The Pathogenesis of Type II Diabetes Mellitus
A Polygenic Disease

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Diabetes mellitus is the most common endocrine disease, consuming almost 15% of annual health care expenditures in the United States. The focus of this review is on type II (non-insulin-dependent) diabetes mellitus, which accounts for approximately 90% of diabetic patients. The current understanding of the pathogenesis of type II diabetes is multifaceted. Complex defects in both insulin action and insulin secretion produce the metabolic derangements responsible for the disease.

Diabetes mellitus is the group of metabolic disorders of carbohydrate metabolism characterized by glucose underutilization and hyperglycemia. Diabetes mellitus is the general name for several distinct disorders with different underlying pathophysiology. There are two major forms: (1) Type I or insulin-dependent diabetes mellitus (IDDM); and (2) Type II or non-insulin-dependent diabetes mellitus (NIDDM). However, significant heterogeneity exists within each group, especially in NIDDM, and clear differentiation between type I and type II is not always feasible.

The prevalence of diabetes mellitus is unknown. It is estimated that there are 6.5 million people in the United States diagnosed as having diabetes mellitus. Because it is believed that approximately half of all cases may have been undiagnosed, the total number may be 13 million (over 5% of the total population). The prevalence of diabetes mellitus increases with age, with about half of all cases found in people older than 55 years, and there is considerable racial predilection. By the age of 65 years, the prevalence in the United States in Hispanics, blacks, and whites is 33%, 25%, and 17%, respectively.

In 1992, diabetes mellitus was estimated to be responsible for almost $92 billion in health care expenditures in the United States. The direct costs in that year were more than $45 billion, which is more than the total annual cost of the British National Health Service. The vast majority, $42.5 billion, is spent on patients admitted to hospitals. Indirect costs were over $46 billion, 63% of which was due to the estimated 150,000 deaths from the disease. Health care expenditures for people with diabetes constituted approximately one in seven health care dollars spent in 1992.

Type I diabetes mellitus (formerly called juvenile-onset diabetes) accounts for 5% to 10% of all cases in the United States. The disease is caused by autoimmune destruction of the β cells of the pancreas, resulting in insulinopenia. Elucidation of the autoimmune mechanisms responsible for the β-cell destruction in type I diabetes mellitus is the subject of intensive investigation and has been reviewed recently and extensively. More than 90% of diabetic patients have type II diabetes mellitus (formerly adult-onset diabetes). In this review, type II diabetes mellitus and NIDDM will be used interchangeably.

The remainder of this review will focus on the current status of research designed to elucidate the pathogenesis of type II diabetes mellitus, which represents a prototypical polygenic disease characteristic of many highly prevalent diseases that affect the human population, such as cardiovascular disease, cancer, osteoporosis, Alzheimer’s disease, and hypertension.

METABOLIC PATHOGENESIS

Glucose homeostasis depends on a balance between glucose production by the liver and glucose use by the peripheral tissues. Regulation is achieved predominantly.
(but not exclusively) by hormones secreted by the pancreas: glucagon from the α-cell and insulin from the β cell. Glucagon promotes glucose production by enhancing gluconeogenesis and glycogenolysis in the liver. An increase in blood glucose levels, from dietary absorption or release from endogenous body stores, produces a negative feedback, inhibiting further glucagon release. Normal glucose disposal depends on: (1) the ability of the pancreas to secrete insulin (which is stimulated by blood glucose); (2) the ability of insulin to promote uptake of glucose in peripheral tissues (insulin sensitivity); and (3) the ability of insulin to suppress hepatic glucose production. The major insulin target cells are adipocytes, skeletal myocytes, and hepatocytes. There are some differences in responses of various target cells to insulin. For example, the hormone stimulates glucose uptake into muscle and fat cells, but not liver cells.

