Role of Glucose Effectiveness in the Determination of Glucose Tolerance

JAMES D. BEST, MD
STEVEN E. KAHN, MB, CHB
MARILYN ADER, PHD
RICHARD M. WATANABE, PHD
TA-CHEN NI, PHD
RICHARD N. BERGMAN, PHD

Insulin secretion and insulin action are major factors in the determination of glucose tolerance, and insulinopenia and insulin resistance cause glucose intolerance and/or NIDDM. Because glucose itself can enhance glucose disposal and suppress endogenous glucose production *independent* of a change in insulin, it is necessary to consider an additional factor in determination of glucose tolerance: glucose effectiveness. This phenomenon represents the ability of glucose per se, under basal insulin conditions, to enhance glucose disposal and to suppress endogenous glucose production. Glucose effectiveness has been measured in many studies in which glucose disposal and output have been quantified at basal insulin but with widely varying glycemia. The effect of glucose on glucose disposal in humans is such that a 100 mg/dl increase in plasma glucose (at basal insulin) will increase glucose disposal by 1.63 $mg \cdot min^{-1} \cdot kg^{-1}$. Similarly, the same 100 mg/dl increment in glucose alone will suppress endogenous glucose output by 0.79 $mg \cdot min^{-1} \cdot kg^{-1}$. Thus, two-thirds of glucose effectiveness in humans is the disposal effect [1.63/(1.63 + 0.79)] and the remaining third is the effect to suppress the liver. Having numerical values for glucose effectiveness makes it possible to calculate the importance of hyperglycemia per se relative to the importance of insulin to disposition of a glucose load. In normal individuals, ~50% of the glucose disposal during an oral glucose tolerance test (OGTT) is due to glucose effectiveness and not to the dynamic insulin response. In the insulin-resistant obese individual, 83% of glucose disposal occurs independent of the dynamic insulin response; in NIDDM, because of severe insulin resistance and relative insulinopenia, 99% of glucose uptake after a carbohydrate meal is due to glucose effectiveness. Thus, glucose effectiveness is a component equal to or greater than insulin itself in the determination of glucose tolerance. Glucose effectiveness can be assessed from the intravenous glucose tolerance test (IVGTT) by using the so-called minimal model approach; the sensitivity parameter that is calculated, the glucose effectiveness index (S_G) represents the sum, or whole-body, effect of hyperglycemia to enhance glucose disposal *and* to suppress endogenous glucose production. Using the model, S_G has been measured multiple times in humans: the average from 18 independent studies is 0.024 min^{-1}. Physical activity and training almost double S_G; states of glucose intolerance are characterized by reduced S_G. For example, S_G is down 33% in offspring of two parents with NIDDM, down by 50% in subjects with impaired glucose tolerance, and reduced as much as 60% in subjects on a very-low-calorie diet. A hallmark of states of reduced S_G appears to be the insulinopenic state, although this hypothesis requires further validation. Whether reduced glucose effectiveness is a true inheritable defect that can enhance risk for and contribute to the onset of NIDDM remains to be investigated. Recent evidence that glucose can enhance glucose uptake not only by mass action and enzyme activation, but also by transporter recruitment suggests that a genetic contribution to reduced glucose effectiveness may be an important heritable cause of NIDDM.

GLUCOSE EFFECTIVENESS, CONCEPTUAL BASIS

The physiological response to carbohydrate administration has long been used as a probe to classify metabolic disease (1). Impaired glucose tolerance is considered a risk factor for macrovascular disease and represents an increased risk of further deterioration to diabetes. The classification of diabetes indicates risk for microvascular as well as macrovascular disease. Thus, it is important to understand the physiological mechanisms that are of significance in the determination of glucose tolerance so as to focus on a potential cause of a variety of chronic illnesses, including cardiovascular disease, that are associated with reduced tolerance to carbohydrate.

Various physiological mechanisms come into play to reestablish basal glycemia after carbohydrate ingestion. The role of the gastrointestinal tract includes absorption of the carbohydrate load, which determines the ascension rate of the blood glucose concentration. The rising glucose contributes to the rapid insulin response, which for normal individuals is central to the renormalization of the blood glucose concentration. Thus, it has been generally assumed that the rate at which glucose is normalized after a carbohydrate load is determined by the amount of insulin secreted in response to the load, as well as the sensitivity of the tissues (liver and periphery) to the secreted hormone. Glucose intolerance, then, has been interpreted to be caused by impaired insulin response and/or insulin resistance. The relative importance of each of these factors in the pathogenesis of NIDDM has been the subject of vigorous debate (2–9).

The question arises as to whether glucose intolerance can be entirely ac-

From the University of Melbourne (J.D.B.), Melbourne, Australia; Veteran's Affairs Puget Sound Health Care System (S.E.K.), Seattle, Washington; and the University of Southern California Medical School (M.A., R.M.W., T.-C.N., R.N.B.), Los Angeles, California.

Address correspondence and reprint requests to Richard N. Bergman, PhD, Chairman, Department of Physiology and Biophysics, USC Medical School, MMR 630, 1333 San Pablo St., Los Angeles, CA 90033.

Received for publication 14 December 1995 and accepted in revised form 2 May 1996.

GDR, glucose disposal rate; HGO, hepatic glucose output; IVGTT, intravenous glucose tolerance test; OGTT, oral glucose tolerance test; NIMGU, non–insulin-mediated glucose uptake; S_G, glucose effectiveness index; S_I, insulin sensitivity index.

counted for by alterations in the plasma insulin response and/or tissue sensitivity. Insulin resistance and/or insulinopenia may result in both impaired suppression of endogenous glucose output and impairment in peripheral glucose uptake. What other mechanisms may be important? While alterations in glucose absorption rate may alter the blood glucose pattern (10), absorption per se has not been implicated in most forms of glucose intolerance. The potentiating effect of the gastrointestinal tract on β-cell secretion may be impaired in NIDDM (11), but this is manifest as a secretory impairment. Given this, it might be assumed that assessment of insulin response and sensitivity, by whatever means, will fully account for variations in glucose tolerance in health or disease. However, it now appears likely that an additional factor, glucose effectiveness, also determines whole-body glucose tolerance, and alterations in glucose effectiveness may contribute to glucose intolerance under certain conditions (12–14).

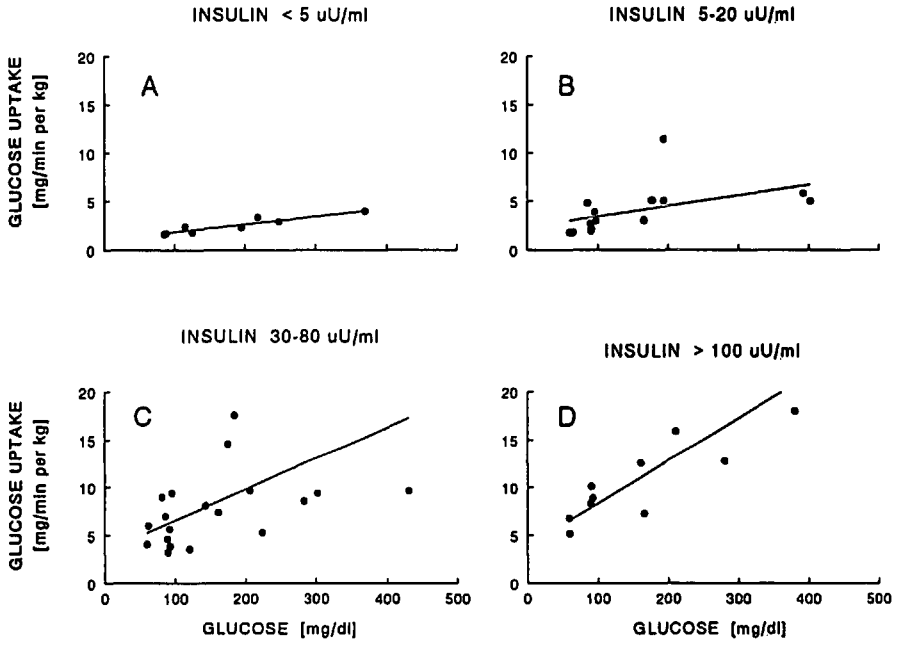

Figure 1—*Glucose uptake rates at different glucose levels and matched insulin concentrations based on data from 15 individual studies (19–33). In most studies, insulin levels are fixed by infusion of somatostatin and exogenous insulin, and the desired glucose level is achieved by infusion of dextrose using the glucose clamp technique. Glucagon was not replaced in any study. Glucose uptake is usually calculated from turnover of radiolabeled glucose. Regression lines relate ability of glucose to enhance glucose uptake at fixed insulin. At subbasal insulin (<5 μU/ml), the increase of glucose uptake with hyperglycemia is very limited. The effect of hyperglycemia increases with increasing insulin concentration so that at high insulin (>100 μU/ml), glucose uptake increases almost threefold with similar hyperglycemia.*

What is glucose effectiveness?

Glucose effectiveness is the influence of glucose at basal insulin to enhance its own utilization and suppress its own endogenous production (15). In this review, the term glucose effectiveness is used as a concept, analogous to insulin sensitivity. Thus, glucose effectiveness can be measured using various techniques, and the measure emanating from a specific methodology would have a unique designation [e.g., S_G, $S_{G(clamp)}$].

