

Irving L. Schwartz Lecture

Pathogenesis and Prediction of Diabetes Mellitus:

Lessons from Integrative Physiology

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Abstract

The molecular revolution in biology is providing an exponentially increasing body of data regarding subcellular events in normal and pathological conditions. The task of integrating even a small part of this deluge of information is a formidable challenge. Many integrative regulatory principles are still unknown. The present article argues that important principles may be discovered by the repetitive experimental testing of simple isomorphic computer or mathematical models of biological regulation. The system regulating the blood glucose is used as an example. Implicit in a “minimal model,” postulated more than 20 years ago, were specific but untested assumptions. These assumptions, which were tested over the ensuing decades, have enriched our understanding of metabolic regulation and the causes of diabetes. Currently accepted concepts emerging from modeling include: (a) the importance of sluggish insulin transport across the capillary endothelium in stimulation of glucose uptake; (b) the “single gateway” concept, that insulin transport across endothelium of adipose tissue suppresses free fatty acids, which act in turn to reduce endogenous glucose production by the liver; (c) the importance of the single gateway mechanism in the metabolic syndrome, whereby increased fat in the abdominal compartment relates to insulin resistance and risk for type 2 diabetes; and (d) the hyperbolic relationship between insulin action and insulin secretion, which provides an accurate prediction of diabetes risk. It is hoped that the experience with the metabolic system will provide a metaphor for other regulatory systems less subjected to critical quantitative analysis. Such analysis may well lead to analogous conceptual understanding of other important integrated biological systems, and provide approaches for early intervention in the pathogenic process of other chronic and devastating diseases.

Key Words: Modeling, minimal model, insulin resistance, cell.

Personal Introductory Remarks

THIS MANUSCRIPT IS BASED ON the Irving L. Schwartz lecture, which I was honored to deliver at the Mount Sinai Medical School on November 9, 2000. In the preparation of such a lecture, it is customary to investigate the relationship between the lecture or lecturer, and the honored faculty member after whom the lecture was named. This provided a challenge to me. I was familiar with Dr. Schwartz' reputation, and his pioneering role in the Physiology Department at the Mount Sinai School of Medicine. But, as I assumed we were in different areas of research, and because I was never a trainee or faculty at Mount Sinai, it was unclear if

I could make a meaningful personal comment regarding our possible relationship. This quandary led me to the latter-day oracle of all knowledge: the internet. I quickly struck cyber-gold. I noted that Dr. Schwartz had published, in 1965, an excellent review article in the *American Journal of Medicine* entitled “Insulin Structure and Function: Reflections on the Present State of the Problem” (1). Schwartz' co-author, Oscar Hechter, rang a large bell for me, as I also had published with him (2) (Fig. 1). More relevant: Oscar Hechter is my uncle! (See pedigree in Fig. 1). This unexpected co-author relationship between Dr. Schwartz and me was a very pleasant surprise; what was even more satisfying was that Irving Schwartz attended my lecture at Mount Sinai, and I think he also found the striking coincidence gratifying. I hope that the lecture and this manuscript will live up to the high standards set by Dr. Schwartz' work, as exemplified in the relevant article.

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About Integrative Biology

There can be no denying the “molecular revolution” in life sciences over the past several



Insulin structure and function. *Reflections on the present state of the problem.*
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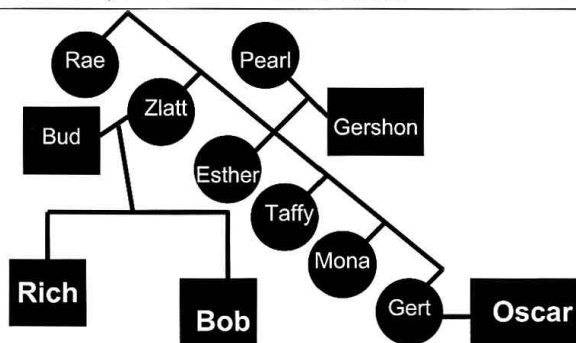


Fig. 1. Somewhat distant relationship between Dr. Irving Schwartz and the author. In 1965 Dr. Schwartz and Dr. Oscar Hechter published the cited manuscript in *American Journal of Medicine*. Bergman and Hechter published together in the *Journal of Biological Chemistry* in 1978. Pedigree diagram is that showing familial relationship between Hechter and Bergman.

decades. Molecular research has led to increasingly more accurate descriptions of the cellular events involved in hormone action. However, the elucidation of the human genome has generated a new and daunting challenge. How does one begin to integrate the mass of information which will emerge in an effort to comprehend biological function? It is clear that the integration of genomic information will profoundly change how life science research proceeds (3). It is also clear that mathematics and computer simulation will be a critical component of genomic studies. A senior investigator such as myself can only marvel at the coming challenges and insights which will emerge.

Ultimately, it will become necessary to integrate the mass of information which is emerging from the new areas of genomics and proteomics. Genome scans have revealed and will continue to reveal new molecules, which in turn will lead to the identification of new pathways. What will we want to know about these complex pathways? Certainly we must understand the “principles of regulation” which will reveal the “control points” that are most critical for alterations in metabolic function and for disease states. Much of the information will be redundant or unimpor-

tant. This has already become clear from transgenic studies; some knockout models are revealing information about human disease — others have led to investigation of models which are less than relevant. One might compare pugilists with scientists — In boxing the knockout is the end of the struggle; in physiology the “knockout” is only the beginning of the struggle!

