Chapter 8

Risk Factors for Insulin-Dependent Diabetes

Janice S. Dorman, PhD; Bridget J. McCarthy, MS; Leslie A. O'Leary, PhD; and Anita N. Koehler, MPH, RD

SUMMARY

Insulin-dependent diabetes mellitus (IDDM) is one of the most common chronic diseases in children; its incidence is increasing in the Americas and around the world. However, the etiology of this disorder remains unclear. Epidemiologic patterns, including the higher IDDM incidence rates in Caucasians compared with African Americans or Hispanics, the increase in risk at puberty, and the more frequent occurrence of the disease during the winter months, suggest that viruses, nutrition, and socioeconomic factors may be involved. These environmental risk factors have been investigated in numerous populations but have yielded conflicting results. This has been due, in part, to a failure to account for host susceptibility in most studies. The genes that confer susceptibility to IDDM are located in the HLA region of chromosome 6. Individuals who carry alleles containing DNA sequences coding for arginine in position 52 of the DQ α chain (DQA1*Arg-52) and an amino acid other than aspartic acid in position 57 of the DQ β chain (DQB1*non-Asp-57) are known to be at high risk for IDDM. Genetically susceptible individuals who also have autoantibodies to islet cell antigens or to glutamic acid decarboxylase are at greatest risk for developing IDDM. Despite our ability to identify several important risk factors, we are currently unable to prevent the occurrence of IDDM, even in those who are genetically susceptible and immunologically compromised. Future epidemiological studies of potential etiologic determinants, focusing on host and environmental risk factors and their interactions, are likely to provide important information regarding the causes of IDDM and lead to approaches for disease prevention.

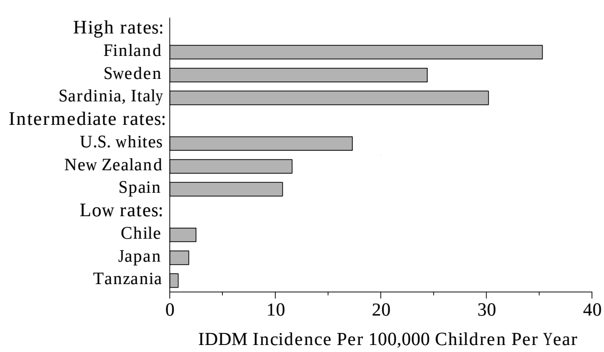
• • • • • • •

POPULATION STUDIES OF IDDM

RACE AND ETHNICITY

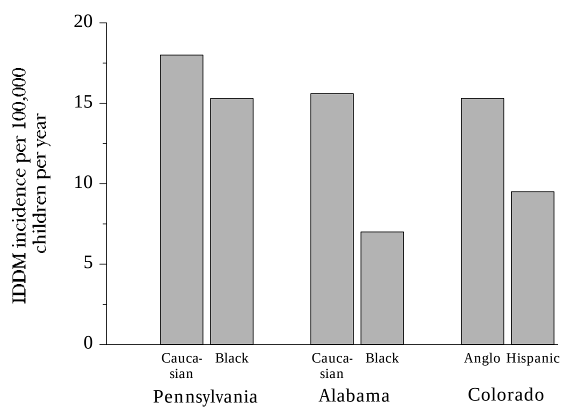
IDDM is one of the most common chronic disorders of childhood (see Chapter 3). Standardized descriptive studies of the epidemiology of IDDM are being conducted around the world, providing much needed information regarding the frequency and potential risk factors for IDDM in developed and developing countries. In many areas, these investigations are being facilitated through the World Health Organization Multinational Project for Childhood Diabetes, known as *Diabete Mondiale* or the DiaMond Project[1], and the EURODIAB ACE Study in Europe[2]. They have provided clear evidence that racial and ethnic background represents one of the most important risk factors for IDDM. As illustrated in Figure 8.1, IDDM incidence is highest (>20 per 100,000 per year) in children in the Scandinavian countries[3-6] and Sardinia, Italy[7], and is intermediate (3-19 per 100,000 per year) in the United States, Spain[8], and Israel[9]. Asian[10-11] and Native American[12] populations, as well as people in

Figure 8.1
Incidence Rates for IDDM in Some International Populations



Source: Reference 3

Figure 8.2
Incidence Rates for IDDM in the U.S. According to Race/Ethnicity



Source: References 18-20

Latin American countries, such as Chile[13] and Mexico[14], have some of the lowest incidence in the world, with rates of <3 per 100,000 per year.

Differences in IDDM incidence within countries have also been observed. More than a sixfold variation in risk exists in Italy[15], where rates range from ~6-7 per 100,000 per year in the northern and central parts of the country[16,17] to 30 per 100,000 per year on the island of Sardinia[7]. Studies in the United States have focused on Caucasians, African Americans, and Hispanics (Figure 8.2). In Allegheny County, PA, the incidence of IDDM in children is higher in Caucasians (18.0 per 100,000 per year) than African Americans (15.3 per 100,000 per year)[18]. An even larger racial difference has been found in Jefferson County, AL (15.6 per 100,000 per year in Caucasians versus 7.0 per 100,000 per year in African Americans)[19]. Among Hispanics in Colorado, the incidence of IDDM is lower than for non-Hispanics (9.5 per 100,000 per year versus 15.3 per 100,000 per year, respectively)[20].

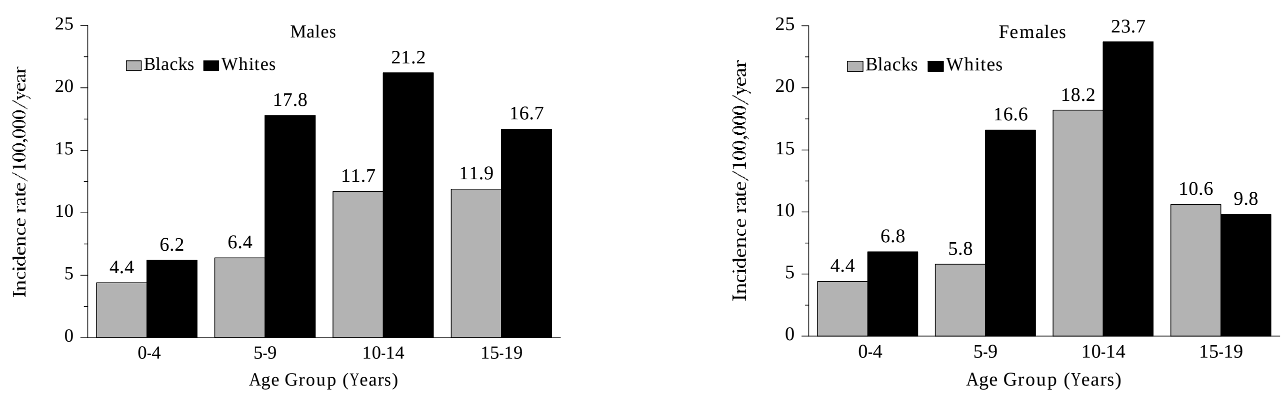
GENDER AND AGE

Gender does not appear to be a significant determinant of IDDM, since incidence rates are generally similar for males and females. The distribution of age at onset for IDDM is also relatively consistent across populations, with a small peak occurring at ~5 years of age in males (Figure 8.3) and a larger peak observed for both sexes occurring near puberty[21-24]. This age pattern may reflect exposure to infectious agents during childhood[21], growth spurts[25], or hormonal changes that occur during adolescence. Interestingly, diabetic children diagnosed before puberty have been reported to be taller at IDDM onset than nondiabetic siblings or control children of the same age[25-27]. Although a decreased growth velocity during the prediabetic period was reported by a recent twin study[28], most published data suggest that immunologic or metabolic factors related to accelerated growth, which is most significant during puberty, contribute to the etiology of IDDM. Thus, the risk of IDDM increases with age during childhood and adolescence. However, there is a decline in incidence of IDDM during adult years.

