Medical Progress

Pathogenesis of Impaired Glucose Tolerance and Type II Diabetes Mellitus—Current Status

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The insulin response to glucose taken orally is increased in patients with impaired glucose tolerance (IGT) but decreased in those with type II diabetes mellitus. The insulin response to meals, however, is normal in patients with type II diabetes, although the glucose concentrations are obviously elevated. The acute insulin response to intravenously administered glucose is absent in cases of both IGT and type II diabetes when the fasting plasma glucose level exceeds 115 mg per dl. On the other hand, the response to other intravenously given secretagogues is either normal or nearly so. The absent acute insulin response to intravenously administered glucose can be restored by α-adrenergic blockade, prostaglandin synthesis inhibition, dopaminergic blockade and euglycemia.

Insulin antagonism characterizes patients with both IGT and type II diabetes. Those with IGT and mild diabetes mellitus (untreated fasting plasma glucose concentrations < 180 mg per dl) have a receptor defect probably due to down regulation. Diabetic patients with more severe type II diabetes show a postreceptor defect. The relation (if any) between receptor and postreceptor defects is unclear.

(Davidson MB: Pathogenesis of impaired glucose tolerance and type II diabetes mellitus—Current status [Medical Progress]. West J Med 1985 Feb; 142:219-229)

Type II or ketosis-resistant diabetes mellitus and impaired glucose tolerance (IGT) are common and are responsible for a great deal of morbidity and mortality in adults. Current treatment is imperfect, reflecting our ignorance of the pathogenesis of these disorders. The lack of appropriate animal models has forced investigations to be carried out in human subjects and necessarily slowed our progress. However, since the advent of the radioimmunoassay for insulin about 25 years ago and the more recent introduction of new in vivo techniques for assessing insulin sensitivity, a great deal of information has emerged in this area. At first glance, the pathogenesis of IGT and diabetes mellitus would seem to be either impaired insulin secretion, impaired insulin action or possibly some combination of the two. In this review I will summarize the information regarding these possibilities, provide enough background material for understanding the data in this rapidly changing area and attempt to draw some tentative (albeit speculative) conclusions based on our current knowledge.

Insulin Secretion

Stimuli Given Orally

The results of the first report[1] comparing insulin responses of patients with ketosis-resistant diabetes mellitus and control subjects are shown in Figure 1. The first obvious conclusion is that insulin lack is not the cause of diabetes in these persons. There are two caveats to this conclusion, however. Many of these patients were obese and subsequent reports[2] have clearly shown that obesity per se is associated with hyperinsulinemia. Therefore, to assess insulin secretion in cases of IGT and diabetes mellitus, weight-matched controls are mandatory. Thus, one cannot conclude from the results shown in Figure 1 whether or not insulin secretion was normal as obese nondiabetic control subjects were not used. The second difference between the diabetic patients and control subjects in Figure 1 is their pattern of insulin responses. The peak concentration of insulin in the nondiabetic persons occurred at one hour while insulin levels peaked later in the diabetic

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patients. This delayed peak of insulin has been found in many, but not all, patients with ketosis-resistant diabetes and seems to be independent of obesity—that is, obese subjects with normal glucose tolerance do not show it and both lean and obese persons with IGT and type II diabetes mellitus may. Its significance in the pathogenesis of altered states of carbohydrate metabolism is unknown.

In hundreds of subsequent publications attempts have been made to determine if insulin secretion in cases of diabetes was increased, normal or decreased when controls of appropriate weight were used. The answer finally seems to be in and involves a strict definition of the groups under study. Patients with IGT according to the criteria of the National Diabetes Data Group—that is, fasting plasma glucose concentrations of less than 140 mg per dl and two-hour values between 140 and 199 mg per dl during a glucose tolerance test[3]—have increased insulin secretion and many of them show a delayed peak to glucose taken orally.[4-6] Patients with overt type II diabetes—that is, fasting plasma glucose concentrations greater than 140 mg per dl and two-hour values greater than 200 mg per dl during a glucose tolerance test—have impaired insulin secretion after glucose is readministered orally.[4-6] These conclusions are substantiated in three cohorts of patients—a group from California (Figure 2), Pima Indians (Figure 3) and a Scandinavian population (Figure 4.)

The total insulin responses in 145 nonobese persons[4] are summarized in Figure 2. Normal glucose tolerance (group N) in this study is defined by the very sensitive Fajans and Conn criteria—that is, one-hour plasma glucose concentrations of less than 185 mg per dl and two-hour plasma values of less than 140 mg per dl. Borderline tolerance (BT) defines a group in which one of these values was exceeded and chemical diabetes (CD) those persons in whom both values were exceeded. The final two groups had mild and moderate fasting hyperglycemia. The results are expressed as the area subtended by the values for plasma glucose and insulin during a three-hour glucose tolerance test. It is apparent that the total insulin response is increased in CD patients and decreased in those with fasting hyperglycemia of greater than 150 mg per dl. A normal total insulin response occurred in those with borderline tolerance and mild fasting hyperglycemia (glucose levels between 110 and 150 mg per dl).

Figure 3 relates the two-hour plasma glucose and insulin concentrations during oral glucose tolerance tests in 396 nonobese and obese (> 125% desirable weight) Pima Indians, none of whom were receiving sulfonylurea agents at the time of the test nor had ever received insulin.[5] The pattern is obvious. As the two-hour glucose value increases up to about 200 mg per dl, the insulin level is greater than normal. Further increases in the two-hour glucose value were associated with a

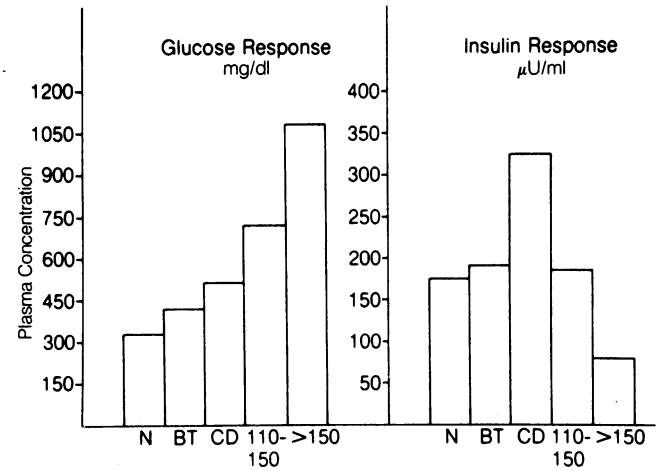

Figure 2.—Total glucose and insulin responses during oral glucose tolerance tests. See text for description of patient groups and method of expressing results. (From Reaven GM, Carbohydrate metabolism in insulin-independent diabetes, The Role of Sulfonylureas in the Treatment of Insulin-Independent Diabetes, published for Pfizer Laboratories Division, Pfizer Inc, by Science and Medicine Inc, 1980, pp 7-12. This figure summarizes data published in Reaven et al.[4])

