Accurate Assessment of β-Cell Function
The Hyperbolic Correction

Richard N. Bergman, Marilyn Ader, Katrin Huecking, and Gregg Van Citters

Only in the last decade did modeling studies predict, and knockout experiments confirm, that type 2 diabetes is a "2-hit" disease in which insulin resistance is necessarily accompanied by β-cell defect(s) preventing the compensatory upregulation of insulin secretion. This long-delayed insight was associated with the development of a constant, the "disposition index," describing the β-cell sensitivity-secretion relationship as a rectangular hyperbola. Shifts in insulin sensitivity are accompanied by compensatory alterations in β-cell sensitivity to glucose. Insulin-sensitive subjects do not require a massive insulin response to exogenous glucose to maintain a normal blood glucose. But if their insulin sensitivity decreases by 80%, as in late pregnancy, they need a fivefold greater insulin response to achieve an identical disposition index. Women with gestational diabetes have an insulin response similar to that of normal volunteers; at first glance, this suggests similar islet function, but the utility of the disposition index is to normalize this response to the amplitude of third trimester insulin resistance, revealing severe β-cell deficiency. The index is a quantitative, convenient, and accurate tool in analyzing epidemiologic data and identifying incipient impaired glucose tolerance. Separate major issues remain, however: the causes of insulin resistance, the causes of the failure of adequate β-cell compensation in type 2 diabetes, and the nature of the signal(s) from insulin-resistant tissues that fail to elicit the appropriate β-cell increment in sensitivity to glucose and other stimuli. The disposition index is likely to remain the most accurate physiologic measure for testing hypotheses and solutions to these challenges in whole organisms. *Diabetes* 51 (Suppl. 1):S212–S220, 2002

Defective function of the pancreatic β-cells is now accepted to be a hallmark of type 1 and type 2 diabetes. The importance of the β-cells in type 1 diabetes has long been accepted. On the contrary, the necessity of a pancreatic defect in type 2 diabetes has only recently been widely appreciated (1,2). For many years, it was considered that insulin resistance alone could engender hyperglycemia in those without immune etiology of disease (3,4). Results based on modeling indicating that β-cell upregulation would compensate for even severe insulin resistance and not result in fasting hyperglycemia (5) were recently supported by the laboratory of C.R. Kahn and colleagues, who demonstrated that knockout of the muscle insulin receptor using Cre-loxP methodology did not result in a diabetic phenotype (6). Compensatory hyperinsulinemia was sufficient to allow for regulation of the blood glucose in the normal range. On the contrary, modeling studies predicted that a β-cell defect in the face of insulin resistance would engender a diabetes phenotype (5). This result was likewise confirmed by knockout of the insulin receptor as well as IRS-1, which led to insulin resistance, β-cell defect, and diabetes (7). Thus, type 2 diabetes is most often a "2-hit" phenomenon, in which insulin resistance is accompanied by a β-cell defect preventing compensatory upregulation of insulin secretion.

The hyperbolic sensitivity-secretion relationship. It is of interest to consider why several decades passed between the demonstration of severe insulin resistance and the recognition of the absolute necessity for a β-cell defect for the pathogenesis of type 2 diabetes. To understand the role of the β-cell, it has been useful to elucidate the quantitative relationship between insulin sensitivity and insulin action as it exists in normal (i.e., not prediabetic) individuals. Some years ago, we postulated that, if β-cells are normal, the sensitivity-secretion relationship could most efficiently be expressed as a rectangular hyperbola (8). The product of insulin sensitivity and insulin secretory response would equal a constant, which we named the "disposition index" (Fig. 1). Based on a limited data set obtained in human volunteers, we postulated that shifts in insulin sensitivity would be accompanied by compensatory alterations in β-cell sensitivity to glucose (Fig. 1). Thus, reduction in insulin action (↑ insulin resistance) should upregulate β-cell sensitivity, whereas enhancement of insulin action (↓ insulin resistance) would downregulate β-cell sensitivity. This is illustrated in Fig. 1. Consider a normal, insulin-sensitive subject, with an insulin sensi-

From the Department of Physiology and Biophysics, Keck School of Medicine, University of Southern California, Los Angeles, California.

Address correspondence and reprint requests to rbergman@usc.edu.

Accepted for publication 13 June 2001.

DI, disposition index; FFA, free fatty acid; GDM, gestational diabetes mellitus; GLP-1, glucagon-like peptide-1; IGT, impaired glucose tolerance; S_I, insulin sensitivity index.

The symposium and the publication of this article were made possible by an unrestricted educational grant from Servier, Paris.

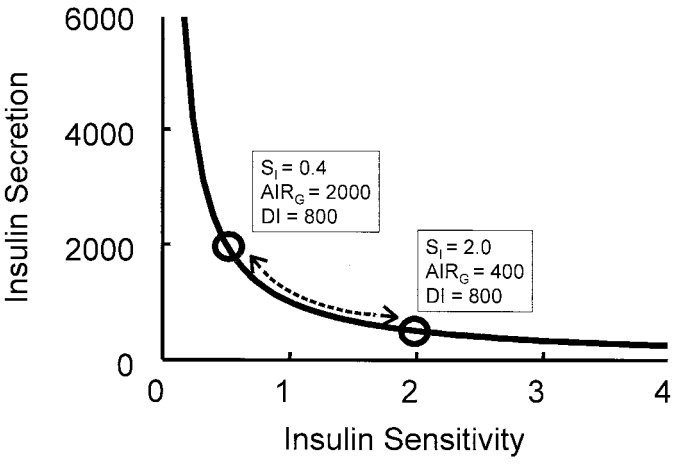

FIG. 1. The hyperbolic sensitivity/secretion curve. It is envisioned that, in the course of environmentally induced reductions in insulin sensitivity, "normal" pancreatic islets would respond by upregulation of the β-cells' sensitivity to glucose. In the example shown, individuals with an S_I of 2.0×10^{-5} min^{-1} per pmol/l and first-phase insulin response (AIR_G) of 400 pmol/l would have a disposition index [defined as the product ($S_I \times AIR_G$)] of 800. Reduction in insulin sensitivity (for example, to 0.4×10^{-5} min^{-1} per pmol/l) would result in upregulation of AIR_G to 2,000 pmol/l, with the DI remaining constant at 800. Reduction in insulin sensitivity may be due to one of several factors, including pregnancy, increased adiposity, and puberty.

