Insulin-dependent diabetes mellitus (IDDM) is caused by destruction of the insulin-secreting β-cells of the islets of Langerhans. It is proposed that the disease is caused by nongenetic, probably environmental, factors operating in a genetically susceptible host to initiate a destructive immune process. These environmental factors may operate over a limited period in early childhood to induce the immune process that destroys the islet β-cell. Thereafter, there is a long prodrome before the onset of clinical diabetes, during which clinical, immune, and metabolic changes can be detected. If these proposals are correct, epidemiological studies should focus on environmental events in early childhood that might induce, or accelerate, the disease process. Moreover, it should be possible to identify, from an early age, changes in the prediabetic period that persist to diagnosis and have predictive value. The variable age of presentation of IDDM may, therefore, reflect different rates of disease progression rather than different ages of exposure to the critical environmental events. Those patients in whom the disease process is slow could present with IDDM as adults, develop diabetes that does not require insulin treatment, or even fail to develop diabetes altogether. These proposed features, if confirmed, would have important implications for the prediction of IDDM and raise the possibility that modulation of the destructive immune process could prevent progression to clinical diabetes. Diabetes 43:843–850, 1994

Ancient texts document the existence of a severe type of diabetes similar to insulin-dependent diabetes mellitus (IDDM), although it appears to have been a rare disease (1). The disease remains extremely rare in primitive hunter-gatherer societies, although the incidence rises with migration to a modern society (2). Indeed, after asthma, IDDM is the second most common chronic childhood illness in developed countries. No country is exempt from IDDM, although the incidence of the disease varies considerably from country to country (3). IDDM is precipitated by the destruction of the insulin-secreting β-cell of the islets of Langerhans and associated with immune changes in the islets and in the peripheral blood. The precise cause of the disease remains unclear, although it is believed to be immune mediated and to involve the interaction of genetic and nongenetic factors.

ROLE FOR GENETIC FACTORS
Heritability reflects gene expression or penetrance in a given environment. The best estimate of heritability can be obtained by determining concordance rates of twins. Both identical and nonidentical twins share a similar environment in childhood, but only identical twins share the same genes. In the classic twin method, the difference between the concordance rates for identical and nonidentical twins is doubled to give an index of heritability. All diabetic twin studies to date indicate a higher concordance rate for IDDM in identical than in nonidentical twins, which is consistent with a genetic influence on the disease (4). An estimate of heritability can be obtained from studies in Finland in which ascertainment was complete (5). Heritability was low (20%), although the true value may become higher as a new study continues (5). Estimates of heritability must be viewed with caution because they are an imprecise measure of the genetic effect, but they clearly indicate that genetic factors are important. The genetic susceptibility to IDDM is mediated in part by genes in the human leukocyte antigen (HLA) region that either predispose or protect people from developing the disease (6). These HLA genes operate as susceptibility factors, not as determining factors, in that the majority of patients with these disease-associated genes do not develop IDDM.

IMPORTANT ROLE FOR NONGENETIC FACTORS
Population studies are of limited value in determining the role of nongenetic factors because it is often difficult to define genetic differences between populations and how such differences might influence the disease rate. An alternative method is to assess changes in disease incidence within a population in which the genetic pool is presumed to remain constant. Two such analyses, which studied increases in the disease incidence within a population and in migrant populations, indicate that nongenetic factors are important. An increasing risk of IDDM for children <15 years of age has been observed in most of Europe and the Western Pacific, although not consistently in North America (2).
incidence of IDDM in children of Asian origin 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, becoming similar to that of the indigenous British population (10.5/100,000 per year) (7). Similarly, IDDM is a rare disease in Western Samoa, but when these Polynesians migrate to New Zealand, the disease incidence abruptly changes from <1 to 7/100,000 per year (8). Such a change in diabetes incidence upon migration within one generation favors an acutely operational environmental change.

