Physiologic Evaluation of Factors Controlling Glucose Tolerance in Man

MEASUREMENT OF INSULIN SENSITIVITY AND β-CELL GLUCOSE SENSITIVITY FROM THE RESPONSE TO INTRAVENOUS GLUCOSE

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ABSTRACT The quantitative contributions of pancreatic responsiveness and insulin sensitivity to glucose tolerance were measured using the "minimal modeling technique" in 18 lean and obese subjects (88–206% ideal body wt). The individual contributions of insulin secretion and action were measured by interpreting the dynamics of plasma glucose and insulin during the intravenous glucose tolerance test in terms of two mathematical models. One, the insulin kinetics model, yields parameters of first-phase (ϕ_1) and second-phase (ϕ_2) responsivity of the β-cells to glucose. The other glucose kinetics model yields the insulin sensitivity parameter, S_I. Lean and obese subjects were subdivided into good ($K_G > 1.5$) and lower ($K_G < 1.5$) glucose tolerance groups. The etiology of lower glucose tolerance was entirely different in lean and obese subjects. Lean, lower tolerance was related to pancreatic insufficiency (ϕ_2 77% lower than in good tolerance controls [$P < 0.03$]), but insulin sensitivity was normal ($P > 0.5$). In contrast, obese lower tolerance was entirely due to insulin resistance (S_I diminished 60% [$P < 0.01$]); pancreatic responsiveness was not different from lean, good tolerance controls (ϕ_1: $P > 0.06$; ϕ_2: $P > 0.40$). Subjects (regardless of weight) could be segregated into good and lower tolerance by the product of second-phase β-cell responsivity and insulin sensitivity ($\phi_2 \cdot S_I$). Thus, these two factors were primarily responsible for overall determination of glucose tolerance.

The effect of ϕ_1 was to modulate the K_G value within those groups whose overall tolerance was determined by $\phi_2 \cdot S_I$. This ϕ_1 modulating influence was more pronounced among insulin sensitive (ϕ_1 vs. K_G, $r = 0.79$) than insulin resistant (obese, low tolerance; ϕ_1 vs. K_G, $r = 0.91$) subjects. This study demonstrates the feasibility of the minimal model technique to determine the etiology of impaired glucose tolerance.

INTRODUCTION

The ability to dispose of carbohydrate depends on the responsiveness of the pancreatic β-cells to glucose and the sensitivity of the glucose utilizing tissues to the secreted insulin. Insulin resistance is an important factor particularly in the etiology of type II, nonketosis prone diabetes (1–5). The primacy of insulin resistance in this state remains controversial, however, and most investigators agree that at least a relative impairment in pancreatic secretory capacity is important in noninsulin-dependent diabetic states (6–8).

Understanding the etiology of the various forms of impaired glucose tolerance requires techniques for measuring both pancreatic responsiveness and insulin sensitivity, and a means to evaluate their relative contributions to overall glucose tolerance. The major difficulty in making independent measures of these two factors is the glucose insulin feedback rela-

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tionship, which tends to complicate glucose/insulin dynamics and obscure the causality of impaired tolerance (9). During the past decade, several laboratories have approached this problem by breaking the feedback relationship, either by pharmacological suppression of pancreatic insulin secretion (10) or by external feedback control (glucose clamp) to circumvent the effect of plasma insulin to change plasma glucose (11). These methods for measuring insulin sensitivity have contributed to understanding the etiology of intolerance, but they require extensive experimental manipulation, entail some risk to the patient, and have been used only in a few clinical research centers.

We have developed a new approach to quantify both pancreatic responsiveness and insulin sensitivity in the intact organism. This method, the "minimal model" technique, uses computer modeling to analyze the plasma glucose and insulin dynamics during an intravenous glucose tolerance test (IVGTT).[1] A mathematical model of pancreatic insulin release and distribution is used to obtain characteristic parameters of insulin secretory responsiveness to glucose (both first phase [ϕ_1] and second phase [ϕ_2]) by predicting the time-course of plasma insulin, when the plasma glucose time-course is supplied (12). Conversely, an index of insulin sensitivity (S_I) is measured from a second model that predicts glucose kinetics, when the insulin time-course is supplied (13). The three characteristic parameters (ϕ_1, ϕ_2, and S_I) represent an integrated metabolic portrait of a single individual. Because it is not necessary to interrupt the glucose-insulin feedback relationship, the experimental manipulations can be performed in a routine clinical setting with minimal patient risk.

In this report we present the first application of the minimal model approach to analysis of glucose tolerance in humans. The purpose of the study was to determine the specific contributions of pancreatic responsiveness and insulin sensitivity to normal and low glucose tolerance in lean and obese subjects.

METHODS

Subjects. IVGTT with frequent sampling was performed on 8 male and 10 female subjects ranging from 88 to 206% of ideal body weight (% IBW) as estimated using Metropolitan Life Insurance tables. Subjects were in good health, euthyroid, and not taking any medication that would alter carbohydrate metabolism. Most lean subjects (88–105% IBW) were outpatient Northwestern University students; most obese subjects (130–206% IBW) were inpatients undergoing metabolic study at the Northwestern University Clinical Research Center. Informed consent was obtained in all cases.

Performance of the IVGTT. Subjects consumed at least 300 g carbohydrate/d for 3 d preceding the test, which was begun at 0800 following an overnight fast. The tests were performed in the Clinical Research Center. A "butterfly" needle (Deseret Company, Sandy, Utah) was inserted into an antecubital vein, and patency was maintained with a slow saline drip. After a 30-min rest period basal samples (2 ml) were taken at −13, −8, and −3 min, following which glucose (300 mg/kg) was injected smoothly over 60 s, starting at time (t) = 0. To define glucose and insulin dynamics precisely, 23 additional 2-ml samples were collected at the following times: 2, 4, 6, 8, 10, 12, 14, 16, 19, 22, 27, 32, 42, 52, 62, 72, 82, 92, 102, 122, 142, 162, and 182 min. Samples were collected within 15 s, and great care was taken to avoid contamination with saline or blood from previous samples. Samples were mixed with 10 U powdered heparin and 1 mg NaF, and centrifuged under refrigeration. Plasma was stored at −20 C until assay for glucose and insulin.

