Quantitative estimation of insulin sensitivity

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BERGMAN, RICHARD N., Y. ZIYA IDER, CHARLES R. BOWDEN, AND CLAUDIO COBELLI. *Quantitative estimation of insulin sensitivity.* Am. J. Physiol., 236(6): E667–E677, 1979 or Am. J. Physiol.: Endocrinol. Metab. Gastrointest. Physiol. 5(6): E667–E677, 1979.—We have evaluated the feasibility of using a mathematical model of glucose disappearance to estimate insulin sensitivity. Glucose was injected into conscious dogs at 100, 200, or 300 mg/kg. The measured time course of insulin was regarded as the "input," and the falling glucose concentration as the "output" of the physiological system storing and using glucose. Seven mathematical models of glucose uptake were compared to identify the representation most capable of simulating glucose disappearance. One specific nonlinear model was superior in that it *1*) predicted the time course of glucose after glucose injection, *2*) had four parameters that could be precisely estimated, and *3*) described individual experiments with similar parameter values. Insulin sensitivity index (S_I), defined as the dependence of fractional glucose disappearance on plasma insulin, was the ratio of two parameters of the chosen model and could be estimated with good reproducibility from the 300 mg/kg injection experiments ($S_I = 7.00 \times 10^{-4} \pm 24\%$ (coefficient of variation) $min^{-1}/(\mu U/ml)$ ($n = 8$)). Thus, from a single glucose injection it is possible to obtain a quantitative index of insulin sensitivity that may have clinical applicability.

carbohydrate metabolism; glucose homeostasis; mathematical modeling; system identification

IN RECENT YEARS, several new techniques have been introduced to quantify the influence of decreased peripheral insulin sensitivity on the impairment of the patient's ability to tolerate a standard glucose load. These techniques allow for observation of the relationship between insulin and glucose utilization under conditions, in which the usual effect of glucose on the β-cells is prevented. This interaction is prevented either by suppression of insulin release by a combined infusion of glucose, epinephrine, and propranolol ("pancreatic suppression test" (PST) (22, 24, 27)) or by manual stabilization of the blood glucose concentration by variable glucose infusion ("glucose clamp" (19, 28)). The PST and glucose-clamp techniques present sizable technical problems and are not likely to achieve widespread use for the estimation of insulin resistance.

In these studies, we are examining the feasibility of a new alternative technique for estimating peripheral insulin sensitivity. This new method involves only frequent sampling of peripheral plasma after an intravenous glucose injection (intravenous glucose-tolerance test, IVGTT) and is therefore less invasive than the PST or clamp methods. The measured time course of plasma insulin concentration is viewed as the "input" and the plasma glucose concentration as the "output" of the system regulating glucose disappearance. From a set of seven proposed mathematical models, one model has been chosen that, according to specific criteria, is the "best" representation of glucose kinetics (KG). The parameters of the model can be estimated from a single IVGTT, and the parameters provide an explicit, quantitative estimate of the insulin sensitivity of the tissues of a given subject.

METHODS

Animal Experiments

Thirteen intravenous glucose tolerance tests (IVGTT) were performed on five mongrel dogs, which weighed between 20.0 and 29.8 kg. Nine experiments on two dogs were used for model comparison; four additional experiments on three other animals were used for estimates of insulin sensitivity (see RESULTS). Under sterile conditions, a polyvinyl chloride catheter was inserted into the right atrium of each dog through the jugular vein. The catheter was filled with sterile heparinized saline and capped. Chronic, indwelling jugular catheters were checked at frequent intervals for patency and were used for injection of glucose and subsequent blood sampling. Dogs were maintained in a controlled kennel environment and were fed Purina dog chow. The animals were fasted overnight before the glucose injections. During the experiments, the animals were conscious and relaxed and were resting on a warm laboratory bench. Experiments consisted of a single injection (over a 1-min period) of a low (100 mg/kg), intermediate (200 mg/kg), or high (300 mg/kg) dose of glucose (α-D-glucose, Mallinkrodt) followed by blood sampling beginning 1.5 min later, at intervals of 1 min or more for a 60-min period. The catheter was flushed with sufficient saline after glucose injection to prevent possible contamination of samples by the injectate. Thirty-two blood samples were collected in each experiment: samples were taken every minute from 1.5 to 17.5 min, every 2.5 min until 50 min, and at 55 and 60 min after injection. Sampling tubes containing

NaF were quickly centrifuged to separate plasma, which was frozen for later measurement of glucose and insulin. Plasma glucose was measured in duplicate on the Beckman glucose analyzer; insulin was measured by radioimmunoassay according to the Herbert technique (17) against a porcine insulin standard. Assay statistics were as follows: coefficients of variation; glucose (± 1.5%), insulin (± 7%).

Data Analysis

A series of distinct mathematical models of utilization was proposed (see MODELS AND RATIONALE) to account for the effect of the changing plasma glucose and insulin on the glucose-disappearance curves. Glucose was represented as the measured value and insulin as the deviation from the preinjection basal value. Parameter values were estimated by using the nonlinear least-squares technique of Marquardt (21). Some models of glucose utilization were insulin dependent. In such cases the insulin data were supplied to the estimation algorithm (together with initial estimates of the parameters) and the time course of glucose concentration was predicted. It was assumed, for purposes of estimation, that the basal values of glucose and insulin were reestablished by 120 min. The goodness-of-fit of a given model was described, as usual, in terms of the sums of squares of the differences between the observed and predicted values (SS_R; see Ref. 3). In addition, SS_R was compared with the estimated contribution of error in glucose measurement (SS_M). Errors in glucose measurement were assumed to be independent and Gaussian, with 0 mean, and with a total measurement error of 2.0%. Errors in insulin measurement were not explicitly considered. The estimation algorithm provided, together with parameter values, an evaluation of parameter precision. (The precision of estimation of an individual parameter for a given model for one experiment is provided by the diagonal elements of the covariance matrix (inverse of the information matrix) that is calculated along with parameter estimation (15).) We considered a parameter to be nonidentifiable if the fractional standard deviation of the parameter estimates (when fitting a single experiment) exceeded 100%.

Along with other criteria for comparing models, we applied the criterion of Akaike (4) to compare the ability of three linear models to simulate the glucose data (*I*, *IV*, *V*; see MODELS AND RATIONALE). This criterion simultaneously takes into account the relative contributions of goodness-of-fit and the number of parameters in evaluating the worth of competing model structures. For a given model and a single experiment, this criterion is calculated as

$$\tfrac{1}{2}\text{AIC} = (N/2) \ln SS_R + n \qquad (1)$$

where N is the number of data points, n is the number of estimated parameters, and ½AIC is the variable of Akaike (4).

RESULTS

Glucose Injection

Nine experiments were used for model evaluation: four at the highest dose, two at the intermediate, and three at the low dose (Table 1). Glucose and insulin values (for 3 experiments only; *animal 1*) are shown in Fig. 1. At each dose, the glucose values are plotted on the upper panel; for comparison, the insulin curves, which differed markedly from each other, are plotted below. At the initial sampling time, 1.5 min after the injection, the glucose values were maximal: 259 ± 11, 236 ± 8, and 171 ± 10 (SE) mg/dl at the three doses (Table 1). At 5.5 min after the beginning of injection, glucose had fallen to 200 ± 6, 158 ± 1, and 125 ± 5 mg/dl, respectively, values at or near the renal threshold (26).[1] There was an average 38 ± 4 mg/100 ml increase in plasma glucose at 5.5 min, per 100 mg/kg injected, and the dose-response relationship was approximately linear ($r = 0.96$).

