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# *Perspectives in Diabetes*

## Age-Dependent Influences on the Origins of Autoimmune Diabetes

### Evidence and Implications

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**A** decade ago we proposed that environmental factors operating in early life lead to type 1 diabetes, outlining the evidence and the implications if the hypothesis was true (1). Today we can be confident that environmental factors can indeed operate in childhood to cause type 1 diabetes, but we now review evidence that this is unlikely to be true in the generality of cases of type 1 diabetes. Indeed, type 1 diabetes presenting in adult life is remarkably distinct from diabetes presenting in children in terms of its genetic, immune, metabolic, and clinical features. If the mechanism and timing of disease induction is also distinct in adult-onset, compared with childhood-onset, type 1 diabetes, then these differences would have implications for our understanding of the disease pathogenesis, prediction, and prevention. The aim of this article is to explore the different influences of genetic and nongenetic factors on type 1 diabetes according to the age of clinical disease onset and the potential consequences of such differences.

Type 1 diabetes is caused by the destruction of insulin-secreting islet cells by an immune-mediated process. This adverse immune response is induced and promoted by the interaction of genetic and environmental factors and is one of a group of autoimmune diseases that affect ~10% of the population in the developed world (2–5).

#### AGE-DEPENDENT ROLE FOR GENETIC FACTORS

Type 1 diabetes is genetically determined as shown by family, twin, and genetic studies. The frequency of type 1 diabetes is higher in siblings of diabetic patients (e.g., 6% by age 30 years in the U.K.) than in the general population (0.4% by age 30 years) (6). Familial clustering could be caused by shared genetic or environmental factors, and to distinguish between them, twin studies have been used.

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IA2, insulinoma-associated 2; IAA, insulin autoantibody; ICAA, islet cell autoantibody; LADA, latent autoimmune diabetes of adults.

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Higher concordance rates for autoimmune diseases in identical compared with nonidentical twins is consistent with a genetic influence on these diseases (7). Of genes implicated in the genetic susceptibility to type 1 diabetes, the most important are in the histocompatibility (HLA) region of chromosome 6 (6,8).

Age-related genetic factors not only influence the risk of type 1 diabetes, but also the presence of diabetes-associated autoantibodies, the rate of progression to clinical diabetes, and the severity of reduced insulin secretory capacity. Not only is the age incidence of type 1 diabetes lower than in children, but the range of incidence across European countries is also reduced (9). Furthermore, there is a male excess in disease incidence that becomes evident during puberty and is most striking in the age-group 25–29 years (9). Survival analysis estimated that nondiabetic identical twins of probands diagnosed with type 1 diabetes <25 years of age had, in one study, a 38% probability of developing diabetes compared with 6% for twins of probands diagnosed later (10–12) (Table 1). Such a remarkably low twin concordance rate for adult-onset type 1 diabetes, lower than that for influenza, implies that the genetic impact in adult-onset diabetes is limited (7).

HLA alleles associated with diabetes susceptibility include HLA DR3, DQB1\*0201 and DR4, DQB1\*0302, whereas others are associated with disease protection, e.g., HLA DR2, DQB1\*0602 (2,6). Type 1 diabetic children show an increased prevalence of the heterozygous alleles HLA DR3, DQB1\*0201 and DR4, DQB1\*0302, with the proportion of heterozygotes declining with age at diagnosis (13–15) (Table 2). Children with the diabetes-protective HLA DR2, DQB1\*0602 are unlikely to develop diabetes, whereas in adult-onset diabetes the same alleles carry less protection (13,14). Patients with HLA DR4, DQB1\*0302 are at particular risk of having insulin autoantibodies (IAAs), and these HLA alleles and IAAs are more prevalent in children with type 1 diabetes (15,16).