Assays. Glucose was measured in triplicate by the glucose oxidase technique on an automated analyzer (Yellow Springs Instrument Co., Yellow Springs, Ohio). The coefficient of variation of a single glucose determination was ±1.5%. Insulin was measured in duplicate by radioimmunoassay, with dextran-charcoal separation using a human insulin standard (Novo Corp., Copenhagen, Denmark). Guinea pig anti-insulin serum was produced in our laboratory; ^{125}I-insulin was purchased on a regular basis from Amersham Corp., Arlington Heights, Ill. Within-assay coefficient of variation was ±7% from 8 to 200 μU/ml; between-assay variation was ±11%.

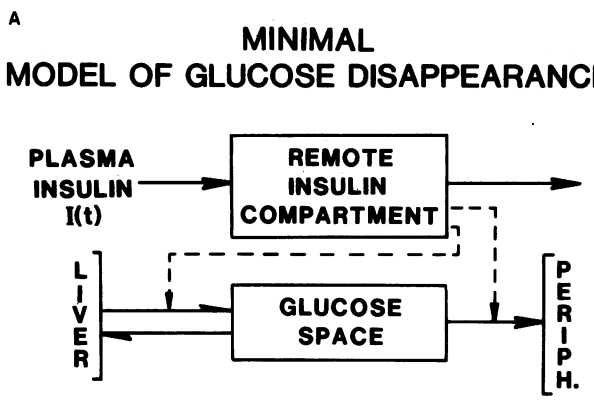
Analysis of data. The theoretical basis underlying estimation of the characteristic parameters from IVGTT results has been published in detail (12–14), and will only be summarized here. K_G values, calculated for purposes of comparison with our parameters, were calculated as the least-squares slope of the ln (glucose concentration) vs. time relationship between 10 and 42 min after glucose injection.

General approach: partition and minimal modeling. The system regulating the glucose concentration is envisioned as being partitioned into two parts: (*a*) the glucose-dependent segment that determines the plasma insulin (the pancreas and insulin-degrading tissues) and (*b*) the insulin-dependent segment which determines the plasma glucose (glucose producing and utilizing tissues). We have previously evolved specific "minimal" mathematical models for each of the two parts. The two minimal models selected have been shown to be the simplest physiologically based representations that can respectively account (*a*) for the observed glucose kinetics when the plasma insulin values are supplied and (*b*) for the observed insulin kinetics when the plasma glucose values are supplied. Using the two independent minimal models to describe the dynamic glucose and insulin responses during IVGTT, characteristic parameters of insulin sensitivity and pancreatic responsivity are generated.

Parameter of insulin sensitivity, S_I. The minimal model of glucose disappearance is diagrammed in Fig. 1a. The coefficients of the minimal model (c.f., reference 13) are estimated for a single individual from the IVGTT data by allowing the model to predict the observed fall in plasma glucose when the (measured) plasma insulin is supplied. In accounting for the glucose kinetics by considering plasma insulin as input and plasma glucose as output it is not necessary to formulate any assumptions as to the mechanisms by which pancreatic insulin secretion is controlled ("partition analysis" [14]). S_I can be calculated (13) for a single individual as the ratio of two of the parameters of the glucose disappearance model. This ratio is proportional to the concentration of "active" insulin in a compartment remote from plasma, and the ability of that insulin to enhance glucose disappearance. The units of S_I, so estimated, are minute^{-1} per microunit per milliliter; that is, the increase in the fractional clearance rate of glucose per unit change in the plasma insulin concentration.

[1] *Abbreviations used in this paper*: IBW, ideal body weight; IVGTT, intravenous glucose tolerance test.

A



B

FIGURE 1 (A) Minimal model of glucose kinetics used to calculate insulin sensitivity from IVGTT. Plasma insulin [I(t)] enters a "remote compartment" where it is active in accelerating glucose disappearance into the periphery and liver, and inhibiting hepatic glucose production. The equations of the minimal model are

$$\frac{dG(t)}{dt} = (P_1 - X)G(t) - P_1Gb,$$

$$\frac{dX(t)}{dt} = P_2X(t) + P_3I(t);$$

where the variable X(t) is proportional to insulin in the remote compartment. Insulin sensitivity index (S_I) is $-P3/P2$; equal to insulin's effect to augment the tendency for glucose self-normalization. The units of S_I are $min^{-1}/\mu U$ per ml (fractional glucose disappearance rate per unit insulin concentration). Explicit definitions of X and the parameters in terms of fractional turnover constants are found in reference (13). (B) Model of insulin kinetics used to calculate pancreatic responsivity parameters ϕ_1 and ϕ_2 (12). G(t) is supplied to this model, which predicts I(t). First-phase insulin release is represented as a bolus of insulin entering the plasma compartment at the time of the glucose injection (30). Sensitivity of the first-phase release to glucose is $\phi_1 = Io/n\Delta G$, where Io is the early peak plasma insulin concentration, n is the time constant for insulin disappearance (min^{-1}) and ΔG is the maximum change in the glucose concentration due to the glucose injection. Second-phase insulin secretion is described by

$$\frac{dI(t)}{dt} = \gamma(G(t) - h)t - nI(t)$$

The rate of increase of second-phase secretion is proportional (by γ) to the degree by which glucose exceeds a threshold level (h). The factor ϕ_2 represents the sensitivity of the rate of rise of the second phase to glucose, and is defined as second-phase pancreatic responsivity.

Parameters of pancreatic responsiveness to glucose, ϕ_1 and ϕ_2. Insulin secretory parameters are calculated for a given individual from the IVGTT by using our minimal model of insulin secretion and disapparance (Fig. 1b). The model assumes that the early peak in insulin secretion represents an "injection" of insulin into plasma by the pancreas in direct proportion to the rise in glucose. First-phase responsivity (ϕ_1) is the amount of insulin (per unit volume) that can be accounted for by this assumed injection, per unit change in plasma glucose. It is assumed in the model that the rate of rise of second-phase insulin secretion is proportional to the plasma glucose; the second-phase responsivity (ϕ_2) is the proportionality factor between glucose and the rate of rise (15, 16).

Methods of parameter estimation. Parameter estimation was performed on a digital computer (IBM 370/168, IBM Corp., White Plains, N. Y.) using a nonlinear least squares technique (17), and accuracy of the parameter estimates was evaluated using the covariance matrix (18). Analysis of the relation between estimated parameters within patient groups was performed using Student's *t* test and regression analysis (19).

RESULTS

Analysis of IVGTT. Characteristics of the 18 subjects are listed in Table I. Basal glucose values were all <115 mg/dl. There were significant positive correlations between the IBW and both basal glucose ($r = 0.59$, $P < 0.01$) and insulin ($r = 0.62$, $P < 0.01$).