TABLE 1. *Dynamic responses to intravenous glucose injection used for model comparison*

Expt	Animal	Glucose Concn, mg/dl: Basal glucose	Initial sample	Initial sample for analysis	First return to basal, min	Final return to basal, min
Dose, 300 mg/kg						
4	1	83	252	196	21	46*
5	1	93	261	202	26	58.5*
6	1	82	236	187	26	53.5*
10	2	80	288	217	26	58.5*
Mean ± SE		85 ± 3	259 ± 11	200 ± 6		
Dose, 200 mg/kg						
7	1	87	243	159	41	
14	2	75	228	157	26	58.5*
Mean ± SE		81 ± 6	236 ± 8	158 ± 1		
Dose, 100 mg/kg						
8	1	86	190	128	23.5	28.5*
9	1	85	166	133	53.5	
12	2	78	158	115	23.5	43.5*
Mean ± SE		83 ± 3	171 ± 10	125 ± 5		

Values are means ± SE. Glucose was injected and the initial sample was 1.5 min later ($t = 0$). Initial sample for analysis was taken at $t = 4$ min. * Experiments in which glucose transiently receded and returned to the final value ("undershoot").

Following the initial peak, glucose concentration fell rapidly, reaching the basal value by 27.5 min. In two experiments (*7* and *9*) no undershoot in the glucose concentration was observed.

In contrast to the rather similar and well-behaved nature of the glucose response, insulin responses were extremely variable (Fig. 1) although the well-known "early peak" (12) was usually observed. However, multiple peaks in insulin were frequently observed, particularly at the high and intermediate doses of glucose. In no case did the first peak in plasma insulin occur before 2.5

[1] Although urine glucose was not measured, it was assumed that significant glucose would not spill during the short period glucose exceeded the expected T_{max} (at the highest dose) after 5.5 min, and disappearance of glucose via renal excretion was not included in any of the 7 models evaluated.

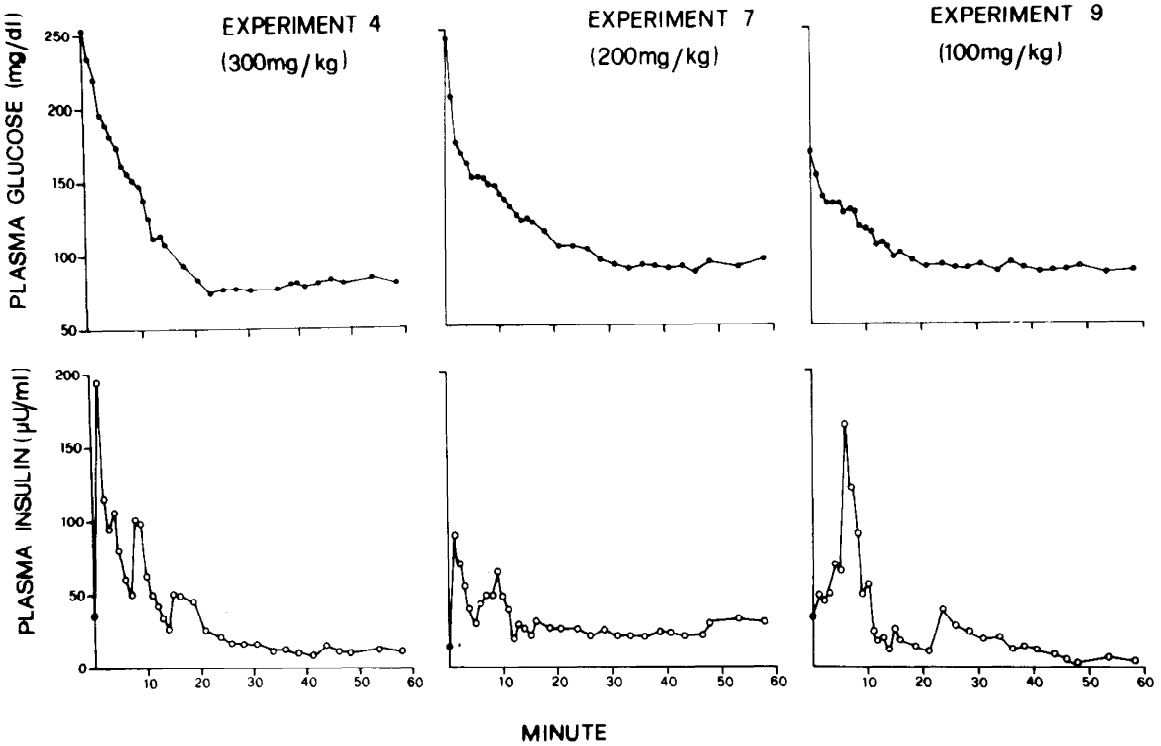

FIG. 1. Responses of plasma glucose and insulin to 3 glucose doses in a single dog. Injection was begun at −1.5 min and lasted about 1 min. Glucose samples at 1, 2, and 3 min were not used for analysis; all insulin values were used. Insulin is plotted below as it is viewed as input to system producing and utilizing plasma glucose.

min although the glucose concentration was invariably already in decline. Also, in most cases, plasma insulin returned to the preinjection value while glucose was still elevated, and a clearly defined insulin undershoot was not generally evident. There was a significant correlation between the integrated insulin response ($\int_{1.5}^{60} I(t)dt$) and the dose of glucose injected ($r = 0.81$, $P < .01$).

MODELS AND RATIONALE

Alternative Structures

Seven distinct models of glucose uptake were proposed to account for the observed glucose kinetics (Table 2, Figs. 2 and 3). The structures were carefully chosen to allow for comparison between classical models and alternative propositions and to establish the limitations of the systems-identification approach in quantifying physiological parameters of glucose regulation.

To evaluate the importance of insulin as a factor in determining the kinetics of glucose disappearance, we examined three models in which glucose disappearance was dependent on glucose only. The results from these models could then be compared with the remaining four models (*IV–VII*) that assume explicit relationships between insulin, glucose, and glucose fluxes. Thus, for estimating parameters for *models IV–VII,* the (measured) time course of insulin was supplied as a model input.

The seven models depicted in Figs. 2 and 3 and summarized in Table 2 are described as follows.

Insulin-Independent Models

Model I. It is assumed in this model that glucose production is constant, that glucose distributes in a single compartment, and that the rate of glucose utilization is a linear function of the plasma glucose concentration. Thus, the parameter k_1 in this model (Fig. 2) represents the classical diagnostic glucose disappearance term KG, which is obtained from a semilogarithmic plot of glucose disappearance kinetics. The success of this model is therefore related to the acceptability of KG as a measure of the glucose disappearance rate.

Model II. This model is identical to *model I,* except that glucose utilization is a saturable process that obeys Michaelis-Menten kinetics and depends on the plasma glucose concentration.

