Control of Blood Glucose in Normal and in Diabetic Subjects

Studies by Compartmental Analysis and Digital Computer Technics

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SUMMARY

A model with two compartments (glucose and insulin) and a negative feedback has been used to fit the values of blood glucose obtained experimentally by infusing intravenously glucose (0.5 gm. min^{-1}) or insulin (0.055 U. min^{-1}) for about 250 minutes. Glucose was infused to normal ambulatory or hospitalized subjects and to diabetic patients; insulin was infused to normal subjects. The model employed fits the data of all the groups. The SAAM program and a digital computer (IBM 7094) were used. The model cannot be solved completely due to the number of degrees of freedom of the system but values related to the transfer constants of the model can be computed, as the damping constant a, the natural frequency w, the natural period T and the free frequency b of the system, which shows damped oscillations in normal subjects; in diabetic patients the system passes through states of overdamping until no oscillations can be seen in the more severe cases. The effect of ten days of treatment with prednisone (25 mg. per day, per os) has been evaluated in a group of normal subjects. Discriminant analysis between normal and diabetic subjects and between glucose and insulin infusion has been carried out by using a BMD program and a digital computer. DIABETES *17*:570-78, September, 1968.

The appraisal of the parameters which characterize the kinetics of glucose utilization and the homeostasis of the glycemia can be obtained through two different approaches: the first is based on methods which do not perturb the steady state of glucose levels, as for instance the intravenous injection of tracer amounts of labeled glucose; the second approach is based on the perturbation of the system and on the analysis of its response which can afford the values of the parameters which participate in the regulatory process.

The first approach has been followed, among others, by Bastenie et al.[6] and by Ooms and others[28,29]; the use of tracer amounts of glucose affords values which validate the figures of glucose utilization obtained by an impulsive load of glucose, but the two methods differ in their approach.

The second method, to which the usual loading curves can be related (including the impulsive intravenous glucose injection) has been followed by Ceresa et al.[15,16] by Ackerman et al.[1-5,20-24] and in other studies.[12-14,26,30]

In the present paper this second approach has been followed and the results have been analysed by means of compartmental analysis, which has been used in the formulation of the model, and of digital computer technics, which have been employed to fit the experimental data to the model and to carry out the multivariate analysis of the compartmental data.

THE MODEL

The model used in the present investigation is identical to that employed in a previous study (Ceresa et al.[15]); this model has also been used by Ackerman et al.[1]

The model is clearly an abstraction of reality: for instance, reactions of first order only have been assumed and many compartments have been lumped into the two compartments which characterize the model (figure 1). But, being aware that this model constitutes a first approximation only, we must nonetheless admit that in any case a simplified model represents a preliminary step to the study of more complex problems; future experience will tell us how far this model can be applied in clinical work.

The formulation of the model is based on the following assumptions:

(1) Glucose and insulin are represented by two compartments (figure 1): compartment I = glucose; com-

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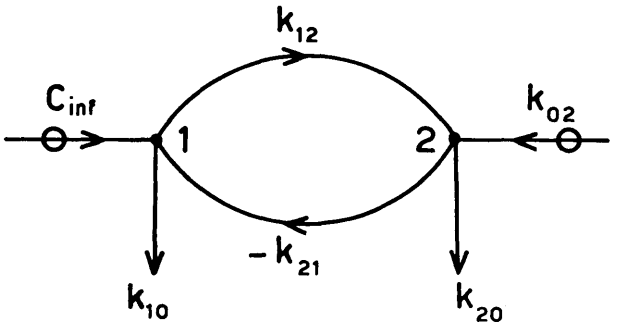


FIG. 1. Compartmental model used to fit the plasma glucose kinetics following intravenous infusion of glucose or insulin. The compartments are indicated by numbers (1 = glucose; 2 = insulin); the transfer constants are indicated by k's (k_{ij} = fractional amount of material in compartment i entering compartment j in one minute); ———c——→ indicates a continuous input.

partment 2 = insulin.

(2) Glucose enters the system at a rate proportional (following coefficient C') to the difference between its concentration in compartment 1 (X_1) and a reference value Z. This linear relationship has been shown to be valid for glucose utilization by the liver (Soskin et al.).[33]

(3) The rate of glucose disappearance is proportional, following coefficient k'_{10}, to its concentration and to insulin concentration (X_2), following coefficient k_{21}.

