# Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus

THE EXPERT COMMITTEE ON THE DIAGNOSIS AND CLASSIFICATION OF DIABETES MELLITUS*

The current classification and diagnosis of diabetes used in the U.S. was developed by the National Diabetes Data Group (NDDG) and published in 1979 (1). The impetus for the classification and diagnosis scheme proposed then holds true today. That is,

> the growth of knowledge regarding the etiology and pathogenesis of diabetes has led many individuals and groups in the diabetes community to express the need for a revision of the nomenclature, diagnostic criteria, and classification of diabetes. As a consequence, it was deemed essential to develop an appropriate, uniform terminology and a functional, working classification of diabetes that reflects the current knowledge about the disease. (1)

It is now considered to be particularly important to move away from a system that appears to base the classification of the disease, in large part, on the type of pharmacological treatment used in its management toward a system based on disease etiology where possible.

An international Expert Committee, working under the sponsorship of the American Diabetes Association, was established in May 1995 to review the scientific literature since 1979 and to decide if changes to the classification and diagnosis of diabetes were warranted. The Committee met on multiple occasions and widely circulated a draft report of their findings and preliminary recommendations to the international diabetes community. Based on the numerous comments and suggestions received, including the opportunity to review unpublished data in detail, the Committee discussed and revised numerous drafts of a manuscript that culminated in this published document.

This report is divided into four sections: definition and description of diabetes, classification of the disease, diagnostic criteria, and testing for diabetes. The aim of this document is to define and describe diabetes as we know it today, present a classification scheme that reflects its etiology and/or pathogenesis, provide guidelines for the diagnosis of the disease, develop recommendations for testing that can help reduce the morbidity and mortality associated with diabetes, and review the diagnosis of gestational diabetes.

## DEFINITION AND DESCRIPTION OF DIABETES MELLITUS

— Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels.

Several pathogenic processes are involved in the development of diabetes. These range from autoimmune destruction of the β-cells of the pancreas with consequent insulin deficiency to abnormalities that result in resistance to insulin action. The basis of the abnormalities in carbohydrate, fat, and protein metabolism in diabetes is deficient action of insulin on target tissues. Deficient insulin action results from inadequate insulin secretion and/or diminished tissue responses to insulin at one or more points in the complex pathways of hormone action. Impairment of insulin secretion and defects in insulin action frequently coexist in the same patient, and it is often unclear which abnormality, if either alone, is the primary cause of the hyperglycemia.

Symptoms of marked hyperglycemia include polyuria, polydipsia, weight loss, sometimes with polyphagia, and blurred vision. Impairment of growth and susceptibility to certain infections may also accompany chronic hyperglycemia. Acute, life-threatening consequences of diabetes are hyperglycemia with ketoacidosis or the nonketotic hyperosmolar syndrome.

Long-term complications of diabetes include retinopathy with potential loss of vision; nephropathy leading to renal failure; peripheral neuropathy with risk of foot ulcers, amputation, and Charcot joints; and autonomic neuropathy causing gastrointestinal, genitourinary, and cardiovascular symptoms and sexual dysfunction. Glycation of tissue proteins and other macromolecules and excess production of polyol compounds from glu-

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**Abbreviations:** ACOG, American College of Obstetricians and Gynecologists; FPG, fasting plasma glucose; GCT, glucose challenge test; GDM, gestational diabetes mellitus; HNF, hepatocyte nuclear factor, IFG, impaired fasting glucose; IGT, impaired glucose tolerance; MODY, maturity-onset diabetes of the young; NDDG, National Diabetes Data Group; NHANES III, Third National Health and Nutrition Examination Survey; OGTT, oral glucose tolerance test; PAI-1, plasminogen activator inhibitor-1; WHO, World Health Organization; 2-h PG, 2-h postload glucose.

cose are among the mechanisms thought to produce tissue damage from chronic hyperglycemia. Patients with diabetes have an increased incidence of atherosclerotic cardiovascular, peripheral vascular, and cerebrovascular disease. Hypertension, abnormalities of lipoprotein metabolism, and periodontal disease are often found in people with diabetes. The emotional and social impact of diabetes and the demands of therapy may cause significant psychosocial dysfunction in patients and their families.

The vast majority of cases of diabetes fall into two broad etiopathogenetic categories (discussed in greater detail below). In one category (type 1 diabetes), the cause is an absolute deficiency of insulin secretion. Individuals at increased risk of developing this type of diabetes can often be identified by serological evidence of an autoimmune pathologic process occurring in the pancreatic islets and by genetic markers. In the other, much more prevalent category (type 2 diabetes), the cause is a combination of resistance to insulin action and an inadequate compensatory insulin secretory response. In the latter category, a degree of hyperglycemia sufficient to cause pathologic and functional changes in various target tissues, but without clinical symptoms, may be present for a long period of time before diabetes is detected. During this asymptomatic period, it is possible to demonstrate an abnormality in carbohydrate metabolism by measurement of plasma glucose in the fasting state or after a challenge with an oral glucose load.

## CLASSIFICATION OF DIABETES MELLITUS AND OTHER CATEGORIES OF GLUCOSE REGULATION

— A major requirement for epidemiological and clinical research and for the clinical management of diabetes is an appropriate system of classification that provides a framework within which to identify and differentiate its various forms and stages. While there have been a number of sets of nomenclature and diagnostic criteria proposed for diabetes, no generally accepted systematic categorization existed until the NDDG classification system was published in 1979 (1). The World Health Organization (WHO) Expert Committee on Diabetes in 1980 and, later, the WHO Study Group on Diabetes Mellitus endorsed the substantive recommendations of the NDDG (2). These groups recognized two major forms of diabetes, which they termed insulin-dependent diabetes mellitus (IDDM, type 1 diabetes) and non-insulin-dependent diabetes mellitus (NIDDM, type 2 diabetes), but their classification system went on to include evidence that diabetes mellitus was an etiologically and clinically heterogeneous group of disorders that share hyperglycemia in common. The overwhelming evidence in favor of this heterogeneity included the following:

1. There are several distinct disorders, most of them rare, in which glucose intolerance is a feature.
2. There are large differences in the prevalence of the major forms of diabetes among various racial or ethnic groups worldwide.
3. Patients with glucose intolerance present with great phenotypic variation; take, for example, the differences between thin, ketosis-prone, insulin-dependent diabetes and obese, nonketotic, insulin-resistant diabetes.
4. Evidence from genetic, immunological, and clinical studies shows that in western countries, the forms of diabetes that have their onset primarily in youth are distinct from those that have their onset mainly in adulthood.
5. A type of non-insulin-requiring diabetes in young people, inherited in an autosomal dominant fashion, is clearly different from the classic acuteonset diabetes that typically occurs in children.
6. In tropical countries, several clinical presentations occur, including diabetes associated with fibrocalcific pancreatitis.

These and other lines of evidence were used to divide diabetes mellitus into five distinct types (IDDM, NIDDM, gestational diabetes mellitus [GDM], malnutritionrelated diabetes, and other types). The different clinical presentations and genetic and environmental etiologic factors of the five types permitted discrimination among them. All five types were characterized by either fasting hyperglycemia or elevated levels of plasma glucose during an oral glucose tolerance test (OGTT). In addition, the 1979 classification included the category of impaired glucose tolerance (IGT), in which plasma glucose levels during an OGTT were above normal but below those defined as diabetes.

The NDDG/WHO classification highlighted the heterogeneity of the diabetic syndrome. Such heterogeneity has had important implications not only for treatment of patients with diabetes but also for biomedical research. This previous classification indicated that the disorders grouped together under the term diabetes differ markedly in pathogenesis, natural history, response to therapy, and prevention. In addition, different genetic and environmental factors can result in forms of diabetes that appear phenotypically similar but may have different etiologies.

The classification published in 1979 was based on knowledge of diabetes at that time and represented some compromises among different points of view. It was based on a combination of clinical manifestations or treatment requirements (e.g., insulin-dependent, non-insulin-dependent) and pathogenesis (e.g., malnutrition-related, "other types," gestational). It was anticipated, however, that as knowledge of diabetes continued to develop, the classification would need revision. When the classification was prepared, a definitive etiology had not been established for any of the diabetes subclasses, except for some of the "other types." Few susceptibility genes for diabetes had been discovered, and an understanding of the immunological basis for most type 1 diabetes was just beginning.

The current Expert Committee has carefully considered the data and rationale for what was accepted in 1979, along with research findings of the last 18 years, and we are now proposing changes to the NDDG/WHO classification scheme (Table 1). The main features of these changes are as follows:

1. The terms insulin-dependent diabetes mellitus and non-insulin-dependent diabetes mellitus and their acronyms, IDDM and NIDDM, are eliminated. These terms have been confusing and have frequently resulted in classifying the patient based on treatment rather than etiology.
2. The terms type 1 and type 2 diabetes are retained, with arabic numerals being used rather than roman numerals. We recommend adop-

**Table 1—*Etiologic classification of diabetes mellitus***

I. Type 1 diabetes* (β-cell destruction, usually leading to absolute insulin deficiency)
  A. Immune mediated
  B. Idiopathic
II. Type 2 diabetes* (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)
III. Other specific types
  A. Genetic defects of β-cell function
    1. Chromosome 12, HNF-1α (MODY3)
    2. Chromosome 7, glucokinase (MODY2)
    3. Chromosome 20, HNF-4α (MODY1)
    4. Mitochondrial DNA
    5. Others
  B. Genetic defects in insulin action
    1. Type A insulin resistance
    2. Leprechaunism
    3. Rabson-Mendenhall syndrome
    4. Lipoatrophic diabetes
    5. Others
  C. Diseases of the exocrine pancreas
    1. Pancreatitis
    2. Trauma/pancreatectomy
    3. Neoplasia
    4. Cystic fibrosis
    5. Hemochromatosis
    6. Fibrocalculous pancreatopathy
    7. Others
  D. Endocrinopathies
    1. Acromegaly
    2. Cushing's syndrome
    3. Glucagonoma
    4. Pheochromocytoma
    5. Hyperthyroidism
    6. Somatostatinoma
    7. Aldosteronoma
    8. Others
  E. Drug- or chemical-induced
    1. Vacor
    2. Pentamidine
    3. Nicotinic acid
    4. Glucocorticoids
    5. Thyroid hormone
    6. Diazoxide
    7. β-adrenergic agonists
    8. Thiazides
    9. Dilantin
    10. α-Interferon
    11. Others
  F. Infections
    1. Congenital rubella
    2. Cytomegalovirus
    3. Others
  G. Uncommon forms of immune-mediated diabetes
    1. "Stiff-man" syndrome
    2. Anti-insulin receptor antibodies
    3. Others
  H. Other genetic syndromes sometimes associated with diabetes
    1. Down's syndrome
    2. Klinefelter's syndrome
    3. Turner's syndrome
    4. Wolfram's syndrome
    5. Friedreich's ataxia
    6. Huntington's chorea
    7. Laurence-Moon-Biedl syndrome
    8. Myotonic dystrophy
    9. Porphyria
    10. Prader-Willi syndrome
    11. Others
IV. Gestational diabetes mellitus (GDM)

*Patients with any form of diabetes may require insulin treatment at some stage of their disease. Such use of insulin does not, of itself, classify the patient.

tion of arabic numerals in part because the roman numeral II can easily be confused by the public as the number 11. The class, or form, named type 1 diabetes encompasses the vast majority of cases that are primarily due to pancreatic islet β-cell destruction and that are prone to ketoacidosis. This form includes those cases currently ascribable to an autoimmune process and those for which an etiology is unknown. It does not include those forms of β-cell destruction or failure for which non-autoimmune-specific causes can be assigned (e.g., cystic fibrosis). While most type 1 diabetes is characterized by the presence of islet cell, GAD, IA-2, IA-2β, or insulin autoantibodies that identify the autoimmune process that leads to β-cell destruction, in some subjects, no evidence of autoimmunity is present; these cases are classified as type 1 idiopathic.