Despite the limited genetic risk implied by twin studies, adult-onset type 1 diabetes shows HLA genetic susceptibility, which is also found in adults presenting with non-insulin-requiring diabetes who have diabetes-associated autoantibodies to GAD (17–19). Such patients, mistakenly diagnosed initially with type 2 diabetes, have autoimmune non-insulin-requiring diabetes, designated latent autoimmune diabetes of adults (LADA), with a re-

TABLE 1  
Concordance for type 1 diabetes in identical twins according to age at clinical onset in the index twin

	Young onset	Older onset
U.K./U.S. (ref. 10)	38 (<25)	6 (>25)
U.S. (ref. 11)	44 (<15)	13 (>15)
Finland (ref. 12)	50 (<10)	23 (>10)

Data are % (years). Note the substantially lower concordance rates in the older-onset twins consistent with a marked non-genetically determined effect causing diabetes in them.

duced frequency of metabolic syndrome compared with other cases of non-insulin-requiring diabetes (17,18). This form of autoimmune diabetes affects ~10% of recently diagnosed non-insulin-requiring European adults, implying that it is more prevalent than childhood type 1 diabetes (18). Moreover, ~90% of LADA patients progress to insulin dependence within 6 years, so that, rates of progression to insulin dependence apart, it is difficult to distinguish between adult-onset type 1 diabetes and LADA (18,19) (Table 2). Even in LADA, older patients progress to insulin dependence more slowly (19). Strikingly, adults with non-insulin-requiring diabetes without GAD autoantibodies have an excess of diabetes-associated HLA alleles and are relatively young and lean (16,17).

#### AGE-DEPENDENT ROLE FOR NONGENETIC FACTORS

The incidence of autoimmune diseases has increased notably over the last 3 decades (5). The current low selection density and relative stability of HLA polymorphisms indicate that this increasing incidence cannot be caused by genetic selection pressures, at least operating through HLA genes, and is most likely the result of nongenetic factors (5,8). Nongenetic factors play a major role in causing type 1 diabetes, as shown by studies of populations that have migrated, of populations with changing disease incidence, and of twins.

Population studies are of limited value in identifying the impact of nongenetic factors because it is difficult to segregate genetic from environmental influences. However, changes in disease incidence within a genetically stable population—or in migrants—are important when disease incidence rises rapidly (5,20). In the U.S. the reported death rates from diabetes in children aged <15 years (by implication the type 1 diabetes incidence because this was before insulin therapy) in 1890 and 1920 were 1.3/100,000 and 3.1/100,000 per year, respectively (21), rising by 1959–1961 in Erie County, New York, to 11.3/100,000 per year, a substantial change within four

generations (22). Such changes have been most striking in children diagnosed at <5 years of age, as in Switzerland, where the incidence rose from 4.5/100,000 in 1965 to 10.5/100,000 in 2000 (23).

Migration studies also support a role for environmental factors influencing disease incidence (3,5). Type 1 diabetes incidence in Asian children who migrated to Britain increased from 3.1/100,000 per year in 1978–1981 to 11.7/100,000 per year in 1988–1990, much higher than in their native Karachi (1/100,000 per year) (24,25). There are no comparable studies of adults.

Increases in disease risk in young children could be caused by an accelerated progression to type 1 diabetes (a proposal encompassed in the accelerator hypothesis and the early spring harvest hypothesis) or to an increased disease risk or both. In support of an increased disease risk, there has been a recent shift in Finland in the HLA genetic susceptibility to include more cases with low- or moderate-risk HLA genotypes (26). In support of accelerated disease progression, the disease incidence rose in the young (age 0–14 years) with a coincident fall later (15–34 or 39 years) (27,28). So perhaps both factors explain the increasing disease incidence in young children. Acceleration of the disease process, or of metabolic decompensation, could result from reduced insulin sensitivity, due either to increased linear growth, which has been linked to diabetes risk, or increased childhood obesity, which has been correlated with age at presentation (29–31). We have previously argued that these non-genetically determined factors are likely to be environmental factors (1).