(4) The rate of insulin formation is proportional to the glucose concentration, following coefficient k_{12}, and its disappearance is proportional to its concentration, following coefficient k_{20}. The additional supposition of a constant rate of insulin formation leads practically to the same system of equations, as shown by Ackerman et al.[1]

The assumptions 1 to 4 lead to the following system of differential, first order equations

$$\begin{cases} dX_1/dt = -k'_{10}X_1 - k_{21}X_2 + C'(Z-X_1) \geq 0 \\ dX_2/dt = k_{12}X_1 - k_{20}X_2 \end{cases} \quad (1)$$

which can be simplified into

$$\begin{cases} dX_1/dt = -k_{10}X_1 - k_{21}X_2 + C_{fast} \\ dX_2/dt = k_{12}X_1 - k_{20}X_2. \end{cases} \quad (2)$$

The linear effect of X_1 upon X_2 and vice versa amounts to assuming that the values of X_1 and X_2 are small in respect to the dissociation constants in the Michaelis formulas which represent the relationship between concentration and effect of each substance upon the other.

It may be noted that, according to assumption 2, C_{fast} corresponds to the endogenous glucose output (presumably almost entirely from the liver), whereas the uptake of glucose by all glucose consuming tissues is included under the term $k_{10}X_1$.

Two different solutions of equations (2) are obtained, depending on whether $(k_{10}-k_{20})^2 < 4\ k_{12}k_{21}$ or $(k_{10}-k_{20})^2 > 4\ k_{12}k_{21}$.

Let us put $X_1(0) = X_2(0) = 0$ as initial conditions, which are impossible from a physiological standpoint but are permissible from a mathematical standpoint; the system of equations 2 with these initial conditions would describe the fasting homeostasis when one starts from a situation where no glucose and no insulin are present in plasma. In this hypothetical case, when $(k_{10}-k_{20})^2 < 4\ k_{12}k_{21}$ the solution for $X_1(t)$ is given by

$$X_1(t) = C_{fast} \int_0^t G(t)\ dt$$

where $G(t) = A\ e^{-at} \cos(bt + c)$ (3)

and

$$\begin{cases} A = [1 + (k_{10}-k_{20})^2/4b^2]^{1/2} \\ a = (k_{10}+k_{20})./2 \\ b = [k_{12}k_{21} - (k_{10}-k_{20})^{2/4}]^{1/2} \\ c = \tan^{-1}(k_{10}-k_{20})/2b \end{cases} \quad (4)$$

(Jennings et al.[27]).

The solution 3 corresponds to damped oscillations, which are characterized by the following parameters

a = damping constant
$w = [k_{10}k_{20} + k_{12}k_{21}]^{1/2}$ = natural frequency
$T = 2\pi/w$ = natural period
$b = [w^2 - a^2]^{1/2}$ = free frequency.

The asymptotic value of X_1 for $t \to \infty$ is equal to

$$X_0 = 100\ C_{fast}\ k_{20}/w^2.* \quad (5)$$

When $(k_{10}-k_{20})^2 > 4\ k_{12}k_{21}$, then the system is overdamped and the solution for $G(t)$ instead of equation (3) is given by

$$G(t) = M_1e^{-m_1t} + M_2e^{-m_2t} \quad (6)$$

where $-m_1$ and $-m_2$ are the roots of equation

$$m^2 + 2am + w^2 = 0$$

and $M_1 = (m_2 - k_{20})/(m_2 - m_1)$ and

$M_2 = -M_1$.

*The coefficient 100 in equation (5) is due to the fact that the glycemia is expressed as mg. per 100 ml.

When the steady state is reached and the value of X_1 is given by X_0 (see equation 5), if one infuses glucose at the rate C_{glu}, then the only change in the system is that the input to compartment 1 is now given by

$$C_{fast} + C_{glu} = C_{inf}$$

because of the superposition principle; a set of equations similar to equations 2 is then obtained, of the following form

$$\begin{cases} dX_1/dt = -k_{10}X_1 - k_{21}X_2 + C_{inf} \\ dX_2/dt = k_{12}X_1 - k_{20}X_2 \end{cases} \quad (7)$$

with $X_1(o) = X_0$ (glycemia in fasting state) and $X_2(o) =$ insulinemia in fasting state as initial conditions.