Model III. The third model assumes two-compartment glucose distribution. Disappearance from either compartment is linearly dependent on glucose concentration in that compartment. Glucose production is constant. Multicompartmental glucose distribution has been widely suggested (cf. Refs. 19 and 23).

TABLE 2. *Models of glucose utilization*

Model	Insulin Dependence	Compartments		Linear	Total Parameters
		Glucose	Insulin		
I	0	1	0	Yes	3
II	0	1	0	No	4
III	0	2	0	Yes	5
IV	+	1	1	Yes	4
V	+	1	2	Yes	5
VI	+	1	2	No	5
VII	+	1	2	No	6

Structures of the 7 models are shown in Figs. 2 and 3. Of the total parameters for each model, one is the estimated initial condition for glucose; the remainder are related to the structure of the system modeled in each case.

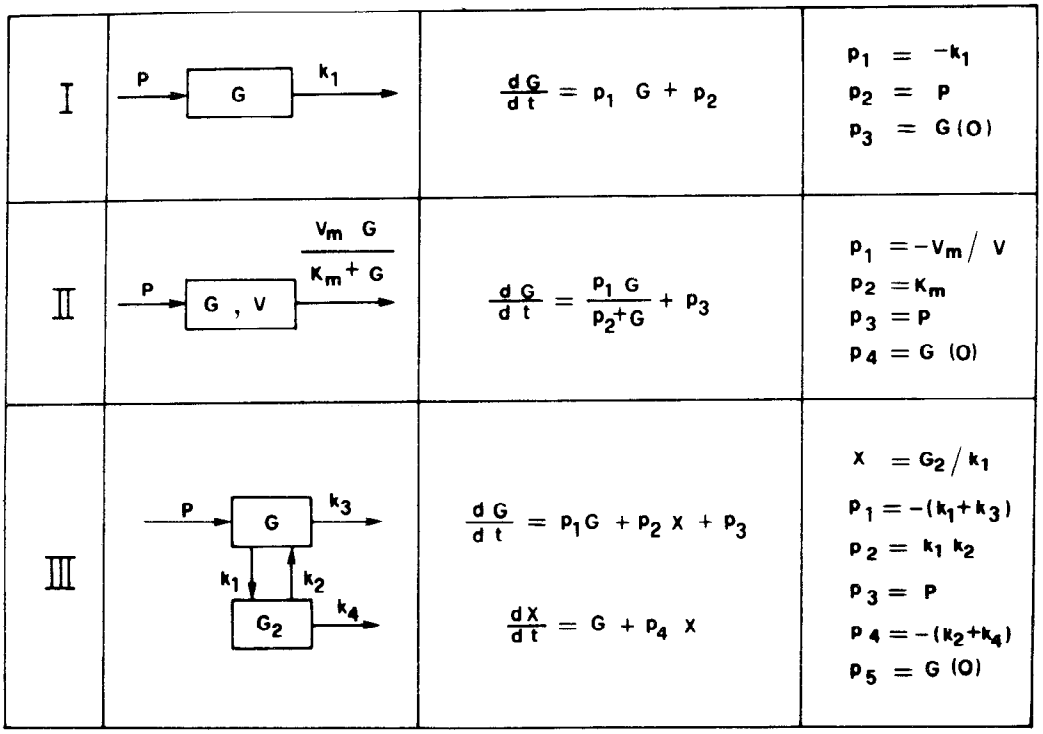

FIG. 2. Three proposed insulin-independent models of glucose metabolism. *Left panel:* proposed structure; *middle panel:* mathematical representation when parameters are defined as shown on *right*. Values of k represent fractional turnover rates (min^{-1}); P, hepatic glucose production; V, glucose space, and V_{max} and K_m, Michaelis-Menten parameters. G(0) is glucose concentration that would obtain immediately after injection assuming no dynamics of mixing in glucose space.

Insulin-Dependent Models

Model IV. Glucose disappearance in this model is linearly dependent on both the plasma glucose and insulin concentrations. Glucose distributes in a single compartment, and the production is assumed constant. The relationships among insulin, glucose, and glucose disappearance used in this model were first proposed by Bolie (10), and have been assumed in a substantial fraction of those studies that have used system identification to analyze glucose kinetics for clinical purposes (1, 2, 10, 13, 14, 25). The extent of success of *model IV* to account for disappearance relates to the potential applicability of the Bolie (10) model (and its descendants) for purposes of diagnosis.

Model V. This model assumes that glucose uptake is directly dependent on the concentration of insulin, not in plasma, but in a second compartment of insulin distribution remote from plasma. This proposition is based on the studies of Insel and his colleagues (19, 28) and is consistent with the existence of a remote receptor pool that is intimately involved in the action of insulin (30). In this model insulin (I(t)) enters the remote compartment (I′), and I′ increases glucose disappearance in a linear, independent fashion. Glucose also accelerates its own disappearance independent of insulin, and glucose production is constant.

In *models I* through *V* glucose production was assumed to be constant at all times. Because it has long been known that insulin inhibits glucose production, we introduced *models VI* and *VII* (see below), in which this interaction was included. Two approaches were used. In *VI,* glucose production and hepatic glucose uptake were lumped together as net hepatic glucose balance. In *model VII* an alternative approach was used, i.e., hepatic and peripheral glucose utilization were lumped together, and absolute glucose production (R_a (cf. Ref. 18)) was represented explicitly.

Model VI. In this model, the rate of change of glucose is the difference between the net hepatic glucose balance, B (which may take on positive (production) or negative (uptake) values), and the disappearance of glucose into peripheral tissues only (U_p). We have previously shown that hepatic glucose balance varies according to a relation of the form (8):

$$B = B_o - (k_5 + k_6 I')G \qquad (2)$$

where B is net glucose balance; and B_o is the net balance expected when plasma glucose concentration is extrapolated to 0 (see Fig. 5, Ref. 8). It is assumed that the insulin acts from a remote compartment, as in *model V.*

For glucose utilization we may write a similar expression

$$U_p = (k_1 + k_4 I')G \qquad (3)$$

where "remote" insulin is envisioned to increase the mobility of glucose across the cell membrane, and this motility potentiates glucose disappearance.

Model VII. In this model, we explicitly represented "absolute" hepatic glucose production (R_a) and the inhibition of this rate by remote insulin. Utilization (which, in this case, includes hepatic and peripheral) is described by a similar nonlinear function as in *model VI.*