#### DISEASE INDUCTION BY ENVIRONMENTAL FACTORS

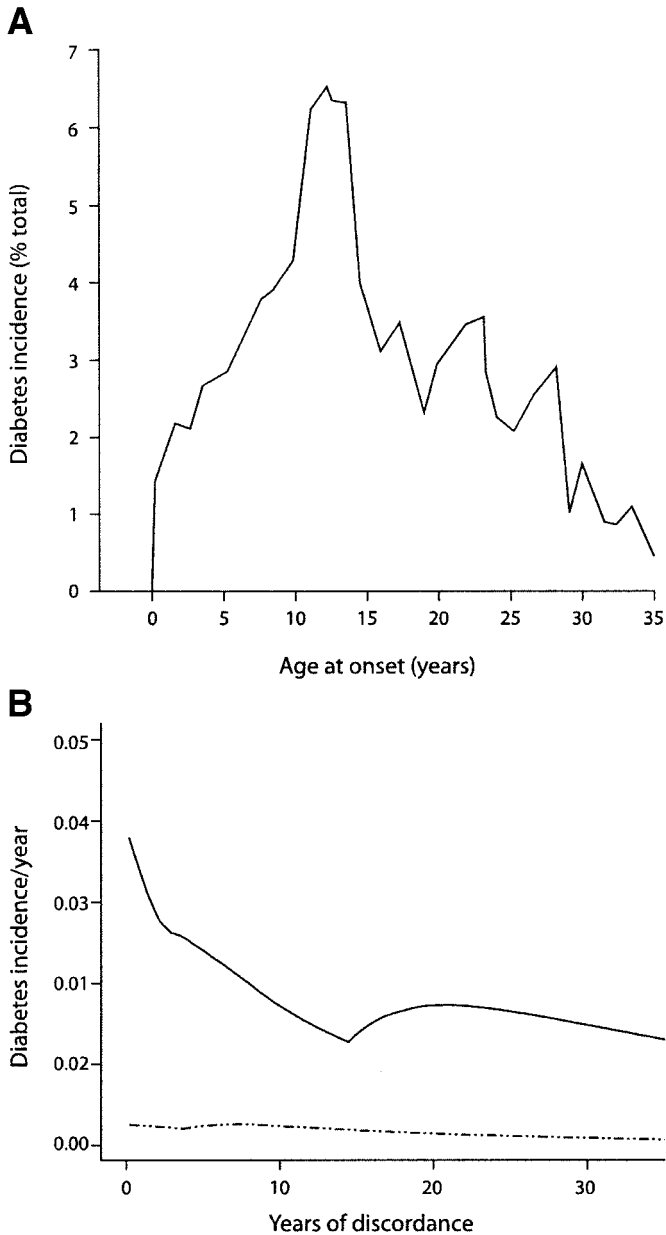
Environmental factors have been implicated in the etiology of autoimmune diseases. These factors include: temperate climate, increased hygiene and decreased rates of infection, vaccinations and antibiotics, and increasing wealth (possibly all relevant for most autoimmune and atopic diseases); however, for type 1 diabetes, factors also include overcrowding in childhood and virus infections, early exposure to cow's milk, reduced rates or duration of breast-feeding, and vitamin D and nitrite consumption (1,5,32–50).

The qualitative age-specific pattern of incidence of type 1 diabetes is similar worldwide, with a peak incidence in childhood and declining sharply thereafter (1) (Fig. 1A). The striking postpubertal decline in disease incidence could be caused by a loss of a genetic or environmental effect. The latter is most likely because there is also a fall in disease risk in identical twins of young diabetic pa-

TABLE 2  
Distinction between childhood-onset and adult-onset type 1 diabetes and LADA

	Children	Adults	LADA
Age at diagnosis	Childhood	Adulthood	Adulthood
Identical twin concordance rate (%)	38	6	—
HLA DR3/ DR4 (%)	37	13	22
Autoantibodies	IAA, GAD, IA-2	GAD, IA-2	GAD, IA-2
Serum insulin levels	Very low	Low	Low

Note that the children, compared with the others, have a higher identical twin concordance rate, frequency of HLA genetic susceptibility heterozygosity and IAAs, and lower serum insulin levels. Data were compiled from different sources (10,15,17,61,66). HLA DR3/4 is found in ~6% of North American and European control populations.



**FIG. 1. A:** Age of onset of type 1 diabetes compiled from several sources to estimate age-specific incidence, but only before 35 years of age (1,85). Note the sharp decline in disease incidence during adolescence. It is important to note that ~25% of type 1 diabetic patients develop the disease after 35 years of age, and a further substantial proportion develop adult-onset non-insulin-requiring autoimmune diabetes, so-called LADA. **B:** Diabetes incidence for the twin cohort from the time of diagnosis of the index twin, according to the age at diagnosis in the index twin when aged 0–6 years ( $n = 38$ ) (solid line) and  $\geq 24$  years ( $n = 40$ ) (dashed line). Note the sharp decline in diabetes incidence in the cotwins of young diabetic twins, but a lower and more stable diabetes incidence in co-twins of adult-onset diabetic twins, and compare this decline with the decline shown in Fig. 1A.