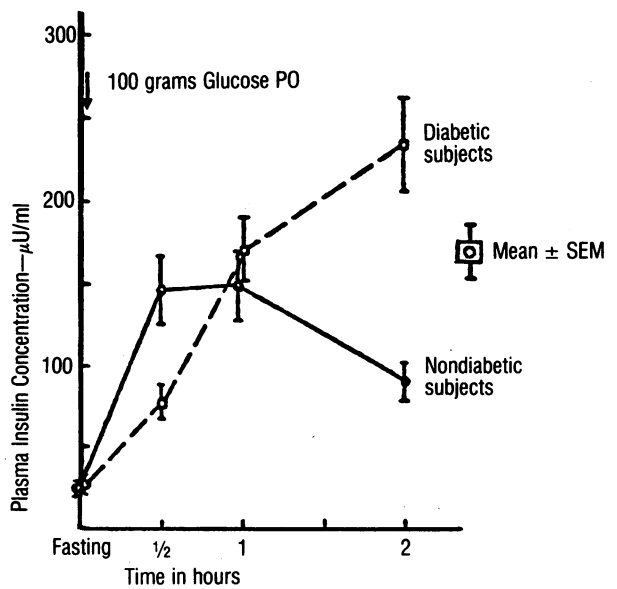

Figure 1.—Insulin response during an oral glucose tolerance test in 17 patients with "early maturity-onset" diabetes and 14 control subjects (from Yalow and Berson[1]). PO = by mouth, SEM = standard error of the mean.

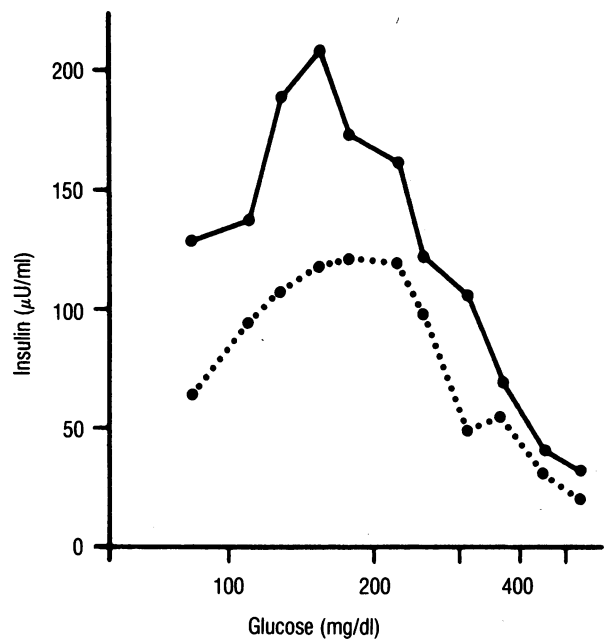

Figure 3.—Mean two-hour serum insulin and glucose concentrations in nonobese (●---●) and obese (●—●) Pima Indians (from Savage et al[5]).

declining insulin level, which soon fell to below normal. Note that although insulin concentrations are increased in obese subjects compared with lean ones as mentioned previously,[2] the same general pattern exists within each group.

The Scandinavian group[6] consisted of 165 control subjects and 85 persons with varying degrees of abnormalities on oral glucose tolerance testing. These latter patients were divided into five groups with progressive deterioration of glucose tolerance (bottom row of Figure 4) and each group was compared with sex- weight- and age-matched control subjects.

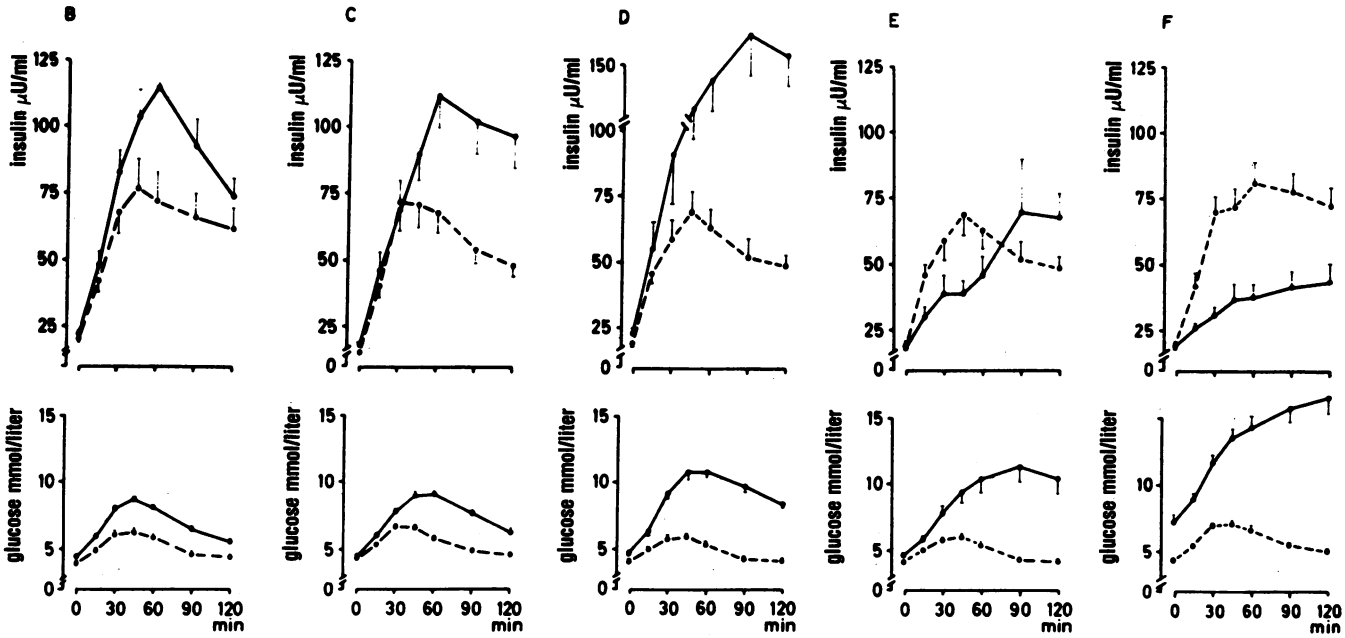

Figure 4.—Glucose and insulin responses during oral glucose tolerance tests in Scandinavian patients, with varying degrees of abnormalities depicted by the solid lines compared with sex-, weight- and age-matched controls depicted by the broken lines (from Luft et al[6]).