SEASONAL VARIATION

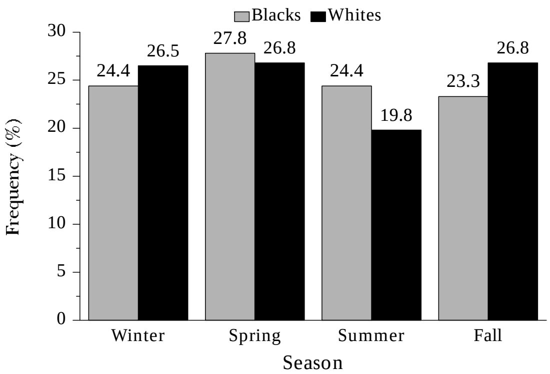
Seasonal variation in the onset of IDDM has been observed worldwide, suggesting that infectious agents are potential risk factors. Data from the Allegheny

Figure 8.3
Incidence Rates for IDDM by Age and Race for Males and Females, Allegheny County, PA, 1965-80



Source: Reference 24

Figure 8.4
Seasonal Distribution of IDDM Cases, by Race, Allegheny County, PA, 1965-80



Source: Reference 24

County, PA IDDM registry are shown in Figure 8.4[24]. Most studies from both the northern and southern hemispheres have found a reduction in the number of cases occurring during the warm summer months[19,23,24,29,30]. These epidemiologic patterns indicate that environmental factors such as viruses, which vary dramatically across populations, contribute to the etiology of IDDM. However, genetic differences also exist across racial groups and countries and appear to be a major determinant of the worldwide patterns of IDDM[31].

GENETIC SUSCEPTIBILITY

RISK OF IDDM IN RELATIVES

More than 80% of cases of IDDM occur in individuals with no family history of the disease. However, in the remaining 20%, IDDM aggregates in families[32]. The overall risk before age 30 years for North American Caucasian siblings, parents, and offspring of individuals with IDDM ranges from 1% to 15% (Table 8.1)[33-43], compared with rates of <1% for individuals without IDDM relatives. Most data on risk of IDDM in family members are from Caucasian populations that have similar incidence rates. There is a paucity of information for other racial groups in the Americas, including African Americans and Hispanics[32]. In Allegheny County, PA, there was a lower risk for developing IDDM in siblings of African-American IDDM patients, compared with Caucasians (2.8% versus 6.5% through age 30 years)[42]. Although the sample size was small for the African-American population, these findings parallel the racial difference in IDDM risk for the general population. There also appears to be an

Table 8.1
Risk of IDDM in First-Degree Relatives of IDDM Cases: Studies from the U.S. and Canada

Ref.	Population	Prevalence in parents	Risk to siblings before age 30 years	Risk to offspring of IDDM fathers and mothers before age 30 years
33	Montreal, Canada	3.2%	4.1% prevalence	
34	Boston, MA	5.7%	4.6% prevalence	
35	Pittsburgh, PA	2.6% 1.4% mothers 3.7% fathers	3.3% prevalence	
36	Minnesota	3.0%	5.5% prevalence	
37	Boston, MA			3.1% (either parent) 1.3% (mother) 6.1% (father)
38	Boston, MA			2.1% (mother)
39	Pittsburgh, PA	2.0% 1.0% mothers 3.0% fathers		
40	Pittsburgh, PA			3.0% (either parent) 1.4% (mother) 4.3% (father)
41	Wisconsin	6.4% 2.9% mothers 3.5% fathers	15.4% prevalence	
42	Pittsburgh, PA		6.3% incidence 6.5% whites 2.8% blacks	
43	Boston, MA			4.8% (either parent) 3.4% (mother) 8.9% (father)

Source: References are listed within the table increased risk of IDDM in relatives of subjects with non-insulin-dependent diabetes mellitus (NIDDM)[44]. This may be related to specific HLA haplotypes that confer susceptibility to both IDDM and NIDDM[45].

For children with IDDM who have an IDDM parent, the father is more likely to have the disease than the mother[35,39,41]. The prevalence of paternal compared with maternal IDDM was 6.2% versus 2.3% in Sweden[46] and 5.7% versus 2.6% in Finland[4]. Prospective studies that ascertained IDDM in the offspring of parents with IDDM have also revealed a higher risk of IDDM in children of affected fathers than mothers (~6% and 2%, respectively; Table 8.1)[37,40,43,47]. Several possible explanations have been proposed for this intriguing finding, including an increase in spontaneous abortion by IDDM mothers of fetuses that might develop IDDM[37], maternal environmental factors that allow the fetus to remain tolerant to autoantigens[38], an increase in the paternal transmission of HLA susceptibility genes for IDDM[48], and differential expression of the disease depending on the sex of the parent transmitting the susceptibility allele[39].

HLA ANTIGENS: SEROLOGICAL AND MOLECULAR STUDIES

The HLA region of chromosome 6 contains genes that encode class I (HLA-A, B, C), class II (HLA-DR, DQ, DP), and class III antigens, as well as numerous other genes that control immune response[49]. Associations between HLA and IDDM began to be documented in the mid-1970s when it was observed that individuals with IDDM were significantly more likely to have genes for HLA-B8 and B15 than nondiabetic individuals[50,51]. It was thought that the genes coding for these antigens may be linked to "true" IDDM susceptibility genes, located in adjacent regions of the chromosome. With the discovery of class II antigens, associations between DR locus antigens and IDDM became apparent. These studies revealed that the relationship between IDDM and DR3 and/or DR4 was stronger than between IDDM and B8 and B15[52,53]. Approximately 95% of IDDM patients in most populations had DR3 and/or DR4, and individuals with both DR3 and DR4 were particularly susceptible to IDDM. However, racial differences in the HLA-IDDM associations were also observed. DR7 in African Americans[54], DR5 in Hispanics[55], and DR9 in Chinese[56] and Japanese[53] also appeared to contribute to IDDM susceptibility.