tients, though notably not in older twins (1,10) (Fig. 1B). Such a declining disease risk in childhood-onset, but not adult-onset, diabetes implies that those critical environmental events causing childhood-onset type 1 diabetes operate preferentially within a limited period in early childhood. Put simply, if two events or “hits” widely separated in time led to diabetes, then the longer the time of follow-up, the more likely would susceptible individuals be to encounter both hits, as happens with cancer, in

**TABLE 3**  
Factors associated with increased risk of type 1 diabetes

Being born to diabetic fathers rather than diabetic mothers
Having a diabetic mother aged <8 years at diagnosis compared with mother diagnosed later
Increasing maternal age at delivery
Being first born
ABO incompatibility with the mother
The season of delivery
Increasing maternal enterovirus infection rate
Early cessation of breast-feeding

which the disease risk rises with time, in contrast with childhood-onset type 1 diabetes after 15 years of age (1,45) (Fig. 1A and B). No such claim can be made currently for adult-onset autoimmune diabetes.

**Maternal-related events influence diabetes risk.** Disproportionate maternal influences on risk of type 1 diabetes suggests that critical disease-inducing environmental events operate very early, even in utero. A number of maternal-related events are associated with an increased disease risk in children but not in adults (Table 3).

Children of diabetic mothers are less likely to develop type 1 diabetes than children of diabetic fathers, and the risk in mothers is less than the expected risk based on their HLA status (46,47). The mean life table risk of diabetes in offspring of diabetic mothers and fathers in one study was 1.3 and 6.1%, respectively (46). This low disease risk is confined to offspring of mothers who had become diabetic after the age of 8 years, perhaps because of reduced transmission of genetic risk. The risk of offspring developing diabetes increases with maternal age at birth, whereas the effect of paternal age is smaller (48). The first born has the highest risk of diabetes, the risk falling thereafter by 15% per child born. Blood group incompatibility between mother and child may also predispose to diabetes, although the cause remains obscure (49). Whereas the size of these studies is limited, a more comprehensive analysis has been made of viral infections during pregnancy and of early cessation of breast-feeding. **Exposure to viruses.** Extensive epidemiological, histological, and immunologic data, largely derived from studies of patients aged <15 years at diagnosis, support the role for a virus or viruses in the pathogenesis of type 1 diabetes (33,38). Attention has focused on enteroviruses, specifically on members of the picornavirus family, which are nonenveloped RNA viruses; for example, coxsackie B virus infection was detected in 64% of young diabetic children as compared with only 4% of control subjects (34).

Maternal viral infections during pregnancy could increase disease risk: levels of group-specific enteroviral IgG and IgM antibodies during pregnancy were higher in 57 mothers of pre-diabetic children than in 203 mothers of control subjects (35), although HLA-DR disease risk alleles were associated with increased humoral responsiveness to enteroviral antigens (36). Two further observations support a viral etiology for type 1 diabetes: there is both seasonality in the appearance of diabetes-associated auto-antibodies, which peak in the autumn and winter (50), and a temporal relationship between diabetes-associated auto-antibodies appearing and enterovirus infections occurring in the preceding 6 months (37).

**Nature of weaning diet.** Early infant diet affects type 1 diabetes development. Non-breast-fed children have a greater risk of developing diabetes than breast-fed children, and breast-feeding for >3 months protects from diabetes (38). This proposed protective effect could operate by providing immune factors, e.g., secretory immunoglobulin A, or it could delay the early introduction of foreign antigens such as cow's milk proteins (38). In either event there appears to be an association between a short period (<2 months) of breast-feeding and the development of diabetes-associated autoantibodies, especially when infants carried the high-diabetes risk HLA DQ\*0302 allele (39). Furthermore, the association between milk consumption and diabetes risk may not be confined to early life because the quantity of cow's milk intake in adults is related to disease risk (32,38).

In summary, epidemiological evidence favors the induction of childhood-onset type 1 diabetes by an environmental event, possibly a virus or dietary factor, operating over a finite period in early childhood. This environmental effect probably operates in the context of various disease susceptibility genes to determine disease outcome. There is no evidence for such environmental effects in patients with adult-onset type 1 diabetes.