The new asymptotic value of X_1 for $t \to \infty$ is now expressed by (5) but with C_{inf} instead of C_{fast}, that is by

$$X_\infty = 100\ C_{inf}k_{20}/w^2. \quad (8)$$

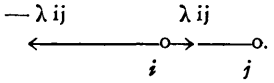
The kinetics of X_1 will be given by

$$X_1(t) = X_0 + C_{inf} \int_0^t G(t)\ dt.$$

When insulin is infused, compartment 2 will have an input given by k_{02} (and the input to compartment 1 will be C_{fast}).

Figure 1 shows the graph which represents the system.

Figure 2 shows the computer representation of the model of figure 1. The transfer constants are here denoted as lambdas instead of kappas; a continuous input to compartment j is indicated as (9)*



Care must be taken of the fact that in figure 1 the transfer constants k_{12} and k_{21} indicate flows of signals and k_{10} and k_{20} indicate flows of materials, whereas in the computer representation of figure 2 the total outflow (of material) from compartment 1 is given by $\lambda_{12} + \lambda_{10}$ and the total outflow of material from compartment 2 is given by $\lambda_{21} + \lambda_{20}$; therefore one must provide the computer with the condition that if $\lambda_{12} \geqq K_{10}$ (rate of glucose disappearance), then $\lambda_{10} \leq o$.

In what follows the lambdas are used to indicate the

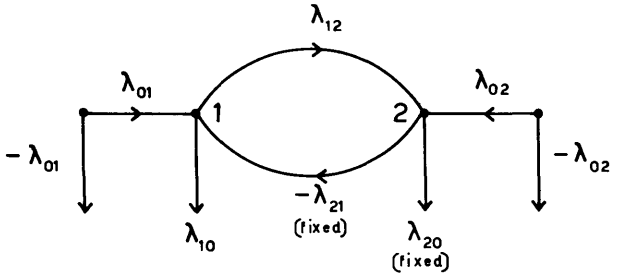


FIG. 2. Computer representation of the model of figure 1; the compartments are indicated by numbers and the transfer constants by λ's (λ_{ij} corresponds to k_{ij}). A continuous input to compartment 1 (glucose infusion) and to compartment 2 (insulin infusion) is represented as explained in the text.

values obtained by the computer and the kappas to indicate the values of the model.

It must be pointed out that by knowing only the glycemic curve resulting from glucose or insulin infusion it is not possible to solve directly all the six degrees of freedom of the model of figure 1.* From equation 4 it is possible to see that from the glycemic curve practically only the parameters a and b can be measured, so that k_{10}, k_{20}, k_{12}, and k_{21} cannot be evaluated independently and only certain relationships among them can be calculated. Therefore in the model representation for the computer the values of λ_{10} and of λ_{21} were taken as fixed.

It can be noted that the curves obtained in normal subjects showed that, in first approximation[15,16]

$$c \simeq o$$

and therefore

$$k_{10} \simeq k_{20}$$
$$a \simeq k_{10}$$
$$b = [k_{12}k_{21}]^{1/2}$$

(see equations 4).

These equations could be used to obtain first approximation values.

It can be observed that the fasting blood glucose level (X_0) is known and that the value of X_∞ (blood glucose level that would be reached at $t \to \infty$ with the infusion) can be calculated by using $X_\infty = 100\ C_{inf}k_{20}/w^2$ (and could be obtained experimentally). It is then possible from equations 5 and 6 to calculate

$$C_{fast} = C_{inf}\frac{X_o}{X_\infty}$$

and

$$C_{glu} = C_{inf} - C_{fast}.$$

*In this paper, for simplicity and for preserving uniformity in the order of the indexes the Berman's order of indexes is reversed.

*In the case of glucose infusion $K_{02} = o$, but $C_{inf} = C_{fast} + C_{glu}$.