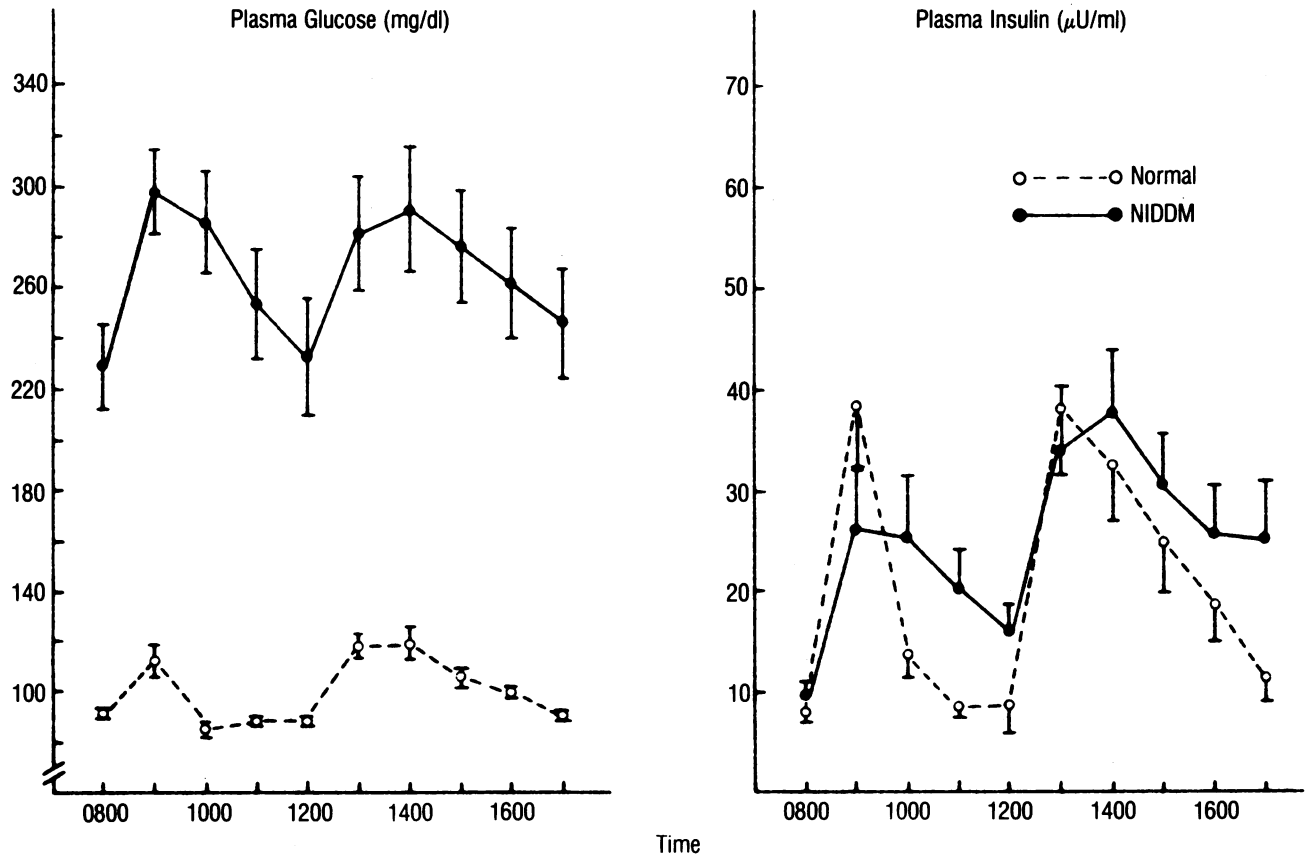

Figure 5.—Plasma glucose and insulin responses (mean ± standard error of the mean) to a mixed meal in 15 patients with type II diabetes and 15 controls. All subjects received breakfast at 0800 and lunch at 1200 (from Liu et al[8]). NIDDM = non-insulin-dependent diabetes mellitus.

The glucose units (mmol per liter) in the figure should be multiplied by 18 to convert them into milligrams per deciliter. The insulin responses are depicted in the top row of Figure 4 and are increased in the the first three groups of patients (B, C and D) with the mildest degrees of abnormality. In group E, the peak levels of insulin are normal, although attainment of the maximum concentration is delayed. Only in group F with the most severe deterioration of the oral glucose tolerance is the total insulin response clearly diminished.

Thus, a spectrum exists. Patients with impaired glucose tolerance (previously termed chemical or mild diabetes) have an enhanced insulin response to oral glucose. As the carbohydrate abnormality worsens, insulin concentrations return to normal and eventually diminish. Because in at least 20% of persons with IGT diabetes mellitus eventually develops,[7] it seems difficult to ascribe the development of clinically evident diabetes solely to a *primary* impairment of insulin secretion. For this to be true, one would have to subscribe to the view that IGT and diabetes mellitus were independent disorders, which does not seem likely.

Further evidence against a *sole primary* defect in insulin secretion as the basic cause of type II diabetes is the fact that the insulin response to meals in these patients is not decreased.[8] The results of two meal tolerance tests (which are obviously much more physiologic than 50 to 100 grams of dextrose) are shown in Figure 5. All sulfonylurea agent therapy in these lean type II diabetic patients was discontinued at least a month before these tests. Furthermore, they had the typical greatly impaired insulin response to glucose taken orally (data not shown) that characterizes these patients. The test meals were solid food of identical composition for breakfast and lunch, consisting of 40% carbohydrate, 40% fat and 20% protein. They provided 20% of the total daily caloric requirement for breakfast and 40% for lunch. The results are clear-cut. The insulin responses to the meals were similar in control and diabetic subjects. Two conclusions can be drawn from these "normal" insulin concentrations in the presence of this degree of hyperglycemia. First, the available insulin is not normally effective, a situation to be discussed below in detail. Second, because a nondiabetic person should be able to mount a much greater insulin response to this degree of hyperglycemia, the β-cell reserve of type II diabetic patients must be diminished. However, the fact remains that the tissues in these persons are exposed to the same levels of insulin throughout a 24-hour period as is the case in nondiabetic persons. Therefore, other factors must be involved in the pathogenesis of type II diabetes in addition to defects in insulin secretion.

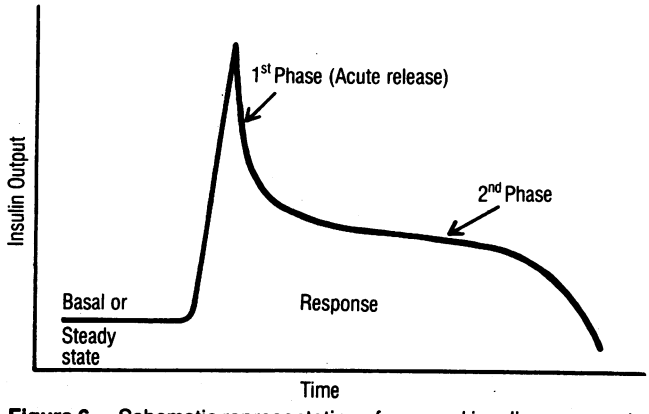

Figure 6.—Schematic representation of a normal insulin response to intravenous administration of glucose (from Pfeifer et al[9]).