The most powerful evidence that IDDM is due to nongenetically determined factors comes from the study of identical twins (4). Differences or discordance between identical twins must be due to nongenetically determined factors. All diabetic identical twin studies, in the U.S., the U.K., Finland, and Japan, showed striking agreement that the majority of co-twins of IDDM patients are not diabetic (5,9-11). This striking discordance between identical twins for IDDM indicates that nongenetically determined factors play an important role in causing the disease.

**Environment or somatic mutation.** Even identical twins can be genetically different for certain genes. Genes can undergo random and ordered rearrangement or mutation and may differ between identical twins. Thus, differences between identical twins could be due to different phenotypic expression of genes through somatic mutations, such as genes defining the characteristics of antibodies. In contrast, genes of the T-cell receptor do not appear to undergo somatic mutation. Because T-cells appear to be responsible for the immune destruction of islet β-cells, somatic mutations are unlikely to cause IDDM. Furthermore, random somatic mutations would not explain the lack of randomness between populations in terms of both the clinical syndrome and the target antigens recognized by antibodies in IDDM patients (12). Therefore, we believe that the disease results from exposure to environmental agents and not somatic mutations.

**ENVIRONMENTAL EFFECT OPERATES IN EARLY CHILDHOOD**

The nature of the putative environmental factor that causes diabetes is unknown. Candidates include viruses, toxins, and dietary factors (13). Whatever the nature of the environmental factor(s), it is likely to be ubiquitous and to operate in childhood. The qualitative age-specific pattern of incidence of IDDM is similar worldwide. The disease is extremely rare before 9 months of age, has a peak incidence between 5 and 15 years of age, and thereafter declines sharply (2,14-16) (Fig. 1). It is likely, therefore, that the environmental factor causing IDDM operates predominantly in childhood. Further, there is clear evidence that, at least in some cases, the process leading to IDDM can be initiated in infancy. About one-quarter of childhood cases present before 5 years of age, and in rare cases due to congenital rubella infection, the diabetic children have been exposed to the rubella virus in utero. For the majority of patients with IDDM, the age of onset of the disease and its long prodrome suggest that the disease process has its origins in early life.

**Evidence for a long metabolic prodrome.** Metabolic changes can precede the onset of IDDM by many months. These changes involve both glucose metabolism and β-cell function. An increase in fasting proinsulin levels has been detected in twins and siblings of diabetic patients several years before they themselves develop diabetes, sometimes even when insulin responses to intravenous glucose are normal (23,24). During the prediabetic period, a decline in insulin secretion can be detected up to 11 years before the clinical onset of IDDM (25). Impaired glucose tolerance has been observed up to 12 years before the diagnosis of diabetes and before changes in fasting glucose (26). These observations indicate that metabolic changes can be detected several years before the clinical onset of IDDM.

**Evidence for a long immune prodrome.** An increase of activated T-cells expressing the HLA-DR antigen or other markers of activation may be found in several autoimmune diseases, including IDDM. When present in a nondiabetic twin of a diabetic patient, this increased level of activated T-cells is a highly sensitive marker for the development of diabetes. Activation of T-cells with increased expression of the HLA-DR antigen has been detected in prediabetic individuals when first ascertained and up to 4 years before they developed diabetes (27). Antigens recognized by serum antibodies in the prediabetic period include islet-cell cytoplasmic antigens (ICAs), insulin, and glutamic acid decarboxylase (GAD) (12). In the prospective sibling and twin
studies, ~90% of the prediabetic subjects had one or more of these antibodies at the time of ascertainment and before they developed IDDM (12,28,29). These humoral immune changes can precede the onset of IDDM by many years; one twin, for example, had ICA and GAD antibodies 153 months before she developed clinical diabetes (12). A sibling of a diabetic patient who subsequently develops IDDM around 13 years of age will typically (but not always) have detectable circulating levels of ICA 5 years or more before the onset of the disease. Of prediabetic cases, ~10% do not show antibodies to these antigens at any time in the prediabetic period. Patients who do not have these antibodies at ascertainment usually remain negative during the prediabetic period. Failure to detect these antibodies initially could be a result of either their absence or their presence at levels below the assay detection limit. In either case, the evidence suggests that those factors that initiated the development of IDDM-associated autoimmune antibodies or enhance the titers of such antibodies usually operate before the time of ascertainment in twin and family studies. Because identical twins may be discordant for antibodies, including ICA and GAD as well as increased levels of activated T-cells, the event initiating the production of these diabetes-associated immune changes is likely to be environmental (30). These observations suggest that the critical environmental event that initiates the diabetes-associated immune changes occurs, in most prediabetic individuals, before ascertainment.