COMPARISON OF MODELS I–VII

Criterion 1: Identifiability

Each of the seven models was individually fitted to the

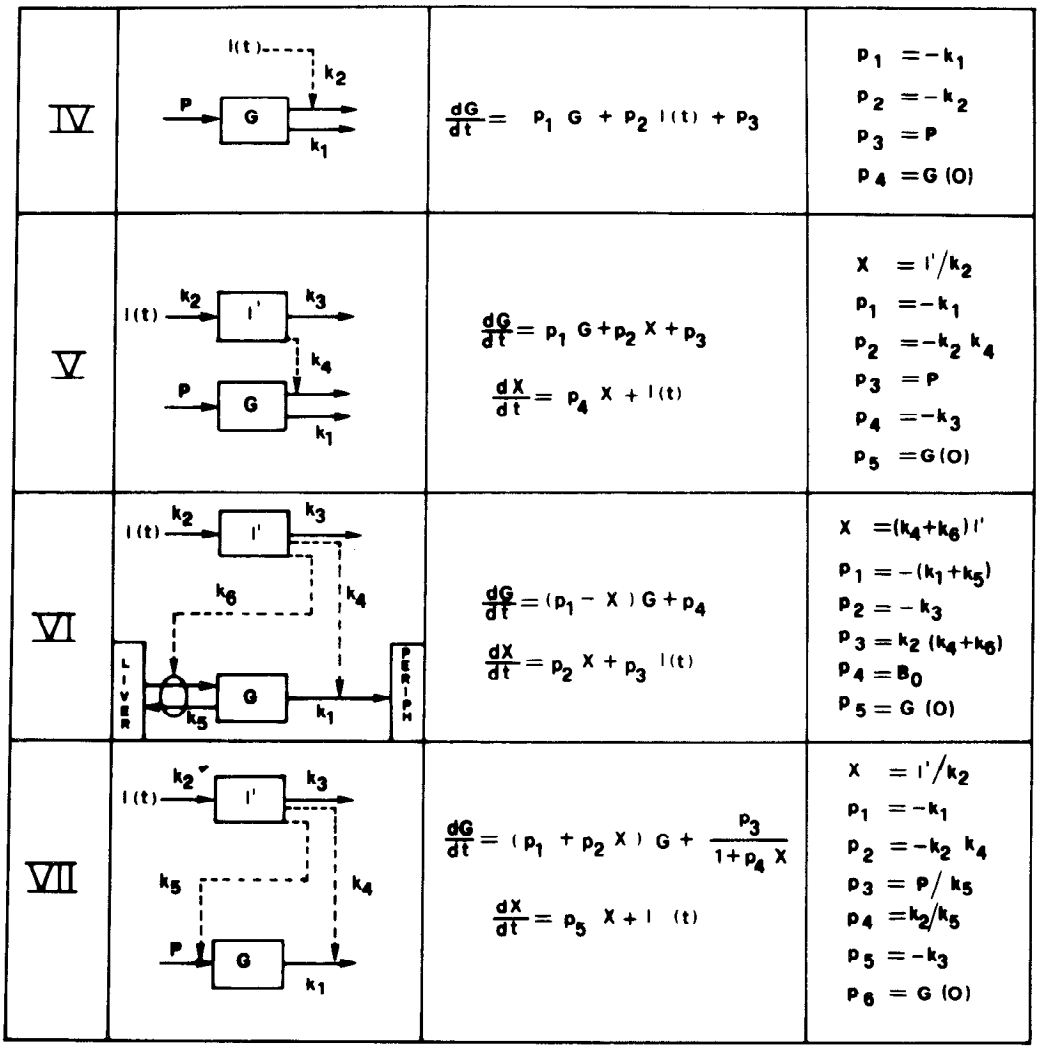

FIG. 3. Four proposed insulin-dependent models of glucose metabolism. I(t), time course of plasma insulin supplied to model; I', concentration of insulin in a compartment remote from plasma. Equations for *model VI* are derived as described in text. B_o, extrapolated hepatic glucose production at 0 glucose concentration.

nine experiments by using parameter estimation as described in METHODS. Parameters of *models II* and *VII* were clearly not identifiable (Table 3) as indicated by the great uncertainty in the estimates of the parameters. All three characteristic parameters of *model II* and three of the five characteristic parameters of *model VII* could not be estimated within 100% of the parameter value. These models were therefore eliminated from further consideration. One parameter of *model III* was not identifiable (p_1); however, because the remaining parameters of *model III* could be estimated, this model was not removed from consideration at this stage. The mean estimates of the parameters for the five remaining models for all nine experiments are given in Table 4.

TABLE 3. *Accuracy of parameter estimates*

Model	Identifiability	Fractional Standard Deviation of Estimate,† %					
		p_1	p_2	p_3	p_4	p_5	p_6
I	Yes	6	7	3†			
II	No	203	306	213	3†		
III	?	367	63	22	43	5†	
IV	Yes	34	22	27	4†		
V	Yes	32	54	32	48	4†	
VI	Yes	73	58	65	67	5†	
VII	No	35	233	36	343	156	16†

* Average for 9 experiments. † Represents initial condition (G(0)); not a characteristic parameter of the model.

Criterion 2: Meaning of Parameters

It was important to consider whether the estimated parameters of the remaining models could be interpreted in a physiologically meaningful way. Close comparison of the estimates shown in Table 4, with the definition of parameters in Figs. 2 and 3, shows that in the case of *model III* the estimated value of one parameter is physiologically absurd. Parameter p_2 of *model III* was negative for all nine experiments, and its value ($-1.25 \pm 0.44 \times 10^{-2}$) was significantly less than 0 (df = 8; $t = -2.85$; $p < 0.025$). A negative p_2 implies that, as glucose increases in the remote compartment, it will decrease the mass flux from G_2 to G, in violation of the law of mass action. This paradoxical prediction of *model III* results from the fact that the role of insulin was ignored in this model, and the inverse dependence on G_2 of $G \rightarrow G_2$ flux compensates for the absence of consideration of the time-dependent insulin effects on glucose utilization.

TABLE 4. *Parameters for identifiable models*

Model	p_1	p_2	p_3	p_4	p_5
I	−1.09 ±0.11 (10^{-1}, SE)	8.5 ±1.10			
III	1.87 ±4.6 (10^{-2})	−1.25 ±0.44 (10^{-2})	9.21 ±1.06	−1.97 ±0.71 (10^{-1})	
IV	−1.44 ±0.35 (10^{-1})	9.15 ±4.0 (10^{-2})	11.3 ±3.1		
V	−6.50 ±0.73 (10^{-2})	−9.10 ±1.73 (10^{-3})	5.97 ±0.70	−1.01 ±0.16 (10^{-1})	
VI	−4.90 ±0.97 (10^{-2})	−9.10 ±1.20 (10^{-2})	8.96 ±1.88 (10^{-5})	4.42 ±0.74	

Final parameter for each model (e.g., p_3 in *model I*) represents the initial glucose concentration and will therefore be expected to vary between doses. This parameter is therefore not reported as this table represents variation between doses.

TABLE 5. *Goodness-of-fit of reasonable models*

Expt	SS_M	SS_R and $\sqrt{SS_R/SS_M}$			
		I (3)	*IV* (4)	*V* (5)	*VI* (5)
High dose					
4	152	1,382	770	426	561
		3.01	2.25	1.67	1.92
5	182	1,163	694	309	398
		2.53	1.90	1.30	1.48
6	157	770	631	336	377
		2.21	2.00	1.46	1.55
10	165	688	418	435	451
		2.04	1.59	1.62	1.65
Intermediate dose					
7	156	361	238	160	159
		1.52	1.24	1.01	1.01
14	119	417	255	146	156
		1.87	1.46	1.11	1.14
Low dose					
8	108	248	139	152	164
		1.52	1.13	1.19	1.23
9	119	196	101	170	167
		1.28	0.92	1.20	1.18
12	88	491	454	166	168
		2.36	2.27	1.37	1.38
Mean $\sqrt{SS_R/SS_M}$ ± SE		2.04 ±0.18	1.6 ±0.16	1.33 ±0.08*	1.39 ±0.10*

Measurement error, SS_M, was computed by assuming an individual coefficient of variation of 2%. This estimate exceeded assay measurements alone (1.5%) because of possible variations due to sampling time, contamination between samples, and system noise. Numbers in parentheses are numbers of experiments. * Significantly better (lower) than for *models I* and *IV* (paired *t* test; see text).