With advances in molecular biology, HLA studies of IDDM are being conducted at the DNA level in populations across the world. Molecular techniques have simplified procedures required for specimen collection from large population-based cohorts. They have also provided researchers with more precise markers of IDDM susceptibility than those afforded by conventional serological techniques. Analyses in a variety of racial and ethnic groups have revealed that DNA sequences in the DQB1 gene coding for the presence of an amino acid other than aspartic acid in the 57th position (non-Asp-57) is highly associated with developing IDDM, whereas sequences coding for aspartic acid appear to confer resistance to IDDM[55,57-64]. This association is much stronger than the association between IDDM and HLA-DR3 and DR4[58] and reflects the results of older HLA-DQ serological studies, which revealed an increase in DQ2 in African Americans with IDDM[65]. The consistency of the results of molecular studies of the DQB1 gene in most populations confirm its importance as a locus determining IDDM susceptibility.

An exception was found for the Japanese and the DR4-DQ4 susceptibility haplotype, which contains DQA1*0301 and DQB1*0401. The latter codes for aspartic acid in position 57 (Asp-57), but the DQA1 gene contains DNA sequences that code for arginine in position 52[62,66,67]. DQA1*0301 is also found in African American but not Caucasian DR7 haplotypes, both of which contain DQB1*0201 (non-Asp-57). Caucasian DR7 haplotypes carry the DQA1*0201 allele (non-Arg-52) and appear to be less diabetogenic. DQA1*Arg-52 genes are associated with IDDM in a variety of racial and ethnic groups and represent consistent independent markers of IDDM susceptibility[60,63,64,66,67]. For example, in Hispanics and non-Hispanics in Colorado, there was an increase in DQA1*0301 (Arg-52), as well as DQB1*0201 and DQB1*0302 (non-Asp-57) in individuals with IDDM compared with nondiabetic individuals[55].

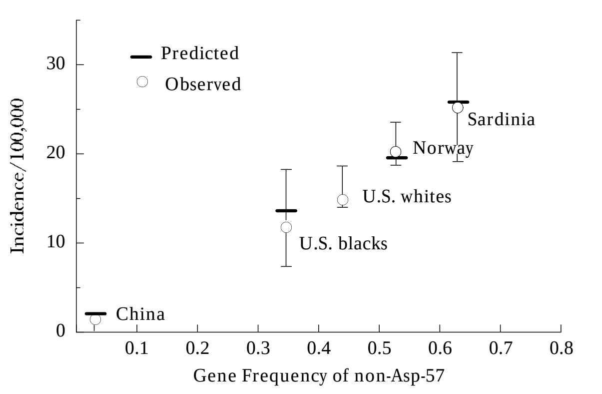
The combination of DQA1*Arg-52 and DQB1*non-Asp-57 alleles seem to be particularly diabetogenic. The associations between these molecular polymorphisms and IDDM may have a biological basis. The presence of aspartic acid in position 57 of the DQ β chain and arginine in position 52 of the DQ α chain affects the peptide binding ability of the HLA molecule, which influences the recognition of the HLA-peptide complex by particular T cell clones[49]. Structural modifications such as these may explain the importance of specific amino acid sequences in determining susceptibility or resistance to IDDM, suggesting that the molecules are directly involved in IDDM etiology.

Immunogenetic studies have been conducted in populations in which the incidence of IDDM has been established from a registry[31], including China[11]; Norway[68]; Sardinia, Italy; and African Americans and Caucasians in Allegheny County, PA. The prevalence of the DQB1*non-Asp-57 genotypes varies significantly in people with IDDM from these five populations (from 6% in China to 100% in Sardinia), as well as in nondiabetic individuals (from 0% in China to 38% in Sardinia), with an increase in non-Asp-57 homozygosity in areas with a high incidence of IDDM[59]. In each of the five populations, the risk of IDDM in non-Asp-57 homozygotes compared with Asp-57 homozygotes was significantly increased, ranging from 14 to 111. For Allegheny County Caucasians, the incidence rate for IDDM was highest for non-Asp-57 homozygotes (47.6 per 100,000 per year), intermediate for heterozygous individuals (13.0 per 100,000 per year), and lowest for Asp-57 homozygotes (0.45 per 100,000 per year), suggesting a dose-response relationship between susceptibility and IDDM risk.

If the geographic differences in risk of IDDM are due to variation in genetic susceptibility to the disease, then incidence rates for IDDM should be similar in persons with the same genotype across populations[59]. Because the statistical properties of these estimates are currently under investigation, this issue was addressed indirectly by applying the genotype-specific incidence rates for Allegheny County Caucasians to the other four populations to predict the overall IDDM incidence rate for each area. Each of the predicted rates fell within the 95% confidence intervals for the rates established through IDDM registries (Figure 8.5).

Both the DQA1 and DQB1 genes are important in determining susceptibility to IDDM[64]. The risk of developing the disease appears to be markedly increased for individuals who are homozygous for both DQB1*non-Asp-57 and DQA1*Arg-52 alleles. Moreover, at least two-thirds of the incidence of IDDM (attributable risk of ≥62%) can be explained by the contribution of these high-risk genes in most populations. In contrast, individuals who are heterozygous at one of the two genetic loci have a risk for IDDM that is similar to that for the general population. These studies emphasize the importance of the complete DQ molecule (composed of an α and a β chain) in the etiology of IDDM.

Figure 8.5
Association Between Observed and Predicted Age-Adjusted Annual IDDM Incidence Rates



The 95% confidence intervals are indicated by the bars associated with each observed incidence value.

Source: Reference 59

In the future, it will be important to directly evaluate the geographic variation in IDDM incidence in genetically homogeneous subgroups and to accurately quantify the contribution of host susceptibility to the global patterns of IDDM. Knowledge of the proportion of susceptible individuals in a population and the magnitude of their risk will provide extremely important information for implementation of prevention strategies and health planning initiatives. The development of the field of molecular IDDM epidemiology will, therefore, test unique hypotheses and achieve a great deal in terms of scientific advancement and public health[31].

ISLET CELL ANTIBODIES, INSULIN AUTOANTIBODIES, AND GAD

Islet cell cytoplasmic antibodies (ICA)[69], as well as antibodies to insulin[70], the 64kD islet cell antigen[71], and the enzyme glutamic acid decarboxylase (GAD)[72], are highly prevalent in persons with IDDM. However, it is unclear whether they play a direct role in the disease process or serve as markers of tissue damage initiated by other etiologic agents. Despite differences in the types of ICAs and variation in laboratory methodology used to detect these molecules, most studies have reported a very high prevalence of ICA (65%-100%) in patients with newly diagnosed IDDM[73]. This high prevalence contrasts with rates of 2%-5% in first-degree relatives (parents, offspring, and siblings) of patients with IDDM, and rates of 0.5% or less in nondiabetic persons[74]. In the United States, prevalence rates for ICA of 0.4%-0.8% have been reported[75,76]. ICAs are potent risk factors for IDDM, and first-degree relatives of patients with IDDM have a risk of developing IDDM that is 50-500 times that of people without ICA[73]. However, most individuals with ICA will never develop the disease. Thus, the predictive value for ICA in identifying which individuals will eventually go on to develop IDDM is low, and has been estimated at ~20%[77].