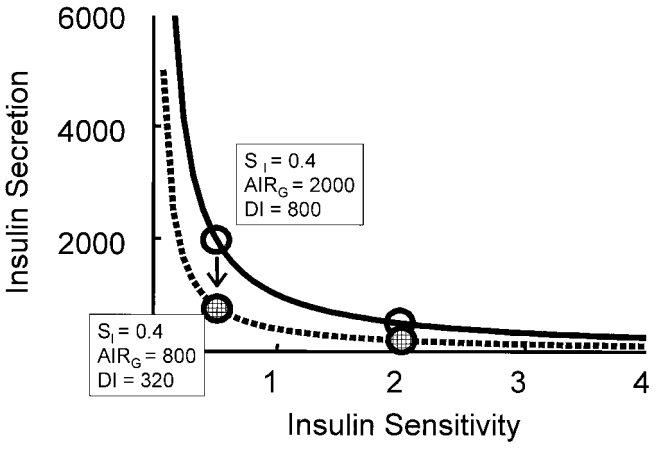

FIG. 2. Curves of "normal" individuals (○) versus individuals with a β-cell defect (⊕). Note that at elevated insulin sensitivity ($S_I \sim 2.0 \times 10^{-5}$ min^{-1} per pmol/l), it would be difficult to detect differences in insulin response, as the AIR_G is relatively low due to the minimal stress on the β-cells. When insulin resistance is present ($S_I = 0.4$), there is a clearer differentiation between AIR_G values, making it easier to differentiate β-cell function in individuals of similar reduced insulin resistance (14).

tivity index (S_I) equal to 2.0×10^{-5} min^{-1} per pmol/l. Such an insulin-sensitive individual would not require a massive insulin response to glucose administration to maintain normal blood glucose and glucose tolerance; first-phase β-cell response in this individual might be 400 pmol/l, yielding a disposition index of 800. A similar individual, experiencing a reduction in insulin sensitivity of 80% due to one of many possible causes (puberty, pregnancy, infection, increased adiposity), would be predicted to mount a fivefold greater insulin response (to 2,000 pmol/l), exhibiting the identical disposition index of 800. The single parameter, the disposition index (DI), can thus be envisioned to predict the normal β-cell response adequate for any degree of insulin resistance. The DI is a measure of the ability of the β-cells to compensate for insulin resistance. It can be considered a measure of the functionality of the pancreas in the intact individual.

The hyperbolic hypothesis was proposed based on a small cohort of subjects. It has been supported by numerous studies in humans, dogs, and recently, rodents (cf., 9–11). S. Kahn and colleagues were the first to confirm the hyperbolic relationship in a cohort of 96 nondiabetic subjects (12), and additional confirmations have emerged from populations in excess of 1,000 (13). It appears that the proposed relationship provides a quantitative and convenient approach to expressing normal metabolic functionality in vivo.

β-Cell defect. What then is to be expected in the case of defective islets? It is reasonable to assume that β-cells would suffer from a reduced ability to upregulate insulin secretion in the face of insulin resistance. On the sensitivity-secretion representation (Fig. 2), this loss of function would be associated with a lower DI, which is represented by a curve shifted closer to the origin (e.g., Fig. 2). Under sensitive conditions (e.g., $S_I = 2.0 \times 10^{-5}$ min^{-1} per pmol/l), it is difficult indeed to distinguish normal from dysfunctional β-cells, because the cells are not challenged by insulin resistance. Under resistant conditions (e.g., $S_I = 0.4 \times 10^{-5}$ min^{-1} per pmol/l), the difference between normal and diseased islets is magnified and easier to detect. This relationship may well explain the failure to detect islet-cell defects in young, normal-weight, and still insulin-sensitive individuals. Later in life, when insulin resistance becomes profound, the presence of a β-cell defect becomes obvious. However, careful assessment of β-cell response, i.e., normalizing the response to resistance by calculating DI, may allow for early prediction of those who will eventually demonstrate type 2 diabetes. In view of recent evidence that sensitization of insulin-dependent tissues by pharmacologic means (9) or lifestyle changes (15) may prevent diabetes, early prediction of at-risk individuals may become extremely important. Thus, an argument may ultimately be made for assessment of the DI in subjects who have familial risk for the disease. Supportive of this assertion is the recent evidence from Elbein et al. (16) that, in a population from Utah, the heritability of DI is 67 ± 3%.

The assertion of the foregoing is that the earliest phenotypic β-cell defect that may be detected in otherwise glucose-tolerant individuals is a reduced DI. It is possible that genetic determinants may be more powerful, and certainly simpler to apply, than phenotypic information to identify at-risk individuals. However, in view of the difficulties in identifying important genetic loci for diabetes risk and explaining them in terms of the coded proteins, the DI may be a useful approach to identifying at-risk individuals for the immediate future.

Masking of islet dysfunction by insulin resistance. Regardless of its potential usefulness for predicting diabetes, the concept of the DI may be used to clarify otherwise conflicting evidence regarding environmental and genetic effects on islet cell function.

Example 1: gestational diabetes mellitus. It is common for islet dysfunction to be accompanied by insulin resistance. While this is not always the case for well-controlled type 1 diabetes, overwhelming evidence exists for two defects in most cases of type 2 diabetes, although

