2))+(X5*Y(1))+X6
      GO TO 15
 82   IF (T-TMAX) 90,90,95
 90   DO 106 M=1,241,10
      T1=M-1.
      IF (T-T1)  15,53,106
106   CONTINUE
 53   J=J+1
      TR(J)=T
      FNC(J,1)=Y(1)
      FNC(J,2)=Y(2)
      GO TO 15
 95   DO 100 L=1,NDAT
      A1=EXP(L,1)
      B1=FNC(L,1)
      C1=(A1-B1)**2
      A2=EXP(L,2)
      B2=FNC(L,2)
      C2=(A2-B2)**2
      SUM=SUM+(C1+C2)
100   CONTINUE
      Z(I)=SUM
      RETURN
      END
```

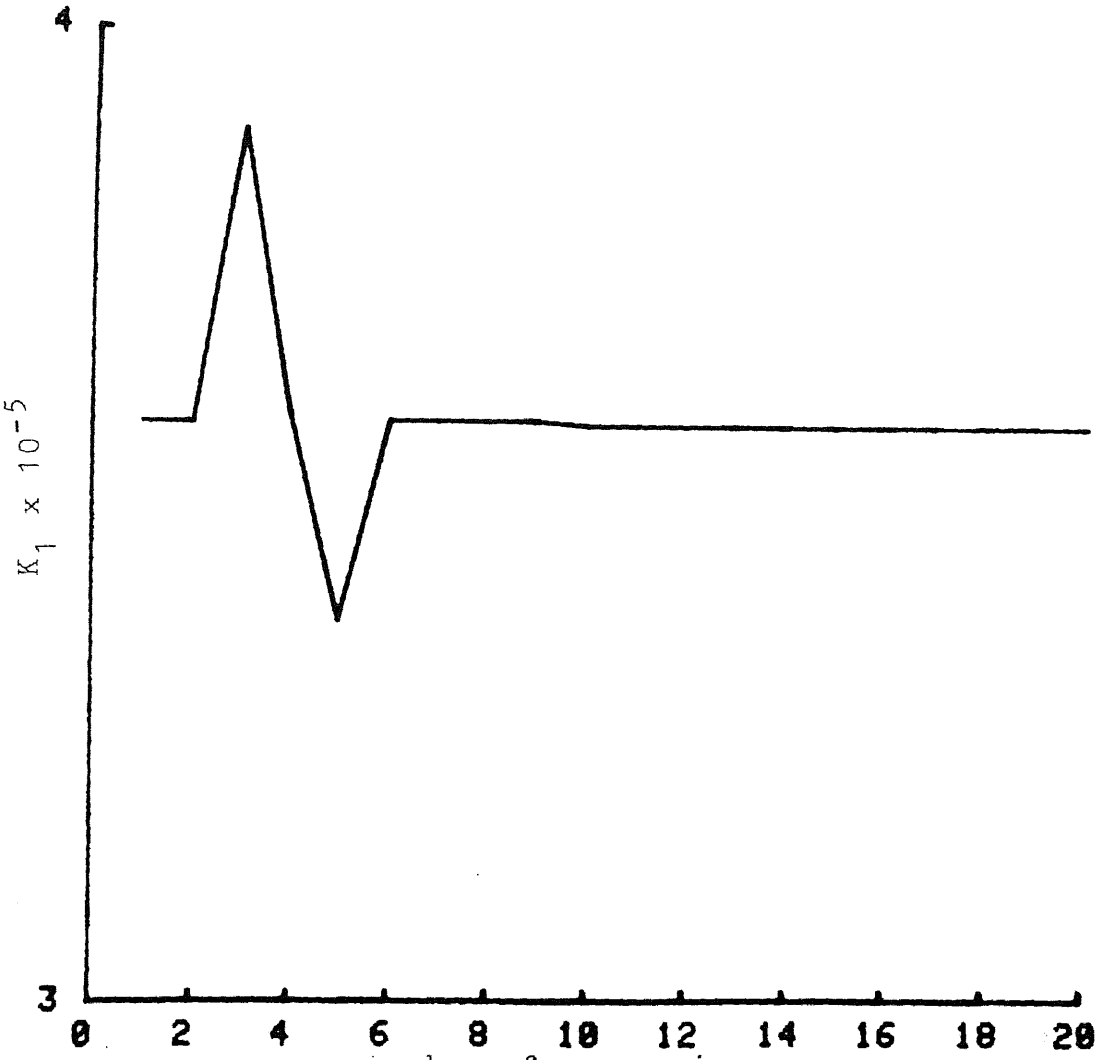

FIG. 15. The last twenty values of K_1 of nonobese normal subjects

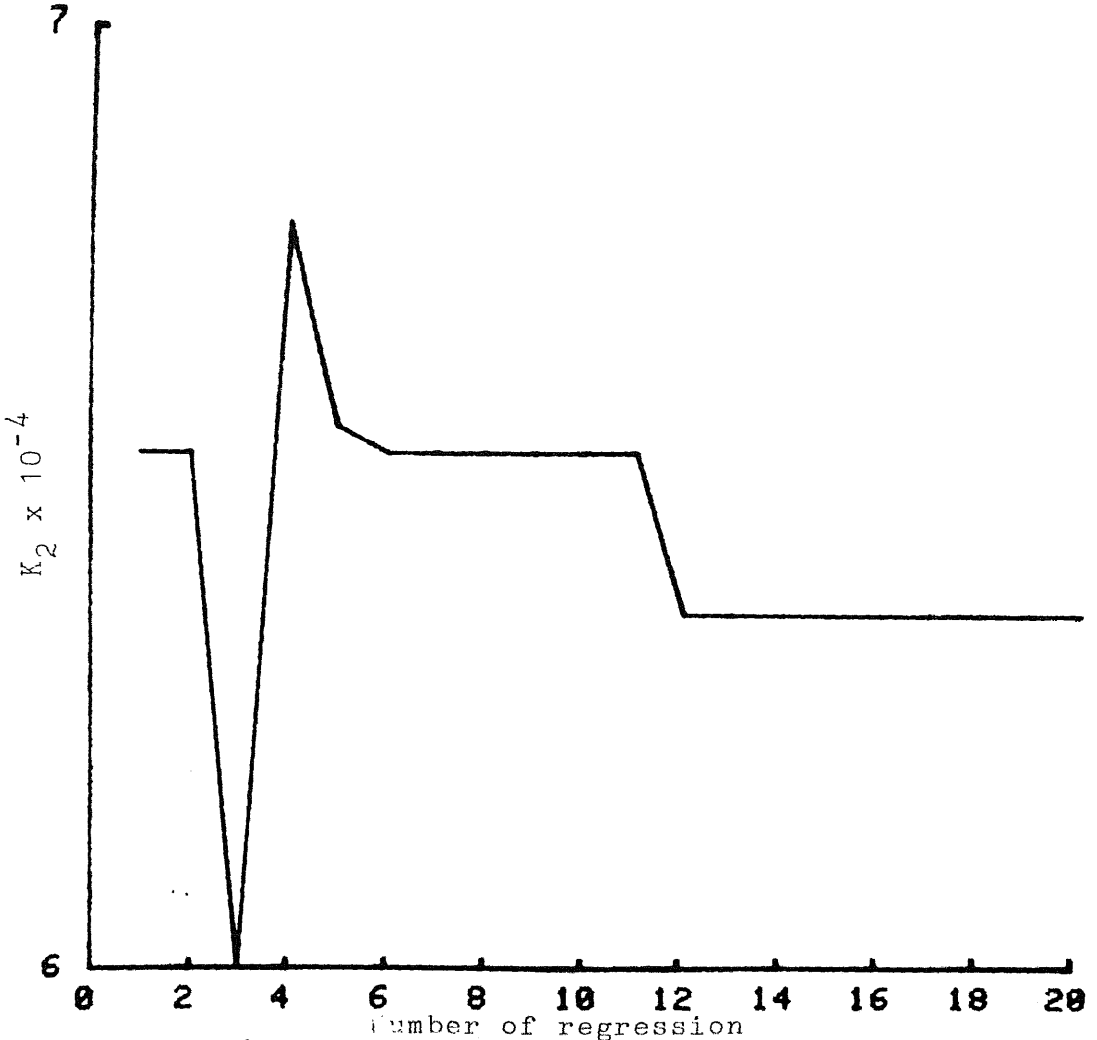