A second paradox is the positive sign of p_2 in *model IV*. This implies that an increase in insulin should decrease glucose uptake. Because p_2 is not significantly greater than 0 at the $P < 0.05$ level (df = 8; $t = 0.92$, $P > 0.1$), we do not reject *model IV* at this stage because of the inconclusive positiveness of this parameter.

Criterion 3: Goodness-of-Fit and Number of Parameters

At this stage of model selection we are left to consider the abilities of *models I, IV, V,* and *VI* to predict glucose kinetics either without (*model I*) or with (*IV, V, VI*) the time course of insulin supplied. These four models could be identified with reasonable parameters of acceptable precision. Table 5 reports the total sums of squares (SS_R) for the four models and for each of the nine experiments. Also reported is $\sqrt{SS_R/SS_M}$, an index of how closely the model can fit the data, given the estimated measurement error (see METHODS). *Models V* and *VI* were able to predict the kinetics of glucose better than either *model IV* ($P < 0.025$ and $P < 0.05$, respectively) or *model I* ($P < 0.0005$; both models, paired *t* tests).

It was of interest to ask whether the improvement in fit in *models V* and *VI* was obtained at the expense of an increase in the number of estimated parameters, *n*. The criterion of Akaike (4) has been recently proposed for comparing models with respect to both the goodness-of-fit and number of estimated parameters (see METHODS). The nonlinearity of *model VI* prevents us from applying Akaike's criterion (4) without redefining the maximum likelihood function; however, we are able to apply it directly to compare *models I, IV,* and *V* (Table 6). The criterion is significantly lower in *model V* than for either *model I* (df = 8; t, = 5.21; $P < 0.005$) or *IV* (df = 8; t, = 1.86; $P < 0.05$); therefore, the improvement in fit in the five-parameter model is obtained not just because of an increase in *n*, but because *model V* is a more likely representation of the structure of the real physiological system than either *model I* or *IV*. Because *models V* and *VI* have the same number of parameters and the mean values of the index $\sqrt{SS_R/SS_M}$ for the five-parameter models were equivalent, we proceed on the assumption that the improvement in goodness-of-fit for *VI* was due to a genuine improvement of the model. A definitive proof of this assumption would require further investigation of the nonlinear case.

Model Comparison: Summary

Only *models V* and *VI* appear acceptable in terms of providing meaningful parameter estimates (Table 7). Given this similarity, we compare *models V* and *VI* from a physiological viewpoint. *Model VI* (like the rejected

TABLE 6. *Comparison of acceptable linear models (I, IV, V)* by criterion of Akaike

Model	Parameter No.	Akaike Criterion (½AIC) Expts									
		4	*5*	*6*	*10*	*7*	*14*	*8*	*9*	*12*	½AIC ± SE
I	3	108.0	105.3	99.4	97.7	88.4	90.5	82.9	79.5	92.8	93.8 ± 3.2
IV	4	100.4	98.9	97.5	91.5	83.3	84.0	75.6	70.9	92.7	88.3 ± 3.5
V	5	92.8	88.1	89.4	93.1	78.6	77.3	77.9	79.5	79.1	84.0 ± 2.2
		Decrement in (½AIC) between models									
V vs. *I*		15.2	17.2	10.0	4.6	9.7	13.2	5.0	0.	13.7	9.8 ± 1.9*
V vs. *IV*		7.6	10.8	8.1	−1.6	4.7	7.1	−2.3	−8.6	13.6	4.4 ± 2.4†

For criterion of Akaike, see Ref. 4. Individual decrements are estimated with SD of ± 1 (*V* vs. *I*) and ± 0.7 (*V* vs. *IV*). * ½AIC different from 0 ($P < 0.025$). † ½AIC different from 0 ($P < 0.05$).

model VII) includes insulin inhibition of liver glucose production (represented as glucose balance), whereas *model V* assumes (incorrectly) constant production in the face of elevated insulin. We therefore selected *model VI*, of all seven models considered, as the best, in that it has acceptable properties from the identification point of view and it is consistent in broad terms with the known physiology of glucose metabolism.

The ability of *model VI* to describe glucose data from three typical experiments with high, medium, and low doses of injected glucose is shown in Fig. 4. Also shown are the predicted time courses of the variable designated X, which is proportional to the concentration of insulin in the remote compartment.

INSULIN SENSITIVITY

It is our goal to define insulin sensitivity formally, in mathematical terms, and estimate it using the parameters of *model VI*.

Definition

Glucose effectiveness (E) is defined as the quantitative enhancement of glucose disappearance due to an increase in the plasma glucose concentration

$$E \equiv -\frac{\partial \dot{G}}{\partial G} \tag{4}$$

where $\dot{G}$ is the time rate of change of the plasma glucose concentration [G].

Insulin sensitivity is then defined (in steady state (SS)) as the quantitative influence of insulin to increase the enhancement of glucose of its own disappearance

$$S \equiv \frac{\partial E_{SS}}{\partial I_{SS}} \tag{5}$$

Insulin Sensitivity Index

It is of interest to estimate insulin sensitivity from the parameters of *model VI* because *1*) *model VI* appears to be a reasonable representation of glucose kinetics, and *2*) the parameters of *model VI* can be readily determined from the insulin and glucose response to a single glucose injection. Applying the definitions of *Eqs. 4* and *5* to *model VI* (see APPENDIX) yields the insulin sensitivity index (S_I)

$$S_I = -\frac{p_3}{p_2} \tag{6}$$

where p_3 and p_2 are parameters of *model VI* defined in Fig. 3, with mean values (for dogs) listed in Table 4. S_I is expressed as $\text{min}^{-1}/(\mu\text{U/ml})$ (fractional glucose disappearance per insulin concentration unit).

Table 8 lists the calculated values of S_I for the (grouped) low- and intermediate-dose experiments and for the high-dose (300 mg/kg) experiments. In addition, glucose at the 300 mg/kg dose was administered in four experiments in three additional animals, and the calcu-

TABLE 7. *Criteria for acceptability of models*

Model	Identifiability	Parameter Absurdity	Goodness-of-Fit	Acceptance
I	OK	OK	NA	No
II	NA	Not considered	Not considered	No
III	?	NA	Not considered	No
IV	OK	?	NA	No
V	OK	OK	OK	Yes
VI	OK	OK	OK	Yes
VII	NA	Not considered	Not considered	No

NA, not acceptable.

