# 2 The Classification and Diagnosis of Diabetes Mellitus

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**Key points**

- The classification of diabetes mellitus is based on four main categories: Type 1, Type 2, other specific types, and gestational diabetes mellitus
- Impaired glucose tolerance and impaired fasting glycemia are high-risk states collectively termed "intermediate hyperglycemia"
- Type 2 diabetes is a diagnosis by exclusion and as more specific causes are found these will move out of the type two category into other specific types
- Measurement of glucose continues to be the mainstay of diagnosis. In the symptomatic person a single abnormal value, either casual or fasting, is often enough to confirm the diagnosis. In asymptomatic individuals two abnormal values are required and an oral glucose tolerance test may be needed
- The diagnosis of diabetes can not be excluded by measuring fasting plasma glucose alone
- $HbA_{1c}$ has major advantages over glucose testing in terms of convenience and lack of variability, although it is not adequately quality assured or standardized in many places, and is costly. Nonetheless, it is already recommended in some countries as an alternative diagnostic test. This is likely to become more widespread

## Introduction

Diabetes mellitus is a disease of antiquity (see Chapter 1). A treatment was described in the Ebers papyrus and as long ago as 600 BC two main types were distinguished. Perhaps the most famous description was by Arateus the Cappadocian who talked of the melting down of flesh into urine and of the end being speedy. Over the ensuing centuries sporadic descriptions were noted, with Maimonides in Egypt pointing out its relative rarity. It was attributed to a salt-losing state although the sweetness of the urine had long been known. Undoubtedly, virtually all of these accounts referred to type 1 (T1DM) or late type 2 diabetes (T2DM).

Diabetes was better recognized in the 17th and 18th centuries, with the association with obesity noted in some cases. The obvious breakthrough came in the 17th century with the demonstration of excess glucose in the urine and later also in blood.

The presence of excess ketones was shown in the 19th century. A clear description of the two main types of diabetes appeared at the end of the 19th century, with the distinction being made between that occurring in young people with a short time course before ketoacidosis supervened, and that found in older people who were obese. Over the next decades these became known as juvenile-onset diabetes and maturity-onset diabetes, although it was generally stated that the latter was just a milder form of the disease. Diagnosis now depended on glucose measurement with some using glucose tolerance tests. There were no standard criteria for these initially, although glucose levels were clearly above normal. Diagnosis usually occurred after clinical development of the disease with the combination of symptoms with raised glucose in the blood or glycosuria being diagnostic, together with ketonuria in the juvenile-onset form.

A further breakthrough occurred with the work of Himsworth in 1936. Himsworth's work showed that people with diabetes could be divided into insulin-resistant and insulin-sensitive types, with the former much more common in those with the maturity-onset variety [1]. The next milestone was the development of the radioimmunoassay for insulin which allowed the unequivocal demonstration of insulin deficiency, or indeed absence, in those with juvenile-onset diabetes while levels were apparently normal or raised in those with maturity-onset diabetes.

At that time, diabetes was still considered to be a relatively uncommon disorder occurring predominantly in Europids. The World Health Organization (WHO) began to take note and held its first Expert Committee meeting in 1964 [2]. The real breakthrough, however, in terms of diagnosis and classification came in 1980 with the publication of the second Expert Committee report [3] shortly after the report from the National Diabetes Data Group (NDDG) in the USA in 1979 [4]. These events form the starting point for the diagnostic criteria and classification used today.

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## Definitions

Diabetes mellitus is a metabolic disorder of multiple etiologies. It is characterized by chronic hyperglycemia together with disturbances of carbohydrate, fat and protein metabolism resulting from defects of insulin secretion, insulin action or both [6]. The relative contribution of these varies between different types of diabetes. These are associated with the development of the specific microvascular complications of retinopathy, which can lead to blindness, nephropathy with potential renal failure, and neuropathy. The latter carries the risk of foot ulcers and amputation and also autonomic nerve dysfunction. Diabetes is also associated with an increased risk of macrovascular disease.

The characteristic clinical presentation is with thirst, polyuria, blurring of vision and weight loss. This can lead to ketoacidosis or hyperosmolar non-ketotic coma (see Chapter 19). Often, symptoms are mild or absent and mild hyperglycemia can persist for years with tissue damage developing, although the person may be totally asymptomatic.