A similar conundrum has existed in the molecular/systemic physiology relationship. This has been a difficult marriage indeed. It is difficult to avoid the siren song of reductionist research — one finding leads to questions regarding the underlying mechanism at a lower level of metabolic organization, with this pattern repeating so that information emerges at progressively greater and greater detail. One example is the insulin signaling pathway, which now is known to involve a surfeit of proteins that can account for multiple different potential signaling pathways. Will these studies reveal the causes of insulin resistance in type 2 diabetes? In this and other regulating systems, it is requisite to ask the question: “Will the principles of regulation of an integrated physiological system emerge from increasingly reductionist research?” It appears that the simple answer is

probably not. We know this from the plethora of nonintuitive results which have emerged from knockout models. For example, knockout of the insulin receptor in skeletal muscle did not result in a murine model of diabetes (4). This outcome, which was a surprise to molecular biologists (5), was not surprising to those who had previously built models of carbohydrate regulation (6). The point is this: as with reductionist research, which marches in lock-step toward ever increasing detail, it is also necessary to study metabolic systems at higher levels of organization. Such studies may reveal principles of regulation which may never emerge from reductionist approaches.

The Role of Modeling — Studies from Our Laboratory

What is the paradigm for elucidating principles of regulation of an integrated physiological system? Endocrinology is an excellent playing field from which to study this question, as negative feedback regulation is part and parcel of regulation of hormones and metabolites. Fuel metabolism is of interest because it is essential to life, and because metabolic dysfunction — diabetes — is a major health problem in Westernized societies, accounting for more than 100 billion dollars in medical costs in the United States. But more important, diabetes is a major component of mortality, morbidity and human suffering in this country. Thus, for some years we have attempted to use concepts of systems analysis and modeling in parallel with experimental design to elucidate underlying principles of metabolic regulation in mammals. We hoped that by doing so we might impact the understanding of the mechanisms and the prevention of diabetes mellitus, and possibly advance therapy of the disease. If we have contributed meaningfully to these goals, we can believe that we have not been wasting our time or effort.

It Started with Minimal Modeling

The so-called “minimal model” has been widely published and widely used (7–9) (Fig. 2). It is interesting that the model was virtually uncited for the first 5 years after it was postulated and published — there are now approximately 50 major studies published per year employing the model, and more than 500 can be found in the literature. (This is a lesson to junior faculty — if you want to gain tenure don’t veer too far from the established research paradigm!) Twenty years ago modeling had little impact on diabetes research, although a few models had

been introduced (10–12). We considered that those models were either too simple or too complex, and hypothesized that a model of “optimal” complexity might exist — complex enough that the model could account for the feedback relationship between insulin and glucose, but simple enough so that it could be used to characterize metabolic function in a single patient with a simple clinical protocol. The history of the model has been written elsewhere (8, 13).

Over time, the minimal model has proven to be more than a clinical tool. The process of quantitative modeling forces explicit assumptions. Inherent in the model were some brazen assumptions unproven at the time the model was postulated. It is correct to say that a majority of the work that my colleagues and I have completed during the last 2 decades followed directly from efforts to test the simple assumptions inherent in the minimal model. The model made quantitative predictions, but the inherent concepts were qualitative in nature. In this article, I hope to relate some of the simple assumptions of the model to the work which emanated from testing these assumptions. While some of the work we have done has ventured far afield, the minimal model was always the basic road map. Of course the minimal model is far from perfect, but it has been an excellent vehicle to provoke some novel ideas and force experimental design.

“minimal” model (sic)

$$\frac{dG}{dt} = - \left\{ S_G + X(t) \right\} * G$$

$$\frac{dX}{dt} = p_2 * I(t) - p_3 * X(t)$$

$$S_I = p_2 / p_3$$

$$\text{GLUCOSE RESTORATION RATE} = - \left\{ \text{GLUCOSE EFFECTIVENESS} + \text{REMOTE INSULIN} \right\} * G$$

$$\text{INCREASE IN REMOTE INSULIN} = p_2 * \text{PLASMA INSULIN} - p_3 * \text{REMOTE INSULIN}$$

Complex model

↩

Simple model

Fig. 2. Equations of the minimal model. The minimal model was a compromise between complex and simplistic representations. The model accounts for the reattainment of basal glucose (G) and insulin (I) following glucose injection. Variable X is proportional to insulin in the remote compartment, now known to be interstitial insulin. Literal equations (top) are described in physiological terms below. First equation accounts for the post-injection decline of glucose in terms of insulin-independent as well as insulin-dependent processes. Second equation represents movement of insulin from plasma to interstitial fluid and internalization/degradation by insulin-sensitive tissues. Transport parameters represented by “p_x.” S_I, insulin sensitivity index; S_G, glucose effectiveness. For details, see (6).

The Time Course of Insulin Action

Our modeling was based upon simple plasma kinetics of glucose and insulin. Surprisingly, in 1979, accurate dynamics of glucose and insulin after glucose injection had not been described, since infrequent sampling had failed to reveal the rich dynamic patterns that follow glucose injection. In the course of modeling frequently sampled data, we were absolutely unable to account for plasma glucose/insulin kinetics without a delay in the action of insulin to stimulate glucose utilization (7). Similarly, Rasio and colleagues described the slowness of insulin action in the dog (14, 15), and Andres and Sherwin and their colleagues implemented this idea in the 1970s in early glucose clamp studies (16, 17). Thus, there is a disconnect between the rapid action of insulin to mobilize glucose uptake *in vitro* versus its sluggish action *in vivo*. What is the explanation for the delay in insulin action to stimulate glucose uptake *in vivo*?