3. The class, or form, named type 2 diabetes includes the most prevalent form of diabetes, which results from insulin resistance with an insulin secretory defect.
4. A recent international meeting reviewed the evidence for and characteristics of malnutrition-related diabetes (3). While it appears that malnutrition may influence the expression of other types of diabetes, the evidence that diabetes can be directly caused by protein deficiency is not convincing. Therefore, the class termed malnutrition-related diabetes mellitus has been eliminated. Fibrocalculous pancreatopathy (formerly a subtype of malnutrition-related diabetes) has been reclassified as a disease of the exocrine pancreas.
5. The stage termed impaired glucose tolerance (IGT) has been retained. The analogous intermediate stage of fasting glucose is named impaired fasting glucose (IFG).
6. The class termed gestational diabetes mellitus (GDM) is retained as defined by the WHO and NDDG, respectively. Selective rather than universal screening for glucose intolerance in pregnancy is now recommended.
7. The degree of hyperglycemia (if any) may change over time, de-

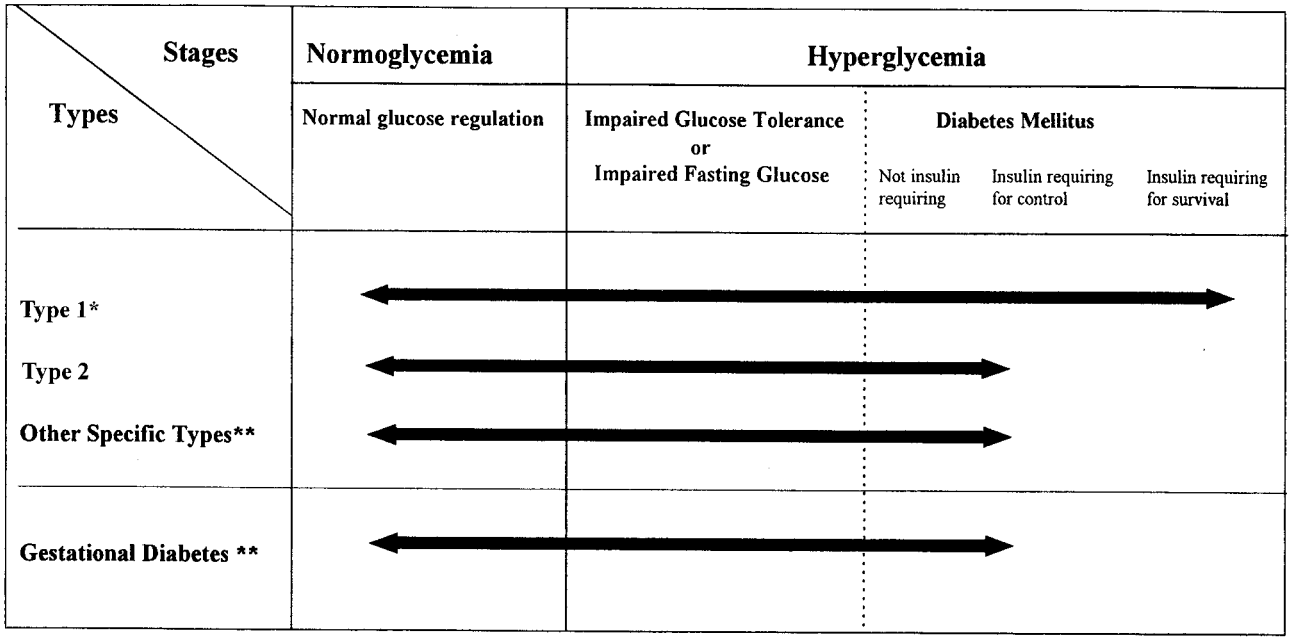


**Figure 1**—*Disorders of glycemia: etiologic types and stages. *Even after presenting in ketoacidosis, these patients can briefly return to normoglycemia without requiring continuous therapy (i.e., "honeymoon" remission); **in rare instances, patients in these categories (e.g., Vacor toxicity, type 1 diabetes presenting in pregnancy) may require insulin for survival.*

pending on the extent of the underlying disease process (Fig. 1). A disease process may be present but may not have progressed far enough to cause hyperglycemia. The same disease process can cause IFG and/or IGT without fulfilling the criteria for the diagnosis of diabetes. In some individuals with diabetes, adequate glycemic control can be achieved with weight reduction, exercise, and/or oral glucose-lowering agents. These individuals therefore do not require insulin. Other individuals, who have some residual insulin secretion but require exogenous insulin for adequate glycemic control, can survive without it. Individuals with extensive β-cell destruction and therefore no residual insulin secretion require insulin for survival. The severity of the metabolic abnormality can progress, regress, or stay the same. Thus, the degree of hyperglycemia reflects the severity of the underlying metabolic process and its treatment more than the nature of the process itself.

8. Assigning a type of diabetes to an individual often depends on the circumstances present at the time of diagnosis, and many diabetic individuals do not easily fit into a single class. For example, a person with GDM may continue to be hyperglycemic after delivery and may be determined to have, in fact, type 1 diabetes. Alternatively, a person who acquires diabetes because of large doses of exogenous steroids may become normoglycemic once the glucocorticoids are discontinued, but then may develop diabetes many years later after recurrent episodes of pancreatitis. Another example would be a person treated with thiazides who develops diabetes years later. Because thiazides in themselves seldom cause severe hyperglycemia, such individuals probably have type 2 diabetes that is exacerbated by the drug. Thus, for the clinician and patient, it is less important to label the particular type of diabetes than it is to understand the pathogenesis of the hyperglycemia and to treat it effectively.

### Type 1 diabetes (β-cell destruction, usually leading to absolute insulin deficiency)

**Immune-mediated diabetes.** This form of diabetes, previously encompassed by the terms insulin-dependent diabetes, type 1 diabetes, or juvenile-onset diabetes, results from a cellular-mediated autoimmune destruction of the β-cells of the pancreas (4). Markers of the immune destruction of the β-cell include islet cell autoantibodies (ICAs), autoantibodies to insulin (IAAs), autoantibodies to glutamic acid decarboxylase ($GAD_{65}$), and autoantibodies to the tyrosine phosphatases IA-2 and IA-2β (5–13). One and usually more of these autoantibodies are present in 85–90% of individuals when fasting hyperglycemia is initially detected. Also, the disease has strong HLA associations, with linkage to the DQA and B genes, and it is influenced by the DRB genes (14,15). These *HLA-DR/DQ* alleles can be either predisposing or protective.

In this form of diabetes, the rate of β-cell destruction is quite variable, being rapid in some individuals (mainly infants and children) and slow in others (mainly adults [16]). Some patients, particularly children and adolescents, may present with ketoacidosis as the first manifestation of the disease. Others have modest fasting hyperglycemia that can rapidly change to severe hyperglycemia and/or ketoacidosis in the presence of infection or other stress. Still others, particularly adults, may retain residual β-cell function sufficient to prevent ketoacidosis for many years. Many such individuals with this form of type 1 diabetes eventually become dependent on insulin for survival

and are at risk for ketoacidosis. At this latter stage of the disease, there is little or no insulin secretion, as manifested by low or undetectable levels of plasma C-peptide. Immune-mediated diabetes commonly occurs in childhood and adolescence, but it can occur at any age, even in the 8th and 9th decades of life.

Autoimmune destruction of β-cells has multiple genetic predispositions and is also related to environmental factors that are still poorly defined. Although patients are rarely obese when they present with this type of diabetes, the presence of obesity is not incompatible with the diagnosis. These patients are also prone to other autoimmune disorders such as Graves' disease, Hashimoto's thyroiditis, Addison's disease, vitiligo, and pernicious anemia.

**Idiopathic diabetes.** Some forms of type 1 diabetes have no known etiologies. Some of these patients have permanent insulinopenia and are prone to ketoacidosis, but have no evidence of autoimmunity. Although only a minority of patients with type 1 diabetes fall into this category, of those who do, most are of African or Asian origin. Individuals with this form of diabetes suffer from episodic ketoacidosis and exhibit varying degrees of insulin deficiency between episodes. This form of diabetes is strongly inherited, lacks immunological evidence for β-cell autoimmunity, and is not HLA associated. An absolute requirement for insulin replacement therapy in affected patients may come and go (17).

### Type 2 diabetes (ranging from predominantly insulin resistance with relative insulin deficiency to predominantly an insulin secretory defect with insulin resistance)

This form of diabetes, previously referred to as non-insulin-dependent diabetes, type 2 diabetes, or adult-onset diabetes, is a term used for individuals who have insulin resistance and usually have relative (rather than absolute) insulin deficiency (18–21). At least initially, and often throughout their lifetime, these individuals do not need insulin treatment to survive. There are probably many different causes of this form of diabetes, and it is likely that the proportion of patients in this category will decrease in the future as identification of specific pathogenic processes and genetic defects permits better differentiation among them and a more definitive subclassification. Although the specific etiologies of this form of diabetes are not known, autoimmune destruction of β-cells does not occur, and patients do not have any of the other causes of diabetes listed above or below.

Most patients with this form of diabetes are obese, and obesity itself causes some degree of insulin resistance (22,23). Patients who are not obese by traditional weight criteria may have an increased percentage of body fat distributed predominantly in the abdominal region (24). Ketoacidosis seldom occurs spontaneously in this type of diabetes; when seen, it usually arises in association with the stress of another illness such as infection (25–27). This form of diabetes frequently goes undiagnosed for many years because the hyperglycemia develops gradually and at earlier stages is often not severe enough for the patient to notice any of the classic symptoms of diabetes (28–30). Nevertheless, such patients are at increased risk of developing macrovascular and microvascular complications (30–34). Whereas patients with this form of diabetes may have insulin levels that appear normal or elevated, the higher blood glucose levels in these diabetic patients would be expected to result in even higher insulin values had their β-cell function been normal (35). Thus, insulin secretion is defective in these patients and insufficient to compensate for the insulin resistance. Insulin resistance may improve with weight reduction and/or pharmacological treatment of hyperglycemia but is seldom restored to normal (36–40). The risk of developing this form of diabetes increases with age, obesity, and lack of physical activity (29,41). It occurs more frequently in women with prior GDM and in individuals with hypertension or dyslipidemia, and its frequency varies in different racial/ethnic subgroups (29,30,41). It is often associated with a strong genetic predisposition, more so than is the autoimmune form of type 1 diabetes (42,43). However, the genetics of this form of diabetes are complex and not clearly defined.

### Other specific types of diabetes

**Genetic defects of the β-cell.** Several forms of diabetes are associated with monogenetic defects in β-cell function. These forms of diabetes are frequently characterized by onset of hyperglycemia at an early age (generally before age 25 years). They are referred to as maturity-onset diabetes of the young (MODY) and are characterized by impaired insulin secretion with minimal or no defects in insulin action (44–46). They are inherited in an autosomal dominant pattern. Abnormalities at three genetic loci on different chromosomes have been identified to date. The most common form is associated with mutations on chromosome 12 in a hepatic transcription factor referred to as hepatocyte nuclear factor (HNF)-1α (47,48). A second form is associated with mutations in the glucokinase gene on chromosome 7p and results in a defective glucokinase molecule (49,50). Glucokinase converts glucose to glucose-6-phosphate, the metabolism of which, in turn, stimulates insulin secretion by the β-cell. Thus, glucokinase serves as the "glucose sensor" for the β-cell. Because of defects in the glucokinase gene, increased plasma levels of glucose are necessary to elicit normal levels of insulin secretion. A third form is associated with a mutation in the HNF-4α gene on chromosome 20q (51,52). HNF-4α is a transcription factor involved in the regulation of the expression of HNF-1α. The specific genetic defects in a substantial number of other individuals who have a similar clinical presentation are currently unknown.

Point mutations in mitochondrial DNA have been found to be associated with diabetes mellitus and deafness (53–55). The most common mutation occurs at position 3243 in the tRNA leucine gene, leading to an A-to-G transition. An identical lesion occurs in the MELAS syndrome (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like syndrome); however, diabetes is not part of this syndrome, suggesting different phenotypic expressions of this genetic lesion (56).

Genetic abnormalities that result in the inability to convert proinsulin to insulin have been identified in a few families, and such traits are inherited in an autosomal dominant pattern (57,58). The resultant glucose intolerance is mild. Similarly, the production of mutant insulin molecules with resultant impaired receptor binding has also been identified in a few families and is associated with an autosomal inheritance and only mildly impaired or even normal glucose metabolism (59–61).