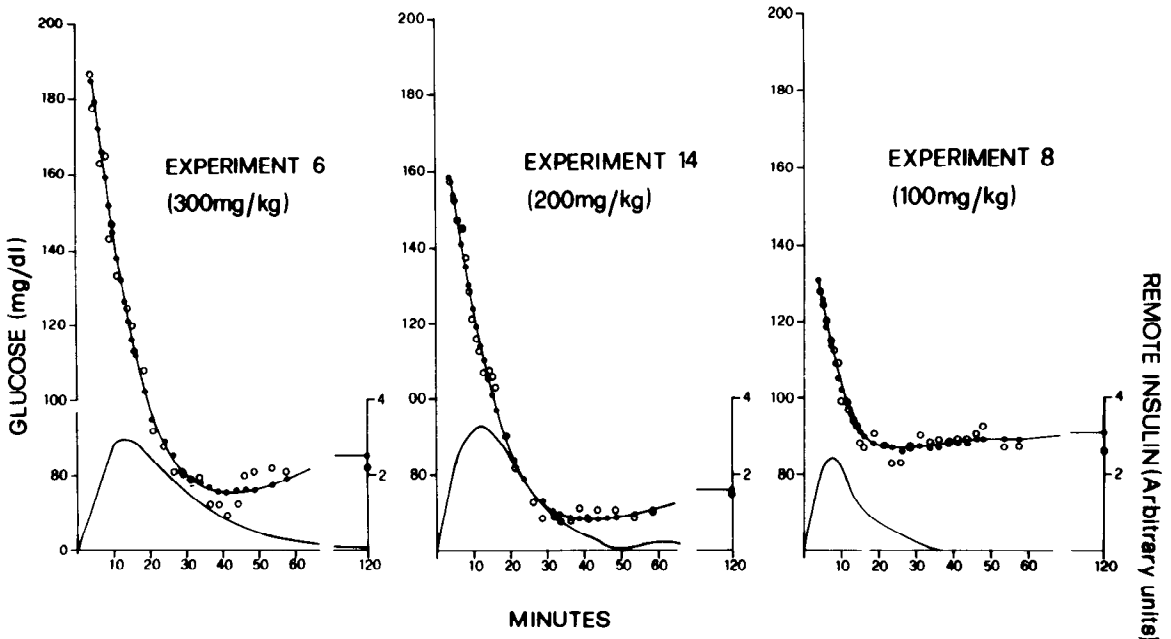

FIG. 4. Ability of *model VI* to predict falling plasma glucose concentration for 3 sample experiments. Closed circles represent fit of model with best parameter values for each experiment; open circles represent measured glucose data beginning at 4 min. Bottom curves are time course of insulin in a compartment remote from plasma that represents time course of insulin action. Glucose concentration at 120 min was assumed to be same as preinjection basal glucose.

lated results are included in Table 8. With the high dose, S_I could be calculated with a high degree of reproducibility ($\bar{S}_I = 7.0 \times 10^{-4}$ min^{-1}/(μU/ml); coefficient of variation = 24%). On the other hand, the reproducibility of the S_I estimate for the lower groups was much worse (coefficient of variation = 86%) although the estimate of S_I from the combined lower-dose group was not different from the S_I value estimated from the high-dose group (df = 11; $P > 0.06$). It is clear from the variation in the estimates of the individual parameters, p_2 and p_3, that the variation in the S_I estimate for the lower-dose group resulted from a wide variation in the estimate of parameter p_3 from the dynamic response to lower doses of glucose. The estimate of this parameter (equal to the disappearance parameter (k_3) for insulin in the remote compartment (I', Fig. 3)) is very sensitive to the "undershoot" dynamics of glucose (Table 1); and the greater prevalence of this undershoot is presumably responsible for the more reproducible estimate of p_3 in the high-dose experiments.

Thus, it is possible to obtain a precise estimate of the insulin sensitivity index from parameters of *model VI*, identified from the dynamic data obtained from an intravenous 300 mg/kg glucose injection.

TABLE 8. *Calculation of insulin sensitivity index from parameters of model VI*

Expt	Animal	Parameters of Model VI		Insulin Sensitivity Index $S_I \times 10^4$ min^{-1}/(μU/ml)
		$-p_{2_1}$ min^{-1}	$p_3 \times 10^4$, min^{-2}/(μU/ml)	
Low- and intermediate-dose expts				
8	*1*	0.13	0.79	5.3
9	*1*	0.13	0.31	2.4
12	*2*	0.14	1.99	15.2
7	*1*	0.04	1.45	33.0
14	*2*	0.09	1.29	14.0
		0.11 ± 0.04 (SD)	1.17 ± 0.64 (SD)	13.9 ± 12.0 (SD)* (CV = 86%)
High-dose expts				
4	*1*	0.10	0.85	8.4
5	*1*	0.06	0.55	9.0
6	*1*	0.07	0.50	7.4
10	*2*	0.06	0.41	6.9
15	*3*	0.08	0.39	4.8
16	*4*	0.08	0.44	5.8
17	*4*	0.08	0.69	8.7
18	*5*	0.18	0.92	5.0
		0.09 ± 0.04 (SD)	0.60 ± 0.20 (SD)	7.00 ± 1.66 (SD) (CV = 24%)

Amounts of glucose injected were: low dose, 100 mg/kg; intermediate; 200; and high-dose, 300. In the first group, 2 dogs were used and in the second 5. * Low- and intermediate-dose experiments were grouped because they yielded widely varying estimates of the insulin sensitivity index. Although the mean estimates of S_I from the low- and intermediate- vs. high-dose groups were not different ($P > 0.06$; df = 11), the variance of the estimate of S_I from the 300 mg/kg dose experiments was higher than that from the other group ($F = 51.9$, $P < 0.0001$).

DISCUSSION

Numerous approaches have been suggested for more effectively delineating the specific tissue changes responsible for glucose intolerance. In particular, it could be of great benefit to quantitatively differentiate in a given pathological situation the extent to which β-cell insensitivity to glucose or peripheral insulin insensitivity ("resistance") is responsible for the inability to dispose of a glucose load. These studies attempt to quantify insulin sensitivity by employing a simple dynamic perturbation, i.e., intravenous glucose injection, and by using the observed system dynamics to identify the parameters of a model of glucose metabolism.

Many workers have proposed simple models of the system regulating the blood glucose concentration (1, 2, 5, 10, 13, 14, 25) and have attempted to relate the model parameters to insulin secretory function and insulin action. Such attempts have frequently been confounded by the inherent difficulty in representing the nonlinear process of insulin secretion. Glucose-stimulated insulin secretion is difficult to model and requires multiple parameters (9, 11, 16, 20), and if the response to several secretagogues or prolonged stimulation is to be modeled, even more complex, nonlinear, and multiparametric models are required (7).

The novelty of the present study is that we circumvented the difficulty of modeling the β-cell response by treating the measured time course of insulin concentration as a model input. This approach allowed us to treat the system as "open-loop" and analyze the interactive effects of insulin and glucose on glucose disappearance without having to simultaneously analyze insulin secretion and without suppressing insulin secretion or manually controlling the blood glucose concentration by variable infusion. It was hoped that a quantitative measure of insulin sensitivity would emerge from this modeling effort because the ability to estimate insulin sensitivity by a simple dynamic perturbation of the system would certainly simplify the study of the physiological regulation of insulin sensitivity in vivo and should be useful in clinical studies.

We systematically investigated seven distinct physiologically based models of glucose disappearance to identify the one or more models that were able to describe the experimental data well with the smallest set of identifiable and meaningful parameters.