Clearly the difference between secreted insulin's action *in vivo* versus its action *in vitro* is the delivery of insulin to the insulin-sensitive tissues in the intact organism. Secreted insulin is distributed via the cardiovascular system to the capillaries of insulin-sensitive tissues (skeletal muscle, fat). The insulin molecule must then traverse the endothelium to gain access to the insulin-sensitive cells. It seemed reasonable that insulin's traversing of the endothelial barrier could account for its slow action *in vivo*.

How should transendothelial transport (TET) of insulin be examined? To study transport, it is necessary to access the compartment from which the peptide is coming and the compartment to which it is going. In the mid-1980s, George King and colleagues pioneered *in vitro* studies examining insulin transport across an endothelial cell monolayer, and suggested that transport was saturable and mediated via insulin-receptor binding on the luminal surface (18, 19). We reasoned that since sluggish insulin action is observed *in vivo*, we should study the transport process in intact animals. The compartments to be examined were blood (easily sampled) and interstitial fluid ("ISF"; difficult to sample *in vivo*) which bathes the insulin-sensitive cells. Following Rasio (14, 15), we used lymph as a surrogate for ISF.

Examining interstitial insulin (in dogs) revealed that even under fasting conditions there is a large insulin concentration gradient across the endothelial barrier (Fig. 3) (20). Under hyperinsulinemic conditions (as in glucose clamps) the gradient is maintained — even at

pharmacological insulin levels (20, 21). Additionally, abrupt increases in plasma insulin provoke only sluggish increases in interstitial insulin, thereby accounting for our inability to model insulin action without a delay in insulin's effect. In contrast to plasma insulin, where the rapid changes were not mirrored by changes in glucose uptake, there was a near-perfect similarity in patterns of change in interstitial insulin compared to glucose utilization (Fig. 3). These data confirm that transendothelial transport of insulin is the primary process which limits the rapidity of changes in glucose disposal in response to changes of insulin in blood.

Thus, modeling led to the understanding that TET is one of the most important factors determining insulin action dynamics. TET insulin delivery is also a critical factor in the efficacy of insulin-like analog molecules (22). The question arises as to whether TET is altered in pathological states. Recently, Hamilton-Wessler and Ellmerer, in our laboratory, have demonstrated that TET may be reduced in a model of insulin-resistant central adiposity (23) (Fig. 4). While these studies require confirmation, it is possible that TET may be a cause of insulin resistance under some conditions, and thus may be an important target for therapy.

The Liver

Normally, insulin response not only stimulates glucose utilization, but squelches endogenous glucose production (EGP) from the liver. If TET is rate limiting for activating glucose uptake, what determines the kinetics of suppression of EGP? Liver capillaries are fenestrated — therefore, following the secretion of insulin into the portal vein, the peptide should reach the liver almost immediately and suppress EGP. It is true that insulin can be detected rapidly at the liver following hormone injection (24) (Fig. 5). Yet, despite rapid accumulation of hormone in liver, EGP is suppressed slowly (25) (Fig. 5). How can the paradox of insulin's rapid accession of hepatocytes, yet relatively sluggish suppression of EGP, be explained?

The discordance between portal insulin concentration and suppression of glucose production led us to hypothesize that there is an intervening signal mediating insulin's action to reduce EGP. We hypothesized that insulin acts first at some "initial recognition" tissue depot with a relatively impermeable endothelial barrier (i.e., not the liver). Following this initial recognition there would be modulation of a sec-