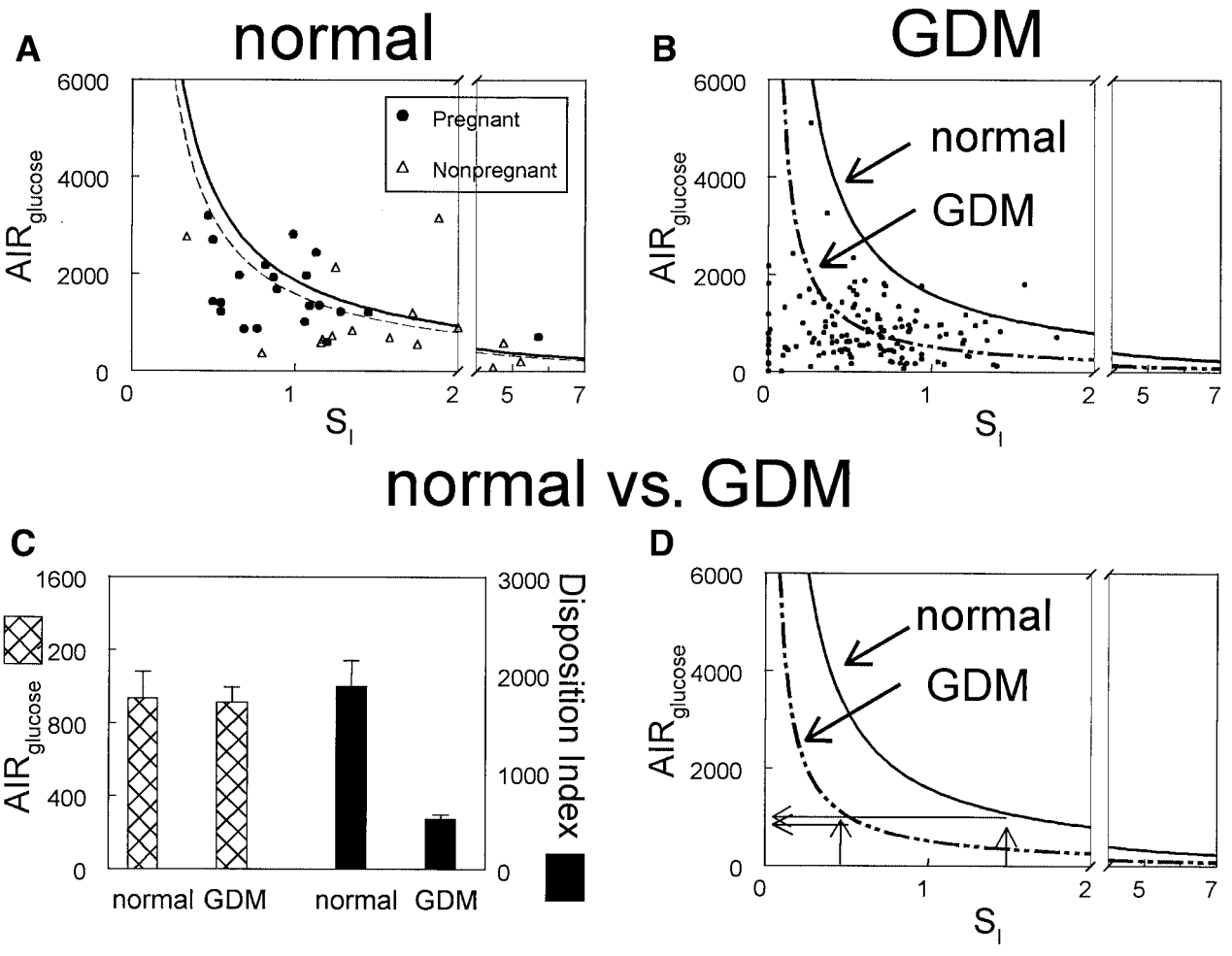

FIG. 3. Importance of expressing β-cell function in terms of disposition index. Note that in normal women (*A*), insulin sensitivity is relatively high (△), so that stress to the β-cells is limited and AIR_G is low. Pregnancy is characterized by lower S_I (●), and AIR_G is increased in response. Best-defined hyperbolas for nonpregnant and pregnant conditions are the same, because the values of the DI for the curves (solid versus dotted) are virtually identical. Women with GDM (*B*), as shown by Xiang et al. (20), have a severe β-cell defect, as reflected in a curve shifted down and to the left, reflecting a lower DI (broken line) relative to the DI observed in normal pregnancy (solid line). Note that because subjects with GDM are insulin resistant (*D*), AIR_G is virtually the same in women with GDM and normal pregnant women, masking the β-cell defect in GDM. However, calculating the DI (*C*) reveals the severe islet cell defect of GDM (20 and Buchanan, unpublished observations).

type 2 diabetes in the absence of insulin resistance has been reported in a few populations (17–19). How may one evaluate the health or lack thereof of the endocrine pancreas in the face of insulin resistance? The difficulty inherent in doing this is illustrated in Fig. 3. This figure exploits data obtained by Buchanan and colleagues (20 and Buchanan, unpublished observations), in which they have examined insulin secretion and action in Hispanic women with gestational diabetes mellitus (GDM).

The hyperbolic relationship is elegantly depicted by the secretion/sensitivity changes during pregnancy (Fig. 3*A*). In normal women, in response to the 75% decrement in S_I during the third trimester, Buchanan and colleagues observed the compensatory tripling of the acute response to intravenous glucose injection (Fig. 3*A*). They also observed that a cohort of women with GDM in whom secretion and sensitivity were assessed after term defined a hyperbolic curve with a reduced disposition index—i.e., the curve was shifted closer to the origin (Fig. 3*B*). Their data suggested that the women with GDM had a substantial β-cell defect (compare with Fig. 2). However, not all investigators have reported islet defects in GDM (21). Why they might reach this conclusion is illustrated by Fig. 3*D*. Note that women with GDM are insulin resistant. The sensitivity-secretion data for these women lie on a lower hyperbolic curve, indicating a substantial β-cell defect. However, in agreement with the hyperbolic hypothesis, the greater resistance of subjects with GDM upregulates β-cell response such that the insulin response for women with GDM is virtually identical to that of normal volunteers. The normal and GDM insulin responses per se would suggest similar islet function. However, normalizing to the degree of insulin resistance with the DI (Fig. 3*C*) reveals the severe deficiency in pancreatic function characteristic of women with GDM (22).

The example of Fig. 3*A–D* emphasizes the inherent difficulty in interpreting β-cell response per se as an index of islet health, without normalizing to the degree of insulin resistance. The example also shows that the DI can accurately reveal islet dysfunction. Clearly, these concepts must be applied to longitudinal studies of the pathogenesis of type 2 diabetes, in which β-cell defects can be masked

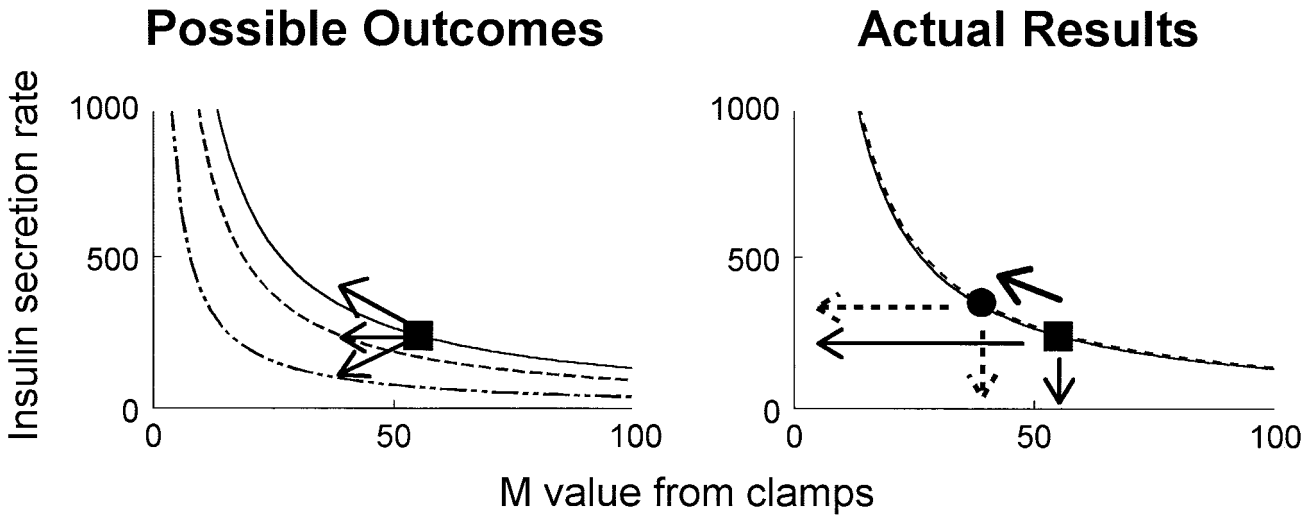

FIG. 4. Interpretation of data from Boden et al. (25) on the effects of lipid infusion on insulin secretion. Liposyn was infused into normal subjects for 48 h, and insulin sensitivity and insulin secretion were determined from euglycemic and hyperglycemic clamps. The left panel suggests possible outcomes on the sensitivity/secretion hyperbolic representation. It is to be expected that lipid infusion will induce insulin resistance (29,30). However, no change in insulin secretion rate (horizontal arrow) or a reduction in insulin secretion rate (downward arrow) would indicate a reduction in islet function, as the DI would be reduced. If islet function were unchanged, data would be represented by the upward arrow—i.e., moving upward and to the left on a single hyperbola (solid line), and a constant DI. In fact, a constant DI is what may be calculated from the data of Boden (right panel, constant DI with insulin resistance and expected β-cell upregulation). From Bergman and Ader (28).

by simultaneous insulin resistance and compensatory upregulation of insulin response to approach that of nonaffected subjects.