**Development of diabetes-associated antibodies.** Initial seroconversion to ICA positivity developed before 5 years of age in 85% of those subjects who showed seroconversion (Fig. 2). Conversion from ICA negativity to positivity during the prediabetic period is rare after 10 years of age (31) (Fig. 2). At birth, the child of a diabetic mother has the islet-specific autoantibodies (ICA, insulin autoantibody [IAA], and GAD antibodies) found in the maternal serum (32). The levels of ICA in cord blood are comparable to the maternal levels, presumably reflecting transplacental passage of maternal immunoglobulin G (IgG) antibodies. These passively acquired antibodies disappear after birth as expected, but they can subsequently be replaced by the infant's own antibodies. In a recent study, 3 of 18 infants of diabetic mothers developed IAA, ICA, and GAD by 2 years of age (32). These observations suggest that the immune process associated with the development of IDDM is usually initiated in early childhood. It is possible that, in some cases, the disease process even starts in utero.

**Disproportionate maternal influence.** Two observations suggest that maternal-related events influence the development of IDDM: 1) the differential risks of developing IDDM according to which parent has diabetes and 2) blood-group incompatibility between mother and infant. Children of diabetic mothers are less likely to develop IDDM than are children of diabetic fathers (33). The mean 20-year life-table risk of diabetes in offspring of diabetic mothers and fathers in one study was 3.4 and 8.9%, respectively (33). This low risk is confined to offspring of mothers who had become diabetic after 8 years of age. It remains unclear whether the reduction in transmission rates is because of genetic or nongenetic factors. Preferential paternal transmission of an allele in the 5′-region of the insulin gene to HLA-DR4-positive diabetic offspring has been described; 38 of 50 HLA-DR4-positive diabetic offspring received this allele from their father as compared with 8 of 21 non-HLA-DR4 offspring (34). These observations raise the possibility that genetic imprinting, or the differential expression of genotypes according to the parental source of the relevant gene, contributes to the risk of developing diabetes.

Blood-group incompatibility between a mother and her child may predispose to IDDM. Children dying of erythroblastosis fetalis because of severe blood-group incompatibility between the mother and child exhibit islet hyperplasia. The nature and implications of this association remain obscure. However, nonfatal blood-group incompatibility, whether to rhesus or ABO blood groups, has been shown to confer an increased risk to the infant for developing diabetes (35).

**Importance of weaning diet.** The early infant diet may affect IDDM onset in later life. A number of epidemiological studies have established that the risk of developing IDDM is higher in non-breast-fed children than in breast-fed children and that breast-feeding for >3 months protects from IDDM (36). Breast-feeding could protect against diabetes by providing immune factors involved in defense against infection, such as specific secretory IgA and cytotoxic T- and B-cells. Alternatively, early cessation of breast-feeding is associated with the early introduction of foreign antigens, such as cow's milk proteins (36-38). In one recent study, the attributable risk was 8% for cow's milk and 25% for solid foods if these factors were introduced after 3 months of age (37). The particular fraction of cow's milk that might be diabetogenic is controversial (37-39). Antibodies to bovine serum albumin (30) may be more common in patients with recently diagnosed diabetes than in control subjects, although this is disputed (40,41). These antibodies recognize a dominant epitope found in bovine, but not in rat or human, albumin. A peptide expressed by human islets, p69, when exposed to γ-interferon in vitro and expressed by an islet β-cell cDNA library shares some limited homology with this bovine epitope (40). The cow's milk theory postulates that individuals genetically susceptible to IDDM can generate antibodies against bovine

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**FIG. 2.** Results of repeated testing for ICA in families with an IDDM proband in Auckland, New Zealand. A total of 3,979 subjects were tested initially, and of those who were ICA-negative, 1,007 were retested; 20 of 1,007 on retesting had converted to ICA-positive (>10 JDF U). The age of those who seroconverted is shown.