**Genetic defects in insulin action.** There are unusual causes of diabetes that result

from genetically determined abnormalities of insulin action. The metabolic abnormalities associated with mutations of the insulin receptor may range from hyperinsulinemia and modest hyperglycemia to severe diabetes (62,63). Some individuals with these mutations may have acanthosis nigricans. Women may be virilized and have enlarged, cystic ovaries (64,65). In the past, this syndrome was termed type A insulin resistance (62). Leprechaunism and the Rabson-Mendenhall syndrome are two pediatric syndromes that have mutations in the insulin receptor gene with subsequent alterations in insulin receptor function and extreme insulin resistance (63). The former has characteristic facial features and is usually fatal in infancy, while the latter is associated with abnormalities of teeth and nails and pineal gland hyperplasia.

Alterations in the structure and function of the insulin receptor cannot be demonstrated in patients with insulin-resistant lipoatrophic diabetes. Therefore, it is assumed that the lesion(s) must reside in the postreceptor signal transduction pathways.

**Diseases of the exocrine pancreas.** Any process that diffusely injures the pancreas can cause diabetes. Acquired processes include pancreatitis, trauma, infection, pancreatectomy, and pancreatic carcinoma (66–68). With the exception of cancer, damage to the pancreas must be extensive for diabetes to occur. However, adenocarcinomas that involve only a small portion of the pancreas have been associated with diabetes. This implies a mechanism other than simple reduction in β-cell mass. If extensive enough, cystic fibrosis and hemochromatosis will also damage β-cells and impair insulin secretion (69,70). Fibrocalculous pancreatopathy may be accompanied by abdominal pain radiating to the back and pancreatic calcifications on X ray (71). Pancreatic fibrosis and calcium stones in the exocrine ducts have been found at autopsy.

**Endocrinopathies.** Several hormones (e.g., growth hormone, cortisol, glucagon, epinephrine) antagonize insulin action. Excess amounts of these hormones (e.g., acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma) can cause diabetes (72–75). This generally occurs in individuals with preexisting defects in insulin secretion, and hyperglycemia typically resolves when the hormone excess is removed.

Somatostatinoma- and aldosteronoma-induced hypokalemia can cause diabetes, at least in part, by inhibiting insulin secretion (75,76). Hyperglycemia generally resolves after successful removal of the tumor.

**Drug- or chemical-induced diabetes.** Many drugs can impair insulin secretion. These drugs may not cause diabetes by themselves, but they may precipitate diabetes in individuals with insulin resistance (77,78). In such cases, the classification is unclear because the sequence or relative importance of β-cell dysfunction and insulin resistance is unknown. Certain toxins such as Vacor (a rat poison) and intravenous pentamidine can permanently destroy pancreatic β-cells (79–82). Such drug reactions fortunately are rare. There are also many drugs and hormones that can impair insulin action. Examples include nicotinic acid and glucocorticoids (77,78). Patients receiving α-interferon have been reported to develop diabetes associated with islet cell antibodies and, in certain instances, severe insulin deficiency (83,84). The list shown in Table 1 is not all-inclusive, but reflects the more commonly recognized drug-, hormone-, or toxin-induced forms of diabetes.

**Infections.** Certain viruses have been associated with β-cell destruction. Diabetes occurs in patients with congenital rubella (85), although most of these patients have HLA and immune markers characteristic of type 1 diabetes. In addition, coxsackievirus B, cytomegalovirus, adenovirus, and mumps have been implicated in inducing certain cases of the disease (86–88).

**Uncommon forms of immune-mediated diabetes.** In this category, there are two known conditions, and others are likely to occur. The stiff-man syndrome is an autoimmune disorder of the central nervous system characterized by stiffness of the axial muscles with painful spasms (89). Patients usually have high titers of the GAD autoantibodies and approximately one-third will develop diabetes.

Anti-insulin receptor antibodies can cause diabetes by binding to the insulin receptor, thereby blocking the binding of insulin to its receptor in target tissues (63). However, in some cases, these antibodies can act as an insulin agonist after binding to the receptor and can thereby cause hypoglycemia. Anti-insulin receptor antibodies are occasionally found in patients with systemic lupus erythematosus and other autoimmune diseases (63). As in other states of extreme insulin resistance, patients with anti-insulin receptor antibodies often have acanthosis nigricans. In the past, this syndrome was termed type B insulin resistance.

**Other genetic syndromes sometimes associated with diabetes.** Many genetic syndromes are accompanied by an increased incidence of diabetes mellitus (90). These include the chromosomal abnormalities of Down's syndrome, Kline-felter's syndrome, and Turner's syndrome. Wolfram's syndrome is an autosomal recessive disorder characterized by insulin-deficient diabetes and the absence of β-cells at autopsy (91). Additional manifestations include diabetes insipidus, hypogonadism, optic atrophy, and neural deafness. Other syndromes are listed in Table 1.

**Gestational diabetes mellitus (GDM)**

GDM is defined as any degree of glucose intolerance with onset or first recognition during pregnancy. The definition applies regardless of whether insulin or only diet modification is used for treatment or whether the condition persists after pregnancy. It does not exclude the possibility that unrecognized glucose intolerance may have antedated or begun concomitantly with the pregnancy (92). Six weeks or more after pregnancy ends, the woman should be reclassified, as described below (see diagnostic criteria for diabetes mellitus), into one of the following categories: 1) diabetes, 2) IFG, 3) IGT, or 4) normoglycemia. In the majority of cases of GDM, glucose regulation will return to normal after delivery.

GDM complicates ~4% of all pregnancies in the U.S., resulting in ~135,000 cases annually (93). The prevalence may range from 1 to 14% of pregnancies, depending on the population studied (93). GDM represents nearly 90% of all pregnancies complicated by diabetes (94). Clinical recognition of GDM is important because therapy, including medical nutrition therapy, insulin when necessary, and antepartum fetal surveillance, can reduce the well-described GDM-associated perinatal morbidity and mortality (95). Maternal complications related to GDM also include an increased rate of cesarean delivery and chronic hypertension (95–97). Although many patients diagnosed with GDM will not develop diabetes later in life, others will be diagnosed many years

**Table 2—*Diagnosis of GDM with a 100-g or 75-g glucose load***

| | mg/dl | mmol/l |
|---|---|---|
| 100-g Glucose load | | |
| Fasting | 95 | 5.3 |
| 1-h | 180 | 10.0 |
| 2-h | 155 | 8.6 |
| 3-h | 140 | 7.8 |
| 75-g Glucose load | | |
| Fasting | 95 | 5.3 |
| 1-h | 180 | 10.0 |
| 2-h | 155 | 8.6 |

Two or more of the venous plasma concentrations must be met or exceeded for a positive diagnosis. The test should be done in the morning after an overnight fast of between 8 and 14 h and after at least 3 days of unrestricted diet (≥150 g carbohydrate per day) and unlimited physical activity. The subject should remain seated and should not smoke throughout the test.

postpartum as having type 1 diabetes, type 2 diabetes, IFG, or IGT (98–103).

Deterioration of glucose tolerance occurs normally during pregnancy, particularly in the 3rd trimester. The criteria for abnormal glucose tolerance in pregnancy, which are widely used in the U.S., were proposed by O'Sullivan and Mahan (98) in 1964 and were based on data obtained from OGTTs performed on 752 pregnant women. Abnormal glucose tolerance was defined as two or more blood glucose values out of four that were greater than or equal to two standard deviations above the mean. These values were set based on the prediction of diabetes developing later in life.

In 1979, the NDDG revised the O'Sullivan and Mahan criteria, converting the whole blood values to plasma values (1). These criteria were adopted by the American Diabetes Association and the American College of Obstetricians and Gynecologists (ACOG) (104), but are at variance with WHO criteria.

Carpenter and Coustan (105) suggested that the NDDG conversion of the O'Sullivan and Mahan values from the original Somogyi-Nelson determinations may have resulted in values that are too high. They proposed cutoff values for plasma glucose that appear to represent more accurately the original O'Sullivan and Mahan determinations. In three studies, these criteria identified more patients with GDM whose infants had perinatal morbidity (106–108). Additional studies have been completed to define abnormal 75-g OGTT values in different populations (109–111). This method has provided values for plasma glucose concentrations that are similar to the Carpenter/Coustan extrapolations of the 100-g OGTT.

Recommendations from the American Diabetes Association's Fourth International Workshop-Conference on Gestational Diabetes Mellitus held in March 1997 support the use of the Carpenter/Coustan diagnostic criteria as well as the alternative use of a diagnostic 75-g 2-h OGTT (111a). These criteria are summarized below.

**Testing for gestational diabetes.** Previous recommendations have been that screening for GDM be performed in all pregnancies. However, there are certain factors that place women at lower risk for the development of glucose intolerance during pregnancy, and it is likely not cost-effective to screen such patients. This low-risk group comprises women who are <25 years of age and of normal body weight, have no family history (i.e., first-degree relative) of diabetes, have no history of abnormal glucose metabolism or poor obstetric outcome, *and* are not members of an ethnic/racial group with a high prevalence of diabetes (e.g., Hispanic American, Native American, Asian American, African-American, Pacific Islander) (112–114). Pregnant women who fulfill *all* of these criteria need not be screened for GDM.

Risk assessment for GDM should be undertaken at the first prenatal visit. Women with clinical characteristics consistent with a high risk of GDM (marked obesity, personal history of GDM, glycosuria, or a strong family history of diabetes) should undergo glucose testing (see below) as soon as feasible. If they are found not to have GDM at that initial screening, they should be retested between 24 and 28 weeks of gestation. Women of average risk should have testing undertaken at 24–28 weeks of gestation.

A fasting plasma glucose level >126 mg/dl (7.0 mmol/l) or a casual plasma glucose >200 mg/dl (11.1 mmol/l) meets the threshold for the diagnosis of diabetes, if confirmed on a subsequent day, and precludes the need for any glucose challenge. In the absence of this degree of hyperglycemia, evaluation for GDM in women with average or high-risk characteristics should follow one of two approaches:

**One-step approach:**
Perform a diagnostic OGTT without prior plasma or serum glucose screening. The one-step approach may be cost-effective in high-risk patients or populations (e.g., some Native-American groups).

**Two-step approach:**
Perform an initial screening by measuring the plasma or serum glucose concentration 1 h after a 50-g oral glucose load (glucose challenge test [GCT]) and perform a diagnostic OGTT on that subset of women exceeding the glucose threshold value on the GCT. When the two-step approach is employed, a glucose threshold value >140 mg/dl (7.8 mmol/l) identifies approximately 80% of women with GDM, and the yield is further increased to 90% by using a cutoff of >130 mg/dl (7.2 mmol/l).

With either approach, the diagnosis of GDM is based on an OGTT. Diagnostic criteria for the 100-g OGTT are derived from the original work of O'Sullivan and Mahan, modified by Carpenter and Coustan, and are shown in the top of Table 2. Alternatively, the diagnosis can be made using a 75-g glucose load and the glucose threshold values listed for fasting, 1 h, and 2 h (Table 2, bottom); however, this test is not as well validated as the 100-g OGTT.

## Impaired glucose tolerance (IGT) and impaired fasting glucose (IFG)

The terms IGT and IFG refer to a metabolic stage intermediate between normal glucose homeostasis and diabetes. This stage includes individuals who have IGT and individuals with fasting glucose levels ≥110 mg/dl (6.1 mmol/l) but <126 mg/dl (7.0 mmol/l) (IFG). The term IFG was coined by Charles et al. (115) to refer to a fasting plasma glucose (FPG) level ≥110 mg/dl (6.1 mmol/l) but <140 mg/dl (7.8 mmol/l). We are using a similar definition, but with the upper end lowered to correspond to the new diagnostic criteria for diabetes. A fasting glucose concentration of 109 mg/dl (6.1 mmol/l) has been chosen as the upper limit of "normal." Although it is recog-

**Table 3—*Criteria for the diagnosis of diabetes mellitus***

1. Symptoms of diabetes plus casual plasma glucose concentration ≥200 mg/dl (11.1 mmol/l). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.

or

2. FPG ≥126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.

or

3. 2-h PG ≥200 mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by WHO (2), using a glucose load containing the equivalent of 75-g anhydrous glucose dissolved in water.

In the absence of unequivocal hyperglycemia with acute metabolic decompensation, these criteria should be confirmed by repeat testing on a different day. The third measure (OGTT) is not recommended for routine clinical use.

nized that this choice is somewhat arbitrary, it is near the level above which acute phase insulin secretion is lost in response to intravenous administration of glucose (116) and is associated with a progressively greater risk of developing micro- and macrovascular complications (117–121).