Stimuli Administered Intravenously

Abnormalities in the insulin response to intravenous administration of glucose occur in patients with both IGT and type II diabetes mellitus, though how they may be related to the altered carbohydrate metabolism in these disorders is not yet clear. The normal insulin response to intravenously given glucose is shown in Figure 6. There is an initial rapid response with peak insulin concentrations reached within the first few minutes. This is called the first-phase or the "acute" insulin response. A more delayed gradual increase (termed the second-phase response) occurs if large amounts of glucose are administered or if the glucose is given continuously. A small pulse of glucose elicits only the first-phase response. Some other agents given intravenously will also stimulate a first-phase response. These include isoproterenol (Isuprel) hydrochloride, which is a β-adrenergic agonist,[10] glucagon,[11] tolbutamide,[12] certain amino acids such as arginine[13] and secretin.[14]

Persons with fasting glucose concentrations exceeding 115 mg per dl have an absent first-phase response to intravenously given glucose (Figure 7).[15] This obviously includes patients with both IGT and type II diabetes. However, the second-phase response to glucose given intravenously remains generally intact until the fasting plasma glucose level exceeds 200 mg per dl.[15]

In contrast to the absent first-phase response to intravenous administration of glucose, patients with both IGT and type II diabetes retain their acute insulin response to other intravenously given secretagogues such as isoproterenol,[10] arginine,[13] glucagon,[11] secretin[16] and tolbutamide.[17] Figure 8 depicts the acute responses to glucose and isoproterenol in normal persons and type II diabetic patients. Although the latter did respond to the β-adrenergic agonist, their mean response was somewhat less than that of normal subjects. More detailed analysis of the results in the diabetic population showed that the response to isoproterenol remained normal until the fasting plasma glucose concentration exceeded 300 mg per dl.[9]

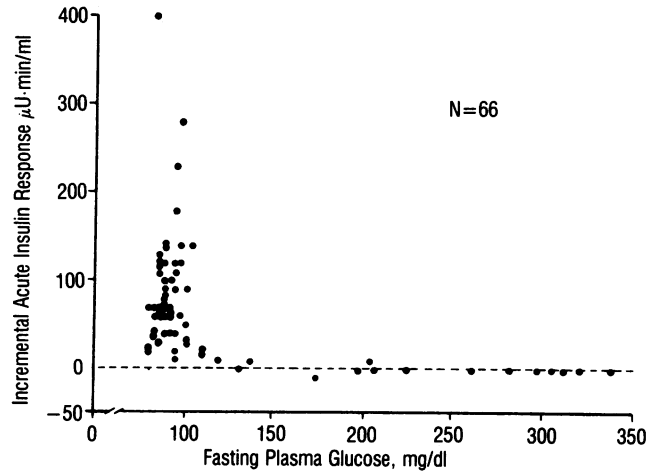

Figure 7.—Relation between fasting plasma glucose concentrations and the first-phase insulin response to intravenously given glucose (from Brunzell et al[15]).

Thus, the second-phase insulin response to intravenous administration of glucose became impaired with moderate decompensation, whereas impairment of the first-phase insulin response to isoproterenol only occurred with severe decompensation. These results suggest that the abnormalities of insulin secretion to intravenously given secretagogues may not be absolute. That is, they may vary depending on the degree of various metabolic or hormonal changes, or both. Indeed, it can be shown that the absent first-phase insulin response to glucose is not irreversible. It can be at least partially restored by the following manipulations: inhibition of prostaglandin synthesis[10]; α-adrenergic blockade[18,19]; opiate-receptor blockade,[20] and return to normal of the fasting glucose concentration by an overnight infusion of insulin.[17]

Because prostaglandin infusions, α-adrenergic agonists and dopaminergic stimulation will all inhibit insulin release in normal subjects, there is a molecular basis for the restoration of insulin secretion by the first three manipulations listed above. There is also a possible molecular basis for the effect of normalizing the fasting glucose concentration in restoring

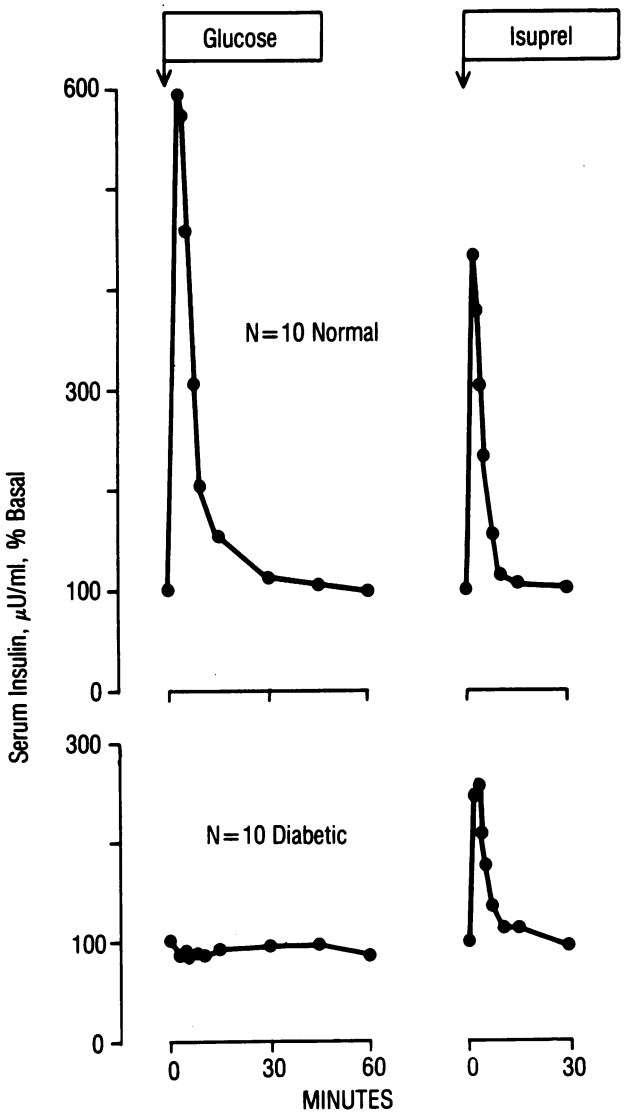

Figure 8.—Comparison of the first-phase insulin response to glucose and isoproterenol hydrochloride given intravenously in type II diabetic patients and controls (from Robertson and Porte[10]).

the acute insulin response to glucose given intravenously. If hyperglycemia is induced in *normal* subjects by a 46-hour infusion of somatostatin and glucagon, the acute insulin responses to glucose and isoproterenol mimic those found in patients with IGT and type II diabetes—an absent response to glucose and a normal response to the β-adrenergic agonist.[21] One interpretation of these results in normal subjects is that the alterations in insulin secretion to intravenous administration of secretagogues in patients with IGT and type II diabetes reflect a reaction to chronic hyperglycemia rather than a primary lesion of the pancreatic β-cell.

Insulin Antagonism

Insulin antagonism or resistance (these terms will be used interchangeably) occurs in any situation in which insulin is unable to exert its normal effect. Until 1970, insulin antagonism in human subjects was usually shown by either indirect means—such as normal or elevated glucose concentrations in the presence of elevated insulin levels following a glucose challenge—or by insulin tolerance tests. However, the latter test was not very sensitive as extremely high plasma insulin concentrations were attained. Furthermore, interpretation was hindered by the fact that different amounts of insulin were often given because of varying body weights. Finally, the contrainsulin (counterregulatory) hormones affect the results and this response is not related to insulin resistance per se.