There are at two major identifiable pathologic defects in patients with type II diabetes (for review, see reference 6). One is a decreased ability of insulin to act on the peripheral tissues. This is called insulin resistance and is thought by many to be the primary underlying pathology. The other is β-cell dysfunction, which is an inability of the pancreas to produce sufficient insulin to compensate for the insulin resistance. Thus, there is a relative deficiency of insulin early in the disease and absolute insulin deficiency late in the disease. The debate over whether NIDDM is primarily the result of a defect in β-cell secretion, peripheral resistance to insulin, or both has been raging for decades. However, there are data to support the concept that insulin resistance is the primary defect, preceding the derangement in insulin secretion and clinical diabetes by as much as 20 years. An example of such data is summarized in Figure 1, which is derived from one of the few long-term longitudinal studies of patients at high risk for type II diabetes mellitus. As can be seen in Figure 1, insulin resistance (Panel A), but not insulin secretion (Panel B), precedes the onset of clinical diabetes by more than 15 years, which is manifest by fasting hyperglycemia (Panel C). In fact, antedating the development of clinical diabetes, there may even be a phase of increased insulin secretion as shown in Figure 1B. Regardless of whether insulin resistance is the primary or secondary defect, it is clear that type II diabetes mellitus is an extremely heterogeneous disease and no single cause is adequate to explain the progression from normal glucose tolerance to NIDDM.

The fundamental defects in insulin resistance and secretion are caused by a combination of genetic and environmental factors that together contribute to the pathogenesis of type II diabetes. The genetic factors may be generally classified into two types: primary diabetesgenes, analogous to the onco genes that are proposed to underlie the pathogenesis of cancer, and secondary or diabetes-related genes, such as those predisposing to obesity.

**Environment**

Environmental factors, such as diet and exercise, are important determinants in the pathogenesis of type II diabetes, but the actual underlying mechanisms are unknown. Both animal and human studies have provided convincing evidence linking obesity to the development of NIDDM. However, the association between these disorders is far from straightforward. Although 60% to 80% of NIDDM subjects are obese, fewer than 15% of obese subjects develop diabetes. Virtually all obese subjects, even those with normal carbohydrate tolerance, have hyperinsulinemia and are insulin-resistant. Other factors, such as family history of NIDDM (genetic predisposition), the duration of obesity and the distribution of fat are important. Non-insulin-dependent diabetes mellitus is 10 times more likely to occur in an obese person with a diabetic parent than an equally obese person without a diabetic family history. Women who gained 8 to 10.9 kg had a relative increased risk for diabetes mellitus of 2.7-fold, whereas loss of more than 5 kg decreased their risk by at least 50%.

A gene that is expressed only in adipose tissue (ob) has been cloned and its protein product, leptin, has been proposed to be a vital signalling factor regulating bodyweight homeostasis and energy balance. Potential interactions between the ob gene and insulin have been described. Plasma levels of leptin are increased in diabetic mice. Moreover, both eating and insulin administration
increased leptin mRNA levels in fasted rats. This latter finding suggests that insulin may be an important mediator of the effects of food intake on ob expression, thus providing a possible genetic link between obesity and NIDDM. However, caution should be exercised in interpreting these findings as extrapolation from animal studies to human disease is often not straightforward and obesity, like diabetes mellitus, is unlikely to have a monogenic basis.

Interestingly, there is an inverse relationship between the level of physical activity and the prevalence of NIDDM. For every 500 kcal increase in daily energy expenditure, there is a 6% decrease in the age-adjusted risk of NIDDM. This effect is unchanged after adjusting for body weight and is independent of parental history of diabetes. The mechanism of the protective effect of exercise is thought to be an increased sensitivity to insulin in skeletal muscle and adipose tissue.

**Loss of β-Cell Function**

The increased β-cell demand induced by insulin resistance is ultimately associated with a progressive loss of β-cell function (Fig. 1). Several hypotheses have been proposed to explain this phenomenon, but the etiology remains unknown. Despite this, it is clear that fasting hyperglycemia does not develop unless β-cell function is impaired (Fig. 1). An increase in blood glucose normally elicits a biphasic release of insulin from the pancreas. The first phase lasts 5 to 10 minutes and is followed by a progressive increase of insulin release that persists for the duration of hyperglycemia (Fig. 2A). A challenge with intravenous glucose in patients with NIDDM demonstrates an absence of the first phase (Fig. 2B). The loss of release of insulin is specific for glucose as the insulin response to other secretagogues (eg, arginine) is unimpaired. This insulin secretory defect is termed selective glucose unresponsiveness. Other insulin secretory abnormalities in NIDDM include disruption of the normal pulsatile release of insulin and an increased ratio of plasma proinsulin to insulin. A number of mechanisms have been proposed to explain the molecular basis for the selective unresponsiveness of the β cells to glucose. None is able to account for all the characteristics of the secretory abnormalities. The accumulated evidence indicates that hyperglycemia renders the β cells increasingly unresponsive to glucose (called glucotoxicity), and the level of dysfunction correlates with both the glucose level and duration of hyperglycemia. Restoration of euglycemia rapidly resolves the defect.