IVGTT results are summarized in Table II. Because the lean control subjects tended to be taller than the obese patients, the dose of glucose based upon IBW was 14% greater in the lean subjects. This difference in dose was reflected in an incremental change in plasma

TABLE I
Human Subjects

Subject No.	Sex	IBW	Basal values	
			Glucose	Insulin
		%	*mg/100 ml*	*μU/ml*
7	M	88	97	3
4	M	95	99	8
6	M	97	98	4
8	M	98	93	6
2	M	100	91	9
5	M	100	93	11
1	M	101	94	17
3	M	105	85	15
14	F	130	92	20
15	F	138	102	81
12	F	142	110	26
11	F	147	96	17
13	F	148	99	21
9	F	153	100	8
18	F	153	103	16
10	F	154	94	15
16	F	172	109	37
17	F	206	104	68

TABLE II
IVGTT Results

Subjects	Dose glucose	K_G*	Glucose(0)‡	ΔGlucose§	Glucose distribution space	$\int_0^\infty I(t)dt$
	g	*min*$^{-1}$	*mg/dl*	*mg/dl*	*dl*	*(μU/ml) min*
Lean						
1	18.8	2.4	298	203	92.6	7.23
2	22.7	1.8	276	181	125.4	2.83
3	21.8	1.9	250	165	132.1	4.02
4	25.8	2.3	337	238	108.4	3.48
5	30.0	2.4	329	235	127.6	3.25
6	20.0	1.4	296	197	101.5	2.35
7	19.1	1.1	248	151	126.5	2.18
8	21.0	1.1	271	178	118.0	2.14
	22.4±1.3	1.8±0.2		194±11	117±5	3.44±0.60
Obese						
9	18.2	1.9	297	196	92.9	3.45
10	16.3	1.8	242	147	110.9	3.98
11	20.4	3.0	348	252	81.0	7.00
12	22.7	1.0	263	141	161.0	3.52
13	19.7	1.1	217	117	168.4	8.32
14	17.8	1.1	224	131	135.4	6.58
15	18.2	1.4	258	156	116.7	25.72
16	24.9	1.3	267	163	152.8	13.75
17	20.5	0.7	242	105	195.2	18.64
18	18.1	0.6	253	124	146.0	4.88
	19.7±0.8 ($P < 0.04$)	1.4±0.2 NS‖		153±14 ($P < 0.025$)	136±11 ($P < 0.025$)	9.58±2.36 ($P < 0.02$)

* K_G is calculated from the regression of ln glucose concentration vs. time 10, 22, 32, and 42 min after glucose injection.

‡ Glucose(0) is the glucose concentration at t = 0 estimated by extrapolating the prediction of the glucose kinetics model to the moment of injection. Thus, cardiovascular mixing is not included.

§ ΔGlucose equals glucose(0) − glucose basal.

‖ K_G value not significantly less for obese subjects (>130% IBW; $P < 0.10$). *P* values compare all obese with all lean subjects.

glucose concentration (Δ glucose) of 194±11 mg/dl in the lean subjects; 21% greater than the increment in the obese (Δ glucose = 153±14 mg/dl; $P < 0.025$). Despite the lesser increase in plasma glucose concentration in the obese, they manifested a 2.8-fold greater integrated insulin response.

No significant overall difference in K_G values was observed in obese vs. lean subjects ($P > 0.09$), although the obese K_G tended to be lower. Thus, to some extent at least, it was apparent that obese patients were able to compensate for overall insulin resistance by means of pancreatic hyperresponsivity. The frequency distribution of K_G for all subjects is shown in Fig. 2. Although the distribution was not absolutely bimodal, there was separation of individuals at $K_G = 1.5$. For purposes of analysis, we chose $K_G > 1.5$ as "good tolerance" and $K_G < 1.5$ as "low tolerance." Five lean and three obese subjects had good tolerance; seven obese and three lean individuals segregated as "low tolerance."

Fig. 3 shows the glucose and insulin during the IVGTT of four patient groups, segregated on the bases of body weight and glucose tolerance: group I (lean, good tolerance); group II (lean, low tolerance); group III (obese, good tolerance) and group IV (obese, low tolerance). In all groups, glucose injection provoked rapid insulin secretory responses characterized by an early peak at 4 min, followed by a prolonged secondary phase; however, qualitative differences in the shapes and magnitudes were observed (Fig. 3). For example, only modest first and second phases were evident in the responses of group II, in contrast to the other three groups. Also, the second phases were prolonged in groups II and IV, when compared with their respective good-tolerance counterparts. The prolonged

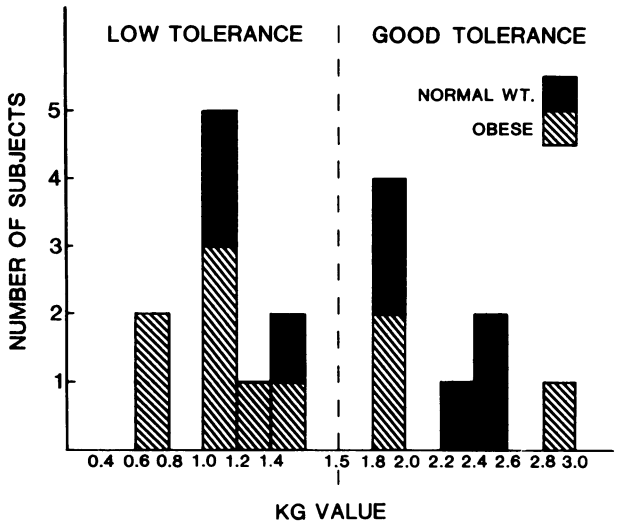


FIGURE 2 Frequency histogram of the K_G values of the 18 subjects under study, calculated from the IVGTT. Because no K_G values were found between 1.4 and 1.8, we arbitrarily divided the population into "good tolerance" and low tolerance at $K_G = 1.5$. Units of K_G: min^{-1}.

second phases corresponded to the extended periods of glucose elevation. In all experiments glucose fell below basal; at 140 min after injection glucose was an average of 10±2 mg/dl below the basal value ($P < 0.001$) but had usually begun renormalization by 180 min. No comparable "undershoot" in plasma insulin was observed.