<table>
<thead>
<tr>
<th>Age at test (yrs)</th>
<th>% ICA Converters</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>17/460</td>
</tr>
<tr>
<td>5-9</td>
<td>3/191</td>
</tr>
<tr>
<td>10-14</td>
<td>0/142</td>
</tr>
<tr>
<td>15-19</td>
<td>0/63</td>
</tr>
<tr>
<td>&gt;20</td>
<td>0/150</td>
</tr>
</tbody>
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albumin that cross-react with p69. The implication that bovine milk is important in causing diabetes finds some support from observations in animal models of spontaneous diabetes in which progression to diabetes can be either markedly reduced, as in the BB rat if L-amino acids are substituted for protein in their diet (39), or totally prevented, as in NOD mice, by hydrolyzing the protein content of the diet (42). The fraction of cow’s milk that promotes diabetes in NOD mice is not albumin but casein. These interesting observations regarding the potential role of cow’s milk in causing IDDM need to be confirmed.

Patients with IDDM in Iceland, as elsewhere, are more likely to present with diabetes during the autumn, with a noticeable excess of male diabetic patients born in October (43). This excess might be because of parental consumption of smoked cured mutton, traditionally eaten around the New Year, which is rich in nitrosamines. Mice fed with cured mutton had male offspring with increased glucose levels and evidence of β-cell destruction (43). Smoked mutton, a rare commodity, can hardly account for the incidence of IDDM worldwide. Nevertheless, the low prevalence of IDDM in primitive societies is worth noting because they do not use food preservatives such as nitrosamines.

If these dietary associations are confirmed, it is possible that the excess disease risk attributed to them may operate only in those subjects genetically at risk of the disease, for example, in those with HLA genetic susceptibility (37). In summary, evidence as disparate as blood-group incompatibility between mother and child and dietary practices in infancy influence the risk of developing IDDM.

**Congenital rubella infection causes IDDM.** There is a precedent for an early environmental event causing IDDM. Congenital rubella infection can cause diabetes of a similar type to both IDDM and non-insulin-dependent diabetes (NIDDM). Diabetes is found in ~20% of patients with the congenital rubella syndrome with a latent period of many years and a median age of onset of 13 years (44,45). As with IDDM, antibodies to ICA and surface antigens are found in ~70% of those who develop diabetes (46). Those patients exposed to congenital rubella who also have the HLA genetic susceptibility associated with IDDM (HLA-DR3 and -DR4) tend to develop diabetes, and as with IDDM, HLA-DR2 is apparently protective (45). Rubella-induced diabetes is rare and cannot account for the general prevalence of patients with IDDM. It remains possible that other maternal viral infections during pregnancy could be important risk determinants for IDDM; for example, levels of group-specific enteroviral IgG and IgM antibodies during pregnancy were higher in 57 mothers of children who later developed IDDM than in 208 mothers of healthy control subjects (47).

**CRITICAL EVENT OPERATES OVER LIMITED PERIOD**

The consistent and striking decline in disease incidence after puberty could be caused by either a loss of the genetic or of the environmental effect (Fig. 1). Loss of the genetic effect could result from attrition of the genetically susceptible pool, but we know from twin studies that the majority of genetically susceptible individuals do not develop the disease (9-11). The decrease in the disease incidence with age is, therefore, likely to be because of a decreased environmental effect. This loss of the environmental effect is even seen in genetically susceptible subjects, given that 94% of the co-twins of diabetic patients who develop diabetes do so within 12 years of the diagnosis of the index twin and most much earlier; thereafter, the chance of the co-twin developing diabetes is small (9). These observations imply that the environmental effect that causes IDDM operates over a limited period in childhood.