Note that many individuals with IGT are euglycemic in their daily lives (122) and may have normal or near normal glycated hemoglobin levels (123). Individuals with IGT often manifest hyperglycemia only when challenged with the oral glucose load used in the standardized OGTT.

In the absence of pregnancy, IFG and IGT are not clinical entities in their own right but rather risk factors for future diabetes and cardiovascular disease (117). They can be observed as intermediate stages in any of the disease processes listed in Table 1. IFG and IGT are associated with the insulin resistance syndrome (also known as syndrome X or the metabolic syndrome), which consists of insulin resistance, compensatory hyperinsulinemia to maintain glucose homeostasis, obesity (especially abdominal or visceral obesity), dyslipidemia of the high-triglyceride and/or low-HDL type, and hypertension (124). Insulin resistance is directly involved in the pathogenesis of type 2 diabetes. IFG and IGT appear as risk factors for this type of diabetes at least in part because of their correlation with insulin resistance. In contrast, the explanation for why IFG and IGT are also risk factors for cardiovascular disease is less clear. The insulin resistance syndrome includes well-recognized cardiovascular risk factors such as low HDL levels and hypertension. In addition, it includes hypertriglyceridemia, which is highly correlated with small dense LDL and increased plasminogen activator inhibitor-1 (PAI-1) levels. The former is thought to have enhanced atherogenicity, perhaps as a result of its greater vulnerability to oxidation than normal LDL. PAI-1 is a cardiovascular risk factor probably because it inhibits fibrinolysis. Thus, the insulin resistance syndrome contains many features that increase cardiovascular risk. IFG and IGT may not in themselves be directly involved in the pathogenesis of cardiovascular disease, but rather may serve as statistical risk factors by association because they correlate with those elements of the insulin resistance syndrome that are cardiovascular risk factors.

## DIAGNOSTIC CRITERIA FOR DIABETES MELLITUS

### The new criteria

The diagnostic criteria for diabetes mellitus have been modified from those previously recommended by the NDDG (1) or WHO (2). The revised criteria for the diagnosis of diabetes are shown in Table 3. Three ways to diagnose diabetes are possible, and each must be confirmed, on a subsequent day, by any one of the three methods given in Table 3. For example, one instance of symptoms with casual plasma glucose ≥200 mg/dl (11.1 mmol/l), confirmed *on a subsequent day* by 1) FPG ≥126 mg/dl (7.0 mmol/l), 2) an OGTT with the 2-h postload value ≥200 mg/dl (11.1 mmol/l), or 3) symptoms with a casual plasma glucose ≥200 mg/dl (11.1 mmol/l), warrants the diagnosis of diabetes.

For epidemiological studies, estimates of diabetes prevalence and incidence should be based on an FPG ≥126 mg/dl (7.0 mmol/l). This recommendation is made in the interest of standardization and also to facilitate field work, particularly where the OGTT may be difficult to perform and where the cost and demands on participants' time may be excessive. This approach will lead to slightly lower estimates of prevalence than would be obtained from the combined use of the FPG and OGTT (Table 4).

The Expert Committee recognizes an intermediate group of subjects whose glucose levels, although not meeting criteria for diabetes, are nevertheless too high to be considered altogether normal. This group is defined as having FPG levels ≥110 mg/dl (6.1 mmol/l) but <126 mg/dl (7.0 mmol/l) *or* 2-h values in the OGTT of ≥140 mg/dl (7.8 mmol/l) but <200 mg/dl (11.1 mmol/l). Thus, the categories of FPG values are as follows:

- FPG <110 mg/dl (6.1 mmol/l) = normal fasting glucose;
- FPG ≥110 (6.1 mmol/l) and <126 mg/dl (7.0 mmol/l) = IFG;

**Table 4—*Estimated prevalence of diabetes in the U.S. in individuals 40–74 years old using data from the NHANES III***

| Diabetes diagnostic criteria | Prevalence (%) of diabetes by glucose criteria without a medical history of diabetes* | Total diabetes prevalence (%)† |
|---|---|---|
| Medical history of diabetes | — | 7.92 |
| WHO (2) criteria for diabetes: FPG ≥140 mg/dl (7.8 mmol/l) or 2-h PG ≥200 mg/dl (11.1 mmol/l) | 6.34 | 14.26 |
| FPG ≥126 mg/dl (7.0 mmol/l) | 4.35 | 12.27 |

Data are from K. Flegal, National Center for Health Statistics, personal communication. *Diabetes prevalence (by glucose criteria) in those without a medical history of diabetes × (100%-prevalence of diabetes by medical history); †first column of data plus 7.92.

- FPG ≥126 mg/dl (7.0 mmol/l) = provisional diagnosis of diabetes (the diagnosis must be confirmed, as described above).

The corresponding categories when the OGTT is used are the following:

- 2-h postload glucose (2-h PG) <140 mg/dl (7.8 mmol/l) = normal glucose tolerance;
- 2-h PG ≥140 (7.8 mmol/l) and <200 mg/dl (11.1 mmol/l) = IGT;
- 2-h PG ≥200 mg/dl (11.1 mmol/l) = provisional diagnosis of diabetes (the diagnosis must be confirmed, as described above).

Since the 2-h OGTT cutoff of 140 mg/dl (7.8 mmol/l) will identify more people as having impaired glucose homeostasis than will the fasting cutoff of 110 mg/d (6.1 mmol/l), it is essential that investigator always report which test was used.

### Rationale for the revised criteria for diagnosing diabetes

The revised criteria are still based on measures of hyperglycemia. Whereas many different diagnostic schemes have been used all have been based on some measurement of blood or urine glucose, as reviewed by McCance et al. (125). The metabolic defects underlying hyperglycemia, such as islet cell autoimmunity or insulin resistance, should be referred to independently from the diagnosis of diabetes, i.e., in the classification of the disease. Determining the optimal diagnostic level of hyperglycemia depends on a balance between the medical, social, and economic costs of making a diagnosis in someone who is not truly at substantial risk of the adverse effects of diabetes and those of failing to diagnose someone who is (126). Unfortunately, not all these data are available, so we relied primarily on medical data.

Plasma glucose concentrations are distributed over a continuum, but there is an approximate threshold separating those subjects who are at substantially increased risk for some adverse outcomes caused by diabetes (e.g., microvascular complications from those who are not. Based in part on estimates of the thresholds for microvascular disease, the previous WHO criteria defined diabetes by FPG ≥140 mg/dl (7.8 mmol/l), 2-h PG

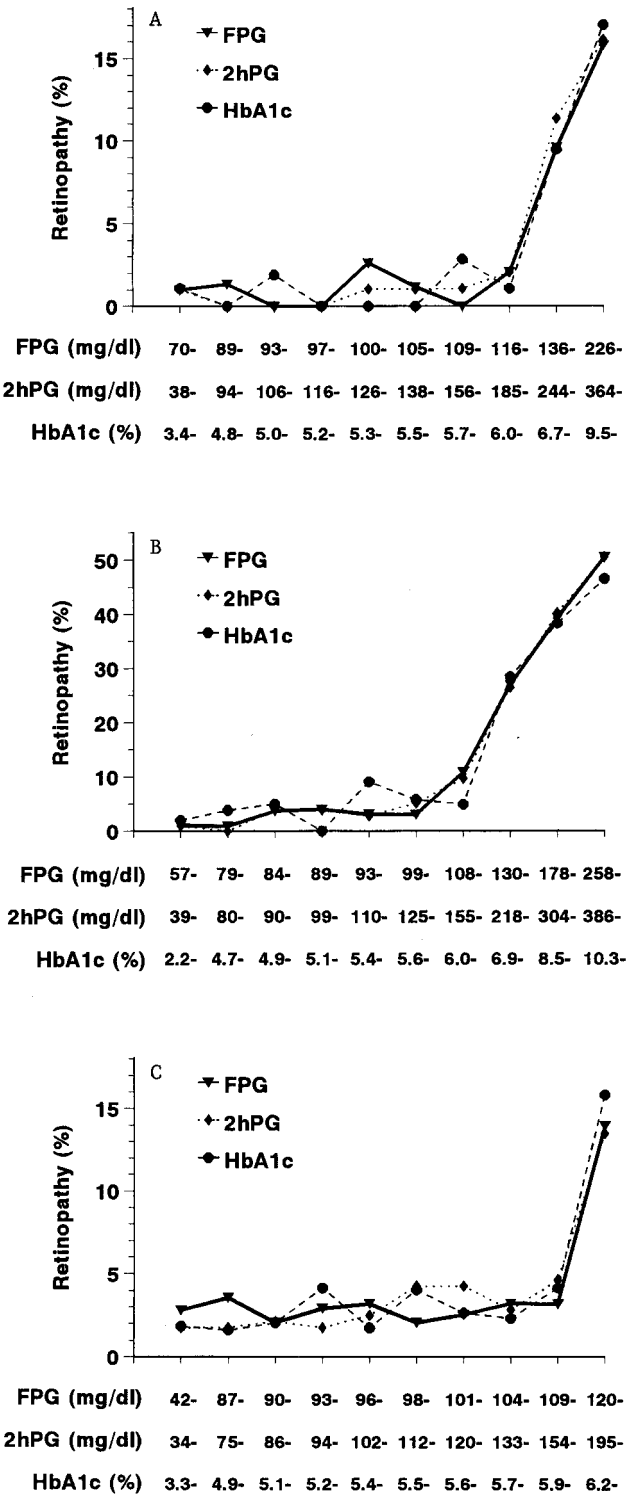


**Figure 2—***Prevalence of retinopathy by deciles of the distribution of FPG, 2-h PG, and $HbA_{1c}$ in Pima Indians (A) described by McCance et al. (129), in Egyptians (B) described by Engelgau et al. (130), and in 40- to 74-year-old participants in NHANES III (C) (K. Flegal, National Center for Health Statistics, personal communication). The x-axis labels indicate the lower limit of each decile group. Note that these deciles and the prevalence rates of retinopathy differ considerably among the studies, especially the Egyptian study, in which diabetic subjects were oversampled. Retinopathy was ascertained by different methods in each study; therefore, the absolute prevalence rates are not comparable between studies, but their relationships with FPG, 2-h PG, and $HbA_{1c}$ are very similar within each population.*

**Table 5—*FPG cutpoints equivalent to the WHO 2-h plasma glucose criterion of 200 mg/dl***

| Study and reference | Method | Fasting plasma glucose* |
|---|---|---|
| Pima Indians (129) | ROC curves† | 123 mg/dl (6.8 mmol/l) |
| Pima Indians (129) | Equal prevalence‡ | 120 mg/dl (6.7 mmol/l) |
| Several Pacific populations (134) | Equal prevalence‡ | 126 mg/dl (7.0 mmol/l) |
| NHANES III§ | Equal prevalence‡ | 121 mg/dl (6.7 mmol/l) |

*The results for the receiver-operating characteristics (ROC) curve analysis of the Pima Indian data and those from the Pacific populations appear in the cited publications (in millimoles per liter). The other results have not been published; †equivalent to the WHO criterion of 2-h PG ≥200 mg/dl (11.1 mmol/l) in sensitivity and specificity for retinopathy from analysis of ROC curves; ‡the method is described by Finch et al. (134); §NHANES III subjects ages 40–74 years, excluding users of insulin and oral hypoglycemic agents, weighted according to sampling plan (K. Flegal, National Center for Health Statistics, personal communication).

≥200 mg/dl (11.1 mmol/l) in the OGTT, or both. These criteria effectively defined diabetes by the 2-h PG alone because the fasting and 2-h cutpoint values are not equivalent. Almost all individuals with FPG ≥140 mg/dl (7.8 mmol/l) have 2-h PG ≥200 mg/dl (11.1 mmol/l) if given an OGTT, whereas only about one-fourth of those with 2-h PG ≥200 mg/dl (11.1 mmol/l) and without previously known diabetes have FPG ≥140 mg/dl (7.8 mmol/l) (127). Thus, the cutpoint of FPG ≥140 mg/dl (7.8 mmol/l) defined a greater degree of hyperglycemia than did the cutpoint of 2-h PG ≥200 mg/dl (11.1 mmol/l). It is the consensus of the Expert Committee that this discrepancy is unwarranted and that the cutpoint values for both tests should reflect a similar degree of hyperglycemia and risk of adverse outcomes.