The goal of our analytic approach is to account for the variations in glucose tolerance in terms of the specific contributions of pancreatic responsiveness and insulin sensitivity. To do this, we used the two minimal models to describe the IVGTT data of each patient. Fig. 4 shows for two patients the ability of the glucose disappearance model (Fig. 1a) to describe glucose kinetics, given insulin, and the ability of the insulin kinetics model (Fig. 1b) to describe insulin kinetics, given glucose. The specific model coefficients obtained from modeling the dynamics of all patients (separated into groups) are given in Table III.

Characteristic metabolic parameters. The coefficients of the two models listed in Table III were reduced to three characteristic metabolic parameters: ϕ_1. ϕ_2, and S_I (Table IV). Low tolerance in lean subjects was associated with insufficient pancreatic responsiveness. Although S_I was the same in the lean good tolerant and lean low tolerant subjects (group I; $S_I = 4.0 \pm 1.0$; group II; $S_I = 5.1 \pm 1.3$ $min^{-1}/\mu U$ per ml; $P > 0.5$), the low tolerance of lean patients (group II) was associated with a 77% lower second-phase responsivity, compared with the lean good tolerant group I ($P < 0.03$). There was also a tendency for first-phase responsivity to be lower in the second group but the difference in ϕ_1 was not significant ($P < 0.08$) because of wide variation in ϕ_1.

In contrast to the lean individuals, low glucose tolerance in the obese patients was related to insulin resistance rather than diminished pancreatic responsiveness. Insulin sensitivity was 60% diminished in group IV obese low tolerance patients (compared with lean, good tolerance group I controls; [$P < 0.01$]), whereas in the group IV patients second-phase responsiveness was not different from group I (31±6 compared with 27±7; $P > 0.4$). As in the lean patients, there was wide variation in ϕ_1 in the group IV patients (range of ϕ_1: 1.0 to 18.2). However, even in those group IV patients for whom ϕ_1 was increased (subjects 13 and 15, for example [Table IV]), the increased first phase responsivity was not sufficient to overcome the intolerance occasioned by normal ϕ_2 coupled with a severely diminished S_I typical of the obese, low tolerance individuals.

Significance of $\phi_2 \cdot S_I$ in determining tolerance. Since impaired tolerance can be associated with either diminished second-phase responsivity or S_I, we examined the hypothesis that the product $\phi_2 \cdot S_I$ ("disposition factor") may be a convenient means for segregating individuals of varying tolerance, regardless of weight. The value of this product was 160±26 for all good tolerance subjects and 40±7 ($P < 0.001$) for the low tolerance subjects (Table IV). Fig. 5 (top) indicates that $\phi_2 \cdot S_I$ for 9 of the 10 low tolerance individuals is below 75, and that the product exceeds 75 for 7 of the 8 good tolerance subjects. Also shown in Fig. 5 is the relationship between S_I and ϕ_2 for all subjects. The hyperbola representing $\phi_2 \cdot S_I = 75$ separates most good tolerant (upper right) from low tolerant (lower left) subjects. Thus, the position of a subject on this plot (above or below the "75" curve) determines not only whether the subject is tolerant, but also the relative contribution of pancreatic responsiveness (ϕ_2) or S_I to the degree of tolerance that the individual exhibits.

Influence of first-phase responsivity on glucose tolerance. The ability to segregate on the basis of tolerance, in terms of the $\phi_2 \cdot S_I$ product alone suggests that these two factors are primarily responsible for glucose tolerance in a given individual. Due to the wide variation of ϕ_1 within groups, it was not possible to obtain clear segregation using $\phi_1 \cdot S_I$ (not shown). Nonetheless, first-phase insulin responsivity appears to play a role in the determination of tolerance within groups whose overall tolerance is determined by $\phi_2 \cdot S_I$. Fig. 6 shows the relation between K_G and ϕ_1 in the four groups. K_G was highly correlated with ϕ_1, in the obese, low tolerance subjects (group IV; $r = 0.91$, $P < 0.001$). Presumably due to the relative insulin resistance of these subjects ($S_I = 2.0 \pm 0.4$ $min^{-1}/\mu U$ per ml), an in-