**Exposure or susceptibility.** It is not possible to be sure whether the loss of the environmental effect with age, even in genetically susceptible subjects, is because of lack of exposure or loss of susceptibility. It is difficult to envisage a ubiquitous environmental factor to which only children are exposed. On the other hand, virus infections can reduce susceptibility to diabetes, at least in an animal model of IDDM (48). It is not known whether IDDM is initiated by single or multiple exposures during the critical period. Diabetes can be produced in animal models using viruses and chemical toxins in combination (49). Cumulative damage, if it were to occur, would probably have to do so over a limited period as outlined above.

**EPIDEMIOLOGICAL IMPLICATIONS OF EARLY EVENTS CAUSING IDDM**

The proposal that an early environmental event initiates the disease process leading to IDDM, if true, could alter the focus of epidemiological research, our understanding of this process, and the nature of therapeutic intervention.

**Focus on early environmental changes.** Epidemiological research has not yet successfully identified relevant environmental factors (2). Evidence summarized here suggests that the critical environmental event may operate several years before the onset of clinical diabetes. Therefore, in seeking critical environmental factors, emphasis has switched to the study of early childhood, such as the observation that early exposure to cow’s milk may play a role in the etiology of IDDM. The potential role of other factors in causing IDDM, including toxins and viruses, does not conflict with the cow’s milk hypothesis because the cause of IDDM may be multifactorial. All of these agents could operate in different ways, either together synergistically or individually, to initiate islet β-cell destruction.

**Environmental factors precipitate clinical onset.** The diagnosis of IDDM is made more often in cooler than in warmer months, and the peak incidence is consistently associated with the peripubertal years (15). If IDDM is caused by an environmental event that operates in early life, these associations would be secondary to the cause of the disease; that is, these environmental factors could precipitate the disease presentation but would not initiate the disease process, which is likely to have occurred many months earlier (13). Supporting this argument is the fact that immune and metabolic changes in prediabetic individuals antedate by many months the season in which the clinical diagnosis is made (12). It remains possible that IDDM is precipitated by multiple environmental “hits,” in which case a seasonal factor could provide the critical insult. However, if this proposal was correct, immune changes would not have as high a predictive value in family studies as they do (28). Finally, both immune and metabolic changes have been clearly demonstrated in twins before their pubertal growth spurt and before they developed diabetes (19). Therefore, it is unlikely that the pubertal growth spurt plays a primary role in the pathogenesis of IDDM. The evidence favors a limited role for seasonal factors and puberty in precipitating the
clinical presentation, perhaps by causing insulin insensitivity in a metabolically compromised patient.

Although we suggest that environmental events in early childhood are a cause of diabetes, we do not rule out the possibility that environmental factors in later life could cause IDDM. However, if our hypothesis is correct, critical exposure to viruses or toxins in later life would be uncommon. One exceptional case suggested direct viral involvement: when a 10-year-old boy died from an overwhelming viral infection and diabetic ketoacidosis, a Coxsackie B4 virus isolated from his pancreas induced diabetes with islet cell damage in mice susceptible to diabetes (50). In addition, a number of structurally diverse toxins are diabetogenic in animals and, in some cases, also in humans. Of these toxins, only N-nitroso derivatives are known to induce acute β-cell destruction and diabetic ketoacidosis; for example, the rat poison Vacor, when taken as an overdose, can induce ICAs and diabetes in those subjects with HLA-DR3 and -DR4 (51).