Several studies have examined the relationship between HLA and ICA. An investigation of German schoolchildren revealed that non-Asp-57 homozygosity was increased in children who were ICA positive, compared with children who were ICA negative[78]. A study of French schoolchildren found a similar distribution of DQB1*non-Asp-57 alleles in ICA positive and negative individuals[79]. These findings are consistent with molecular studies of ICA positive and negative Caucasian family members from Allegheny County, PA[80]. Although the proportions of first-degree relatives who were homozygous for both DQB1*non-Asp-57 and DQA1*Arg-52 were similar in those with (19%) and without (15%) ICA, the subsequent development of IDDM was restricted to individuals who were both ICA positive and genetically susceptible.

Insulin autoantibodies (IAA) are another immune marker for IDDM. However, methodologic variabilities and the ability to detect IAA in only ~50% of those who later develop IDDM limits their utility in identifying individuals at high risk for IDDM[81,82].

The most promising of the immune markers for IDDM are antibodies to GAD, originally identified as a 64,000-M islet cell antigen[72,83]. Several studies have examined the prevalence of GAD in IDDM and nondiabetic subjects. In U.S. Caucasians, 84% of newly diagnosed IDDM patients and 82% of ICA-positive first-degree relatives had GAD antibodies[84]. These antibodies were not detected in any nondiabetic subjects and in only one of the ICA-negative first-degree relatives. GAD may also help discriminate between NIDDM and IDDM. In one study, 69% of patients with a short duration of IDDM were positive for GAD antibodies, while only 5% of individuals with NIDDM and none of the nondiabetic subjects were GAD positive[85]. Accordingly, GAD potentially has the best ability to predict the development of IDDM[84]. However, prospective investigations and studies of the general population are required to determine the accuracy of this marker in identifying individuals who will subsequently develop IDDM. By evaluating the presence or absence of high-risk IDDM susceptibility genes and organ-specific autoantibodies, future population-based family and case-control studies will assess both the relative and absolute risks associated with these potential determinants of the disease.

ENVIRONMENTAL RISK FACTORS

Twin studies have shown that genetic susceptibility to IDDM appears to be necessary, but is not sufficient to cause the development of the disease, because concordance for IDDM occurs in only ~36% of monozygous twin pairs[86]. Thus, there must be a role for environmental factors in the etiology of IDDM. Nutrition and viruses have been suggested as potential determinants of the disease.

NUTRITION

Various nutrients and nutritional practices have been associated with the development of IDDM. Animal studies have consistently shown that diets containing intact protein, in contrast to diets with protein hydrolysates or an amino acid mixture, contribute to high rates of diabetes in susceptible animals[87,88]. Studies in humans have revealed less dramatic effects. However, a positive association between ingestion of smoked/cured mutton by Icelandic women at conception and subsequent development of IDDM in their offspring was reported[89]. In addition, the intake of foods containing high amounts of nitrosamines appears to be related to the etiology of the disease[90]. Moreover, an ecologic relationship between nitrate level in potable water supplies and IDDM incidence has been reported[91].

Studies have also examined the effect of nicotinamide, a water-soluble vitamin, on maintaining insulin secretion in newly diagnosed IDDM cases[92-94], but results have been inconsistent. Individuals with high ICA titres and low first-phase insulin response were significantly less likely to develop IDDM if they received daily doses of nicotinamide[95]. However, longer followup of individuals in well-controlled clinical trials is needed before the efficacy of nicotinamide for preventing IDDM can be advocated.

The most widely studied nutritional risk factor for IDDM is breast-feeding and exposure to cow's milk protein[96-101] (Table 8.2). In the early 1980s, an inverse relationship between breast-feeding and IDDM incidence was observed, suggesting that breast-feeding was a protective factor[102]. The incidence of IDDM is highly correlated with the amount of cow's milk consumed in various countries[103]. Also, a positive correlation has been found between IDDM incidence and intake of unfermented cow's milk, and a negative correlation with the prevalence of breast-feeding through at least age 3 months[104]. Studies in Canada, the United States, and other countries have corroborated these findings[96-99,105,106], showing a decreased IDDM risk in individuals who had a longer duration of breast-feeding, particularly those who were exclusively breast-fed.

A study of African Americans and Caucasians in Allegheny County, PA revealed that Caucasian children

Table 8.2
IDDM and Infant Nutrition: Studies from the U.S. and Canada

Ref.	Population	Exposure	Odds Ratio (95% CI)
96	IDDM patients from New York diabetic clinic; nondiabetic individuals were friends.	No breast-feeding vs. some breast-feeding	1.00 (0.45-2.24)
97	IDDM patients from Colorado registry; nondiabetic individuals from office practices and an unrelated study.	Breast-feeding <3 months vs. ≥3 months	1.47 (0.85-2.56)
98	IDDM patients from Montreal, Canada, registry; nondiabetic individuals were friends and relatives.	No breast-feeding vs. some breast-feeding	1.30 (0.70-2.50)
99	IDDM patients from Allegheny County, PA and Children's Hospital registries; nondiabetic individuals were siblings.	No breast-feeding vs. some breast-feeding	
		Caucasians:	2.00 (1.11- 3.33)
		African Americans:	2.00 (0.71-5.00)
100	IDDM patients from Colorado registry; nondiabetic individuals from licensed drivers.	No breast-feeding vs. some breast-feeding	1.09 (0.68-1.76)
		Cow's milk before age 3 months vs. after age 3 months	4.50 (0.90-21.40)
101	Meta-analysis	Breast-fed <3 months vs. ≥3 months	1.43 (1.15-1.77)

CI, confidence interval

Source: References are listed within the table

with IDDM were 50% less likely to have been breast-fed than those without IDDM[99]. Although duration of breast-feeding did not differ by diabetes status for Caucasians or African Americans, African Americans with IDDM were more likely to have received breast milk substitutes at an earlier age than those without IDDM (5.1 weeks versus 11.9 weeks, p=0.02). This association, however, was not significant for Caucasians (5.5 weeks versus 7.1 weeks, p=0.18), which may indicate a larger genetic influence in Caucasians or the contribution of other environmental factors to the etiology of IDDM.

Meta-analysis of selected studies on breast-feeding or early exposure to cow's milk and the development of IDDM revealed that patients with IDDM were 43% more likely to have been breast-fed <3 months and 63% more likely to have been exposed to cow's milk before age 3-4 months[101]. Thus, early exposure to cow's milk may be an important risk factor for IDDM and appears to increase the risk ~50%.

The relationship between exposure to cow's milk and IDDM has been investigated in genetically high- and low-risk Caucasian IDDM cases in Colorado[100]. Exposure to cow's milk at age <3 months was 11-fold higher in persons with IDDM, compared with nondiabetic persons among high-risk cases, defined as DQB1*non-Asp-57 homozygotes. This association was not found in low-risk individuals. These data suggest that there is an interaction between the genetics of the individual (DQB1*non-Asp-57) and an environmental factor (cow's milk) in the development of IDDM. However, additional studies are needed to confirm these findings in other ethnic groups in the Americas.