It has been known since the time of Soskin et al. (16) that glucose could influence its own metabolism independent of changes in the plasma insulin level. In fact, in 1971, Vranic et al. (17) demonstrated this insulin-independent effect directly in pancreatectomized dogs tested at basal insulin (plasma glucagon levels remained normal because of enteric secretion). Evaluation of this phenomenon in normal animals and estimation of its contribution to glucose tolerance was first performed by Ader et al. (18). They demonstrated that even when the insulin response to glucose injection is prevented pharmacologically (with basal insulin and glucagon replaced intraportally), hyperglycemia is rapidly renormalized to preinjection levels, although the rate of normalization is slower than that seen with the insulin response intact. Thus, there must exist mechanisms to enhance the utilization of glucose and/or to suppress glucose output that are not dependent on the stimulation of β-cell release of insulin.

EVIDENCE FOR GLUCOSE EFFECTIVENESS

Studies of glucose effectiveness in humans: glucose disposal

One approach to quantitation of glucose's role independent of hyperinsulinemia is the glucose clamp method. By the use of somatostatin as an islet-suppressing agent, it has been possible to examine glucose uptake under steady-state conditions at different insulin and glucose levels. Using the glucose clamp approach, many different groups have confirmed the relationship among glucose, insulin, and glucose uptake reported by Best et al. (19) in 1981. Data from 15 of these laboratories are summarized in Fig. 1 (19–33).

With islet suppression and without insulin replacement (i.e., at insulin indistinguishable from zero), glucose alone can enhance glucose utilization (Fig. 1*A*). In fact, the slope of the best-fit line garnered from available data was 0.005 min^{-1}. (Note that the term 1.69 times the glucose is included so that glucose effectiveness and insulin sensitivity can be expressed in terms of the fractional change of the glucose pool, in units of min^{-1}.) At insulin near basal fasting levels, this slope increases to 0.012 min^{-1} (Fig. 1*B*). This latter slope represents the effect of glucose itself to enhance glucose disposal at basal insulin and is therefore a measure of the component of glucose effectiveness related to glucose disposal. We refer to the slope of Fig. 1*B* as $S_{G(DCLAMP)}$. S_G is used as the generic terminology for glucose effectiveness defined at basal insulin. The letter *D* refers to disposal of glucose, and the word *clamp* delineates the value calculated from a clamp study. By analogy, the term referring to the effect of glucose per se to suppress glucose appearance (i.e., endogenous glucose production) we have delineated $S_{G(ACLAMP)}$, for which *A* delineates appearance of glucose. The total effect of glucose to enhance glucose disposal and suppress glucose appearance during a glucose clamp experiment done at basal insulin is whole-body

Table 1—*Relative contribution of glucose effectiveness to total glucose uptake (% total)*

Insulin (μU/ml)	Glucose level (mg/dl)		
	80	120	160
12	60	69	75
40	36	40	41
80	29	31	32
120	26	28	29

glucose effectiveness, represented as $S_{G(CLAMP)}$.

With increased insulin, as expected, the slope of the glucose uptake versus glucose concentration relationship increases substantially, to a near-maximal value of 0.045 min^{-1} (Fig. 1*D*), or four times the glucose uptake component of glucose effectiveness [$\sim 4 \times S_{GD(CLAMP)}$]. It is convenient to express the relationships among glucose, insulin, and glucose uptake shown in Fig. 1 with a simple algebraic equation (Eqs. 1 and 2, below). In these equations, GDR is glucose disposal rate, and $R_d(0)$ is the intercept on the *y*-axis, that is, the apparent glucose uptake at zero glucose concentration. [Of course, there can be no glucose uptake at zero glucose. Rather, $R_d(0)$ represents that saturable component of glucose uptake that would be added to uptake rate at all glucose levels.] Disposal glucose effectiveness [$S_{GD(CLAMP)}$] represents the effect of glucose to enhance glucose disposal at basal fasting insulin; under such a condition, the increment in insulin above basal is 0 (Δinsulin = 0). Above basal insulin (Δinsulin > 0), the slope of the relationship between glucose concentration and glucose uptake increases with insulin; the rate of increase of glucose disposal with insulin is represented by the insulin sensitivity in Eq. 1. This latter insulin sensitivity index was previously defined as $S_{IP(CLAMP)}$ (34). The effect of insulin to increase the slope has a tendency to saturate; this saturation is accounted for by Michaelis-Menten parameter K_m.

$$GDR = R_d(0) + \left[\text{glucose effectiveness} + \text{insulin sensitivity}\left(\frac{\Delta \text{insulin}}{\Delta \text{insulin} + K_m}\right)\right] \bullet \text{glucose} \bullet V_d \quad (1)$$

or

$$GDR = R_d(0) + \left[S_{GD(CLAMP)} + S_{IP(CLAMP)}\left(\frac{\Delta \text{insulin}}{\Delta \text{insulin} + K_m}\right)\right] \bullet \text{glucose} \bullet V_d \quad (2)$$

The actual best-fit equation describing all the glucose clamp data collated from the many laboratories is shown above (Eq. 3). In this equation, glucose represents the plasma glucose concentration, insulin is in microunits per milliliter, glucose effectiveness is in units of reciprocal minutes, and GDR is represented in milligrams per minute per kilogram. Note that Eq. 3 allows the estimation of glucose utilization for the overall population of normal individuals studied in the many experiments. This uptake value can be calculated at any fasting and/or elevated steady-state plasma insulin and glucose concentration.

$$GDR = 1.03 + \left[0.012 + 0.038\left(\frac{\Delta \text{insulin}}{\Delta \text{insulin} + 55}\right)\right] \bullet 1.69 \bullet \text{glucose} \quad (3)$$

Baron et al. (25) have previously examined the physiological and pathophysiological regulation of non–insulin-mediated glucose uptake (NIMGU). However, NIMGU and glucose effectiveness are different concepts. NIMGU is the truly insulin-independent glucose uptake. It is usually determined at fasting glucose, but can be determined at hyperglycemia. At fasting glucose, NIMGU is approximately equal to $R_d(0)$ (1.03 $mg \cdot min^{-1} \cdot kg^{-1}$). Disposal glucose effectiveness, however, is the change in glucose uptake with increasing glucose level, calculated at basal insulin. Disposal glucose effectiveness [$S_{GD(CLAMP)}$] can be calculated from clamps by taking the difference between glucose uptake at basal insulin and hyperglycemia minus glucose uptake at basal insulin and euglycemia. Thus, unlike NIMGU, which is approximately equal to $R_d(0)$, $S_{GD(CLAMP)}$ is independent of $R_d(0)$.

Components of disposal glucose utilization

Expressing all glucose uptake data in Eq. 2 allows one to calculate the contributions to glucose disposal of three components: *1)* $R_d(0)$, or the component that is independent of glucose *and* insulin; 2) the contribution of glucose effectiveness; and 3) the additional contribution of incremental plasma insulin. The $R_d(0)$ component is constant at 1.03 $mg \cdot min^{-1} \cdot kg^{-1}$. However, the relative contribution of glucose effectiveness to glucose uptake changes substantially at steady state with increasing insulin (Table 1).

At basal, fully 60% of glucose uptake is due to glucose effectiveness; this proportion reduces to <30% with insulin in excess of 100 μU/ml. During the normal glucose tolerance test, glucose may reach 160 mg/dl and insulin frequently reaches 80 μU/ml; under this condition, if steady state were to be reached, it could be estimated that ~70% of the glucose uptake would be due to the insulin component and $R_d(0)$ and that only ~30% could be ascribed to glucose effectiveness. However, as we shall see, this estimate of the minor contribution of glucose effectiveness is an underestimate, and glucose effectiveness is more important in disposal of carbohydrate than is indicated by Table 1.

Dynamic effects: disposal glucose effectiveness

When carbohydrate is taken by mouth or injected by vein, steady-state conditions do not apply; that is, both glucose and insulin are changing during the period after carbohydrate administration. Because they are changing, the contribution of glucose effectiveness to glucose disposal is considerably greater than is indicated in Table 1. It is now abundantly clear that insulin acts slowly in vivo to enhance glucose utilization (35,36). This sluggishness is in contrast to the rapid onset of insulin action in vitro. In recent years, the cause