Changes persist after critical exposure. The destructive immune process, once initiated, would have to pursue a chronic progressive course of β-cell destruction if the initiating event occurred over a short period some considerable time before the clinical onset of the disease. Such a chronic course is consistent with what is known of the prediabetic period. Changes can be detected up to 14 years before the onset of diabetes, during which period immune, metabolic, and clinical changes may herald the onset of clinical diabetes (12,19,25). These immune and metabolic changes tend to persist throughout this period, which is consistent with the progressive and continuous nature of the destructive process (52). Increased levels of activated T-cells expressing the HLA-DR antigen and either ICA or IAA were found in all of 10 prediabetic twins in a total of 39 of 40 samples tested during the prediabetic period (27).

Variable rate of disease progression. If the critical initiating event usually operates before 5 years of age, then the rate of progression of the disease process must vary widely, being rapid in patients presenting <5 years of age and slow in those presenting at >30 years of age. Perhaps the most striking evidence that the disease rate can be variable comes from the study of disease recurrence in pancreas grafts (53). A pancreas isograft in a diabetic patient can result in the temporary amelioration of hyperglycemia. However, recurrence of the diabetic process can occur, particularly if the graft is from an identical twin. Recurrence can be very rapid, with diabetes developing within as little as 6 weeks (53). There is clear histological evidence for a variable rate of progression (54). Not all the insulin-secreting β-cells in a patient with IDDM are destroyed; even in long-standing diabetic patients, ~10% of the islets can have insulin-containing cells (55). This observation implies that the destructive process does not involve all cells simultaneously and that, in some, the destructive process may progress at variable rates, even after the clinical onset of diabetes. In keeping with this proposal and with the concept of a more aggressive disease process in younger patients, histological studies show that β-cells tend to be absent within 12 months of diagnosis in patients <7 years of age, but are often present for longer in older patients (54).

Further evidence that there is variability in the rates of progression to IDDM come from studies of immunological changes during the prediabetic period. Life-table analysis reveals that >50% of first-degree relatives with ICA >40 Juvenile Diabetes Foundation Units (JDF U) progress to diabetes within 5 years compared with only 15% of those with ICA between 20 and 40 JDF U (28). There is a particularly striking relationship between a rapid rate of progression to IDDM and the presence of IAA. Levels of IAA, reflecting the affinity and capacity of the autoantibodies for insulin, correlate positively with the rate of developing the clinical disease and form a critical component of the dual parameter model that seeks to predict rates of progression to diabetes (52,56).

Genetic factors may affect disease rate. Rates of disease progression could be determined by genetic or nongenetic factors. There is evidence that genetic factors are important in determining whether IDDM presents in early or later life. Concordance rates for IDDM in identical and nonidentical twins approximate when the index twin is diagnosed at >15 years of age but are substantially higher in identical twins when the index twin was diagnosed at <10 years of age (10). These observations suggest that the genetic influence causing IDDM is greatest in early-onset cases. In keeping with this proposal, patients with IDDM diagnosed before 10 years of age are more likely to have HLA susceptibility genes, notably the HLA-DQA1*0301-DQB1*0302 haplotype, than are patients diagnosed at an older age (57). It is possible, therefore, that certain HLA haplotypes and, perhaps, other unrecognized genetic elements determine the rate of disease progression.

Disease process could lead to NIDDM. Because clear evidence exists that the islet β-cells can be damaged without IDDM developing, it is reasonable to anticipate that, in some individuals, the damage may be sufficient to cause impaired glucose tolerance, even diabetes, without absolute insulin deficiency. Until more is known of those immune features that clearly define the process associated with IDDM, this argument will remain hypothetical. There is evidence, however, that in some patients who present with NIDDM and later become frankly insulin-dependent, the pathogenesis, like IDDM, has an immune basis. In families with a NIDDM parent and an IDDM child, shared genetic factors linked to HLA-DR4 seem to be important determinants of disease in both (58). Of patients who develop IDDM, ~25% do so after 35 years of age (16). In addition, up to 1% of patients with NIDDM each year become insulin deficient, and these patients have many features of IDDM, including low or normal body weight, ICA, antibodies to GAD, and high rates of HLA-DR3 and -DR4 (59). Patients not treated with insulin but who have persistent ICA and HLA-DR4 are at particular risk of progressing to insulin dependence; of 32 ICA-positive "NIDDM" patients, 7 of 22 with persistent ICA became insulin-dependent compared with none of the 10 in whom ICA became undetectable (60).