Now C_{glu} corresponds to the fractional input of glucose to compartment 1 when the infusion rate is equal to 0.5 gm. min^{-1}; it is then possible to calculate the volume V_1 (in liters) of compartment 1 as equal to

$$V_1 = (0.5/C_{glu}) \cdot (100/X_{\infty}).$$

Of course not too much confidence can be placed on this value, because of the approximations and errors involved in its calculation.*

COMPUTATION

The model of figure 2 was solved by using the SAAM program (Berman et al.[7-9]) and a digital computer (IBM 7094). A subroutine of SAAM program was used by which a direct solving procedure is employed with a least squares iterative procedure and which affords directly the parameters of the model with their standard deviations. The experimental data were weighted by assigning to them a fractional deviation equal to the 10 per cent of the observed values. The accuracy of the fitting was judged by means of the deviations between calculated and observed values, their ratio, and by means of the sum of the squares of the deviations as well as by inspection of the plot of the calculated and observed values; all these data were provided by the computer.

As initial condition for compartment 1 the plasma glucose level of each subject at the beginning of the experiment (X_0) was used; for compartment 2 an arbitrary value (100) was used; if the true value of plasma insulin concentration had been available, then the transformation of this arbitrary value into the true one would have been possible. The initial conditions of compartments 3 and 4 (this last when present) of the computer representation were set as equal to 100.

Figure 3 shows an example of such a calculation.

In order to validate the model the superposition principle was tested: in one case an infusion of 0.8 gm. min^{-1} of glucose was performed as well as the perfusion at the usual rate (0.5 gm. min^{-1}); the values obtained for the constants of figure 2 are in good agreement (case A.M. of group A):

Infusion rate	a	b	w^2	T	C_{inf}	C_{fast}	X_0
0.5	0.0065	0.030	0.00094	202	0.120	0.094	100
0.8	0.0085	0.027	0.00080	223	0.130	0.097	122.

*If one takes the mean values for the normal subjects shown in table 5, then one obtains $X_{\infty} = 133$; $C_{glu} = 0.03$; $V_1 = 12.5$ liters.

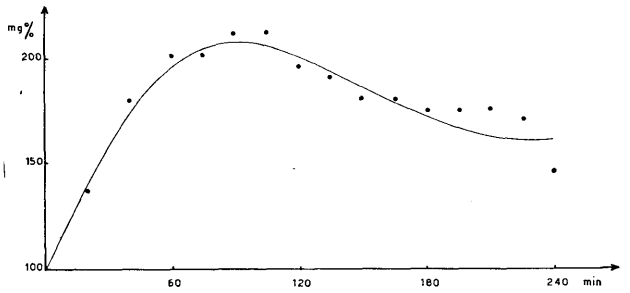


FIG. 3. Example of the fitting obtained from an experiment (case 3 i of table 2): ordinates = glycemia in mg. per cent; abscissae = minutes. The dots correspond to the experimental data, the continuous line represents the curve generated by the computer. The values of the variable parameters, obtained after three iterations, are (in parentheses the standard deviations):
$\lambda_{01} = 0.0989$ (± 0.00478)
$\lambda_{12} = 0.00698$ (± 0.000172)
$\lambda_{10} = 0.00167$ (± 0.00267).
The fixed parameters were:
$\lambda_{21} = -0.07$
$\lambda_{20} = 0.08$.
The initial conditions were: compartment 1 (X_0) = 102; compartment 2 = 100; compartment 3 (introduced to generate the continuous input to compartment 1) = 100. The calculated parameters are shown in table 2. The sum of the squares of the deviations between the found and calculated values, after three iterations is equal to 950, with a sigma equal to 79.

In a similar way the values obtained from an experiment of glucose infusion were compared with those obtained from an experiment of impulsive glucose injection (intravenous dose of 30 gm. of glucose injected rapidly, blood sampled every ten minutes for 110 minutes) (case F.C. of Group A) and solved with the same model:

	a	b	w^2	T	C_{inf}	C_{fast}	X_0
Infusion	0.020	0.022	0.00090	218	0.120	0.049	100
Impulse	0.016	0.036	0.0020	155	—	0.076	100.

It must be noted that in the case of the impulse one obtains directly the value of C_{fast} instead of that of C_{inf}.

The values of the parameters obtained for the several groups of subjects were submitted to the multivariate analysis, in particular to the stepwise discriminant analysis by using the BMD programs (Dixon[17]) and the IBM 7094.)