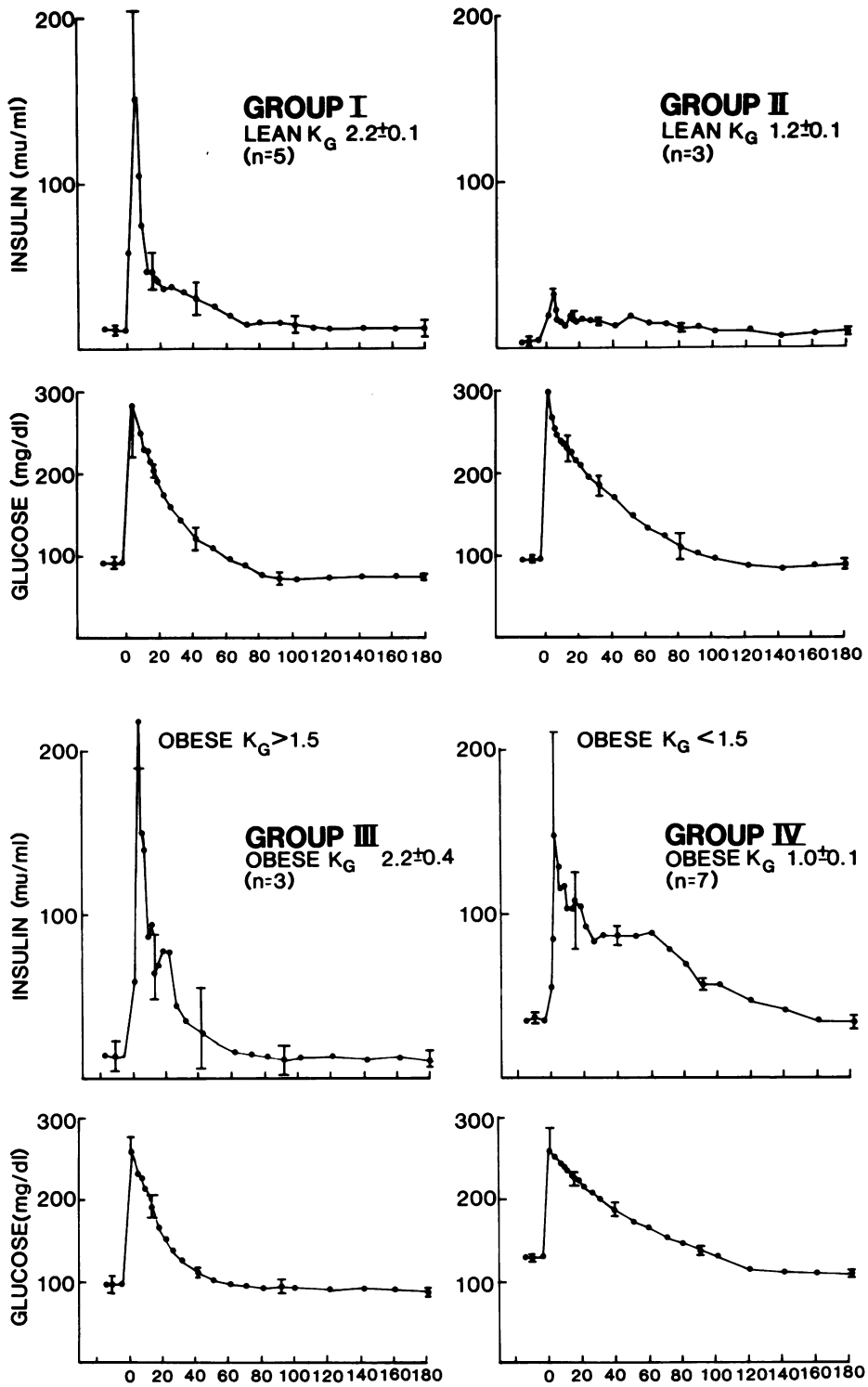


FIGURE 3 IVGTT results for four groups of subjects: lean, good tolerance (group I), lean lower tolerance (group II), obese, good tolerance (group III), obese, lower tolerance (group IV). In all cases, good tolerance implied $K_G > 1.5$; lower tolerance, $K_G < 1.5$. Glucose (330 mg/kg) was injected over 1 min starting at t = 0. Vertical bars represent SEM.

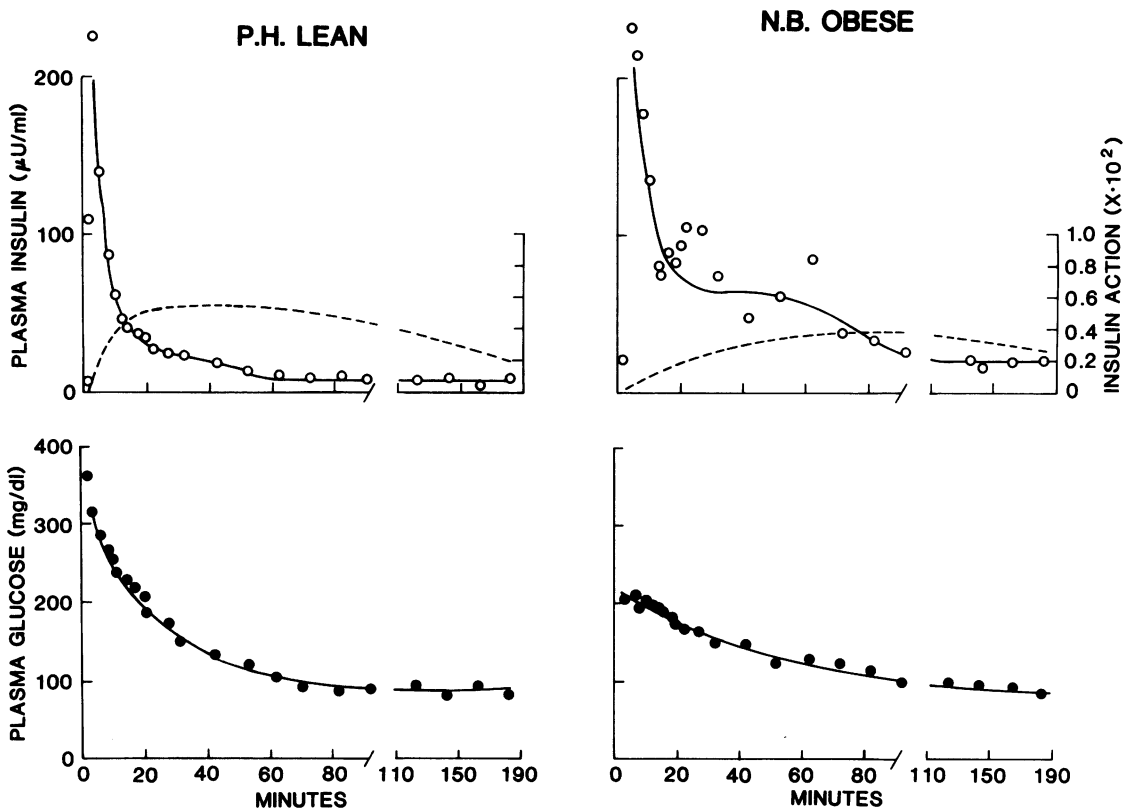


FIGURE 4 Ability of the minimal models to describe glucose and insulin kinetics during the IVGTT (examples). Insulin and glucose data are represented by open (○) and filled (●) circles. Prediction of the insulin kinetics model are the solid curves; upper panels. Glucose kinetics model predicts the time-course of plasma glucose (solid curves, lower panels) as well as the time-course of "insulin action" (dashed line upper panels; remote insulin [X] in the model of Fig. 1a).

crease of ϕ_1 from 1 to 10 was associated with an increase in K_G of only 0.3 min^{-1}. In contrast, in the other subjects (groups I, II and III), for whom insulin resistance was not a general characteristic (n = 11, S_I = 5.1 ±0.7) a similar increase in ϕ_1 was associated with an increase in K_G of 0.9 min^{-1}. Thus, the difference in S_I between these groups is reflected in the extent to which the variation in first phase secretion can result in altered K_G. That the differences in K_G within these populations can be accounted for by S_I and not ϕ_2 is indicated by the fact that the mean second phase sensitivities in these two populations were not different (ϕ_2 = 27±6 (nonresistant); = 31±6 (resistant); $P > 0.4$).

In addition to insulin-related factors the tolerance to glucose is dependent upon mechanisms related to the levels of glucose per se: hepatic glucose autoregulation (20); and insulin-independent glucose uptake (21). We have referred to the sum of these factors as "glucose effectiveness" (13). It is of interest to consider whether alterations in glucose effectiveness contribute to the glucose intolerance of the obese subjects.

