

Mathematical modelling of insulin kinetics

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We review a general mathematical model which incorporates beta-cell kinetics and a gastrointestinal absorption term for glucose into a glucose–insulin feedback system. The model comprises of a set of four nonlinear, coupled ordinary differential equations. Numerical simulations lead to time variations of plasma glucose and insulin levels that are consistent with clinical observations in normal groups. The results obtained after suitable changes in some of the parameters are in agreement with the clinical profiles and laboratory data in all the clinical categories of diabetes mellitus, viz. insulin-dependent diabetes mellitus, non-insulin-dependent diabetes mellitus, and malnutrition related diabetes mellitus, in response to a glucose challenge. Linear stability analysis in each case gives an indication of the metabolic factor(s) responsible for the particular disorder. Finally, the possible use of sensitivity analysis in the therapy of diabetes mellitus is discussed.

THE secretion of insulin and its biological effectiveness in response to a glucose load are determined mainly by the beta cell number and function in the pancreas and peripheral resistance to insulin action. A reduced secretory response of insulin, with or without an increase in peripheral resistance to its action, leads to glucose intolerance which is the hallmark of diabetes mellitus.

Diabetes mellitus can be clinically categorized into three distinct types according to the WHO classification¹. These are (i) insulin-dependent diabetes mellitus (IDDM), (ii) non-insulin dependent diabetes mellitus (NIDDM), and (iii) malnutrition-related diabetes mellitus (MRDM). Whereas a reduction in or a loss of insulin secretion by the beta cells is a feature of IDDM, a significant decrease in the biological effectiveness of the hormone occurs in NIDDM. NIDDM is clinically categorized as obese and non-obese. Patients with obese NIDDM exhibit varying degrees of glucose intolerance, even though plasma insulin levels are generally elevated when compared to non-obese controls. There is thus a resistance to insulin action and this is known to be mainly at, or beyond the insulin receptors located on the plasma membranes of target cells. The third type of diabetes mellitus (MRDM) is prevalent in the developing countries. Experimental observations on a sub-type of MRDM, namely protein-deficient diabetes mellitus (PDDM) indicate a sub-optimal response of the beta cells, but the pathophysiology is not well understood.

In an attempt to gain a better insight into the patho-

physiology and to identify the primary metabolic factor(s) responsible for the particular type of diabetes mellitus, it is desirable to formulate an integrated mathematical model that incorporates beta-cell kinetics into a glucose–insulin feedback relationship. The model should be such that the same set of equations, with suitably adjusted parameter values should lead to results that are consistent with the clinical and metabolic profiles of glucose and insulin in normal controls as well as in subjects with the three types of diabetes mellitus.

Among the earliest mathematical models, the simplified model proposed by Ackerman *et al.*² and its modifications^{3,4} have been successful in describing the mathematical relationship between the kinetics of glucose and insulin in plasma. A survey of these earlier methods was made by Atkins⁵ who observed that these models were based on very small and short data sets, and were not consistent with known physiological data. A very significant contribution towards the physiological understanding of glucose tolerance with the help of mathematical modelling was made by Bergman *et al.*⁶. Based on the frequently sampled intravenous glucose tolerance test (FSIGT), a minimal model was proposed for the estimation of the physiological parameters in the model equations for a single individual from a single FSIGT. The glucose levels predicted from the model with the insulin time course as the input are compared with the measured glucose levels. Values of the equation parameters are then adjusted automatically until the glucose pattern is fitted, based on known insulin.

None of the above models explicitly includes either beta-cell kinetics, or a gastrointestinal absorption term which is necessary for modelling the oral glucose tolerance test (OGTT), the most commonly used diagnostic procedure for estimating glucose tolerance.

We present here a mathematical model^{7,8}, which incorporates both the beta-cell kinetics and a gastrointestinal absorption term into a glucose–insulin feedback relationship.

The mathematical model

The starting point of the model is the glucose–insulin feedback relationship proposed by Ackerman *et al.*², which is described by the following differential equations:

$$\begin{aligned} \frac{dH}{dt} &= -l_1 H + l_2 + l_3 G \\ \frac{dG}{dt} &= -l_4 G + l_5 - l_6 H, \end{aligned} \quad (1)$$

where G and H are the plasma glucose and insulin levels respectively, and l_1 through l_6 are parameters.

If G and H are replaced by the difference from the corresponding fasting levels, the equations simplify to

$$\frac{dh}{dt} = -l_1 h + l_3 g$$

$$\frac{dg}{dt} = -l_4 g - l_6 h,$$

where $h = H - H_F$, $g = G - G_F$, H_F and G_F being the fasting concentrations, which in this case have been taken to be the same as the steady state values. However, this may not be true as pointed out by some authors⁹, who have demonstrated the existence of oscillations in the basal (fasting) levels of glucose and insulin.

Assuming the fasting concentrations to differ from the steady state values by constant values, equations (1) simplify to

$$\frac{dh}{dt} = -l_1 h + l_3 g + C_2, \tag{2}$$

$$\frac{dg}{dt} = -l_4 g - l_6 h + C_2,$$

where C_1 and C_2 are constants.

We consider the beta cell kinetics from the point of view of transformation to the proliferation phase, multiplication and elimination, which can be modelled by the following differential equation:

$$\frac{db}{dt} = R_1 g(T - b) + R_2 b(T - b) - R_3 b, \tag{3}$$

where b is the number of beta cells in the proliferation phase, T is the total number of beta cells, and R_1, R_2, R_3 are parameters. The parameters are chosen in such a way that the numerical solution of eq. (3), in response to a constant glucose stimulus, gives steady state saturation values consistent with those obtained by Swenn¹⁰.

In order to incorporate beta cell kinetics, we consider the model of Turner *et al.*¹¹, according to which, if there is a decrease in insulin secretion due to a reduction to $1/N$ of the normal number, x , of beta cells the basal plasma glucose increases until near normal basal insulin levels are obtained. Thus, the basal plasma glucose level is a function of the beta cell capacity (N/x). We make use of this relationship in the glucose-dependent loss term ($-l_4 g$) of eq. (2). The model for the intravenous glucose tolerance test (IVGTT) is then given by

$$\begin{aligned} \frac{db}{dt} &= R_1 g(T - b) + R_2 b(T - b) - R_3 b \\ \frac{dg}{dt} &= R_4 N/b - R_5 h + C_1 \\ \frac{dh}{dt} &= R_6 g - R_7 h + C_2 \end{aligned} \tag{4}$$

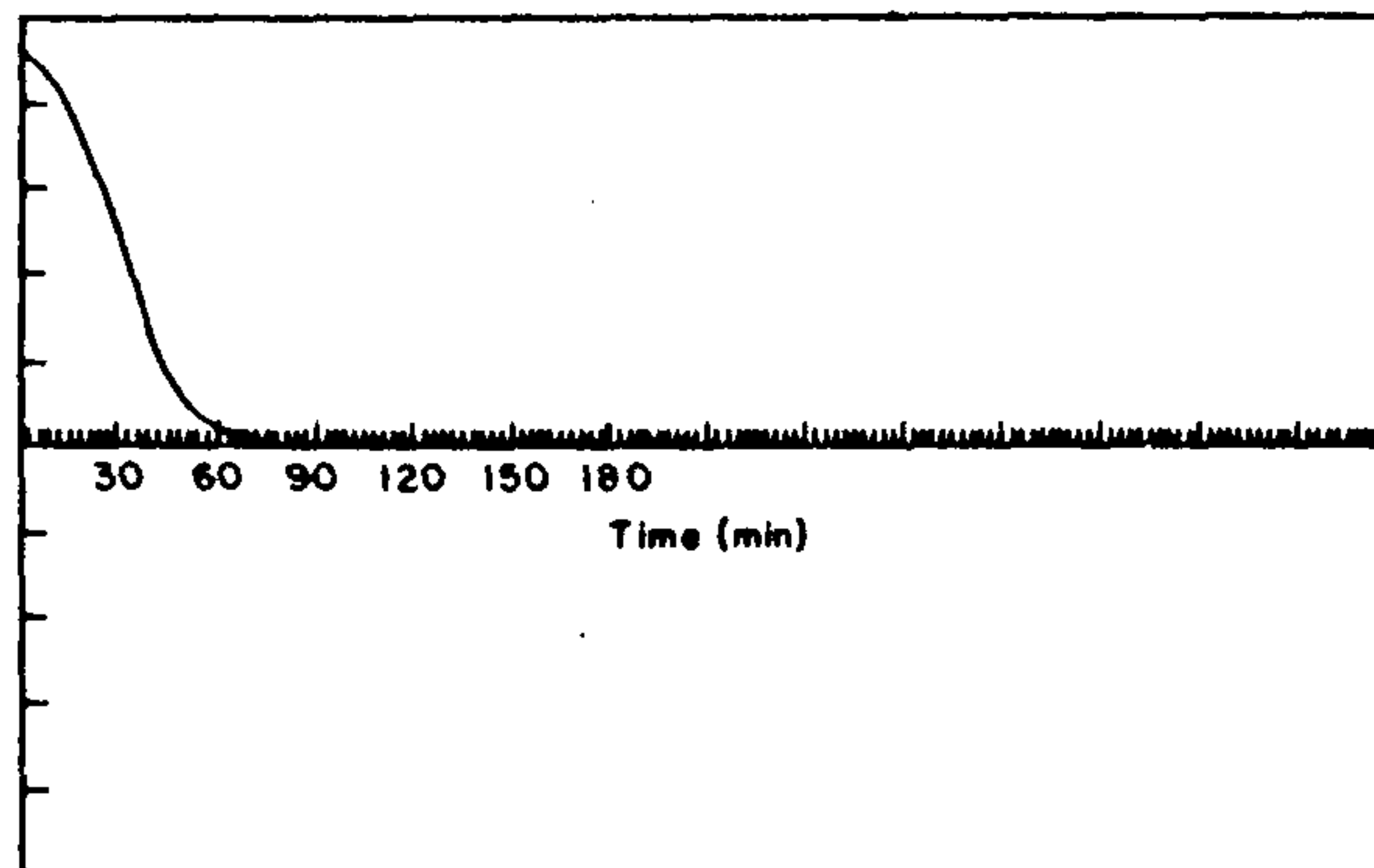


Figure 1. Time variation of rate of absorption, w , of glucose. (One division on the y axis is equal to 0.01 units.)

where R_1 through R_7 are parameters.

The parameters of the model have a meaning in terms of the pathophysiology of glucose metabolism and insulin kinetics. As explained earlier, R_4 represents beta-cell capacity. The parameter R_5 is related to the peripheral resistance to insulin action. The smaller the value of R_5 , the larger is the resistance (the sensitivity to insulin is smaller). R_6 represents the insulin secretory function of beta cells in response to change in glucose levels, while R_7 represents the glucose-independent insulin loss.

The gastrointestinal absorption term

In order to model OGTT, we introduce in the time variation of glucose (g), a term proportional to g with a rate constant w , which is itself a function of the form

$$\frac{dw}{dt} = -aw + apw^2, \tag{5}$$

where a and p are constants. The solution of this equation is given by

$$w = 1/(p + e^{at})$$

and the graphical representation of this function is shown in Figure 1.

The inclusion of the glucose absorption term then leads to the following mathematical model

$$\begin{aligned} \frac{db}{dt} &= R_1 g(T - b) + R_2 b(T - b) - R_3 b \\ \frac{dg}{dt} &= R_4 N/B - R_5 h + C_1 + wg \\ \frac{dh}{dt} &= R_6 g - R_7 h + C_2 \\ \frac{dw}{dt} &= -aw + apw^2. \end{aligned} \tag{6}$$

It can be seen that, by setting $w=0$, the model reduces to that for IVGTT.

Data

The values of the parameters R_1 , R_2 and R_3 were chosen as described above. The values for R_5 and R_6 were taken from observed data on normal humans¹², and the value of R_7 was chosen to be of the same order as R_5 . The values of NR_4 , C_1 , C_2 and T were arbitrarily chosen, while those of a and p were chosen to give results consistent with laboratory data in normal humans. The complete set of parameters and assigned values for normal controls are given in Table 1.

Numerical simulations

The set of four nonlinear, coupled ordinary differential equations (6) were solved numerically on a PC-486 by the Runge-Kutta-Merson scheme.

Results in normal controls

Basal glucose and insulin concentrations. The eqs (6) were integrated with initial conditions $b=20$, $g=h=w=0$, and the resulting curves are shown in Figure 2. The glucose and insulin levels are seen to oscillate before reaching the steady state values. In addition, the

glucose oscillations are seen to lead the insulin oscillations. This is in accordance with the observations of Goodner *et al.*⁹.

Glucose and insulin levels in response to an intravenous glucose stimulus. The initial conditions in this case are $b=20$, $g=20$, $b=w=0$ and the results are shown in Figure 3. The glucose curve is seen to contain a minimum whose value is less than the steady state concentration, in agreement with experimental normal glucose-tolerance curves⁵. Also seen in the same figure is the biphasic (two maxima) nature of the insulin curve, a feature which has been experimentally reported by Kanazawa *et al.*¹³. The second insulin peak becomes more pronounced if the value of R_5 is increased. This is clearly visible in Figure 4, for a three-fold increase in R_5 . Most of the earlier models were unable to give this biphasic response. Another point of agreement with experiment¹⁴ is that the insulin concentration (Figure 3) reaches its maximum value within about 6 min and this value is about 6 times the steady state value.

Glucose levels in response to an intravenous injection of insulin. The insulin sensitivity test was simulated by using initial conditions $b=20$, $g=w=0$, and $h=20$, and the results are shown in Figure 5. A fall in glucose concentration to about 40% of the steady state concentration is seen which is in good agreement with the experimental value of about 38% (ref. 15).