Example 2: lipid infusion. Considerable debate has centered on possible stimulatory effects of plasma free fatty acids on β-cell function (23,24). Other data have supported a "lipotoxic" effect (25,26). To examine this controversy, Boden et al. (27) performed elegant studies of the effects of lipid infusion on insulin response in human subjects. After a 48-h infusion of Liposyn, they observed an apparent doubling of β-cell response (Fig. 4). This enhancement may at first glance be considered supportive of a direct effect of free fatty acids (FFAs) to stimulate the β-cells. However, it is well documented that FFAs induce insulin resistance (29,30). The studies of Boden et al. confirm the insulin resistance: infusion of Liposyn reduced insulin sensitivity from 74 to 38 $\mu mol \cdot min^{-1} \cdot kg^{-1}$ (assessed in glucose clamps). What is the effect on β-cell function? Lipid infusion upregulated insulin secretory response from 300 to 600 $pmol \cdot l^{-1} \cdot min^{-1}$, exactly in concert with a constant DI value of ~22,200 (74 × 300 or 38 × 600). Therefore, it is reasonable to conclude that the FFA infusion directly affected insulin action only, and the increase in insulin secretion was the normal pancreatic compensation for enhanced insulin resistance. While Boden et al. may have understood this relationship between sensitivity and secretion, their data will be misunderstood by others and interpreted as supporting a direct effect of FFAs on insulin release in vivo. No direct effect on the pancreas was obvious.

Failure to take into account the hyperbolic relationship may also lead to misinterpretation of population studies. Table 1 lists preliminary results from the Insulin Resistance and Atherosclerosis Study (IRAS), in which insulin sensitivity and secretion were measured in a total of 1,524 subjects with normal glucose tolerance, impaired glucose tolerance (IGT), or type 2 diabetes (31). The relative defect in acute insulin response in subjects with IGT was 36%—this could well be interpreted as a mild impairment. However, subjects with IGT were also insulin resistant: S_I was 43% reduced. If a subject with normally functioning β-cells were insulin resistant to that extent, one would expect an increase in acute insulin response—similar to the finding of Boden et al. with lipid infusion. However, the reduction in acute insulin response in the face of insulin resistance suggests a much more substantial reduction in islet health; in fact the DI, which corrects insulin response to resistance, was reduced by nearly 70%, confirming a severe defect in islet function in IGT (32). This reduction matches similar severe β-cell defects in subjects with IGT reported by other workers who employed the DI concept (33,34). Failure to take the hyperbolic relationship into account in this case would greatly underestimate the β-cell defect in subjects with IGT—the reduction in acute insulin response was only 35%. It is likely that populations of insulin-resistant subjects with apparently normal insulin secretion exist where the secretory defect is masked by upregulation of insulin response due to the insulin resistance. Given recent efforts to prevent or delay the development of type 2 diabetes, it is incumbent on the diabetes research community to identify individuals with the earliest islet cell defects.

Unmasking β-cell defects. The two examples stated, plus a third confirming reduced β-cell function in aging,

TABLE 1
Preliminary results from the Insulin Resistance and Atherosclerosis Study (IRAS)

	Relative Defect		
	NGT	IGT	Type 2 diabetes
Insulin sensitivity (S_I)	0	43%	67%
Insulin response ($AIR_{glucose}$)	0	35%	92%
Disposition index (β-cell function)	0	67%	98%

NGT, normal glucose tolerance.

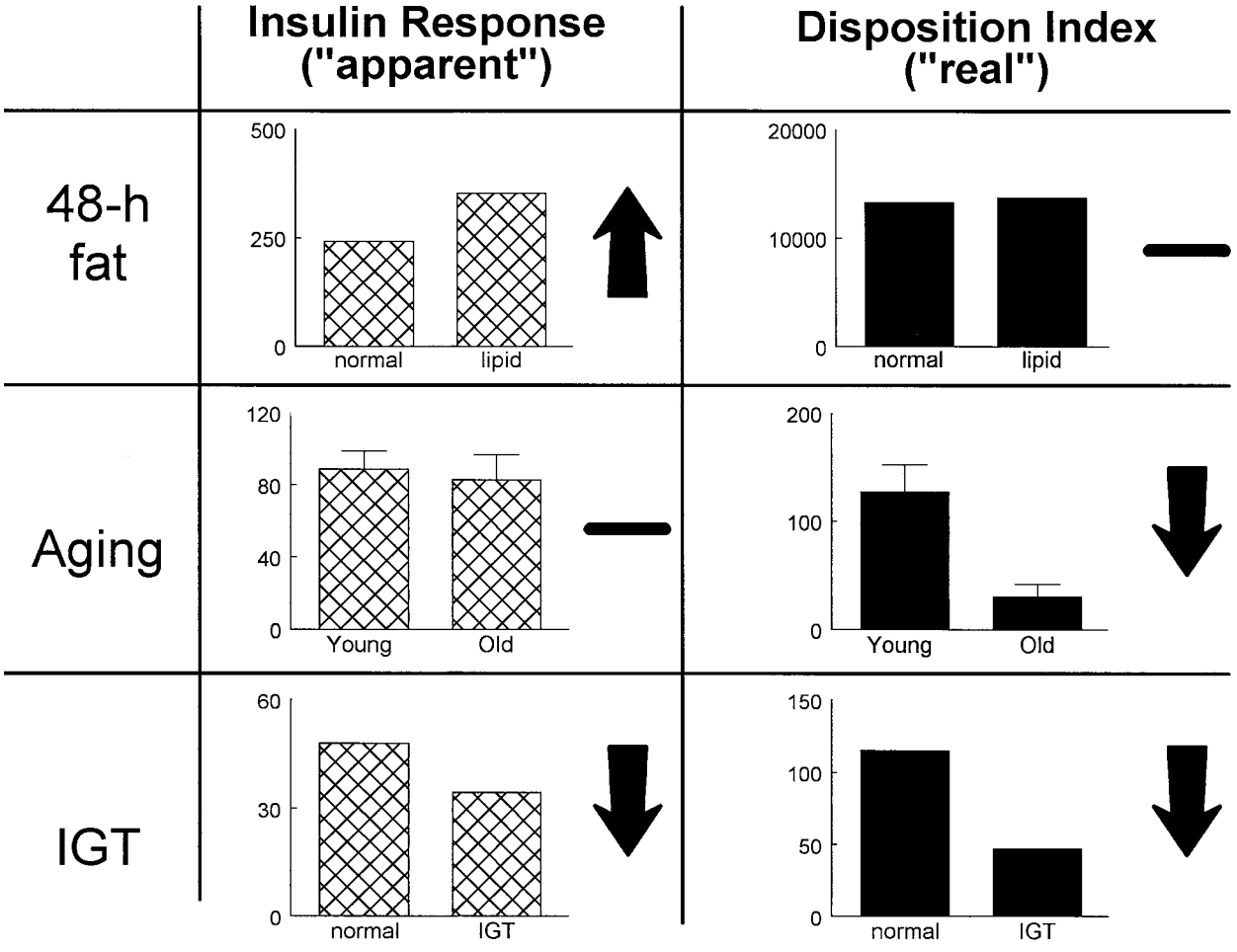

FIG. 5. Possible interpretations of insulin secretory function if the hyperbolic relationship between secretion and sensitivity is not considered. Data in upper panel are from the Boden study (cf, Fig. 4; 27) in which increase in insulin secretory response (left) reflects a constant disposition index (DI) (top right; lipid infusion had no effect per se on β-cell sensitivity to glucose). The middle panel reflects measures of insulin sensitivity and β-cell response in young versus elderly subjects (35). Whereas the secretory response was similar in both groups, when the age-dependent reduction in insulin sensitivity is accounted for (middle row, right panel), a severe β-cell defect is revealed (notice the 75% lower DI in the elderly subjects). The bottom panel reflects measurements in normal versus subjects with IGT (31). A relatively small reduction in insulin response (lower left panel) underestimates the severe β-cell defect in subjects with IGT which is masked by insulin resistance. DI values in the subjects with IGT were reduced by nearly 70%.