Under the previous WHO and the NDDG criteria, the diagnosis of diabetes is largely a function of which test is performed. Many individuals who would have 2-h PG ≥200 mg/dl (11.1 mmol/l) in an OGTT are not tested with an OGTT because they lack symptoms or because they have an FPG <140 mg/dl (7.8 mmol/l). Thus, if it is desired that all people with diabetes be diagnosed and the previous criteria are followed, OGTTs must be performed periodically in everyone. However, in ordinary practice, not only is the OGTT performed infrequently, but it is usually not used even to confirm suspected cases (128). In summary, the diagnostic criteria are now revised to *1*) avoid the discrepancy between the FPG and 2-h PG cutpoint values and 2) facilitate and encourage the use of a simpler and equally accurate test—fasting plasma glucose—for diagnosing diabetes.

The cutpoint for the 2-h PG has been justified largely because at approximately that point the prevalence of the microvascular complications considered specific for diabetes (i.e., retinopathy and nephropathy) increases dramatically. This property of the 2-h PG has been compared with the FPG in population studies of the Pima Indians in the U.S., among Egyptians, and in the Third National Health and Nutrition Examination Survey (NHANES III) in the U.S. In other studies, the relationships between glycemia and macrovascular disease have also been examined.

The relationships of FPG and 2-h PG to the development of retinopathy were evaluated in Pima Indians over a wide range of plasma glucose cutpoints (Fig. 2A) (129). Both variables were similarly associated with retinopathy, indicating that by this criterion, each could work equally well for diagnosing diabetes. The authors concluded that both measures were equivalent in terms of the properties previously used to justify diagnostic criteria.

These findings were confirmed in a similar study in Egypt, in which the FPG and 2-h PG were each strongly and equally associated with retinopathy (Fig. 2B) (130). For both the FPG and the 2-h PG, the prevalence of retinopathy was markedly higher above the point of intersection of the two components of the bimodal frequency distribution (FPG = 129 mg/dl [7.2 mmol/l] and 2-h PG = 207 mg/dl [11.5 mmol/l]).

In the NHANES III, 2,821 individuals aged 40–74 years received an OGTT, a measurement of $HbA_{1c}$, and an assessment of retinopathy by fundus photography (K. Flegal, personal communication). Figure 2*C* shows that all three measures of glycemia (FPG, 2-h PG, and $HbA_{1c}$) are strongly associated with retinopathy, which is similar to the relationships found in the Pima Indians (129) and Egyptians (130), although the relationship was strongest for 2-h PG. As in other studies, the prevalence rose dramatically in the highest decile of each variable, corresponding to FPG ≥120 mg/dl (6.7 mmol/l), 2-h PG ≥195 mg/dl (10.8 mmol/l), and $HbA_{1c}$ ≥6.2%. As in the Pima Indian (129) and Egyptian (130) studies, estimates of these "thresholds" for retinopathy are somewhat imprecise. More precision cannot easily be obtained by using narrower glycemic intervals (e.g., 20 instead of the 10 shown in Fig. 2) because of the limited numbers of cases of retinopathy in each sample (32 cases in the Pima study, 146 in the Egyptian study, and 111 in NHANES III). There are no absolute thresholds because some retinopathy occurred at all glucose levels, presumably because of measurement or disease variability and because of nondiabetic causes of retinopathy.

The associations between FPG and 2-h PG and macrovascular disease have been examined in adults without known diabetes (131). The 2-h PG was somewhat more closely associated with major coronary heart disease, but there was no significant difference in the association of the FPG or the 2-h PG with other indexes of macrovascular disease. Similarly, the relationship between glycemia and peripheral arterial disease was studied in 50- to 74-year-old Caucasians (132). The prevalence of arterial disease was strongly related to the FPG and 2-h PG. The associations appeared to be of the same strength for both variables.

In a recent analysis of the Paris Prospective Study, the incidence of fatal coronary heart disease was related to both FPG and 2-h PG determined at a baseline examination (118). Incidence rates were markedly increased at FPG ≥125 mg/dl (6.9 mmol/l) or 2-h PG ≥140 mg/dl (7.8 mmol/l). Similarly, the incidence of coronary artery disease and the all-cause mortality rates were predicted by the FPG in the Baltimore Longitudinal Study of Aging (R. Andres, C. Coleman, D. Elahi, J. Fleg, D.C. Muller, J.D. Sorkin, J.D. Tobin, personal communication). The incidence rates of both these outcomes increased markedly and almost linearly above FPG levels in the range of 110–120 mg/dl (6.1–6.7 mmol/l). In conclusion, both the FPG and 2-h PG provide important information regarding risk of both micro- and macrovascular disease, and the approximate thresholds for increased risk

correspond with those for retinopathy and with the revised diagnostic criteria.

Reproducibility is another important property of a diagnostic test, a property for which the FPG appears to be preferable. When OGTTs were repeated in adults during a 2- to 6-week interval, the intra-individual coefficients of variation were 6.4% for the FPG and 16.7% for the 2-h PG (133).

It is important to review the rationale for retaining the diagnostic cutpoint of 200 mg/dl (11.1 mmol/l) for the 2-h PG. This cutpoint was originally adopted for three reasons (1,2). First, 200 mg/dl (11.1 mmol/l) has been found to approximate the cutpoint separating the two components of the bimodal distribution of 2-h PG. Second, in several studies, the prevalence of microvascular disease sharply increased above 2-h PG levels of ~200 mg/dl (11.1 mmol/l). Third, an enormous body of clinical and epidemiological data has been collected based on the 2-h PG cutpoint of 200 mg/dl (11.1 mmol/l). Thus, this value has been retained for the diagnosis of diabetes because it would be very disruptive, and add little benefit, to alter the well-accepted 2-h PG diagnostic level of ≥200 mg/dl (11.1 mmol/l).

Changing the diagnostic cutpoint for the FPG to 126 mg/dl (7.0 mmol/l) is based on the belief that the cutpoints for the FPG and 2-h PG should diagnose similar conditions, given the equivalence of the FPG and the 2-h PG in their associations with vascular complications and their discrimination between two components of a bimodal frequency distribution (129,130). McCance et al. (129) computed the FPG level equivalent (in sensitivity and specificity for retinopathy) to the 1985 WHO criterion of the 2-h PG ≥200 mg/dl (11.1 mmol/l) and found it to be an FPG of ≥123 mg/dl (6.8 mmol/l) (Table 5). Finch et al. (134) approached the problem in each of 13 Pacific populations surveyed with OGTTs by determining the value in the FPG that, when used alone as a diagnostic criterion, gave the same prevalence of diabetes as did 2-h PG ≥200 mg/dl (11.1 mmol/l). The summary estimate from all these populations was a cutpoint of 126 mg/dl (7.0 mmol/l). The same method was applied to data derived from the Pima Indians and resulted in an FPG cutpoint of 120 mg/dl (6.7 mmol/l). In NHANES III, the corresponding cutpoint was 121 mg/dl (6.7 mmol/l) (Table 5). These values and the 2-h PG cutpoint of 200 mg/dl (11.1 mmol/l) are also quite similar to the values of FPG 129 mg/dl (7.2 mmol/l) and 2-h PG 207 mg/dl (11.5 mmol/l) that separated the components of the bimodal frequency distributions and identified individuals with a high prevalence of retinopathy among Egyptians (130). Because the standard errors of these estimates are not known, the small differences in the estimates shown in Table 5 may be consistent with sampling variability.

We chose a cutpoint at the upper end of these estimates (FPG ≥126 mg/dl, 7.0 mmol/l). This value is slightly higher than most of the estimated cutpoints that would give the same prevalence of diabetes as the criterion of 2-h PG ≥200 mg/dl (11.1 mmol/l). That is, slightly fewer people will be diagnosed with diabetes if the new FPG criterion is used alone than if either the FPG or the OGTT is used and interpreted by the previous WHO and NDDG criteria (Table 4).

As noted above, although the OGTT is an acceptable diagnostic test and has been an invaluable tool in research, it is not recommended for routine use. Because of its inconvenience to patients and the perception by many physicians that it is unnecessary, the OGTT is already not widely used for diagnosing diabetes. In addition, it is more costly and time-consuming than the FPG, and the repeat test reproducibility of the 2-h PG is worse than that of the FPG (133). If the OGTT is used, either for clinical or research purposes, the test procedure methods recommended by the WHO (2) and the diagnostic criterion in Table 3 should be employed.

$HbA_{1c}$ measurement is not currently recommended for diagnosis of diabetes, although some studies have shown that the frequency distributions for $HbA_{1c}$ have characteristics similar to those of the FPG and the 2-h PG. Moreover, these studies have defined an $HbA_{1c}$ level above which the likelihood of having or developing macro- or microvascular disease rises sharply (Fig. 2) (129–132). Furthermore, $HbA_{1c}$ and FPG (in type 2 diabetes) have become the measurements of choice in monitoring the treatment of diabetes, and decisions on when and how to implement therapy are often made on the basis of $HbA_{1c}$. These observations have led some to recommend $HbA_{1c}$ measurement as a diagnostic test (126,135).

On the other hand, there are many different methods for the measurement of $HbA_{1c}$ and other glycosylated proteins, and nationwide standardization of the $HbA_{1c}$ test has just begun (136). Studies of the utility of the test compared with the FPG and 2-h PG have used different assays, thereby making it difficult to assign an appropriate cutpoint. Also, the FPG, 2-h PG, and $HbA_{1c}$ tests are imperfectly correlated. In most clinical laboratories, a "normal" $HbA_{1c}$ is usually based on a statistical sampling of healthy, presumably nondiabetic individuals. In conclusion, $HbA_{1c}$ remains a valuable tool for monitoring glycemia, but it is not currently recommended for the diagnosis of diabetes.

The revised criteria are for *diagnosis* and are *not* treatment criteria or goals of therapy. No change is made in the American Diabetes Association's recommendations of FPG <120 mg/dl (6.7 mmol/l) and $HbA_{1c}$ <7% as treatment goals (137). The new diagnostic cutpoint (FPG ≥126 mg/dl [7.0 mmol/l]) is based on the ob-

**Table 6—*Criteria for testing for diabetes in asymptomatic, undiagnosed individuals***

1. Testing for diabetes should be considered in all individuals at age 45 years and above and, if normal, it should be repeated at 3-year intervals.
2. Testing should be considered at a younger age or be carried out more frequently in individuals who:
   - are overweight (BMI ≥25 kg/m$^2$)
   - have a first-degree relative with diabetes
   - are members of a high-risk ethnic population (e.g., African-American, Hispanic American, Native American, Asian American, Pacific Islander)
   - have delivered a baby weighing >9 lb or have been diagnosed with GDM
   - are hypertensive (≥140/90)
   - have an HDL cholesterol level ≤35 mg/dl (0.90 mmol/l) and/or a triglyceride level ≥250 mg/dl (2.82 mmol/l).
   - on previous testing, had IGT or IFG

The OGTT or FPG test may be used to diagnose diabetes; however, in clinical settings the FPG test is greatly preferred because of ease of administration, convenience, acceptability to patients, and lower cost.

servation that this degree of hyperglycemia usually reflects a serious metabolic abnormality that has been shown to be associated with serious complications. The treatment of nonpregnant patients with hyperglycemia near the cutpoint should begin with an individualized lifestyle-modification regimen (i.e., meal planning and exercise). Initiation of pharmacological therapy in these patients has not yet been shown to improve prognosis and may lead to an unacceptably high incidence of hypoglycemic reactions with certain drugs (e.g., sulfonylureas, insulin).

The new criteria have implications for estimates of the prevalence of diabetes. Although an FPG ≥126 mg/dl (7.0 mmol/l) and a 2-h PG ≥200 mg/dl (11.1 mmol/l) have similar predictive value for adverse outcomes, the two tests are not perfectly correlated with each other. A given person may have one glucose value above one cutpoint and another value below the other cutpoint. Thus, simultaneous measurement of both FPG and 2-h PG will inevitably lead to some diagnostic discrepancies and dilemmas. Although diagnosing diabetes by either test will result in a similar number of "cases," different individuals in different hyperglycemic stages may be identified. (This situation would be even more complicated if a third diagnostic test, such as $HbA_{1c}$, were used.) However, according to the data reviewed above, there is no basis for concluding that the 2-h PG is more reliable than the FPG. Thus, the FPG alone should be used for estimating the comparative prevalence of diabetes in different populations.