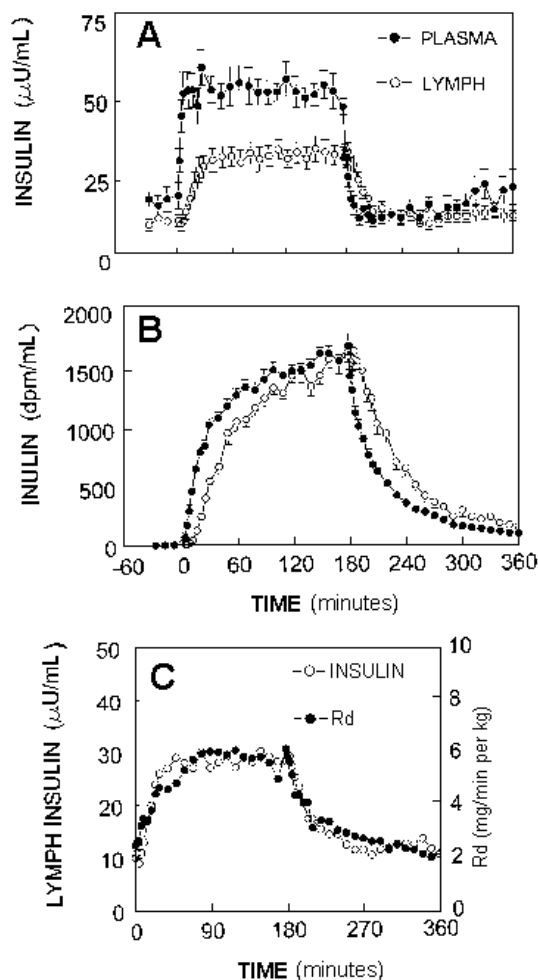


Fig. 3. Results from euglycemic glucose clamps. Insulin (A) and inulin (B) were infused intravenously under euglycemic conditions. Samples were collected in plasma as well as lymph (surrogate for interstitial fluid). Insulin levels in interstitium were lower than in plasma (“attenuation”) at basal and during activation period of clamps. Insulin rises rapidly in plasma, but slowly in interstitium, reflecting delay in transendothelial insulin transport. Unlike insulin, there is no steady-state plasma:interstitium gradient for inulin due to lack of cellular uptake of the inert compound. C. Hand-in-glove similarity between interstitial insulin and glucose uptake (Rd). Adapted from (20).

ondary signal, which then itself controls glucose output. We considered several recognition tissues and secondary candidates (Fig. 6). One favored candidate emerged: under a variety of conditions, a remarkable correlation was observed between plasma free fatty acids (FFA) and glucose production rates (22, 26–29) (Fig. 7). FFA in blood under fasting conditions emanates from triglycerides stored in adipose tissue depots. Because adipocytes have an impermeable endothelial barrier similar to skeletal muscle, the sluggish effect of insulin could be explained by slow permeation into adipocytes,

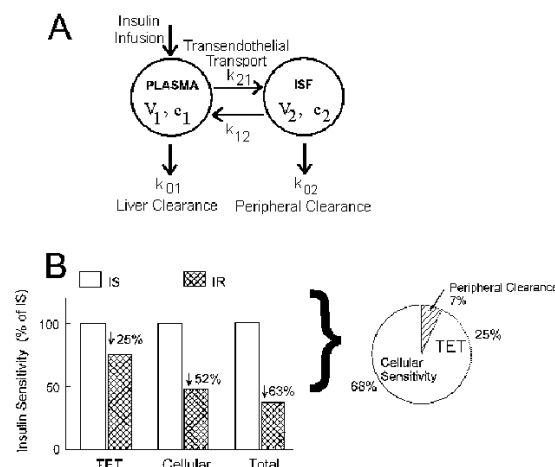


Fig. 4. Role of transendothelial transport (TET) defect in insulin resistance of obesity. A. Compartment model representing flux between plasma and interstitial fluid (ISF). “k” parameters are fractional transport coefficients. “V” are volumes of distribution for insulin, and “c” are concentrations. B. Bar graph shows estimated contribution of TET defect compared to defect in insulin-sensitive cells to overall insulin sensitivity. IS = insulin-sensitive group; IR = insulin-resistant group.

slow suppression of lipolysis, reduction in plasma FFA, and ultimately reduction in EGP (“single gateway hypothesis”) (25, 30, 31) (Fig. 8). Thus, plasma FFA has emerged as a potentially important regulator of glucose production, which can be modulated by insulin.

Importance of FFA Control of Endogenous Glucose Production

The scientific journey leading to postulation of FFA as an important moment-to-moment controller of liver glucose output was founded in our inability to account for effects of insulin on glucose uptake and production without postulating a delay in the effect of the hormone. Thus, it was an indirect outcome of the need to postulate the delay in insulin action on EGP in the minimal model. However, the concept of FFA regulation of glucose production has important implications for the pathogenesis of type 2 diabetes.

Population studies have revealed a striking relationship between central, or visceral, adiposity and the risk for both type 2 diabetes and cardiovascular disease (32, 33). While obesity is generally associated with insulin resistance (34), the correlation between central adiposity and resistance is even stronger (35). We considered the possibility that there is a causal relationship between visceral fat and insulin resistance, and that this relationship is due to the role of FFA in controlling liver glucose output.