THE METHOD

Several groups of subjects were infused intravenously (infusion pump: Braun Unita II) with glucose (25 per cent solution) at the rate of 0.5 gm. min^{-1} for

240 to 300 minutes. Blood samples were withdrawn at the following times: 0 (control), 20, 40, 60 min. and thereafter every 15 min. Blood glucose was determined by the method of Folin and the values were expressed in mg. per 100 ml.

The subjects infused with glucose were all in fasting conditions and grouped as follows:

Group A: normal ambulatory subjects (seven subjects, five males and two females aged from twenty to fifty years);

Group B: hospitalized (for diagnostic purposes): five subjects, two males and three females aged from twenty-seven to fifty years;

Group C: diabetic patients: twenty-one cases, five males and sixteen females, aged from nineteen to seventy years.

A fourth group *(Group D)* was formed by nine normal subjects infused intravenously with insulin (soluble insulin Squibb) at the rate of 0.055 U. min^{-1} for 180-240 minutes and sampled as for the other groups. This group is composed of females aged from twenty to fifty-six years.

The diagnosis of diabetes in group C was based on the following criteria: fasting blood glucose levels of 130 mg. per 100 ml. or more, glycosuria, glycemic values during a standard glucose load exceeding accepted criteria for normal subjects. The subjects were on insulin therapy, which was withdrawn twenty-four hours before the test. During the glucose infusion the normal subjects and most diabetic subjects did not show any glycosuria; only a few diabetic patients showed a moderate glycosuria never exceeding three to four grams during the whole test.

The subjects of group B after the first infusion with glucose were treated for ten days with prednisone (25 mg. per day, per os) and infused again with glucose, prednisone having been withdrawn forty-eight hours before.

RESULTS

The values of the parameters obtained by solving the model for the four groups of subjects are shown in tables 1, 2, 3, and 4. The values of group C are partitioned into two subgroups: those that give $b^2 > 0$ and correspond to damped oscillations in the solution of the system of equations (2), and those that give $b^2 < 0$ and correspond to their exponential solution (6).

A stepwise discriminant analysis (BMD Dixon[17]) has been carried out for all the normal values (group A and group B, before treatment) versus the value of the diabetic subjects (group C, subgroup that shows oscillations). Table 5 shows the means and the standard deviations of the values for normal and diabetic subjects and summarizes also the results by indicating the parameters entered at each step (and added to the previous ones), and the F-values in the comparison between the two groups. All the F-values are highly significant at the 0.1 per cent level. The parameter C_{inf} was not entered in the computation because at the last step the F-level was insufficient for further computation. Therefore the parameters shown in the table (b, $b + w^2$, $b + w^2 + C_{fast}$, and so on) give a good discrimination between the two groups.

TABLE 1

Group A

Normal ambulatory subjects

	a	b	w^2	T	C_{inf}	C_{fast}	X_o
M.L.	0.0255	0.020	0.00106	195	0.130	0.107	101
A.V.	0.0099	0.026	0.00072	231	0.094	0.074	104
Z.L.	0.0180	0.031	0.00130	174	0.141	0.121	101
G.B.	0.0112	0.029	0.00083	215	0.093	0.073	88
F.C.	0.0205	0.022	0.00090	218	0.120	0.049	100
M.M.	0.0135	0.030	0.00111	190	0.106	0.090	91
A.M.	0.0065	0.030	0.00094	202	0.120	0.120	100

a = damping constant

b = free frequency

w = natural frequency

T = natural period

C_{inf} = fractional input to compartment *1* when glucose is infused

C_{fast} = fractional input to compartment 1 in fasting condition

X_o = initial glycemic value.