Table 4 shows the effect of the new diagnostic criteria on the estimated prevalence of diabetes in the U.S. population aged 40–74 years using data from NHANES III. Diagnosing diabetes in those without a medical history of diabetes by using only the FPG test would result in a lower prevalence of diabetes than would using WHO criteria (4.35 vs. 6.34%). The total prevalence of diabetes (including those with a medical history) would be 12.27%, or 14% lower than the prevalence of 14.26% by the WHO criteria. Of note, these prevalence estimates refer to results of testing on one occasion. The prevalence of diabetes confirmed by a second test will be lower regardless of which criteria are used.

Widespread adoption of the new criteria may, however, have a large impact on the number of people actually diagnosed with diabetes. Presently, about half the adults with diabetes in the U.S. are undiagnosed (127), but many might now be diagnosed if the simpler FPG test were always used.

## TESTING FOR DIABETES IN PRESUMABLY HEALTHY INDIVIDUALS

— Type 1 diabetes is usually an autoimmune disease, characterized by the presence of a variety of autoantibodies to protein epitopes on the surface of or within the β-cells of the pancreas. The presence of such markers before the development of overt disease can identify patients at risk (138). For example, those with more than one autoantibody (i.e., ICA, IAA, GAD, IA-2) are at high risk (139–141). At this time, however, many reasons preclude the recommendation to test individuals routinely for the presence of any of the immune markers outside of a clinical trials setting. First, cutoff values for some of the assays for immune markers have not been completely established for clinical settings. Second, there is no consensus yet as to what action should be taken when a positive autoantibody test is obtained. Thus, autoantibody testing may identify people at risk of developing type 1 diabetes without offering any proven measures that might prevent or delay the clinical onset of disease. Of note, however, is that there are a number of ongoing well-controlled clinical studies testing various means of preventing type 1 diabetes. These studies conducted in high-risk subjects may one day offer an effective means to prevent type 1 diabetes, in which case screening may become appropriate. Last, because the incidence of type 1 diabetes is low, routine testing of healthy children will identify only the small number (<0.5%) who at that moment may be "prediabetic." Thus, the cost-effectiveness of such screening is questionable, at least until an effective therapy is available. For the above reasons, the clinical testing of individuals for autoantibodies related to type 1 diabetes, outside of research studies, cannot be recommended at this time. Similarly, antibody testing of high-risk individuals (e.g., siblings of type 1 patients) is also not recommended until the efficacy and safety of therapies to prevent or delay type 1 diabetes have been demonstrated. On the other hand, the autoantibody tests may be of value to identify which newly diagnosed patients have immune-mediated type 1 diabetes in circumstances where it is not obvious, particularly when therapies become available to preserve β-cell mass.

Undiagnosed type 2 diabetes is common in the U.S. As many as 50% of the people with the disease, or about 8 million individuals, are undiagnosed (127). Of concern, there is epidemiological evidence that retinopathy begins to develop at least 7 years before the clinical diagnosis of type 2 diabetes is made (142). Because hyperglycemia in type 2 diabetes causes microvascular disease and may cause or contribute to macrovascular disease, undiagnosed diabetes is a serious condition. Patients with undiagnosed type 2 diabetes are at significantly increased risk for coronary heart disease, stroke, and peripheral vascular disease. In addition, they have a greater likelihood of having dyslipidemia, hypertension, and obesity (143).

Thus, early detection, and consequently early treatment, might well reduce the burden of type 2 diabetes and its complications. However, to increase the cost-effectiveness of testing undiagnosed, otherwise healthy individuals, testing should be considered in high-risk populations. Suggested criteria for testing are given in Table 6. Factors leading to these recommendations include: *1*) the steep rise in the incidence of the disease after age 45 years, *2*) the negligible likelihood of developing any of the complications of diabetes within a 3-year interval of a negative screening test, and *3*) knowledge of the well-documented risk factors for the disease. Although the OGTT and FPG are both suitable tests, in clinical settings, the FPG is strongly recommended because it is easier and faster to perform, more convenient and acceptable to patients, more reproducible, and less expensive.

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**References**

1. National Diabetes Data Group: Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes* 28:1039–1057, 1979
2. World Health Organization: *Diabetes Mellitus: Report of a WHO Study Group*. Geneva, World Health Org., 1985 (Tech. Rep. Ser., no. 727)
3. Hoet JJ, Tripathy BB, Rao RH, Yajnik CS: Malnutrition and diabetes in the tropics. *Diabetes Care* 19:1014–1017, 1996
4. Atkinson MA, Maclaren NK: The pathogenesis of insulin dependent diabetes. *N Engl J Med* 331:1428–1436, 1994
5. Baekkeskov S, Neilsen JH, Marner B, Bilde T, Ludvigsson J, Lernmark A: Autoantibodies in newly diagnosed diabetic children with immunoprecipitate human pancreatic islet cell proteins. *Nature* 298:167–169, 1982
6. Atkinson MA, Maclaren NK, Riley WJ, Winter WE, Fisk DD, Spillar RP: Are insulin autoantibodies markers for insulin-dependent mellitus? *Diabetes* 35: 894–898, 1986
7. Kaufman D, Erlander M, Clare-Salzler M, Atkinson M, Maclaren N, Tobin A: Autoimmunity to two forms of glutamate decarboxylase in insulin-dependent mellitus. *J Clin Invest* 89:283–292, 1992
8. Christie MR, Tun RY, Lo SSS, Cassidy D, Brown TJ, Hollands J, Shattock M, Bottazzo GF, Leslie RDG: Antibodies to GAD and tryptic fragments of islet 64K antigen as distinct markers for development of IDDM: studies with identical twins. *Diabetes* 41:782–787, 1992
9. Schott M, Schatz D, Atkinson M, Krischer J, Mehta H, Vold B, Maclaren N: $GAD_{65}$ autoantibodies increase the predictability but not the sensitivity of islet cell and insulin autoantibodies for developing insulin dependent diabetes mellitus. *J Autoimmunity* 7:865–872, 1994
10. Schmidli RS, Colman PG, Harrison LC: Do glutamic acid decarboxylase antibodies improve the prediction of IDDM in first-degree relatives at risk for IDDM? *J Autoimmunity* 7:873–879, 1994
11. Myers MA, Rabin DU, Rowley MJ: Pancreatic islet cell cytoplasmic antibody in diabetes is represented by antibodies to islet cell antigen 512 and glutamic acid decarboxylase. *Diabetes* 44:1290–1295, 1995
12. Lan MS, Wasserfall C, Maclaren NK, Notkins AL: IA-2, a transmembrane protein of the protein tyrosine phosphatase family, is a major autoantigen in insulindependent diabetes mellitus. *Proc Natl Acad Sci USA* 93:6367–6370, 1996
13. Lu J, Li Q, Xie H, Chen Z, Borovitskaya AE, Maclaren NK, Notkins AL, Lan MS: Identification of a second transmembrane protein tyrosine phosphatase, IA-2β, as an autoantigen in insulin-dependent diabetes mellitus: precursor of the 37-kDa tryptic fragment. *Proc Natl Acad Sci USA* 93: 2307–2311, 1996
14. Cantor AB, Krischer JP, Cuthbertson DD, Schatz DA, Riley WJ, Malone J, Schwartz S, Quattrin T, Maclaren NK: Age and family relationship accentuate the risk of IDDM in relatives of patients with insulin dependent diabetes. *J Clin Endocrinol Metab* 80:3739–3743, 1995
15. Huang W, Connor E, DelaRosa T, Muir A, Schatz D, Silverstein J, Crockett S, She JX, Maclaren NK: Although DR3-DQB1* may be associated with multiple component diseases of the autoimmune polyglandular syndromes, the human leukocyte antigen DR4-DQB110302 haplotype is implicated only in beta cell autoimmunity. *J Clin Endocrinol Metab* 81:1–5, 1996
16. Zimmet PZ, Tuomi T, Mackay R, Rowley MJ, Knowles W, Cohen M, Lang DA: Latent autoimmune diabetes mellitus in adults (LADA): the role of antibodies to glutamic acid decarboxylase in diagnosis and prediction of insulin dependency. *Diabet Med* 11:299–303, 1994
17. Banerji M, Lebovitz H: Insulin sensitive and insulin resistant variants in IDDM. *Diabetes* 38:784–792, 1989
18. Reaven GM, Bernstein R, Davis B, Olefsky JM: Nonketotic diabetes mellitus: insulin deficiency or insulin resistance? *Am J Med* 60:80–88, 1976
19. Olefsky JM, Kolterman OG, Scarlett, JA: Insulin action and resistance in obesity and noninsulin-dependent type II diabetes mellitus. *Am J Physiol* 243:E15–E30, 1982
20. DeFronzo R, Deibert D, Hendler R, Felig P: Insulin sensitivity and insulin binding to monocytes in maturity-onset diabetes. *J Clin Invest* 63:939–946, 1979
21. Turner RC, Holman, RR, Matthews D, Hockaday TDR, Peto J: Insulin deficiency and insulin resistance interaction in diabetes: estimation of their relative contribution by feedback analysis from basal plasma insulin and glucose concentrations. *Metabolism* 28:1086–1096, 1979
22. Kolterman OG, Gray RS, Griffin J, Burstein P, Insel J, Scarlett JA, Olefsky JM: Receptor and postreceptor defects contribute to the insulin resistance in noninsulin-dependent diabetes mellitus. *J Clin Invest* 68:957–969, 1981
23. Bogardus C, Lillioja S, Mott DM, Hollenbeck C, Reaven G: Relationship between degree of obesity and in vivo insulin action in man. *Am J Physiol* 248:E286–E291, 1985
24. Kissebah AH, Vydelingum N, Murray R, Evans DF, Hartz AJ, Kalkhoff RK, Adams PW: Relationship of body fat distribution to metabolic complications of obesity. *J Clin Endocrinol Metab* 54:254–260, 1982
25. Butkiewicz EK, Leibson C, O'Brien PC, Palumbo PJ, Rizza RA: Insulin therapy for diabetic ketoacidosis. *Diabetes Care* 18:1187–1190, 1995
26. Banerji MA, Chaiken RL, Huey H, Tuomi T, Norin AJ, Mackay IR, Rowley MJ, Zimmet P, Lebovitz H: GAD antibody negative NIDDM in adult black subjects with diabetic ketoacidosis and increased frequency of human leukocyte antigen DR3 and DR4. *Diabetes* 43:741–745, 1994
27. Umpierrez GE, Casals MMC, Gebhart SSP, Mizon PS, Clark WS, Phillips LS: Diabetic ketoacidosis in obese African-Americans. *Diabetes* 44:79–85, 1995
28. Harris MI: Impaired glucose tolerance in the U.S. population. *Diabetes Care* 12: 464–474, 1989
29. Zimmet PZ: Kelly West Lecture 1991: challenges in diabetes epidemiology: from west to the rest. *Diabetes Care* 15: 232–252, 1992
30. Fujimoto WY, Leonetti DL, Kinyoun JL, Shuman WP, Stolov WC, Wahl PW: Prevalence of complications among second-generation Japanese-American men with diabetes, impaired glucose tolerance or normal glucose tolerance. *Diabetes* 36:730–739, 1987
31. Moss SE, Klein R, Klein BEK, Meuer MS: The association of glycemia and cause-specific mortality in a diabetic population. *Arch Int Med* 154:2473–2479, 1984
32. Kuusisto J, Mykknen L, Pyörälä K, Laakso M: NIDDM and its metabolic control predict coronary heart disease in elderly subjects. *Diabetes* 43:960–967, 1994
33. Andersson DKG, Svaardsudd K: Long-term glycemic control relates to mortality in type II diabetes. *Diabetes Care* 18: 1534–1543, 1995
34. Uusitupaa MIJ, Niskanen LK, Siitonen O, Voutilainen E, Pyörälä K: Ten year cardiovascular mortality in relation to risk factors and abnormalities in lipoprotein composition in type 2 (non-insulin-dependent) diabetic and non-diabetic subjects. *Diabetologia* 11:1175–1184, 1993
35. Polonsky KS, Sturis J, Bell GI: Non-insulin-dependent diabetes mellitus: a genetically programmed failure of the beta cell to compensate for insulin resistance. *N Engl J Med* 334:777–784, 1996
36. Scarlett JA, Gray RS, Griffin J, Olefsky JM, Kolterman OG: Insulin treatment reverses the insulin resistance of type II diabetes mellitus. *Diabetes Care* 5:353–363, 1982