Table 1. Values of parameters for normal controls

R_1	R_2	R_3	NR_4	R_5	R_6	R_7	C_1	C_2	T
0.0003	0.0001	0.0025	15.03	0.05	0.054	0.055	0.1	0.3	1000

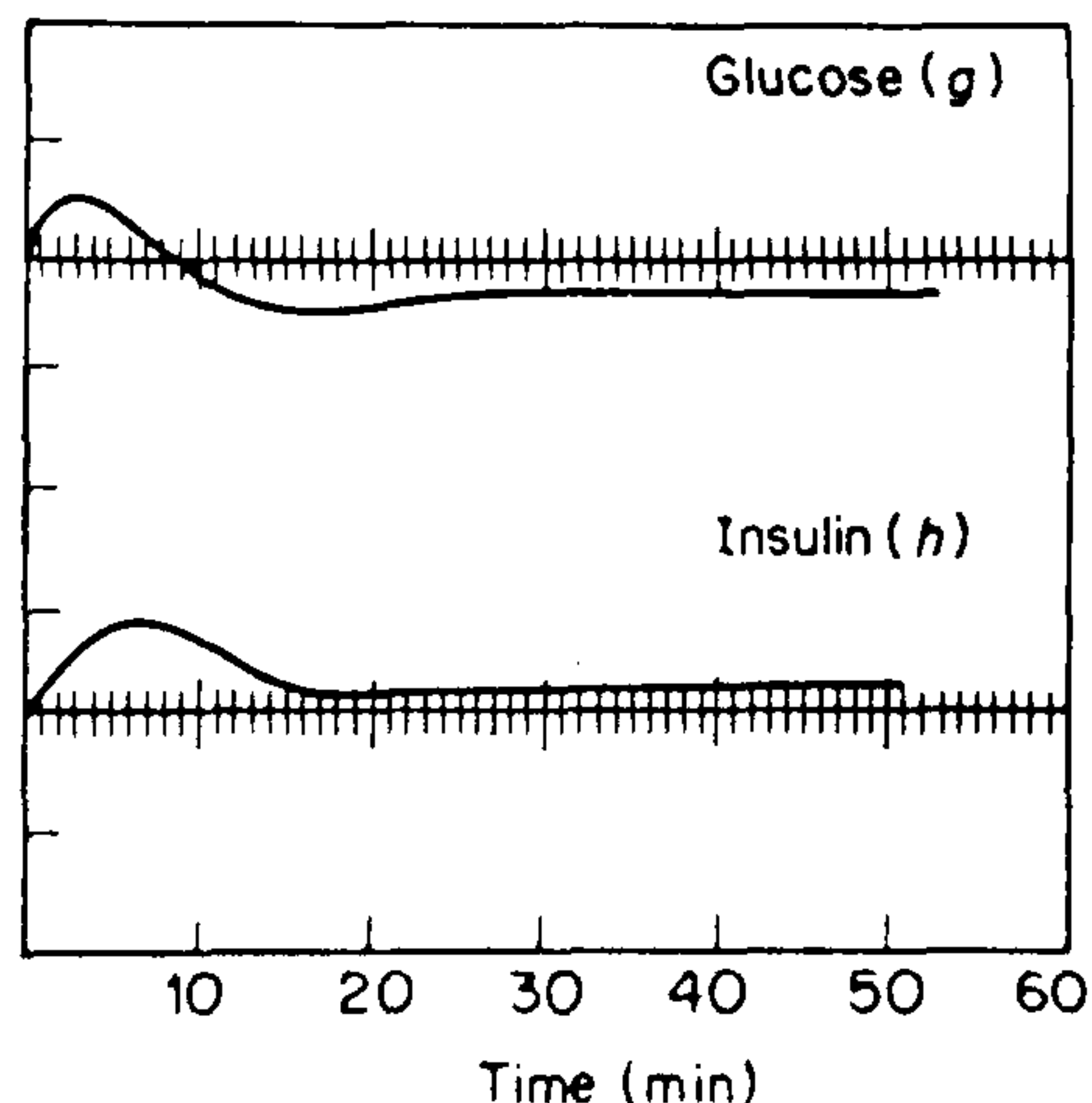


Figure 2. Theoretical basal glucose (g) and insulin (h) levels in normal controls. Glucose and insulin values are in arbitrary units. (One division on y-axis = 10 units).

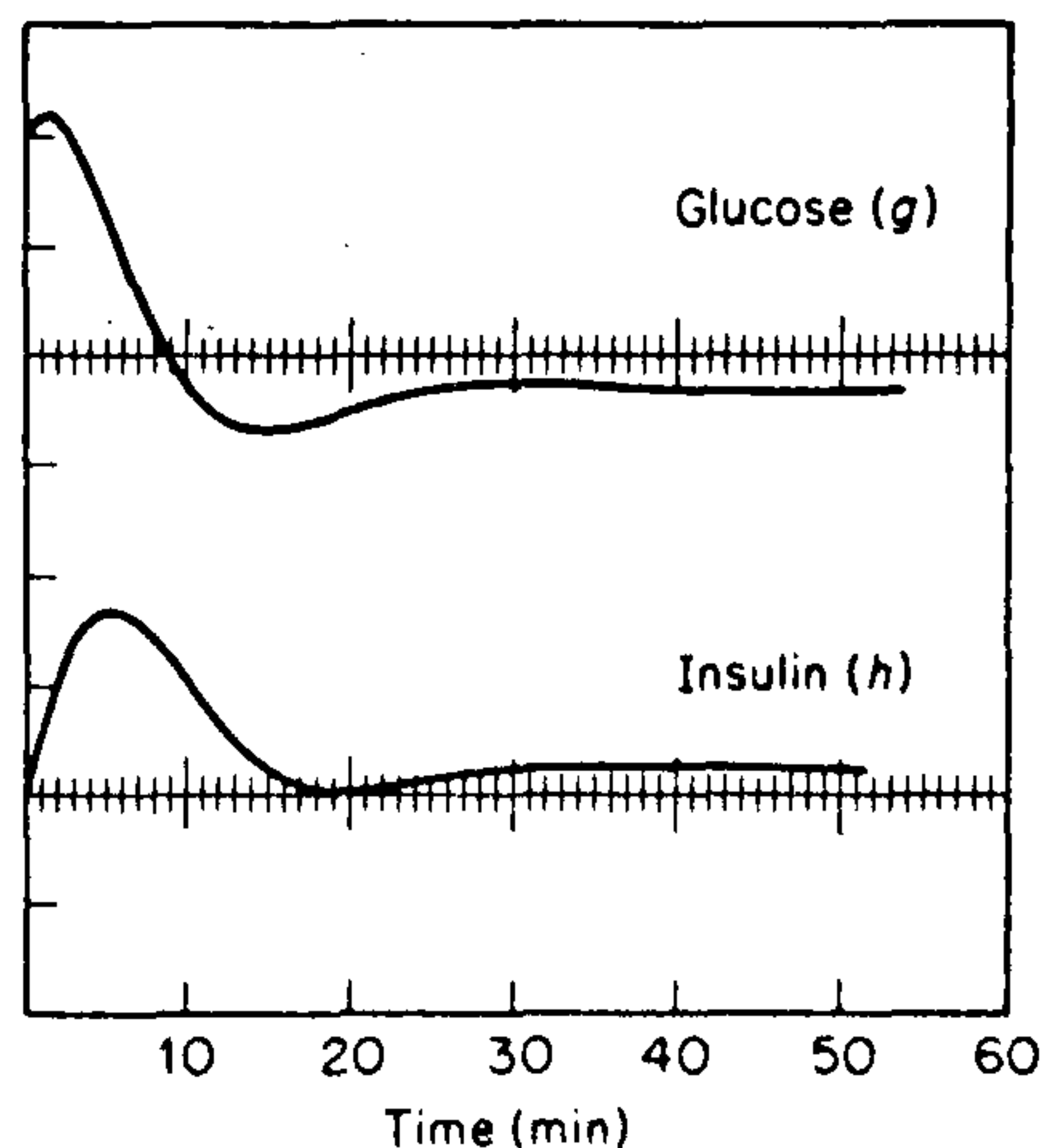


Figure 3. Theoretical time behaviour of glucose and insulin levels in response to an IV glucose load in normal controls (Axes as in Figure 2).

Application to IDDM

Evidence suggests that IDDM is a slowly progressive disorder characterized by a genetic susceptibility to develop immune-mediated inflammation in the islets of Langerhans, eventually leading to a complete beta-cell destruction¹⁶. At the time of clinical presentation, moderate to severe hyperglycemia is invariably present on account of marked insulinopenia, both in the basal state as well as following meals. The patients therefore require exogenous administration of insulin for survival; hence the term insulin-dependent diabetes mellitus.

The endocrinic and metabolic profiles of blood glucose and plasma insulin in IDDM and the corresponding profiles of age, sex and weight matched normal controls

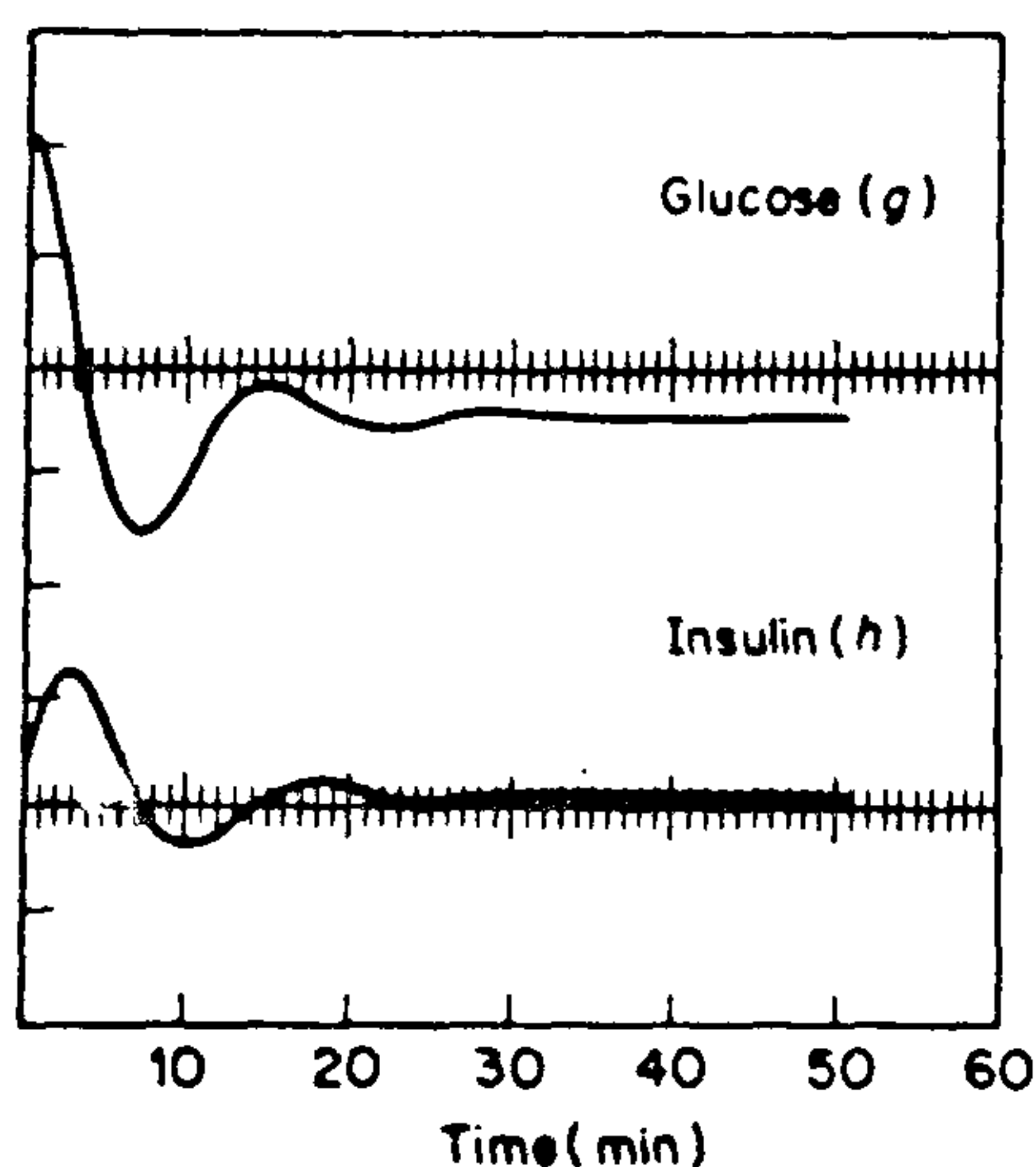


Figure 4. Theoretical time behaviour of glucose and insulin levels in response to an IV glucose load in normal controls, but with R_5 equal to three times the value in Figure 3 (Axes as in Figure 2).

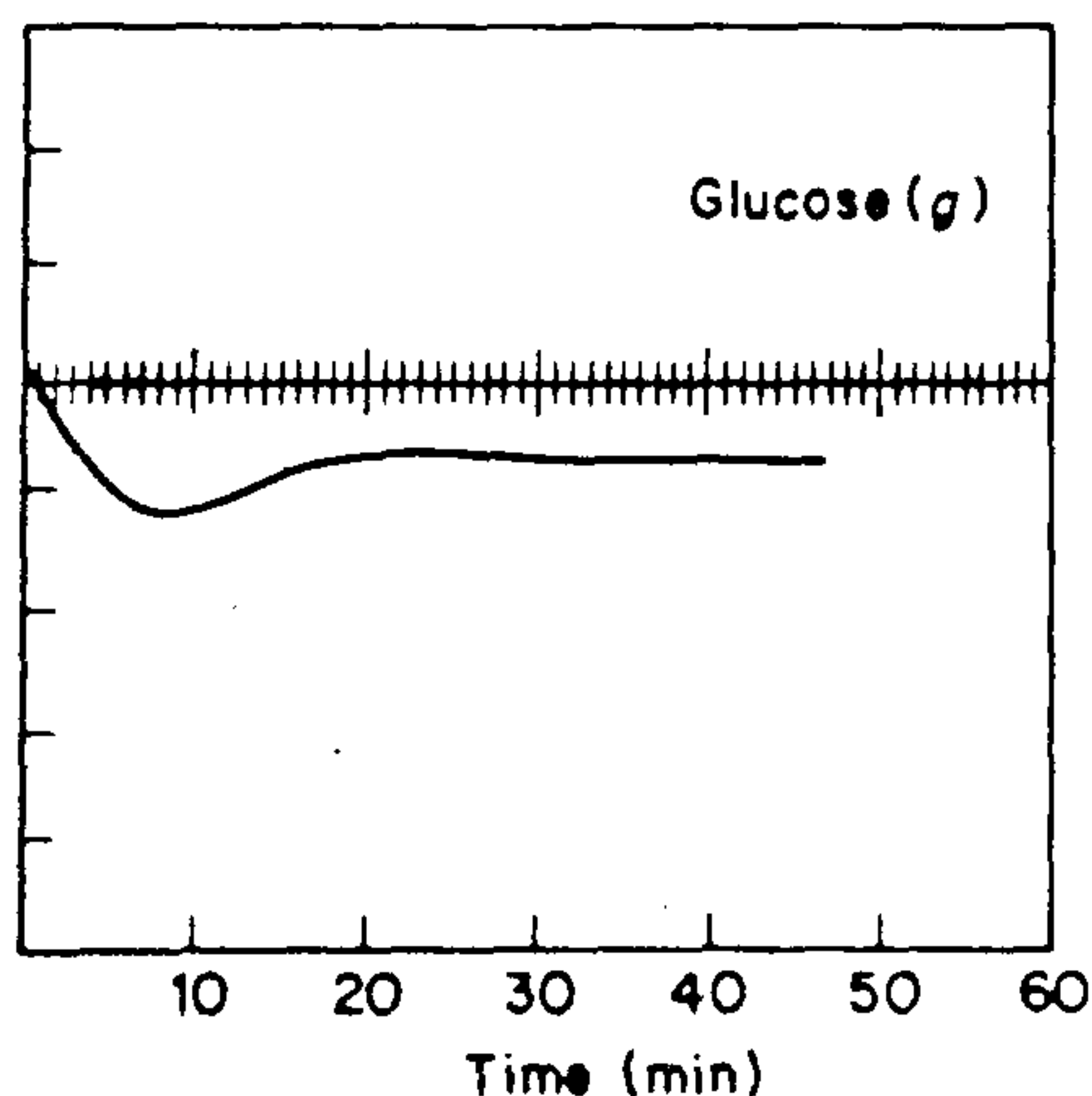


Figure 5. Theoretical fall in blood glucose level after IV injection of insulin in normal controls. (One division on y-axis = 5 units).

are shown in Figures 6 and 7. It can be seen that in the basal state there is marked hyperglycemia and insulinopenia. Following oral administration of glucose, there is a further exacerbation of hyperglycemia without significant rise in plasma insulin.

Parameter values for normal controls

It was found that the same set of parameter values as given in Table 1, along with two additional parameters, $a=0.06$ and $p=20.7$ gave results consistent with the glucose and insulin profiles of normal controls during OGTT.

Parameter values in IDDM

The parameters of the model were varied (increased or decreased from the 'normal' values) in order to determine which parameter(s) could discriminate between normal controls and cases of IDDM. It was found that the results for IDDM were obtained by the following variations in the parameters:

$$NR_4 = (NR_4^0)/4, R_5 = R_5^0/2.5, R_6 = R_6^0/20, T = T^0/5,$$

$$C_1 = 0.03C_1^0, C_2 = 0.01C_2^0,$$

where the symbols with superscript 0 refer to the corresponding 'normal' values.