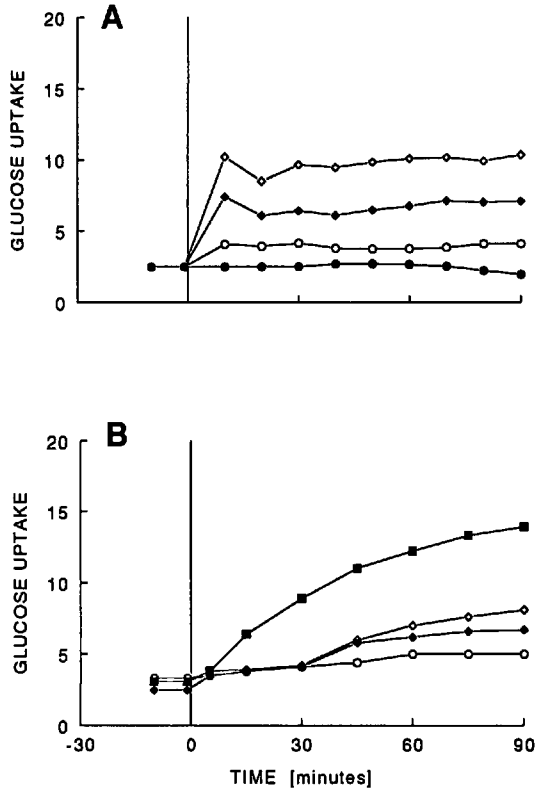

Figure 2—*Dynamics of glucose uptake due to isolated effects of hyperglycemia or hyperinsulinemia in dogs.* A: *effects of glucose per se. Glucose clamps were performed during somatostatin and basal insulin and glucagon replacement at glucose levels of 100 (●), 150 (○), 225 (◆), or 300 (◇) mg/dl.* B: *Effects of insulin per se. Euglycemic clamps were performed at insulin levels of 15 (○), 35 (◆), 53 (◇), or 131 (■) μU/ml. While the stimulatory effects of hyperglycemia are quite rapid, insulin's action to increase glucose uptake is delayed because of relatively slow movement of insulin across the capillary endothelial barrier. From Bergman et al. (41).*

of this phenomenon has been delineated: it is due to the relatively slow movement of the insulin molecule across the capillary endothelium of most insulin-sensitive tissues, including muscle and adipose tissue. In contrast to what happens when insulin changes, when glucose increases (Fig. 2), glucose uptake is enhanced almost instantaneously, even in vivo. Glucose readily crosses the capillary because of its small size and uncharged status; thus, it can readily enter the cell through specific transporter molecules and be stored or catabolized. In contrast to transendothelial movement of glucose, the slowness with which insulin reaches the insulin-sensitive tissues such as muscle and fat limits the overall influence of insulin to enhance glucose uptake after a carbohydrate meal or glucose injection.

We have measured the time course of interstitial fluid insulin during glucose clamps in dogs (37–39) as well as in humans (40). As expected, despite a rapid increment in plasma insulin, interstitial fluid insulin (as reflected by insulin in lymph exiting the leg) rises slowly, with a half-time of ~41 min (39). In addition, insulin concentration in lymph, even at steady state, is little more than half the concentration in plasma. Thus, there is both an attenuation and a retardation of the insulin signal as it crosses from the blood to the interstitium. This alteration in the insulin signal has important implications for the relative importance of glucose effectiveness versus insulin action in stimulation of glucose utilization.

As stated previously, during a glucose clamp, interstitial insulin increases slowly to a steady state over a 3-h period. While the time course of interstitial insulin during the OGTT has not been measured, computer simulation allows us to predict the insulin concentration in interstitial fluid (i.e., at the site of insulin action) during the OGTT and compare it to that during the clamp (Fig. 3). Because of the changing plasma insulin during the OGTT and the attenuation/retardation phenomenon discussed above, the peak level of insulin reached at the insulin-sensitive tissues themselves in normal individuals is <50% of that achieved at the end of a 3-h clamp (cf. Fig. 3*A* and *B*). During a clamp in which plasma insulin is 100 μU/ml, the increment in interstitial insulin is ~50 μU/ml. During the OGTT, plasma insulin peaks at ~100 μU/ml, equaling the maximal plasma insulin during the clamp. However, because of the slow dynamics of insulin transport, it is predicted that interstitial insulin peaks at just 24 μU/ml above basal (total, ~30 μU/ml). Additionally, mean insulin during the 3-h test is but 15 μU/ml above basal (mean total, ~21 μU/ml). More important, the total increase in the *amount* of insulin appearing in the interstitial compartment during the OGTT is predicted to be only 40% of the extra amount that has been measured to appear in the interstitium during a clamp. Similar differences are predicted between the glucose clamp and interstitial insulin during the OGTT for individuals with impaired glucose tolerance (Fig. 3*C*).

That insulin does not achieve steady state during the OGTT limits its total effect on glucose uptake (41). In fact, glucose effectiveness in normal individuals can be calculated to account for an equivalent amount of glucose uptake as insulin action after a glucose load (Fig. 4*A*). The relative importance of glucose effectiveness is even greater in insulin-resistant states when the time to achieve insulin action is increased compared with normal states (half-time ~75 min [42]) and the overall effect of insulin is reduced because of cellular insulin resistance. In fact, in the insulin-resistant obese individual, the estimated contribution of glucose effectiveness compared to that of insulin action is 83% compared with just 17% (Fig. 4*B*).

Thus, it appears that glucose effectiveness has significance equal to and possibly greater than the influence of insulin itself to enhance glucose uptake after a glucose load, and that the importance of glucose effectiveness is even greater in insulin-resistant states such as obesity.

Appearance versus disposal components of glucose effectiveness

Even at basal insulin, the effect of glucose infusion can include not only glucose enhancement of its own disposal, but also

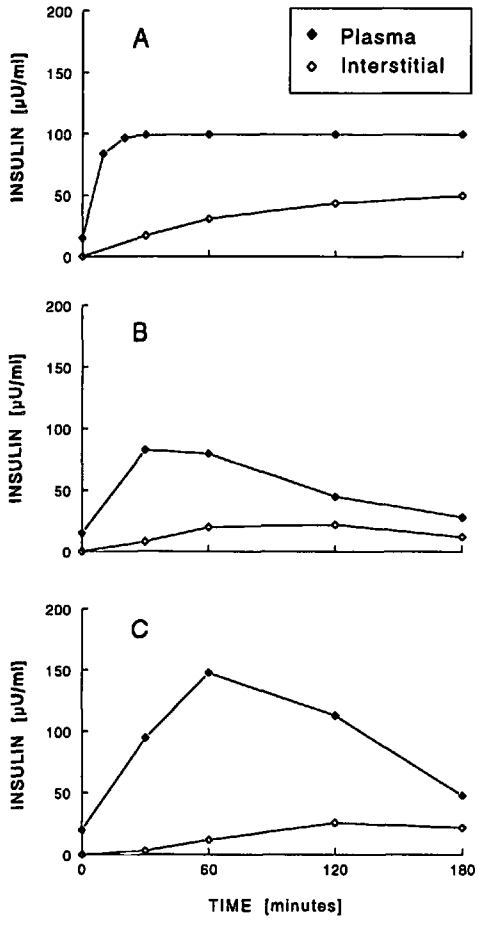

Figure 3—*Concentrations of insulin in plasma (actual) and interstitial fluid (predicted) during the hyperinsulinemic-euglycemic clamps (A), OGTTs in normal subjects (B), and OGTTs in subjects with impaired glucose tolerance (C). Plasma insulin is shown in solid symbols, and interstitial insulin in open symbols. To simulate the interstitial insulin profile from the time course of plasma insulin, the half-time for appearance of insulin in the interstitial space was assumed to be 45 min in normal and 74 min in subjects with impaired glucose tolerance (39). The ratio of insulin concentrations between plasma and interstitial fluid is assumed to be 2.0 in normal subjects (39) and 2.2 in subjects with impaired glucose tolerance (40). Plasma insulin data from clamps and OGTTs were obtained from Castillo et al. (40) and Reaven and Miller (100), respectively.*

suppression of endogenous glucose production (primarily from liver) (27,43,44). The overall effect of hyperglycemia to alter glucose economy is the sum of the increase in glucose disposal and the decrease in glucose production. During glucose clamps, the sum of these two effects is equal to the requisite glucose infusion rate to maintain target glycemia. We may extend our definition of glucose effectiveness from just the disposal component [$S_{GD(CLAMP)}$] to also include the effect of glucose to suppress endogenous glucose appearance [$S_{GA(CLAMP)}$]. Thus, we define whole-body glucose effectiveness from the glucose clamp [$S_{G(CLAMP)}$] as the relationship between glycemia and the rate of glucose infusion required to maintain that glycemia. Therefore,

$$S_{G(CLAMP)} = S_{GD(CLAMP)} + S_{GA(CLAMP)} \quad (4)$$

For example, let us assume that at basal glucose (95 mg/dl), hepatic glucose output equaled 2.5 mg · min^{-1} · kg^{-1} and that clamping glucose at 175 mg/dl, at basal insulin, suppressed endogenous hepatic glucose output (HGO) by 1.0 mg · min^{-1} · kg^{-1} and increased disposal by 2.0 mg · kg^{-1} · min^{-1}. The overall effect of glucose would be 1.0 + 2.0 = 3.0 mg · kg^{-1} · min^{-1} and would equal the requisite glucose infusion rate. Whole-body glucose effectiveness, then, would be equal to the requisite glucose infusion rate divided by the glucose increment:

$$S_{G(CLAMP)} = \frac{\Delta \text{ HGO} + \Delta R_d}{\Delta \text{ glucose}} \quad (5)$$

and

$$S_{G(CLAMP)} = \frac{1.0 + 2.0}{175 - 95} = 0.0375 \text{ dl} \cdot \text{min}^{-1} \cdot \text{kg}^{-1} \quad (6)$$

Note that this definition of whole-body glucose effectiveness will exceed peripheral glucose effectiveness by the degree to which glucose suppresses hepatic glucose output. [In this example, $S_{GD(CLAMP)}$ would have been 2.0/(175 − 95) = 0.025 dl · min^{-1} · kg^{-1}.] We shall return to a discussion of whole-body glucose effectiveness below, after discussion of the calculation of glucose effectiveness from the minimal model.

Glucose injection

The concept that glucose effectiveness is as important as incremental insulin action to enhance glucose disposal, demonstrated for clamps and the OGTT, has also been demonstrated for the IVGTT. In particular, the glucose effectiveness concept was incorporated into the minimal model (15). This model was the simplest mathematical construct that could account for intravenous glucose dynamics. It was not possible to account for glucose dynamics without including glucose effectiveness, further evidence for the importance of this concept.