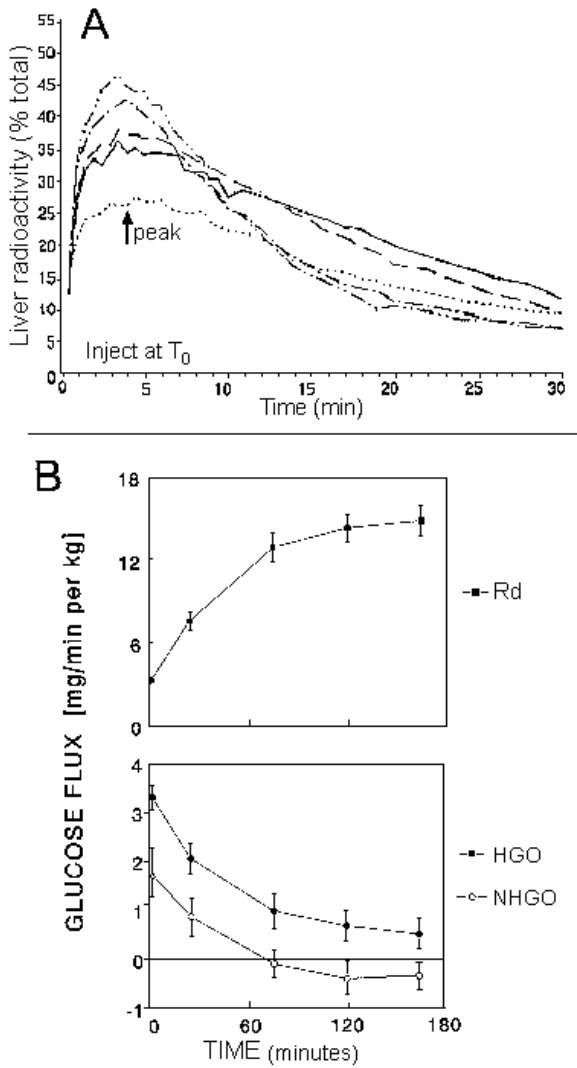


Fig. 5. **A.** Rapid distribution of injected radioactively labeled insulin in liver (modified from Jensen et al.) (24). **B** (top). Comparatively sluggish increase in glucose uptake (Rd) and equivalently slow suppression of glucose production (bottom) in dogs during euglycemic clamps. HGO and NHGO = hepatic and net hepatic glucose output, respectively. Insulin administered at 20 pmol/min per kg. From (25).

To examine the role of central lipid accumulation we introduced a model of visceral adiposity in the dog (36). We increased the fat content of the diet by 2 g/kg per day, which is a modest amount, especially when compared with diets used by other laboratories (37, 38). This modest increment in fat intake produced a canine model of the “insulin resistance syndrome” (Fig. 9). To establish the causality of changes in metabolic function induced by dietary fat, we used the minimal model to measure insulin sensitivity at 2-week intervals for 12 weeks of fat feeding. The pattern of changes was interesting and unanticipated. As expected, with fat feed-

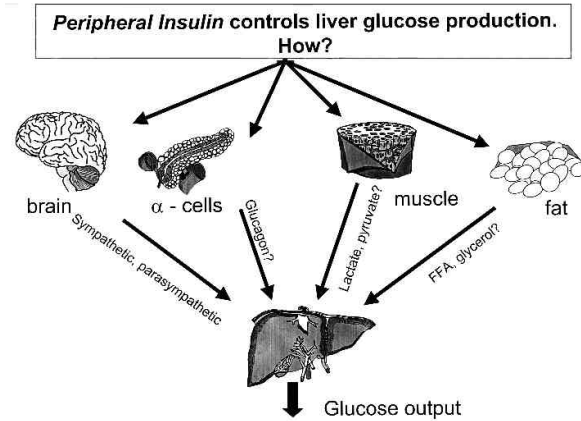


Fig. 6. Possible signals by which peripheral insulin may regulate endogenous glucose production. FFA= free fatty acids.

ing, insulin sensitivity declined within 1 week to a level of 40% of normal. Unexpectedly, insulin secretory compensation to the insulin resistance was not observed until the second week. First-phase insulin release maximized at week 6, but then receded, reaching a value slightly higher than basal by the 12th week. Despite this pattern of changes, there was little change in glucose tolerance. The question arises: how was insulinemic compensation for insulin resistance maintained despite only a transient increase in secretion by the β -cells?

Interestingly, after 6 weeks of increased fat in the diet, the need for increased insulin secretion was mitigated by a very substantial reduction in metabolic clearance rate of the hormone. Most insulin is cleared by the liver. Fat feeding induces a reduction in first-pass hepatic clearance of insulin, mirrored by a reduction in the number of insulin receptors (39). The reduction in receptor-mediated insulin clearance is a very important component of the integrated metabolic response to compensate for insulin resistance. Thus, the liver acts as a “gate-keeper,” titrating the proportion of newly secreted insulin reaching the systemic circulation and insulin-sensitive tissues (muscle and fat). This physiological role of the liver can be viewed teleologically — it can explain why evolution has provided that insulin is secreted into the portal vein — with the liver modulating release of newly secreted insulin into the systemic vessels. It is clear that normal function of this gate-keeping function can relieve the β -cells of hypersecretion of insulin. Is it possible that failure of the liver to regulate insulin clearance in proportion to physiological need may stress the β -cells and contribute to the pathogenesis of Type 2 diabetes?

