Perspectives in Diabetes
Insulin Resistance or Insulin Deficiency
Which Is the Primary Cause of NIDDM?

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Extensive investigations of the pathophysiology of non-insulin-dependent diabetes mellitus (NIDDM) have identified two defects in endocrine function: insulin resistance and insulin deficiency. Despite general agreement that both defects are present in most patients with established NIDDM, many authorities have debated the question of which defect is the primary cause of NIDDM. Many interesting physiological studies have been conducted in an effort to address the following questions: Which defect can be detected earliest in the course of the disease? Which defect is more important in the pathogenesis of NIDDM? These clinical investigations have provided valuable insights into the pathophysiology of NIDDM. However, like many productive scientific investigations, they have raised as many questions as they have answered. Fortunately, after years of spirited debate, methods are becoming available that are likely to resolve the controversy. Genetic factors contribute importantly to the predisposition to develop NIDDM. Nevertheless, abundant evidence suggests that environmental factors (e.g., nutrition, physical exercise, etc.) may also modulate the expression of the diabetic phenotype. (Such interactions between genetics and the environment are commonly observed in many genetic diseases. For example, patients with mild forms of glucose-6-phosphate dehydrogenase deficiency are usually asymptomatic unless they are exposed to environmental stresses [e.g., administration of certain drugs, infections, etc.].) Inasmuch as NIDDM is a genetic disease, the identity of the cause of the disease is encrypted in the sequence of nucleotides in the patients' DNA. To learn the secret of the disease, we need to decipher the code. With the development of powerful methods of molecular genetic analysis, the time is rapidly approaching when identification of the primary genetic defects that render an individual susceptible to NIDDM will be possible. In this perspective, we review the evidence supporting the balanced view that both insulin resistance and insulin deficiency contribute to the pathogenesis of NIDDM but that the relative importance of each factor may vary from patient to patient. Before attempting to discuss the more controversial areas, we will begin by reviewing the points about which there is general agreement.

Insulin resistance. Insulin is a pluripotent hormone that elicits multiple biological responses. Among its important biological actions, insulin accelerates glucose transport in muscle and adipose tissue, regulates the activities of intracellular enzymes, and regulates the transcription of selected genes. Insulin resistance is a pathological condition in which the magnitude of the biological response to insulin is decreased (1). The impaired response to insulin may be observed either over the entire range of insulin concentrations or only at low concentrations of the hormone. Two types of evidence support the conclusion that patients with NIDDM are resistant to the biological actions of insulin. First, patients with NIDDM have a diminished response to exogenously administered insulin. Sophisticated methods have been developed to measure insulin action in vivo, e.g., euglycemic insulin clamps (2) and minimal model analysis of frequently sampled intravenous glucose tolerance tests (FSIVGTTs) (3). These methods have documented that all the major target tissues are resistant to the biological actions of insulin. For example, insulin is impaired in its ability to promote glucose utilization by skeletal muscle, to inhibit glucose production in liver, and to inhibit lipolysis in adipose tissue (4,5).

The second line of evidence is based on the observation that patients with NIDDM are resistant to the action of endogenously secreted insulin. Hyperinsulinemia in the fasting state is one of the laboratory abnormalities observed relatively early in the natural history of NIDDM. Both cross-sectional and longitudinal studies have demonstrated that patients are hyperinsulinemic even before the plasma glucose has become elevated to the point where it satisfies the diagnostic criteria for diabetes (4-9). For example, in patients with impaired glucose tolerance (IGT) (a group of patients at increased risk of developing NIDDM in the future), plasma insulin levels are elevated throughout the course of an oral glucose tolerance test (OGTT) (Fig. 1) (10). The fact that the hyperinsulinemia does not induce hypoglycemia demonstrates that the patient is resistant to the hypoglycemic action of endogenous insulin secreted by the pancreas.

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NIDDM, non-insulin-dependent diabetes mellitus; OGTT, oral glucose tolerance test; IGT, impaired glucose tolerance; IDDM, insulin-dependent diabetes mellitus; FSIVGTT, frequently sampled intravenous glucose tolerance test; IVGTT, intravenous glucose tolerance test; FPG, fasting plasma glucose.

