The Pathogenesis and Prevention of Diabetes in Adults

Genes, autoimmunity, and demography

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HOW MANY FACES HAS DIABETES IN ADULTS?— Life would be much easier for researchers and clinicians if there were only one type of diabetes. The reality, however, is that diabetes is not one disease. From the most simple viewpoint, there are two major forms, insulin-dependent diabetes mellitus (IDDM), or type I diabetes, and non-insulin-dependent diabetes mellitus (NIDDM), or type II diabetes (1,2). Both forms are heterogenous, particularly NIDDM, and in addition, there are several less important forms from a numerical perspective (1). Controversy abounds on the current classification of diabetes, and while this may not be a major problem in children, it certainly presents a major challenge for researchers and clinicians in the diagnosis of diabetes in adults, particularly in young adults (3).

IDDM

IDDM is relatively easy to explain and diagnose. It is a relatively discrete disorder and has an autoimmune basis, and there is evidence of genetic susceptibility interacting with as yet unknown environmental agents (4). Viruses have been implicated in some instances, and molecular mimicry between the PC-2 protein of the coxsackievirus and glutamic acid decarboxylase (GAD) is a possible initiator of the events that lead to pancreatic β-cell destruction (4). An alternative hypothesis proposed by Nerup et al. (5) is that a viral infection or some other environmental insult generates cytokines and other inflammatory mediators that ultimately destroy the β-cells. It is plausible that β-cell antigens might be chemically modified (e.g., dimerization or some other structural change) by superoxide anions that result from this process, thus rendering them antigenic.

IDDM occurs at all ages (6), and the clinical presentation can vary with age (7,8). It generally has a classical dramatic clinical and biochemical presentation, especially in children, and failure to treat immediately with insulin can be life-threatening (2). Usually, the onset is explosive, and rapid deterioration occurs unless insulin therapy is introduced immediately. However, in adults, it can masquerade as NIDDM at presentation, with a slow deterioration in metabolic control, and later progress to insulin dependency (7–9).

IDDM is not a rare disease in the elderly, and it may develop at any age. In a recent Danish study from Mølbak et al. (6), the cumulative incidence from the age of 30 years onwards was stable, and they concluded that the lifetime risk of developing IDDM is higher than has previously been recognized. They suggested that the reported substantial differences in IDDM incidence between countries may be related to age at onset rather than lifetime risk.

Currently, there is enormous interest and debate not only in relation to the pathogenesis of IDDM (4,5,10) but also concerning the role of GAD as the putative autoantigen (4,7,11). In addition, the role of the measurement of antibodies to this ubiquitous enzyme in classification and prediction of future IDDM and insulin dependency in both adults and children is under intense investigation (12–14) and will be addressed later in this article.

NIDDM

There is now a global epidemic of NIDDM with a projected morbidity and mortality of enormous magnitude (15–17). It is not as easy to explain or describe NIDDM as it is IDDM (18). The disorder shows heterogeneity in numerous respects (Table 1). In the majority of cases, it is a lifestyle disorder, with the highest prevalence seen in populations that have a heightened genetic susceptibility, and environmental factors associated with lifestyle unmask the disease (19).

A major challenge at present is that our current concept of NIDDM is undergoing a radical change (18). Previously, it was regarded as a relatively dis-

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anti-GAD, GAD autoantibody; CVD, cardiovascular disease; GAD, glutamic acid decarboxylase; GDM, gestational diabetes mellitus; HLA, human leukocyte antigen; IAA, insulin autoantibody; ICA, islet cell antibody; IDDM, insulin-dependent diabetes mellitus; IGT, impaired glucose tolerance; LADA, latent autoimmune diabetes in adults; MODY, maturity-onset diabetes of the young; NIDDM, non-insulin-dependent diabetes mellitus; WHO, World Health Organization; YODM, youth-onset diabetes of maturity.

Table 1—*Facets of the heterogeneity of NIDDM and diabetes in adults*

Genotype
Environmental determinants
Age of onset
Patterns of insulin secretion
Overlap with autoimmune IDDM
Differences in clinical presentation
Differences based on ethnicity
Differences in geographic distribution
Diabetes associated with pregnancy
Associations with other CVD risk factors, e.g., Metabolic Syndrome

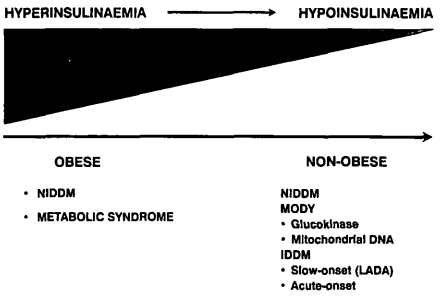

Figure 1—*The spectrum of diabetes in adults in relation to insulin levels and obesity.*

tinct disease entity, but in reality, NIDDM (and its associated hyperglycemia) is just a broad descriptive term and a manifestation of a much broader underlying disorder (15,20). This includes a number of different etiological entities, which are discussed below. It probably also includes Syndrome X (21) or the Metabolic Syndrome (18,20), a cluster of cardiovascular disease (CVD) risk factors, which, apart from hyperglycemia (manifesting as NIDDM or impaired glucose tolerance [IGT]), includes hyperinsulinemia, dyslipidemia, hypertension, and central obesity.

As Diamond (17) has so clearly stated, the lifestyle-related NIDDM arises from the collision of our old hunter-gatherer genes with our new 20th century way of life. The western lifestyle must have unmasked the effects of preexisting genes because the consistent result has been NIDDM within a few decades. This is occurring too quickly to be the result of altered gene frequencies (17), and the significance of this will be discussed in greater detail later.

NIDDM is unmasked by social, behavioral, and environmental risk factors (18,22). The epidemic in many countries, particularly developing and newly industrialized nations, appears to be the result of change in lifestyle from traditional to modern, a process labeled "Coca-colonization" by the late Arthur Koestler (23). Oversecretion of insulin (hyperinsulinemia) and insulin resistance characterize this group of NIDDM subjects, although β-cell failure occurs within the natural history of the disorder (20).