Equations 7 and 8 comprise the minimal model:

$$\frac{dG(t)}{dt} = -[S_G + X(t)] \cdot G(t) + S_G G_b \quad (7)$$

$$\frac{dI(t)}{dt} = -p_2 X(t) + p_3 I(t) \quad (8)$$

$I(t)$ and $G(t)$ are plasma insulin and glucose, respectively, after glucose injection. $X(t)$ represents the "remote" insulin compartment, now identified as interstitial insulin (37,38). I_b and G_b are insulin and glucose at basal, before glucose injection, and S_G is the glucose effectiveness index. (In all previous literature, parameter S_G has been referred to as glucose effectiveness because the latter had not been measured other ways. However, now that the

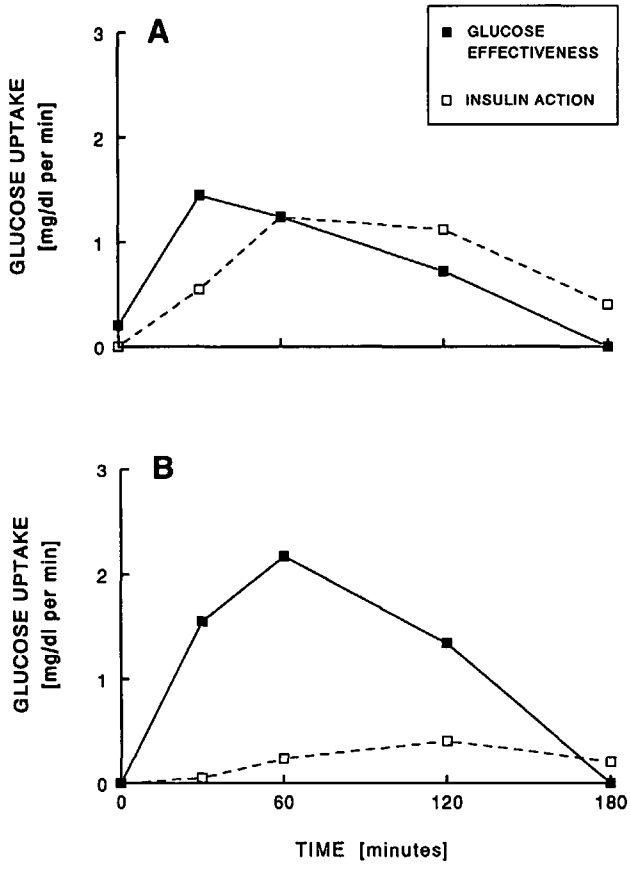

Figure 4—*Relative contribution of glucose effectiveness and insulin action during the OGTT for normal subjects (A) or subjects with impaired glucose tolerance (B). Glucose kinetics were characterized by a two-compartment distribution model, with insulin action affecting glucose uptake from the slow compartment (41). OGTT data were obtained from Reaven and Miller (100). Half-time for insulin action is 45 min for normal subjects and 74 min for subjects with impaired glucose tolerance (42).*

glucose clamp and the minimal model approach are being used to assess the effectiveness concept [50,101], we refer to S_G as the glucose effectiveness index, analogous to the insulin sensitivity index, S_I.) Parameters S_G, p_2, and p_3 are characteristic of individual subjects and are calculated from the performance of a frequently sampled IVGTT.

The minimal model partitions the return of plasma glucose after glucose injection into two individual components: one that depends on the dynamic insulin response (incremental insulin action) and a second that depends on glucose per se, at basal insulin (glucose effectiveness). The former component is quantitated as the product of the dynamic insulin response and the insulin sensitivity $[\int(I(t) - I_b)dt \cdot S_I]$. The latter component is quantified as S_G. This parameter has the same theoretical definition as whole-body glucose effectiveness discussed earlier. Of course, since $S_{G(CLAMP)}$ and S_G are calculated from different techniques (the clamp versus the minimal model), it remains to be proven that they are, in fact, equivalent.

In principle, the value of S_G from the minimal model should be equivalent to the S_G value determined from the IVGTT where the dynamic insulin response is suppressed. This can be understood by examination of Eqs. 7 and 8. At basal insulin, X (which represents any *increment* in interstitial insulin associated with a dynamic insulin response) is defined as zero.

Under this condition, Eq. 7 reduces to Eq. 9

$$\frac{dG(t)}{dt} = -S_G[G(t) - G_b] \quad (9)$$

and Eq. 10

$$G(0) = G_b + \Delta G \quad (10)$$

$G(t)$ is plasma glucose, $G(0)$ is the predicted glucose concentration immediately after glucose injection, G_b is the preinjection glucose concentration, and S_G is a rate constant defining the decline in plasma glucose. (Parameter S_G was originally termed p_1, but was renamed to establish its similarity to the insulin sensitivity index, S_I. The terminology S_G will be used throughout this review.)

The solution to Eq. 9 is Eq. 11:

$$G(t) = G_b + \Delta G e^{-S_G t} \quad (11)$$

According to Eq. 11, when the dynamic insulin response is suppressed and basal insulin is maintained, the minimal model predicts that the response to glucose injection should be approximately exponential, with a time constant equal to S_G. In other words, the half-time for glucose to return to its preinjection basal value (after initial mixing in the extracellular fluid) should be $0.693/S_G$. Thus, for example, if $S_G = 0.025$, the half-time for glucose disappearance, if the dynamic insulin response is inhibited, would be 27.7 min (0.693/0.025).

Ader et al. (18) examined the response to glucose injection at basal insulin. They used normal dogs, with somatostatin suppression of endogenous insulin, and basal insulin replacement. As predicted from the minimal model, with constant basal insulinemia, after glucose injection, the rate of decline of plasma glucose followed a single exponential. Glucose effectiveness, quantitated as the time constant of the renormalization of glucose, averaged 0.025 ± 0.004 min^{-1} in their experiments.

Note that glucose effectiveness from Ader's analysis exceeds the $S_{G(CLAMP)}$ value of 0.012 min^{-1} presented above for human volunteers. There are several possible explanations for this difference. First, the value of whole-body glucose effectiveness from Ader's analysis represents the effect of glucose to enhance *net* glucose disappearance. This includes two components: the glucose effect to increase glucose disposal (disposal component) and the effect of glucose to suppress endogenous glucose output (endogenous appearance component). The data presented above for humans represented the disposal component only. Second, the possibility must be considered that glucose effectiveness in dogs exceeds that in humans.

The measure of glucose effectiveness derived from the minimal model

Table 2—*Calculation of glucose effectiveness from glucose clamp studies in dogs*

Glucose (mg/dl)		Glucose effectiveness (dl · min^{-1} · kg^{-1})		
		Disposal	Whole-body	Difference
Basal	Elevated	$\left(\frac{\Delta R_d}{\Delta G}\right)$	$\left(\frac{\text{GINF}}{\Delta G}\right)$	
127	213	0.0273	0.0451	0.0178
92	227	0.0219	0.0352	0.0133
99	234	0.0309	0.0336	0.0270
98	270	0.0228	0.0438	0.0210
104 ± 8	236 ± 12	0.026 ± 0.002	0.039 ± 0.003	0.013 ± 0.004
per unit distribution volume (min^{-1})		0.015 ± 0.001 (67%)	0.023 ± 0.002 (100%)	0.008 ± 0.002 (33%)

Data from individual animals are shown. Based on data from Cherrington et al. (47).

analysis of IVGTT data includes glucose's effects to enhance utilization *and* to suppress glucose output. Therefore, the minimal model definition of glucose effectiveness is analogous to the definition of whole-body glucose effectiveness from glucose clamps at basal insulin. The minimal model parameter S_G is the fractional increase in glucose utilization, normalized to the glucose pool, and expressed in units of reciprocal minutes. Clamp-based glucose effectiveness at basal insulin can be converted to a value equivalent to S_G by dividing by the glucose space; that is, Eq. 12:

$$S_G = \text{glucose effectiveness from clamps/distribution volume} \quad (12)$$

Assuming a glucose distribution volume of 0.65 × 2.6 dl/kg (45,46), we have

$$S_G = \text{clamp glucose effectiveness at basal insulin}/1.69 \quad (13)$$

Table 2 shows data from glucose clamp studies in dogs, with whole-body and disposal glucose effectiveness values calculated at basal insulin (16 μU/ml), extracted from a study by Cherrington et al. (47). Converting to minimal model units, S_G is 0.023 ± 0.002 min^{-1} (corrected for glucose space, bottom of 4th column in Table 2). Cherrington used tracer dilution to calculate peripheral glucose uptake, allowing for additional calculation of the peripheral component of glucose effectiveness from their data. Note that whole-body effectiveness (0.039 dl · min^{-1} · kg^{-1}, 0.023 min^{-1} after correction to glucose space) can be separated into the disposal component (0.026 dl · min^{-1} · kg^{-1}, 0.015 min^{-1} after correction, 67%) and the remainder (0.013 dl · min^{-1} · kg^{-1}, 0.008 min^{-1}, 33%), which is presumably the effect of glucose at basal insulin to suppress hepatic glucose output (the appearance component of glucose effectiveness). These data in Table 2 indicate that, based on tracer dilution measurements, at basal insulin, about two-thirds of the effect of glucose to enhance *net* glucose uptake is due to the disposal effect, with the remainder apparently accounted for by an effect of glucose to suppress the liver. This proportion—two-thirds disposal and one-third production—is very similar to results calculated from human data (Table 3) except that whole-body glucose effectiveness in the dog appears to be somewhat greater than that reported for humans (0.039 compared to 0.024 dl · min^{-1} · kg^{-1}).