are summarized in Fig. 5. Note the apparent increase in β-cell response in the 48-h lipid-infused subject; DI was not changed, indicating no change in β-cell function. In aging, no apparent change in islet function masks a severe β-cell dysfunction, which is evident when insulin resistance of aging is taken into consideration. The DI was reduced >75%. β-Cell dysfunction may be an important component in the glucose intolerance associated with aging. Finally, the defect in islet function in subjects with IGT is substantially underestimated without correcting for resistance, as employed in the disposition index approach. The data in Fig. 5 emphasize the importance of calculating DI or some similar parameter to unmask the "real" β-cell function in studies employing intact organisms including human volunteers.

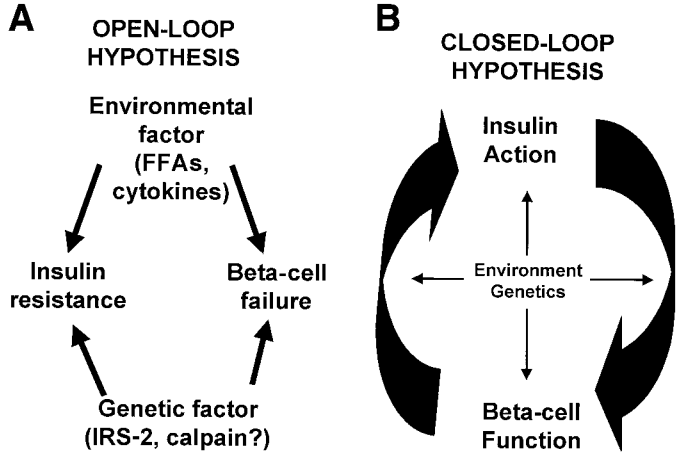

FIG. 6. Two possible scenarios for pathogenesis of diabetes. *A*: Independent causality for insulin resistance and β-cell dysregulation. Both genetic predisposition and environmental factors may induce insulin resistance and simultaneously lead to inability of the β-cells to compensate adequately for insulin resistance. In most cases, both defects will be necessary and sufficient for final conversion to diabetes. Genes for diabetes have not yet been clearly defined. *B*: Diabetes seen as dysfunction of the closed-loop relationship between insulin resistance and insulin secretory response. All signals relating secretion and action have not been defined; thus, it is not yet clear why β-cells upregulate their function when faced with insulin resistance. Diabetes may result from failure of appropriate signaling between insulin-sensitive and insulin-secreting cells. IRS-2, insulin receptor substrate 2.

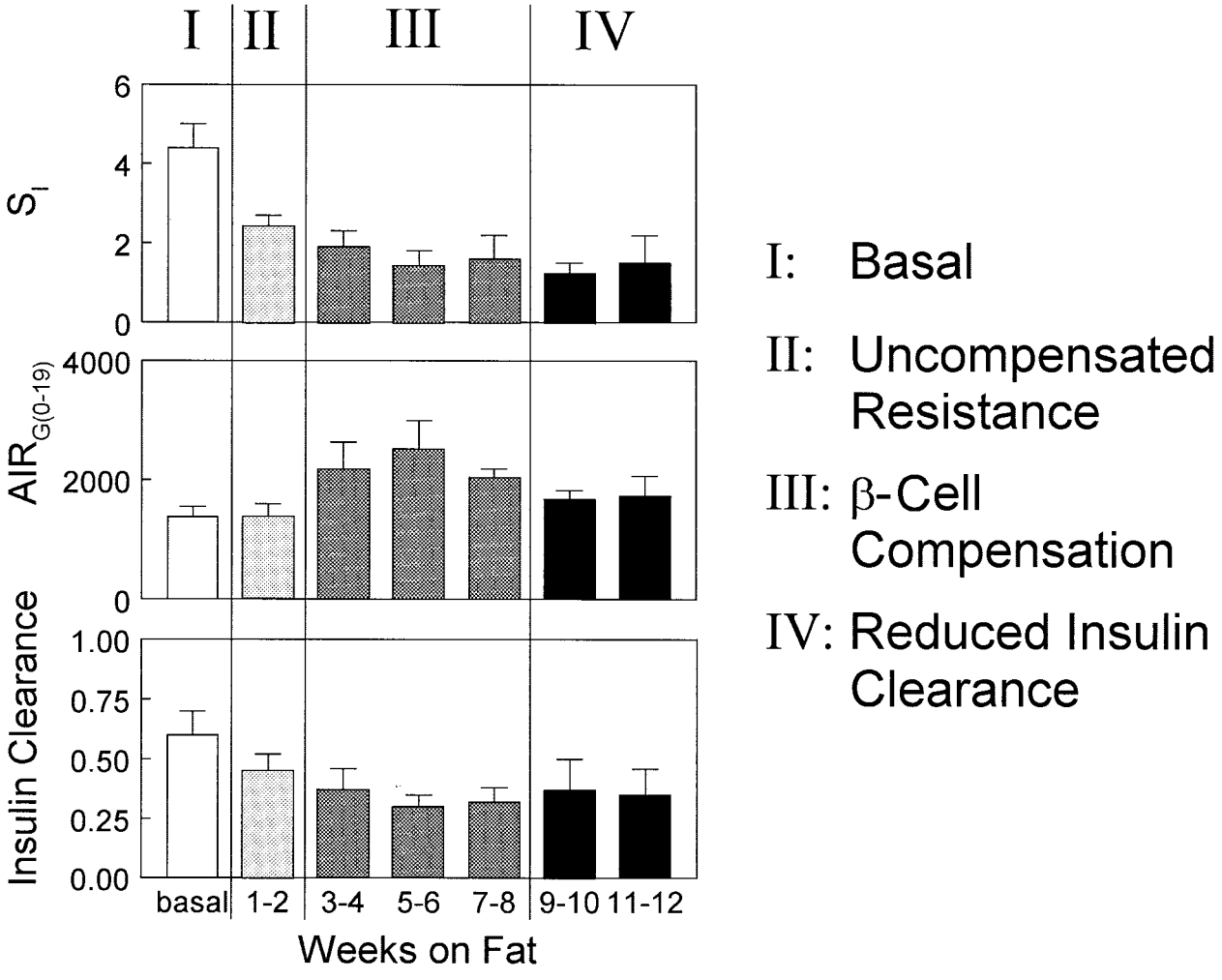

FIG. 7. Time course of compensation for feeding of moderate amounts of fat (10). After basal observations (phase I), dogs were fed a modest (+50 g/day) fat diet which resulted in increased visceral adiposity. Initial insulin resistance (phase II) was compensated during phase III by upregulation of insulin response (AIR_G). However, reduced extraction of insulin by the liver (insulin clearance) delivered more of secreted molecules to the systemic circulation, sparing β-cells from having to chronically oversecrete insulin. This reduced hepatic insulin extraction mechanism may protect β-cells from exhaustion in normal individuals.