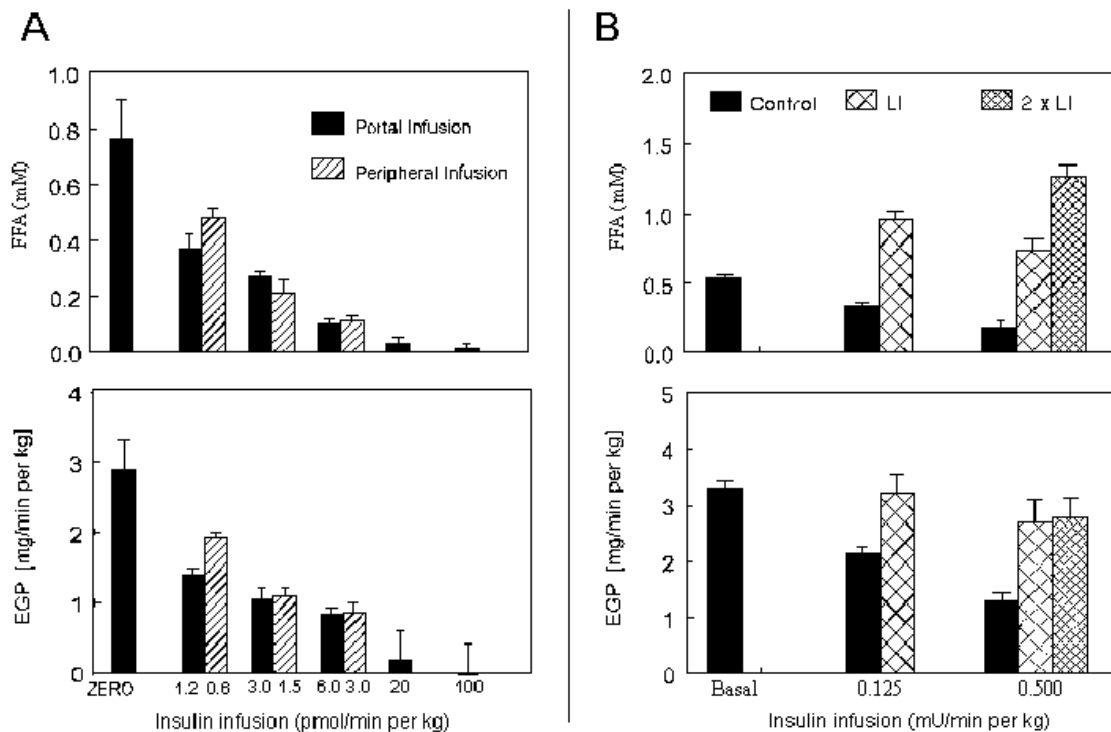


Fig. 7. Data supporting free fatty acids (FFA) as the peripheral signal regulating liver glucose production. **A.** Insulin was infused in conscious dogs either into the portal vein (black bars) or into a peripheral vein (striped bars) at rates selected to yield similar peripheral insulin levels. Infusion rates were approximately doubled for portal infusion to compensate for first-pass hepatic clearance of insulin. Note the striking similarity in pattern between effects of insulin on plasma FFA (top) compared with endogenous glucose production (EGP, bottom). From (26). **B.** Infusion of Liposyn with heparin (LI) (hatched bars) prevented the fall in FFA as well as the decline in glucose production, further supporting FFA role as signal to the liver. From (27). [Editor's Note: LI = 20% safflower oil emulsion administered at 0.5 mL/min, 2 × LI = the same solution administered at 1.0 mL/min.]

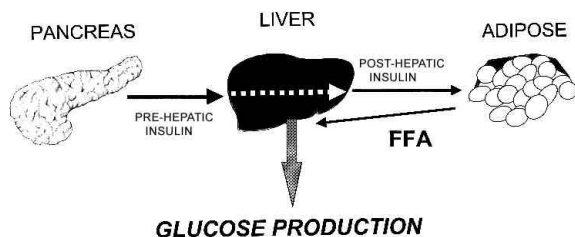


Fig. 8. The "single gateway hypothesis." Insulin is envisioned as controlling glucose output indirectly. The hormone is secreted by the β -cells of the pancreas, from which it enters the liver. While insulin may have a direct acute effect to suppress EGP, much of it survives first-pass degradation and enters the systemic circulation where lipolysis is suppressed in adipocytes. Reduction of plasma FFA is a major factor lowering liver glucose production. Because adipocyte endothelium is relatively impermeable to insulin, this mechanism can explain the surprisingly slow effect of any increase in insulin to suppress EGP. For details, see (30).

Thus, visceral adiposity contributes to increased flux of FFA to liver, reducing insulin clearance and potentially stimulating glucose production. In fact, both Joyce Richey and

Stella Kim have recently demonstrated, in the rat and the dog, respectively, that after chronically increased fat intake, glucose production by the liver is rendered totally resistant to insulin, such that a physiological increase in the portal level of the hormone fails completely to suppress steady-state glucose output (40, 41). The insulin resistance explained by increased portal fatty acid flux is exacerbated by the extreme insulin resistance of the visceral adipocytes, shown *in vitro* (42) and recently confirmed *in vivo* (43). Thus, portal FFA flux to the liver can account for the relationship between visceral adiposity and insulin resistance. Other molecules emanating from adipocytes may also bear responsibility for insulin resistance, including cytokines such as tumor necrosis factor (TNF)- α or interleukin-6. Newly described peptides such as resistin (44) or adiponectin (45) may also play a role. However, we continue to support the concept that it is the enhanced turnover of visceral FFA, resulting in fat accumulation in the liver, which plays the primary role.