#### ACTIVATION OF THE DIABETES-ASSOCIATED IMMUNE RESPONSE

If the critical event that induces the destructive immune process operates in early childhood, it follows that diabetes-associated immune changes, which reflect that process, may also be detected at an early age. Timing of the onset of autoimmunity is a prerequisite for unmasking triggers in the pathogenesis of this disease. At birth, children of diabetic mothers often have islet cell autoantibodies (ICAAs), IAAs, and GAD autoantibodies. But these autoantibodies can also be found in the maternal serum and are probably placentally transferred to the child because autoantibody specificities are similar in mother and cord blood and are not usually detected in the infants of mothers without such autoantibodies (51–53). Passively acquired maternal autoantibodies disappear after birth, as expected, but they can subsequently be replaced by the infant's own autoantibodies. In one study, 3 of 58 infants of diabetic mothers developed IAAs, ICAAs, and GAD autoantibodies de novo by 2 years of age, and only then were autoantibodies associated with diabetes risk (51). Cumulative risk of type 1 diabetes in 1,353 offspring of diabetic parents was 18% at age 5 years but 50% in those with more than one diabetes-associated autoantibody (51).

Although cord blood autoantibodies are mainly transplacentally acquired, diabetes-associated autoantibodies can appear at a very young age. For example, 85% of New Zealand schoolchildren who seroconverted to ICAA did so before 5 years of age (1). Of 137 children with ICAAs from a prospective Finnish study of 4,590 consecutive newborns with the disease risk HLA-DQB1 allele, IAAs and GAD autoantibodies usually appeared before ICAAs, whereas insulinoma-associated 2 (IA2) autoantibodies usually appeared afterward (54). Strikingly, 95% of seroconversions to IAAs or GAD or IA2 autoantibodies occurred in a cluster (–12 to +8 months) around the time of ICAA seroconversion. Children at high genetic risk sero-

converted steadily at approximately twice the rate of those at moderate risk (54). Thus, induction and activation of diabetes-associated autoantibodies is not confined to early childhood, and seroconversion may be detected up to at least 10 years of age.

Taken together, these observations suggest that activation, possibly by viruses, of the diabetes-associated immune process can occur in early childhood. However, seroconversion is not confined to early childhood, so neither, by implication, is activation of the diabetes-associated immune response.

#### DESTRUCTION BY THE DIABETES-ASSOCIATED IMMUNE RESPONSE

Loss of insulin secretory capacity is variable and age dependent, being more rapid in childhood-onset diabetes than in adults. Variation in rates of disease progression appears to be substantially genetically determined and associated with obesity.

**Variable rate of disease progression.** If the critical initiating environmental event were to operate exclusively in childhood, then the subsequent rate of progression to clinical disease would be rapid in patients presenting at <5 years of age and slow in those presenting much later (1). Histological evidence supports this contention; islet  $\beta$ -cells tend to be absent within 12 months of diagnosis in patients aged <7 years, but they are detected for longer periods in older patients (55). Even when immune changes are activated in very young children, there can be variability in progression to clinical diabetes; remarkably, of children identified between 1 and 5 years of age with diabetes-associated autoantibodies and subnormal insulin responses, half of them progressed rapidly to diabetes, whereas the remainder were not diabetic up to 4 years later (56). This observation implies variable disease progression even among very young children with similar HLA genetic susceptibility, numbers of diabetes-associated autoantibodies, and degree of metabolic disturbance. Other studies have emphasized such variable progression being more rapid in children in the presence of diabetes-associated autoantibodies but being independent of autoantibody type and the degree of insulin secretory loss and being more rapid in obese than lean children (31,57,58).

**Genetic factors affect disease rate.** Genetic factors determine when type 1 diabetes presents. Identical twins develop the disease at a similar age, which is for them also at a similar time, with a heritability for age at diagnosis of 74% (12,59). Family studies comparing affected siblings show a correlation in them with age at diagnosis, and not with time of diagnosis (59). Lack of correlation between siblings for time of diagnosis argues against a common environmental exposure precipitating diabetes and favors a distinct environmental event (59). Given clustering in time between siblings for immune activation, as judged by autoantibody seroconversion, as well as clustering by age at time of diagnosis, the rate of progression of the destructive process during the intervening pre-diabetic period is probably, to a degree, genetically determined in both children and adults.