During the last decade, the explosion of research has shown that there are other forms of NIDDM that do not appear to fit the pattern described above, and decreased insulin secretion (hypoinsulinemia) is seen (24,25). Some of this group clearly have cases of NIDDM where hyperinsulinemia was present at an earlier stage; and they have now traversed the Starling Curve of the Pancreas (26,27), perhaps better described as Reaven's Curve after the person who originally described this phenomenon (28), and represent secondary forms of an insulin-secretory defect as the result of β-cell exhaustion. There are other forms that are associated with mutations of the insulin (29), insulin-receptor (30) and glucokinase (25,31) genes and mitochondrial DNA (32), while other cases are actually slow-onset IDDM masquerading as NIDDM (7–9). Thus, diabetes in adults has many faces and covers a broad spectrum of genotypes and phenotypes as illustrated in Fig. 1.

It is for these reasons that the term NIDDM and its usage has inherent weaknesses. It provides a mixed expression of genotype, phenotype, and etiology. Thus, while the classification of IDDM is not too difficult, it has become more difficult to define the limits of NIDDM or diabetes presenting in adulthood (3,18,33). This paper will cover many of these aspects and review the understanding of causes of the main forms of diabetes in adults. This knowledge can help with the development of primary prevention strategies for a disorder that now affects over 100 million people worldwide and is likely to increase to over 230 million people by the year 2010 (16).

Potentially, the problems in classification of diabetes in adults may eventually be simplified by new knowledge and technology in several areas, which include:

- genetic studies relating to the glucokinase, mitochondrial DNA, and other gene mutations (29–32)
- the development of a simple radioimmunoassay for antibodies to GAD (12)
- longitudinal epidemiological studies of the natural history of NIDDM as are being performed in a number of diverse ethnic groups in developing and newly industrialized societies (34)
- studies of the Metabolic Syndrome and its relationship to glucose intolerance and hyperinsulinemia (20)
- studies on the natural history of gestational diabetes mellitus (GDM) (35)
- studies leading to a better understanding of the feast and famine/thrifty genotype (36) and low birth weight/thrifty phenotype (37) scenarios.

This review attempts to provide a broad perspective of these issues and how they can influence current and future efforts to classify, understand the pathogenesis of, and prevent diabetes in adults.

NEW CHALLENGES AND PROGRESS IN THE CLASSIFICATION OF DIABETES IN ADULTS

Attempts at classification: potential flaws

Several international expert groups, including the World Health Organization (WHO) (1,38) and the National Diabetes Data Group (2), have attempted the classification of diabetes. However, the application of these classifications has had se-

vere limitations (3,18,33,39). They have not been capable of providing clear-cut and mutually exclusive differentiation between IDDM and NIDDM, and they have been based on a mixture of etiological and clinical criteria. On the other hand, these initiatives have been important in terms of providing direction for improving classification for epidemiological studies and, to a certain extent, differentiation for clinical research and management.

While the current classification of NIDDM places the emphasis on phenotype and severity rather than genotype and etiology, new discoveries have repeatedly drawn attention to the deficiencies of the latest consensus. For example, the last WHO Study Group to consider the classification they proposed of diabetes met in 1985 (38), and the last decade has seen an explosion in genetic, autoimmune, and demographic findings relating to diabetes in adults. To the credit of the 1985 WHO Study Group, they realized that the classification they proposed was interim and that discovery of further heterogeneity in both etiology and pathogenesis was inevitable (38).

In adult-onset diabetes, and indeed NIDDM, there is a wide spectrum of insulin levels from hyperinsulinemia to hypoinsulinemia and also variations in insulin sensitivity/resistance (20,24,40, 41). The association of hyperinsulinemia with other metabolic abnormalities to form the Metabolic Syndrome or Syndrome X (20,21) provides yet another dimension to the spectrum. Here, the syndrome can be likened to a shopping basket of disorders, and depending on the circumstances, the patient may first be diagnosed with IGT, NIDDM, hypertension, dyslipidemia, or central obesity in isolation, or a combination of two or more, and the other abnormalities may emerge progressively with time.

With this genotypic and phenotypic heterogeneity, it is not surprising that it is still common for the physician to be faced with the diagnostic dilemma in adults with diabetes: which form is present—IDDM or NIDDM? However, before discussing hyperinsulinemic obese NIDDM, which is the predominant type of diabetes in adults, some other forms of adult-onset diabetes will be reviewed.

THE MANY FACES OF DIABETES IN ADULTS: AN ETIOLOGICAL AND EPIDEMIOLOGICAL PERSPECTIVE

IDDM

Acute-onset IDDM. This is the classic form of IDDM seen in young children and adolescents. Genetic susceptibility to the disorder is conveyed by genes associated with the human leukocyte antigen (HLA) DQ region, and autoimmune destruction of the β-cells of the pancreas occurs in susceptible individuals due to as yet unknown environmental agents (4). In the prediabetic phase, antibodies to a number of islet β-cell constituents including islet cell antigen (islet cell antibody [ICA]) (42), insulin (insulin autoantibody [IAA]) (43), and GAD (anti-GAD) (12,13,44) can be detected for up to 10 years before clinical diagnosis. IDDM can have an acute onset even in the elderly, but it may also be insidious in onset (45).

One of the most important discoveries in diabetes in the last 50 years has been the identification of the 64-kDa antigen as the enzyme GAD by Baekkeskov et al. (46) in 1991. It has renewed and stimulated the interest in the search for the autoantigen(s) for IDDM (Table 2). Research in this area had been hampered by available technology as the immunofluorescent assay for ICA and immunoprecipitation assay for 64-kDa antibodies are technically difficult and labor-intensive (47). In addition, both proteins lacked an identity. That situation changed within several years with the discovery that the 64-kDa protein was GAD (46) and the development of a simple radioimmunoprecipitation assay for antibodies to GAD (12,48). This opened the way for more detailed epidemiological research into the possible role of GAD in the etiology of IDDM as well as the use of the anti-GAD assay for the prediction of future IDDM at all ages and insulin dependency in adults presenting with diabetes, including women presenting with GDM (12–14,48,49).