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Insulin deficiency. Pancreatic insulin secretion is subject to regulation by multiple factors. Although the concentration of glucose in the plasma is the most important regulator of insulin secretion, other regulatory influences are important as well (e.g., amino acids, circulating hormones, neurotransmitters, paracrine factors). Insulin deficiency is defined as a pathological condition in which there is an inappropriate decrease in the rate at which the β-cell secretes insulin. Most commonly, normal ranges for the concentration of insulin in plasma are defined as a function of the concentration of glucose in plasma. Nevertheless, because insulin secretion is a dynamic process, the levels of insulin in plasma are not constant, but vary from minute to minute throughout the day. Thus, subtle defects in β-cell function may possibly manifest as abnormalities in the rate at which insulin concentrations change as a function of time (11,12).

As discussed above, most patients are hyperinsulinemic early in the natural history of NIDDM (4–9). However, plasma insulin levels usually decline later in the course of the disease, around the time when a patient develops overt NIDDM. Indeed, the progressive deterioration of pancreatic insulin secretion has been implicated as the proximate cause of the progressive increase in plasma glucose levels. (According to the hypothesis that NIDDM is a genetic disease, it is appropriate to consider the natural history of NIDDM as beginning early in life, even from the time of conception. Thus, the development of overt diabetes is a relatively late event in the natural history of the disease.) Thus, by the time patients have developed fasting hyperglycemia, demonstration of impaired insulin secretion is usually straightforward. For example, plasma insulin levels are decreased throughout the course of an OGTT in patients with NIDDM associated with a fasting plasma glucose (FPG) >8.3 mM (150 mg/dl) (Fig. 1). Furthermore, a marked decrease in the first phase of insulin secretion occurs in response to intravenous glucose (12). Similarly, sophisticated tests of β-cell function based on deconvolution analysis of the kinetics of C-peptide turnover in the plasma also demonstrate that insulin secretion is reduced in patients with NIDDM (11).

OVERVIEW OF THE AREAS OF CONTROVERSY
It is reassuring that there is considerable agreement about the description of the pathophysiology of patients with severe hyperglycemia—the patients in whom the defects are most severe and, therefore, most easily quantitated. Much of the controversy relates to investigations of prediabetic patients. By definition, these are individuals who are not yet diabetic, but are destined to develop NIDDM in the future. Thus, these studies have the potential to identify defects that occur early in the course of the natural history of the disease, even before the time that patients develop hyperglycemia. It seems reasonable to postulate that the primary cause(s) of NIDDM must appear early in the natural history, before the onset of overt hyperglycemia. Although this approach may seem straightforward, it is bedeviled by experimental difficulties that have engendered much of the disagreement and controversy.

Identification of prediabetic individuals. Strictly speaking, prediabetes is a retrospective diagnosis that can be made only after the patient has actually developed overt diabetes. Thus, in an optimal experimental design, it would be desirable to identify a cohort of nondiabetic individuals and study them prospectively. At the end of the study, the individuals who ultimately developed diabetes would be labeled retrospectively as prediabetic. Even in this type of idealized study, the diagnosis of “normal” is conditional; one cannot be certain that apparently nondiabetic individuals would not have developed NIDDM had they been followed for a longer time.

Because a population-based prospective study of this type requires a prohibitive amount of resources, most investigators have limited the scope of the study to obtain data in a more reasonable time frame. Accordingly, study subjects have been drawn from groups at high risk of developing NIDDM—e.g., Pima Indians (8,9), Mexican Americans (13), or offspring of two parents with NIDDM (6,7,14). These individuals have such a high risk of developing NIDDM that it has been possible to conduct true prospective studies. On the other hand, there is no guarantee that these groups are representative of the total universe of patients with NIDDM.
Another approach has been to study first-degree relatives of patients with NIDDM (15-18). This group includes many individuals who are destined ultimately to develop NIDDM. However, because most studies of first-degree relatives have not been long-term prospective studies, these studies are usually limited by one of two problems. In some studies, first-degree relatives of patients with NIDDM are compared with normal individuals without any family history of diabetes (15-18). In this study design, neither group is homogeneous. Although the relatives of patients with NIDDM are at increased risk of developing NIDDM, the risk is considerably <100%; furthermore, the control group almost certainly contains some prediabetic individuals. The inability to obtain homogeneous groups tends to blur the distinctions between prediabetic and normal individuals. An alternative study design is to compare the group of first-degree relatives with IGT to the group of first-degree relatives with normal glucose tolerance (18). However, by the time patients have developed IGT, the investigator can no longer be certain that any physiological defect is primary rather than a secondary consequence of the acquired metabolic abnormality. 