Five models (*I, II, III, IV,* and *VII*) were judged unacceptable by the criterion of parameter identification. The first three models failed to perform well, presumably because they included the erroneous implicit assumption that glucose disappearance is independent of insulin. Thus identification may be difficult when flagrantly incorrect assumptions are incorporated into the model structure.

The failure of *model IV* is of particular interest because it includes the dependence of glucose disappearance on plasma insulin. The formulation of glucose disappearance in *model IV* (i.e., disappearance as a linear function of plasma insulin and glucose) was first introduced by Bolie (10) and has since been implemented by various groups who have identified the parameters of glucose metabolism for clinical purposes. The introduction of a remote compartment for insulin action (I') into those earlier models might have improved their ability to describe the available data.

Model VII, a reasonable representation of glucose kinetics, was not identifiable from the available data, indicating the difficulty of separately quantitating (from glucose-tolerance test data) insulin inhibition of glucose production on the one hand and the potentiation of hepatic and peripheral glucose uptake on the other. Nevertheless, we were able to include insulin inhibition of glucose production as a component of net hepatic glucose balance in *model VI.*

The improvement in identifiability between *model IV* on the one hand and *models V* and *VI* on the other came about by the introduction of an insulin compartment (I′) remote from plasma on which glucose disappearance is dependent. This dependence was first demonstrated by Insel, Sherwin, and their colleagues (19, 28) in their kinetic analysis of glucose-clamp studies. Our studies strongly confirm the earlier analyses; this agreement with their studies illustrates that artificially maintaining a constant glucose concentration is not required to deduce the steady-state relationship between insulin and glucose uptake. The glucose-clamp studies clarified the effect of insulin on glucose disappearance when glucose was constant and close to a normal fasting level; the present technique extends beyond that limited objective by distinguishing between possible alternative quantitative representations of the interactive effects of glucose and insulin on disappearance while both signals are elevated and changing with time.

The choice of *model VI* over *V* for estimating sensitivity was made because *VI* is the more realistic model physiologically in that it includes the insulin inhibition of hepatic glucose balance. Thus, we were able to define the insulin sensitivity index, S_I, and estimate it from *model VI* as a function of system parameters that are representative of the sensitivity of both the liver and the periphery to insulin.

We have formulated an unambiguous, mathematically precise definition of insulin sensitivity. In *model VI*, S_I is independent of glucose and insulin, and equal to $(-p_3/p_2)$. By definition of p_3 and p_2 therefore (Fig. 3), S_I is equal to $(k_2/k_3)(k_4 + k_6)$, and I′ (or *X*) is representative of the time course of insulin action. Thus, it is possible to suggest that the remote insulin compartment, I′, represents a receptor "pool" for insulin bound to peripheral tissues (30), for which the forward binding constant times the number of binding sites is related to k_2, the dissociation constant is k_3, and the "effectiveness" of the insulin-receptor complex is related to both k_4 and k_6. If this suggestion were valid, S_I would represent a composite measure of the amount of receptor-bound insulin and the combined effectiveness of bound insulin on glucose efflux and hepatic glucose balance.

It is important to compare the insulin sensitivity index, estimated by our technique, with the insulin effectiveness parameter previously introduced by Insel et al. (19). Their technique involves the identification of 12 parameters of a combined glucose ("hot" and "cold") and insulin model. It was necessary to perform three separate experiments on a single subject to determine the parameters for that single individual: *1*) the pulse injection of insulin to identify a three-compartment model of insulin kinetics, *2*) the primed continuous infusion or pulse injection of [^{14}C]glucose for determination of the transfer coefficients of a three-compartment glucose model, and *3*) the "clamping" of the plasma glucose concentration by variable glucose infusion to clarify the relationship between the insulin concentration in three compartments and the rate of disappearance of glucose. They defined the insulin effectiveness as the derivative of glucose utilization with respect to the insulin concentration in a compartment remote from plasma because evidence was presented showing that utilization was dynamically differentiated from plasma insulin and the temporal pattern of utilization bore some resemblance to the time course of remote insulin. Obviously, the technique presented here is sufficiently simple to be performed on a routine basis as it requires only the performance of an intravenous glucose-tolerance test and the accurate identification of a five-parameter model. We may therefore compare the sensitivity estimates of the Insel technique with our own. By a simple conversion of their effectiveness definition to ours,[2] one may calculate that they report an average sensitivity index of $12 \pm 7 \times 10^{-4}$ (±SD) $min^{-1}/(\mu U/ml)$, for six human subjects, surprisingly close to the average $7.0 \pm 1.7 \times 10^{-4}$ (±SD) $min^{-1}/(\mu U/ml)$, which we found for dogs using 300 mg/kg glucose (Table 8). Therefore, it appears possible to obtain a reasonable estimate of insulin sensitivity with a much simpler experimental protocol and a model greatly reduced in size.

Despite the similarity of these estimates, it is important to recognize a fundamental difference between the insulin effectiveness of Insel et al. (19) and the sensitivity index proposed in our study. In their experiments, sensitivity is limited to the lumped effect of insulin on glucose uptake by periphery and liver because hepatic glucose production during glucose clamping and insulin infusion is at a constant level below the fasting value. Our index includes the effect of insulin not only to augment glucose uptake by periphery and liver, but also to inhibit hepatic glucose production. The similarity of the sensitivity estimates of the two groups may indicate that the sensitivity index estimate is dominated by the effect of insulin on glucose uptake.

S_I is attractive in that it is normalized to body size, is independent of the plasma glucose concentration, and is based on glucose disappearance as a function of insulin in plasma. Thus, this has the potential for comparing individuals of varying size, weight, and body composition. In fact, due to the generosity of Drs. Ferranini, Navalesi, and Pilo of the University of Pisa, Italy, we have been able to obtain plasma glucose and insulin measurements on normal human subjects whose blood was sampled frequently after intravenous glucose injections (330 mg/kg body wt). S_I for this group of normal subjects was 6.5 ± 3.9 (SD) $\times 10^{-4}$ $min^{-1}/(\mu U/ml)$. Thus, the S_I value for normal human subjects appears to be similar to the estimated value in normal dogs, given a similar intravenous glucose load.

The meaning of S_I can be shown by the following example. A sensitivity index of 0.00070 $min^{-1}/(\mu U/ml)$ (Table 8) implies that for each 10 $\mu U/ml$ increase in plasma insulin, there will be an increase of 0.7%/min in

[2] S_I can be calculated from insulin sensitivity (Table 4, Ref. 19) by assuming sensitivity equal to B in *Eq.* 7 of Ref. 19; assuming $I_3/I_1 \cong 2$ (Fig. 2, Ref. 19) and $M_6 \cong 5$ g (Table 3, Ref. 19).

fractional glucose disappearance. Of course, it must be understood that *i*) this index may only apply over a limited range of glucose and insulin concentration, and *ii*) glucose disappearance in this sense refers to all the combined effects of glucose to lower the plasma glucose concentration (i.e., inhibition of production, and augmentation of uptake by liver and periphery).