Steady-State Plasma Glucose Technique

In 1970 Reaven and colleagues[22] reported a method that could show directly in human subjects more subtle degrees of insulin resistance. With this approach, termed the pancreatic suppression test, insulin suppression test or the steady-state plasma glucose technique, an infusion of insulin, glucose, propranolol hydrochloride and epinephrine is used. Insulin and glucose reach steady-state concentrations after 90 minutes and remain stable for at least an hour. The insulin level, termed the steady-state plasma insulin, is the same in all subjects, with the value depending on the rate of insulin infusion. The steady-state plasma glucose level is inversely related to the effectiveness of the infused insulin. Lower glucose concentrations reflect more effective insulin action whereas higher glucose values denote insensitivity to insulin. With this technique, Reaven and colleagues[2,22-30] found increasing insulin antagonism in lean subjects who have abnormalities in carbohydrate metabolism progressing from minor impairments of glucose tolerance through to overt diabetes mellitus (Figure 9). These results have been confirmed by other investigators in lean subjects with both impaired glucose tolerance[31] and overt diabetes.[32] However, because the unopposed α-adrenergic effect of propranolol and epinephrine can cause arrhythmias and hypertension,[33] this particular approach is now seldom used. More recently, somatostatin has been substituted for epinephrine and propranolol to block endogenous insulin secretion. Insulin resistance was again observed in lean and obese patients with both borderline glucose tolerance and overt diabetes.[34-37]

Euglycemic Glucose Clamp Technique

Recently, a more sophisticated method has been used to measure insulin sensitivity. With this approach, called the euglycemic clamp technique, a constant infusion of insulin (after an initial bolus) is given and variable rates of glucose

administered to maintain the glucose concentration at the basal value—that is, the glucose level is "clamped." This is accomplished by rapidly measuring glucose concentrations in blood specimens drawn every five minutes and adjusting the glucose infusion rate to maintain the desired concentration according to a predetermined algorithm.[38] The total amount of glucose administered is directly related to the effectiveness of the infused insulin; higher amounts of administered glucose reflect sensitivity to insulin whereas lower amounts indicate insulin resistance. Because the glucose concentrations remain constant, the rate at which glucose is disposed of is equal to the rate at which it is delivered into the circulation. This is the sum of the exogenous glucose administered by vein and the endogenous glucose produced by the liver. However, hepatic glucose production is suppressed by about 95% (even in diabetic persons) by these amounts of glucose and insulin and can

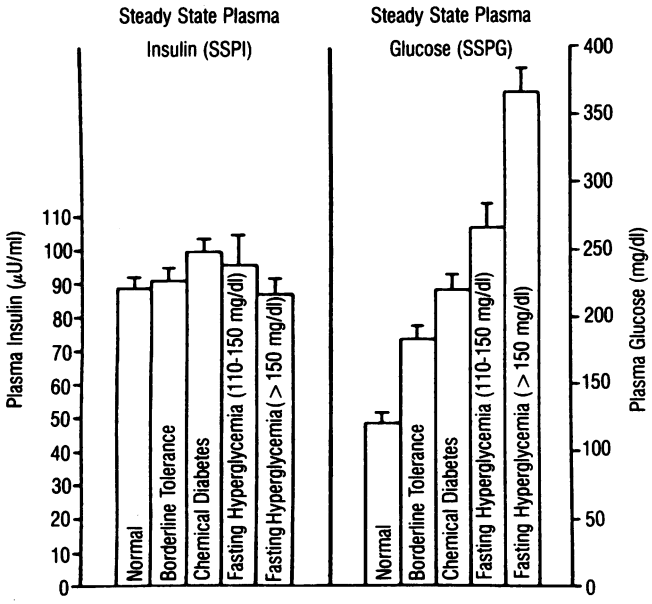

Figure 9.—Mean (± standard error of the mean) steady-state plasma insulin (SSPI) and glucose (SSPG) levels during the infusion of epinephrine (6 μg per minute), propranolol hydrochloride (0.08 mg per kg of body weight per minute), insulin (80 mU per minute) and glucose (6 mg per kg per minute) in five groups of patients. These patient groups are the same as those defined for Figure 2 (from Reaven et al[4]).

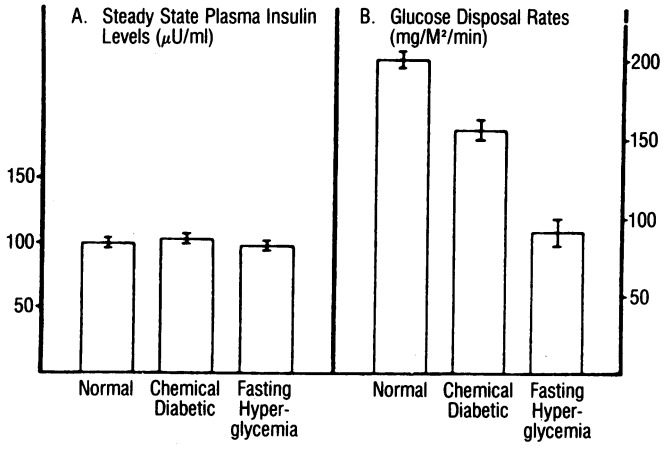

Figure 10.—Mean steady-state plasma insulin levels (A) and glucose disposal rates (B) in normal subjects, patients with impaired glucose tolerance (chemical diabetes) and type II diabetes (from Olefsky[40]).

therefore be ignored. If the renal threshold is exceeded, however, the amount of glucose lost in the urine must be taken into consideration. The results are often expressed as the glucose disposal rate and, in the absence of glucosuria, is simply equal to the rate of administration of exogenous glucose.

Increasing insulin antagonism has also been shown with the clamp technique as impaired glucose tolerance (chemical diabetes) worsens to overt diabetes (Figure 10).[30,39-45] Although obesity per se is associated with insulin resistance, once diabetes supervenes, the degree of insulin antagonism is similar in obese and nonobese persons with type II diabetes when measured by the clamp technique.[43]

Thus, a number of in vivo studies[2,22-37,39-45] have clearly established that insulin antagonism characterizes impaired glucose tolerance and type II diabetes mellitus. Unraveling the mechanism of this insulin resistance, however, has not been easy. Part of the reason involves the complicated set of circumstances governing insulin action and insulin antagonism. An understanding of these sophisticated concepts is necessary before assessing the current state of knowledge of the mechanism of insulin antagonism in patients with abnormal carbohydrate metabolism.