## Classification

There was awareness of different grades of severity of diabetes for many centuries; however, the possibility that there were two distinct types only emerged at the beginning of the 20th century. Even then there was no real clue to distinct etiologies. In the 1930s, Himsworth suggested that there were two phenotypes. The first real attempt to classify diabetes came with the first WHO Expert Committee on Diabetes Mellitus which felt that the only reliable classification was by age of onset and divided diabetes into juvenile-onset and maturity-onset disease [2]. There were many other phenotypes in vogue at that time including brittle, gestational, pancreatic, endocrine, insulin-resistant and iatrogenic diabetes, but for most cases there was no clear indication of etiology. Clarity began to emerge in the 1970s with the discovery of the human leukocyte antigen (HLA) genotypes common in juvenile-onset diabetes and the discovery of islet call antibodies. This gave a clear indication that younger patients with diabetes, all of whom required insulin therapy, had an autoimmune disorder.

The beginning of the modern era came with the second WHO Expert Committee [3] which reviewed and modified the revised classification published by the National Diabetes Data Group [4]. This proposed two main classes of diabetes: insulin-dependent diabetes mellitus (IDDM; type 1) and non-insulin-dependent diabetes (NIDDM; type 2) together with "other types" and gestational diabetes. There were also two risk classes: previous abnormality of glucose intolerance (PrevAGT) and potential abnormality of glucose tolerance (PotAGT) which replaced previous types known as pre-diabetes or potential diabetes.

The 1980 classification was revised further in 1985 [5] and reverted to clinical descriptions with retention of IDDM and NIDDM but omission of type 1 and type 2. Malnutrition-related diabetes mellitus was also introduced in recognition of a different phenotype found particularly in Asia and sub-Saharan Africa. Impaired glucose tolerance (IGT) was also introduced as a high risk class.

**Table 2.1** Etiologic classification of disorders of glycemia. Adapted from World Health Organization [6].

| |
|---|
| Type 1 diabetes (β-cell destruction) |
| • Autoimmune |
| • Idiopathic |
| Type 2 diabetes (insulin resistance with insulin hyposecretion) |
| Other specific types (Table 2.2) |
| Gestational diabetes (includes former categories of gestational IGT and gestational diabetes) |

IGT, impaired glucose tolerance.

Based on increasing knowledge, WHO revisited the classification in 1999 [6] as did the American Diabetes Association (ADA) [7]. It was recognized that the terms IDDM and NIDDM, although superficially appealing, were often confusing and unhelpful – as in patients with insulin-treated T2DM. The new classification attempted to encompass both etiology and clinical stages of the disease as well as being useful clinically. This was based on the suggestion of Kuzuya and Matsuda [8]. This acknowledges that diabetes may progress through several clinical stages (e.g. from normoglycemia to ketoacidosis) while having a single etiologic process such as autoimmune attack on the β-cells. Similarly, it is possible that someone with T2DM can move from insulin requirement to no pharmaceutical intervention through modification of lifestyle. The main classes are T1DM, T2DM, other specific types and gestational diabetes (Table 2.1). It should be noted that T2DM is largely categorization by exclusion. As new causes are discovered so they will be included under "other specific types" as has occurred for maturity-onset diabetes of the young (MODY).

The classification was revisited by WHO in 2006, but no further modification was introduced, and it will be examined again in 2010 when at most minor amendments will be made. IGT was removed from the formal classification of types of diabetes – logically, as it is not diabetes – but was retained as a risk state. Impaired fasting glycemia (IFG) was introduced as another risk state. This was particularly important in many countries where glucose tolerance tests are rarely performed in practice outside of pregnancy so that IGT was not diagnosed and IFG, although not strictly equivalent, has been used as an easily obtained risk marker.