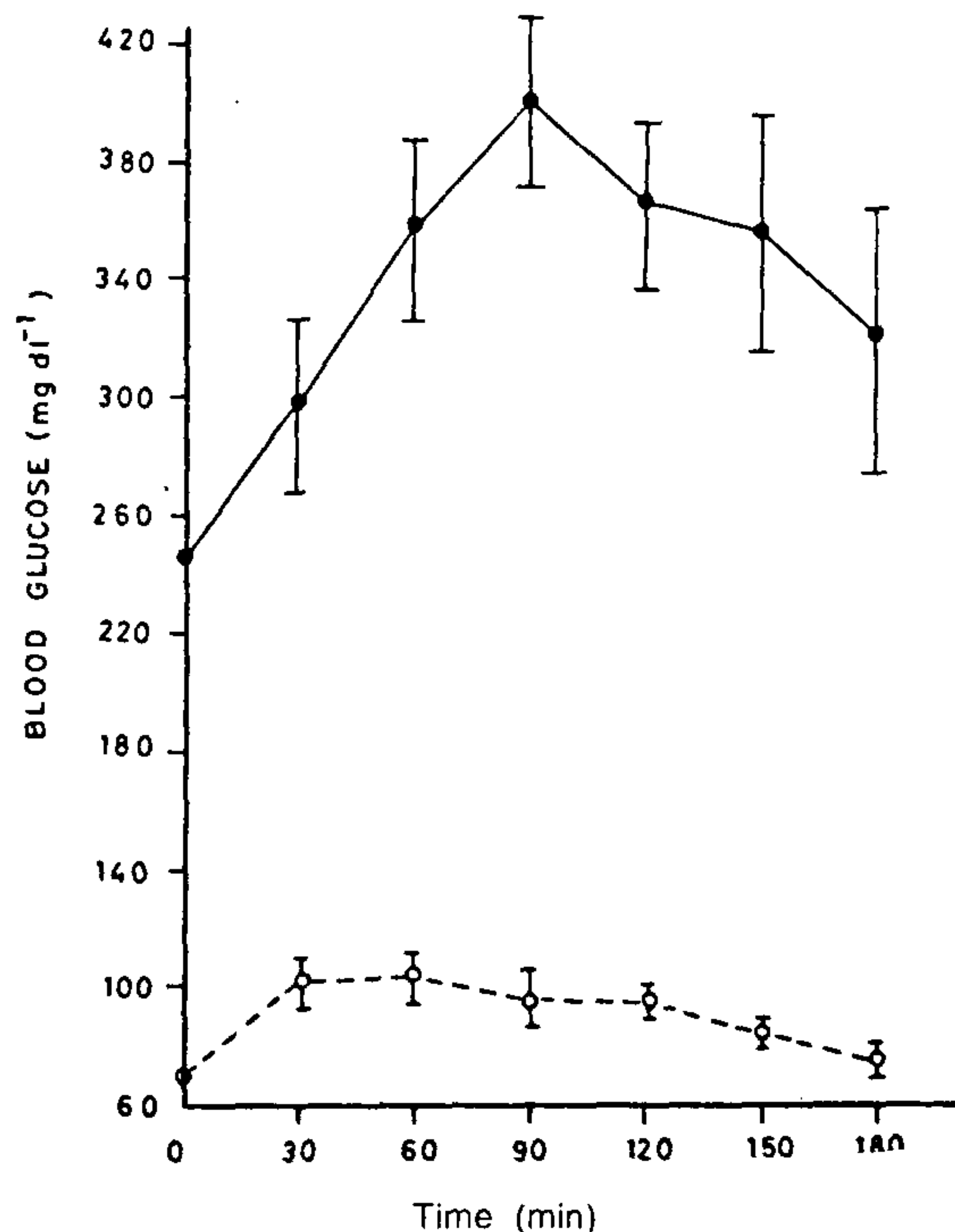


Figure 6. Oral glucose tolerance test (OGTT) in normal controls (O---O) and IDDM (●—●) showing significantly higher levels of glucose in IDDM compared to normal.

Results of numerical simulations

Basal glucose and insulin concentrations

Equations (6) were integrated with initial conditions $b=20$, $g=h=w=0$. The resulting glucose and insulin levels in IDDM and their comparison with the normal levels are shown in Figure 8. The curves indicate a higher fasting level of glucose and a lower fasting level of insulin in IDDM in accordance with the observed endocrinal and metabolic profile of these subjects.

Glucose and insulin levels during OGTT

The initial conditions used in this case were $b=20$, $g=h=0$, $w=0.046$. The results are shown in

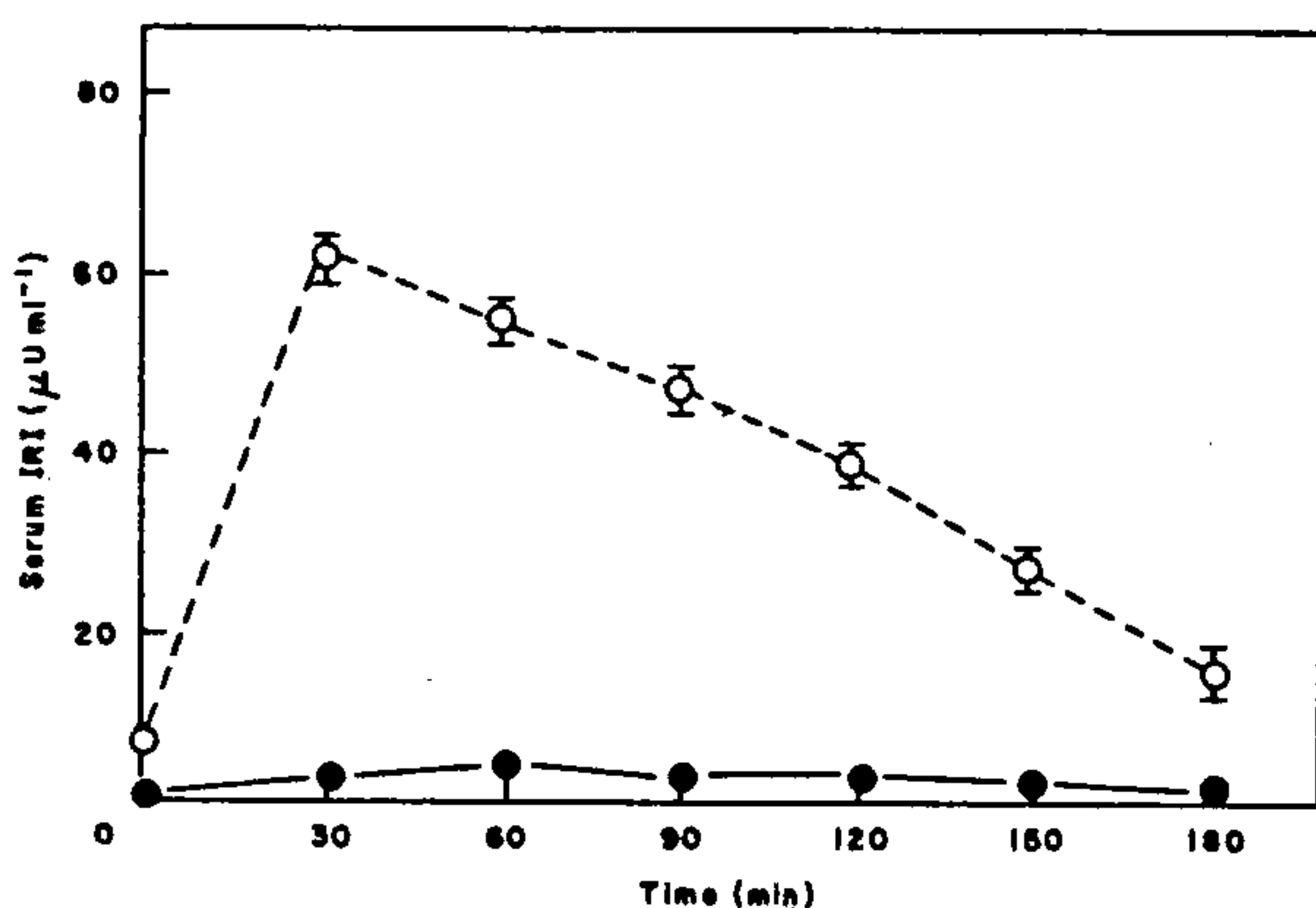


Figure 7. Serum insulin during OGTT showing a lower fasting level and an insignificant rise in IDDM. Normal (o---o) and IDDM (●—●).

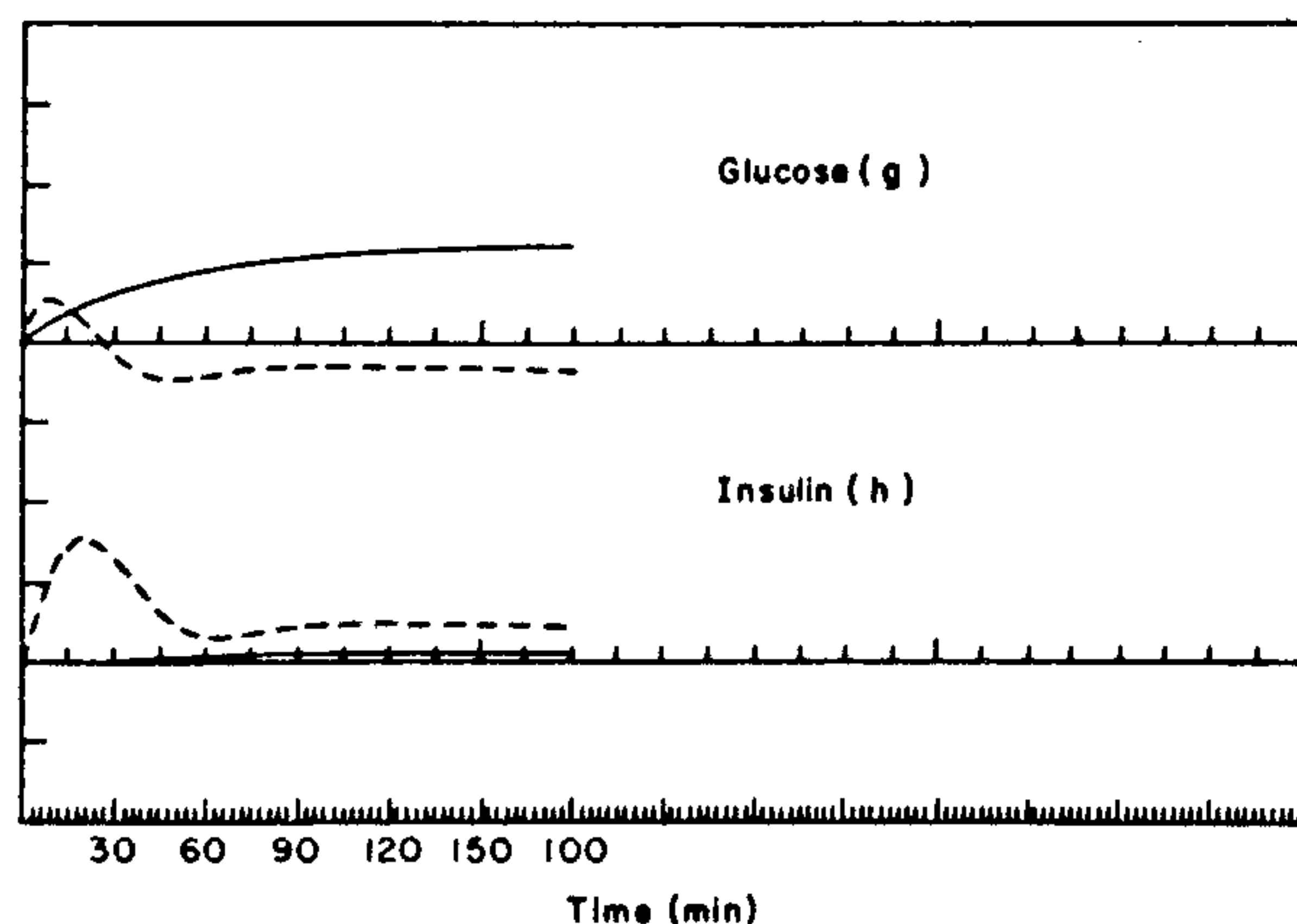


Figure 8. Theoretical basal glucose and insulin levels showing a higher steady state value of glucose and a lower steady state value of insulin in IDDM. Normal (---), IDDM (—). Glucose and insulin values are in arbitrary units. (One division on y-axis equals 10 units for glucose and 5 units for insulin.)

Figure 9. There is approximately a three-fold increase in the maximum glucose concentration and a six-fold increase in the maximum insulin concentration as compared to the normal controls. The sluggish insulin response can also be seen. Thus, numerical simulations using the model are found to be consistent with clinical observations on glucose and insulin levels in the normal group as well as in IDDM, under different experimental conditions, viz. basal levels without any perturbations and during OGTT.

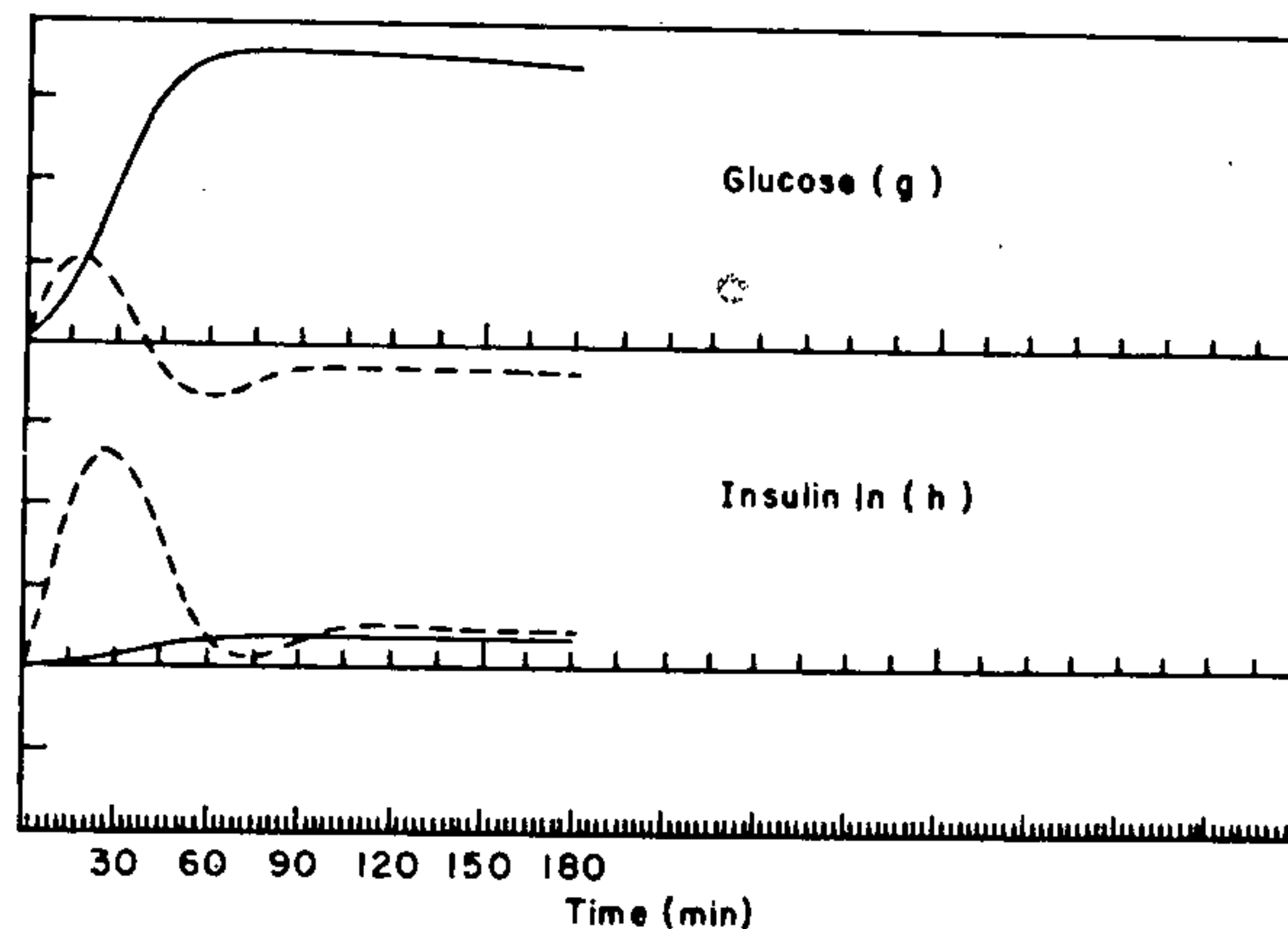


Figure 9. Theoretical time behaviour of glucose and insulin levels in response to oral glucose administration, showing very high levels of glucose and a very small and sluggish insulin response in IDDM. (Axes as in Figure 8) Normal (---). IDDM (—).