Mechanisms of β-cell upregulation and role in pathogenesis of disease. What message relating to pathogenesis of disease emanates from the hyperbolic relationship? The concept of the 2-hit causality implies that different environmental and/or genetic causes will determine insulin action and β-cell function and their individual contributions to disease (Fig. 6*A*). Thus, we presuppose that environmental factors such as glycemia itself, FFAs, cytokines (tumor necrosis factor α, leptin, interleukin-6?), and/or islet amyloid polypeptide (36) may slowly damage β-cells. Simultaneously, obesity, FFAs, and genetic predisposition result in insulin resistance. When the sinister combination of reduced islet function and insulin resistance reach a critical juncture, diabetes ensues. It may be argued, however, that to understand diabetes we must understand the signals that relate insulin resistance to pancreatic response in normal subjects (Fig. 6*B*). Possibly the cause of diabetes is related to a failure of signaling from the insulin-resistant tissues to elicit the appropriate β-cell increment in sensitivity to glucose and other stimuli. But are these signals known?

The glucose hypothesis. It is reasonable to propose that glucose itself is the critical signal by which the peripheral tissues communicate. By this concept, insulin resistance will engender a subtle glucose intolerance. The elevated glucose—either fasting or prandial—will, in turn, stimulate the β-cells over time to be more sensitive to glucose as well as other secretagogues, thus enhancing the insulin response and mitigating the degree of intolerance. This hypothesis cannot at present be rejected. However, there are few data directly implicating glucose itself as the signal upregulating islet responsiveness with mild to moderate insulin resistance. Certain considerations indicate that other signals may play a role. In normal pregnancy, for example, severe insulin resistance and enhanced β-cell sensitivity prevent glucose intolerance despite a reduction in fasting glucose (37). Is it possible that signals other than glucose play a role in upregulation of islets during moderate insulin resistance? May failure of this system play a role in development of diabetes?

GLP-1 as a "compensatrin." We have recently introduced a model of moderate visceral adiposity in the dog

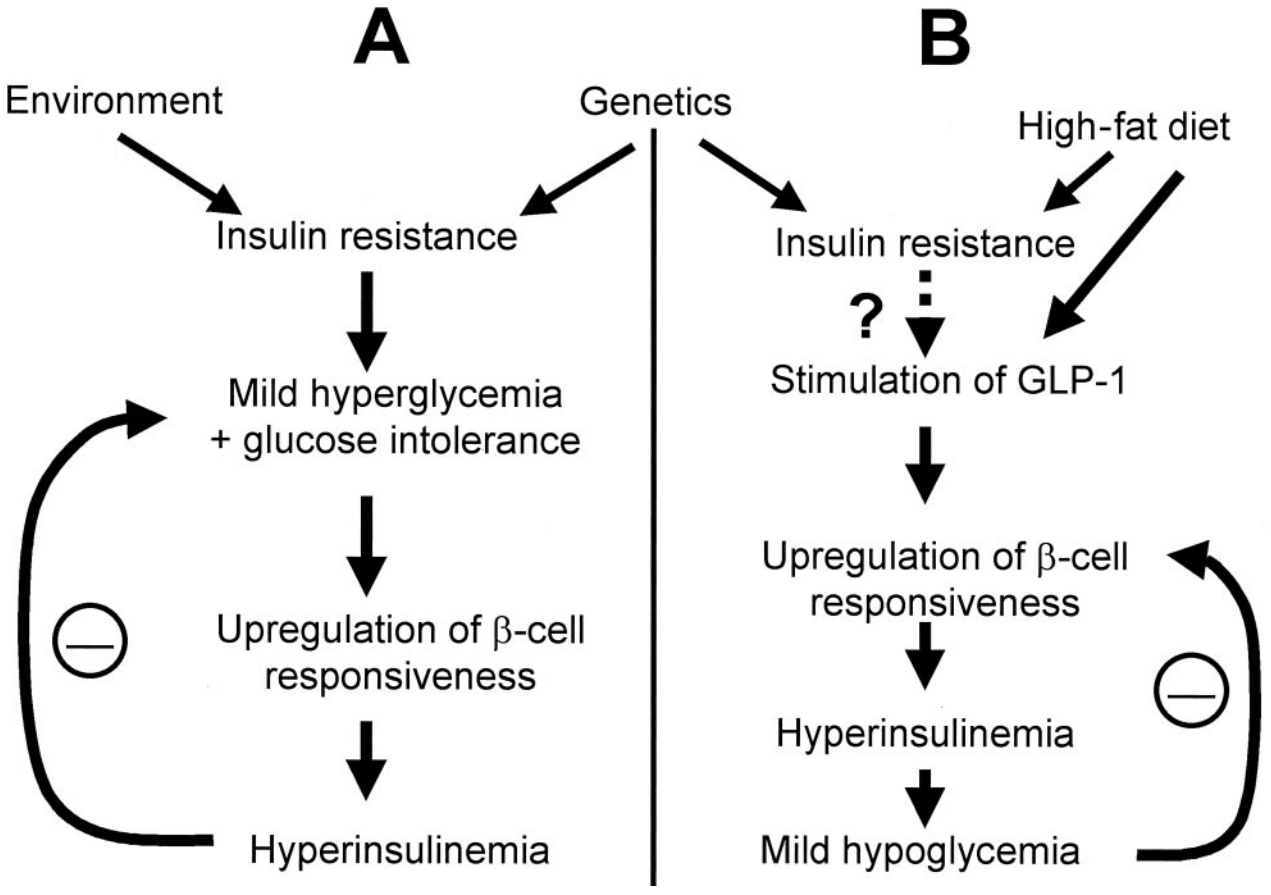

FIG. 8. Two possible scenarios of compensation for insulin resistance. *A*: Conventional wisdom. Insulin resistance is assumed to lead to mild hyperglycemia and glucose intolerance which enhances glucose sensitivity of β-cells, leading to hyperinsulinemia. In the alternative scenario (*B*), insulin resistance or the fat diet itself leads to "incretin" release (GLP-1, glucose-dependent insulinotropic polypeptide, others?) which is the signal responsible for β-cell upregulation. In this scenario, response is associated with a mild hypoglycemia. This is the response we have observed (see text).