Table 2—*Antigens against which autoantibodies have been found in IDDM subjects*

GAD (64-kDa)
Islet cell antigen, e.g., sulphatide
Insulin
Carboxypeptidase H
37-kDa
38-kDa
Heat shock protein 65
Bovine serum albumin
Others, e.g., islet cell antigens 69, 12, and 512

We have made a number of new and important observations using the assay, most of which have now been confirmed by other groups. The prevalence of anti-GAD at the time of diagnosis of IDDM ranges from 69 to 74% in three independent Australian series from Melbourne (12), Perth (49), and New South Wales (50). Higher rates of positivity are seen in females (49,50).

As the majority of newly diagnosed IDDM patients have been shown to be anti-GAD positive, is it possible to detect anti-GAD in the majority of preclinical IDDM subjects? In fact, this is so, and in Europids from New Zealand at high risk of IDDM, e.g., ICA-positive first-degree relatives, 78% were anti-GAD positive up to 4 years before the clinical onset of diabetes (51). In addition, 100% of those >15 years of age at onset of IDDM were anti-GAD positive compared with 72% with younger age of onset (Table 3). The reverse situation was seen for IAAs (i.e., 57.1 vs. 76%). Thus, the appearance of least anti-GAD and IAA in IDDM can be related to age of onset of diabetes (45,51) as well as sex (50,51), and the frequency of anti-GAD positivity is lower in IDDM subjects from Asian countries (55,56). This suggests that the stimuli to autoimmunity may operate differently at various ages, and they may also be both sex- and ethnicity-related.

Table 3—*Frequency of autoantibodies to GAD (anti-GAD) and insulin (IAA) in prediabetic subjects according to age at eventual time of diagnosis of IDDM*

Autoantigen positive	Age of onset (years)			
	≤10	>10	≤15	>15
n	14	18	25	7
Anti-GAD	71.4 (10)	83.3 (15)	72 (18)	100 (7)
IAA	92.9 (13)	55.6 (10)	76 (19)	57.1 (4)

Data are % (*n*) of patients. Data is stratified for onset of symptomatic IDDM at ≤10 or >10 and ≤15 or >15 years of age. $\chi^2 = 5.42$ ($P = 0.02$) for IAA in ≤10- vs. >10-year-old age-groups.

Latent autoimmune diabetes in adults (LADA)—the new kid on the block. It is usually assumed that an adult presenting with diabetes has NIDDM. It is now clear that IDDM is more common in adults than formerly believed (6,45,52) and, in fact, close to 60% of cases are of patients who develop it after the age of 20 (53). However, it may not present in the classic manner (9,54) so that it is often difficult to classify the 35- to 50-year-old nonobese diabetic patient, and there may be a variety of different etiologies in this group. We have recently become very interested in this category of patients, referred to as LADA (55), a subcategory of diabetes patients who might constitute a significant, but as yet undefined, proportion of diabetes in adults.

We have shown that high anti-GAD levels remain for up to 40 years after diagnosis of IDDM (12), in comparison with ICA and IAA, which fall quite soon after diagnosis (47). The high persistent anti-GAD levels are not the result of diabetic neuropathy (58) as was suggested by Kaufman et al. based on a very small series of patients (59). While the true explanation is unclear, this phenomenon is important because the persistence of the high anti-GAD levels for years after diagnosis makes it a useful marker for future insulin dependency in adults as the diagnosis of diabetes is often delayed (60).

Our recent report, from a study of Finnish women ages 15–35 (13), has shown that high levels of anti-GAD can be detected in 82% of IDDM cases up to 10 years before clinical presentation (Table 4). A positive test for anti-GAD predicted future IDDM with 82.1% sensitivity and 100% specificity. This is a unique, albeit retrospective, study that was possible because of the policy to test and store sera from all pregnancies in Finland since 1983. As registration with the National Public Health Institute of all cases of diabetes in the age group of 15–39 years was instituted in 1992, we were able to trace back sera from the women who were registered. In addition to the results in IDDM, we found that 15% of women with GDM who received insulin during their pregnancy were also anti-GAD positive (13). This was 15 times the frequency in those treated with diet alone.

There also appears to be an ethnic difference in anti-GAD positivity with higher frequency in Europid than in Chinese, Thai, and Korean patients (56,57). We are not certain as to whether this bears any relationship to the fact that IDDM is seen less frequently in Asian ethnic groups (61). We have also studied African-Americans from Flatbush, a borough of New York. In adults presenting with diabetic ketoacidosis (typical of IDDM), yet with a subsequent natural history of diabetes akin to NIDDM and often treated with diet only, anti-GAD negativity was found (62).

We have now reported on LADA in Finland (9), Australia (55), New Zealand (63), U.S. (64), Hong Kong (65) and the People's Republic of China (Pan Xioren, unpublished observations), and Mexico (Gomez Perez, unpublished observations). Similar findings have also been reported in Sweden (14) and Japan (66).

It is with the LADA group that real problems exist in classification between IDDM and NIDDM in adults. From our own studies (3,9,55) and those of others (14,63), it appears that between 10 and 20% of adult-onset diabetic patients have IDDM with autoimmune etiology. Many of these individuals can maintain good metabolic control with diet and oral hypoglycemic therapy for years before they become insulin-dependent (7–9,14). This suggests that the autoimmune process can proceed quite slowly over many years in older patients (54).