Insulin Binding

Binding of insulin to its receptor is the critical first step of insulin action. The interaction between hormones and receptors is influenced by two general properties: the number of available receptors (also termed the binding capacity) and the affinity or "attraction" between the hormone and its receptor. Hormonal binding affinities and capacities are usually quantitated by plotting the ratio of the bound hormone divided by the free hormone against the amount of hormone bound to the receptor at equilibrium.[46] Examples of this relationship (termed the Scatchard plot) for growth hormone and insulin are shown in Figure 11. Interpreting Scatchard plots is straightforward and calculations of the properties of hormonal binding are simple if a straight line relationship is obtained as in the case of growth hormone. The X intercept represents the total binding capacity and the slope of the curve defines the affinity. Evaluating curvilinear Scatchard plots, which characterize insulin binding, is more controversial. The two current leading interpretations are that the curve depicts either two classes of receptors[48] or a single class of receptors whose affinity for insulin diminishes as more and more insulin becomes bound.[47] However, binding capacities are still represented by the intersection with the X axis and the affinities by the slope of the curve. Because the validity of the

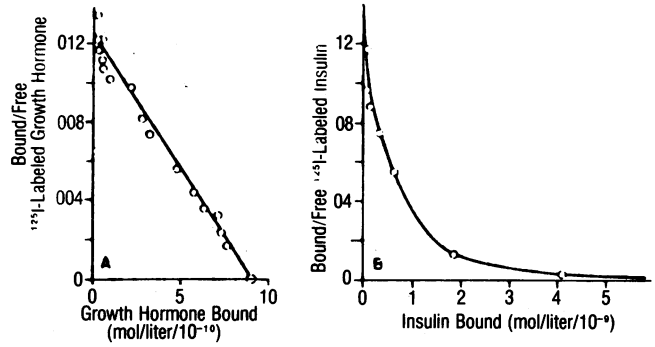

Figure 11.—Scatchard plots of growth hormone and insulin binding in cultured human lymphocytes (from de Meyts et al[47]).

Scatchard plot for insulin binding has been challenged,[49] the data concerning insulin binding (especially binding capacities) in type II diabetes (see below) should be interpreted cautiously.

There is an inverse relationship between circulating insulin concentrations and insulin binding. The "down regulation" of binding in the presence of increased levels of insulin[50] and "up regulation" when insulin concentrations are low[51] are an intrinsic characteristic of cells because lymphocytes in culture also show diminished insulin binding when exposed to high concentrations of insulin in vitro.[52] The reciprocal relationship between insulin concentrations and insulin binding is probably explained by the sequence of events that occurs after insulin binds to its receptor. The insulin-receptor complex is internalized into the cell where the hormone and, to some extent, the receptor are degraded in lysosomal structures.[53] Enhanced insulin binding in response to higher plasma insulin concentrations increases this process, which presumably leaves less available insulin receptors on the surface of the cell for subsequent binding.

Insulin-sensitive tissues contain spare or excess insulin receptors. Only 2% to 10% of the receptors on fat cells need to be occupied for insulin to exert its maximal effect[54]; for muscle, the proportion is 20%[55] and, for liver, 35%.[56] Thus, about 90% to 98%, 80% and 65% of the receptors on fat, muscle and liver, respectively, are spare or extra.

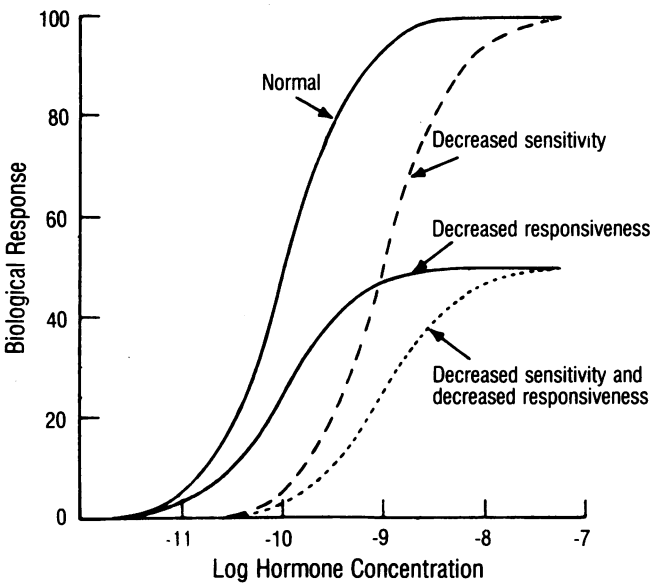

Figure 12.—Tissue sensitivity and responsiveness to hormonal stimulation (from Kahn[57]).

Tissue Sensitivity and Responsiveness

In a seminal paper in 1978, Kahn[57] discussed insulin resistance in terms of decreased sensitivity or responsiveness (or both). Characterization of insulin antagonism in these terms requires a full dose-response curve (Figure 12). If the curve is shifted to the right but the maximal effect is eventually attained, decreased sensitivity is present. That is, at submaximal concentrations of insulin, the effect is blunted, but at maximal levels a normal response is seen. Dose-response curves can be compared easily in terms of sensitivity by ascertaining the concentrations of insulin that cause 50% of the maximal effect. A higher value denotes insensitivity compared with the appropriate control situation. If a normal maximal effect is not attained regardless of how high an insulin concentration is used, decreased responsiveness is present (Figure 12). Decreased sensitivity and decreased responsiveness can occur separately or together (Figure 12).

Evaluating insulin antagonism in terms of decreased sensitivity or decreased resistance or both helps to delineate the mechanism(s) involved. A receptor defect (decreased insulin binding capacity) was postulated to cause diminished sensitivity whereas a postreceptor defect caused impaired responsiveness.[40] The reasoning is as follows. The interaction between a hormone and its receptor can be viewed as a random event. As the number of receptors decreases, it is less likely that an insulin molecule will find and interact with its receptor at a given hormone concentration. Therefore, an increased concentration of insulin is necessary in this situation to ensure that on a random basis the same number of receptors is occupied as in the normal state. This is consistent with the observations defining decreased sensitivity—that is, to obtain commensurate effects of insulin at submaximal levels, higher concentrations are needed until a maximal effect is reached (Figure 12).

To understand the mechanism underlying decreased responsiveness, a series of chemical reactions of a metabolic pathway within a cell may be represented as A → B → C → D → E. If the rate-determining step in this sequence is the C → D reaction, no matter how much or how fast substrate A is converted to compound C, the appearance of E will depend on the rate of C → D. To translate this into the series of events that occurs when insulin acts on peripheral tissues, the A → B reaction represents insulin binding to its receptor; B → C, the transport of glucose into the cell, and C → D, a number of intracellular reactions that eventually lead to the final reaction, D → E. This reaction culminates in the appearance of substance E whose production is increased by insulin (Figure 13). Therefore, if one of the rate-determining intracellular

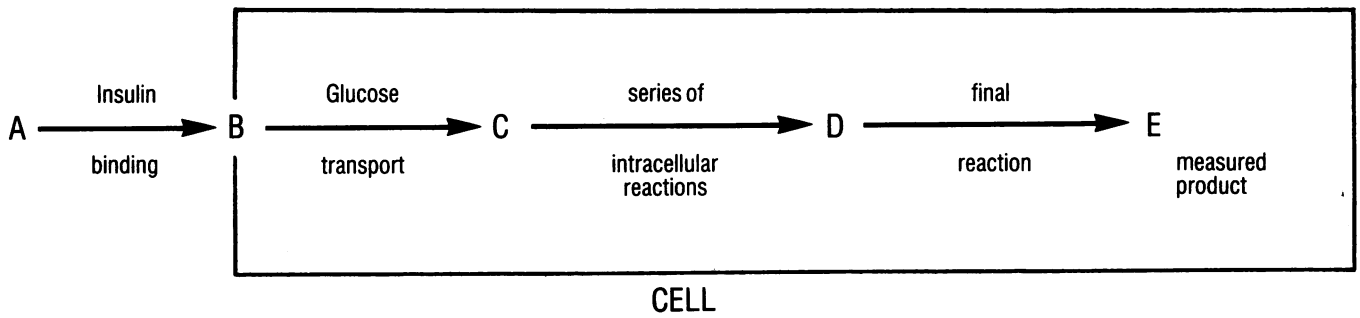

Figure 13.—Representation of insulin-stimulated intracellular metabolic pathway.