TABLE 2

Group B

Effect of prednisone treatment on subjects hospitalized for diagnostic purposes*

		a	b	w^2	T	C_{inf}	C_{fast}	X_o
1	i	0.0265	0.020	0.00111	190	0.150	0.126	115
	ii	0.0096	0.024	0.00065	250	0.106	0.065	100
2	i	0.0146	0.026	0.00088	215	0.120	0.099	100
	ii	0.0093	0.024	0.00059	260	0.104	0.069	106
3	i	0.0093	0.022	0.00057	260	0.099	0.058	102
	ii	0.0089	0.020	0.00049	284	0.100	0.048	100
4	i	0.0192	0.033	0.00074	232	0.150	0.085	115
	ii	0.0064	0.021	0.00049	284	0.092	0.053	119
5	i	0.0100	0.016	0.00067	240	0.107	0.070	106
	ii	0.0115	0.022	0.00065	250	0.102	0.067	102

i = before prednisone treatment

ii = after prednisone treatment

*All the patients were in good general condition without either metabolic disorders or fever. For the symbols see table 1.

TABLE 3

Group C

Diabetic patients

	a	b	w^2	T	C_{inf}	C_{fast}	X_o
With oscillations							
Go	0.0090	0.0030	0.00009	660	0.050	0.021	232
Qu	0.0200	0.0077	0.00046	291	0.103	0.091	200
Pa	0.0075	0.0069	0.00010	615	0.131	0.007	140
Dap	0.0087	0.0014	0.00008	712	0.144	0.010	140
Ti	0.0078	0.0026	0.00007	765	0.049	0.024	352
Fi	0.0036	0.0106	0.00012	560	0.032	0.017	137
Ba	0.0035	0.0020	0.00002	999	0.032	0.003	180
Ma	0.0035	0.0020	0.00002	999	0.026	0.003	207

Without oscillations	a	$-m_1$	$-m_2$	C_{inf}	C_{fast}	X_o
Bi	0.0661	0.1239	0.0083	0.032	0.016	198
Bu	0.0175	0.0174	0.0176	0.076	0.029	172
Si	0.0068	0.0116	0.0020	0.056	0.030	133
Ma	0.0056	0.0017	0.0085	0.042	0.034	245
Br	0.0113	0.0179	0.0047	0.072	0.029	140
Bia	0.0180	0.0300	0.0060	0.100	0.079	198
Ra	0.0112	0.0090	0.0134	0.053	0.033	245
Va	0.0416	0.0550	0.0270	0.054	0.041	177
Ras	0.0255	0.0360	0.0150	0.089	0.025	185
Co	0.0237	0.0322	0.0152	0.055	0.025	166
Na	0.0078	0.0124	0.0034	0.075	0.061	157
Li	0.0135	0.0182	0.0088	0.071	0.028	170
Fo	0.0490	0.0780	0.0200	0.096	0.062	280

For the symbols see table 1, for the meaning of the two exponents $-m_1$ and $-m_2$ see equation **6.**

TABLE 4

Group D

Normal subjects infused intravenously with insulin*

	a	b	w	T	C_{fast}	k_{02}	X_o
Bo	0.0246	—(†)	0.00420	96	0.072	0.0097	108
Dc	0.0171	0.027	0.00101	195	0.088	0.0010	98
Tm	0.0172	—(†)	0.00028	368	0.077	0.0091	115
Nm	0.0414	0.013	0.00161	157	0.150	0.0043	105
Lg	0.0375	0.010	0.00032	347	0.081	0.0088	104
Po	0.0157	—(†)	0.00025	392	0.070	0.0095	82
Rl	0.0157	0.025	0.00080	223	0.087	0.0043	115
Cc	0.0131	0.039	0.00274	120	0.123	0.0100	93
Pl	0.0341	0.022	0.00191	146	0.150	0.0010	70

*For the symbols see table 1 and figure 1.
†Too small to be determined with confidence.

The evaluation of the effect of prednisone treatment in group B (table 2) evidently cannot be obtained through the discriminant analysis between two groups, but it is necessary to resort to the Student t test; by this procedure, only the differences in the parameter a and C_{fast}, respectively equal to 2.8 and to 2.7, reach the level of statistical significance ($t = 2.78$ for $P = 0.05$).

Table 6 shows the results of the discriminant analysis between the effect of glucose infusion and the effect of insulin infusion in normal subjects.