In the glucose kinetics model (Fig. 1b) the coefficient P1 is the insulin-independent fractional turnover constant for glucose disposition (cf., reference 13); P1 is equal to glucose effectiveness when insulin remains at the basal level. This coefficient was significantly lower in subjects with low tolerance than in good tolerance individuals (1.4±0.2 vs. 3.6±0.3%/min; $P < 0.01$). Thus, not only are pancreatic responsivity (ϕ_2) or insulin sensitivity (S_I) attenuated in the low tolerance individuals, but insulin-independent glucose normalization mechanisms are apparently diminished as well.

S_I and basal insulin. It has been suggested that since there is an inverse correlation between insulin levels and S_I, basal insulin may provide a measure of the degree of insulin resistance (22, 23). Fig. 7 demonstrates that for those patients for whom S_I is <3.0 $min^{-1}/\mu U$ per ml, basal insulin is correlated with S_I (r = 0.65, $P < .03$). However, over the range of insulin sensitivities from 3.0–10.0 min^{-1} μU per ml the correlation was not observed (r = 0.08).

TABLE III
Parameters of Models

	Glucose kinetics model					Insulin kinetics model			
	K_G*	G(0)	$-P_1$ ($\times 10^2$)	$-P_2$ ($\times 10^2$)	P_3 ($\times 10^6$)	I(0)	$\gamma \times 10^5$	h	n‡
		mg/dl	*min*$^{-1}$	*min*$^{-1}$	*min*$^{-2}$/*μU/ml*	*μU/ml*	*μU/mg min*^{2}	*mg/dl*	*min*$^{-1}$
Group I									
Lean, good tolerance									
1	2.4	298 (2%)§	2.96 (14)	1.86 (14)	6.51 (11)	333	5.36 (23)	90.9 (1)	0.23 (16)
2	1.8	276 (2)	1.92 (4)	2.62 (18)	14.7 (22)	69	1.40 (32)	100.0 (4)	0.18 (24)
3	1.9	250 (1)	3.74 (7)	4.78 (77)	8.73 (92)	33	2.93 (27)	87.5 (1)	0.30 (22)
4	2.3	337 (2)	3.63 (6)	0.81 (31)	4.01 (18)	192	2.40 (15)	93 (1)	0.23 (8)
5	2.4	329 (2)	4.64 (3)	0.38 (38)	3.61 (11)	73	1.69 (50)	119 (1)	0.13 (21)
	2.2±0.1	†							
Group II									
Lean, low tolerance									
6	1.4	296 (1)	1.36 (15)	3.41 (31)	17.3 (34)	50	0.89 (7.6)	90.9 (1)	0.22*
7	1.1	248 (2)	1.51 (13)	3.13 (60)	9.7 (62)	15	0.69 (11)	82.6 (3)	0.22*
8	1.1	271 (2)	2.17 (10)	2.92 (43)	19.1 (41)	14	0.28 (32)	87.3 (2)	0.11 (15)
	1.2±0.1								
Group III									
Obese, good tolerance									
9	1.9	297 (2)	4.00 (5)	0.42 (42)	2.56 (15)	209	3.72 (34)	154 (4)	0.22 (19)
10	1.8	242 (2)	3.23 (5)	0.34 (41)	2.67 (13)	104	3.46 (24)	145 (3)	0.19 (17)
11	3.0	348 (7)	4.66 (34)	6.76 (48)	16.1 (51)	264	7.47 (125)	186 (3)	0.09 (14)
	2.2±0.4								
Group IV									
Obese, low tolerance									
12	1.0	256 (1)	1.80 (8)	1.08 (26)	2.29 (16)	99	3.42 (6)	153 (1)	0.13*
13	1.1	217 (5)	1.13 (5)	0.34 (22)	0.97 (9)	225	3.30 (27)	122 (2)	0.14 (18)
14	1.1	224 (3)	1.13 (55)	2.40 (32)	4.89 (51)	185	1.36 (12)	123 (2)	0.11 (6)
15	1.4	258 (1)	2.46 (5)	0.69 (23)	0.55 (11)	337	2.70 (19)	175 (4)	0.13*
16	1.3	267 (2)	1.00 (28)	1.66 (31)	2.02 (29)	248	3.40 (85)	108 (2)	0.13*
17	0.7	242 (1)	0.71 (21)	1.25 (26)	1.58 (15)	20	6.11 (13)	143 (3)	0.13*
18	0.6	254 (1)	0.93 (15)	2.00 (26)	7.78 (21)	16	1.19 (8)	132 (3)	0.13*
	1.0±0.1								

* K_G, glucose disappearance rate (min^{-1}) calculated as the negative slope of ln (glucose) between 10 and 42 min after the glucose injection; P_1, P_2, and P_3, are parameters of the glucose kinetics model defined in Fig. 1A and reference 13; γ and h are parameters of insulin kinetics model of Fig. 1B and reference 12.

‡ Parameter n is the fractional clearance of insulin (min^{-1}); the value of n was assumed for those subjects for whom there was no significant first-phase insulin secretion. The parameter was assumed equal to the average n for the patients with a first phase with matched body weights (lean or obese).

§ Number in parentheses is the average percent fractional SD of the parameter (CV × 100).

DISCUSSION

In the present study, we have demonstrated the feasibility of a new approach to relating pancreatic responsiveness and insulin sensitivity to the glucose tolerance of human subjects. These metabolic features, expressed in terms of the three metabolic parameters ϕ_1, ϕ_2, and S_I can usually be measured by using the precise insulin and glucose dynamics during an IVGTT to estimate the coefficients of two mathematical models: one of glucose kinetics and a second of insulin kinetics. The utility of our approach is demonstrated by its ability to differentiate the causality of observed low glucose tolerance between lean and obese subjects. In the lean intolerant individuals, S_I was identical with that of lean tolerants; intolerance was related to pancreatic insufficiency