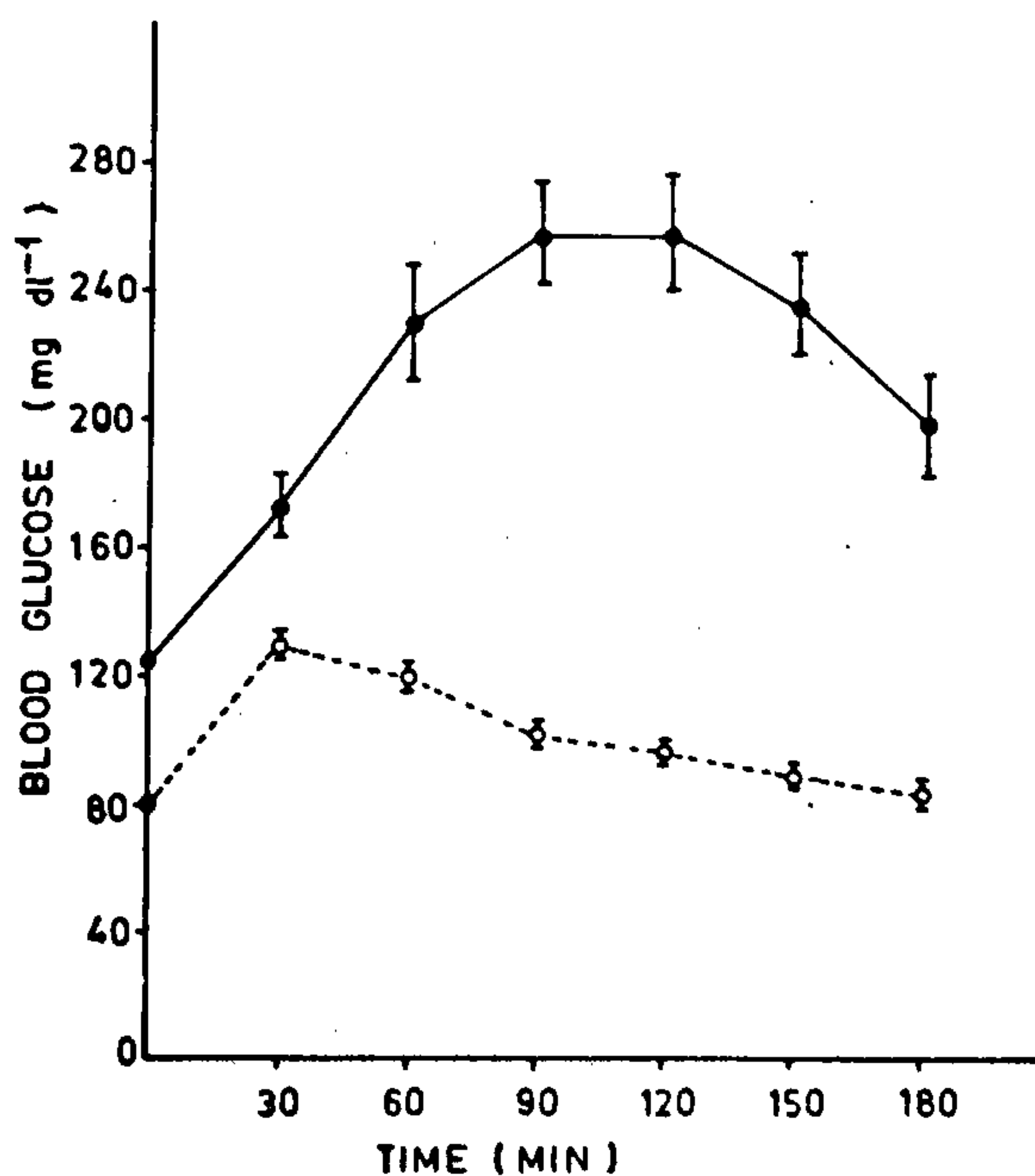


Figure 10. OGTT in normal controls (o---o) and non-obese NIDDM (●—●) showing higher glucose levels with a delayed peak compared to normal controls.

Predictions of the model. Since many parameters had to be changed, identifying the primary metabolic factor responsible for the onset of IDDM is not straightforward. On doing a linear stability analysis of the model for the normal and IDDM cases, the nature of the stability was found to be different. In order to identify which parameter(s) contributed to the change in the nature of the stability, each of the parameters NR_4 , R_5 , R_6 , T , C_1 and C_2 were changed to the corresponding IDDM value, keeping all the others fixed at their normal values. It was found that the critical parameter was R_6 . This would suggest that there is a critical value of the beta-cell function represented by R_6 at which there is a transition to the IDDM state. Evidence suggests that there is a pre-hyperglycemic stage in the natural history of IDDM, during which there is a slow progressive immune-mediated destruction of beta cells, at times indicated by a slow and progressive loss of early phase insulin release¹⁷. However, in such subjects, normoglycemia continues to exist, possibly because of compensating mechanisms. The pre-hyperglycemic stage may last as long as eight years, after which, through a stage of progressively decreasing beta-cell function, the hyperglycemic phase of IDDM manifests itself. The decrease in T is consistent with clinical and pathological findings that IDDM is characterized by inflammation and resulting destruction of beta cells. Consequently, in trying to maintain normal levels of glucose, the residual beta cells are stressed, leading to a diminution in both beta cell capacity and function, i.e. a reduction in NR_4 and R_6 , as found in our model.

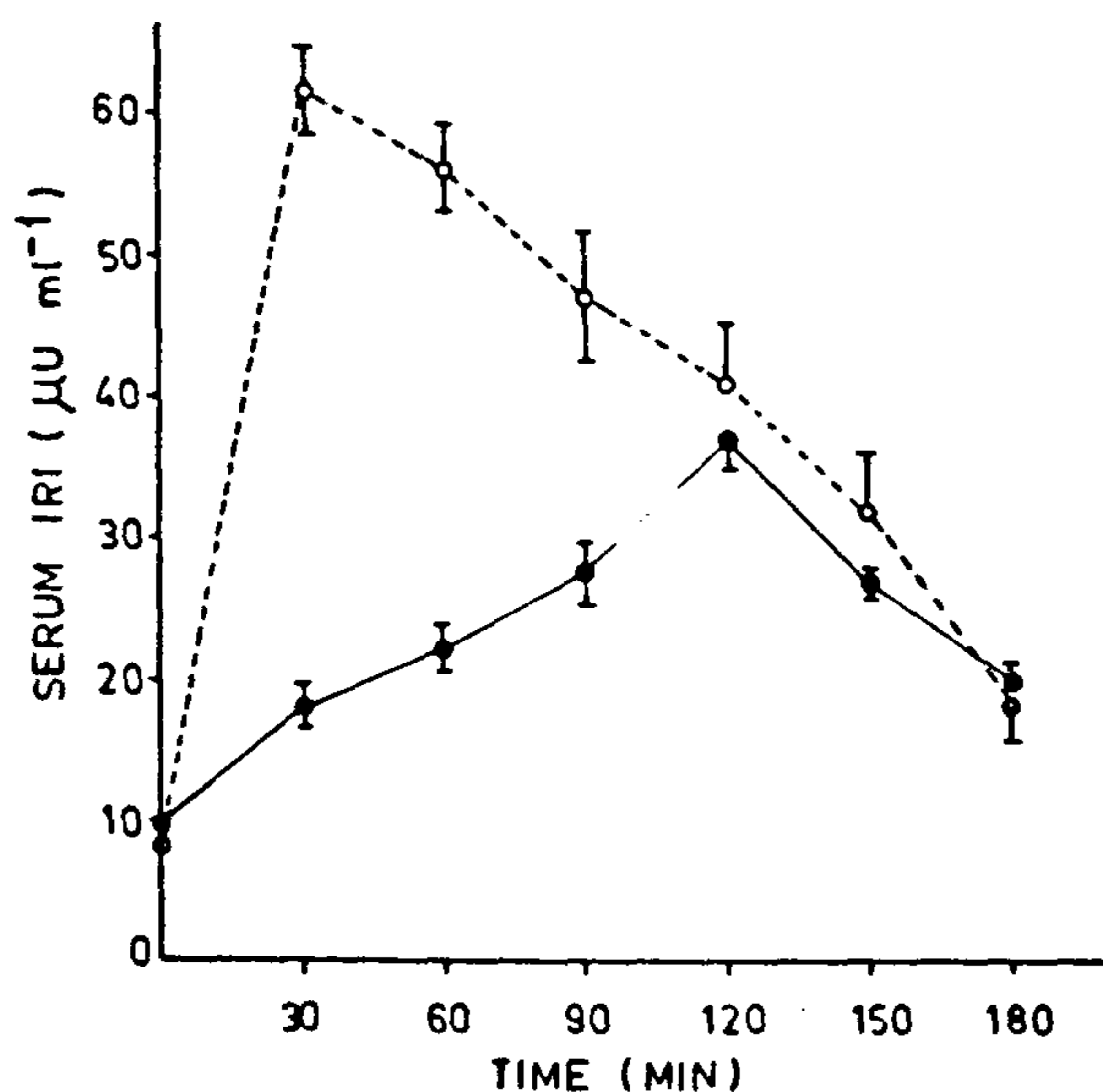


Figure 11. Serum insulin during OGTT. Normal (o---o) and non-obese NIDDM (●—●).

Application to NIDDM

Non-obese NIDDM

The time variations in blood glucose and plasma insulin concentrations in patients with non-obese NIDDM and the corresponding profiles for the controls are shown in Figures 10 and 11. It can be seen that higher glucose levels with a delayed peak compared to the controls are present at all times in the non-obese NIDDM cases. The glucose levels do not return to normal levels even beyond 180 min. The insulin levels, on the other hand, are lower than normal to begin with and approach the normal levels beyond 180 min. A sluggish rise in insulin levels in NIDDM can be seen.

The observed data can be fitted with the following choice of parameters:

$$NR_4 = (NR_4^0)/4; R_5 = R_5^0/1.25; R_6 = R_6^0/2.5 \text{ and } R_7 = 2.5R_7^0$$

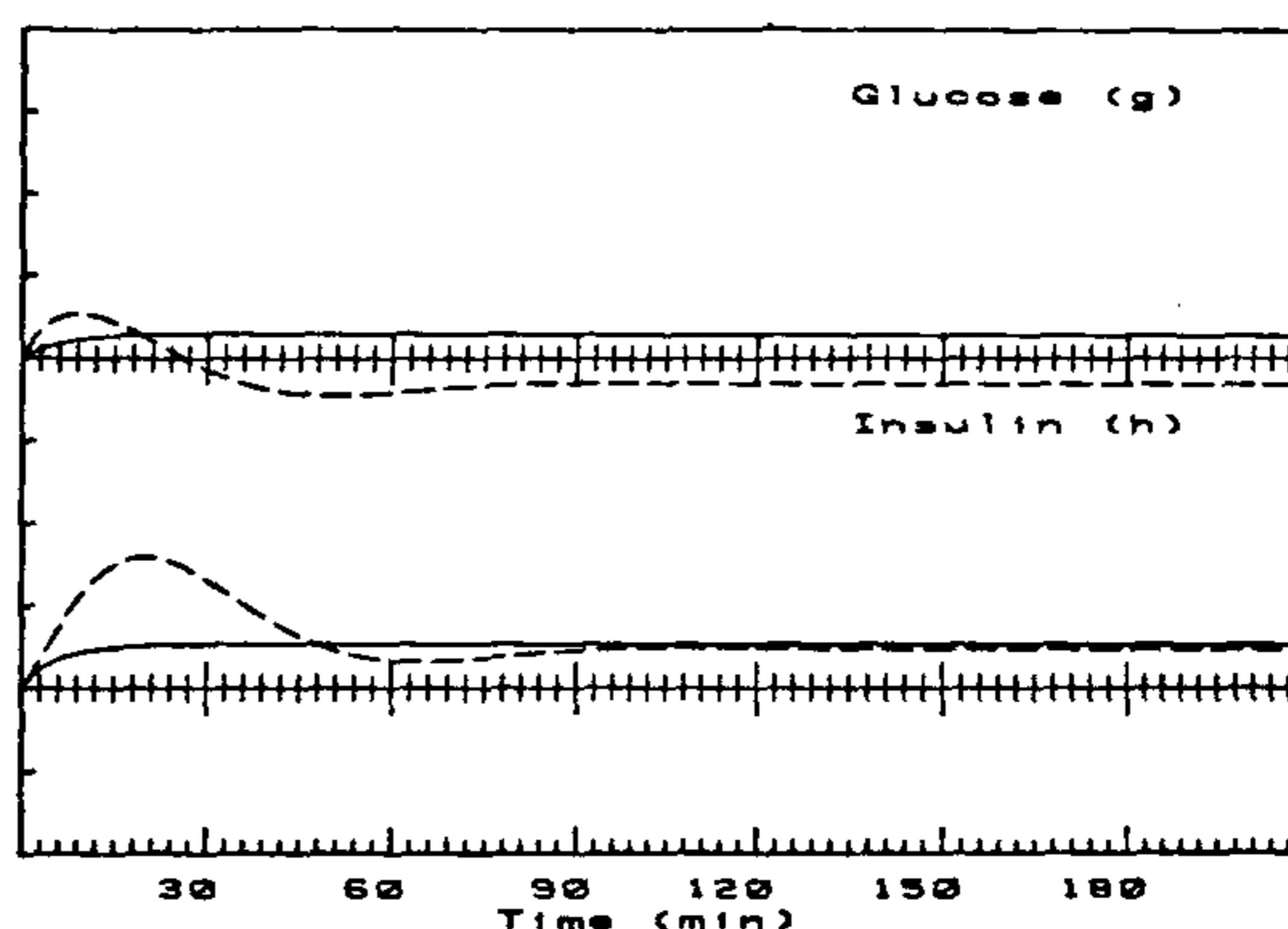


Figure 12. Theoretical basal glucose and insulin levels. Normal (---) and non-obese NIDDM (—).