### Type 1 diabetes

T1DM is primarily caused by β-cell destruction although some insulin resistance is also present (see Chapter 9). After the initial stages, insulin is required for survival. In Europids >90% show evidence of autoimmunity with anti-glutamine acid decarboxylase (anti-GAD), anti-insulin and/or islet cell antibodies detectable. It shows strong association with specific alleles at the DQ-A

and DQ-B loci of the HLA complex [9]. Not all subjects with the clinical characteristics of T1DM show these associations with autoimmunity although they are ketosis-prone, non-obese and generally under the age of 30 years. In non-Europid populations, up to 80% may show no measurable autoantibodies [10]; these are referred to as having idiopathic T1DM. As with autoimmune diabetes, however, there is clear loss of β-cell function as measured by low or absent C-peptide secretion. Diabetes occurring before the age of 6 months is most likely to be monogenic neonatal diabetes rather than autoimmune T1DM (see Chapter 15) [11].

In addition to the typically young people with acute-onset T1DM, there is an older group with slower onset disease. They may present in middle age with apparent T2DM but have evidence of autoimmunity as assessed by GAD antibody measurements and ultimately become insulin-dependent. This is referred to as latent autoimmune diabetes of adults (LADA) [12].

## Type 2 diabetes

By far the majority of people with diabetes worldwide have T2DM. This is characterized by insulin resistance with relative insulin deficiency (i.e. patients secrete insulin, but not enough to overcome the insulin resistance) (see Chapters 10 and 11). Typically, they do not require insulin to survive but often will eventually need insulin to maintain reasonable glycemia control, often after many years.

The precise molecular mechanisms underlying T2DM are not known. Major efforts have been made to discover underlying genetic abnormalities but with only modest success (see Chapter 12). The most promising to be date has been TCF7L2 [13] which may have a role in insulin secretion but this does not explain diabetes susceptibility in the majority of subjects. What is clear is that T2DM is closely associated with obesity and physical inactivity, and the westernization of lifestyles. The dramatic increase in T2DM over the past two decades has been closely paralleled by the rise in obesity worldwide. Both obesity, particularly visceral adiposity, and physical inactivity cause insulin resistance which will result in diabetes in those with only a small capacity to increase insulin secretion. The incidence of T2DM also increases with age, which may be related to decrease in exercise and muscle mass; however, as the incidence increases so T2DM is being found at younger ages and it is now not uncommon in adolescence in many ethnic groups.

T2DM occurs in families so that those with a first-degree relative with diabetes have an almost 50% life-time risk. There is also marked variation between different ethnic groups. Thus, those of Polynesian, Micronesian, South Asian, sub-Saharan African, Arabian and Native American origin are much more prone to develop diabetes than Europids.

T2DM is a diagnosis by exclusion and the prevalence may fall as causes are identified, but this is likely to be a slow process.

## Other specific types of diabetes

Diabetes occurs both as a result of specific genetic defects in insulin secretion and action and in a range of other conditions (Table 2.2).

**Table 2.2** Other specific types of diabetes. Adapted from World Health Organization [6].

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|---|
| **Genetic defects of β-cell function** |
| Chromosome 20, HNF4α (MODY 1) |
| Chromosome 7, glucokinase (MODY 2) |
| Chromosome 12, HNF1α (MODY 3) |
| Chromosome 13, IPF-1 (MODY 4) |
| Mitochondrial DNA 3243 mutation |
| Others |
| **Genetic defects in insulin action** |
| Type A insulin resistance |
| Leprechaunism |
| Rabson–Mendenhall syndrome |
| Lipoatrophic diabetes |
| Others |
| **Disease of the endocrine pancreas** |
| Fibrocalculous pancreatopathy |
| Pancreatitis (particularly chronic) |
| Trauma/pancreatectomy |
| Neoplasia |
| Cystic fibrosis |
| Hemachromatosis |
| Others |
| **Endocrinopathies** |
| Cushing syndrome |
| Acromegaly |
| Pheochromocytoma |
| Glucagonoma |
| Somatostatinoma |
| Others |
| **Drug- or chemical-induced** |
| Nicotinic acid |
| Glucocorticoids |
| Thyroxine/triiodothyronine |
| α-Adrenergic agonists |
| Thiazides |
| Pentamidine |
| Vacor |
| Others |
| **Infections** |
| Congenital rubella |
| Cytomegalovirus |
| Mumps |
| Others |
| **Uncommon forms of immune-mediated disease** |
| Insulin autoimmune syndrome |
| Anti-insulin receptor antibodies |
| "Stiff man" syndrome |
| Others |
| **Other genetic syndromes** |
| (see Table 2.3) |

The best known of the defects in insulin secretion are the MODY family, which are a group of autosomal-dominant inherited disorders where there is hyperglycemia at an early age, generally of a mild nature. The most common concerns a mutation in the HNF-1α gene on chromosome 12 (MODY 3) while another is caused by mutations in the glucokinase gene on chromosome 7p. These account for a small number of people with diabetes but are important in determining therapeutic approaches.