Assigning a full third of the effect of glucose on net glucose disappearance to suppression of hepatic glucose output is consistent with reports of glucose's effect on glucose output. Sacca et al. (43) reported a 35–40% suppression of hepatic glucose output in normal subjects at basal insulin when glycemia increased to 183 mg/dl (43); the ratio of suppression of production to increment in glucose concentration in their study was 0.95 mg · min^{-1} · kg^{-1} per 94 mg/dl = 0.010 dl · min^{-1} · kg^{-1}. This is similar to the prediction from human data (Table 3) that the hepatic component of glucose effectiveness would be 0.008 dl · min^{-1} · kg^{-1}. Similarly, Adkins et al. (48) assessed the effect of peripheral glycemia on net hepatic glucose balance in dogs, measured by arteriovenous difference and tracer methods. Glucose effectiveness from their data was [(3.50 −1.29 mg · min^{-1} · kg^{-1})/(200 −100 mg/dl)] = 0.022 dl · min^{-1} · kg^{-1}, confirming that the hepatic component of glucose effectiveness in dogs exceeds that in humans in absolute value and that it accounts for at least one-third of the total effect of elevated glycemia to alter net glucose disposition when plasma insulin is at a basal fasting level.

Recently, Ader and colleagues (49) used tracer modeling as well as glucose clamps to separate glucose effectiveness into its two components. They report that in dogs about two-thirds of glucose effectiveness is due to disposal and one-third is due to glucose suppression of the liver (49). Christopher et al. (50) have also reported a predominance of the disposal effect in dogs. Thus, it is clear that the value of glucose effectiveness in dogs (18) exceeded the estimated value in humans for at least two reasons: the liver component contributes an additional one-third factor to whole-body glucose effectiveness, and the peripheral glucose effectiveness component appears to be greater in dogs than in humans.

GLUCOSE EFFECTIVENESS IN DIFFERENT STATES

S_G from the minimal model

Measuring glucose effectiveness directly, whether by glucose clamp or by the intra-

Table 3—*Calculation of glucose effectiveness from clamps in subjects with normal glucose tolerance*

Glucose (mg/dl)		Mean insulin	Glucose effectiveness ($dl \cdot min^{-1} \cdot kg^{-1}$)		
Basal	Elevated	($\mu U/ml$)	Disposal	Whole-body	Difference
100	309	11	0.016 ± 0.004 (67%)	0.024 ± 0.005 (100%)	0.008 ± 0.001 (33%)

Data are summarized from six data sets (24,27,29–32).

venous protocol introduced by Ader et al. (18), is a time-consuming and labor-intensive process. An alternative is the direct use of the minimal model itself. A stereotypical protocol is used in which glucose (usually 300 mg/kg) is injected, followed by either tolbutamide or insulin 20 min later. Samples are taken over 3 h, and glucose and insulin measurements are used to estimate the parameters of the minimal model (Eqs. 7 and 8). From this analysis emerges the insulin sensitivity index, S_I, as well as the glucose effectiveness index, S_G. The great preponderance of data on glucose effectiveness is based on estimates emerging from minimal model usage.

Glucose effectiveness has been measured using the minimal model in over 50 individual studies in the recent past. Some of these studies are summarized in Table 4, in which we have listed only the mean normal S_G value from 18 studies, and values of S_G from all studies that deviated measurably from the normal value. While individual values of insulin sensitivity (S_I) varied widely among individual studies (coefficient of variation 58%, data not shown), the S_G in 18 studies (average value 0.024 min^{-1}) varied much less (coefficient of variation 32%). Also, S_G is reduced in certain specific subject groups, ranging from a minor reduction in polycystic ovarian disease (S_G = 0.018 min^{-1}) to a substantial reduction in subjects on a very-low-calorie diet (S_G = 0.010 min^{-1}). Note that S_G is reduced in IDDM as well as NIDDM patients.

In three groups, a substantial *increase* in S_G was noted: with acute exercise, with glucagon-like peptide 1 treatment, and with physical training, although the training effect on S_G has not been universally observed (51).

Commonality in groups with S_G reduction

A common thread in many but certainly not all groups with reduced S_G is reduced insulin secretion and/or hypoinsulinemia. Thus, reduced insulin response is expected in pancreas transplant subjects and subjects treated with octreotide, as well as in NIDDM and IDDM patients and in patients on a very-low-calorie diet. Two possibilities may be considered: first, that insulin itself, on a chronic basis, is a regulator of glucose effectiveness. Consistent with this notion are studies in animals reporting reduced S_G with experimental β-cell damage (83,84). A second possibility must also be considered, namely, that S_G estimation from the minimal model may be distorted in subjects with reduced insulin response. Finegood and Tzur (85) have suggested this latter possibility based on animal experiments. Clearly, clarification of whether a bias in the S_G estimate exists based on insulin response deserves further attention, and reduced S_G in diabetic states awaits further analysis.

Importance of glucose effectiveness in NIDDM

Regardless of the exact value of glucose effectiveness, it is an important factor in the glucose regulation of NIDDM patients. As discussed earlier, there are three components that determine glucose disposition: $R_d(0)$, glucose effectiveness, and secreted insulin acting through the insulin action cascade. However, NIDDM subjects are highly insulin resistant (4,7); in addition, NIDDM patients have severely depressed insulin secretion (6,9), especially for their degree of insulin resistance. The combination of these two defects results in insulin itself making little if any contribution to the increase in glucose disposal after carbohydrate ingestion. $R_d(0)$ does not increase with glycemia; therefore, it is only the glucose effectiveness that can account for glucose utilization increasing after carbohydrate ingestion in the NIDDM patient. It is glucose effectiveness, then, that represents the last resort for glucose regulation in these patients. Given this, it is important to understand the regulation of glucose effectiveness in diabetic patients because the value of this parameter may well influence the mortality and morbidity related to lack of glucose regulation in such patients.

Table 4—*Glucose effectiveness index for human subjects*

Condition	S_G (min^{-1})	Reference
Acute exercise	0.044	52
Physical training	0.030	53
Glucagon-like peptide 1	0.027	54
Normal subjects	**0.024**	**55–72**
Polycystic ovarian disease	0.018	56
Pancreas transplant	0.016	73
Offspring of 2 NIDDM parents	0.016	74
NIDDM	0.015	75–77
Anorexia nervosa	0.015	78
Impaired glucose tolerance	0.015	79,80
IDDM	0.013	63,70
High-dose oral contraceptive	0.011	81
Octreotide treatment (7 days)	0.010	66
Very-low-calorie diet	0.010	82

Value of S_G for normal subjects represents mean of control values published in 18 separate studies (55–72). In all studies, S_G obtained from the test conditions was statistically different from that of their respective control conditions.

MECHANISMS

Given the present observations that glucose effectiveness contributes substantially to carbohydrate disposal and is reduced in diabetic states, it is of interest to consider the underlying mechanisms that are responsible for glucose uptake at basal insulin. It will also be of interest to study the alterations in these mechanisms in pathological states.

Peripheral component

The most obvious contributor to glucose effectiveness is the mass-action effect of glucose itself. At basal insulin, there are finite populations of insulin-independent glucose transporters GLUT1 and GLUT2 on the cell membrane and presumably a small number of so-called insulin-dependent transporters, GLUT4 (86–88). Thus, it is straightforward that hyperglycemia, even at basal insulin, will, by the law of mass action, enhance the flux of glucose across the capillary endothelium and into cells. This flux should be large for liver, which is replete with GLUT2 transporters. Interestingly, since glucose effectiveness is the *increase* in glucose uptake with hyperglycemia, the central nervous system contributes little or nothing because glucose uptake by the brain is saturated at the fasting glucose level (89,90). Additionally, it is to be expected that increased uptake with hyperglycemia would occur in muscle, which not only has GLUT1 transporters on the membrane but accounts for 50% of body mass.

However, it is not likely that mass action is the only contributing factor to glucose effectiveness. It has long been known that certain rate-limiting enzymes, particularly in the liver, are allosterically activated by glucose. For example, glucokinase, rate limiting for hepatic glucose uptake and therefore glycogen synthesis, is a glucose-dependent enzyme (91,92). Thus, glucose should enhance glycogen synthesis in liver beyond the mere mass-action uptake of the hexose. There is both a "push" and a "pull" enhancement of glycogen synthesis in the liver, and these mechanisms will contribute to whole-body glucose disappearance independent of a change in insulin.

Finally, exciting new results indicate that glucose itself may mimic insulin by directly enhancing recruitment of GLUT4 glucose transporters to the surface of skeletal muscle. In fact, Galante et al. (93) reported that in vitro and in vivo glucose transporter abundance at the cell membrane could be doubled by hyperglycemia without hyperinsulinemia. Also Nolte et al. (94) demonstrated that the glucose-dependent activation of glucose transport is mechanistically distinct from the insulin-dependent mechanism. Glucose acts via a Ca^{2+}-dependent mechanism, whereas the insulin mechanism is mediated via phosphatidylinositol 3-kinase. This recent report of glucose-stimulated transporter recruitment, if confirmed, should lead to continued investigation of the mechanism by which glucose acts to increase cellular metabolism independent of a change in insulin.