Vicious cycle of insulin resistance and insulin deficiency. It is essentially impossible to isolate insulin deficiency from insulin resistance. For example, in insulin-dependent diabetes mellitus (IDDM), it is well accepted that the primary defect is insulin deficiency caused by autoimmune destruction of pancreatic $\beta$-cells (19). Nevertheless, even in IDDM, chronic insulin deficiency renders the target tissues resistant to the acute actions of insulin. Similarly, in patients with NIDDM, the insulin deficiency exacerbates the severity of the underlying insulin resistance (20). In fact, aggressive replacement therapy with insulin can markedly increase insulin action in vivo (20). Conversely, just as insulin deficiency can cause insulin resistance, insulin resistance can lead to insulin deficiency. To the extent that insulin resistance can lead to chronic hyperglycemia, this can impair $\beta$-cell function as a result of glucose toxicity (21). In short, there is a vicious cycle involving insulin resistance and insulin deficiency. Thus, when both insulin resistance and insulin deficiency are present, it is difficult to know whether both abnormalities are independent primary defects, or whether one defect is secondary to the other. In an effort to circumvent this problem, Porte and collaborators (14) have defined a relationship between parameters of insulin secretion as a function of parameters of insulin sensitivity. Using this functional relationship, they concluded that offspring of two parents with NIDDM have a defect in insulin secretion relative to their observed insulin sensitivity when compared with a matched group of normal individuals without a family history of diabetes (14). Thus, they concluded that the genetic predisposition to develop NIDDM is caused by a defect in the ability of the $\beta$-cell to secrete insulin. In contrast, Martin et al. (7) conducted prospective studies on a similar population—the offspring of two parents with NIDDM. In this larger study, insulin resistance and hyperinsulinemia were the most powerful predictors of future development of NIDDM. Indeed, even when first-phase insulin secretion was stratified according to the quintile of insulin sensitivity, Martin et al. (7) did not observe a decrease in first-phase insulin secretion among the offspring who later developed NIDDM. Although these two studies differed with respect to their detailed methodology, whether these differences are sufficient to account for the diametrically opposed conclusions is not clear. Nevertheless, the discrepancies illustrate the difficulties in obtaining definitive data in this area.

Difficulty in designing relevant tests of physiological function

Insulin action. Two tests are commonly used to measure insulin action in vivo: the euglycemic insulin clamp (22) and minimal model analysis of FSIVGTTS (3). While each approach has its advocates, convincing data are available that validate the use of both tests to identify physiological abnormalities that predict the future development of NIDDM. In prospective studies of Pima Indians, the euglycemic insulin clamp provided measurements of peripheral glucose utilization in the presence of maximally effective insulin concentrations. The risk of future development of NIDDM was primarily related to the severity of the insulin resistance (8,9,22). Similarly, Martin et al. (7) used the FSIVGTT to measure insulin sensitivity in a prospective study of offspring of two parents with NIDDM. This study confirmed that insulin resistance was the best predictor of future risk of developing NIDDM.

Insulin deficiency. Tests of $\beta$-cell function are more problematic. The IVGTT is among the most commonly used tests. First-phase insulin secretion (measured during the first 10 min of the test) is markedly impaired in patients with established NIDDM (12). The response to other secretagogues is more difficult to measure because their effectiveness is modulated by the ambient level of plasma glucose (12). When all individuals are studied at comparable levels of glucose in plasma, patients with NIDDM also have diminished insulin secretion in response to other secretagogues such as arginine and $\beta$-adrenergic agonists (12). Polonsky et al. (11) used a more physiological test in which they measured the rate of insulin secretion during a 24-h period, during which time the individual was eating normal meals and doing relatively normal physical activities. These investigators confirmed the conclusion that NIDDM is associated with a defect in insulin secretion (11). However, in apparent conflict with the data obtained with the IVGTT (12), first-phase insulin secretion appeared to be relatively normal, while second phase insulin secretion was the locus of the major defect (11).