The association of diabetes with defects in insulin action has long been known, particularly in type A insulin resistance, leprechaunism and lipoatrophic diabetes. Not surprisingly, diseases of the exocrine pancreas often cause diabetes through destruction of the islets. Pancreatitis secondary to alcohol is probably the most common of these (see Chapter 18). Hemochromatosis and cystic fibrosis also commonly result in diabetes.

Fibrocalculous pancreatitis is also included in this category. Originally, this was part of malnutrition-related diabetes mellitus where there were two proposed variants: one associated with cassava consumption in malnourished people but without evidence of calculi, while the other was found after tropical pancreatitis and presented with fibrocalculous disease. The latter is akin to the diabetes found with other forms of chronic pancreatitis. In 1999 it was felt that this latter form would fit into the category of "other specific types" and that more evidence was needed before a specific malnutrition-related diabetes category could be included.

Several endocrinopathies are associated with diabetes: Cushing syndrome, acromegaly, pheochromocytoma, glucagonoma and hyperthyroidism (see Chapter 17). In general, the diabetes will disappear if the endocrinopathy is treated. Many drugs and chemicals cause diabetes (Table 2.2, Chapter 16). Some of these cause β-cell destruction but others will cause diabetes by increasing insulin resistance in susceptible individuals.

Infections are also associated with the development of diabetes; classically, mumps, congenital rubella, coxsackie B and cytomegalovirus are the main ones implicated. Many genetic syndromes are also associated with diabetes (Table 2.4).

There are other types of diabetes that do not fit conveniently into any of the current classes. These include "Flatbush" diabetes found in Afro-Americans [14] and so-called ketosis-prone T2DM found in Africans in sub-Saharan Africa [15]. These are both characterized by periods of ketosis with absolute insulin dependence and other times when the diabetes can be controlled by diet alone.

## Gestational diabetes mellitus

Gestational diabetes mellitus (GDM) is hyperglycemia first detected during pregnancy (see Chapter 53). This is distinct from women with diabetes undergoing pregnancy, who have diabetes in pregnancy rather than gestational diabetes. Plasma glucose levels, both fasting and post-prandial, are lower than normal in early pregnancy so that raised levels at this stage are almost certainly caused by previously undetected T2DM. Screening for GDM is generally undertaken at around 28 weeks (see below for diagnostic criteria). There is significant morbidity associated with GDM including intrauterine fetal death, congenital malformations, neonatal hypoglycemia, jaundice, prematurity and macrosomia. Risk factors for GDM include certain ethnic groups, those with previous GDM or abnormalities of glucose tolerance, age, obesity and previous large babies.

## Risk states

Prior to the 1979 and 1980 reports, the state of "borderline" diabetes had been recognized for cases where there was uncertainty about the diagnosis of diabetes but where plasma glucose was above accepted normal levels. This was formalized by the NDDG and WHO [3,4] as IGT, a higher than normal plasma

**Table 2.3** Other genetic syndromes associated with diabetes. Adapted from World Health Organization [6].

| |
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| Down syndrome |
| Friedreich ataxia |
| Huntington chorea |
| Klinefelter syndrome |
| Lawrence–Moon–Biedl syndrome |
| Myotonic dystrophy |
| Porphyria |
| Prader–Willi syndrome |
| Turner syndrome |
| Wolfram syndrome |
| Others |

**Table 2.4** World Health Organization (WHO) recommended criteria for the diagnosis of diabetes and intermediate hyperglycemia.