Lactoglobulin (casein), the major portion of protein in cow's milk, was significantly associated with an increased risk of IDDM in Sweden[107]. A Finnish study also found significantly higher levels of antibodies to both cow's milk and to lactoglobulin in IDDM children, compared with nondiabetic siblings and unrelated nondiabetic individuals[108]. Antibody levels were especially high in IDDM children age <3 years, suggesting that cow's milk proteins may have a particularly significant effect on the development of IDDM in young children.

The whey protein, bovine serum albumin (BSA), is the suspected milk protein trigger of an autoimmune response in genetically susceptible individuals. Antibodies to a 17-amino acid section of the BSA molecule (ABBOS), which react with a β-cell surface protein[109], have been found in children with IDDM. Since infants have an immature digestive system, exposure to large proteins such as BSA may allow these molecules to pass directly into the bloodstream. It has been proposed that genetically susceptible children who have been exposed to cow's milk at age 3-12 months (prior to gut closure) may develop antibodies to ABBOS. On exposure to viral infections at a later time, the sensitized immune system may mistake the β-cell protein for ABBOS and contribute to the β-cell destruction that occurs in IDDM[109]. Similar studies in Caucasians, African Americans, and Hispanics living in the Americas are needed to fully evaluate the nutritional etiology of IDDM.

VIRUSES

Strong arguments have been made for the role of recent exposure to the Coxsackie B virus in IDDM etiology. Coxsackie viruses B2, B3, B4, and B5 have all been isolated from the sera of persons with newly diagnosed IDDM[110,111]. The Coxsackie B4 virus has most often been associated with the disease, but the findings are not consistent[112]. Although it is unknown whether the virus may initiate or accelerate β-cell destruction, it is hypothesized that variants of the Coxsackie B virus have different potential in causing diabetes. However, the majority of IDDM cases show no evidence of recent viral infection at diagnosis of IDDM[113]. Interestingly, Coxsackie B virus infections were more prevalent in IDDM patients in Wisconsin who were DR3 positive, compared with those who were DR3 negative, thus suggesting a potential host-environment interaction contributing to the development of IDDM[114].

Attention has recently focused on persistent viral infections as possible triggers of autoimmune disease[115]. The incorporation of human cytomegalovirus (CMV) gene segments into genomic DNA has been significantly associated with IDDM in newly diagnosed patients[116], and a relationship between CMV genome positivity and islet cell antibodies has also been reported[116,117]. Persistent CMV infection may lead to the expression of viral or host antigens on the β-cells of the pancreas, resulting in the production of ICA. Alternatively, molecular mimicry may contribute to the production of antibodies that recognize both viral and host antigens. Aberrant β-cell expression of HLA class II molecules may also contribute to the beginning of an autoimmune response, particularly in the presence of DQB1*non-Asp-57 and DQA1*Arg-52. These issues need to be further explored in etiologic research.

Congenital rubella syndrome (CRS), which results from maternal exposure to the virus causing measles during pregnancy, has been associated with the development of IDDM. Approximately 20% of CRS patients in the United States also have IDDM[118]. The highest frequency of IDDM occurred in CRS cases with HLA-DR3 and/or DR4[119,120]. In addition, islet cell surface antibodies occurred in 20% of individuals with CRS, which is consistent with the frequency of these antibodies in patients with IDDM. It has therefore been hypothesized that exposure to rubella infection *in utero* triggers an autoimmune mechanism in genetically susceptible individuals, subsequently resulting in IDDM.

Several case reports have described a temporal relationship between mumps virus infection and the development of IDDM[121,122]. Epidemiological studies validating this observation have met with limited success. The incidence of IDDM parallels that of mumps, after allowing for a 4-year lag period in Erie County, NY, and ~50% of children with IDDM in this population had mumps or exposure to mumps ~4 years prior to IDDM onset[123]. However, no evidence of antecedent mumps infection and subsequent onset of IDDM was found in residents of Montreal, Canada[124]. As with Coxsackie B virus, it has been suggested that a particular variant of the mumps virus in combination with genetic susceptibility is necessary for development of IDDM. If mumps is a cause of IDDM, it is likely to be so in only a small proportion of cases.

OTHER POTENTIAL RISK FACTORS

In addition to nutrition and viruses, other potential IDDM risk factors include stress, maternal age, birth order, and socioeconomic status. Several investigators noted that life events such as accidents, pregnancy, and personal problems frequently occurred during the year prior to IDDM onset[125]. These observations were supported by a family study that revealed an increase in the reporting of at least one serious life event during the 6 months prior to disease onset in IDDM compared with nondiabetic siblings[126]. Although investigations of stress and IDDM have, in general, reported positive associations, most studies have been retrospective and suffered from methodological difficulties in assessing stress and measuring its frequency, intensity, and duration[127,128]. Thus, prospective evaluations of the interaction among stress, the immune system, and the occurrence of autoimmune diseases are warranted.

Characteristics such as older maternal age at birth and higher birth order have also been associated with increased IDDM risk. Several Caucasian studies have reported a higher prevalence of IDDM in children born to older mothers and in children with a higher birth order[107,129,130]. These investigations concluded that of the two related potential determinants of IDDM risk, advanced maternal age (i.e., age ≥35 years at the child's birth) was the more significant risk factor. Reasons for this association are unclear, but it has been suggested that it may be related to the intrauterine environment. Interestingly, a study from southern India failed to corroborate these findings and, in fact, reported opposite results, with an increased IDDM risk for children with lower birth order and children born to younger mothers[131]. Additional investigations in other ethnic groups, such as African Americans, Asians, and Hispanics, are needed to determine the etiologic significance of these potential risk factors.

Studies of deprivational differences in IDDM risk emphasize the importance of socioeconomic factors in the etiology of IDDM. In northern England, IDDM incidence rates were highest in the most deprived areas and lowest in the least deprived areas[132]. The deprivation index employed for this study assessed levels of unemployment, car ownership, home ownership, and overcrowding. However, a study from Scotland reported conflicting results, with higher IDDM incidence rates in affluent areas[133]. The authors, therefore, concluded that deprivation appeared to confer significant protection from developing IDDM. These studies reflect earlier conflicting reports indicating that either high[134] or low[135] socioeconomic status was related to IDDM incidence. Such discrepancies may be related to methodologic differences, including different assessments of socioeconomic status or deprivation, which may reflect the influence of different environmental agents in different populations.