## IMPLICATIONS FOR DISEASE PATHOGENESIS

Complex disorders tend to present clinically in adult life, whereas ~80% of Mendelian disorders present in childhood (60). Thus, the diverse ages at which autoimmune diabetes presents clinically could reflect differences in the disease pathogenesis. We have already noted differences in the impact of genetic and nongenetic factors with age at diagnosis in autoimmune diabetes. From these observations it follows that there should be a spectrum in rates of metabolic decompensation during the pre-diabetic period. Such a metabolic spectrum has been well documented.

**Age-dependent variation in disease progression.** Insulin secretory capacity is less compromised in adults at diagnosis than in children, and after diagnosis it deteriorates less rapidly. A study of 235 consecutive cases with newly diagnosed type 1 diabetes found that those aged <7 years had the lowest baseline residual insulin secretion and required the highest insulin dose for optimal control, whereas the older the age at diagnosis, the higher the basal C-peptide level (61). Decreased insulin sensitivity in puberty and in adulthood could also be relevant to metabolic decompensation, leading to frank diabetes (Fig. 1A). Post-diagnosis, there is a decline in both fasting and stimulated C-peptide; however, persistent C-peptide secretion, implying less aggressive disease, is detected in more adults than adolescents and in more adolescents than prepubertal diabetic children (62–64).

Pre-diabetic individuals pass through a stage of impaired glucose tolerance or even non-insulin-requiring diabetes before becoming frankly insulin dependent. DPT-1 (Diabetes Prevention Trial of Type 1 Diabetes) detected 585 relatives of type 1 diabetic patients who had ICAAs plus either IAAs or low first-phase insulin response to intravenous glucose; of them, 427 had normal glucose tolerance, 87 had impaired glucose tolerance, and 61 were diabetic—yet asymptomatic—on glucose tolerance testing (65). Of these latter, those with impaired fasting glucose were significantly older (mean age 21 years) than those with normal fasting glucose (mean age 12 years). It follows that some patients with autoimmune diabetes (i.e., with diabetes-associated autoantibodies) pass through a phase of non-insulin-requiring diabetes before becoming insulin dependent. Numerous studies worldwide have identified such cases as LADA patients and have shown that they have a similar clinical and immunogenetic profile to adult-onset type 1 diabetes (Table 2) (17–19). Of these LADA patients, 94% required insulin treatment by 6 years as compared with only 14% without either GAD autoantibodies or ICAAs. Consistent with an age effect on rates of disease progression, even in adults progression to insulin dependence in LADA is more rapid in those aged <45 years than in older cases (19). Furthermore, patients of a similar age with LADA and adult-onset type 1 diabetes have similar C-peptide levels at clinical onset, although C-peptide levels fall more rapidly in the latter after diagnosis (66).

It remains to be established whether LADA has the same disease process as adult type 1 diabetes, but the argument could be semantic and in the present context only serves to illustrate the wide clinical spectrum associated with the immunogenetic features of autoimmune diabetes and the age at which it presents. How broad that spectrum could be

remains uncertain, but, as described earlier, a proportion of non-insulin-requiring patients who do not have GAD autoantibodies may have a disease process similar to LADA in that they also show an association with diabetes-associated HLA alleles, just as for others with diabetes-associated autoantibodies, clinical diabetes many never develop (1,2). This observation is in keeping with other studies identifying an increased risk of diabetes-associated HLA alleles in patients with non-insulin-requiring diabetes (67–69).

**Age-dependent variation in growth.** Changes in growth and weight gain can occur shortly before the onset of type 1 diabetes. However, these clinical changes are distinct in early- and late-onset cases. Although identical twins normally grow at the same rate and to approximately the same final height (70), a diabetic twin aged  $\geq 9$  years at diagnosis is often shorter than their nondiabetic cotwin, probably because of growth delay in the pre-diabetic period (71). On the other hand, twins and siblings of diabetic patients aged <9 years at diagnosis are not shorter, suggesting a more rapid disease process (72,73). Decreasing insulin sensitivity during puberty could be relevant to the increased disease incidence at this time (Fig. 1A).