| |
|---|
| **Diabetes** |
| Fasting plasma glucose ≥7.0 mmol/L (126 mg/dL) |
| and/or |
| 2-hour post-glucose load ≥11.1 mmol/L (200 mg/dL) |
| plasma glucose |
| **Impaired glucose tolerance** |
| Fasting plasma glucose <7.0 mmol/L (126 mg/dL) |
| and |
| 2-hour post-glucose load |
| plasma glucose ≥7.8 and <11.1 mmol/L (140 and 200 mg/dL) |
| **Impaired fasting glycemia** |
| Fasting plasma glucose 6.1–6.9 mmol/L (110–125 mg/dL) |
| and (if measured) |
| 2-hour post-glucose load <7.8 mmol/L (140 mg/dL) |
| plasma glucose |

NB. All values refer to venous plasma glucose. Capillary plasma glucose values would be the same fasting but 1 mmol/L (18 mg/dL) higher than venous levels after the glucose load. The glucose load is 75 g anhydrous glucose.

glucose 2 hours after a glucose load but below the diagnostic cutoff for diabetes. Later, both the ADA and WHO introduced the concept of IFG as a fasting plasma glucose above normal but below the diabetes diagnostic level [6,7]. Both IFG and IGT are associated with a two- to threefold increased risk of developing diabetes, while IGT is also a cardiovascular risk marker. IFG was welcomed as it could indicate an at-risk individual without the need to perform a glucose tolerance test. Collectively, IFG and IGT became known as "pre-diabetes" – a misleading term as not everyone with pre-diabetes develops diabetes, and it diminishes the importance of other risk markers such as family history. The term "intermediate hyperglycemia" is preferred by WHO [16]. IGT and IFG are more likely in older people, those who are obese, people from particular high risk ethnic groups and those with cardiovascular disease or other features of the metabolic syndrome, such as dyslipidemia, hypertension or visceral adiposity.

## Diagnostic criteria

The diagnosis of diabetes mellitus has lifelong implications for the individual. Thus, both the clinician, and person tested, must have full confidence in the diagnosis. In the symptomatic individual this is easier but in asymptomatic people once an abnormal test has been found it must be confirmed by a further test. This is increasingly important as screening programs spread and also because 30–50% of people with T2DM are asymptomatic and unaware that they have the disorder.

### Clinical diagnosis of diabetes in symptomatic individuals

The search for diabetes in an individual is often driven by the presence of characteristic symptoms such as thirst, polyuria, weight loss, recurrent infections and, in more severe cases, precoma. In such individuals, a single elevated casual plasma glucose value is sufficient to confirm the diagnosis. A definite diagnosis can be assumed if the venous plasma glucose level is greater than 11.1 mmol/L (200 mg/dL) or 12.2 mmol/L (220 mg/dL) in capillary plasma [5]. WHO describes values of 5.0–11.0 mmol/L as uncertain. Further testing is then required as described below.

### Diagnostic tests for diabetes

A raised blood glucose has been the hallmark of diabetes mellitus for over 100 years. The oral glucose tolerance test (OGTT) was developed in the early years of the 19th century but only came into common use as methods for measuring blood glucose became easier. When the first WHO Expert Committee on Diabetes reviewed diagnostic tests [2] they first of all stated that glycosuria was an unsatisfactory test and that neither the presence of glycosuria nor its absence could rule in or rule out diabetes. They also commented on the wide range of glucose tolerance tests available at the time and recommended strongly that only the 50-g or the 100-g OGTT should be used. They suggested that a fasting venous blood glucose level over 130 mg/dL (7.2 mmol/L) indicated the probability of diabetes. This was for whole blood so that in terms of plasma this would equate to about 150 mg/dL (8.3 mmol/L); however, at that time, most blood glucose chemical tests in use overestimated true glucose by at least 20 mg/dL (1.1 mmol/L). They placed most reliance on the OGTT. They examined both values at 1 and at 2 hours after the glucose load but decided that the 2-hour value on its own was adequate – and this was the key diagnostic test suggested. The value selected was 130 mg/dL (7.2 mmol/L) for venous whole blood and that was to be applied regardless of whether the 50-g or the 100-g glucose load was given. They also introduced the important concept of "borderline" diabetes – the forerunner of IGT – where values were to be above normal but less than those diagnostic for diabetes: 110 mg/dL (6.1 mmol/L) to 129 mg/dL (7.2 mmol/L) for venous whole blood 2 hours after the glucose load.