Disease process need not result in diabetes. Although an imbalance between destruction and recovery of the islet cells can lead to IDDM, it might be possible for the destructive process to be so slow that diabetes never develops. Immune changes associated with IDDM do not always lead to diabetes (61). Increased levels of activated T-cells have been detected in the majority of nondiabetic identical twins of recently diagnosed diabetic patients, who were then followed for up to 10 years without developing diabetes themselves (30). Autoantibodies to islet cells, insulin, GAD, and tryptic fragments of the 64K islet antigen have also been detected in nondiabetic twins and siblings of diabetic pa-
tients who were unlikely to develop diabetes themselves (12,28). In both twin and population-based studies, ICA can remit without progression to diabetes (30,62).

Islet β-cells can also be functionally damaged without progression to IDDM. Impaired glucose tolerance was observed in 5 of 41 identical twins of patients with IDDM, all of whom now have normal glucose tolerance (26). Some of these nondiabetic twins as well as siblings had a decreased insulin response to intravenous glucose and an altered insulin-to-glucose dose-response relationship (63,64). Finally, increased peripheral blood levels of proinsulin have been found in twins and siblings of diabetic patients many years after the diagnosis of the index case, when they themselves are unlikely to develop IDDM (24,65). We have known for some years that immune changes in organ-orientated diseases such as thyroiditis need not lead to destruction of the target cells. It now looks as if the disease process associated with IDDM also encompasses a wide spectrum of immune and metabolic changes that do not lead to diabetes.

IMPLICATION FOR PREDICTION OF IDDM

Immune changes may be predictive. If the destructive process that leads to IDDM develops in early life, one would anticipate that certain immune and metabolic changes associated with this process would have a high predictive value. Certainly, if the destructive process is initiated before 5 years of age, screening a population should identify most of those who develop IDDM; that is to say, the marker should have a high sensitivity as a predictor. Alternatively, if the disease process was caused by multiple events operating over many years right up to the weeks and months preceding the onset of clinical diabetes, then the predictive value of any changes should be limited, with low sensitivity, because only a fraction of those who develop diabetes would be identified. Certain immune and metabolic changes are, indeed, sensitive, and not necessarily specific, predictors of IDDM. ICAs are detectable in 5–8% of first-degree relatives (28,29); the majority of future cases of IDDM will come from this ICA-positive subgroup, and the positive predictive value of ICA >80 JDF U is as high as 90% (31). Antibodies to a 64K antigen were detected in samples from 34 of 42 patients tested up to 91 months before the onset of IDDM (66,67). Antibodies to GAD, which constitute some or all of the 64K antigen, appear in some 80% of high-risk relatives before they develop IDDM (12). When immune changes are considered in association with metabolic changes, they can predict IDDM with a high degree of certainty (68). Predictive values for immune or metabolic changes may differ in twin, family, or population studies even though there is no direct evidence that familial cases of IDDM differ from sporadic cases (69). It is proposed, however, that any difference in predictive values for ICA between family and population studies will not be because of its loss of sensitivity as a predictor; rather, it is likely to be because of loss of specificity (70).

Persistent immune changes and prediction. The extent and persistence of immune changes may be important as predictors of IDDM. In a 10-year prospective study of a cohort of 25 nondiabetic twins, 10 of whom developed IDDM, both increased levels of activated T-cells and either ICA or IAA distinguished twins who developed IDDM from those who did not (27).