The typical patient with LADA is 35 years or older, nonobese, and presenting with what appears to be NIDDM (33). The diabetes is often controlled with diet, but within a short period, from months to a few years, metabolic control fails and oral agents are required, and subsequent progress to insulin-dependency may be

Table 4—*Subjects positive for antibodies to GAD during pregnancies before the diagnosis of diabetes among and in a random sample of young women in Finland*

Type of diabetes	*n*	Anti-GAD positive (%)	Age (years)
IDDM	28	82	30 (23-39)
NIDDM	11	34	32 (22-39)
GDM—insulin-treated	32	15	32 (22-40)
GDM—diet alone	80	1	32 (20-45)
Normal control subjects	100	0	36 (25-45)

For age, data are mean (range).

quite rapid. This form of diabetes was previously labeled as "Type 1 1/2" diabetes (33). Among Europeans, it has been shown to be a late-onset and slowly evolving form of IDDM, since studies have shown the presence of markers of autoimmunity, including ICA, and also the typical high IDDM susceptibility HLA haplotypes (7,67). In several recent reports mentioned above (9,14,55,57,63–65), there is a high frequency of anti-GAD positivity in this category of patients over a wide range of ethnic groups.

These studies confirm that autoimmune IDDM in adults is much more common than formerly believed. As many as 15–20% of all adult diabetics may have LADA, and LADA may constitute as many as 50% of nonobese NIDDM. This figure may be even higher as anti-GAD positivity may not be the sole marker of autoimmunity in this group, given that ~25% do not have antibodies to GAD. Not all those who show the LADA phenotype will necessarily be anti-GAD positive, and other markers of autoimmune diabetes such as ICA, IAA, or 37-kDa (4) may be present when more detailed investigations take place. Other workers have come to a similar conclusion, and Orchard (3) has proposed that up to one-third of NIDDM cases may be what he has labeled as youth-onset diabetes of maturity (YODM). The cases he described were all identified from families having an IDDM proband.

If these findings in LADA are confirmed in other populations, a routine test for anti-GAD becomes a very likely scenario for all adults presenting with NIDDM, particularly the nonobese form. This would provide physicians with important information about the possibility of future insulin dependency. Earlier treatment with insulin may improve their immediate well-being, but also, as is discussed later, this treatment has important implications for post-primary intervention with immunotherapy. There is a chance of preserving remaining β-cell function and thereby lessening the risks of long-term microvascular complications of diabetes (68).

NIDDM with known gene associations

In recent years, there has been an explosion of studies relating to specific gene mutations including glucokinase (31,69), mitochondrial DNA (32), and rarer mutations of insulin (29), insulin receptor (30), and other genes (70–73) in NIDDM. The other genes found in association with NIDDM in certain populations include glycogen synthase (70), β-3 adrenergic receptor (71), and apolipoprotein D (72,73) genes, but in general, these associations are not very strong (71).

Recent reports of maturity-onset diabetes of the young (MODY), a familial condition with autosomal dominant inheritance, have shown that the disorder is frequently linked to the glucokinase gene on chromosome 7 (25,34,69) and to the region of the adenosine deaminase gene on chromosome 20 (74). Numerous mutations (at least 22 thus far) of this gene, in association with MODY, have now been reported (69,71). Glucokinase is a key enzyme in mediating the insulin secretory response to glucose (75), and it has now been shown that many MODY subjects have an insulin secretory defect (25,76).

A single point mutation in the mitochondrial $tRNA^{Leu(UUR)}$ gene has been described in Europid (77,78) and Japanese (79,80) families, and the diabetes phenotype is similar to MODY but is also accompanied by nerve deafness. The same mutation has been linked to a syndrome of mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS). How this one genotype can give rise to such different phenotypes is not yet clear.

The mitochondria are the powerhouse of the cell and are responsible for generating 90% of its energy. Oxidative mitochondrial metabolism plays a very important role in the regulation of insulin production, and there is evidence that there may be a defect of insulin secretion or release rather than β-cell sensing (80), as is the case for glucokinase mutations (25,76). In a landmark paper in 1962, Luft et al. (81) described the first patient with a mitochondrial disorder (Luft disease). This paper was the forerunner to a new branch of medicine. Luft has recently reviewed the subject of mitochondrial medicine, and primary defects in mitochondrial function are now implicated in more than 100 diseases (82). While pointing out that it is unlikely that specific mutations of mtDNA would explain the majority of cases of NIDDM, Luft suggests that an age-related decline in the capacity for oxidative phosphorylation and its consequences could play a significant role in the pathophysiology of this disorder.

These specific gene mutations probably represent only 2–4% of all cases of diabetes presenting in adult life but constitute an important model for the understanding of the genetics of NIDDM and for further research. They may have important implications for future therapeutic and prevention strategies.

NIDDM with as yet unknown genetic basis (genes in waiting)

NIDDM is now an epidemic in many populations in the developing and newly industrialized world (17,19,83), particularly in communities where way of life has changed most dramatically toward a modern lifestyle. In these communities, the previous dependency on hunting and gathering and the later subsistence agriculture was replaced with a modern pattern, characterized by sedentary way of life and a diet of energy-dense processed foods with high levels of saturated fat (19). Numerous epidemiological studies (Fig. 2) have highlighted the spectacularly high susceptibility of Micronesian, Polynesian and certain Melanesian Pacific islanders (84), Australian Aborigines (85,86), North American Indians (61), African-Americans (87) and other black populations (88), Hispanics (89), and migrant Asian Indians and Chinese (88) to NIDDM and lesser degrees of glucose intolerance. The lowest prevalence is seen