TABLE 1—*Relationship Among Insulin Binding, Sensitivity and Responsiveness in Various Clinical and Experimental Situations*

	Insulin Binding	Dose-Response Curves* Sensitivity	Responsiveness	Defect	References
A	Decreased	Right-shifted	Normal	Receptor	41, 42, 59
B	Normal	Normal	Decreased	Postreceptor	60, 61
C	Decreased	Right-shifted	Decreased	Receptor and postreceptor	59, 62-64
D	Normal	Right-shifted	Decreased	Postreceptor	65-67
E	Normal	Right-shifted	Normal	Postreceptor	68-71

*Insulin action versus extracellular insulin concentration.

reactions (C → D) is inhibited, no matter what concentration of insulin to which the tissue is exposed or what changes occur in the initial step of insulin binding, the maximal response to insulin (measured as the production of E) cannot be raised to normal. Thus, decreased responsiveness to insulin is thought to be due to alterations in the reactions within the cell and is therefore labeled a postreceptor defect.

Decreased responsiveness could theoretically also be caused by a diminished binding capacity if the number of receptors fell below the percent that had to be occupied to give a maximal response. Because of the presence of spare or excess receptors, this would mean a decrease to less than about 90% of normal in fat,[54] 80% in muscle[55] and 65% in liver.[56] With the exception of a few rare situations[58] not involving cases of type II diabetes mellitus, decrements in insulin binding capacities have been less than 50%. Therefore, a postreceptor defect remains a valid explanation for decreased responsiveness.

Since the initial formulations concerning the relationships among sensitivity and responsiveness and receptor and postreceptor defects were reported,[40] a number of other combinations have been described (Table 1). The first three situations in Table 1 were the ones discussed above. The remaining two situations in Table 1 (D and E) show that postreceptor defects can also cause decreased sensitivity and the last situation shows that a postreceptor defect may cause *only* decreased sensitivity—that is, responsiveness is normal. Reviewing all of the reported combinations in Table 1 suggests that the following simpler approach to assigning receptor or postreceptor defects (or both) to states of insulin resistance may be valid. If decreased binding is present, there is a receptor defect. If binding is normal, a postreceptor defect must be the cause of the insulin antagonism. In the presence of a receptor defect (decreased binding), a postreceptor defect is also present if decreased responsiveness (impaired maximal response) can be shown. With this formulation, it would be unnecessary to determine whether the dose-response curves were shifted to the right to delineate the site of insulin antagonism.

Application to Patients With Impaired Glucose Tolerance and Type II Diabetes

With these fundamental concepts regarding insulin binding and action in mind, let us turn to the situation in patients with abnormal carbohydrate metabolism. Some of the earlier studies did not differentiate between overt and chemical diabetes (now termed impaired glucose tolerance) but wherever possible they have been separated here. Insulin binding to monocytes[26] and adipocytes[41,72] removed from lean subjects with impaired glucose tolerance was decreased

TABLE 2—*Relationship Among Fasting Insulin Concentration, Insulin Binding and Insulin Action*

	Insulin Concentration	Binding	Action	References
A	Increased	Decreased	Decreased	26, 41
B	Normal	Decreased	Decreased	39, 42
C	Normal	Normal	Decreased	26, 32, 35,* 81, 84

*Fasting insulin levels were elevated.

and Scatchard plot analysis in all three reports showed diminished binding capacities. Insulin binding was normal, however, in obese patients with impaired glucose tolerance.[35] Insulin binding (only tracer binding was measured) was also decreased in monocytes from lean subjects with normal results on oral glucose tolerance testing but with a family history of diabetes.[73] Diminished insulin binding was also noted in cases of overt type II diabetes. Specifically, it was decreased in monocytes,[26,39,42,74,75] erythrocytes[76-78] and adipocytes[41] from lean patients and monocytes,[73] erythrocytes,[79] adipocytes[41] and T lymphocytes activated in vitro[80] from obese diabetic persons. Normal insulin binding, however, has been noted in some studies.[26,32,45,81-86] One wonders whether normal insulin binding in patients with altered carbohydrate metabolism may be more common but unreported in view of the number of published papers in which decreased binding has been observed. Scatchard plot analysis showed a diminished binding capacity and no change in binding affinities in all cases in which binding was decreased.[39,41,42,74,77,78,80] In one study in which tracer binding was normal, a decreased capacity was offset by an increased affinity.[83]

Insulin concentrations were measured in many of these studies. After oral glucose was administered, they were elevated in patients with impaired glucose tolerance[26,85] and decreased in those with overt diabetes.[26,32,82,83] Fasting levels were either normal[26,32,39,78,81-84,87] or elevated.[26,35,41,74-77,80,87] Because impaired insulin action was also found in some of these same studies,* it is instructive to examine the relationship among insulin concentrations, binding and action (Table 2). No consistent pattern is apparent. In situation A of Table 2, decreased insulin binding could contribute to the insulin antagonism possibly through the mechanism of down regulation. Diminished insulin binding could also be involved in the insulin resistance depicted in situation B, but it is not due to down regulation. However, situation C shows that the insulin antagonism associated with abnormal carbohydrate metabolism can occur in the presence of normal insulin binding.

Several other observations suggest that decreased insulin binding may not contribute fundamentally to the insulin resistance of these patients. Cultured skin fibroblasts from patients

*References 26, 32, 35, 39, 41, 42, 81, 84.

with overt type II diabetes[88] or maturity-onset diabetes of youth[89] bind insulin normally. In two studies (in which insulin action was not assessed),[87,90] the patients were divided into three groups depending on their insulin response to an oral glucose tolerance test. Insulin binding was increased in the low insulin responders, normal in the patients with a normal response and decreased in those with an enhanced response. Similarly, in a study in which insulin action was measured,[26] patients with considerable insulin resistance and normal fasting insulin levels had normal insulin binding, whereas other patients had less severe insulin antagonism, elevated fasting insulin concentrations and depressed insulin binding. These observations suggest that although changes in insulin binding may reflect local environmental factors—that is, insulin concentration—they do not constitute a primary abnormality in type II diabetes.