TABLE IV
Characteristic Metabolic Parameters of Subjects

Subjects	Pancreatic responsivity* Phase 1 ϕ_1 $\left(\frac{Io}{n\Delta G}\right)$	Pancreatic responsivity* Phase 2 ϕ_2 ($\gamma \times 10^4$)	Insulin sensitivity‡ S_I $\left(\frac{-P3}{P2} \times 10^4\right)$	K_G	Disposition factor $\phi_2 \cdot S_I$
Group I Lean, tolerant					
1	6.91	53	3.5	2.4	186
2	1.56	14	5.6	1.8	78
3	0.73	29	1.8	1.9	52
4	3.13	24	4.9	2.3	118
5	2.87	17	9.6	2.4	163
	3.0±1.1	27±7	5.1±1.3		119±25
Group II Lean, low tolerance					
6	1.06	8.9	5.1	1.4	4.5
7	0.23	6.9	3.1	1.1	21
8	0.78	2.8	6.5	1.1	18
	0.69±0.2	6.2±1.7	4.9±1.0		28±9
Group III Obese, tolerant					
9	4.88	37	6.1	1.9	225
10	4.59	35	7.9	1.8	276
11	16.1	75	2.4	3.0	180
	8.6±4	49±13	5.5±1.6		227±28
Group IV Obese, low tolerance					
12	9.5	34	2.1	1.0	71
13	13.3	33	0.8	1.1	26
14	9.9	14	2.0	1.1	28
15	18.2	27	0.8	1.4	22
16	9.5	34	1.2	1.3	41
17	1.0	61	1.3	0.7	79
18	1.0	12	3.9	0.6	47
	9.0±2.3	31±6	2.0±0.4		45±8
All normal tolerance (Groups I and III)					160±26
All low tolerance (Groups II and IV)					40±7

* Pancreatic responsivity parameters ϕ_1 and ϕ_2 represent relative responsiveness of first and second phase insulin release to glucose and are calculated from the coefficients of the insulin secretion model (see text).

‡ Insulin sensitivity parameter S_I, the effect of insulin to increase fractional glucose disappearance, is calculated from the coefficients of the glucose kinetics model (see text).

which was most significant for the second phase of insulin secretion. The lean, low tolerant patients had K_G values within the normal range (1.2±0.1) and are apparently able to successfully dispose of administered carbohydrate with only a very modest insulin response.

The present results confirm the existence of insulin resistance in low tolerant obese individuals, (5, 24–26); in fact, sensitivity was diminished 60% in our obese subjects, compared with the lean individuals. Using the "insulin clamp" technique, DeFronzo et al.

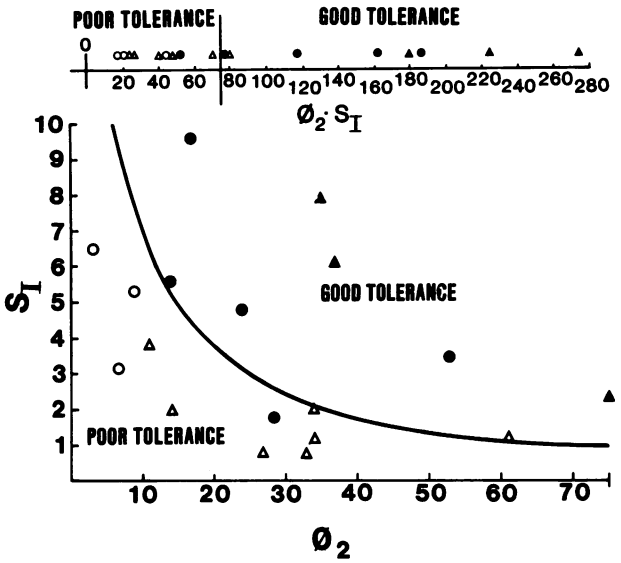


FIGURE 5 Relationship between pancreatic responsiveness (ϕ_2; second phase) and S_I in all subjects: groups I (●), II (○), III (▲), and IV (△). Top: subjects are segregated according to the $S_I \cdot \phi_2$ product. Bottom: subjects represented on the S_I vs. ϕ_2 plot. The solid line represents $\phi_2 \cdot S_I = 75$; this "tolerance boundary" separates the upper "good tolerance" region from the "poor" tolerance region.

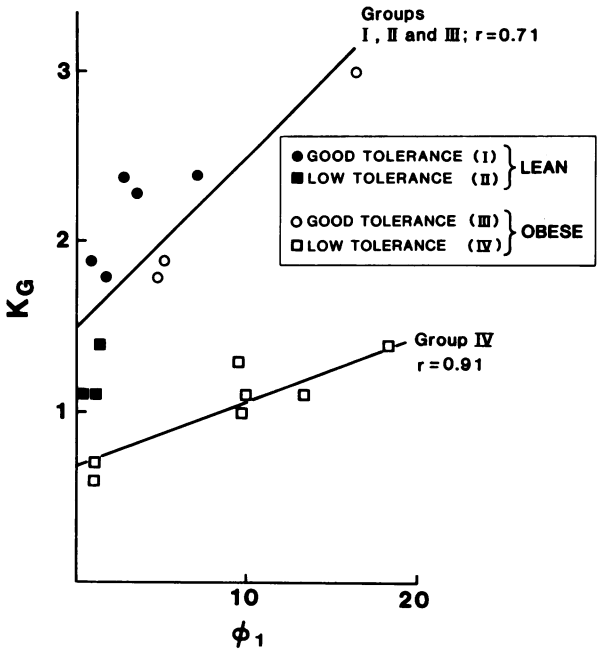


FIGURE 6 Dependence of K_G upon ϕ_1 in subjects from groups I, II, and III (upper line, $n = 11$, $S_I = 5.1 \pm 0.7$ min$^{-1}/\mu$U per ml) and group IV (lower line, $n = 7$, $S_I = 2.0 \pm 0.4$ min$^{-1}/\mu$U per ml). Insulin resistance was characteristic of group IV, but not I, II and III (Table III). Slopes of the two lines are significantly different ($P < 0.01$).

(25) reported a diminution in S_I[2] of 53% in obese (158–265% IBW) compared to lean subjects (5); remarkably similar to the 60% we calculated from the IVGTT. Thus, our results are consistent with the diminished S_I of obese subjects elucidated by both qualitative (26) and quantitative techniques (25).

It is important to consider whether the lower value of S_I for obese subjects was related to an actual difference in sensitivity of the insulin-responsive tissues, rather than simply increased patient mass. The increased mass of heavier subjects would normally result in a proportional increase in glucose distribution space. However, because our control group tended to be taller than the obese subjects, the obese glucose space exceeded the space of lean individuals by only 16% (Table II). Because of this, there was only a 26% difference in the change in plasma glucose occasioned by injection in the obese vs. lean subjects. It is certainly possible that the glucose kinetics may not be applicable with the same set of parameters for a given individual, over the entire range of possible glucose doses. However, it seems a reasonable assumption that our model with a unique parameter set may well apply over a dose range which induces glucose increments from 153 to 194 mg/dl, particularly in view of the ability of this model to simulate a wide variety of glucose dynamic patterns (13). It is doubtful the 60% diminution in insulin sensitivity in the obese can be an artifact of a 26% difference in glucose increment. Nonetheless, we believe that a more complete study of the range of doses over which the model is applicable would be worthwhile.