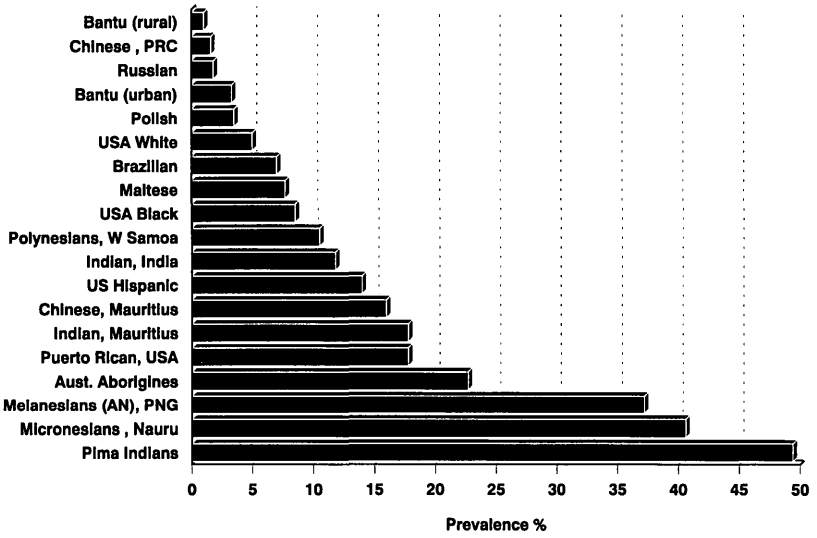

Figure 2—*Prevalence of NIDDM age-standardized to Segi's world population in selected populations aged 30–64 years. Adapted from King et al. (61).*

in rural Bantu in Africa and in the People's Republic of China (61).

A comprehensive review of the age-standardized prevalence of these and other selected populations around the world allowing comparisons has recently been published (61). The highest prevalences (age-standardized for adults 25 and over) are 42.2% in the Pima Indians of Arizona and 39.5% in Nauruans from Micronesia. This latest, and rather spectacular, high age-standardized prevalence of 37.3% has just been reported in urbanized Melanesians of coastal Papua New Guineans (83). This community is the latest to join the high-prevalence group, and the rate of diabetes has doubled in the 14 years between 1977 and 1991. The above-listed rates compare with those of 3% in Australians of European origin (90) and 1.6% in people from People's Republic of China (91).

While NIDDM in Europeans is usually characterized by onset after age 50, in Pacific islanders and the other high-prevalence groups, onset in the 20- to 30-year-old group is common (34,84,92), and the socioeconomic and health impact on society is much greater. The high genetic susceptibility to NIDDM in these former traditional living groups has been attributed to an evolutionary phenomenon, namely the "thrifty genotype" (93), and this is discussed later in this review. It has also been suggested that this phenomenon may explain the association of the Metabolic Syndrome with hyperinsulinemia, glucose intolerance, and the other features of this cluster (20).

The Metabolic Syndrome and NIDDM

A major diagnostic and treatment challenge for the diabetologist is the person with either NIDDM or IGT and/or hypertension, central (upper body) obesity, and dyslipidemia. This group of patients is at very high risk of coronary artery, cerebrovascular, and peripheral vascular disease (18–21) as each one in its own right is an important CVD risk factor, and they also contribute cumulatively to macrovascular disease (94,95).

Often, a patient with one of these conditions, e.g., NIDDM or upper body obesity, will be found to have at least one or more of the other CVD risk components (94,95). This clustering has been labeled the Deadly Quartet (96) or Syndrome X (21), and when the group of risk factors is widened, the Metabolic Syndrome (20) or Insulin Resistance Syndrome (97).

Epidemiological studies confirm that the Metabolic Syndrome does occur commonly in a number of ethnic groups, including Europids (20,21), African-Americans (95,98), Mexican-Americans (99), Asian Indians and Chinese (95), Australian Aborigines (100), and Polynesians and Micronesians (101). The syndrome was first described over 20 years ago and has been attributed to various people including Crepaldi, Vague, Welborn, and Modan (102). However, in 1988, Reaven (21) refocused attention on the cluster and named it Syndrome X. It is much more common to have central obesity as part of the cluster and because Reaven omitted it from his original description, the term Metabolic Syndrome is now favored (102).

Hyperinsulinemia and/or insulin resistance and the Metabolic Syndrome. Hyperinsulinemia is a predictor of both NIDDM and coronary artery disease (20,34,89) in a number of epidemiological studies. Evidence is accumulating that insulin resistance and/or hyperinsulinemia may be the common etiological factor(s) for the components of the Metabolic Syndrome (20,21,97), although there appears to be heterogeneity in this relationship between populations.

Two-thirds of NIDDM patients die from CVD (103). The clustering of NIDDM, a well-documented risk determinant for CVD, with the other risk factors that constitute the Metabolic Syndrome is now well established (20,21,94, 95). This seems the most likely explanation for this increased mortality due to CVD in people with NIDDM. Alone, each component of the cluster conveys increased CVD risk, but as a combination, they become a "time bomb" (16,20). This means that the management of NIDDM should focus not only on tight blood glucose control but also strategies for reduction of the other CVD risk factors (20).

It is now well documented that the other features of the Metabolic Syndrome can be present up to 10 years be-

fore diagnosis of NIDDM (102,104,105). This assumes great importance in relation with our understanding of the etiology of NIDDM and the associated CVD risk as well as the potential to prevent CVD and its morbidity and mortality in persons with glucose intolerance. In other words, the risk and the actual development of CVD starts many years before glucose intolerance manifests, and Haffner et al. (104) have posed the very relevant question: when does the clock actually start ticking for CVD in people with diabetes?

Thus, paradoxically, the prevention of CVD in patients with NIDDM should commence before their diabetes is diagnosed; however, is this really feasible at our current state of knowledge? However, the diagnosis of the Metabolic Syndrome without NIDDM provides a group at very high risk of future NIDDM. Thus, aggressive early management of the syndrome may have a significant impact on both the prevention of NIDDM and CVD mortality (20,39).

GDM—a distinct entity or potpourri?

Another form of diabetes seen in adult life, albeit only in women, is GDM. This term is restricted to pregnant women in whom the onset or first recognition of glucose intolerance occurs during pregnancy and the lifetime risk for IGT and NIDDM is substantially increased (33). What is not clear is what the actual risk of future IDDM is, although it has been estimated that ~2% of women with GDM will progress to IDDM over 15 years (13).