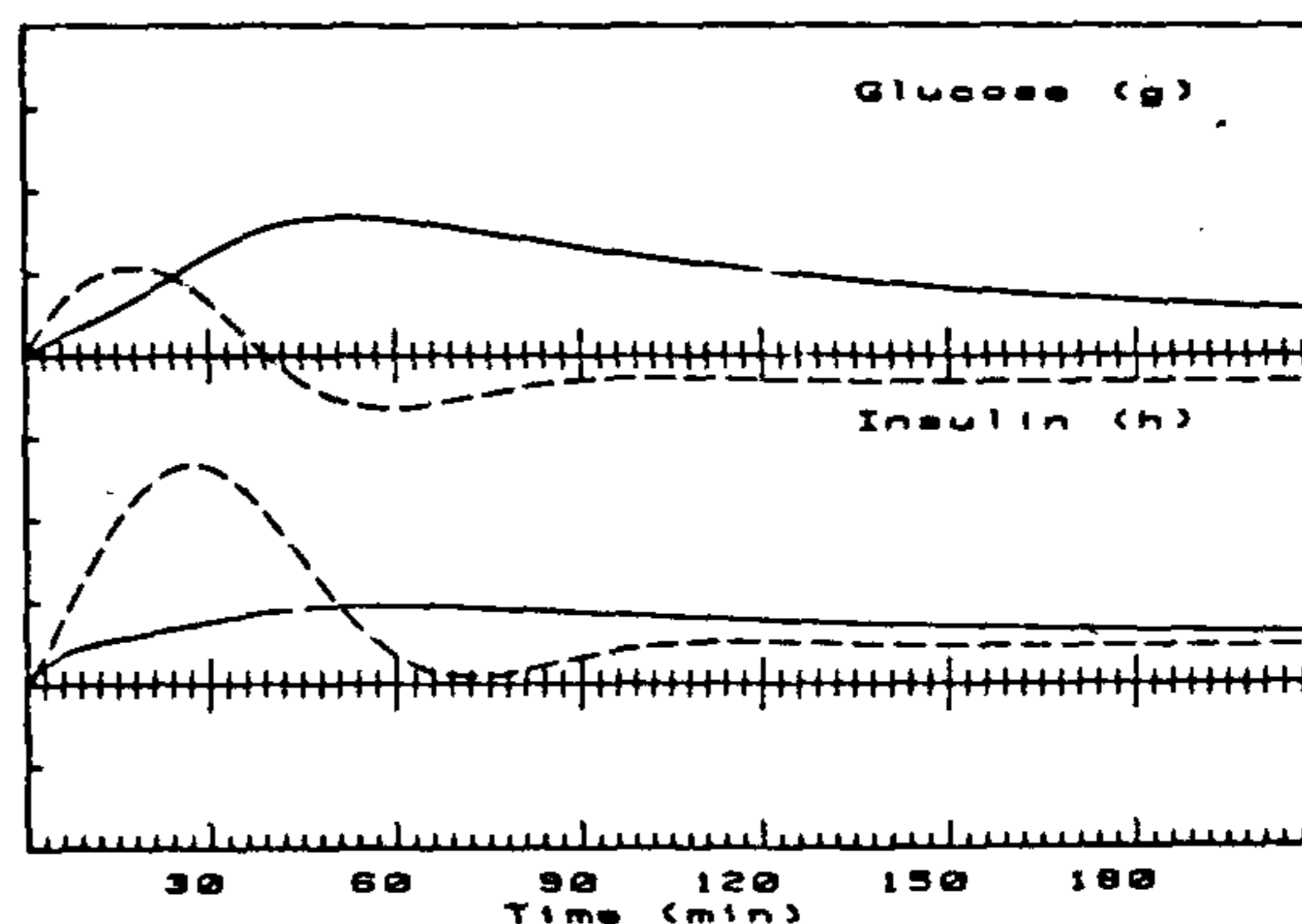


Figure 13. Theoretical glucose and insulin levels in response to a glucose load. Normal (---) and non-obese NIDDM (—).

with an initial rate of absorption, $w_0 = 0.046$. The resulting curves are shown in Figures 12 and 13.

Obese controls and obese NIDDM

The observed data (Figures 14 and 15) show that, whereas the glucose levels in obese controls are not too different from those in non-obese controls, there is a three-fold increase in the insulin peak with no delay compared to non-obese controls. In the case of obese NIDDM, the insulin peak is almost as high, but delayed compared to obese controls. Glucose levels are also elevated two-fold, with the peak being delayed compared to obese controls. Furthermore, both the glucose and insulin levels in obese NIDDM remain elevated at all times and do not return to normal levels even after 180 min. The observations can be modelled by the following changes in parameters.

Obese controls

$$R_5 = R_5^0/2.5; R_6 = 4R_6^0; R_7 = 1.75R_7^0; C_2 = 3C_2^0;$$

$$w_0 = 0.048.$$

Obese NIDDM

$$NR_4 = (NR_4)^0/10; R_5 = R_5^0/6.75; R_6 = 2R_6^0;$$

$$R_7 = 1.75R_7^0; a = 0.095; w_0 = 0.048;$$

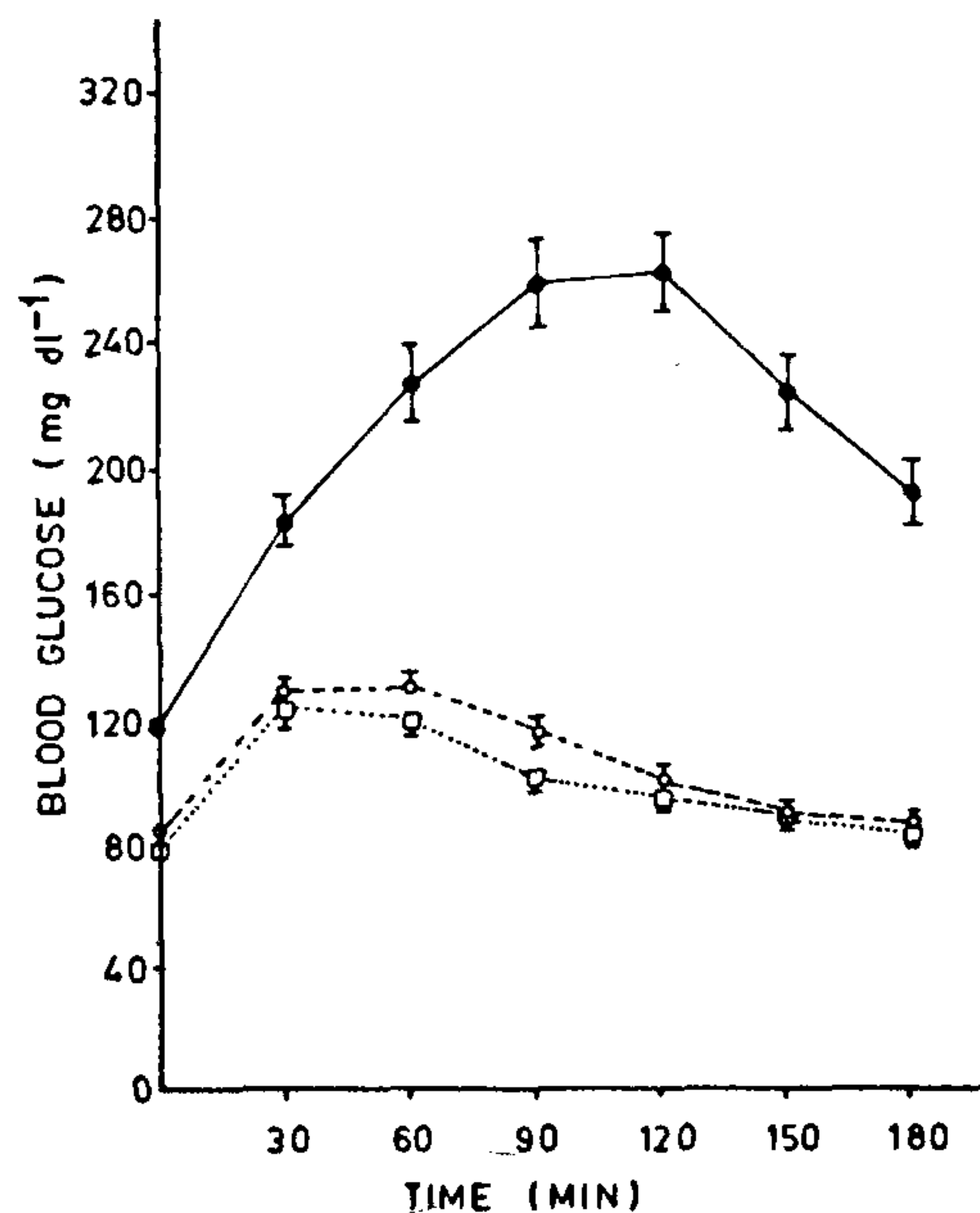


Figure 14. OGTT in obese NIDDM. Normal (□---□), obese normal (o---o), obese NIDDM (●—●).

The results for the basal levels and OGTT are shown in Figures 16 and 17. Thus obese controls are characterized by a four-fold increase in beta-cell function, an increased peripheral resistance in insulin action and an increased initial rate of gastro-intestinal absorption of glucose compared to non-obese controls. These changes correlate well with patho-physiological findings¹⁸.

In comparison with the corresponding controls, both obese and non-obese NIDDM appear to occur as a result of decreased beta-cell capacity and function and an increased peripheral resistance to insulin action. An

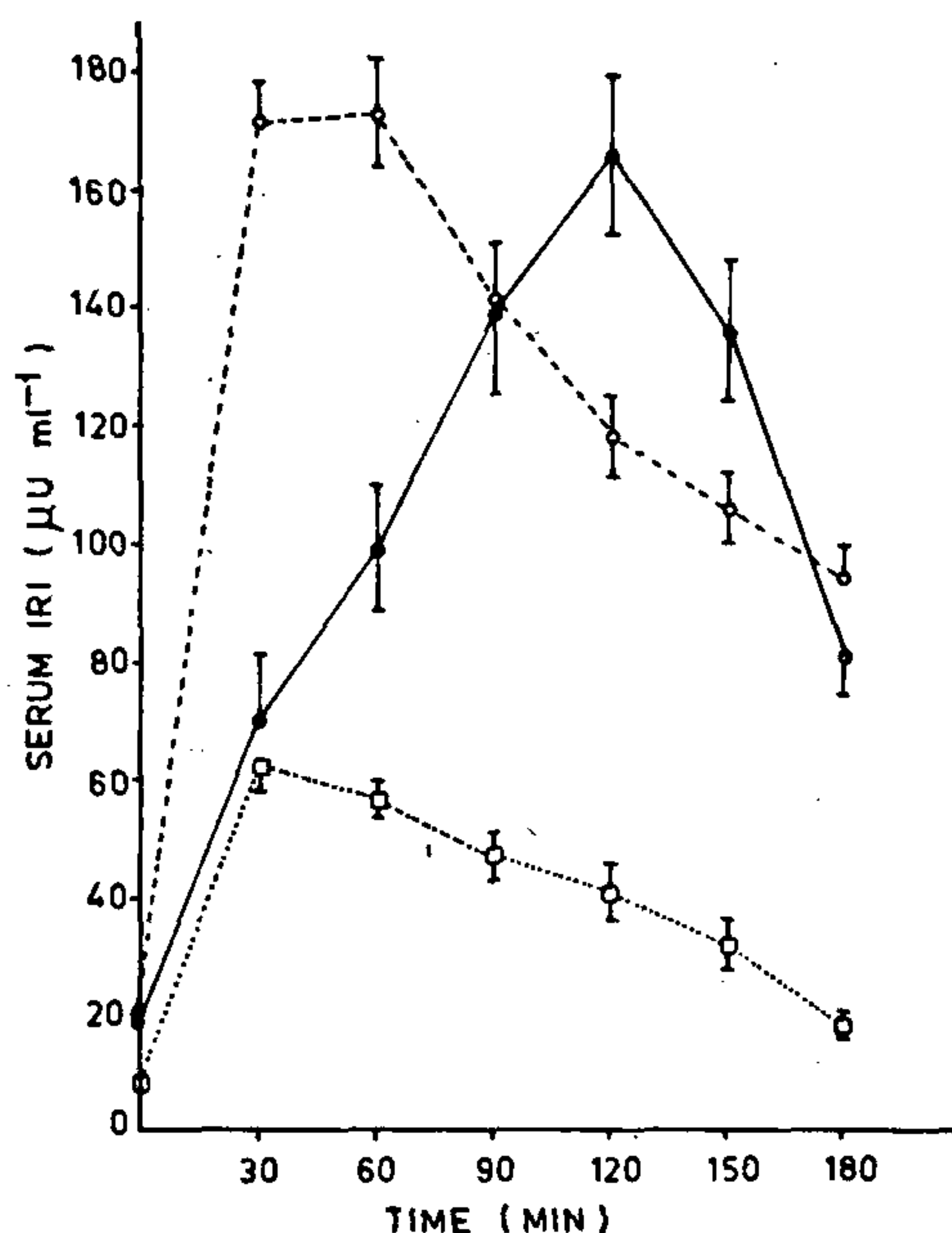


Figure 15. Serum insulin levels during OGTT. Normal (□---□), obese normal (o---o) and obese NIDDM (●—●).

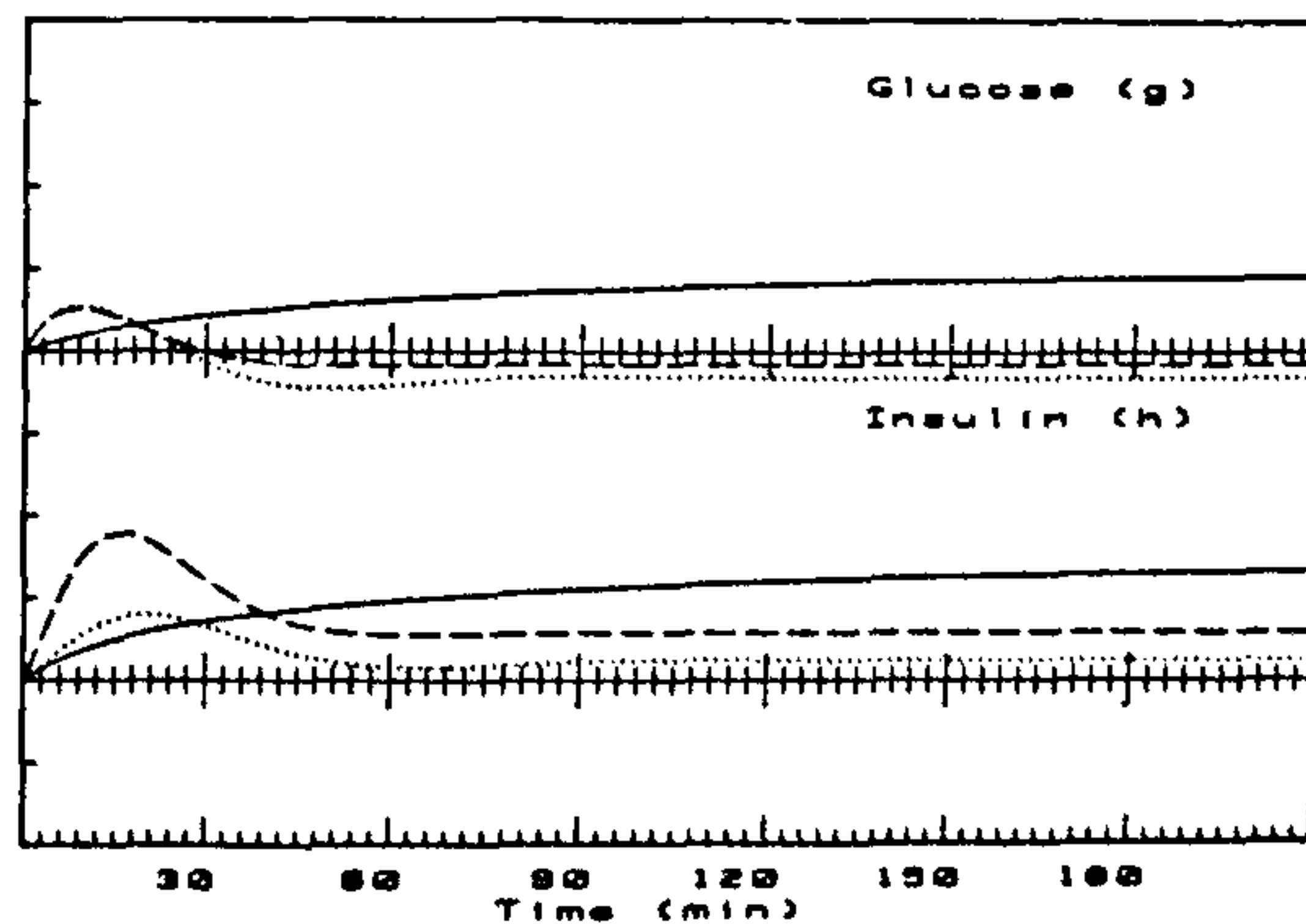


Figure 16. Theoretical basal glucose and insulin levels. Normal (...), obese normal (---) and obese NIDDM (—).

increase in non glucose-dependent insulin loss is also a key feature in non-obese NIDDM. The results of a linear stability analysis shows that there is no change in the nature of the stability between obese and non-obese controls. However there is a change in going from the controls to the corresponding NIDDM case. As done in the case of IDDM, the critical parameter in the obese case seems to be peripheral resistance to insulin while in the non-obese case it appears to be R_7 , the non glucose-dependent insulin loss. This is in agreement with the results of the model proposed by Bergman *et al.*⁶.