Predictors of disease rate. Given the widely different ages at diagnosis of IDDM and the evidence that the critical initiating event occurs within a limited period in early childhood, striking differences should be seen in rates of β-cell destruction between prediabetic subjects. Destruction of the insulin-secreting β-cells can be estimated using the insulin response to intravenous glucose. The first-phase insulin response to intravenous glucose declines before the onset of diabetes in most cases. ICA-positive relatives with insulin responses below the first percentile developed diabetes faster (0.48 per subject-year of follow-up) than did those with higher insulin responses (0.05 per subject-year) (71). The presence of IAA has also been reported to correlate with time to diabetes onset (56). These observations led to the development of the dual-parameter model using IAA and the first-phase insulin response to intravenous glucose to produce a simple linear regression model for predicting the time to overt diabetes (52,68). Of 40 ICA-positive nondiabetic relatives, 12 developed diabetes on follow-up, 11 of them within the 95% time limit provided by the model's equation (68). This model, although yet to be independently validated, encapsulates the concept that prediction of disease rate should be feasible.

Approaches to prediction. Screening and intervention in the population at large must be our goal. Strategies for disease prevention will involve identification of high-risk individuals using the genetic markers as well as the immune and metabolic changes associated with the disease. If the immune process associated with the development of IDDM is initiated in early childhood, several implications become important for the prediction of the disease. First it should be possible to identify individuals at risk of developing IDDM by screening a population at an age after which the environmental effect is thought to operate. Screening a nondiabetic population at, for instance, the age of 5 years for ICA, IAA, and GAD antibodies should identify most of those individuals who will later develop diabetes. Such a strategy could identify with high sensitivity those subjects who will develop IDDM. To improve the specificity of prediction, a separate strategy might employ a two-test and two-sample approach to make use of the observation that immune changes, once induced, usually persist up to the clinical onset of diabetes. Thus, an initial test of high sensitivity (for example, ICA) can be linked with more specific tests that could be repeated after a period which remains to be defined. Not all those with persistent disease-associated immune changes can be expected to develop IDDM, and so it is likely that the specificity of these changes will not approach 100%. Immune studies could be used in conjunction with metabolic changes to increase the certainty of prediction. Trials of intervention will have to take account of the potentially variable rate of progression of the disease process. It will be necessary to stratify subjects entered into intervention trials according to markers of rates of β-cell destruction.

IMPLICATIONS FOR PREVENTION

We have proposed that IDDM can be regarded as a chronic destructive disease of the islet β-cell in which the destructive process is initiated at an early age by an environmental event. A primary prevention strategy for IDDM requires that critical environmental factors are recognized and removed or their effect negated. Given the early age at which these
risk factors may operate, it would be imperative to intervene early. Only three potentially modifiable factors have been identified so far, adenoviruses, smoked mutton, and cow's milk. Primary intervention programs in the general population or in high-risk groups might aim to eliminate or modify the response to these agents. For example, such programs might include the late introduction of cow's milk into the diets of neonates or the elimination of bovine albumin from cow's milk. A study to be started in Finland will assess the introduction of a non-bovine-based infant formula in all children <9 months of age after breast-feeding. If, as we propose, the environmental factor causing diabetes has its effect predominantly in early life, then primary prevention strategies need operate only in the young.

Secondary prevention of IDDM would involve the identification of high-risk subjects, a feasible strategy given the evidence for a long prediabetic prodrome. Early identification of these prediabetic subjects should enable us to intervene at a stage when the residual $\beta$-cell mass is sufficient to sustain normoglycemia. It is possible that some natural regulatory system may, in some cases, limit progression to the disease, because many of the immune and metabolic changes associated with IDDM can occur without leading to clinical diabetes. Tilting the balance of this immune regulation away from destruction might be sufficient to prevent the onset of diabetes. The prospects of prediction and prevention would be strengthened by finding that the disease process is usually initiated in early life and that the destruction of insulin-secreting cells can be limited, even halted. The decade to come promises further developments that should bring us closer to determining the validity of this concept, as well as toward deciding when, whom, and with what we should treat to prevent this potentially devastating disease.

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