There is clearly heterogeneity within GDM (107), and there is no reason to believe that the etiological spectrum of this disorder is any different from that of adult diabetes in the nonpregnant state as illustrated in Fig. 1. The dilemma for the managing physician is whether GDM could be the initial presentation of NIDDM or IDDM or which type of diabetes the GDM will progress to in the future.

We have been interested in finding the extent of markers of autoimmune IDDM in women with GDM and whether the presence or absence of markers such as ICA and anti-GAD is associated with the need for insulin either during pregnancy or with onset of IDDM in the longer term. In a study of Hispanic and African-American women in New York, McEvoy et al. (107) found that 31% of women with GDM and 48% of those requiring insulin were ICA positive (107). Others have reported between 10 and 38% ICA positivity (108–110). This wide range is most likely due to variation in both sample selection and the assays used in these studies.

In fact, a more recent report by Catalano et al. (111) found 1.6% ICA positivity in women with previous GDM. We found 1.8% frequency of anti-GAD under similar circumstances (N. Beischer, P. Wein, I. Mackay, P.Z., unpublished observations). These data support the concept that there is a subgroup of women with GDM who have a slowly evolving type of IDDM, similar to the slowly progressive IDDM or LADA, or that they have diabetes in pregnancy associated with autoantibodies other than anti-GAD.

Therefore, pregnancy allows the recognition, and perhaps the unmasking, of IDDM earlier than would normally have occurred. Recently, Damm et al. (112) investigated the predictive value of ICA for development of diabetes in women with previous GDM, and 2.9% were ICA positive. Three of these women later developed IDDM (follow-up was ~6 years after the index pregnancy) giving a positive predictive value of 75%. More recently, we found that 5% of GDM patients from Finland were anti-GAD positive (13), and most of the anti-GAD–positive women with GDM (5 of 6) required insulin treatment during their pregnancy. How many of these will develop IDDM in the longer term must still be established, and this aspect is the subject of our ongoing research.

These findings have very important implications for the management and follow-up of women with GDM. Freinkel (113) has highlighted GDM as a unique syndrome, not only because of the opportunity for an aggressive approach for diagnosis and management, but also as a special arena for preventive medicine. If safe immune intervention therapy for IDDM becomes available, a likely scenario is that routine screening of GDM for anti-GAD and/or other markers of autoimmunity would select those women most likely to develop IDDM, and they would be an important target group for primary prevention (39). The possibility remains that in many instances, GDM is not actually caused by the pregnancy, and its discovery is coincidental (114). Therefore, the significance of the detection of autoimmune markers such as ICA and anti-GAD during pregnancy should be further studied.

At the present time, it appears that testing for ICA or anti-GAD detects those most likely to require insulin during the current pregnancy (13), and given evidence that this may protect β-cell function as insulin therapy can induce β-cell rest (4,68), there may already be a rationale for screening all women with GDM with the anti-GAD assay to ensure the optimal management during that pregnancy.

Other types of diabetes

There are other forms of diabetes in adults that are associated with pancreatic disease, endocrine syndromes, drug therapy, malnutrition, and rare genetic syndromes (1,2,33). These together constitute no more than 5% of cases of diabetes in adults.

Malnutrition-related diabetes, confined almost exclusively to the tropics, was listed as a possible third major category of diabetes by the 1985 WHO Study Group (38), but its true frequency is unknown (33).

GENES AND/OR DEMOGRAPHIC FACTORS IN THE ETIOLOGY OF NIDDM—A THRIFTY GENOTYPE

— The high prevalence of obesity and NIDDM in certain ethnic groups including the American Indians,

Australian Aborigines, and Pacific islanders such as the Micronesian Nauruans has been ascribed to a thrifty genotype (36). The hypothesis, first proposed by Neel (93) in 1962, is attractive, plausible, and yet difficult to prove or disprove (36,115). However, there are animal models that provide strong experimental support (116). Shafrir (116) and Barnett et al. (117) have demonstrated in the westernized Israeli sand rat (Psammomys obesus), which develops obesity and diabetes in association with hyperinsulinemia and insulin resistance, that food restriction can lead to a reversal of the hyperinsulinemia and associated metabolic abnormalities.

The basis for the susceptibility to obesity and NIDDM is unclear but could be a result of a thrifty gene that promoted fat deposition and storage of calories in times of plenty and provided a positive selective advantage during periods of food shortage and starvation (118). As a consequence, the populations that formerly were most subject to such adverse circumstance are where the thrifty genotype frequency would be highest and are the ones that now have the highest incidence of NIDDM, such as the Pima Indians and the Nauruans.

The concept of a thrifty gene is not without precedent. There are other classic examples of the thrifty genotype. Genetic traits such as sickle cell anemia and glucose-6-phosphate dehydrogenase deficiency, two of the commonest single-gene diseases in humans, have been selected in a variety of populations where malaria exists (119). Their persistence in certain regions of the globe, given their potential lethal nature, has been ascribed to the fact that heterozygotes are protected against malaria, one of the major environmental hazards in many tropical and developing countries.

The search for the elusive NIDDM gene(s) has not produced any major candidate either for NIDDM or the thrifty gene (34,120). In fact, there could be a number of different thrifty genes that developed under different environmental circumstances through the millennia (121). The complexity of human metabolism, controlled by multiple interacting genetic and physiological mechanisms, has possibly resulted in many potential beneficial mutations, deletions, recombinations, and opportunities for natural selection relating to the feast and famine scenario. Thus, the thrifty gene(s) may vary in presence, intensity, and genetic control systems across almost all the world's human populations.

McGarvey (121) suggests that the thrifty genotype is not a single gene coding for a protein product and setting overall control for energy balance. Rather, there are numerous gene systems involved, which influence adiposity, energy metabolism, and risk of associated diseases, and the thrifty genotype hypothesis provides a convenient umbrella for considering the evolutionary significance of hyperinsulinemia and insulin resistance (20,121,122).