Progression of Obesity

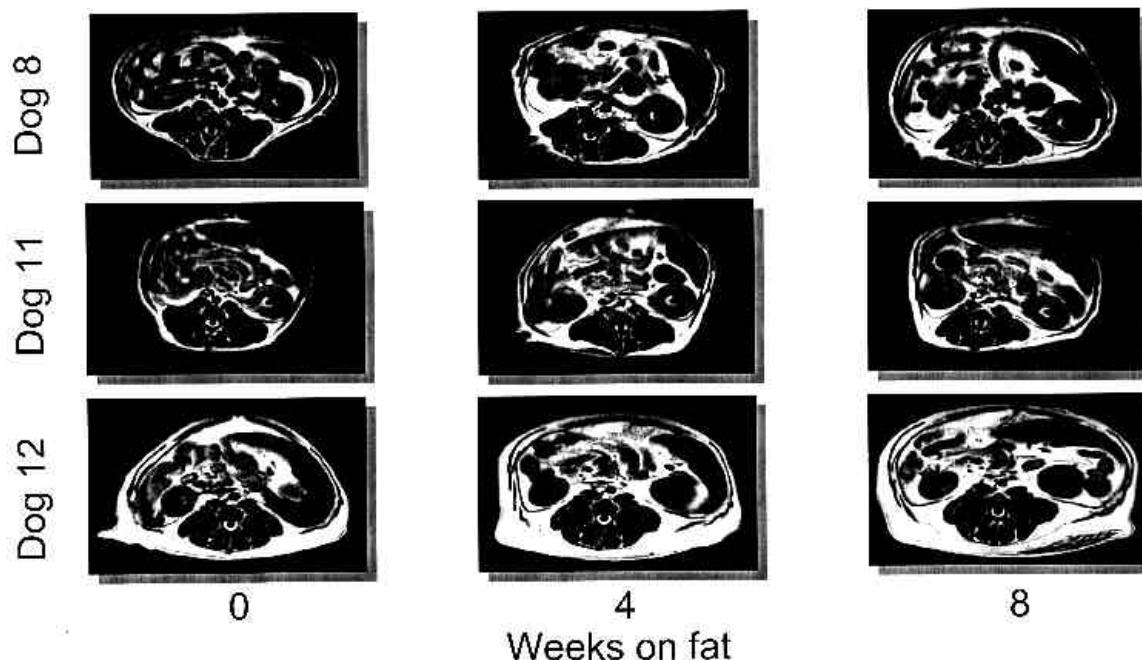


Fig. 9. Progression of central obesity in the dog with a modest fat diet. Diet was increased by 2 g/kg per day of fat. Note increase in visceral as well as subcutaneous fat (white area) from magnetic resonance images (MRI) collected before diet and at 4 and 8 weeks.

Our studies of the importance of central fat are an indirect result of trying to explain why suppression of glucose production of liver in response to hyperinsulinemia occurs slowly — a necessary assumption of the minimal model!

The Hyperbolic Law of Glucose Tolerance

Great battles die hard. In the glucose regulation area, one of the primary battlefields has been the relative importance of insulin resistance versus pancreatic β -cell dysfunction in the pathogenesis of type 2 diabetes (46–48). The surprising hyperinsulinemia of obese patients following glucose ingestion, first identified in New York by Berson and Yalow (49), was suggestive of insulin resistance — elevated insulin with reduced glucose tolerance. Perley and Kipnis, however, demonstrated that when the blood glucose signal was carefully matched, noninsulin-dependent diabetic patients had reduced plasma insulin values (50). The introduction of accurate methods for measuring insulin sensitivity, including the minimal model (6, 51) as well as β -cell response (52–54), did not resolve the controversy over the importance of insulin resistance versus β -cell dysfunction.

We believe that dynamic modeling contributed to the present truce (resolution) regarding the resistance/dysfunction controversy. The resolution emerged from a well-accepted engineering concept known as the “closed loop gain,” which is calculated from a closed-loop negative feedback system (such as the glucose regulating system) and reflects the contribution of all compensatory elements to the ability of the system to regulate itself. With respect to glucose regulation, while many factors can contribute to glucose disposal, insulin secretion and insulin action are the primary elements which determine the ability of the intact organism to respond to provision of fuel. Clearly, insulin resistance can be compensated by enhanced secretion, and a secretory defect will be less significant when there is robust insulin sensitivity. We therefore defined the “disposition index (DI)” as the product of insulin response and insulin sensitivity. Because insulin resistance is compensated in healthy individuals by an increase in β -cell responsiveness (36, 55, 56), DI can be interpreted as the responsiveness of the β -cell normalized to the degree of insulin resistance.

The DI can best be appreciated by plotting the relationship, for a group of individuals, be-

tween secretory response and insulin sensitivity (Fig. 10). Because we envision the β -cells compensating for insulin resistance (rather than the reverse), we plot sensitivity as the independent variable and β -cell function as the dependent variable. The hyperbola (Fig. 10) represented by:

$$\text{Insulin sensitivity} \times \text{Insulin Secretion} = \text{DI}$$

(or the “DI-perbola”), encompasses the idea that reduction in insulin sensitivity due to environmental factors (e.g., infection, obesity, pregnancy, puberty, aging) will be compensated by a proportional increase in β -cell response. In a given individual, the ability of the β -cells to upregulate sensitivity to glucose in response to a decrement in insulin sensitivity is quantitated by the DI value for that individual. A population DI can also be calculated (57). What then characterizes disease?

Risk for diabetes can be characterized as a reduced ability of the β -cells to compensate, i.e., a reduced DI. We hypothesize that the DI value for subjects at risk for diabetes will be lower than normal — even under insulin-sensitive conditions. We may therefore be able to identify subjects at risk for type 2 diabetes long before onset of the disorder by measuring insulin sensitivity and β -cell response, calculating the product, and comparing the result with a similar product from a “normal” (i.e., not at-risk) population.