(10). Diet was supplemented with 50 g fat per day—much less than that employed in earlier studies (38,39). This diet caused accumulation of central and subcutaneous fat. Metabolic changes included a 50% reduction in insulin sensitivity within a fortnight, which was maintained through 12 weeks of the elevated fat diet. Accompanying insulin resistance was upregulation of first-phase insulin response, as well as reduction in insulin clearance (Fig. 7). In a recent study, we addressed the question of the signal that might explain the islet upregulation. With fat feeding in the dog, we measured the expected fasting hyperinsulinemia, suggesting insulin resistance. Surprisingly, fasting glucose did not increase, nor did glucose tolerance worsen. In fact, fasting glucose values were significantly reduced, despite fasting hyperinsulinemia (10,40). This outcome is reminiscent of pregnancy, in which insulin resistance and hyperinsulinemia are associated with a paradoxical decline in fasting glycemia. These data suggest that glucose itself may not be the only signal that can upregulate islet sensitivity in insulin-resistant states.

We envision two possible mechanisms that can upregulate the β-cells. One is the expected impairment of glucose tolerance associated with insulin resistance (Fig. 8*A*), which leads to chronic glycemic stimulation. An alternative (Fig. 8*B*), which may apply in dietary fat–induced resistance, is primary nutrient stimulation of the L-cells of the gut, leading to increased glucagon-like peptide-1 (GLP-1) which, in turn, potentiates the β-cells to oversecrete insulin. The oversecretion drives the glucose levels paradoxically lower. Thus, gut factors such as GLP-1 may not only serve to enhance insulin release during food ingestion acting as incretins, but they may also play a role in establishing hyperinsulinemia to compensate for diet-induced insulin resistance. Thus, they may be not only incretins, but in the compensating role, we may refer to them as "compensatrins."

Final points. Maintenance of glucose tolerance is an important protective mechanism for vertebrates. Reduced glucose endangers function of the central nervous system, leading to inability to compute appropriate responses to environmental risk. Elevated glucose leads to protein glycation and general organ failure. It is no surprise that a complex and robust feedback system has evolved to constrain glycemia within narrow limits.

A fundamental principle of glycemic regulation in higher organisms is the insulin feedback system. Whereas the moment-to-moment importance of insulin in re-regulating glucose after nutrient ingestion has long been appreciated, equally important is the slower compensatory relationship between insulin secretion and action which optimize blood glucose and minimize periodic absorptive hyperglycemia. In this sense, glucose regulation is reminiscent of regulation of body fuel stores, which depends on an acute

system regulating hunger and a slower system re-regulating adipose stores after periods of fuel scarcity (41).

Central to long-term glucose regulation is the dialectic between insulin secretion and insulin action. The long period of dialectic debate as to whether insulin resistance or β-cell defect was primary has given way to the consensus that both are important and usually necessary for type 2 diabetes. Not enough emphasis, however, has previously focused on the normal interaction between these biological processes and the robust ability of the normal islet cells to compensate. This compensation was of little significance in a world of limited food supply. Given the relative abundance of energy supply in much of the Westernized world, the compensatory ability of the β-cells is the single physiological process that protects well-fed individuals from the scourge of type 2 diabetes. It is apparent that while European populations that have long been able to muster adequate food supplies can usually exist with elevated insulinemia but glycemic regulation, populations only recently exposed to extensive energy supply are not able in many cases to compensate, and are thus at greater risk for disease (42).

Important questions remain about islet compensation. As discussed, there may be several molecules that signal the islets to increase sensitivity to stimulation in insulin-resistant conditions. If such signals are identified (glucose, GLP-1?, glucose-dependent insulinotropic polypeptide?), it will be necessary to determine whether resistance of muscle or diet itself is the primary stimulus to β-cell compensation.

It is possible that the insulin sensitivity of muscle, liver, and adipose tissue may themselves play a regulatory role and are sensitized by insulin to ultimately reduce the hyperinsulinemia necessary to keep glycemia within normal ranges. The relative importance of β-cell upregulation versus insulin-mediated sensitization of target tissues to overall maintenance of glucose tolerance remains to be clarified.

It is implied in these discussions that the DI is constant for a single individual at a single point in life. However, if glucose is the primary stimulus to upregulation of islets, it is likely that the DI will be reduced as insulin resistance increases, thus maintaining a glycemic stimulus to the β-cells to oversecrete (C. Bogardus, personal communication). However, if signals other than glucose are invoked as pancreatic sensitizers, then the DI might remain constant. Careful longitudinal studies will be required to examine the efficiency of compensation in single individuals and the changes in the compensatory processes in those at risk.

Finally, and potentially most important, are questions regarding why islets fail to adequately compensate for insulin resistance in those truly at risk for type 2 diabetes. It appears unlikely that defects in the process of compensation will be revealed from short-term studies of insulin release but will be centered on the more complex pathways of chronic regulation of islet granule content and constitutive secretion. These questions of long-term compensation are difficult to address, particularly in the in vivo situation. Possibly studies of the genetics of the heritable DI may ultimately identify genes that code for the critical protein or proteins that play the pivotal role in the compensatory process. Clearly, much needs to be done.

ACKNOWLEDGMENTS

The work presented herein was supported by grants from the National Institutes of Health to Drs. Richard Bergman (DK27619 and DK29867) and Marilyn Ader (AG15111).