37. Firth RG, Bell PM, Rizza RM: Effects of tolazamide and exogenous insulin on insulin action in patients with non-insulin-dependent diabetes mellitus. *N Engl J Med* 314:1280–1286, 1986
38. Simonson DC, Ferrannini E, Bevilacqua S, Smith D, Barrett E, Carlson R, DeFronzo RA: Mechanism of improvement in glucose metabolism after chronic glyburide therapy. *Diabetes* 33:838–845, 1984
39. Henry RR, Wallace P, Olefsky JM: Effects of weight loss on mechanisms of hyperglycemia in obese non-insulin-dependent diabetes mellitus. *Diabetes* 35:990–998, 1986
40. Wing RR, Blair EH, Bononi P, Marcus MD, Watanabe R, Bergman RN: Caloric restriction per se is a significant factor in improvements in glycemic control and insulin sensitivity during weight loss in obese NIDDM patients. *Diabetes Care* 17:30–36, 1994
41. Harris MI, Couric CC, Reiber G, Boyko E, Stern M, Bennett P (Eds.): *Diabetes in America*. 2nd ed. Washington, DC, U.S. Govt. Printing Office, 1995 (NIH publ. no. 95–1468)
42. Newman B, Selby JV, Slemenda C, Fabsitz R, Friedman GD: Concordance for type 2 (non-insulin-dependent) diabetes mellitus in male twins. *Diabetologia* 30: 763–738, 1987
43. Barnett AH, Eff C, Leslie RDG, Pyke DA: Diabetes in identical twins. *Diabetologia* 20:87–93, 1981
44. Herman WH, Fajans SS, Oritz FJ, Smith MJ, Sturis J, Bell GI, Polonsky KS, Halter JB: Abnormal insulin secretion, not insulin resistance, is the genetic or primary defect of MODY in the RW pedigree. *Diabetes* 43:40–46, 1994
45. Byrne MM, Sturis J, Menzel S, Yamagata K, Fajans SS, Dronsfield MJ, Bain SC, Hattersley AT, Velho G, Froguel P, Bell GI, Polonsky KS: Altered insulin secretory response to glucose in diabetic and nondiabetic subjects with mutations in the diabetes susceptibility gene MODY3 on chromosome 12. *Diabetes* 45:1503–1510, 1996
46. Clement K, Pueyo ME, Vaxillaire M, Rakotoambinina B, Thuillier F, Passa P, Froguel P, Roberts J, Velho G: Assessment of insulin sensitivity in glucokinase-deficient subjects. *Diabetologia* 39: 82–90, 1996
47. Vaxillaire M, Boccio V, Philippi A, Vigouroux C, Terwilliger J, Passa P, Beckman JS, Velho G, Lathrop GM, Froguel P: A gene for maturity onset diabetes of the young (MODY) maps to chromosome 12q. *Nature Genet* 9:418–423, 1995
48. Yamagata K, Oda N, Kaisaki PJ, Menzel S, Furuta H, Vaxillaire M, Southarm L, Cox RD, Lathrop GM, Boriraj VV, Chen X, Cox NJ, Oda Y, Yano H, Le Beau MM, Yamada S, Nishigori H, Takeda J, Fajans SS, Hattersley AT, Iwasaki N, Hansen T, Pedersen O, Polonsky KS, Bell GI: Mutations in the hepatocyte nuclear factor-1α gene in maturity-onset diabetes of the young (MODY 3). *Nature* 384: 455–458, 1996
49. Froguel P, Vaxillaire M, Sun F, Velho G, Zouali H, Butel MO, Lesage S, Vionnet N, Clement K, Fougerousse F, et al.: Close linkage of glucokinase locus on chromosome 7p to early-onset non-insulin-dependent diabetes mellitus. *Nature* 356:162–164, 1992
50. Vionnet N, Stoffel M, Takeda J, Yasuda K, Bell GI, Zouali H, Lesage S, Velho G, Iris F, Passa P, et al.: Nonsense mutation in the glucokinase gene causes early-onset non-insulin-dependent diabetes mellitus. *Nature* 356:721–722, 1992
51. Bell GI, Xiang K, Newman MV, Wu S, Wright LG, Fajans SS, Spielman RS, Cox NJ: Gene for non-insulin-dependent diabetes mellitus (maturity-onset diabetes of the young subtype) is linked to DNA polymorphism on human chromosome 20q. *Proc Natl Acad Sci* 88:1484–1488, 1991
52. Yamagata K, Furuta H, Oda N, Kaisaki PJ, Menzel S, Cox NJ, Fajans SS, Signorini S, Stoffel M, Bell GI: Mutations in the hepatocyte factor-4α gene in maturity-onset diabetes of the young (MODY 1). *Nature* 384:458–460, 1996
53. Reardon W, Ross RJM, Sweeney MG, Luxon LM, Pembrey ME, Harding AE, Trembath RC: Diabetes mellitus associated with a pathogenic point mutation in mitochondrial DNA. *Lancet* 340:1376–1379, 1992
54. van den Ouwenland JMW, Lemkes HHPJ, Ruitenbeek W, Sandkuijl LA, de Vijlder MF, Struyvenberg PAA, van de Kamp, Maassen JA: Mutation in mitochondrial tRNA (Leu(URR) gene in a large pedigree with maternally transmitted type II diabetes mellitus and deafness. *Nature Genet* 1:368–371, 1992
55. Kadowaki T, Kadowaki H, Mori Y, Tobe K, Sakuta R, Suzuki Y, Tanabe Y, Sakura H, Awata T, Goto Y, et al.: A subtype of diabetes mellitus associated with a mutation of mitochondrial DNA. *N Engl J Med* 330:962–968, 1994
56. Johns DR: Mitochondrial DNA and disease. *N Engl J Med* 333:638–644, 1995
57. Gruppuso PA, Gorden P, Kahn CR, Cornblath M, Zeller WP, Schwartz R: Familial hyperproinsulinemia due to a proposed defect in conversion of proinsulin to insulin. *N Engl J Med* 311:629–634, 1984
58. Robbins DC, Shoelson SE, Rubenstein AH, Tager HS: Familial hyperproinsulinemia: two cohorts secreting indistinguishable type II intermediates of proinsulin conversion. *J Clin Invest* 73: 714–719, 1984
59. Tager H, Given B, Baldwin D, Mako M, Markese J, Rubenstein A, Olefsky J, Kobayashi M, Kolterman O, Poucher R: A structurally abnormal insulin causing human diabetes. *Nature* 281:122–125, 1979
60. Haneda M, Chan SJ, Kwok SCM, Rubenstein AH, Steiner DF: Studies on mutant human insulin genes: identification and sequence analysis of a gene encoding [Ser$^{B24}$]insulin. *Proc Natl Acad Sci USA* 80:6366–6370, 1983
61. Given BD, Mako ME, Tager HS, Baldwin D, Markese J, Rubenstein AH, Olefsky J, Kobayashi M, Kolterman O, Poucher R: Diabetes due to secretion of an abnormal insulin. *N Engl J Med* 302:129–135, 1980
62. Kahn CR, Flier JS, Bar RS, Archer JA, Gorden P, Martin MM, Roth J: The syndromes of insulin resistance and acanthosis nigricans. *N Engl J Med* 294:739–745, 1976
63. Taylor SI: Lilly Lecture: molecular mechanisms of insulin resistance: lessons from patients with mutations in the insulin-receptor gene. *Diabetes* 41: 1473–1490, 1992
64. Ciaraldi TP, El-Roeiy A, Madar Z, Reichart D, Olefsky JM, Yen SSC: Cellular mechanisms of insulin resistance in polycystic ovarian syndrome. *J Clin Endocrinol Metab* 75:577–583, 1992
65. Dunaif A, Segal KR, Shelley DR, Green G, Dobrjansky A, Licholai T: Evidence for distinctive and intrinsic defects in insulin action in polycystic ovary syndrome. *Diabetes* 41:1257–1266, 1992
66. Schwartz SS, Zeidler A, Moossa AR, Kuku SF, Rubenstein AH: A prospective study of glucose tolerance, insulin, C-peptide, and glucagon responses in patients with pancreatic carcinoma. *Digestive Dis* 23:1107–1114, 1978
67. Cersosimo E, Pister PWT, Pesola G, McDermott K, Bajorunas D, Brennan MF: Insulin secretion and action in patients with pancreatic cancer. *Cancer* 67:486–493, 1991
68. Larsen S, Hilsted J, Tronier B, Worning H: Metabolic control and B cell function in patients with insulin-dependent diabetes mellitus secondary to chronic pancreatitis. *Metabolism* 36:964–967, 1987
69. Phelps G, Chapman I, Hall P, Braund W, Mackinnon M: Prevalence of genetic haemochromatosis among diabetic patients. *Lancet* ii:233–234, 1989
70. Handwerger S, Roth J, Gorden P, Di Sant' Agnese P, Carpenter DF, Peter G: Glucose intolerance in cystic fibrosis. *N Engl J Med* 281:451–461, 1969