What is interesting about the three mechanisms by which glucose can accelerate glucose utilization—mass action, enzyme activation, and transporter recruitment—is that these mechanisms are synergistic. Thus, increased mass action coupled with increased transporter recruitment will have a multiplicative effect to increase the utilization of glucose. It is apparent that exciting work regarding the mechanism of glucose effectiveness lies in the near future.

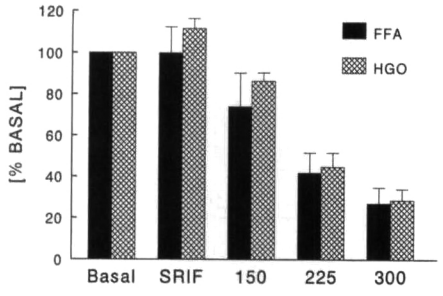

Figure 5—*Suppression of plasma free fatty acid (FFA) and HGO by hyperglycemia alone. Stepwise hyperglycemic clamps (three levels per clamp) were performed in normal dogs during somatostatin and fixed basal insulin and glucagon. Data were obtained at basal, during euglycemic basal insulin and glucagon (SRIF), and at glucose levels of 150, 225, and 300 mg/dl, and are presented as percentages of respective basal values. There was clear similarity in the degree of suppression of free fatty acid and HGO by hyperglycemia, consistent with the possibility that glucose autoregulation may occur through indirect actions on the adipocyte to suppress lipolysis. Data were obtained from Ader and Bergman (102).*

Hepatic suppression component

Classically, it has been known that glucose has an autoregulatory effect to suppress glucose output (43,44,95,96). However, evidence indicates that while glucose suppresses the net rate of glucose output in in vitro systems, the appearance of newly formed glucose (e.g., from gluconeogenesis and glycogen breakdown) is not influenced by glucose (97). In vivo, however, it is very clear that the appearance of newly formed glucose is inhibited by hyperglycemia.

Recent data has emanated from our laboratory that can explain the hepatic suppression component of glucose effectiveness: the dose-dependent reduction in hepatic glucose output that can be seen in vivo. We have reported that insulin has only a minor *direct* effect to suppress hepatic glucose production (98); in fact, the primary mechanism by which liver glucose output is regulated by insulin is at the adipocyte. Thus, insulin suppresses lipolysis, and this, in turn, lowers the liver glucose production (99). Figure 5 reports preliminary data from Ader and Bergman (102) in which a dose-dependent reduction in plasma free fatty acids was stimulated by hyperglycemia, despite maintaining plasma insulin at basal. Thus, glucose, as well as insulin, may suppress hepatic glucose production by an indirect mechanism: Glucose acts to suppress lipolysis (possibly by enhancement of reesterification); this in turn reduces the free fatty acid signal to the liver, and glucose production falls. The ability of glucose to suppress lipolysis and lower plasma free fatty acids may determine the value of the hepatic suppression component of glucose effectiveness. Future studies will be designed to investigate this possibility further.

It is apparent that glucose effectiveness may be the summed effect of many separate physiological mechanisms, acting at the liver as well as the periphery to enhance glucose utilization and suppress glucose output and to help regulate the blood glucose concentration. At this time little is known, but more should be delineated, regarding alterations in these mechanisms in the prediabetic and diabetic states.

FINAL COMMENTS

Understanding the role of insulin secretion and insulin sensitivity in the ability to dispose of carbohydrate is relatively straightforward. It is considerably more difficult to comprehend what glucose ef-

Table 5—*Glossary*

Concept or parameter	Name	Definition
"Glucose effectiveness" (the concept)		The ability of glucose per se to increase glucose disposal and to inhibit endogenous glucose appearance.
$S_{GD(CLAMP)}$	Disposal glucose effectiveness	The effect of increased glucose per se, at basal insulin, to enhance glucose disposal during a glucose clamp.
$S_{GA(CLAMP)}$	Appearance glucose effectiveness	The effect of increased glucose per se, at basal insulin, to suppress endogenous glucose appearance during a glucose clamp.
$S_{G(CLAMP)}$	Whole-body glucose effectiveness	The total effect of increased glucose, at basal insulin, to enhance glucose disposal and to suppress endogenous glucose appearance during a glucose clamp.
S_G	Glucose effectiveness index	The effect of glucose per se to enhance disposal and suppress endogenous glucose appearance during an IVGTT.

fectiveness is and to understand its possible role in glucose intolerance and diabetes.

Glucose effectiveness is an important and previously underappreciated contributor to glucose tolerance in vivo. It appears to be an equal contributor, along with insulin action, to the degree of glucose tolerance in normal individuals under a variety of circumstances. Glucose action is similar among many different subject groups, and it represents a last line of defense, providing glucose disposal even when insulin action is compromised. However, glucose effectiveness has been shown to be reduced in states of glucose intolerance, including diabetes, although whether it is causal or a result of the diabetic state requires further investigation.

Thus, glucose effectiveness is the hidden conspirator in the glucose tolerance regulating system. Its quantitative importance will inevitably lead to further study of the factors that determine it and of whether it has a separable genetic determination from insulin secretion and insulin sensitivity. If the latter is found to be so, then we may look to the proteins that regulate insulin-independent glucose utilization for additional candidate genes that may lead to inherited states of reduced glucose tolerance and diabetes.

Acknowledgments— We gratefully acknowledge support from the National Institutes of Health (NIH) of the U.S., which provides support to R.N.B. (NIH-DK29867 and DK27619) and M.A. (AG00544). R.N.B. is also supported by the Salerni Collegium of the University of Southern California. S.E.K. is supported in part by the Office of Medical Research, Department of Veterans Affairs, and the NIH (DK12829 and DK17047).

APPENDIX

A glossary is presented in Table 5.

References

1. National Diabetes Data Group: Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes* 28:1039–1057, 1979
2. Cerasi E, Luft R: "What is inherited–what is added" hypothesis for the pathogenesis of diabetes mellitus. *Diabetes* 16: 615–627, 1967
3. Perley M, Kipnis DM: Plasma insulin responses to glucose and tolbutamide of normal weight and obese diabetic and nondiabetic subjects. *Diabetes* 15:867–874, 1966
4. Reaven GM, Bernstein R, Davis B, Olefsky JM: Nonketotic diabetes mellitus: insulin deficiency or insulin resistance. *Am J Med* 60:80–88, 1976
5. Turner RC, Holman RR, Matthews D, Hockaday TDR, Peto J: Insulin deficiency and insulin resistance interaction in diabetes: estimation of their relative contribution by feedback analysis from basal plasma insulin and glucose concentrations. *Metabolism* 28:1086–1096, 1979
6. Weir GC: Non-insulin dependent diabetes mellitus: interplay between β-cell inadequacy and insulin resistance. *Am J Med* 73:461–464, 1982
7. DeFronzo RA: The triumvirate: β-cell, muscle, liver: a collusion responsible for NIDDM. *Diabetes* 37:667–687, 1987
8. Cahill GF Jr: Beta-cell deficiency, insulin resistance or both? *N Engl J Med* 318: 1268–1270, 1991
9. Porte D Jr: β-cells in type II diabetes mellitus (Banting Lecture). *Diabetes* 40:166–180, 1991
10. Heine RJ, Hanning I, Morgan L, Alberti KGMM: The oral glucose tolerance test (OGTT): effect of rate of ingestion of carbohydrate and different carbohydrate preparations. *Diabetes Care* 6:441–445, 1983
11. Nauck M, Stockmann F, Ebert R, Creutzfeldt W: Reduced incretin effect in type 2 (non-insulin-dependent) diabetes. *Diabetologia* 29:46–52, 1986
12. Bergman RN: Toward physiological understanding of glucose tolerance: minimal-model approach (Lilly Lecture). *Diabetes* 38:1512–1527, 1989
13. Osei K: Predicting type II diabetes in persons at risk. *Ann Intern Med* 113:905–907, 1990
14. Rudenski AS, Matthews DR, Levy JC, Turner RC: Understanding "insulin resistance": both glucose resistance and insulin resistance are required to model human diabetes. *Metabolism* 40:908–917, 1991
15. Bergman RN, Ider YZ, Bowden CR, Cobelli C: Quantitative estimation of insulin sensitivity. *Am J Physiol* 236:E667–E677, 1979
16. Soskin S, Allweiss MD, Cohn DJ: Influence of the pancreas and the liver upon the dextrose tolerance test. *Am J Physiol* 109:155–165, 1934
17. Vranic M, Fono P, Kovacevic N, Lin BJ: Glucose kinetics and fatty acids in dogs on matched insulin infusion after glucose load. *Metabolism* 20:954–967, 1971
18. Ader M, Pacini G, Yang YJ, Bergman RN: Importance of glucose per se to intravenous glucose tolerance: comparison of the minimal model prediction with direct measurements. *Diabetes* 34:1092–1103, 1985
19. Best JD, Taborsky GJ Jr, Halter JB, Porte D Jr: Glucose disposal is not proportional to plasma glucose level in man.