CONCLUSIONS

Dr. Kelly West, the founder of diabetes epidemiology, said in his landmark book, *Epidemiology of Diabetes and Its Vascular Lesions*, "It has become evident that many factors contribute in an important way in increasing or decreasing susceptibility to diabetes, and that systematic epidemiologic study has great potential for elucidating mechanisms by which both diabetes and its specific manifestations are caused or prevented"[136]. Since that time, much has been learned about the epidemiologic patterns of IDDM in racial and ethnic groups around the world. In the Americas and other continents, new data are emerging for Caucasians, African Americans, and Hispanics regarding potential risk factors for IDDM. These studies are also employing molecular technology to study both genetic and environmental determinants of the disease and will provide critically important information regarding IDDM etiology during the next decade. It is hoped this will lead to the prevention of the disease through risk factor modification in individuals who are genetically susceptible. With the continued efforts of scientists and clinicians in the United States, and the rapid progression of the field of diabetes epidemiology, Dr. Kelly West's vision will be achieved.

Dr. Janice S. Dorman is Associate Professor, Bridget J. McCarthy is Doctoral Student, Dr. Leslie A. O'Leary is Research Associate, and Anita N. Koehler is Doctoral Student, Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA. Ms. Koehler is also affiliated with the Department of Nutrition, Children's Hospital of Pittsburgh, Pittsburgh, PA.

REFERENCES

1. WHO DIAMOND Project Group: WHO multinational project for childhood diabetes. *Diabetes Care* 13:1062-68, 1990
2. Green A, Gale EAM, Patterson CC: Incidence of childhood-onset insulin-dependent diabetes mellitus: The EURODIAB ACE study. *Lancet* 339:905-09, 1992
3. Karvonen M, Tuomilehto J, Libman I, et al: A review of the recent epidemiological data on the worldwide incidence of Type I (insulin-dependent) diabetes mellitus. *Diabetologia* 36:883-92, 1993
4. Tuomilehto J, Lounamaa R, Tuomilehto-Wolf E, et al: Epidemiology of childhood diabetes in Finland—background of a nationwide study of type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 35:70-76, 1992
5. Dahlquist G, Blom L, Holmgren G, et al: The epidemiology of diabetes in Swedish children 0-14 years—a six year prospective study. *Diabetologia* 28:802-8, 1985
6. Joner G, Sovik O: Increasing incidence of diabetes mellitus in Norwegian children 0-14 years of age, 1973-1982. *Diabetologia* 32:79-83, 1989
7. Muntoni S, Songini M, et al: High incidence rate of IDDM in Sardinia. *Diabetes Care* 15:1317-22, 1992
8. Serrano Rios M, Moy CS, Martin Serrano R, et al: Incidence of Type 1 (insulin-dependent) diabetes mellitus in subjects 0-14 years of age in the Comunidad of Madrid, Spain. *Diabetologia* 33:422-24, 1990
9. Laron Z, Karp M, Modan M: The incidence of insulin-dependent diabetes mellitus in Israeli children and adolescents 0-20 years of age: A retrospective study 1975-1980. *Diabetes Care* 6 (Suppl. l):24-28, 1985
10. Diabetes Epidemiology Research International Group: Geographic patterns of childhood insulin-dependent diabetes mellitus. *Diabetes* 37:1113-19, 1988
11. Bao MZ, Wang JX, Dorman JS, et al: HLA-DQ beta non-Asp-57 allele and incidence of diabetes in China and the USA. *Lancet* ii:497-98, 1989
12. Savage PJ, Bennett PH, Senter RG, Miller M: High prevalence of diabetes in young Pima Indians: Evidence for phenotype variation in a genetically isolated population. *Diabetes* 28:927-42, 1979
13. Carrasco E, Lopez G, Garcia de los Rios M, et al: Incidencia de diabetes mellitus insulinodependiente en la region metropolitana. *Rev Med Chile* 119:709-14, 1991
14. Robles Valdes C, Cornejo BJ, Dorantes AL, et al: Incidencia de la diabetes mellitus tipo I 1984-1986 en el D.F. y area metropolitana (A.M.). In *Proc Soc Mex Nutr Endocrinol Merida*, 1987
15. Diabetes Epidemiology Research International Group: The epidemiology and immunogenetics of IDDM in Italian-heritage populations. *Diab Metab Rev* 6:63-69, 1990
16. Bruno G, Merletti F, Pisu E, et al: Incidence of IDDM during 1984-1986 in population aged yr. residents of Turin Italy. *Diabetes Care* 13:1051-56, 1990
17. Calori G, Gallus G, Garancini P, et al: Identification of the cohort of type 1 diabetes presenting in Lombardy in 1983-84: A validated assessment. *Diabetic Medicine* 7:595-99, 1990
18. Dokheel TM: Personal communication, 1992
19. Wagenknecht LE, Roseman JM, Alexander WJ: Epidemiology of IDDM in black and white children in Jefferson County, Alabama, 1979-1985. *Diabetes* 38:629-33, 1989
20. Gay EC, Hamman RF, Carosone-Link PJ: Colorado IDDM Registry: Lower incidence of IDDM in Hispanics—comparisons of disease characteristics and care patterns in biethnic population. *Diabetes Care* 12:701-08, 1989
21. Gamble DR: The epidemiology of insulin-dependent diabetes with particular reference to the relationship of virus infection to its etiology. *Epidemiol Reviews* 2:49-70, 1980
22. Fleegler FM, Rogers KD, Drash A, et al: Age, sex and season of onset of juvenile diabetes in different geographic areas. *Pediatrics* 63:374-79, 1979
23. Joner G, Sovik O: Incidence, age at onset and seasonal variation of diabetes mellitus in Norwegian children. *Acta Paediatr Scand* 70:329-35, 1981
24. LaPorte RE, Tajima N, Dorman JS, et al: Black/white differences in the epidemiology of insulin-dependent diabetes mellitus (IDDM) in Allegheny County, PA. *Am J Epidemiol* 123:592-603, 1986
25. Blom L, Persson LA, Dahlquist G: A high linear growth is associated with an increased risk of childhood diabetes mellitus. *Diabetologia* 35:528-33, 1992
26. Songer TJ, LaPorte RE, Tajima N, et al: Height at diagnosis of insulin-dependent diabetes in patients and their non-diabetic family members. *Brit Med J* 292:1419-22, 1986
27. Price DE, Burden AC: Growth of children before onset of diabetes. *Diabetes Care* 15:1393-95, 1992
28. Leslie RD, Lo S, Millward BA, Honour J, Pyke DA: Decreased growth velocity before IDDM onset. *Diabetes* 40:211-16, 1991
29. Fishbein HA, LaPorte RE, Orchard TJ, et al: The Pittsburgh insulin-dependent diabetes mellitus registry: Seasonal incidence. *Diabetologia* 23:83-85, 1982
30. Elamin A, Omer MIA, Zein K, et al: Epidemiology of childhood type I diabetes in Sudan, 1987-1990. *Diabetes Care* 15:1556-59, 1992
31. Dorman JS: Genetic epidemiology of insulin-dependent diabetes mellitus: International comparisons using molecular genetics. *Ann Med* 24:393-99, 1992
32. WHO DIAMOND Project Group: Familial IDDM epidemiology: Standardization of data for the DIAMOND Project. *Bull WHO* 69:767-77, 1991
33. West R, Belmonte M, Colle E, et al: Epidemiologic survey of juvenile-onset diabetics in Montreal. *Diabetes* 28:690-93, 1979
34. Gottleib MS: Diabetes in offspring and siblings of juvenile- and maturity-onset-type diabetics. *J Chron Dis* 33:331-39, 1980
35. Wagener DK, Sacks JM, LaPorte RE, et al: The Pittsburgh study of insulin-dependent diabetes mellitus: Risk for diabetes among relatives of IDDM. *Diabetes* 31:136-44, 1982
36. Chern MM, Anderson VE, Barbosa J: Empirical risk for insulin-dependent diabetes (IDD) in sibs: Further definition of genetic heterogeneity. *Diabetes* 31:1115-18, 1982
37. Warram JH, Krolewski AS, Gottlieb MS, et al: Differences in risk of insulin-dependent diabetes in offspring of diabetic mothers and diabetic fathers. *New Engl J Med* 311:149-52, 1984
38. Warram JH, Krolewski AS, Kahn CR: Determinants of IDDM

and perinatal mortality in children of diabetic mothers. *Diabetes* 37:1328-34, 1988