**Insulin Resistance and Insulin Action**

Insulin resistance is defined as a decreased biologic response to a normal amount of insulin (for reviews, see references 14 and 15). Unlike glucose or cholesterol, insulin resistance is difficult to measure in a routine clinical setting. Surrogate measures, namely fasting insulin concentration or the insulin response to glucose, are used to provide an indirect assessment of insulin function. The clinical spectrum of insulin resistance is broad, ranging from normal blood glucose levels (though marked elevations in endogenous insulin) to hyperglycemia despite large doses of exogenous insulin. Several rare clinical syndromes are associated with insulin resistance. The prototype is the Type A insulin-resistance syndrome, which is characterized by hyperinsulinemia, acanthosis nigricans, and ovarian hyperandrogenism. Several variants of the Type A syndrome (eg, Rabson-Mendenhall syndrome), which have additional clinical features, have been described. The classical syndrome occurs in adolescent girls who present with features of hyperandrogenism (ie, amenorrhea and hirsutism). Several patients with the Type A syndrome have mutations in the insulin receptor that cause defects in the expression of the receptor on the cell surface and/or in the ability of the receptor to signal. One of the potentially most important clinical syndromes associated with insulin resistance has been called “Syndrome X.” Patients exhibit resistance to insulin, hyperinsulinemia, lipid abnormalities with increased VLDL and decreased HDL, and hypertension. All of these features are associated with an increased incidence of coronary artery disease. Despite the identification of this potential pathophysiologic link between the common diseases, diabetes mellitus and hypertension, there has been relatively little impact of this finding on the care of patients with these diseases.
Because insulin resistance is the earliest detectable metabolic lesion in type II diabetes, it is essential to understand the molecular mechanisms of normal insulin action. Although the effects produced by insulin are well known, the precise mechanism of insulin action is not fully understood. It is generally accepted that the initial event is the binding of insulin to specific receptors in the plasma membrane (for reviews, see references 16 and 17). The human insulin receptor is encoded by a single gene, located on chromosome 19. The receptor is heterotetramer consisting of two subunits (Fig. 3). The \( \alpha \) subunit, which has a molecular mass of 135,000, is located on the outer surface of the plasma membrane and contains the site where insulin binds. The \( \beta \) subunit has a molecular mass of 95,000. This subunit extends intracellularly through the plasma membrane and contains an enzyme, a tyrosine kinase, on its intracellular domain. Binding of insulin to the \( \alpha \) subunits produces a conformational change in the receptor, resulting in activation of the tyrosine kinase that phosphorylates proteins on tyrosine residues. One of the major substrates for this tyrosine kinase is the receptor itself. Phosphorylation of the \( \beta \) subunit of the insulin receptor occurs in three domains. These are tyrosine 960 in the juxtamembrane region, tyrosines 1146, 1150, and 1151 in the regulatory region and tyrosines 1316 and 1322 located in the carboxyl terminal tail. A substantial body of evidence has been accumulated demonstrating that the tyrosine kinase activity of the insulin receptor is essential for signalling. For example, mutation of lysine 1018 prevents ATP binding and therefore eliminates tyrosine kinase activity. This mutant receptor is not able to mediate the growth and metabolic effects of insulin.

In addition to phosphorylating itself, the insulin receptor catalyzes the phosphorylation of a number of selected intracellular proteins on tyrosine residues (Fig. 4). Some of these proteins bind to other signalling molecules, leading to the activation of a series of serine/threonine kinases that ultimately result in the well-known biologic effects of insulin. One important substrate for the insulin receptor tyrosine kinase is insulin receptor substrate-1 (IRS-1). When IRS-1 is phosphorylated by the insulin receptor, it acts as a docking protein, interacting with many intracellular signal transducer proteins (Fig. 4). Several of these proteins contain Src homology 2 (SH2) domains. The SH2 domain, a sequence of approximately 100 amino acids, recognizes phosphorylated tyrosine. Sequence differences in the SH2 domain dictate the specificity of binding. In Figure 4, SH2-containing proteins include those labelled PI3-kinase and GRB2, which are thought to mediate downstream signal transduction events, some of which are listed in Figure 4. In addition to IRS-1 phosphorylation, the insulin receptor probably activates other pathways, including most prominently glucose transport through an IRS-1 independent mechanism. The pathways are elaborate and although several components have been identified, there remain considerable gaps in our knowledge and understanding. Recent studies have clarified one fundamental concept, that the insulin-mediated signaling events are highly redundant. For example, when two key insulin