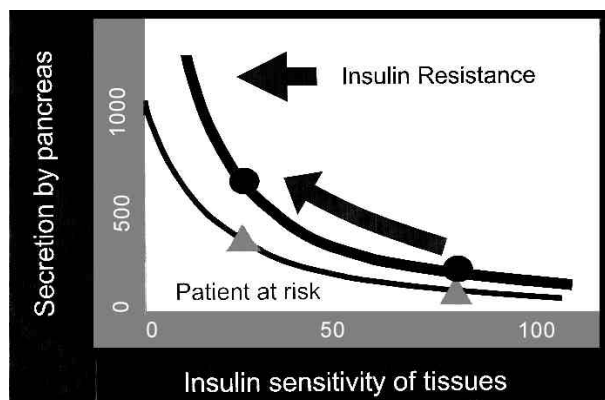


Fig. 10. The “DI-perbola,” the classical hyperbolic relationship between insulin secretion and insulin sensitivity. In normal individuals (thick hyperbola, black dots) arrow indicates shift from insulin-sensitive to insulin-resistant state. With insulin resistance, increased β -cell sensitivity will compensate, thus maintaining glucose tolerance in the normal range. In subjects at risk for diabetes, a similar shift to insulin resistance (thinner hyperbola, triangles) should cause a lesser increase in secretory function, signaling a subtle β -cell defect. The equation of either hyperbola is $\text{Secretion} \times \text{Sensitivity} = \text{Disposition Index}$ (“DI”); the value of the DI is lower for an at-risk individual.

DI also emanated conceptually from the minimal model. We were able to calculate a parameter of insulin sensitivity by fitting the model to intravenous glucose/insulin dynamics. This insulin sensitivity index, S_I , has been widely regarded as a quasi-universal measure of insulin action (58). S_I measures the ability of a given increment in plasma insulin to enhance net glucose clearance. The mean value in a normal population is approximately $5 \times 10^{-4}/\text{min}$ per $\mu\text{U}/\text{mL}$.

DI has been a useful concept. Bogardus, Pratley and colleagues have demonstrated that the risk for type 2 diabetes in the Pima Native Americans is about 20 times greater for the lowest 10% compared to the highest 10% of values of DI (56). Elbein, Kahn and colleagues have demonstrated that DI is heritable (59). Thus, DI, a concept which emerged from minimal modeling considerations, is presently one of the most useful parameters for expressing future risk of type 2 diabetes. Given the difficulty in finding one, or even several, major risk factor genes for type 2 diabetes, it is probable that DI which emerges from a clinical test may well be our most potent weapon for predicting type 2 diabetes in the near future.

Final Comments

Quantification is a final and crucial step to the history of any scientific endeavor. The importance of quantification is not questioned in physical science — we are in awe of the revolutionary transition from the “qualitative” science of Archimedes to the quantitative physics of Newton and Einstein. Conceptualization and quantification of entropy were fundamental to chemistry as well as to information theory. It is less appreciated that quantification may well lead to a similar revolution in biological science. In many ways biological science is just now entering its quantitative era. This is abundantly clear in molecular genetics, which is a close relative of information sciences. In genetics, measurements which are critical to a quantitatively based theory are easily made. However, it is difficult to measure the plethora of protein signals emerging from the genome. It will be even more difficult to integrate the mountains of data which will emerge when the relationships between the genome and the families of proteins can be exploited.

The purpose of this article is to point out that emergent principles can be elucidated from complex systems at any level of integration. We were fortunate to benefit from concepts in systems engineering as well as from biology, to

try to comprehend some of the underlying principles which maintain the supply of fuel to higher organisms. The process of modeling and quantification forced us to define in quantitative terms the most important state variables in glucose regulation, including insulin sensitivity, first-pass hepatic insulin clearance and β -cell responsiveness. In the process of examining the relationship among these variables certain important relationships were realized, including insulin's slow effect, temporal changes in insulin clearance, and the hyperbolic relationship between insulin action and insulin secretion. It is of interest, for example, that sluggish insulin action ultimately led to the importance of FFA in the "metabolic syndrome" (Fig. 11). For us it has been a long, somewhat tortuous, but exciting conceptual journey. I can only hope that I can add to the outstanding contributions of Dr. Irving Schwartz, and that our journey might provide a template for a more junior population who will have to deal with the really hard problems.

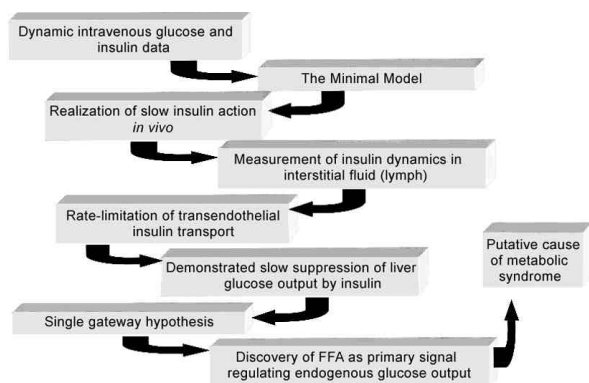


Fig. 11. Historical progression of research in our laboratory. The minimal model was based upon frequent measurements of glucose and insulin in plasma following glucose injection. Slowness of insulin action was a necessary postulate in the model; this led to realization of slow transendothelial transport of insulin, as reflected in sluggish changes in interstitial insulin concentrations. Similar slow dynamics of insulin action on liver glucose output and glucose uptake revealed extrahepatic site of insulin action and indirect effect of insulin to suppress glucose output. Realization that FFA were a signal controlling liver glucose output may explain the negative effect of central adiposity on insulin sensitivity, and risk for diabetes and other chronic diseases (metabolic syndrome).

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