Application to PDDM

The experimental observations in this case comprise of

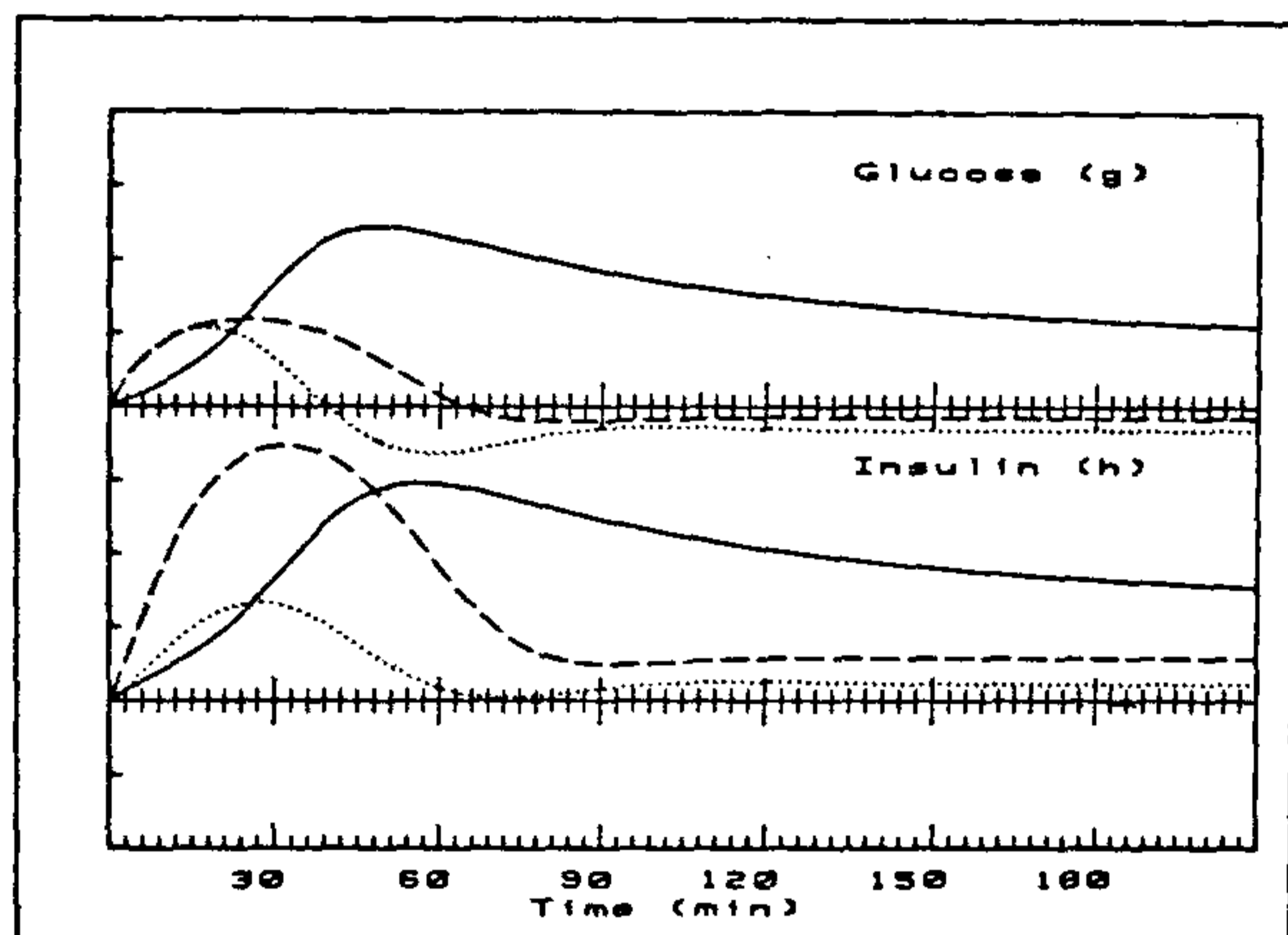


Figure 17. Theoretical glucose and insulin levels in response to an oral glucose load. Normal (....), obese normal (---) and obese NIDDM (—).

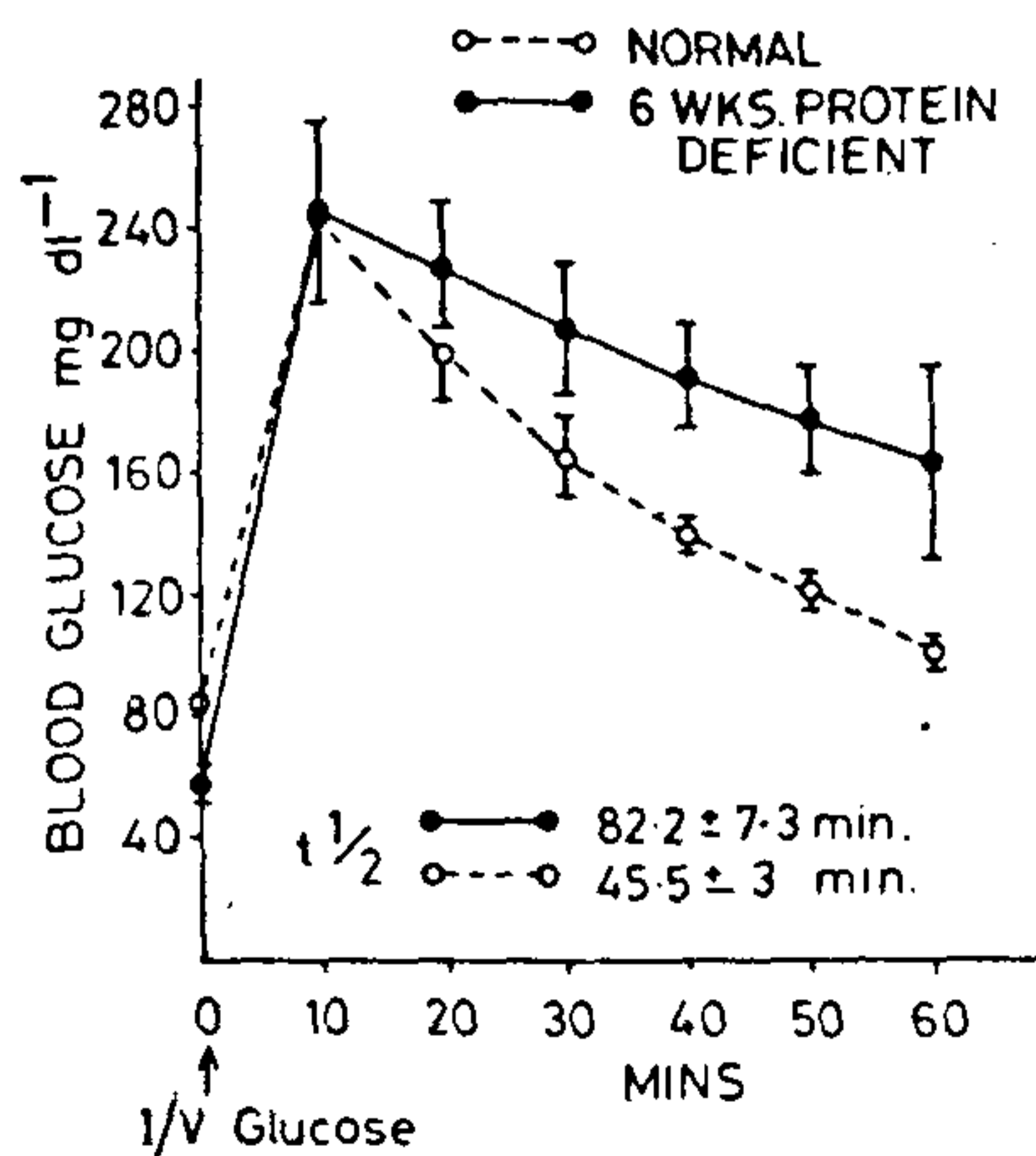


Figure 18. IVGTT in normal (control, o---o) and protein-deficient (experimental, ●—●) groups.

laboratory data on animal experiments using a model of protein malnutrition in the rhesus monkey, which were conducted to investigate the effect of isocaloric diets, identical in all respects but selectively deficient in protein^{19,20}. Previous morphological and pathological studies had shown that classical changes of protein malnutrition were established by six weeks of protein-deficient diet²¹.

The glucose and insulin profiles following intravenous (IV) injection of glucose are shown in Figures 18 and 19. The fasting blood glucose and serum insulin are lower than normal. Following the IV glucose challenge, the glucose levels are higher than normal while there is a significant reduction in the insulinogenic response.

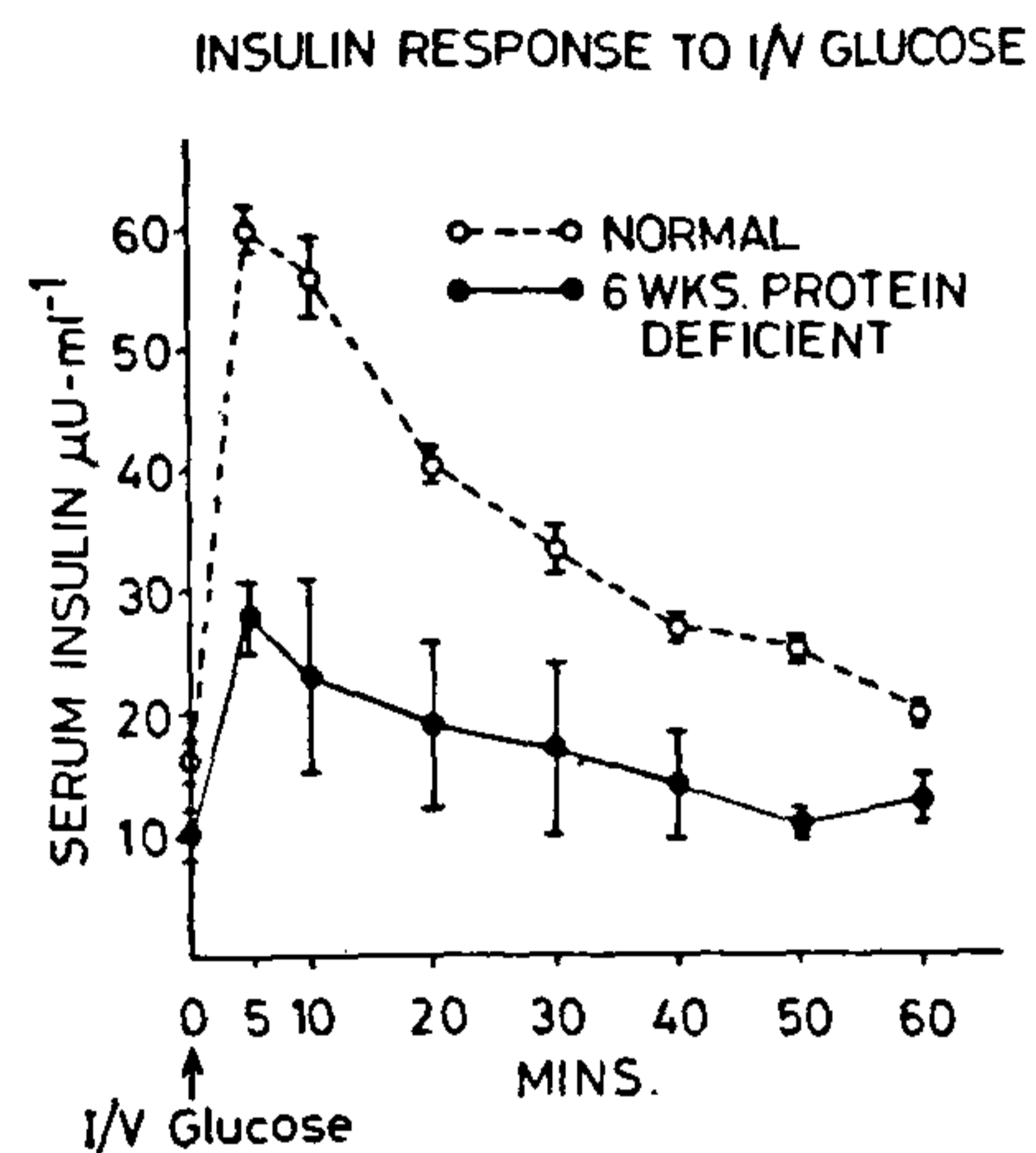


Figure 19. Serum insulin during IVGTT showing significant reduction in the insulinogenic response in protein-deficient groups, but without any delay in the first phase of insulin release. Normal (o---o), protein deficient (●—●).

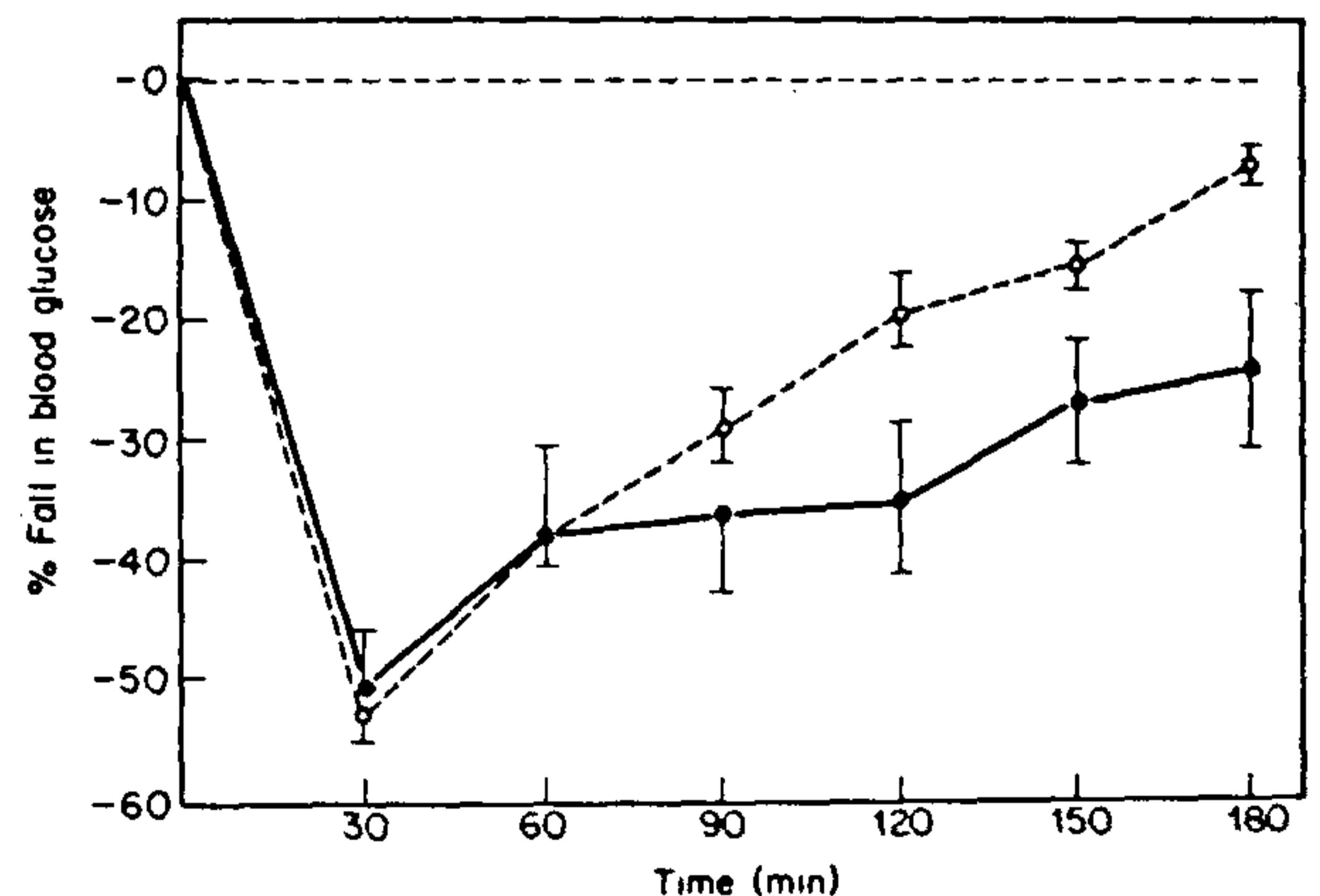


Figure 20. Fall in blood glucose level on IV administration of insulin showing a persistence of hypoglycemia in the protein-deficient group. Normal (o---o), protein-deficient (●—●).