39. McCarthy BJ, Dorman JS, Aston CE, et al: Investigating genomic imprinting and susceptibility to insulin-dependent diabetes mellitus (IDDM): An epidemiologic approach. *Genetic Epidemiol* 8:177-86, 1991
40. McCarthy B, Dorman J, Aston C, et al: The incidence of insulin-dependent diabetes mellitus (IDDM) among offspring of diabetic parents: A prospective study. Abstract, 14th IDF Congress epidemiology satellite, Williamsburg, VA, 1991
41. Allen C, Palta M, D'Alessio J: Risk of diabetes in siblings and other relatives of IDDM subjects. *Diabetes* 40:831-36, 1991
42. Gavard JA, Dorman JS, LaPorte RE, et al: Sex differences in secondary attack rate of IDDM to siblings of probands through older ages. *Diabetes Care* 15:559-61, 1992
43. Bleich D, Polak M, Eisenbarth GS, et al: Decreased risk of Type I diabetes in offspring of mothers who acquire diabetes during adrenarchy. *Diabetes* 42:1433-39, 1993
44. Rotter JI, Vadheim CM, Rimoin DL: Genetics of diabetes mellitus. In *Diabetes Mellitus: Theory and Practice*, Rifkin H, Porte D, eds. Elsevier, 1990, p. 378-413
45. Tuomilehto-Wolf E, Tuomilehto J, Hitman GA, et al: Genetic susceptibility to non-insulin dependent diabetes mellitus and glucose intolerance are located in HLA region. *Brit Med J* 307:155-59, 1993
46. Dahlquist G, Blom L, Tuvemo T, et al: The Swedish childhood diabetes study. Results from a nine year case registry and a one year case-referent study indicating that Type I (insulin-dependent) diabetes mellitus is associated with both Type II (non-insulin-dependent diabetes mellitus) and autoimmune disorders. *Diabetologia* 32:2-6, 1989
47. Tillil H, Kobberling J: Age-corrected empirical genetic risk estimates for first degree relatives of IDDM patients. *Diabetes* 36:93-99, 1987
48. Vadheim CM, Rotter JI, Maclaren NK, et al: Preferential transmission of diabetic alleles within the HLA gene complex. *New Eng J Med* 315:1314-18, 1986
49. Trucco M: To be or not to be ASP 57, that is the question. *Diabetes Care* 15:705-15, 1992
50. Nerup J, Platz P, Anderson O, et al: HLA antigens and diabetes mellitus. *Lancet* ii:864-67, 1974
51. Cudworth AG, Woodrow JD: Genetic susceptibility in diabetes mellitus: Analyses of the HLA association. *Br Med J* 2:846-68, 1976
52. Wolf E, Spencer KM, Cudworth AG: The genetic susceptibility to Type I (insulin-dependent) diabetes: Analyses of the HLA-DR associations. *Diabetologia* 23:224-49, 1983
53. Bertram J, Baur M: Insulin-dependent diabetes mellitus. In *Histocompatibility Testing*. Springer-Verlag, Heidelberg, 1984, p. 348-68
54. Reitnauer PJ, Roseman JM, Barger BO, et al: HLA associations with insulin-dependent diabetes mellitus in a sample of the American black population. *Tissue Antigens* 17:286-93, 1981
55. Cruickshanks KJ, Jobim LF, Lawler-Heavner J, et al: Ethnic differences in human leukocyte antigen markers of susceptibility to IDDM. *Diabetes Care* 17:132-37, 1994
56. Hawkins BR, Lam KS, Ma JT, et al: Strong associations of HLA-DR3/DRw9 heterozygosity with early onset insulin-dependent diabetes mellitus in Chinese. *Diabetes* 36:1297-1300, 1987
57. Todd JA, Bell JL, McDevitt HL: HLA-DQ beta gene contributes to susceptibility and resistance to insulin-dependent diabetes mellitus. *Nature* 329:559-604, 1985
58. Morel PA, Dorman JS, Todd JA, et al: Aspartic acid at position 57 of the HLA-DQ beta chain protects against Type 1 diabetes. *Proc Natl Acad Sci* 85:8111-16, 1988
59. Dorman JS, LaPorte RE, Stone RA, et al: Worldwide differences in the incidence of type I diabetes are associated with amino acid variation at position 57 of the HLA-DQ β chain. *Proc Natl Acad Sci* 87:7370-74, 1990
60. Mijovic CH, Jenkins D, Jacobs KH, et al: HLA-DQA1 and -DQB1 alleles associated with genetic susceptibility to IDDM in a black population. *Diabetes* 40:748-53, 1991
61. Contu L, Carcassi C, Trucco M: Diabetes susceptibility in Sardinia. *Lancet* 338:65, 1991
62. Ronningen KS, Gjertsen HA, Iwe T, et al: Particular HLA-DQ α β heterodimer associated with IDDM susceptibility in both DR4-DQw4 Japanese and DR4-DQw8/DRw8-DQw4 whites. *Diabetes* 40:759-63, 1991
63. Khalil I, Deschamps I, Lepage V, et al: Dose effect of cis- and trans-encoded HLA-DQ α β heterodimers in IDDM susceptibility. *Diabetes* 41:378-84, 1992
64. Gutierrez-Lopez MD, Bertera S, Chantres MT, et al: Susceptibility to Type 1 (insulin-dependent) diabetes mellitus in Spanish patients correlates quantitatively with expression of HLA-DAα Arg 52 and HLA-DQβ non-Asp 57 alleles. *Diabetologia* 35:583-88, 1992
65. Dunston GM, Henry LW, Christian J, et al: HLA-DR3 DQ heterogeneity in American blacks is associated with susceptibility and resistance to insulin dependent diabetes mellitus. *Transplant Proc* 21:653-55, 1989
66. Todd JA, Fukul Y, Kitagawa T, et al: The A3 allele of the HLA-DQA1 locus is associated with susceptibility to Type 1 diabetes in Japanese. *Proc Natl Acad Sci* 87:1094-99, 1990
67. Awata T, Kuzuya T, Matsuda A, et al: Genetic analysis of HLA class II alleles and susceptibility to Type 1 (insulin-dependent) diabetes mellitus in Japanese subjects. *Diabetologia* 35:419-24, 1992
68. Ronningen LS, Halstensen TS, Spurkland A, et al: The amino acid at position 57 of the HLA-DQ beta chain and susceptibility to develop insulin-dependent diabetes mellitus. *Human Immunol* 26:215-25, 1989
69. Bottazzo GF, Florin-Christensen A, Doniach D: Islet cell antibodies in diabetes mellitus with autoimmune polyendocrine deficiencies. *Lancet* ii:1279-82, 1974
70. Palmer JP, Asplin CM, Clemons P, et al: Insulin antibodies in insulin-dependent diabetes before insulin treatment. *Science* 222:1337-39, 1983
71. Baekkeskov S, Nielsen JH, Marner B, et al: Autoantibodies in newly diagnosed diabetic children immunoprecipitate human pancreatic islet cell proteins. *Nature* 298:167-69, 1982
72. Baekkeskov S, Aanstoot H-K, Christgau S, et al: Identification of the 64K autoantigen in insulin-dependent diabetes as the GABA-synthesizing enzyme glutamic acid decarboxylase. *Nature* 347:151-56, 1990
73. Lipton RB, LaPorte RE: Epidemiology of islet cell antibodies. *Epidemiol Rev* 11:182-203, 1989
74. Bruining GJ, Molenaar JL, Grobbee DE, et al: Ten-year follow-up study of islet cell antibodies and childhood diabetes mellitus. *Lancet* i:1100-13, 1989