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**Fig. 3.** Model of the insulin receptor. (Right) Location of critical regulatory domains are depicted. (Left) Sites of identified point mutations (O) are indicated. The solid horizontal line represents the plasma membrane.
Diabetes Mellitus

**Pathogenesis of Type II Diabetes Mellitus**

Insulin

**Fig. 4.** Model of insulin signalling. Protein phosphorylation is indicated by —P. Identified pathways are indicated by solid lines; hypothesized pathways are depicted by broken lines.

signalling molecules, IRS-1 and GLUT 4 (the insulin-sensitive glucose transporter), have been knocked out in transgenic mouse experiments, the results were not overtly diabetic animals, but rather animals that had minor metabolic defects.20,21

### DIABETOGENES

The genetics of type I diabetes mellitus have been the subject of an excellent recent review22 and the focus here will be confined to type II diabetes. It is widely acknowledged that genetic factors contribute to the development of NIDDM (reviewed in references 7 and 23). For example, the concordance rate for NIDDM in identical twins approaches 100%.24 However, despite considerable investigation, the mode of inheritance remains uncertain. There are several reasons for this. Some diseases, usually less common (eg, cystic fibrosis or Duchenne’s muscular dystrophy), appear to be caused by mutations at a single locus. The common diseases such as diabetes mellitus, schizophrenia, atherosclerosis, hypertension, and osteoporosis are not inherited according to Mendelian rules. These diseases are genetically more complex and multiple genetic factors interact with exogenous influences (such as environmental factors) to produce the phenotype. In contrast to single gene disorders, identification of the genes responsible for common polygenic disorders is associated with numerous problems.25,26

Some of these difficulties are listed in Table 1. Genetic heterogeneity occurs because mutations in any one of several genes may result in identical phenotypes with the same pathology. In a population with a high incidence of disease-prone genes (eg, Alzheimer’s disease or NIDDM), some genes may not contribute to the disease process. The small contribution of individual genes necessitates large sample sizes for studies. If the suspect genomic region is excessively large, identification of the specific role of individual genes is difficult. Replication of correct results is always a potential problem in these investigations, requiring considerable reliance on statistical analysis. Animal models, such as transgenic mice, may not correlate with human studies and precautions must be taken to control for genetic background, linked genes and variable gene expression in mutant mice.27

With regard to type II diabetes mellitus, these and additional factors complicate the search for diabetogenes. The relatively late onset of type II diabetes mellitus and the premature mortality make it difficult to detect transmission because few multigenerational families are available. Second, the pathophysiology is complex and clinical manifestation of the disease requires impairment of both insulin action and insulin secretion. Thus, defects at a minimum of two loci are required to develop NIDDM. Third, absence of a clear pathophysiology prevents identifying diabetogenes by the easy route (ie, tracing back from a defective protein to a defective gene). Fourth, type II diabetes is rarely symptomatic in its early