Neel (93), in his original description, proposed that those individuals with the genotype had an exaggerated insulin response to food. This would lead to an increase in stored energy because of increased deposition of adipose tissue during feast periods. The thrifty gene provided a selective survival advantage in times of fluctuating food availability, such as during long canoe voyages or times of famine and climatic change. This scenario is consistent with a hypothesis that storage of fat provides a cushion against food shortages (17), particularly for women for successful conception, during pregnancy and lactation. Thus, the thrifty gene would contribute to increased fat storage during feast periods and would protect reproductive function during famines. In modern times, where the scenario of social and cultural factors favor feasting with a preference for energy-dense processed foods and a sedentary lifestyle, the selective advantage is lost (36).

In the past, with the continued feast situation, the genotype would probably have been eradicated through natural selection as diabetic individuals would have died at a young age through complications including retinopathy, renal failure, and obstetric complications (115). In addition, the rates of congenital anomalies and perinatal deaths are substantially higher in diabetic pregnancies (123), and the fertility rates are lower in diabetic women (115). The combined effect of these events would be a reduction in the gene pool.

In the special populations mentioned above, my group has shown, with others, that physical inactivity and markers of dietary change such as urbanization and improved socioeconomic status are independent risk factors for obesity (19,84,124). Furthermore, both generalized and central obesity as well as physical inactivity are independently associated with IGT and NIDDM (89), probably acting to a large extent in affecting insulin sensitivity/action and causing insulin resistance (16,20). Today, with food aplenty, the thrifty gene becomes deleterious, there is an accentuation of insulin resistance, and those communities where it is present develop high prevalence of obesity and NIDDM (118).

In this context, the relatively low prevalence of NIDDM in European populations is of some interest. It might be due to the fact that there has been less selection in favor of the thrifty genotype as there were not the repeated food shortages seen elsewhere, so there might have been a strong negative selective force against the thrifty (diabetes) gene if it was present. For example, the prevalence of diabetes in the U.K. is ~2% (125) compared with 8% in the U.S. (87). It is tempting to conclude that the people who left Europe to cross the Atlantic Ocean by sea to populate America with all the associated adversity, and who survived, might yet be another example of the thrifty gene scenario!

This suggestion may explain why the prevalence of diabetes in Europids in the U.S., Canada, and Australia is higher than that in the U.K. On the other hand, the difference may just be the result of different levels of environmental risk de-

terminants, such as nutritional factors, exercise, and obesity between these communities (19), or genetic admixture over the centuries as occurred in Europe and the Near East. The latter possibility could have negated the effects of famine and other natural disasters by diluting the thrifty genotype.

Thrifty genotype or thrifty phenotype?

A low birth weight has recently been proposed as a new risk factor for NIDDM (37). Studies in the U.K. have demonstrated an inverse relationship between birth weight and glucose tolerance in adult life (126). This concept of a "thrifty phenotype" has created considerable interest, but does it hold up against available evidence?

Hales and Barker (37) have suggested that low birth weight, a reflection of nutritional deficiency in utero, is related to the later development of glucose intolerance, either IGT or NIDDM, independent of current body mass index and social class. Their interpretation of these findings is that impaired development of the endocrine pancreas and other tissues results from the long-term effects of the nutritional deprivation affecting fetal and infant growth and suggested that this scenario applies in high prevalence communities such as the Nauruans. They then propose the thrifty phenotype hypothesis, claiming that NIDDM is mainly the result of environmental determinants and that genetic factors play little or no role (37).

Dowse et al. (127), Waldhäusl and Fasching (128), and McCance et al. (129) have questioned this interpretation. Paradoxically, the data provided to support the thrifty phenotype concept are also consistent with the thrifty genotype hypothesis. It is likely that the fetuses carrying a thrifty gene in an environment of intra-uterine malnutrition were more likely to survive (128,129). This possibility is, in fact, consistent with the thrifty genotype and is based on the proposal that the U.K. study (126) is of necessity limited to survivors (small infants genetically predisposed to insulin resistance and NIDDM), and the thrifty phenotype hypotheses takes no account of the high mortality associated with a low birth weight.

The Pima Indians show a U-shaped association between birth weight and subsequent NIDDM, with highest diabetes prevalence in both high and low birth weight infants (129). However, diabetes associated with low birth weight only accounts for 6% of diabetes in this population. This suggests that irrespective of the mechanism of the low birth weight association, it is not a major contributor to NIDDM frequency.

CONCLUSIONS

Implications for research and clinical practice

In the past, diabetes presenting in adult life was usually assumed to be NIDDM. It is clear that this was an oversimplification, and the true situation is much more complex (3,7–9). While the majority of adults with diabetes do have lifestyle-associated NIDDM with or without the Metabolic Syndrome (18), a significant percentage, ~10–20%, have LADA with its insidious-onset of insulin dependency. The remainder have hypoinsulinemia due to specific gene mutations (an estimated 2–4%), the most common of which is glucokinase, or one of the other numerically less important forms of diabetes.

Research issues. Testing for anti-GAD, and indeed gene mutations, will become very important for researchers studying NIDDM. Adults within any experimental group are likely to have different etiologies for their diabetes, and this is likely to affect both the results and the interpretation of epidemiological, genetic, and clinical research studies. Apart from the necessity to define diabetes correctly from an epidemiological perspective, the total success of the current thrust to define crucial genes for both IDDM and NIDDM depends on this.

To date, we have failed the geneticists badly, providing samples from patients who may not be truly representative of IDDM and NIDDM. The geneticists regard diabetes as a nightmare (120), and it is no wonder when one considers that clinicians have been asking them to find the diabetes gene(s) yet supplying them with samples from poorly defined groups. The search for the gene(s) is already hard enough without this additional handicap. Furthermore, a major problem presented by the poor classification of diabetes in adults is that many clinical research studies on NIDDM may be fatally flawed. Therapeutic trials of new oral agents, studies of the impact of improved metabolic control, and other clinical studies of NIDDM are likely to have been polluted by the inclusion of adults with slowly progressing IDDM.