71. Yajnik CS, Shelgikar KM, Naik SS, Kanitkar SV, Orskov H, Alberti KGMM, Hockaday TDR: The ketoacidosis-resistance in fibro-calculous-pancreatic-diabetes. *Diabetes Res Clin Pract* 15:149–156, 1992
72. Soffer LJ, Iannaccone A, Gabrilove JL: Cushing's syndrome. *Am J Med* 30:129–146, 1961
73. Jadresic A, Banks LM, Child DF, Diamant L, Doyle FH, Fraser TR, Joplin GF: The acromegaly syndrome. *QJ Med* 202: 189–204, 1982
74. Stenstrom G, Ernest I, Tisell L: Long-term results in 64 patients operated upon for pheochromocytoma. *Acta Med Scan* 223:345–352, 1988
75. Berelowitz M, Eugene HG: Non-insulin dependent diabetes mellitus secondary to other endocrine disorders. In *Diabetes Mellitus*. LeRoith D, Taylor SI, Olefsky JM, Eds. New York, Lippincott-Raven, 1996, p. 496–502
76. Conn JW: Hypertension, the potassium ion and impaired carbohydrate tolerance. *N Engl J Med* 273:1135–1143, 1965
77. Pandit MK, Burke J, Gustafson AB, Minocha A, Peiris AN: Drug-induced disorders of glucose tolerance. *Ann Int Med* 118:529–540, 1993
78. O'Byrne S, Feely J: Effects of drugs on glucose tolerance in non-insulin-dependent diabetes (parts I and II). *Drugs* 40: 203–219, 1990
79. Bouchard P, Sai P, Reach G, Caubarrere I, Ganeval D, Assan R: Diabetes mellitus following pentamidine-induced hypoglycemia in humans. *Diabetes* 31:40–45, 1982
80. Assan R, Perronne C, Assan D, Chotard L, Mayaud C, Matheron S, Zucman D: Pentamidine-induced derangements of glucose homeostasis. *Diabetes Care* 18: 47–55, 1995
81. Gallanosa AG, Spyker DA, Curnow RT: Diabetes mellitus associated with autonomic and peripheral neuropathy after Vacor poisoning: a review. *Clin Toxicol* 18:441–449, 1981
82. Esposti MD, Ngo A, Myers MA: Inhibition of mitochondrial complex I may account for IDDM induced by intoxication with rodenticide Vacor. *Diabetes* 45: 1531–1534, 1996
83. Fabris P, Betterle C, Floreani A, Greggio NA, de Lazzari F, Naccarato R, Chiaramonte M: Development of type 1 diabetes mellitus during interferon alpha therapy for chronic HCV hepatitis. *Lancet* 340:548, 1992
84. Shiba T, Morino Y, Tagawa K, Fujino H, Unuma T: Onset of diabetes with high titer anti-GAD antibody after IFN therapy for chronic hepatitis. *Diabetes Res Clin Pract* 30:237–241, 1996
85. Forrest, JA, Menser MA, Burgess JA: High frequency of diabetes mellitus in young patients with congenital rubella; *Lancet* ii:332–334, 1971
86. King ML, Bidwell D, Shaikh A, Voller A, Banatvala JE: Coxsackie-B-virus-specific IgM responses in children with insulin-dependent (juvenile-onset; type I) diabetes mellitus. *Lancet* i:1397–1399, 1983
87. Karjalainen J, Knip M, Hyoty H, Linikki P, Ilonen J, Kaar M-L, Akerblom HK: Relationship between serum insulin antibodies, islet cell antibodies and Coxsackie-B4 and mumps virus-specific antibodies at the clinical manifestation of type I (insulin-dependent) diabetes. *Diabetologia* 31:146–152, 1988
88. Pak CY, Eun H, McArthur RG, Yoon J: Association of cytomegalovirus-infection with autoimmune type 1 diabetes. *Lancet* ii:1–4, 1988
89. Solimena M, Folli, Aparisi R, Pozza G, De Camilli P: Autoantibodies to GABA-nergic neurons and pancreatic beta cells in stiffman syndrome. *N Engl J Med* 41: 347–353, 1992
90. Rimoin DL: Genetic syndromes associated with glucose intolerance. In *The Genetics of Diabetes Mellitus*. Berlin, Springer-Verlag, 1976
91. Barrett TG, Bundey SE, Macleod AF: Neurodegeneration and diabetes: UK nationwide study of Wolfram (DIDMOAD) syndrome. *Lancet* 346:1458–1463, 1995
92. Metzger BE, Organizing Committee: Summary and recommendations of the Third International Workshop-Conference on Gestational Diabetes Mellitus. *Diabetes* 40:197–201, 1991
93. Engelgau MM, Herman WH, Smith PJ, German RR, Aubert RE: The epidemiology of diabetes and pregnancy in the U.S., 1988. *Diabetes Care* 18:1029–1033, 1995
94. Coustan DR: Gestational diabetes. In *Diabetes in America*. 2nd ed. Washington, DC, U.S. Govt. Printing Office, 1995 (NIH publ. no. 95–1468), p. 703–717
95. Langer O, Rodriguez DA, Xenakis EMJ, McFarland MB, Berkus MD, Arrendondo F: Intensified versus conventional management of gestational diabetes. *Am J Obstet Gynecol* 170:1036–1047, 1994
96. Magee MS, Walden CE, Benedetti TJ: Influence of diagnostic criteria on the incidence of gestational diabetes and perinatal morbidity. *JAMA* 269:609–615, 1993
97. Cousins L: Obstetric complications. In *Diabetes Mellitus and Pregnancy: Principles and Practice*. 2nd ed. New York, Churchill Livingstone, 1995, p. 455–468
98. O'Sullivan JB, Mahan CM: Criteria for the oral glucose tolerance test in pregnancy. *Diabetes* 13:278, 1964
99. O'Sullivan JB: The Boston Gestational Diabetes Studies: review and perspective. In *Carbohydrate Metabolism in Pregnancy and the Newborn*. Sutherland HW, Stowers JM, Pearson DWM, Eds. London, Springer-Verlag, 1989, p. 187–294
100. O'Sullivan JB: Diabetes after GDM. *Diabetes* 40 (Suppl. 2):131–135, 1991
101. Metzger BE, Cho NH, Roston SM, Radvany R: Prepregnancy weight and antepartum insulin secretion predict glucose tolerance five years after gestational diabetes mellitus. *Diabetes Care* 16:1598–1605, 1993
102. Coustan DR, Carpenter MW, O'Sullivan PS, Carr SR: Gestational diabetes: predictors of subsequent disordered glucose metabolism. *Am J Obstet Gynecol* 168: 1139–1145, 1993
103. Kjos SL, Buchanan TA, Greenspoon JS, Montoro M, Bernstein GS, Mestman JH: Gestational diabetes: the prevalence of glucose intolerance and diabetes mellitus in the first two months postpartum. *Am J Obstet Gynecol* 163:93–98, 1990
104. Diabetes and pregnancy. In *ACOG Technical Bulletin* 200, 1994
105. Carpenter MW, Coustan DR: Criteria for screening tests for gestational diabetes. *Am J Obstet Gynecol* 144:768–773, 1982
106. Sacks DA, Abu-Fadil S, Greenspoon JS: Do the current standards for glucose tolerance testing in pregnancy represent a valid conversion of O'Sullivan's original criteria? *Am J Obstet Gynecol* 161:638–641, 1989
107. Neiger R, Coustan DR: Are the current ACOG glucose tolerance test criteria sensitive enough? *Obstet Gynecol* 78: 1117–1120, 1991
108. Naylor CD, Sermer M, Chen E, Sykora K: Caesarean delivery in relation to birth weight and gestational glucose tolerance. *JAMA* 275:1265–1270, 1996
109. Pettitt DJ, Bennett PH, Hanson RL, Narayan KMV, Knowler WC: Comparison of World Health Organization and National Diabetes Data Group procedures to detect abnormalities of glucose tolerance during pregnancy. *Diabetes Care* 17:1264–1268, 1994
110. Sacks DA, Greenspoon JS, Abu-Fadil S, Henry HM, Wolde-Tsadik G, Yao JF: Toward universal criteria for gestational diabetes: the 75-gram glucose tolerance test in pregnancy. *Am J Obstet Gynecol* 172:607–614, 1995
111. Deerochanawong C, Putiyanum C, Wongsuryrat M, Serirat S, Jinayon P: Comparison of National Diabetes Data Group and World Health Organization criteria for detecting gestational diabetes mellitus. *Diabetologia* 39:1070–1073, 1996

111a. Metzger BE, Coustan DR: Summary and recommendations of the Fourth Interna-

tional Workshop-Conference on Gestational Diabetes Mellitus. *Diabetes Care* 21 (Suppl. 2):B161–B167, 1998
112. Marquette GP, Klein VR, Niebyl JR: Efficacy of screening for gestational diabetes. *Am J Perinatology* 2:7–14, 1985
113. Dietrich ML, Dolnicek TF, Rayburn WR: Gestational diabetes screening in a private, midwestern American population. *Am J Obstet Gynecol* 156:1403–1408, 1987
114. Lucas MJ, Lowe TW, Bowe L, McIntire DD: Class $A_1$ gestational diabetes: a meaningful diagnosis? *Obstet Gynecol* 82:260–265, 1993
115. Charles MA, Fontboune A, Thibult N, Warnet JM, Rosselin GE, Eschwege E: Risk factors for NIDDM in white population: Paris Prospective Study. *Diabetes* 40:796–799, 1991
116. Brunzell JD, Robertson RP, Lerner RL, Hazzard WR, Ensink JW, Bierman EL, Porte D Jr: Relationships between fasting plasma glucose levels and insulin secretion during intravenous glucose tolerance tests. *J Clin Endocrinol Metab* 42:222–229, 1976
117. Fuller JH, Shipley MJ, Rose G, Jarrett RJ, Keen H: Coronary-heart disease risk and impaired glucose tolerance: the Whitehall Study. *Lancet* i:1373–1376, 1980
118. Charles MA, Balkau B, Vauzelle-Kervöeden F, Thibult N, Eschwège E: Revision of diagnostic criteria for diabetes (Letter). *Lancet* 348:1657–1658, 1996
119. Jarrett RJ, Kahn H: Hyperglycemia and diabetes mellitus. *Lancet* ii:1009–1012, 1976
120. Klein R, Comor EB, Blount BA, Wingard DL: Visual impairment and retinopathy in people with normal glucose tolerance, impaired glucose tolerance and newly diagnosed NIDDM. *Diabetes Care* 14:914–918, 1991
121. McCartney P, Keen H, Jarrett RJ: The Bedford Survey: observations on retina and lens of subjects with impaired glucose tolerance and in controls with normal glucose tolerance. *Diabete Metab* 9:303–305, 1983
122. Reaven GM, Olefsky J, Farquhar JW: Does hyperglycemia or hyperinsulinaemia characterize the patient with chemical diabetes? *Lancet* i:1247–1249, 1972
123. Little RR, England JD, Wiedmeyer H-M, McKenzie EM, Pettit DJ, Knowler WC, Goldstein DE: Relationship of glycosylated hemoglobin to oral glucose tolerance: implications for diabetes screening. *Diabetes* 37:60–64, 1988
124. Reaven GM: Role of insulin resistance in human disease. *Diabetes* 37:1595–607, 1988
125. McCance, DR, Hanson RL, Pettitt DJ, Bennett PH, Hadden DR, Knowler WC: Diagnosing diabetes mellitus: do we need new criteria? *Diabetologia* 40:247–255, 1997
126. Knowler, WC: Screening for NIDDM: opportunities for detection, treatment and prevention. *Diabetes Care* 17:445–450, 1994
127. Harris MI, Hadden WC, Knowler WC, Bennett PH: Prevalence of diabetes and impaired glucose tolerance and plasma glucose levels in the U.S. population aged 20–74 yr. *Diabetes* 36:523–534, 1987
128. Stolk RP, Orchard TJ, Grobbee DE: Why use the oral glucose tolerance test? *Diabetes Care* 18:1045–1049; 1995
129. McCance DR, Hanson RL, Charles MA, Jacobsson LTH, Pettitt DJ, Bennett PH, Knowler WC: Comparison of tests for glycated haemoglobin and fasting and two hour plasma glucose concentrations as diagnostic methods for diabetes. *BMJ* 308:1323–1328, 1994
130. Engelgau MM, Thompson TJ, Herman WH, Boyle JP, Aubert RE, Kenny SJ, Badran A, Sous ES, Ali MA: Comparison of fasting and 2-hour glucose and $HbA_{1c}$ levels for diagnosing diabetes: diagnostic criteria and performance revisited. *Diabetes Care* 20:785–791, 1997
131. Jackson CA, Yudkin JS, Forrest RD: A comparison of the relationships of the glucose tolerance test and the glycated haemoglobin assay with diabetic vascular disease in the community: the Islington Diabetes Survey. *Diabetes Res Clin Pract* 17:111–123, 1992
132. Beks PJ, Mackay AJC, de Neeling JND, de Vries H, Bouter LM, Heine RJ: Peripheral arterial disease in relation to glycaemic level in elderly Caucasian population: the Hoorn Study. *Diabetologia* 38:86–96, 1995
133. Mooy JM, Gootenhuis PA, de Vries H, Kostense PJ, Popp-Snijders C, Bouter LM, Heine RJ: Intra-individual variation of glucose, specific insulin and proinsulin concentrations measured by two oral glucose tolerance tests in general Caucasian population: the Hoorn Study. *Diabetologia* 39:298–305, 1996
134. Finch CF, Zimmet PA, Alberti KGMM: Determining diabetes prevalence: a rational basis for the use of fasting plasma glucose concentrations? *Diabet Med* 7:603–610, 1990
135. Peters AL, Davidson MB, Schriger DL, Hasselblad V, the Meta-analysis Research Group on the Diagnosis of Diabetes Using Glycated Hemoglobin Levels 1996: A clinical approach for the diagnosis of diabetes mellitus: an analysis using glycated hemoglobin levels. *JAMA* 276:1246–1252, 1996
136. American Diabetes Association: Tests of glycemia in diabetes (Position Statement). *Diabetes Care* 25 (Suppl. 1):S97–S99, 2002
137. American Diabetes Association: Standards of medical care for patients with diabetes mellitus (Position Statement). *Diabetes Care* 25 (Suppl. 1):S33–S49, 2002
138. Mayrhofer M, Rabin DU, Messenger L, Standl E, Ziegler AG: Value of ICA512 antibodies for prediction and diagnosis of type 1 diabetes. *Exp Clin Endocrinol Diab* 104:228–234, 1996
139. Bingley PJ, Christie MR, Bonifacio E, Bonfanti R, Shattock M, Fonte M-T, Bottazzo G-F, Gale EAM: Combined analyses of autoantibodies improves prediction of IDDM in islet cell antibody-positive relatives. *Diabetes* 43: 1304–1310, 1994
140. Verge CF, Gianani R, Kawasaki E, Chase H, Eisenbarth GS: Prediction of type 1 diabetes in first degree relatives using a combination of insulin, GAD and ICA512bc/ IA-2 autoantibodies. *Diabetes* 45:926–933, 1996
141. Hagopian WA, Sanjeevi CB, Kockum I, Landin-Olsson M, Karlsen AE, Sundkvist G, Dahlquist G, Palmer J, Lernmark A: Glutamate decarboxylase-, insulin-, and islet cell-antibodies and HLA typing to detect diabetes in a general population-based study of Swedish children. *J Clin Invest* 95:1505–1511, 1995
142. Harris MI: Undiagnosed NIDDM: clinical and public health issues. *Diabetes Care* 16:642–652, 1993
143. Klein R: Hyperglycemia and microvascular and macrovascular disease in diabetes. *Diabetes Care* 18:258–268, 1995