**Table 1. Difficulties Identifying Specific Gene Variations in Complex Polygene Disorders**

<table>
<thead>
<tr>
<th>Difficulty</th>
<th>Example</th>
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<tbody>
<tr>
<td>Genetic heterogeneity</td>
<td>Genetic heterogeneity</td>
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<tr>
<td>High incidence of disease-prone genes</td>
<td>High incidence of disease-prone genes</td>
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<tr>
<td>Small contribution of individual genes</td>
<td>Small contribution of individual genes</td>
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<tr>
<td>Correct patient diagnosis/classification often difficult and ambiguous</td>
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<tr>
<td>Excessively large suspect genomic region renders identification difficult</td>
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<tr>
<td>Linkage between candidate genes may affect resolution</td>
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<tr>
<td>Difficulty in replicating results requires multiple repeat analyses</td>
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<tr>
<td>Discordance between animal models and human disease</td>
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Adapted from S. M. Weissman (ref 26).
stages and the criteria for diagnosis of “prediabetic” or “impaired glucose tolerance” states are controversial. Different definitions in clinical studies complicate comparisons. It is thus important to clearly and uniformly define the phenotype before embarking on genetic and molecular biologic analyses. Fifth, environmental factors, such as obesity and exercise, modulate the expression of an underlying genetic predisposition, further confusing the issue. Thus, NIDDM is a complex syndrome that probably arises from the cumulative defects of a number of gene products involved as critical components in glucose homeostasis. As such, the search for diabetogenes in diabetes mellitus is a model for the identification of the genetic basis of many common polygenic multifactorial diseases.

Achondroplasia, hemophilia, and many other serious but uncommon diseases are caused by rare, highly penetrant mutations and are thus tightly clustered in families. The risk of a sibling developing the disease significantly exceeds the population frequency (λs ratio) (Fig. 5). These mutations often follow simple Mendelian inheritance as the presence of the mutation results in disease. The majority of these diseases occur at low frequency due to natural selection. In contrast, oligogenic or polygenic diseases (eg, diabetes mellitus) are common, but have significantly lower familial clustering (Fig. 5). For example, λs is 15 and 3.5 for type I and type II diabetes, respectively. For diseases with a low λs, cloning of the genes involved and identification of the etiological polymorphism are fraught with difficulties.

Type II diabetes has been described as a “geneticist’s nightmare.” The complexities of the disease, described above, and the lack of identification of the pathophysiology suggest that multiple genetic strategies are necessary to identify the genetic determinants of type II diabetes (reviewed in reference 23). The two major approaches that have been used are studies of candidate genes and positional searches. The candidate gene method involves the examination of specific cloned genes that may be involved in insulin secretion or insulin action. The frequency of a polymorphism in or near a candidate gene is examined. This method is confined to genes that have been characterized. Positional searching involves the use of probes to “walk” along a chromosome. If a marker is identified, the gene(s) in that a region of the chromosomes are identified by positional cloning. In this approach, the protein product of the gene is not known.

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**Candidate Insulin Secretion Genes**

Pancreatic islet cells contain a glucose transporter, GLUT2, that couples plasma glucose to insulin secretion (Table 2). Although potentially important, little evi-

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**TABLE 2. CANDIDATE GENES—INSULIN SECRETION**

<table>
<thead>
<tr>
<th>Candidate Insulin Secretion Genes</th>
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<tbody>
<tr>
<td>1. Glucose sensing</td>
</tr>
<tr>
<td>Islet glucose transporter (GLUT2)</td>
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<tr>
<td>Glucokinase</td>
</tr>
<tr>
<td>2. Insulin synthesis and release</td>
</tr>
<tr>
<td>Chromosome 20q—adenosine deaminase</td>
</tr>
<tr>
<td>Mitochondria</td>
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<tr>
<td>3. Insulin</td>
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<tr>
<td>4. Other islet cell candidates</td>
</tr>
<tr>
<td>Amylin</td>
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<tr>
<td>Glucagon-like peptide-1 receptor</td>
</tr>
<tr>
<td>Glucokinase regulatory protein</td>
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<tr>
<td>Islet-1</td>
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Table 3. Candidate Genes—Insulin Resistance