TABLE 5

Discriminant analysis between normal subjects and diabetic patients*

	a	b	w^2	T	C_{inf}	C_{fast}	X_o	
Normal subjects (formed by the cases of group A and group B before treatment)								
Means	0.01539	0.02542	0.00090	203.5	0.11942	0.08933	101.92	
Standard deviations	0.00654	0.00535	0.00021	24.64	0.02035	0.02558	7.91	
Coefficients for the discriminant function	816	1759	15552	0.06	—	29.4	0.04	—45.48 (constant)
Diabetic patients								
Means	0.00795	0.00452	0.00012	700.12	0.07087	0.02200	198.50	
Standard deviations	0.00542	0.00341	0.00014	232.65	0.04773	0.02899	71.44	
Coefficients for the discriminant function	973	1159	—11495	0.06	—	129	0.06	—37.52 (constant)

Discriminant analysis

Step	Parameter entered	F-value	Degrees of freedom
1	b	95	1,18
2	w^2	64	2,17
3	C_{fast}	43	3,16
4	T	32	4,15
5	a	24	5,14
6	X_o	19	6,13

*For the symbols see table 1.

TABLE 6

Comparison of glucose and insulin infusion effect on the parameters in normal subjects*

	a	w^2	T	C_{fast}	X_o
Glucose infusion					
Means	0.01539	0.00090	213.5	0.08933	101.9
Standard deviation	0.00654	0.00021	24.64	0.02558	7.91
Insulin infusion					
Means	0.02394	0.00146	227.11	0.09978	98.89
Standard deviation	0.01092	0.00133	113.25	0.03243	15.09

Discriminant analysis

Step	Parameter entered	F-value	Degrees of freedom
1	a	4.4	1.19
2	w^2	2.7	2.18
3	T	5.3	3.17
4	C_{fast}	4.5	4.16
5	X_o	3.4	5.15

For the symbols see table 1.

DISCUSSION

The model used in the present work, even if oversimplified, can afford interesting numerical data for the physiopathological interpretation of blood glucose regulation. It is known that either glucose kinetics and insulin kinetics require more than one compartment each (Farquhar et al.,[19] Segal et al.,[32] Berson et al.[10]); however the lumping of these compartments into one compartment for glucose and one for insulin is compatible with the experimental data of blood glucose levels during glucose infusion. The model of figure 1 fits the experimental data quite well and is supported by a series of considerations; the validity of the superposition principle, the fitting of the impulsive glucose data, the validity of the model also for insulin infusion. The model implies that glucose infusion elicits an increase of blood insulin levels; this has been experimentally observed (Yalow et al.[34,35]) as well as a rapid release of insulin by isolated pancreas in response to a pulse of glucose (Grodsky et al.[25]).

We tried also to fit the data to the following mathematical model

$$\begin{cases} dX_1/dt = -k_{10}X_1 - k_{21}X_1X_2 + C_{inf} \\ dX_2/dt = k_{12}X_1X_2 - k_{20}X_2 \end{cases}$$

instead of system (2); the goodness of fit of the data to this nonlinear model with the SAAM program is satisfactory, but the meaning of the parameters corresponding to this system of equations is not equally obvious and the nonlinear model does not seem to give distinctive advantage over the linear one, which was therefore preferred in the analysis.

Whereas the model employed in the present work corresponds to that of Ceresa et al.,[15,16] of Ackerman et al.,[1-5] and of Bolie,[11] it shows distinctive features with respect to that of McLean[28] and of Seed et al.[31] The diagram drawn by McLean[28] to depict the processes which take part to glucose regulation is a complex diagram that cannot be amended to a form useful for practical applications; the model of Seed et al.[31] cannot fit the experimental data of blood glucose being formed by four compartments and having therefore too many degrees of freedom; moreover in this model insulin does not enter as a member of the negative feedback, whereas there is conclusive evidence for assigning to this hormone such a role. In the present work, during the fitting procedure of the data to the model the small oscillations of the glycemic curves that were taken into account in previous papers[15,16] were disregarded.

The model employed by Cerasi[12] to study the insulin response to glucose infusion after a priming dose of glucose differs from ours mainly because the release of stored insulin is distinct from the release of the newly formed insulin and because the effect of glucose uptake by the tissues on glucose pool is delayed.