Moreover, as summarized above, studies of prediabetic individuals are even more confusing. Most studies have demonstrated that prediabetic individuals are hyperinsulinemic (7,9), but some studies have suggested the existence of impaired insulin secretion (15-17). Several sophisticated approaches have suggested the existence of subtle abnormalities in $\beta$-cell function early in the course of the disease, even before the development of overt diabetes. For example, in normal individuals there are rapid oscillations (with a periodicity of ~10 min) in the level of insulin in plasma. O'Rahilly et al. (16) reported that these rapid oscillations are absent in first-degree relatives of patients with NIDDM. These observations may provide a marker for a defect in $\beta$-cell function that occurs very early in the natural history of NIDDM. In a similar effort to identify subtle defects in $\beta$-cell function, several investigators have analyzed the nature of immunoreactive insulin in plasma. This approach has led to the conclusion that the percentage of proinsulin-like components in the plasma of patients with NIDDM is increased (23,24). In conclusion, although the data are not definitive, several lines of evidence suggest that subtle defects in $\beta$-cell
function may be detected before the development of overt diabetes and hyperglycemia.

**NIDDM is a syndrome of multiple diseases with different causes.** In recent years, it has become obvious that the syndrome of NIDDM is not a single disease, but a collection of multiple diseases with different causes. For example, specific mutations have been identified in a small percentage of patients with unusual variants of NIDDM (Table 1). Mutations in some genes (e.g., insulin receptor, insulin receptor substrate-1) appear to cause insulin resistance (25-27), and mutations in other genes (e.g., insulin, glucokinase) impair β-cell function (28-31). However, specific mutations have not yet been identified in the majority of patients with NIDDM. In addition, there appears to be another source of diversity. Especially in populations with a high prevalence of IDDM (e.g., in Scandinavia), some patients who appear to have NIDDM may actually have a mild form of autoimmune disease causing partial destruction of pancreatic β-cells (32-34). In some patients, this may eventually progress to IDDM. Nevertheless, insulin deficiency seems likely to be the primary pathophysiological defect in NIDDM caused by autoimmune destruction of pancreatic β-cells. Obviously, with this degree of diversity, it is hardly surprising that clinical investigators have not reached agreement as to the identity of the primary cause of NIDDM.

**LESSONS FROM MOLECULAR GENETICS**

Molecular genetics provides an opportunity to identify mutations in specific genes that are responsible for causing disease. So far, several genes have been identified as the locus of mutations that cause syndromes associated with non-insulin-dependent forms of diabetes (Table 1). Because the nature of the mutation is known precisely, there can be little doubt as to the causal role of the genetic defect in the pathogenesis of the disease in these patients. These genetic defects can viewed as primary causes of diabetes. (The term primary is appropriate in the sense that the presence of the mutation is not secondary to some other cause of diabetes.) Nevertheless, because the common form of NIDDM is likely to have polygenic inheritance, an individual with NIDDM is likely to have mutations in more than one gene. In that sense, there may be more than one primary cause of NIDDM, even in an individual patient. Thus, these patients provide illustrations of what is possible. Is it possible for a patient to become diabetic as the result of insulin resistance in the absence of insulin deficiency? Is it possible for mild insulin deficiency to cause diabetes in the absence of insulin resistance?

**Insulin resistance can cause diabetes.** Numerous patients have been reported to develop diabetes as a result of mutations in the insulin receptor gene (25). Not only are these patients severely resistant to insulin, but they generally have striking elevations of plasma insulin (e.g., fasting plasma insulin >100 μU/ml). Thus, these patients provide unambiguous evidence that insulin resistance can be a sufficient cause of diabetes despite supranormal levels of insulin. Moreover, these patients have many clinical characteristics that resemble the common forms of diabetes—including a predisposition to develop such chronic complications as retinopathy, nephropathy, and neuropathy. Nevertheless, it is equally striking that many of these severely insulin resistant patients with mutations in the insulin receptor gene are not diabetic (25). Moreover, even among those patients who ultimately become diabetic, the diabetes is not necessarily present during childhood. Because her medical history is particularly instructive in this regard, we will briefly summarize the case of one patient (patient A-5) with the syndrome of type A insulin resistance caused by a homozygous missense mutation in the insulin receptor gene. When she was 8 years old, her fasting plasma insulin level was extremely high (~900 μU/ml) although her FPG level was within normal limits (35). However, by the time she was 17 years of age, her FPG had risen to 12.3 mM (221 mg/dl) and her fasting plasma insulin had fallen to 360 μU/ml (36). At this time, therapy with insulin was instituted, and she required in excess of 2,000 U per day of insulin to regulate her plasma glucose. Thus, even in this severely insulin resistant patient, her pancreas was able to provide sufficient insulin to prevent diabetes for nearly two decades. Furthermore, even at the time she became diabetic, she was hardly insulin deficient given her fasting plasma insulin of 360 μU/ml. Nevertheless, it is tempting to speculate that the development of diabetes was precipitated by the relative decline in her pancreatic function. Clearly, knowing the cause of the deterioration of her β-cell function in late adolescence would be of interest.