One further important comment is the need for people to be prepared for the OGTT with at least 250 g carbohydrate consumed for 3 days before the test. This still applies and is rarely adhered to, which may explain the large number of older people with normal fasting glucose but elevated 2-hour values. Many of these could well have "starvation" diabetes rather than genuine diabetes.

#### The modern era

The big change and rationalization came in 1979 and 1980 with the work of NDDG and WHO [3,4]. They reviewed all available data and concluded that a 75-g load would be appropriate and that this should be consumed in 300 mL water over 5 minutes. They based the diagnostic levels for fasting and 2-hour values largely on bimodality observations in high prevalence groups such as the Pima Indians and on some observations of risk for retinopathy. Fasting and 2-hour venous plasma levels of 140 mg/dL (7.8 mmol/L) and 200 mg/dL (11.1 mmol/L) were recommended by NDDG and these were – somewhat unfortunately – rounded up to 8 mmol/L and 11 mmol/L by the WHO Committee. IGT was defined as a fasting venous plasma value <8 mmol/L with a 2-hour value of 8–11 mmol/L. Confusion was rife and a further evaluation took place in 1985 [5] when the WHO group adjusted their values to match the NDDG values precisely.

The next big change occurred in 1997 and 1999 with the publication of the ADA and the new WHO report. This time a considerable amount of data were available to look at risk of retinopathy at different glucose levels. The data were cross-sectional but reasonable agreement was shown between studies of Egyptians, US citizens from NHANES III and Pima Indians (for review see Expert Committee on the Diagnosis and Classification of Diabetes Mellitus [7]). Although there was some tolerance on the precise values, the existing 2-hour cut point of 11.1 mmol/L (200 mg/dL) seemed reasonable but the fasting value was lowered to 7.0 mmol/L (126 mg/dL; Table 2.4). At the same time, the concept of IFG was introduced. This was equivalent to IGT but for the fasting state and was meant to indicate a risk state for diabetes. The values chosen were 6.1–6.9 mmol/L (110–125 mg/dL).

There was one major difference between the ADA and WHO proposals. ADA recommended that a fasting glucose alone could be used for diagnostic purposes and that an OGTT was unnecessary. Similarly, the implication was that fasting glucose could be used as a screening test to identify people at risk without requiring a glucose tolerance test. This was not agreed by the WHO group who continued to promote the use of the OGTT where necessary. Part of the reason is that a considerable number of people with diabetes by the 2-hour value have normal or IFG values when fasting.

The final changes came in 2003 when a new ADA group recommended lowering the threshold for IFG to 100 mg/dL (5.6 mmol/L) which was considered by WHO in 2006 but not supported [17].

## Problems with glucose tests

Measurement of glucose has been the cornerstone and bedrock of diabetes diagnosis for the last 100 years; however, it does have problems. Initially, the assays measured reducing sugars and were not specific. Enzyme assays have largely negated this problem. Accuracy and precision are not problems in well-run laboratories with appropriate quality assurance in place but the advent of glucose meters has caused problems. They are efficient if carefully used, properly controlled and calibrated but the coefficient of variation can often be as high as 20% in field use, making them unsuitable for diagnostic purposes. There are other problems: unless blood is separated immediately after withdrawal from the subject there is a steady loss of glucose even when fluoride or other preservatives are present. This can range from 5 to 20%.

There are also potential problems with the subject tested. Fasting glucose is reasonably reproducible but can be influenced by drugs or coexisting conditions, or the patient may not have fasted appropriately. The OGTT is notoriously variable from day to day within the same individual and is unreliable when they are close to the threshold for diagnosis. It has long been deemed the gold standard but this is more by common usage and because there was no alternative. This has become more important as more screening programs take place and people with asymptomatic diabetes are sought.