The values of the parameters obtained by solving the model of figure 1 agree with the figures which can be found in other works; for instance, in normal subjects the value of a is equal to 0.015; now within the approximation $k_{10} \simeq k_{20}$, and therefore $a \cong k_{10}$ (see "The Model") such a value of a agrees with that of Ooms et al.[29] for the utilization coefficient of glucose, obtained with labeled glucose, and which is equal to 0.018. The values that Ackerman et al.[1] reported for the parameters of their model in a normal case agree with the values shown in table 5 for normal subjects, being $a = 0.014$; $b = 0.04$; $w^2 = 0.0019$.

Our model implies that in diabetes the feed-back mechanism between compartments 1 and 2 could be impaired; this corresponds to the conclusion reached by Yalow et al.[35] by studying the insulin response to glucose load.

Moreover our model permits one to assess the effect of a prednisone treatment, which is employed for detecting the prediabetic states (Fajans[18]); such a treatment brings about a change of some of the parameters of the model (see table 2) which is directed toward the values observed in the diabetic subjects, that is a decrease of

the parameter *a*, a decrease of C_{fast} and an increase of *T* (this last change is however of poor statistical significance). The model of figure 1 suggests many possible mechanisms for an impairment of blood glucose control: a change of each transfer constant of the model could bring the system from a state of efficient control to a state of severe impairment. The two subgroups of diabetics of table 3 show an example of such changes; in the first subgroup, where glucose oscillations still exist a change of some transfer constants leads to a decrease of *a* and to an increase of *T* that corresponds to a longer oscillation period with the attainment of higher glucose levels; the extreme cases of this subgroup pass into the second subgroup where $b^2 < 0$ and the control fails, no oscillations can be seen, and the glycemia during the infusion attains very high levels, with glycosuria. Because of the noteworthy glycosuria and probably because of the high value of k_{20} (due to the higher levels of blood insulin shown generally by these cases) (Yalow et al.[34]) the value of *a* is higher than in the previous group and attains levels near the group of normal subjects (Group A and B).

The value of *a* reaches high levels in group D, and this finding agrees with the known effect of insulin on glucose utilization. This increase of *a* is of prominent importance in separating the insulin infusion group from the glucose infusion group (table 6), the other parameters being not too different.

The discrimination between normal and diabetic patients is based firstly on the sign of b^2. If negative, then no oscillations occur in the glycemic curves during glucose infusion. In this case, because of the fact that the solution of system (2) has a different analytical form, the discrimination is self evident; if b^2 is positive, then a discriminant analysis between normal and diabetic subjects may be carried out as shown in table 5, which indicates also that parameter *b* is the most important in the discrimination. The discrimination of the two groups permits one to assign to each group all the cases belonging to it. Figure 4 shows the plot of the two groups of cases of table 5 when the variables are transformed into the canonical ones; the plot indicates that the separation of the two groups is fairly good.

In conclusion it is possible to state that even the very simplified model of figure 1 can provide a theoretical framework by which the experimental data of blood glucose after glucose and insulin infusion and after glucose impulsive injection can be interpreted and by which a discrimination between normal and diabetic subjects can be carried out. Moreover the model permits one to foresee a more subtle clinical classification of diabetic cases and clarifies some of the physiopathological mechanisms that play a role in this disease.

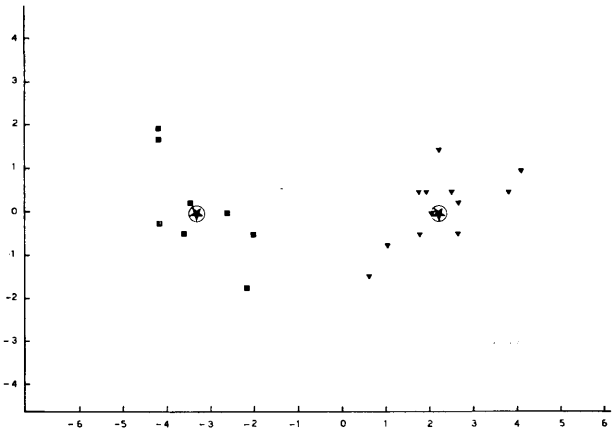


FIG. 4. Plot of the normal and of the diabetic cases obtained with the discriminant analysis and the transformation of the parameters into two canonical variables (the ordinates and the abscissae).
▲ normal subjects; ■ diabetic patients; circled star = mean of each group.

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