**Diabetes caused by insulin deficiency.** IDDM provides the clearest example that severe insulin deficiency can cause diabetes. Furthermore, at least two genetic diseases provide evidence that partial impairment of β-cell function can contribute to the cause of a non-insulin-dependent form of diabetes: mutations in the insulin gene (28) and maturity-onset type diabetes of the young caused by mutations in the glucokinase gene (29-31). Mutations in the insulin gene lead to the synthesis of an insulin molecule with impaired biological activity. Mutations in the glucokinase gene impair insulin secretion by compromising the function of the glucose-sensing mechanism in the β-cell. Thus far, mutations in the insulin and glucokinase genes have only been identified in the heterozygous state; homozygotes have not been identified. The presence of a normal allele in all affected individuals permits preservation of ~50% of normal function. Accordingly, patients with mutations in either of these genes

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**TABLE 1**

Defined genetic loci at which mutations have been reported as primary causes of NIDDM

<table>
<thead>
<tr>
<th>Genetic locus</th>
<th>Pathophysiological defect</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td>Insulin</td>
<td>Impaired insulin secretion (insulin molecule with decreased bioactivity)</td>
<td>28</td>
</tr>
<tr>
<td>Insulin receptor</td>
<td>Insulin resistance (defect in first step of insulin action)</td>
<td>25</td>
</tr>
<tr>
<td>Glucokinase</td>
<td>Impaired insulin secretion (defect in glucose-sensing mechanism of β-cell)</td>
<td>29-31</td>
</tr>
<tr>
<td>Insulin receptor substrate-1</td>
<td>Insulin resistance (? defect in one branch of pathway of insulin action within the target cell)</td>
<td>26, 27</td>
</tr>
<tr>
<td>Mitochondrial DNA</td>
<td>? Impaired insulin secretion</td>
<td>37, 38</td>
</tr>
</tbody>
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are at risk of developing a mild form of NIDDM. However, there is only incomplete penetrance of the phenotype of overt diabetes. For example, only half of individuals with mutations in the glucokinase gene are diabetic (30). Moreover, the metabolic abnormality appears not to be progressive, i.e., the prevalence of diabetes appears not to increase with age. What determines which patients with mutations in the insulin or glucokinase genes will become diabetic is not clear. Nevertheless, susceptibility to develop diabetes may be modulated by other genetic factors, e.g., other genes that affect either insulin sensitivity or β-cell function. Furthermore, it is virtually certain that environmental factors (e.g., nutrition and physical exercise) can modulate the expression of the diabetic phenotype.

CONCLUSIONS
A large body of evidence demonstrates that both insulin resistance and insulin deficiency contribute to the pathogenesis of NIDDM. In selected cases, mutations in single genes have been identified as the cause of diabetes. These patients demonstrate the fact that, when the defect is severe, a selective defect in either insulin action or in insulin secretion is sufficient to cause diabetes. However, in most patients with the common form of NIDDM, the primary causes of the disease have not been identified at a molecular level. Nevertheless, there is general agreement that the majority of patients with NIDDM are insulin resistant, and that the development of insulin resistance is an early event in the natural history of the disease. Indeed, insulin resistance is probably the single best predictor of the future development of NIDDM in populations at high risk of developing the disease (7–9). Furthermore, several lines of evidence strongly suggest that genetic factors contribute importantly to determining an individual’s sensitivity to insulin, and that insulin resistance contributes as a cause of NIDDM in most patients.

In addition, there is general agreement that insulin secretion is impaired in most patients with overt NIDDM (11,12,16). However, whether the defect in insulin secretion develops in the disease remains controversial. In addition, the most recent studies have suggested that impaired insulin secretion is not a powerful predictor of future development of NIDDM (7,8). On the other hand, these epidemiological studies do not definitively address the question of whether an independent genetic defect may lead to impaired β-cell function. Nevertheless, many insulin-resistant individuals may secrete sufficient insulin to prevent the development of NIDDM for many years. How, then, can one explain the fact that β-cell function deteriorates in the patients who ultimately develop NIDDM? Although not proven, genetic factors seem likely to be the primary determinants of impaired insulin secretion in these individuals. Fortunately, one can be optimistic that future molecular genetic studies will eventually resolve this debate by precisely identifying the primary causes of NIDDM at a molecular level.

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