REFERENCES

1. Mauvais-Jarvis F, Virkamaki A, Michael MD, Winnay JN, Zisman A, Kulkarni RN, Kahn CR: A model to explore the interaction between muscle insulin resistance and beta-cell dysfunction in the development of type 2 diabetes. *Diabetes* 49:2126–2134, 2000
2. Withers DJ, Gutierrez JS, Towery H, Burks DJ, Ren JM, Previs S, Zhang Y, Bernal D, Pons S, Shulman GI, Bonner-Weir S, White MF: Disruption of IRS-2 causes type 2 diabetes in mice. *Nature* 391:900–904, 1998
3. Reaven GM, Bernstein R, Davis B, Olefsky JM: Nonketotic diabetes mellitus: insulin deficiency or insulin resistance. *Am J Med* 60:80–88, 1976
4. 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
5. Bergman RN: Toward physiological understanding of glucose tolerance: minimal-model approach (Lilly Lecture). *Diabetes* 38:1512–1527, 1989
6. Lauro D, Kido Y, Castle AL, Zarnowski MJ, Hayashi H, Ebina Y, Accili D: Impaired glucose tolerance in mice with a targeted impairment of insulin action in muscle and adipose tissue. *Nat Genet* 20:294–298, 1998
7. Bruning JC, Winnay J, Bonner-Weir S, Taylor SI, Accili D, Kahn CR: Development of a novel polygenic model of NIDDM in mice heterozygous for IR and IRS-1 null alleles. *Cell* 88:561–572, 1997
8. Bergman RN, Phillips LS, Cobelli C: Physiologic evaluation of factors controlling glucose tolerance in man: measurement of insulin sensitivity and B-cell glucose sensitivity from the response to intravenous glucose. *J Clin Invest* 68:1456–1467, 1981
9. Buchanan TA, Xiang AH, Peters RK, Kjos SL, Berkowitz K, Marroquin A, Goico J, Ochoa C, Azen SP: Response of pancreatic beta-cells to improved insulin sensitivity in women at high risk for type 2 diabetes. *Diabetes* 49:782–788, 2000
10. Mittelman SD, van Citters GW, Kim SP, Davis DA, Dea MK, Bergman RN: The longitudinal compensation for fat induced insulin resistance includes reduced insulin clearance and enhanced beta-cell response. *Diabetes* 49:2116–2125, 2000
11. Filipsson K, Pacini G, Scheurink AJW, Ahren B: PACAP stimulates insulin secretion but inhibits insulin sensitivity in mice. *Am J Physiol* 274:E834–E842, 1998
12. Kahn SE, Prigeon RL, McCulloch DK, Boyko EJ, Bergman RN, Schwartz MW, Neifing JL, Ward WK, Beard JC, Palmer JP, Porte D Jr: Quantification of the relationship between insulin sensitivity and beta-cell function in human subjects: evidence for a hyperbolic function. *Diabetes* 42:1663–1672, 1993
13. Wagenknecht LE, Meyer EJ, Rewers M, Haffner S, Selby J, Borok GM, Henkin L, Howard G, Savage PJ, Saad MF, Bergman RN, Hamman R: The Insulin Resistance Atherosclerosis Study (IRAS): objectives, design, and recruitment results. *Annals Epidemiol* 5:464–472, 1996
14. Ahren B, Pacini G: Impaired adaptation of first-phase insulin secretion in postmenopausal women with glucose intolerance. *Am J Physiol* 273:E701–E710, 1997
15. Uusitupa M, Louheranta A, Lindstrom J, Valle T, Sundvall J, Eriksson J, Tuomilehto J: The Finnish diabetes prevention study. *BMJ* 83 (Suppl. 1):S137–S142, 2000
16. Elbein SC, Hasstedt SJ, Wegner K, Kahn SE: Heritability of pancreatic beta-cell function among nondiabetic members of Caucasian familial type 2 diabetic kindreds. *J Clin Endocrinol Metab* 84:1398–1403, 1999
17. 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
18. Arner P, Pollare T, Lithell H: Different aetiologies of type 2 (non-insulin-dependent) diabetes mellitus in obese and non-obese subjects. *Diabetologia* 34:483–487, 1991
19. Chaiken RL, Banerji MA, Pasmantier R, Huey H, Hirsch S, Lebovitz HE: Patterns of glucose and lipid abnormalities in black NIDDM subjects. *Diabetes Care* 14:1036–1042, 1991
20. Xiang A, Peters RK, Trigo E, Kjos SL, Lee WP, Buchanan TA: Multiple metabolic defects during late pregnancy in women at high risk for type 2 diabetes mellitus. *Diabetes* 48:848–854, 1999

21. Bowes SB, Hennessy TR, Umpleby AM, Benn JJ, Jackson NC, Boroujerdi MA, Sönksen PH, Lowy C: Measurement of glucose metabolism and insulin secretion during normal pregnancy and pregnancy complicated by gestational diabetes. *Diabetologia* 39:976–983, 1996
22. Buchanan TA: Pancreatic B-cell defects in gestational diabetes: implications for the pathogenesis and prevention of type 2 diabetes. *J Clin Endocrinol Metab* 8:989–993, 2001
23. Boden G, Chen X: Effects of fatty acids and ketone bodies on basal insulin secretion in type 2 diabetes. *Diabetes* 48:577–583, 1999
24. Stein DT, Esser V, Stevenson BE, Lane KE, Whiteside JH, Daniels MB, Chen S, McGarry JD: Essentiality of circulating fatty acids for glucose-stimulated insulin secretion in the fasted rat. *J Clin Invest* 97:2728–2735, 1996
25. Lee Y, Hirose H, Ohneda M, Johnson JH, McGarry JD, Unger RH: Beta-cell lipotoxicity in the pathogenesis of non-insulin-dependent diabetes mellitus of obese rats: impairment in adipocyte-beta-cell relationships. *Proc Natl Acad Sci U S A* 91:10878–10882, 1994
26. McGarry JD, Dobbins RL: Fatty acids, lipotoxicity and insulin secretion. *Diabetologia* 42:128–138, 1999
27. Boden G, Chen X, Rosner J, Barton M: Effects of a 48 hour fat infusion on insulin secretion and glucose utilization. *Diabetes* 44:1239–1242, 1995
28. Bergman RN, Ader M: Free fatty acids and the pathogenesis of type 2 diabetes mellitus. *Trends Endocrinol Metab* 11:351–356, 2000
29. Ferrannini E, Barrett EJ, Bevilacqua S, DeFronzo RA: Effect of fatty acids on glucose production and utilization in man. *J Clin Invest* 72:1737–1747, 1983
30. Boden G, Chen X, Ruiz J, White JV, Rossetti L: Mechanisms of fatty acid-induced inhibition of glucose uptake. *J Clin Invest* 93:2438–2446, 1994
31. Haffner SM, Howard G, Mayer E, Bergman RN, Savage PJ, Rewers M, Mykkanen L, Karter AJ, Hamman R, Saad MF: Insulin sensitivity and acute insulin response in African-Americans, non-Hispanic whites, and Hispanics with NIDDM. *Diabetes* 46:63–69, 1997
32. Watanabe RM, Laws A, Rewers M, Bergman R, for the IRAS Investigators: Impaired glucose tolerant subjects exhibit a β-cell defect despite normal fasting glycemia. *Diabetes* 44 (Suppl. 1):5A, 1995
33. Larsson H, Ahrén B: Failure to adequately adapt to reduced insulin sensitivity with increased insulin secretion in women with impaired glucose tolerance. *Diabetologia* 39:1099–1107, 1996
34. Weyer C, Hanson K, Bogardus C, Pratley RE: Long-term changes in insulin action and insulin secretion associated with gain, loss, regain and maintenance of body weight. *Diabetologia* 43:36–46, 2000
35. Chen M, Bergman RN, Pacini G, Porte D Jr: Pathogenesis of age-related glucose intolerance in man: insulin resistance and decreased B-cell function. *J Clin Endocrinol Metab* 60:13–20, 1985
36. Janson J, Ashley RH, Harrison D, McIntyre S, Butler PC: The mechanism of islet amyloid polypeptide toxicity is membrane disruption by intermediate-sized toxic amyloid particles. *Diabetes* 48:491–498, 1999
37. Freinkel N: Of pregnancy and progeny (Banting Lecture). *Diabetes* 29: 1023–1035, 1980
38. Kaiyala K, Prigeon RL, Kahn SE, Woods SC, Porte D Jr, Schwartz MW: Reduced beta-cell function contributes to impaired glucose tolerance in dogs made obese by high-fat feeding. *Am J Physiol* 277:E659–E667, 1999
39. Rocchini AP, Marker P, Cervenka T: Time course of insulin resistance associated with feeding dogs a high-fat diet. *Am J Physiol* 272:E147–E154, 1997
40. van Citters GW, Kim SP, Mittelman SD, Dea MK, Bergman RN: Glucose per se is not involved in upregulation of the beta cell in insulin resistance (Abstract). *Diabetes* 49 (Suppl. 1):A431, 2000
41. Schwartz MW, Woods SC, Porte D Jr, Seeley RJ, Baskin DG: Central nervous system control of food intake. *Nature* 404:661–671, 2000
42. Joffe B, Zimmet P: The thrifty genotype in type 2 diabetes: an unfinished symphony moving to its finale? *Endocrine* 9:139–141, 1998