**Age-dependent variation in disease outcome.** Once diabetes is established, age at onset is associated with the microvascular complication rate. The EURODIAB Prospective Complications Study found that diabetes developing before puberty (arbitrarily taken at 12 years of age) was associated with a higher risk of progression to proliferative diabetic retinopathy and diabetic nephropathy independent of diabetes duration (74,75).

It follows that there is a broad spectrum of immunogenetic, metabolic, and clinical features associated with autoimmune diabetes, and many aspects of that spectrum are age dependent (Table 2). Current studies, focusing on events early in childhood, may well miss those events inducing adult-onset type 1 diabetes and LADA.

## IMPLICATIONS FOR PREDICTION

Accurate disease prediction is vital for secondary disease prevention, so that therapy is only given to individuals who are otherwise likely to develop diabetes. Strategies for disease prevention involve identification of high-risk individuals, using both genetic markers and disease-associated immune and metabolic changes. If the immune process associated with the development of type 1 diabetes is sometimes initiated in early childhood, but later in others, population screening will have to be performed at different ages to detect induction of diabetes-associated autoantibodies in the pre-diabetic period (54,76). Indeed, GAD or IA2 autoantibodies at birth may protect against future autoimmunity or diabetes (77). Furthermore, current studies to either detect critical environmental factors (e.g., DIPP [Diabetes Prediction and Prevention], DAISY [Diabetes AutoImmunity Study of the Young]) or prevent diabetes by reducing critical exposure (e.g., TRIGR [Trial to Reduce IDDM in the Genetically at Risk]) each confine themselves to children and may not be relevant to autoimmune diabetes presenting in adults (50,78,79). A search for autoantibody seroconversion in families with adult-onset autoimmune diabetes could be valuable.

Maximal predictive sensitivity and specificity in population screening will require testing of different sets of

autoantibodies at different ages (80); for example, a study of recently diagnosed type 1 diabetic patients detected multiple autoantibodies in 60% of patients aged <16 years but in only 37% of older cases (81). Identification of combinations of diabetes-associated autoantibodies will therefore be less valuable in screening adults compared with infants, whereas testing for GAD autoantibodies as disease predictors in the former will be more valuable than testing for IAAs, and vice versa. Because autoantibodies to different antigens appear sequentially, disease risk based on autoantibody combinations requires repeated screening with different combinations, given that the predictive value of an autoantibody combination varies with age (15,80). Thus, screening strategies need to be flexible.

#### IMPLICATIONS FOR PREVENTION

The aim of disease prediction is disease prevention. Type 1 diabetes could be prevented by avoiding those environmental factors that cause the disease process (primary prevention) or modulating the destructive process before the onset of clinical diabetes (secondary prevention). A primary prevention strategy for type 1 diabetes requires that critical environmental factors such as diet or viruses are recognized and removed, or their effect negated, while remembering that infections could be protective (79,82,83). Intervention at an early age is therefore imperative for some; for example, the TRIGR study is assessing the prevention of type 1 diabetes by introducing different supplemental formula feeds in the first 6 months of infant life (79). However, if environmental factors causing diabetes can operate later, then these factors might be different and could induce a different type of destructive immune process. In that case, primary and secondary prevention strategies might also differ from those that are used for childhood-onset diabetes (79,84). Given the differences between childhood- and adult-onset autoimmune diabetes, therapy to modify the disease process could also differ; for example, antigen-specific therapy might involve insulin-related compounds in children, whereas in adults GAD- or IA2-related strategies could be more relevant. Future strategies may benefit from incorporating the patient's age at diagnosis into the study design.

We have come a long way since the possibility was first discussed that type 1 diabetes could be induced early in life. Recent developments are bringing us close to determining the utility of this concept. In time, we must move toward a more sophisticated understanding of this disease, including the relationship between clinical diabetes, HLA-mediated genetic susceptibility, and the presence of serum GAD autoantibodies, which in children at diagnosis are together associated with insulin dependence but in adults are probably more frequently associated with diabetes that does not initially require insulin therapy. To this end we will have to consider the relevance of disease induction through environmental events at different ages, as well as the impact such events can have on the dynamic stability of our physiology. Only then will we understand how inappropriate cell destruction can arise and lead to clinical diabetes, and only then will we be able to clarify decisions about how, when, and whom we should treat to prevent autoimmune diabetes.

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