<table>
<thead>
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<th>Candidate Insulin Resistance Genes</th>
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<tbody>
<tr>
<td>1. Insulin receptor</td>
</tr>
<tr>
<td>Binding (α-subunit)</td>
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<tr>
<td>Tyrosine kinase (β-subunit)</td>
</tr>
<tr>
<td>2. Substrates of the insulin receptor</td>
</tr>
<tr>
<td>3. Glucose disposal</td>
</tr>
<tr>
<td>Insulin-sensitive glucose transporter (GLUT4)</td>
</tr>
<tr>
<td>Glycogen synthase</td>
</tr>
<tr>
<td>4. Other</td>
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<tr>
<td>Rad</td>
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...evidence supports a role for GLUT2 defects in NIDDM. The greatest success in the search for diabetogenes has been with glucokinase, an enzyme that phosphorylates glucose after it enters the β cell and has been proposed as a glucose sensor. Early-onset NIDDM (a rare variant of NIDDM, also called maturity-onset diabetes of the young, MODY) was demonstrated to be closely linked to the glucokinase gene on chromosome 7p. The mutations produce relative insulin deficiency by increasing the threshold for glucose-induced insulin secretion. More recently, it was demonstrated that disruption of the glucokinase gene produces a phenotype similar to MODY in heterozygous mice, emphasizing the essential role of glucokinase in the maintenance of glucose homeostasis. However, searches for mutations of the glucokinase gene in older-onset, typical NIDDM patients have not yielded success. Therefore, although the glucokinase gene is important in MODY, it does not appear to have a significant role in common NIDDM. Maturity-onset diabetes of the young has also been linked in a single family to loci on chromosome 20q in the region of the locus for adenosine deaminase. The exact locus is unknown and the mutation has not been identified in other families. A third MODY locus has very recently been shown to be tightly linked to markers on chromosome 12q, but this is not a major gene for late-onset NIDDM.

Mutations or increased expression of islet mitochondrial encoded genes have been identified by several investigators. Like other inherited mitochondrial defects, these are transmitted exclusively by the mother. Defects in the insulin gene have also been reported in NIDDM but are rare. Other candidates include those genes that are expressed in β cells and may be associated with NIDDM, including amylin, glucagon-like peptide-1 receptor, glucokinase regulatory protein, and islet-1 protein.

**Candidate Insulin Resistance Genes**

Even more prevalent than candidate insulin secretion genes are candidate genes implicated in insulin action (Table 3). A large number of mutations of the insulin receptor have been identified (Fig. 3) (reviewed in reference 17). In Figure 3, a number of specific mutations associated with insulin resistance and/or a diabetic phenotype are shown on the left side. Mutations in the α subunit alter insulin binding or recycling of the receptor. β subunit mutations decrease the activity of the tyrosine kinase. Many patients with these defects have extreme insulin resistance. However, these mutations are extremely rare and are usually found in only one patient or a single family. Mutations of substrates for the insulin receptor that cause diabetes are not known. Although polymorphisms occur in the gene for IRS-1, these do not appear to be pathogenic as they are not associated with insulin resistance and occur with the same frequency in NIDDM and healthy subjects.

The insulin-sensitive glucose transporter, GLUT4, is found in adipose tissue and both cardiac and skeletal muscle where it mediates insulin-stimulated glucose uptake. Although a very likely candidate for a defect in NIDDM, few mutations in GLUT4 have been described. Moreover, expression of GLUT4 is not decreased in skeletal muscle of diabetic patients. In fact, genetic ablation of GLUT4 in mice resulted in minimal changes in blood glucose and fasting insulin levels. The major metabolic abnormality was postprandial hyperinsulinemia. Glycogen synthase catalyzes the rate-limiting reaction in glycogen synthesis, which is the predominant pathway of insulin-stimulated glucose disposal in skeletal muscle. Diabetic subjects exhibit a decrease in both glycogen synthase activity and in glycogen formation. Despite extensive searching, no abnormalities in the glycogen synthase gene have been identified. Subtraction cloning identified a gene called a Rad (Ras-associated with diabetes). Northern blot analysis demonstrated that Rad is overexpressed in skeletal muscle of type II diabetes patients by 3- to 18-fold compared to normal subjects. Levels in type I diabetes are the same as in healthy individuals. It is not yet known how Rad might be related to insulin resistance.

Despite considerable investigative effort to identify the genetic basis of type II diabetes mellitus, genetic defects identified to date account for fewer than 5% of patients with NIDDM. Therefore, the gene or genes causing the common forms of type II diabetes remain unknown.

**SUMMARY**

Type II diabetes mellitus or NIDDM is a polygenic heterogeneous disease with a complex pathophysiologic basis, involving defects in both insulin action and insulin secretion. As such, it is prototypical of many common heterogeneous diseases and the underlying defects are those in cellular signal transduction, both in the periph-
eral tissues and in the islet cells of the pancreas. Although there has been considerable progress in the comprehension of the pathophysiologic bases for NIDDM, this knowledge has yet to yield major new advances in understanding the genetic basis for most cases of NIDDM.

Acknowledgments. The authors thank Tina Brown and Marsha Moore for their expert editorial assistance.

REFERENCES