It is possible to construct dose-response curves in vivo using the clamp technique by infusing insulin at increasing rates to achieve circulating concentrations between 100 and 10,000 μU per ml on either different days or sequentially on the same day. The amount of glucose necessary to maintain the basal glucose concentration will increase in proportion to the insulin infusion rate and, when plotted against the plasma insulin level achieved at equilibrium, a typical sigmoidal dose-response curve is generated. Two groups have used this in vivo approach in patients with abnormal carbohydrate metabolism. Kolterman and co-workers[41] separated their patients into two groups of IGT and overt diabetes and found normal responsiveness in the former and decreased responsiveness in the latter (Figure 14). Rizza and associates[42] studied a single group of ten patients evenly split between having IGT and overt diabetes and they found normal responsiveness (Figure 15). Both studies showed decreased insulin binding and sensitivity in all groups of patients. Therefore, Kolterman and colleagues[41] concluded that a receptor defect characterized impaired glucose tolerance and both a receptor and a postreceptor defect were associated with overt diabetes. Rizza and co-workers[42] concluded that only a receptor defect caused the insulin antagonism of type II diabetes. Because the mean fasting plasma glucose concentration of Kolterman's patients with type II diabetes was 255 mg per dl, whereas the ten patients studied by Rizza and associates had an average fasting glucose level of 182 mg per dl, the resolution of these apparently discrepant conclusions may be that a receptor defect causes the insulin antagonism in patients with impaired glucose tolerance and mild type II diabetes and a postreceptor defect is responsible in patients with more severe decompensation.

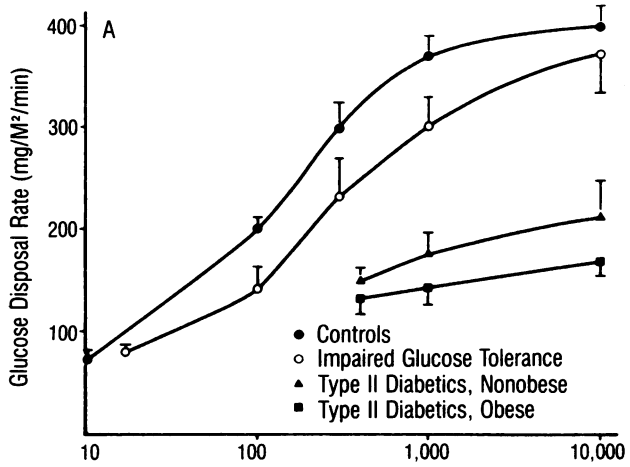

Figure 14.—Mean (± standard error of the mean) in vivo dose-response curves using the clamp technique (from Kolterman et al[41]).

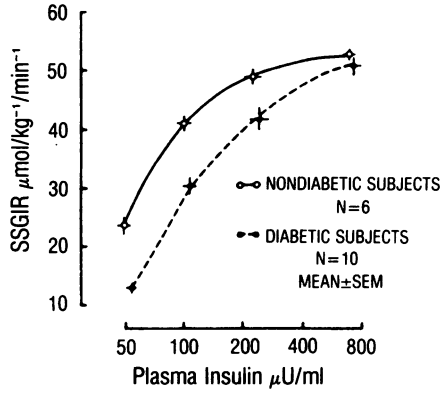

Figure 15.—Mean (± standard error of the mean) in vivo dose-response curves using the clamp technique (from Rizza et al[42]). SSGIR = steady-state glucose infusion rate

In vitro measurement of insulin binding and action in adipose tissue removed from patients with type II diabetes has also been used to evaluate the mechanism of insulin antagonism. This approach has failed to yield clear-cut answers as well. First, insulin binding has been reported to be both decreased[41] and normal.[84-86] Second, although the basal level of glucose transport in these adipocytes was depressed, the percent increase due to insulin has been normal.[86,90-92] Kahn[57] has pointed out the difficulty of evaluating the effect of insulin in the presence of differing baselines. A third difficulty is that antilipolysis responded normally to insulin whereas glucose utilization did not.[84,85] This discrepancy in the response of separate insulin-mediated pathways points toward a postreceptor defect.

Thus, the available information certainly indicates that insulin antagonism characterizes impaired glucose tolerance and type II diabetes. An important point to be considered is whether this insulin resistance is secondary to the altered carbohydrate metabolism or whether it constitutes a primary abnormality in these patients.

In several recent studies insulin binding and insulin action in patients with type II diabetes have been examined after one to eight weeks of intensive treatment with insulin. Greatly improved diabetic control was obtained with fasting glucose concentrations ranging from 70 to 140 mg per dl. The results have been mixed. The impaired insulin action before treatment was either mostly unchanged[32,93,94] or improved substantially but did not return to normal.[95-99] Insulin binding was either unchanged[32,95,98] or increased.[79,100] However, there was no correlation between changes in insulin binding and in vivo insulin action,[32,95,98] casting further doubt on the primacy of decreased insulin binding in causing insulin antagonism in type II diabetes.

Summary and Conclusions

The insulin response to glucose taken by mouth is increased in patients with IGT but decreased in those with type II diabetes. However, the insulin response to meals is normal in patients with type II diabetes, though the glucose concentrations are obviously much higher. The acute insulin re-

sponse to intravenously given glucose is absent in cases of both IGT and type II diabetes as long as the fasting plasma glucose concentration exceeds 115 mg per dl. On the other hand, the response to other intravenously given secretagogues, such as arginine, isoproterenol, tolbutamide, glucagon and secretin, is either normal or nearly so. The absent acute insulin response to intravenous administration of glucose can be restored by α-adrenergic blockade, prostaglandin synthesis inhibition, dopaminergic blockade and euglycemia.

Insulin antagonism characterizes patients with both IGT and type II diabetes. Because decreased sensitivity (a shift of the dose-response curve to the right) can be associated with both receptor or postreceptor defects, it does not seem necessary to measure full dose-response curves to differentiate between the two. Rather, decreased insulin binding defines a receptor defect and decreased responsiveness (impaired maximal insulin action) signifies a postreceptor defect. In general, a receptor defect (possibly related to down regulation of the insulin receptor) is associated with IGT and a postreceptor defect with type II diabetes. The relation (if any) between the two is unclear.

The following (tentative) conclusions seem warranted from the information currently available. For unknown reasons, in persons destined to have IGT and type II diabetes, insulin antagonism develops. Those whose pancreatic β-cells can meet this challenge by secreting increased amounts of insulin continue to have normal glucose concentration or IGT at the expense of hyperinsulinemia. Only in those with a genetic predisposition will type II diabetes develop. This predisposition involves a limited ability of the β-cells to continue to synthesize and secrete the extra insulin demanded of them. Thus, type II diabetes ensues when the β-cells can no longer respond well enough to prevent fasting hyperglycemia. This scenario is supported by a recent study[101] in which insulin secretion, insulin action and insulin binding in type II diabetic patients were evaluated by factor analysis and partial correlation analysis. The authors concluded that impairments of insulin secretion and action were of equal importance in causing the fasting hyperglycemia in type II diabetes, whereas decreased insulin binding was probably a secondary phenomenon.

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