Diabetes 30:847–850, 1981
20. Verdonk CA, Rizza RA, Gerich JE: Effects of plasma glucose concentration on glucose utilization and glucose clearance in normal man. *Diabetes* 30:535–537, 1981
21. DeFronzo RA, Ferrannini E, Hendler R, Felig P, Wahren J: Regulation of splanchnic and peripheral glucose uptake by insulin and hyperglycemia in man. *Diabetes* 32:35–45, 1983
22. DeFronzo RA, Ferrannini E: Influence of plasma glucose and insulin concentration on plasma glucose clearance in man. *Diabetes* 31:683–688, 1982
23. Gottesman I, Mandarino L, Verdonk C, Rizza R, Gerich J: Insulin increases the maximum velocity for glucose uptake without altering the Michaelis constant in man. *J Clin Invest* 70:1310–1314, 1982
24. Proietto J, Nankervis A, Aitken P, Caruso G, Harewood M, Alford FP: The physiologic action of insulin on glucose uptake and its relevance to the interpretation of the metabolic clearance rate of glucose. *Metabolism* 32:1022–1028, 1983
25. Baron AD, Kolterman OG, Bell J, Mandarino LJ, Olefsky JM: Rates of noninsulin-mediated glucose uptake are elevated in type II diabetic subjects. *J Clin Invest* 76:1782–1788, 1985
26. Hansen IL, Cryer PE, Rizza RA: Comparison of insulin-mediated and glucose-mediated glucose disposal in patients with insulin-dependent diabetes mellitus and in nondiabetic subjects. *Diabetes* 34:751–755, 1985
27. Bell PM, Firth RG, Rizza RA: Effects of hyperglycemia on glucose production and utilization in humans: measurement with [2-^{3}H]-, [3-^{3}H]-, and [6-^{14}C]glucose. *Diabetes* 35:642–648, 1986
28. Fink RI, Wallace P, Olefsky JM: Effects of aging on glucose-mediated glucose disposal and glucose transport. *J Clin Invest* 77:2034–2041, 1986
29. Yki-Jarvinen H, Bogardus C, Howard BV: Hyperglycemia stimulates carbohydrate oxidation in humans. *Am J Physiol* 253:E376–E382, 1987
30. Arnfred J, Schmitz O, Hother-Nielsen O, Orskov C, Beck-Nielsen H, Hermansen K, Christiansen JS, Alberti KGMM, Orskov H: Marked impairment of the effect of hyperglycemia on glucose uptake and glucose production in insulin-dependent diabetes. *Diabetic Med* 5:755–760, 1988
31. Thorburn AW, Gumbiner B, Brechtel G, Henry RR: Effect of hyperinsulinemia and hyperglycemia on intracellular glucose and fat metabolism in healthy subjects. *Diabetes* 39:22–30, 1990
32. Edelman SV, Laakso M, Wallace P, Brechtel G, Olefsky JM, Baron AD: Kinetics of insulin-mediated and non-insulin-mediated glucose uptake in humans. *Diabetes* 39:955–964, 1990
33. Davis BM, Bernstein R, Kolterman O, Olefsky JM, Reaven GM: Defect in glucose removal in nonketotic diabetic patients with fasting hyperglycemia. *Diabetes* 28:32–34, 1979
34. Bergman RN, Finegood DT, Ader M: Assessment of insulin sensitivity in vivo. *Endocrine Rev* 6:45–86, 1985
35. Sherwin RS, Kramer KJ, Tobin JD, Insel PA, Liljenquist JE, Berman M, Andres R: A model of the kinetics of insulin in man. *J Clin Invest* 53:1481–1492, 1974
36. Doberne L, Greenfield MS, Schulz B, Reaven GM: Enhanced glucose utilization during prolonged glucose clamp studies. *Diabetes* 30:829–835, 1981
37. Yang YJ, Hope ID, Ader M, Bergman RN: Insulin transport across capillaries is rate limiting for insulin action in dogs. *J Clin Invest* 84:1620–1628, 1989
38. Ader M, Poulin RA, Yang YJ, Bergman RN: Dose response relationship between lymph insulin and glucose uptake reveals enhanced insulin sensitivity of peripheral tissues. *Diabetes* 41:241–253, 1992
39. Poulin RA, Steil GM, Moore DM, Ader M, Bergman RN: Dynamics of glucose production and uptake are more closely related to insulin in hindlimb lymph than in thoracic duct lymph. *Diabetes* 43:180–190, 1994
40. Castillo C, Bogardus C, Bergman R, Thuillez P, Lillioja S: Interstitial insulin concentrations determine glucose uptake rates but not insulin resistance in lean and obese men. *J Clin Invest* 93:10–16, 1994
41. Bergman RN, Ni T-C, Ader M: Glucose effectiveness. In *Clinical Research in Diabetes*. Draznin B, Rizza RA, Eds. Totowa, NJ, Humana, 1996
42. Prager R, Wallace P, Olefsky JM: In vivo kinetics of insulin action on peripheral glucose disposal and hepatic glucose output in normal and obese subjects. *J Clin Invest* 78:472–481, 1986
43. Sacca L, Hendler R, Sherwin RS: Hyperglycemia inhibits glucose production in man independent of changes in glucoregulatory hormones. *J Clin Endocrinol Metab* 47:1160–1163, 1978
44. Liljenquist JE, Mueller GL, Cherrington AD, Perry JM, Rabinowitz D: Hyperglycemia per se (insulin and glucagon withdrawn) can inhibit hepatic glucose production in man. *J Clin Endocrinol Metab* 48:171–175, 1979
45. Altszuler N, Steele R, Wall JS, Dunn A, deBodo RC: Effect of growth hormone on carbohydrate metabolism in normal and hypophysectomized dogs; studies with C-14-glucose. *Am J Physiol* 196: 121–124, 1959
46. Caviezel F, Cattaneo AG, Marini G, Pozza G, Capani F, Sensi S: Diurnal rhythm of blood glucose and insulin levels in obese subjects with or without impaired glucose tolerance. In *Recent Advances in Obesity and Diabetes Research*. Melchionda N, Ed. New York, Raven, 1984, p. 49–54
47. Cherrington AD, Williams PE, Harris MS: Relationship between the plasma glucose level and glucose uptake in the conscious dog. *Metabolism* 27:787–791, 1978
48. Adkins BA, Myers SR, Hendrick GK, Stevenson RW, Williams PE, Cherrington AD: Importance of the route of intravenous glucose delivery to hepatic glucose balance in the conscious dog. *J Clin Invest* 79:557–565, 1987
49. Ader M, Bergman RN: Experimental dissection of metabolic processes accounting for glucose-dependent glucose disappearance (Abstract). *J Invest Med* 43: 170A, 1995
50. Christopher MJ, Rantzau C, Ward GM, Alford FP: Insulinopenia and hyperglycemia influence the in vivo partitioning of GE and SI. *Am J Physiol* 268:E410–E421, 1995
51. Kahn SE, Larson VG, Schwartz RS, Beard JC, Cain KC, Fellingham GW, Stratton JR, Cerqueira MD, Abrass IB: Exercise training delineates the importance of β-cell dysfunction to the glucose intolerance of human aging. *J Clin Endocrinol Metab* 74:1336–1342, 1992
52. Brun JF, Guintrand-Hugret R, Boegner C, Bouix O, Orsetti A: Influence of short-term submaximal exercise on parameters of glucose assimilation analyzed with the minimal model. *Metabolism* 44: 833–840, 1995
53. Tokuyama K, Higaki Y, Fujitani J, Kiyonaga A, Tanaka H, Shindo M, Fukushima M, Nakai Y, Imura H, Nagata I, Taniguchi A: Intravenous glucose tolerance test–derived glucose effectiveness in physically trained humans. *Am J Physiol* 265:E298–E303, 1993
54. D'Alessio DA, Kahn SE, Leusner CR, Ensinck JW: Glucagon-like peptide 1 enhances glucose tolerance both by stimulation of insulin release and by increasing insulin-independent glucose disposal. *J Clin Invest* 93:2263–2266, 1994
55. Kahn SE, Prigeon RL, McCulloch DK, Boyko EJ, Bergman RN, Schwartz MW, Neifing JL, Ward WK, Beard JC, Palmer JP, Porte D Jr: The contribution of insulin-dependent and insulin-independent glucose uptake to intravenous glucose tolerance in healthy human subjects. *Diabetes* 43:587–592, 1994
56. Falcone T, Little AB, Morris D: Impaired glucose effectiveness in patients with polycystic ovary syndrome. *Human Reprod* 7:922–925, 1992