## Use of $HbA_{1c}$ as a diagnostic test for diabetes

The introduction of $HbA_{1c}$ as a means to test glycemic control has had an enormous impact on patient care. It has been proposed many times that it could prove a useful means of diagnosing diabetes as it requires neither fasting nor an OGTT. It also represents glycemic status over weeks and gives real certainty that a person is indeed hyperglycemic. It is also subject to fewer errors within an individual patient although it can obviously be affected by conditions such as anemias and hemoglobinopathies. The arguments against, which were reaffirmed by WHO in 2006 and ADA in 2003, were that the test was not sufficiently standardized, the quality of assays was variable, the test is expensive and it is not available at all in many parts of the world.

Recently, the situation has changed. There is now an international standard that is coming into widespread use and assays are reliable and show only small variation within and between assays in good laboratories. In the USA, the situation has been helped by the National Glycohemoglobin Standardization Program which has promoted standardized assays based on data from the Diabetes Control and Complications Trial. Several other countries also have standardized programs in place.

A groundswell of support has appeared suggesting that it would indeed be a useful addition to the diagnostic armamentarium for diabetes. Several authors have suggested its use in addition to fasting glucose [18]. In particular, an Expert Committee led by the ADA has endorsed the use of $HbA_{1c}$ as a new means of diagnosing diabetes and identifying those at high risk of developing the disorder [19]. One problem concerns the appropriate diagnostic level at which to diagnose diabetes. Many suggestions have been made but that proposed by the Expert Committee [18] of 6.5% (47.5 mmol/mol) is gaining acceptance. This is based primarily on three cross-sectional studies that looked at fasting glucose, 2-hour glucose and $HbA_{1c}$ in relation to retinopathy [7,20,21]. These were the same studies that were used to confirm the diagnostic glucose levels, fasting and after a glucose load. This has been supported by a recent analysis of 13 studies including the earlier three which showed that moderate retinopathy was virtually never found at levels below 6.5% (<47.5 mmol/mol) [22]. One problem is that the methods to detect retinopathy are much more sensitive now than previously and recent studies show background retinopathy occurs in 10% of normoglycemic individuals [23]. It is thus probably wise to use moderate retinopathy to determine cutoff diagnostic values. It has also been suggested that $HbA_{1c}$ levels of 6.0–6.4% (42–47 mmol/mol) or 5.7–6.4% (39–47 mmol/mol) could be used to indicate those at high risk – similar to the use of IGT and IFG.

It seems likely that $HbA_{1c}$ will be accepted for use as a diagnostic test. This should only be done in countries where stringent quality assurance and standardization against international standards are possible. It is also unsuitable in pregnancy. A new WHO Expert Committee has met to consider the use of $HbA_{1c}$ but has not yet reported. Nevertheless, there are still various concerns about the use of $HbA_{1c}$. It is likely that some different individuals will be identified by $HbA_{1c}$ and glucose. There is also the likelihood that prevalences of diabetes will be different. It is assumed by many that the glucose derived data are correct but the 2-hour glucose is a somewhat tarnished gold standard. It is indeed possible that $HbA_{1c}$ will give more accurate diagnosis as it reflects a longer period of hyperglycemia rather than a single point in time and it is not subject to the same analytical and preanalytical problems as glucose.

In most places glucose – casual, fasting and after a glucose load – will continue to be used routinely for the diagnosis of diabetes; in some countries (e.g. USA, Australia, Japan and Northern European countries), however, $HbA_{1c}$ is likely to be the preferred test in the near future. This has indeed now been recommended by the ADA [24].

### Gestational diabetes mellitus

Two different tests are widely used for the diagnosis of GDM. WHO recommends that the normal 75-g glucose load be given after an overnight fast and that those with either IGT or diabetes by non-pregnant criteria are deemed to have GDM [6].

In the USA, a two-step procedure is employed. First, a 50-g glucose load is given. If the 1-hour venous plasma glucose is ≥140 mg/dL (7.8 mmol/L) then the patient returns for a further test using either a 100 or 75 g glucose load. The cutoffs for venous plasma glucose are 95 mg/dL (5.3 mmol/L) fasting, 180 mg/dL (10 mmol/L) at 1 hour and 155 mg/dL (8.6 mmol/L) at 2 hours, regardless of which glucose load is used [17]. The WHO protocol is obviously simpler and has gained widespread acceptance; however, new recommendations are expected imminently in light of the results from the recent Hyperglycemia and Pregnancy Outcomes Study [25].

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