FIG. 16. The last twenty values of K_2 of nonobese normals

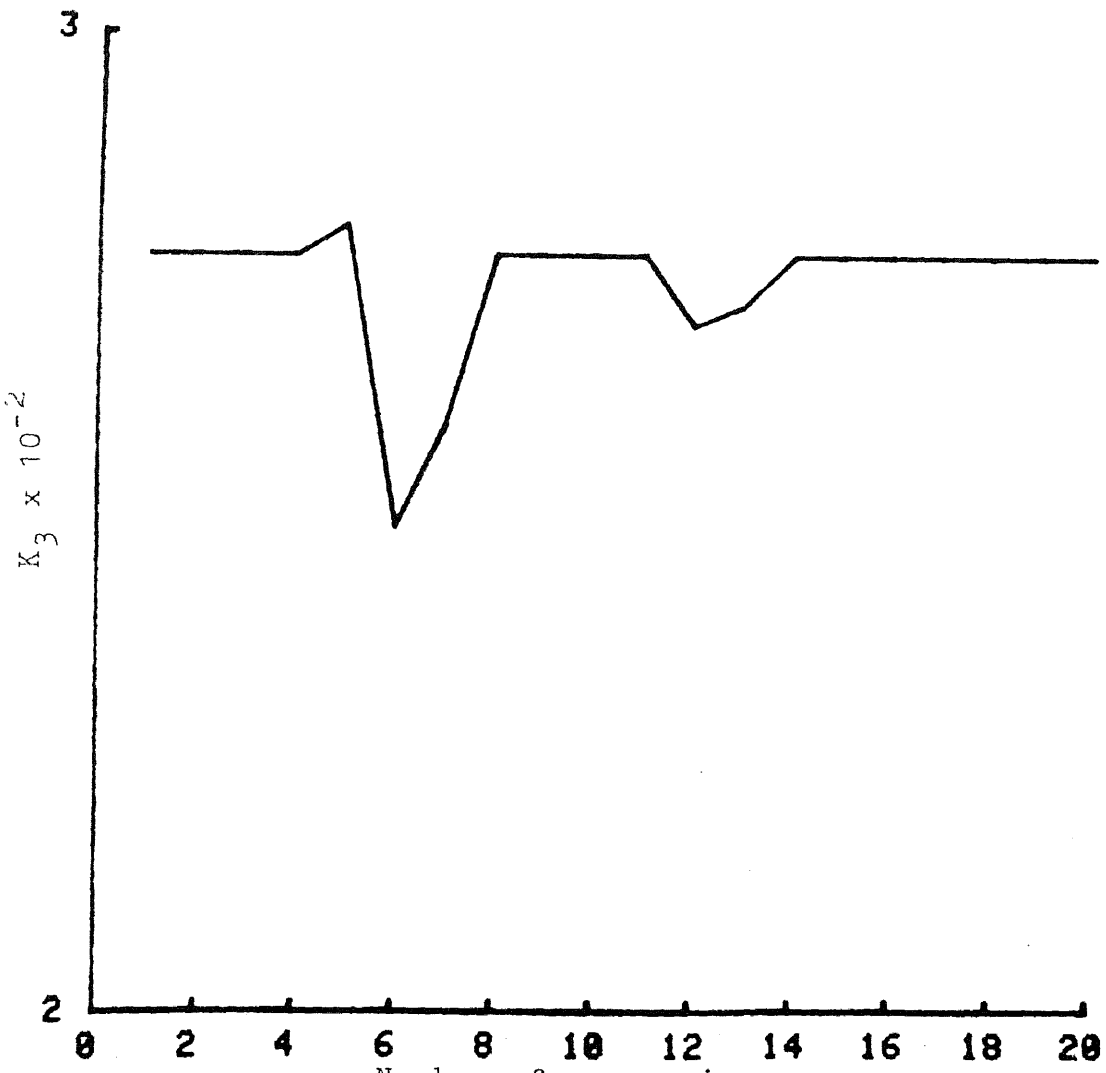

FIG. 17. The last twenty values of K_3 of nonobese normal subjects

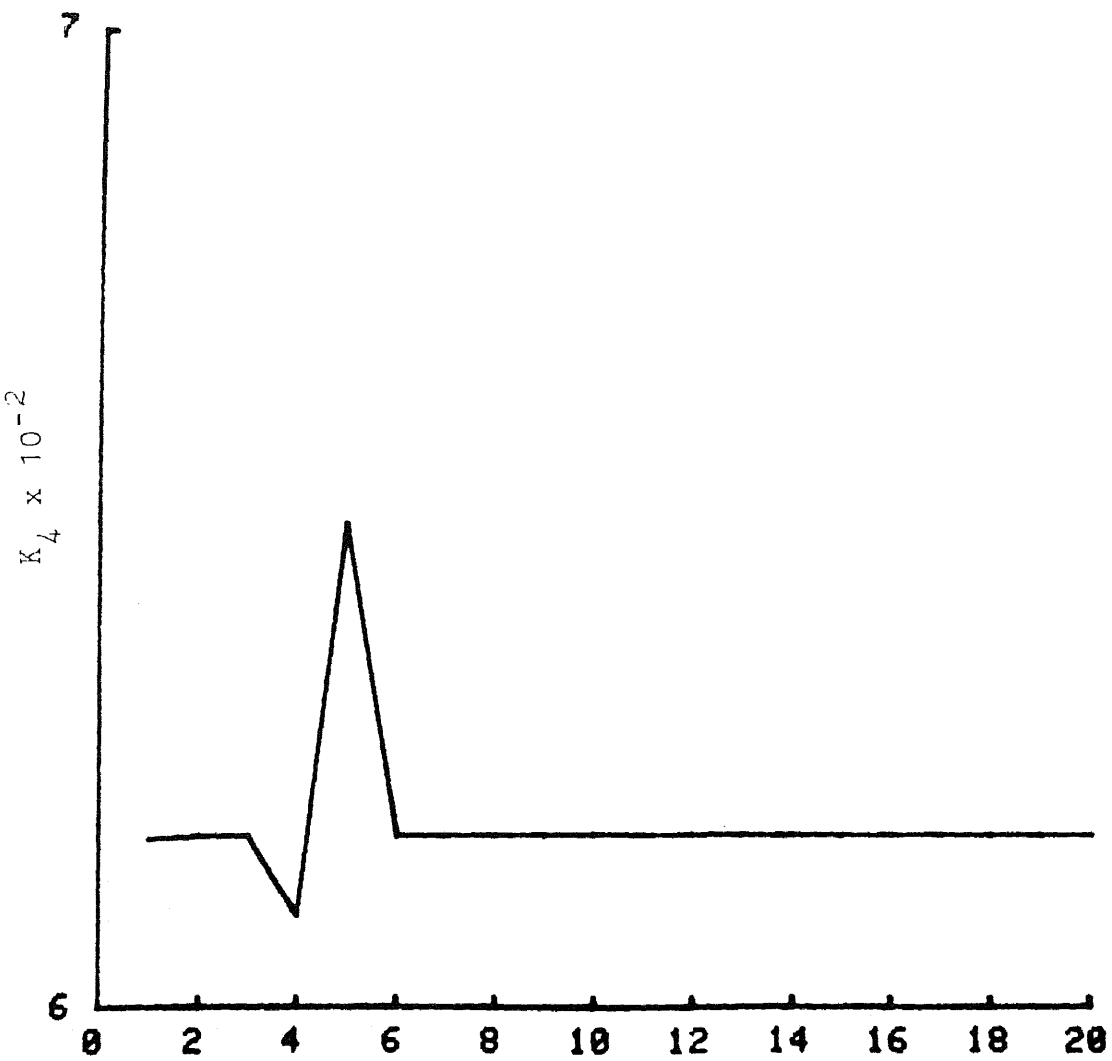