Thus, using *model VI*, it appears possible to estimate insulin sensitivity with good precision, from the response to a simple intravenous glucose injection. The estimated value of S_I appears to characterize the responses to different glucose doses and may be characteristic of a normal population of animals. Future experimental studies, in which insulin sensitivity is simultaneously estimated in different ways, are required to validate the proposed technique and to determine whether this technique is sufficiently sensitive to be of use in monitoring changes in insulin sensitivity (possibly receptor number) that may occur in altered metabolic states, such as starvation (6), exercise (29), and (in man) maturity-onset diabetes mellitus.

APPENDIX

Estimation of Insulin Sensitivity for Model VI

Applying the definition of S to *model VI* (*Eq. 5*, Fig. 3), we can say that, because

$$\dot{G} = (p_1 - X)G + p_4 \qquad (A1)$$

then (by *Eq. 4*)

$$E = X - p_1 \qquad (A2)$$

Also (by Fig. 3), at steady state

$$X_{SS} = \frac{-p_3}{p_2} I_{SS} \qquad (A3)$$

so that

$$E_{SS} = \frac{-p_3}{p_2} I_{SS} - p_1 \qquad (A4)$$

Therefore, by *Eq. 5*, we define the insulin sensitivity index

$$S_I = \frac{-p_3}{p_2} \qquad (A5)$$

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REFERENCES

1. ACKERMAN, E., L. C. GATEWOOD, J. W. ROSEVEAR, AND G. D. MOLNAR. Model studies of blood-glucose regulation. *Bull. Math. Biophys.* 27: 21–37, 1965.
2. ACKERMAN, E., J. W. ROSEVEAR, AND W. F. MCGUCKIN. A mathematical model for the glucose tolerance test. *Phys. Med. Biol.* 9: 203–213, 1964.
3. AFIFI, A. A., AND S. P. AZEN. *Statistical Analysis. A Computer Oriented Approach.* New York: Academic, 1972.
4. AKAIKE, H. A new look at the statistical model identification. *IEEE Trans. Autom. Control* 19: 716–723, 1974.
5. ATKINS, G. L. Investigation of some theoretical models relating the concentration of glucose and insulin in plasma. *J. Theor. Biol.* 32: 471–494, 1971.
6. BAR, R. S., P. GORDEN, J. ROTH, C. R. KAHN, AND P. DEMEYTS. Fluctuations in the affinity and concentration of insulin receptors on circulating monocytes of obese patients; effects of starvation, refeeding and dieting. *J. Clin. Invest.* 58: 1123–1135, 1976.
7. BERGMAN, R. N., AND R. J. BUCOLO. Nonlinear metabolic dynamics of the pancreas and liver. ASME J *Dynamic Systems Measurement Control* 95: 296–300, 1973.
8. BERGMAN, R. N., AND R. J. BUCOLO. Interaction of insulin and glucose in the control of hepatic glucose balance. *Am. J. Physiol.* 227: 1314–1322, 1974.
9. BERGMAN, R. N., AND J. URQUHART. The pilot gland approach to the study of insulin secretory dynamics. *Recent Prog. Horm. Res.* 27: 583–605, 1971.
10. BOLIE, V. W. Coefficients of normal blood glucose regulation. *J. Appl. Physiol.* 16: 783–788, 1961.
11. CERASI, E. Insulin secretion mechanism of the stimulation by glucose. *Q. Rev. Biophys.* 8: 1–41, 1975.
12. CURRY, D. L., L. L. BENNETT, AND G. K. GRODSKY. Dynamics of insulin secretion by the perfused rat pancreas. *Endocrinology* 83: 572–584, 1968.
13. DELLA CORTE, S., M. R. ROMANO, M. R. VOEGHELIN, AND M. SERIO. On a mathematical model for the analysis of the glucose tolerance curve. *Diabetes* 19: 445–449, 1970.
14. GATEWOOD, L. C., E. ACKERMAN, J. W. ROSEVEAR, AND G. D. MOLNAR. Simulation studies of blood-glucose regulatory system. *Comput. Biomed. Res.* 2: 1–14, 1968.
15. GOODWIN, C., AND R. L. PAYNE. *Dynamic System Identification.* New York: Academic, 1977.
16. GRODSKY, G. M. A threshold distribution hypothesis for packet storage of insulin and its mathematical modelling. *J. Clin. Invest.* 51: 2047–2059, 1972.
17. HERBERT, V., K. LAW, C. GOTTLIEB, AND S. BLEICHER. Coated charcoal immunoassay of insulin. *J. Clin. Endocrinol. Metab.* 25: 1375–1384, 1965.
18. HETENYI, G., JR., AND K. H. NORWICH. Validity of the rates of production and utilization of metabolites as determined by tracer methods in intact animals. *Federation Proc.* 33: 1841–1848, 1974.
19. INSEL, P. A., J. E. LILJENQUIST, J. D. TOBIN, R. S. SHERWIN, P. WATKINS, R. ANDRES, AND M. BERMAN. Insulin control of glucose metabolism in man. *J. Clin. Invest.* 55: 1057–1066, 1975.
20. LICKO, V., AND A. SILVERS. Open-loop glucose insulin control with threshold secretory mechanism: analysis of intravenous tolerance tests in man. *Math. Biosci.* 27: 319–322, 1975.
21. MARQUARDT, D. W. An algorithm for least squares estimation of nonlinear parameters. *J. Soc. Ind. Appl. Math.* 11: 431–441, 1963.
22. OLEFSKY, J., J. W. FARQUHAR, G. M. REAVEN. Relationship between fasting plasma insulin level and resistance to insulin mediated glucose uptake in normal and diabetic subjects. *Diabetes* 22: 507–513, 1973.
23. RADZIUK, J., K. H. NORWICH, AND M. VRANIC. Measurement and validation of nonsteady turnover rates with applications to the insulin and glucose systems. *Federation Proc.* 33: 1855–1964, 1974.
24. REAVEN, G. M., W. S. SAGEMAN, AND R. S. SWENSON. Development of insulin resistance in normal dogs following alloxan-induced insulin deficiency. *Diabetologia* 13: 459–462, 1977.

25. SEGRE, G., G. L. TURCO, AND G. VARCELLONE. Modelling blood glucose and insulin kinetics in normal, diabetic and obese subjects. *Diabetes* 22: 94–103, 1973.
26. SHANNON, J. A. Renal tubular excretion. *Physiol. Rev.* 19: 63, 1939.
27. SHEN, S.-W., G. M. REAVEN, AND J. W. FARQUHAR. Comparison of impedance to insulin mediated glucose uptake in normal and diabetic subjects. *J. Clin. Invest.* 49: 2151–2160, 1970.
28. SHERWIN, R. S., K. J. KRAMER, J. D. TOBIN, P. A. INSEL, J. E. LILJENQUIST, M. BERMAN, AND R. ANDRES. A model of the kinetics of insulin in man. *J. Clin. Invest.* 53: 1481–1492, 1974.
29. VRANIC, M., R. KAWAMORI, S. PEK, N. KOVACEVIC, AND G. A. WRENSHALL. The essentiality of insulin and the role of glucagon in regulating glucose utilization and production during strenuous exercise in dogs. *J. Clin. Invest.* 57: 245–255, 1976.
30. ZELEZNIK, A. J., AND J. ROTH. Demonstration of the insulin receptor in vivo in rabbits and its possible role as a reservoir for the plasma hormone. *J. Clin. Invest.* 61: 1363–1374, 1978.