Management issues. The fact that the anti-GAD assay has an important role now in differentiation of adult diabetes should see its use expand. The immunofluorescent test for ICA has major drawbacks that have limited its widespread use (47,55). It is time consuming and difficult to standardize and reproduce consistently in all but a limited number of centers, and it is dependent on a continuous supply of human pancreatic tissue.

There is already a defined clinical utility for the anti-GAD assay in NIDDM and GDM, as has been discussed earlier. Several publications from our group highlight the fact that at least 10–15% of adult patients presenting with diabetes and considered to have NIDDM on clinical grounds (7,55,63,64) have a natural history proceeding to insulin dependency over a period of months or years. This group has been shown to have IDDM, but in a slowly evolving form, i.e., LADA. We have already demonstrated that testing for anti-GAD is superior to the traditionally used ICA in distinguishing those adult-onset diabetics who fit into the IDDM or LADA category (7), and there seems no reason to believe that this would not also be the case in GDM.

There now arises a very important practical and clinical question as to

whether anti-GAD measurements should be performed routinely in NIDDM and GDM at the time of diagnosis. On the basis of a number of studies in different populations (9,14,55,63–66), it would seem that testing for anti-GAD should be a regular procedure in adult nonobese diabetic patients to assist with correct classification and appropriate therapy. Evidence is mounting to suggest that anti-GAD should also be measured routinely in GDM (13,111,112,130).

This has important implications for prevention, particularly for making the distinction between NIDDM and conditions such as LADA (55) and YODM (3). The former requires a healthy lifestyle intervention (131), while the latter two may require immune intervention, i.e., similar to that for childhood IDDM (68).

The prevention of diabetes in adults

IDDM. Prevention of IDDM is dealt with in greater detail elsewhere (4,39,68,132), but current strategies include nicotinamide, cyclosporine and other immunosuppressive agents, insulin, GAD, and tuberculin. As GAD_{65} can be produced in large amounts through recombinant gene technology, it should soon be possible to test whether treatment with GAD will preserve residual β-cell function, halt the autoimmune process, and indeed, progress to overt clinical IDDM.

LADA can be identified using the anti-GAD assay since a high proportion (70–80%) are likely to be positive (9,14,55). Their identification could lead to the earlier institution of insulin therapy, with preservation of residual β-cell function. This, in turn, may permit better metabolic control of diabetes, possibly reducing the risk of long-term microvascular complications of diabetes (68).

Similarly, the identification of a subgroup of patients with GDM who are positive for anti-GAD has the same implications. These women would be the subset most likely to develop IDDM at a later time (13,111,112). In addition, they are the group most likely to require and benefit from insulin therapy during pregnancy (13).

NIDDM. As for prevention of NIDDM, the thrifty gene scenario provides real hope. A trait that was previously advantageous and allowed survival during famine, i.e., favored conservation and storage of energy as fat, now leads to insulin resistance, NIDDM, and obesity in times of affluence (36). Thus, healthy diet and exercise resulting in reduced energy intake and increased energy expenditure provide the logical means of prevention (39,131).

There are no detailed published studies yet of successful population-based intervention for IGT and NIDDM. Two studies, one in Australian Aborigines (133) and the other in native Hawaiians (134), have demonstrated the potential benefits of a return to traditional dietary patterns in terms of improved CVD risk factor profile, including blood glucose and lipids. A recent dietary intervention study in primates (135) and several exercise intervention studies (136–140) provide evidence that such interventions could be successful in a community setting. Hansen and Bodkin (135) have shown that caloric restriction that maintains lean body weight in adult monkeys with a high propensity to develop obesity and NIDDM can substantially delay and possibly prevent NIDDM. As the majority of cases of NIDDM appear to be lifestyle related (19), NIDDM could be seen as an exercise-deficiency or dietary excess disorder and is potentially preventable through the pursuit of a healthy way of life (131).

No large-scale studies have yet been published that show that a healthy lifestyle intervention can prevent IGT and/or NIDDM. However, the preliminary results of a successful diet and exercise intervention in China have recently been reported (142). Here, the incidence of IGT to NIDDM was reduced by a third in the intervention group compared with control subjects. Given the projected epidemic of diabetes in China (15,16), the largest population in the world, such a cost-effective intervention provides good news.

We have also demonstrated that a similar community-based lifestyle approach in Mauritius could reduce some of the key risk-factor determinants for NIDDM and CVD (140). This nation has close to the highest rates for NIDDM and CVD in the world (88).

What is clear is that epidemiological studies have provided a basis for understanding the environmental determinants of NIDDM. However, molecular genetic research directed at linking susceptibility to putative gene(s) has a vital role in determining high-risk individuals, the group where more targeted intervention would be possible for the primary prevention of NIDDM.

A high priority that remains is the research needed to help with a scientifically based classification of the diabetes

Table 5—*Proposed new classification of diabetes for debate, not including IGT and allied disorders*

IDDM
Known genetic contribution: HLA-DR and -DQ
• Acute-onset
• LADA
• Nonautoimmune
NIDDM
Known genetic contribution (sufficiently proven)
• Glucokinase
• Mitochondrial DNA
• Insulin receptor
• Insulin gene
Unknown genetic basis (in most cases)
• Insulin resistance
• Insulin secretory defect
GDM (e.g., transitory)
• Transitory
• Insulin-dependent
• Non-insulin-dependent
Other types
• Pancreatic
• Endocrine
• Malnutrition-related, etc.
• Drug-induced
• Rare genetic syndromes, etc.

syndrome, as the current means for separating IDDM and NIDDM for both clinicians and researchers is based on rather thin ice. A starting point for this is the classification featured in Table 5.

This proposal results from the crystal ball gazing of my colleagues Gary Dowse, Peter Bennett, and Leif Groop as well as myself. This attempts to separate IDDM and NIDDM more clearly to aid investigators, and it is clear that the WHO classification (38) is now in need of urgent revision. Until this happens, the many faces of diabetes, both genotypically and phenotypically, will continue to frustrate those striving so hard to treat and prevent this increasing global problem.

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