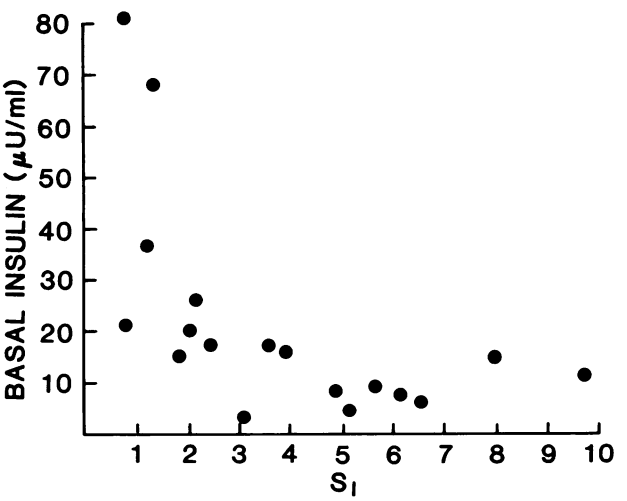


FIGURE 7 Relationship between S_I and basal insulin in all patients studied. Basal insulin is significantly correlated with S_I when insulin resistance is manifest ($S_I < 3.0$; $r = 0.65$) but not in the sensitivity range 3.0–9.6 ($r = 0.08$).

[2] Measured as the infusion rate of glucose necessary to maintain euglycemia in the face of moderate (100 μU/ml) hyperinsulinemia.

The evident primacy of ϕ_2 and S_I in the determination of tolerance between groups led us to propose the product of these two factors, $\phi_2 \cdot S_I$, as a "disposition index," a measure of tolerance which includes within it the quantitative contributions of the individual factors related to the observed tolerance. It is important to reconcile our view that ϕ_2 and S_I are the primary determinants of glucose tolerance with evidence that the initial peak is an important factor if not the major determinant of the value of the K_G (6, 7, 27). In these studies we found that within the lean or obese groups of individuals the ϕ_2 and S_I values were rather consistent, however there was large variation in ϕ_1 within each group and large overlap in ϕ_1 values between different groups. The results of this study lead to the view that phase 1 and phase 2 pancreatic responsivity have differing roles in the determination of the K_G: ϕ_2 functions to establish an overall range of tolerance according to body weight, for example; ϕ_1 determines where within that range a given individual will lie.

The metabolic status of an individual patient can be represented by his position on the S_I vs. ϕ_2 plot (Fig. 5). The location on the $S_I \cdot \phi_2$ plane indicates not only the degree of tolerance (whether the individual lies "above" or "below" the $\phi_2 \cdot S_I = 75$ tolerance boundary) but the relative importance of the pancreas and insulin-sensitive tissues in the etiology of observed glucose tolerance. An approach to optimal treatment of insulin-independent diabetes could be based upon the ability of individual therapies to alter the position of a given individual on the ϕ_2/S_I plot. Application of this approach to therapy for a single individual would include measurement of ϕ_2 and S_I from the IVGTT and determination of the therapy vector (or direction and magnitude of change in S_I and ϕ_2) needed to return the intolerant individual to a region of tolerance. Having characterized the vectors for the available therapies (e.g., sulfonylurea treatment, weight loss, insulin, etc.) it may be possible on this basis to design the therapy best suited to each individual patient.

An interesting relationship that emerged from the present studies was that intolerant subjects were characterized by diminished glucose "effectiveness": that is, glucose had impaired ability to normalize its own concentration under hyperglycemic conditions in the absence of an acute insulin response. This result is consistent with the finding of Olefsky et al. (28) who showed that glucose utilization at basal glucose levels was diminished in obese, diabetic, individuals. Because the diminished glucose effectiveness of obese subjects is independent of acute changes in insulin it may be related to the influence of basal insulin concentration on the levels of those enzymes that are dependent upon a constant insulin environment for their activities, such as glucokinase and glycogen synthase in the liver (29, 30) and glucose transport units in tissues for which glucose transport is insulin dependent (31). Thus, the diminished glucose effectiveness may be related to insulin resistance in that it could be a secondary manifestation of the resistance of tissues to the "permissive" rather than acute effects of the hormone.

The present results provide the opportunity to examine whether basal insulin levels represent a good measure of insulin sensitivity (22, 23). A good negative correlation between basal insulin and S_I was observed under conditions of frank insulin resistance ($S_I < 3.0$); however, over the large range of S_I in normal, tolerant subjects ($3.0 < S_I < 10.0$) a significant correlation between basal insulin and measured resistance was not observed. (That sensitivity can vary over such a large range in normal individuals was originally reported by Sherwin and his colleagues [32], and we have a similar experience in normal dogs [13]). It is not surprising, however, that in normal individuals, basal insulin is not a simple function of S_I, but also depends on factors which may themselves change with insulin resistance. Insulin levels are also determined by basal pancreatic insulin secretion, insulin clearance, and neural mechanisms (33). When frank insulin resistance is manifest, it is reasonable that the resistance effect can overwhelm other mechanisms that control basal insulin, and hyperinsulinemia in proportion to the resistance is observed. However, when S_I is in the normal range, it is only one of several possibly equipotent factors which determine basal insulin, and the clear correlation between S_I and basal insulin disappears. Therefore, although there may be a correlation between basal insulin and S_I, particularly in the insulin resistant state, the former apparently cannot be viewed as an accurate measure of the latter under all conditions.

The present studies demonstrate that the minimal model approach may be applicable to studying the etiology of altered carbohydrate metabolism in man. In addition to comparative validation with other techniques, it will be useful to explore whether the IVGTT is the optimal perturbation to be used to estimate metabolic parameters. Present studies have been limited to evaluation of IVGTT results. It remains to be proven whether the model and its parameters will apply and can be obtained from other doses and other stimulus patterns. Possibly future studies will yield a better temporal pattern of glucose and/or insulin administration that will lead to easier estimation of metabolic parameters. In any event, complete validation of the model and optimal input patterns will be required before the approach can be proposed as a clinical tool.

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