FIG. 18. The last twenty values of K_4 of nonobese normal subjects

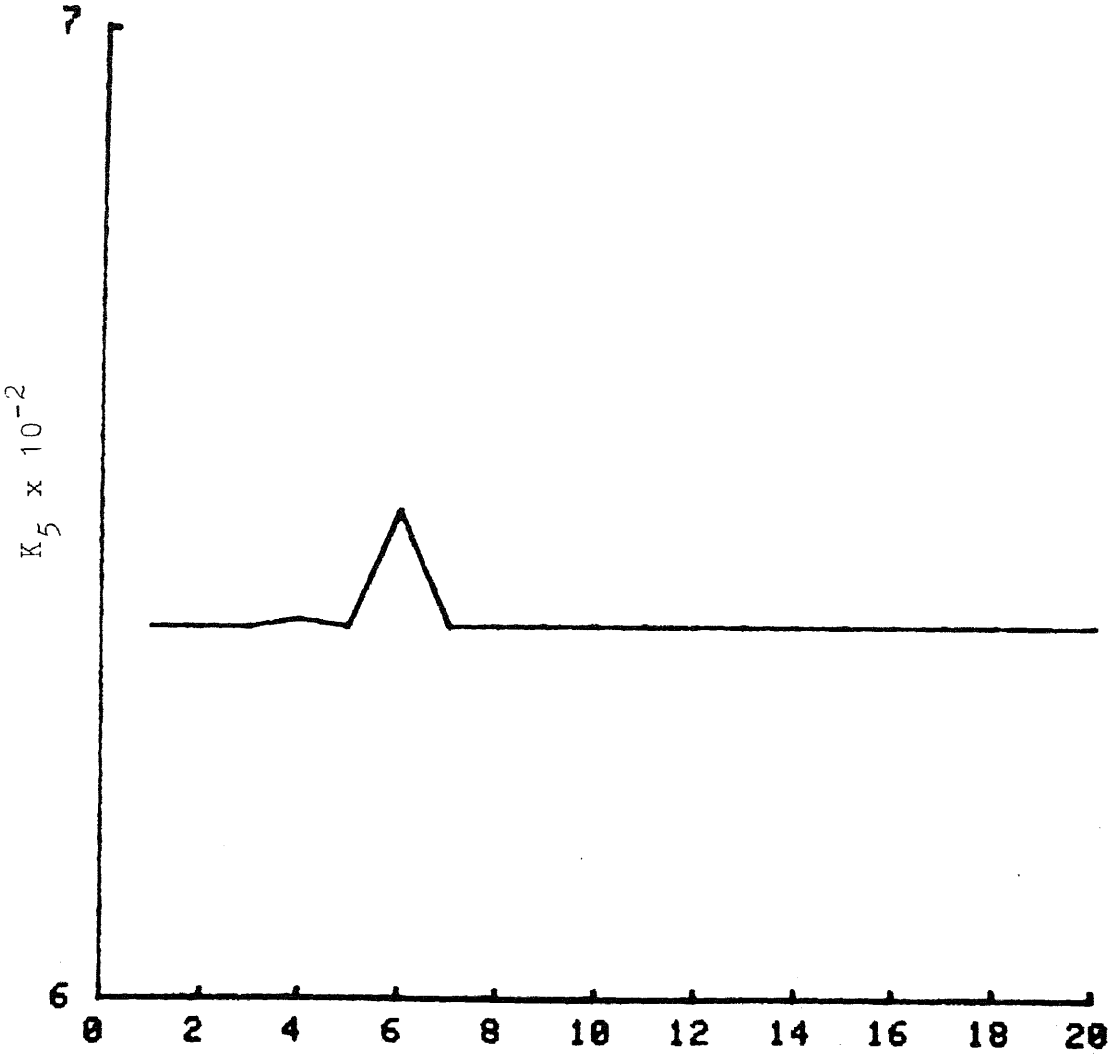

FIG. 19. The last twenty values of K_5 of nonobese normal subjects

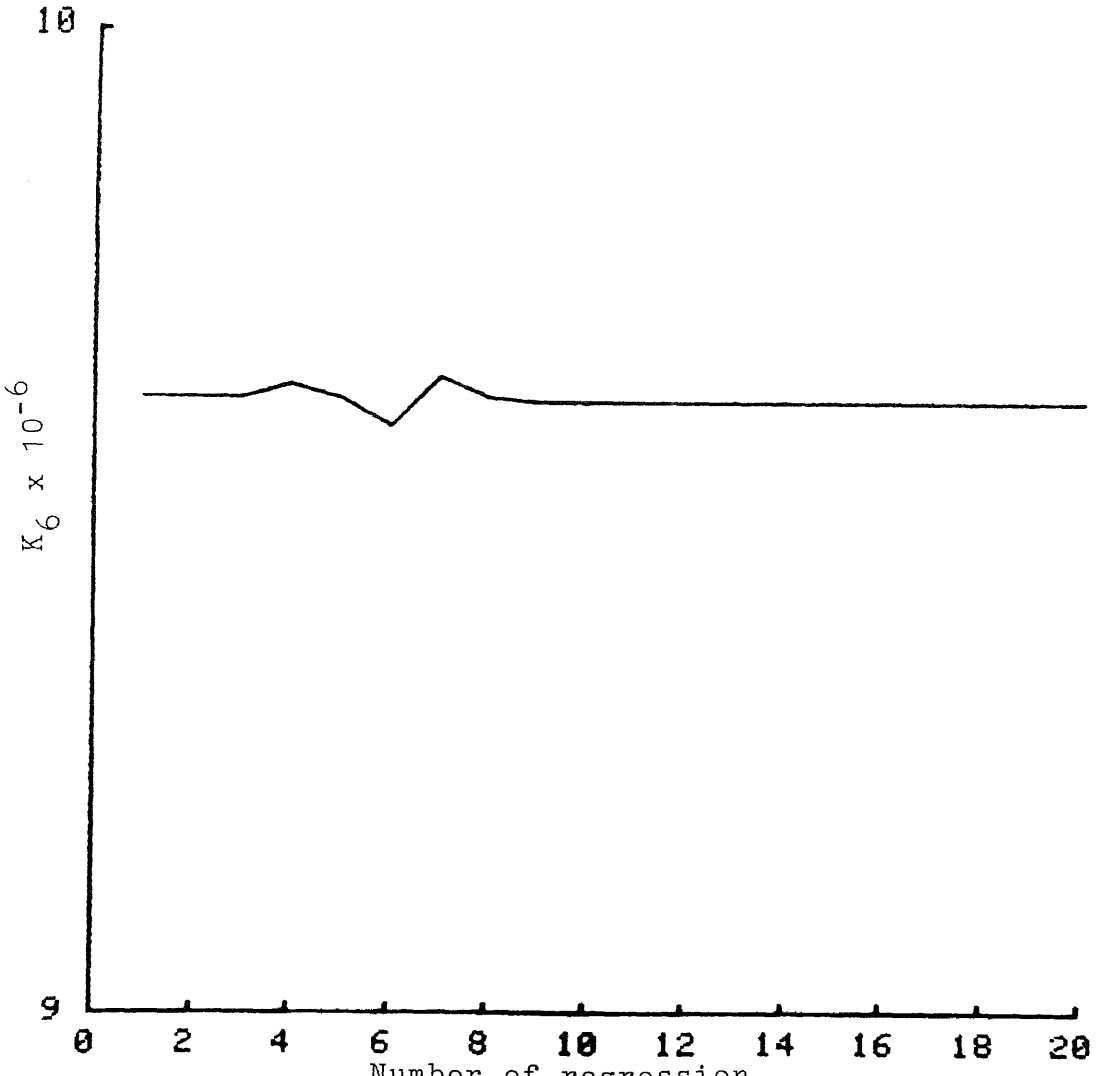

FIG. 20. The last twenty values of K_6 of nonobese normal subjects

FIG. 21. The last twenty values of K_7 of nonobese normal subjects

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