Figure 20 depicts the fall in glucose levels following IV injection of insulin. A significant decrease in blood glucose and persistence of hypoglycemia is observed in the experimental group after six weeks of malnutrition. The observations indicate a sub-optimal response of the beta-cells in PDDM which may be due to several factors, leading to a reduction in either beta-cell number or function or both. No conclusive experimental evidence exists in favour of any one of the three possibilities.

Change of parameters for PDDM

It was found that the results could be obtained by changing only one parameter, R_g to half its normal value. The results of numerical simulation are shown in Figures 21 and 22. They are entirely consistent with the experimental findings that: i) The steady-state values after the initial oscillations in the basal concentrations

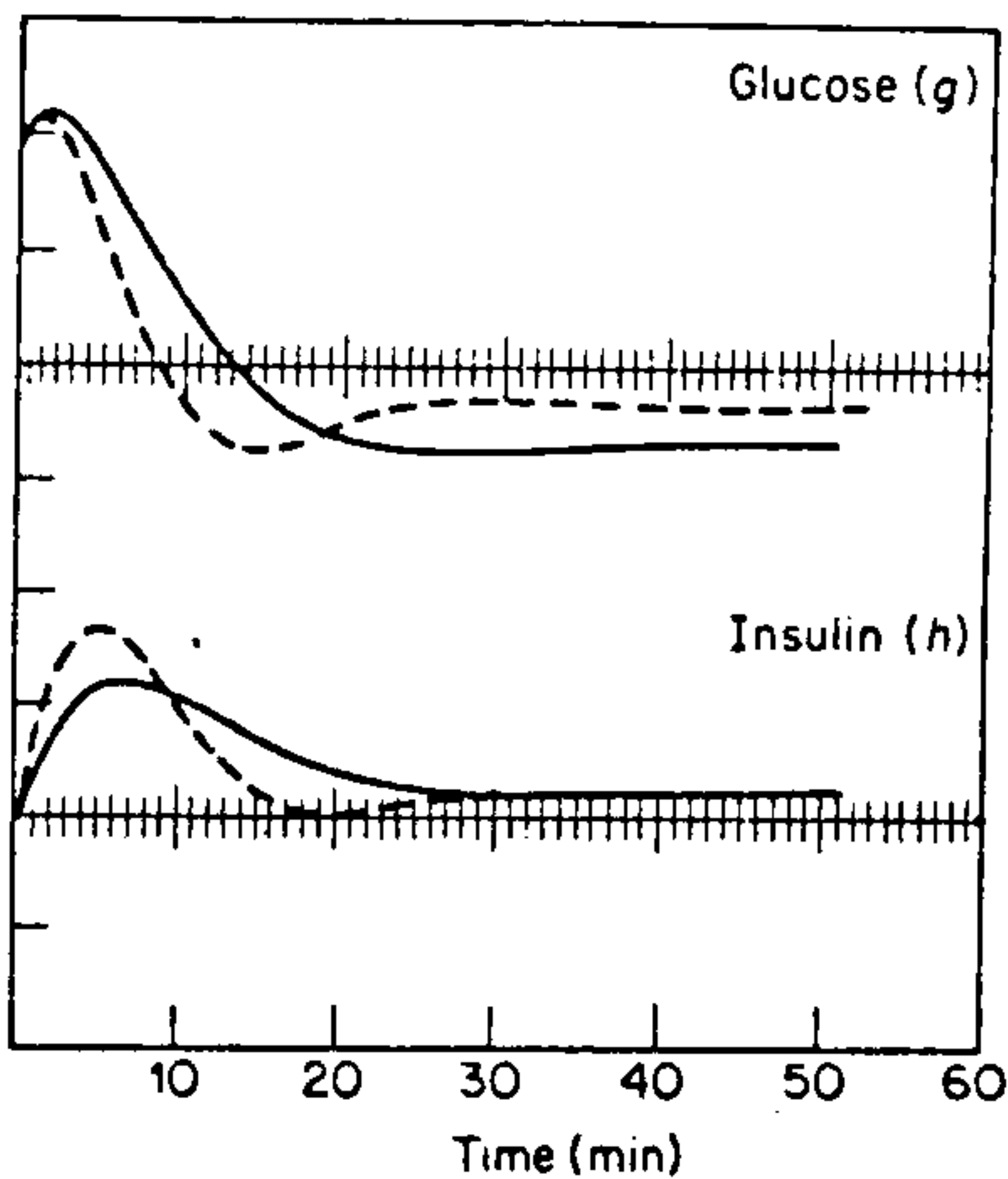


Figure 21. Theoretical time behaviour of glucose and insulin levels in response to an IV glucose load. Normal (---), PDDM (—).

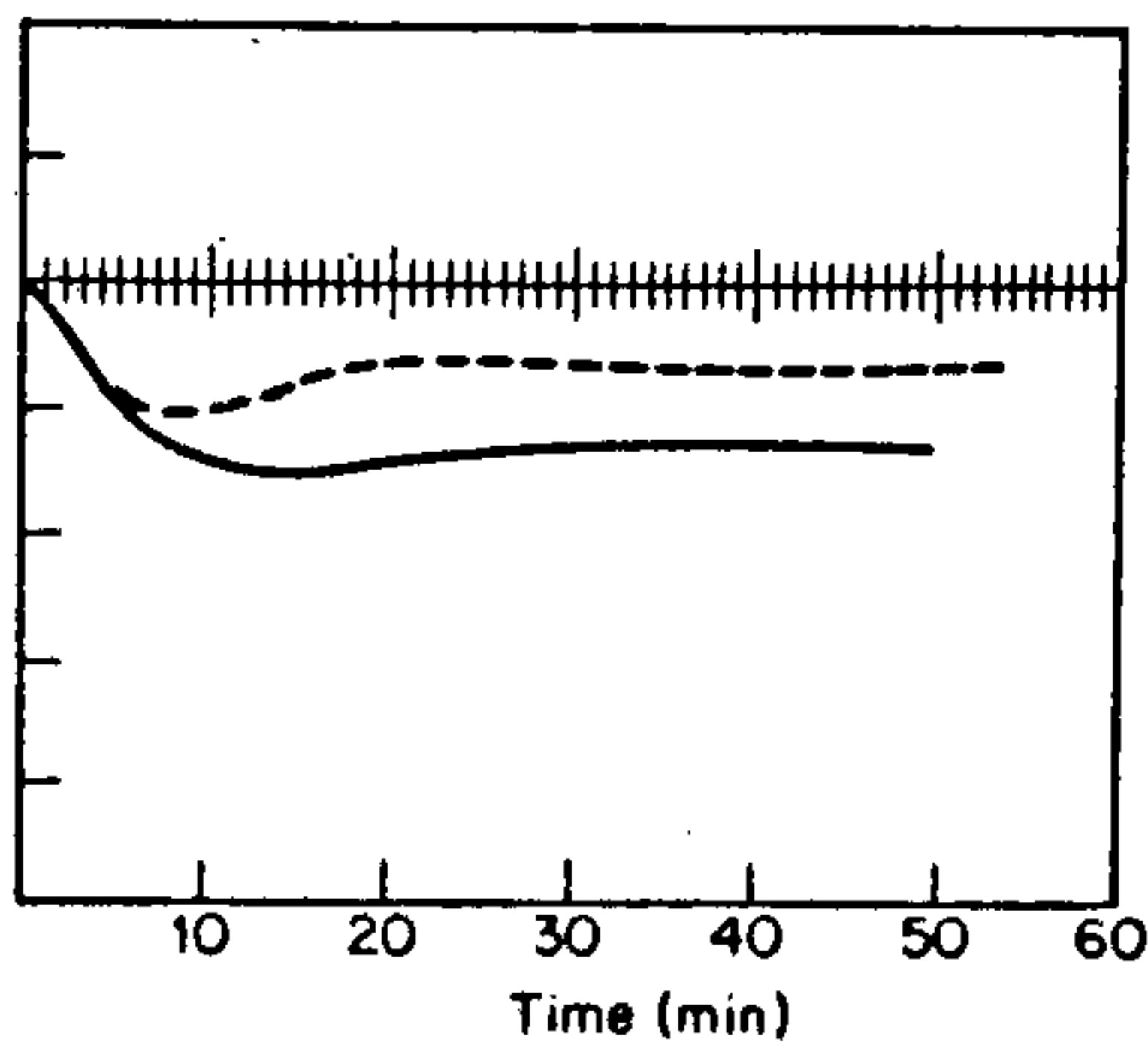


Figure 22. Theoretical fall in blood glucose level after IV injection of insulin. Normal (---), malnutrition (—).

of glucose are lower in PDDM; ii) Insulin response following a glucose challenge is reduced; iii) There is a significant drop in glucose levels following an IV injection of insulin and persistence of hypoglycemia in malnutrition.

Thus the model predicts that it is the beta cell function and not the number which gets diminished in protein malnutrition. Linear stability analysis of the equations indicates that the nature of stability does not change with a decrease in R_g .

Sensitivity analysis

Sensitivity analysis of the equations gives an idea of how the glucose and insulin concentrations will vary with small changes in parameter values and initial conditions. Sensitivity to changes in parameter values provides an insight into the pathophysiology of diabetes mellitus, while that to changes in initial conditions gives an indication of how sensitive the system is to the oral glucose challenge, for example.

The utility of sensitivity analysis in the design and interpretation of tracer experiments has been discussed by Bogumil²². Sensitivity analysis with respect to a single parameter has been used in the minimal model of glucose disappearance²³. In both these applications the direct differential method has been used. A more efficient method when the number of parametric sensitivities to be determined is greater than the number of variables has been used here²⁴.

Results

The model solution and the normalized sensitivities

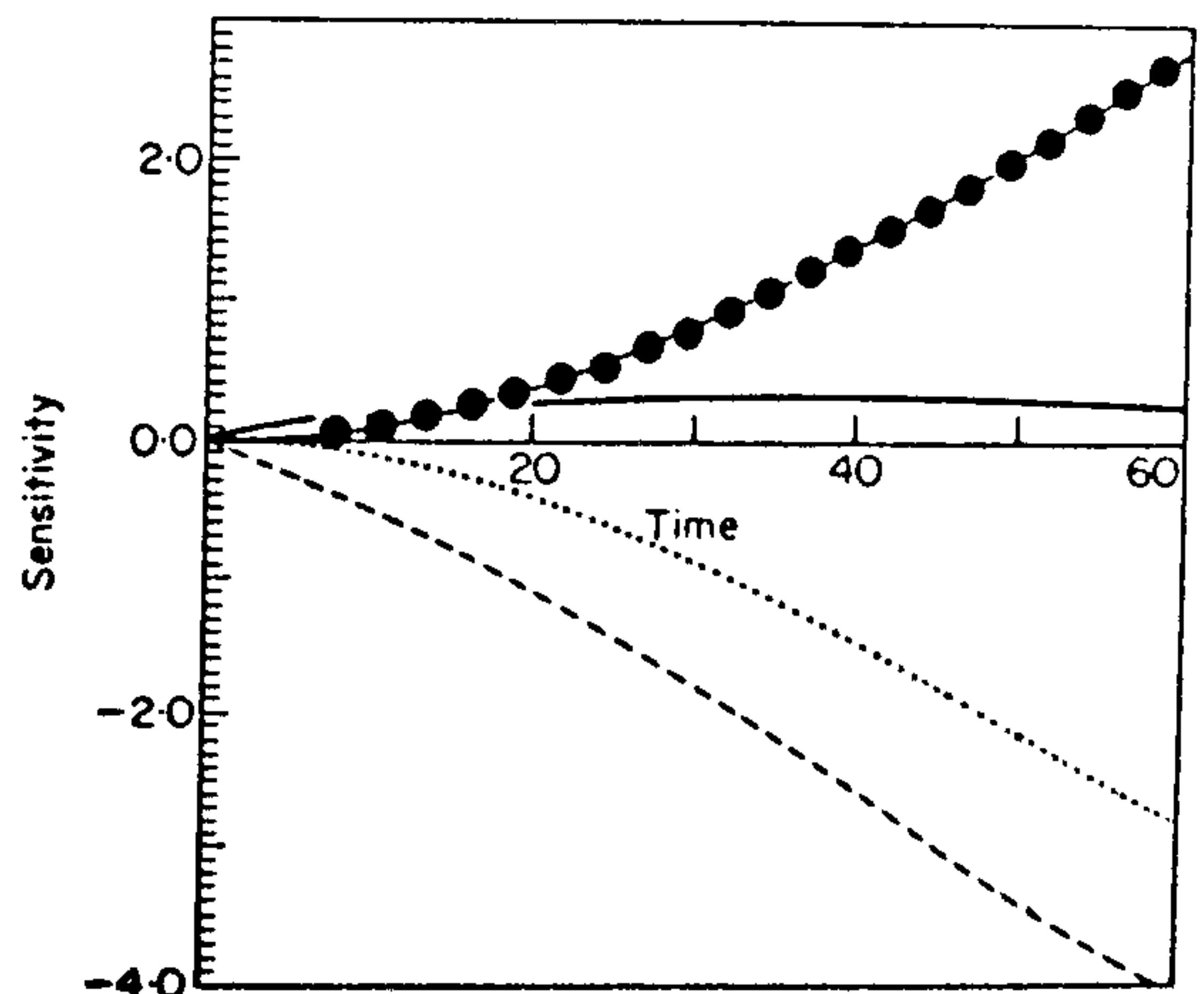


Figure 23. Normalized parametric sensitivity (linear) of glucose level (g) to the parameters R_4 (—), R_5 (---), R_6 (....) and R_7 (•—•—•).

(dg/g , dh/h) to the parameters R_4 , R_5 , R_6 and R_7 were computed for non-obese controls with initial conditions $b = 20$, $g = 0$, $h = 0$ and $w_0 = 0.046$. The results are shown in Figures 23 and 24.

It can be seen that the normal glucose concentration shows a small and constant positive sensitivity to R_4 , a positive and rapidly increasing sensitivity to R_7 and negative, rapidly increasing sensitivities to R_5 and R_6 . Consequently, a small increase in R_7 , or a small decrease in either R_5 or R_6 from the corresponding normal values would result in increasing hyperglycemia, while a small increase in R_4 would result in a constant increment in circulating glucose.