57. Caumo A, Giacca A, Morgese M, Pozza G, Micossi P, Cobelli C: Minimal models of glucose disappearance: lessons from the labelled IVGTT. *Diabetic Med* 8:822–832, 1991
58. Piccardo MG, Pacini G, Rosa M, Vichi R: Insulin resistance in myotonic dystrophy. *Enzyme* 45:14–22, 1991
59. Pestell R, Alford F, Ramos R, Sawyer S, Best J, Ward G: Insulin secretion, insulin sensitivity and glucose-mediated glucose disposal in thyrotoxicosis: a minimal model analysis. *Clin Endocrinol* 33: 481–493, 1990
60. Walton C, Godsland IF, Proudler AJ, Felton C, Wynn V: Evaluation of four mathematical models of glucose and insulin dynamics with analysis of effects of age and obesity. *Am J Physiol* 262:E755–E762, 1992
61. Ward GM, Walters JM, Aitken PM, Best JD, Alford FP: Effects of prolonged pulsatile hyperinsulinemia in humans: enhancement of insulin sensitivity. *Diabetes* 39:501–507, 1990
62. Welch S, Gebhart SSP, Bergman RN, Phillips LS: Minimal model analysis of intravenous glucose tolerance test-derived insulin sensitivity in diabetic subjects. *J Clin Endocrinol Metab* 71:1508–1518, 1990
63. Finegood DT, Hramiak IM, Dupre J: A modified protocol for estimation of insulin sensitivity with the minimal model of glucose kinetics in patients with insulin-dependent diabetes. *J Clin Endocrinol Metab* 70:1538–1549, 1990
64. Osei K, Cottrell DA, Henry ML, Tesi RJ, Ferguson RM, O'Dorisio TM: Minimal model analysis of insulin sensitivity and glucose-mediated glucose disposal in type 1 (insulin-dependent) diabetic pancreas allograft recipients. *Diabetologia* 35:676–680, 1992
65. Kahn SE, Beard JC, Schwartz MW, Ward WK, Ding HL, Bergman RN, Taborsky GJ Jr, Porte D Jr: Increased β-cell secretory capacity as mechanism for islet adaptation to nicotinic-acid-induced insulin resistance. *Diabetes* 38:562–568, 1989
66. Kahn SE, Klaff LJ, Schwartz MW, Beard JC, Bergman RN, Taborsky GJ Jr, Porte D Jr: Treatment with a somatostatin analog decreases pancreatic β-cell and whole body sensitivity to glucose. *J Clin Endocrinol Metab* 71:994–1002, 1990
67. Kahn SE, Bergman RN, Schwartz MW, Taborsky GJ Jr, Porte D Jr: Short-term hyperglycemia and hyperinsulinemia improve insulin action but do not alter glucose action in normal humans. *Am J Physiol* 262:E518–E523, 1992
68. Marchesini G, Pacini G, Bianchi G, Patrono D, Cobelli C: Glucose disposal, β-cell secretion, and hepatic insulin extraction in cirrhosis: a minimal model assessment. *Gastroenterology* 99:1715–1722, 1990
69. Kautzky-Willer A, Pacini G, Niederle B, Schernthaner G, Prager R: Insulin secretion, insulin sensitivity and hepatic insulin extraction in primary hyperparathyroidism before and after surgery. *Clin Endocrinol* 37:147–155, 1992
70. Ward GM, Weber KM, Walters IM, Aitken PM, Lee B, Best JD, Boston RC, Alford FP: A modified minimal model analysis of insulin sensitivity and glucose-mediated glucose disposal in insulin-dependent diabetes. *Metabolism* 40: 4–9, 1991
71. Marangou AG, Weber KM, Boston RC, Aitken PM, Heggie JCP, Kirsner RLG, Best JD, Alford FP: Metabolic consequences of prolonged hyperinsulinemia in humans: evidence for induction of insulin insensitivity. *Diabetes* 35:1383–1389, 1986
72. Marangou AG, Alford FP, Ward G, Liskaser F, Aitken PM, Weber KM, Boston RC, Best JD: Hormonal effects of norepinephrine on acute glucose disposal in humans: a minimal model analysis. *Metabolism* 37:885–891, 1988
73. Christiansen E, Tibell A, Volund A, Rasmussen K, Tyden G, Pedersen O, Christensen NJ, Madsbad S: Insulin secretion, insulin action and non-insulin-dependent glucose uptake in pancreas transplant recipients. *J Clin Endocrinol Metab* 79:1561–1569, 1994
74. Martin BC, Warram JH, Krolewski AS, Bergman RN, Soeldner JS, Kahn CR: Role of glucose and insulin resistance in development of type 2 diabetes mellitus: results of a 25-year follow-up study. *Lancet* 340:925–929, 1992
75. Coates PA, Ollerton RL, Luzio SD, Ismail IS, Owens DR: Reduced sampling protocols in estimation of insulin sensitivity and glucose effectiveness using the minimal model in NIDDM. *Diabetes* 42: 1635–1641, 1993
76. Kruszynska YT, Harry DS, Bergman RN, McIntyre N: Insulin sensitivity, insulin secretion and glucose effectiveness in diabetic and non-diabetic cirrhotic patients. *Diabetologia* 36:121–128, 1993
77. Taniguchi A, Nakai Y, Fukushima M, Kawamura H, Imura H, Nagata I, Tokuyama K: Pathogenic factors responsible for glucose intolerance in patients with NIDDM. *Diabetes* 41:1540–1546, 1992
78. Fukushima M, Nakai Y, Taniguchi A, Imura H, Nagata I, Tokuyama K: Insulin sensitivity, insulin secretion, and glucose effectiveness in anorexia nervosa: a minimal model analysis. *Metabolism* 42: 1164–1168, 1993
79. Kautzky-Willer A, Pacini G, Ludvik B, Schernthaner G, Prager R: β-cell hypersecretion and not reduced hepatic insulin extraction is the main cause of hyperinsulinemia in obese nondiabetic subjects. *Metabolism* 41:1304–1312, 1992
80. Taniguchi A, Nakai Y, Fukushima M, Imura H, Kawamura H, Nagata I, Florant GL, Tokuyama K: Insulin sensitivity, insulin secretion, and glucose effectiveness in subjects with impaired glucose tolerance: a minimal model analysis. *Metabolism* 43:714–718, 1994
81. Watanabe RM, Azen CG, Roy S, Perlman JA, Bergman RN: Defects in carbohydrate metabolism in oral contraceptive users without apparent metabolic risk factors. *J Clin Endocrinol Metab* 79:1277–1283, 1994
82. Nakai Y, Taniguchi A, Fukushima M, Kawamura H, Morita T, Imura H, Nagata I, Tokuyama K: Insulin sensitivity during very-low-calorie diets assessed by minimal modeling. *Am J Clin Nutr* 56: 179S–181S, 1992
83. Tobin BL, DT Finegood: Reduced insulin secretion by repeated low doses of STZ impairs glucose effectiveness but does not induce insulin resistance in dogs. *Diabetes* 42:474–483, 1993
84. Ader M, RN Bergman: Marked diminution in glucose effectiveness contributes to glucose intolerance in experimental diabetes (Abstract). *Diabetologia* 36:A147, 1993
85. Finegood DT, Tzur D: Estimation of glucose effectiveness by the minimal model is dependent on the endogenous insulin secretory response (Abstract). *Diabetes* 44:192A, 1995
86. Mueckler M: Family of glucose-transporter genes: implications for glucose homeostasis and diabetes. *Diabetes* 39: 6–11, 1990
87. Bell GI, Kayano T, Buse JB, Burant CF, Takeda J, Lin D, Fukumoto H, Seino S: Molecular biology of mammalian glucose transporters. *Diabetes Care* 13:198–208, 1990
88. Carruthers A: Facilitated diffusion of glucose. *Physiol Rev* 70:1135–1176, 1990
89. Crone C: Facilitated transfer of glucose from blood into brain tissue. *J Physiol* 181:103–113, 1965
90. Lang CH: Rates and tissue sites of non-insulin and insulin-mediated glucose uptake in diabetic rats. *Proc Soc Exp Biol Med* 199:81–89, 1992
91. Printz RL, Magnuson MA, Granner DK: Mammalian glucokinase. *Ann Rev Nutr* 13:463–496, 1993
92. Meglasson MD, Matschinsky FM: Pancreatic islet glucose metabolism and regulation of insulin secretion. *Diabetes Metab Rev* 2:163–214, 1986
93. Galante P, Mosthaf L, Kellerer M, Berti L, Tippmer S, Bossenmaier B, Fujiwara T,

Okuno A, Horikoshi H, Haring HU: Acute hyperglycemia provides an insulin-independent inducer for GLUT4 translocation in C_2C_{12} myotubes and rat skeletal muscle. *Diabetes* 44:646–651, 1995
94. Nolte LA, Rincon J, Wahlstrom EO, Craig BW, Zierath JR, Wallberg-Henriksson H: Hyperglycemia activates glucose transport in rat skeletal muscle via a Ca^{2+}-dependent mechanism. *Diabetes* 44:1345–1348, 1995
95. Bucolo RJ, Bergman RN, Marsh DJ, Yates FE: Dynamics of glucose autoregulation in the isolated, blood-perfused canine liver. *Am J Physiol* 227: 209–217, 1974
96. Bergman RN, Bucolo RJ: Interaction of insulin and glucose in the control of hepatic glucose balance. *Am J Physiol* 227: 1314–1322, 1974
97. Ruderman NB, Herrera MG: Glucose regulation of hepatic gluconeogenesis. *Am J Physiol* 214:1346–1351, 1968
98. Ader M, Bergman RN: Peripheral effects of insulin dominate suppression of fasting hepatic glucose production. *Am J Physiol* 258:E1020–E1032, 1990
99. Rebrin K, Steil GM, Getty L, Bergman RN: Free fatty acid as a link in the regulation of hepatic glucose output by peripheral insulin. *Diabetes* 44:1038–1045, 1995
100. Reaven GM, Miller R: Study of the relationship between glucose and insulin responses to an oral glucose load in man. *Diabetes* 17:560–569, 1968
101. Ader M, Bergman RN: Experimental dissection of metabolic processes accounting for glucose-dependent glucose disappearance (Abstract). *J Invest Med* 43: 170A, 1995
102. Ader M, Bergman RN: Evidence that "autoregulation" of hepatic glucose output is mediated by free fatty acids (Abstract). *Diabetes* 45:245A, 1996