The normal insulin concentration, on the other hand, exhibits a negative, rapidly increasing sensitivity to R_5 , a small positive and constant sensitivity to R_4 , a small, positive, slowly increasing and then decreasing sensitivity to R_6 and a small, positive, slowly decreasing and then increasing sensitivity to R_7 . Consequently, a small decrease in R_5 from the normal value would considerably raise the plasma insulin levels, while a small decrease in R_4 or R_6 , or a small increase in R_7 would lead to insulinopaenia.

These results are entirely consistent with the clinical and pathophysiological findings that

(i) the hyperglycemic state is a consequence of either reduced beta-cell function (represented by the parameter R_6 in our model) and/or an increased peripheral resistance to insulin action (that is, a decrease in parameter R_5 in our model);

(ii) an increase in peripheral resistance to insulin action leads to elevated plasma insulin levels, and;

(iii) insulinopaenia is a consequence of a decrease in either beta-cell function or capacity (represented by the

parameter NR_4 in our model) or both, and/or by an increase in glucose-independent insulin loss (represented by the parameter R_7 in our model).

A study of the sensitivity of glucose and insulin concentrations to initial conditions in normal controls (both obese and non-obese), as well as in subjects with IDDM or NIDDM, obese and non-obese, was done. Analysis was carried out with respect to the following sets of initial conditions:

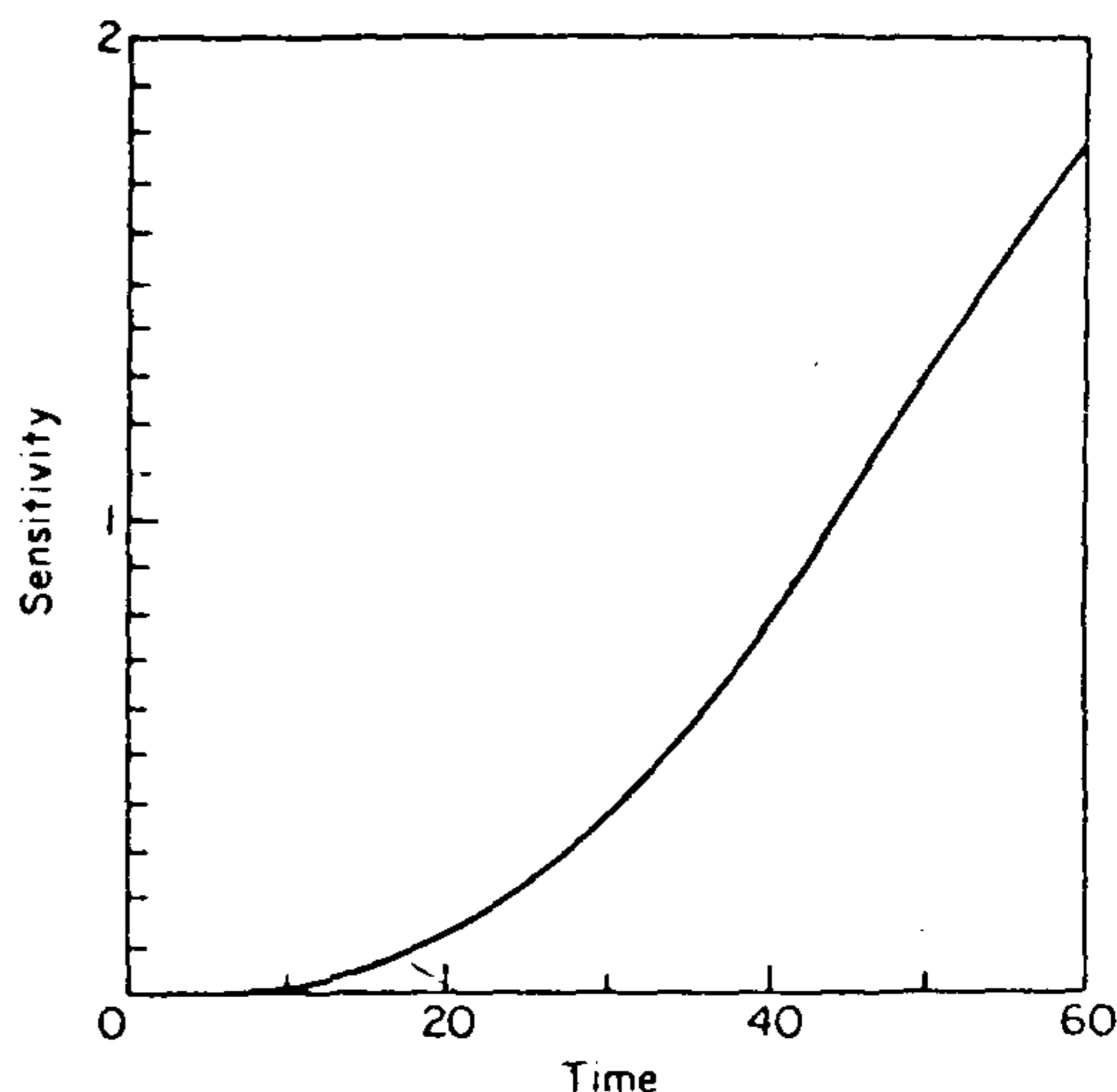


Figure 25. Sensitivity (normalized, linear) of plasma insulin level to initial rate of gastrointestinal absorption in normal obese subjects.

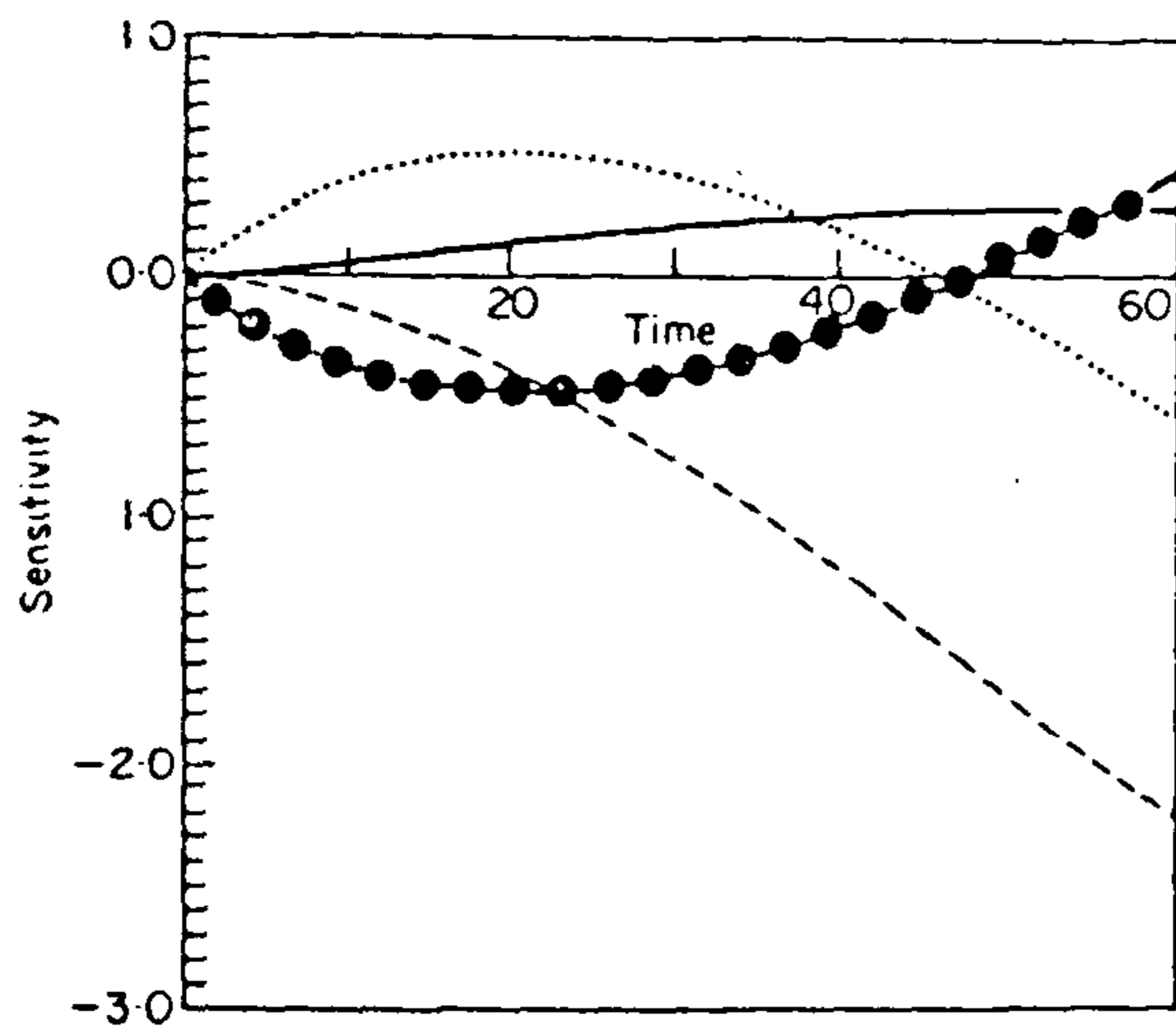


Figure 24. Normalized parametric sensitivity (linear) of insulin level (h) to the parameters R_4 (—), R_5 (---), R_6 (...) and R_7 (●—●—●).

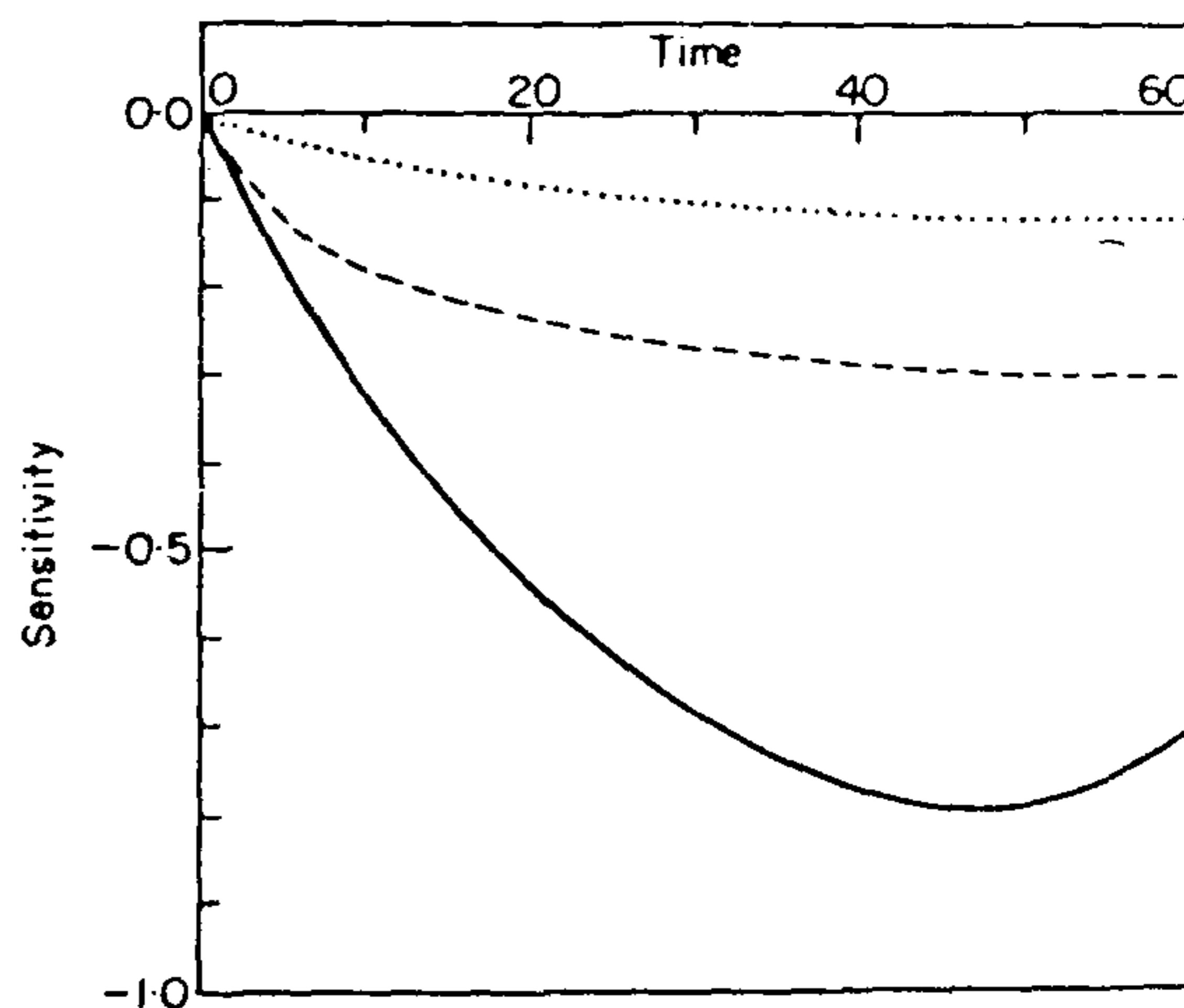


Figure 26. Sensitivity (normalized, linear) of glucose level to changes in insulin level in obese controls and non-obese controls as well as obese diabetics. Normal control (—), normal obese (---), obese diabetic (...).

(i) $b = 20$, $g = 0$, $h = 0$, $w = 0$ (viz. basal levels without perturbation)

(ii) $b = 20$, $g = 0$, $h = 0$, $w \neq 0$ (viz. an oral glucose challenge).

The sensitivity of glucose and insulin concentrations to perturbations in initial conditions for each of the variables was calculated and plotted as a function of time for a period of 60 min. The main results are as follows:

(a) The plasma insulin concentration exhibits a positive, rapidly increasing sensitivity to the initial rate of gastrointestinal absorption in normal controls (Figure 25), while the glucose concentration exhibits a comparable negative, increasing sensitivity to insulin concentration (Figure 26, solid line). These imply that a small increase in the oral glucose challenge would result in an increase in plasma insulin concentration. Also, that an increase in insulin concentration would lead to a lower concentration of glucose. These results are in accordance with the findings of Hollenbeck *et al.*²⁵ that there is a significant relationship in normal subjects between the plasma insulin response to oral glucose challenge and insulin-stimulated glucose utilization as measured by the euglycemic clamp.

(b) As is clinically well established¹⁸, obese controls and obese subjects with NIDDM are characterized by an increase in peripheral resistance to insulin action at target tissues, and consequently, by a vanishingly small sensitivity of glucose concentration to changes in insulin concentration. The results of sensitivity analysis entirely corroborate these facts. As can be seen from Figure 26 (broken line and dotted line) the glucose concentration is relatively insensitive to changes in insulin concentration in obese controls as well as in obese diabetics.

Discussion and future prospects

The model proposed by us is found to give results that are consistent with all the three clinical categories of diabetes mellitus, and has all the desirable features required of a mathematical model for insulin kinetics. Another significant feature is that the model also leads to oscillations in the glucose and insulin levels. As can be seen from the results of normal, non-obese controls, the time period of oscillations is about 90 min and the glucose peak precedes the insulin peak by about 6 min. These results are in very good agreement with observations in humans²⁶.

The results obtained from sensitivity analysis of the

model suggest that by studying the sensitivity of the glucose concentration to an insulin injection and a concomitant glucose challenge, one could make predictions regarding future directions in the therapy of diabetes mellitus, thereby obviating the possible necessity of expensive hospitalization.

In the model reviewed here, insulin secretion has been modelled as a continuous process. However, there is evidence to suggest that insulin may be secreted in pulses. This can be taken into account by introducing a stochastic term in the expression for dh/dt .

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