75. Riley W, Maclaren N: Islet cell antibodies are seldom transient. *Lancet* 1:1352, 1984

76. Maclaren NK, Riley WJ, Horne G, et al: Pancreatic islet cell autoantibodies in US schoolchildren. *Diabetes* 34 (Suppl.):84, 1985

77. Riley WJ, Maclaren NK, Krischer J, et al: A prospective study of the development of diabetes in relatives of patients with insulin-dependent diabetes. *N Engl J Med* 323:1167-72, 1990

78. Boehm BB, Manfras B, Seibler J, et al: Epidemiology and immunogenetic background of islet cell antibody—positive nondiabetic schoolchildren. *Diabetes* 40:1435-39, 1991

79. Levy-Marchal C, Tichet J, Fajardy I, et al: Islet cell antibodies in normal French schoolchildren. *Diabetologia* 35:577-82, 1992

80. Lipton RB, Kocova M, LaPorte RE, et al: Autoimmunity and genetics contribute to the risk of insulin-dependent diabetes mellitus in families: Islet cell antibodies and HLA DQ heterodimers. *Am J Epidemiol* 136:503-12, 1992

81. Dean BM, Becker E, McNally JM, et al: Insulin autoantibodies in the prediabetic period: Correlation with islet cell antibodies and development of diabetes. *Diabetologia* 29:339-42, 1986

82. Wilkin TJ: Antibodies as predictors of Type 1 diabetes. *Compr Ther* 17:3-10, 1991

83. Baekkeskov S, Kristensen JK, Srikanta S, et al: Antibodies to a M 64,000 human islet cell antigen precede the clinical onset of insulin-dependent diabetes. *J Clin Invest* 479:926-34, 1987

84. Atkinson MA, Maclaren NK, Scharp DW, et al: 64000 M[1] autoantibodies as predictors of insulin-dependent diabetes. *Lancet* 335:1357-60, 1990

85. Rowley MJ, Mackay IR, Chen Q-Y, et al: Antibodies to glutamic acid decarboxylase discriminate major types of diabetes mellitus. *Diabetes* 41:548-51, 1992

86. Olmos P, A'Hern R, Heaton DA, et al: The significance of concordance rate for type 1 (insulin-dependent) diabetes in identical twins. *Diabetologia* 31:747-50, 1988

87. Elliot RB, Martin JM: Dietary protein: A trigger of insulin-dependent diabetes in the BB rat? *Diabetologia* 26:297-99, 1984

88. Scott FW, Mongeau R, Kardish M, et al: Diet can prevent diabetes in BB rat. *Diabetes* 34:1959-62, 1985

89. Helgason T, Jonasson MR: Evidence for a food additive as a cause of ketosis-prone diabetes. *Lancet* ii:716-20, 1981

90. Dahlquist GG, Blom LG, Persson L, et al: Dietary factors and the risk of developing insulin dependent diabetes in childhood. *Br Med J* 300:1302-06, 1990

91. Kostraba JN, Gay EC, Rewers M, et al: Nitrate levels in community drinking water and risk of IDDM. *Diabetes Care* 15:1505-08, 1992

92. Vague P, Picq R, Bernal M, et al: Effect of nicotinamide treatment on the residual insulin secretion in type 1 (insulin-dependent) diabetic patients. *Diabetologia* 32:316-21, 1989

93. Chase HP, Butler-Simon N, Garg S, et al: A trial of nicotinamide in newly diagnosed patients with type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 33:444-46, 1990

94. Lewis CM, Canafax DM, Sprafka JM, et al: Double-blind randomized trial of nicotinamide on early-onset diabetes. *Diabetes Care* 15:121-23, 1992

95. Elliott RB, Chase HP: Prevention or delay of type 1 (insulin-dependent) diabetes mellitus in children using nicotinamide. *Diabetologia* 34:362-65, 1991

96. Fort P, Lanes R, Dahlem S, et al: Breast feeding and insulin-dependent diabetes mellitus in children. *J Am Coll Nutr* 5:439-41, 1986

97. Mayer EJ, Hamman RF, Gay EC, et al: Reduced risk of IDDM among breast-fed children. *Diabetes* 37:1625-32, 1988

98. Siemiatycki J, Colle E, Campbell S, et al: Case-control study of IDDM. *Diabetes Care* 12:209-16, 1989

99. Kostraba JN, Dorman JS, LaPorte RE, et al: Early infant diet and risk of IDDM in blacks and whites. *Diabetes Care* 15:626-31, 1992

100. Kostraba JN, Cruickshanks KJ, Lawler-Heavner J, et al: Early exposure to cow's milk and solid foods in infancy, genetic predisposition, and risk of IDDM. *Diabetes* 42:288-95, 1993

101. Gerstein HC: Cow's milk exposure and Type 1 diabetes mellitus: A critical overview of the clinical literature. *Diabetes Care* 17:13-19, 1994

102. Borch-Johnsen K, Mandrup-Poulsen T, Zachau-Christiansen B, et al: Relation between breast feeding and incidence rates of insulin-dependent diabetes mellitus. *Lancet* 2:1083-86, 1984

103. Dahl-Jorgensen K, Joner G, Hanssen K: Relationship between cow's milk consumption and incidence of IDDM in childhood. *Diabetes Care* 14:1081-83, 1991

104. Scott F: Cow milk and insulin-dependent diabetes mellitus: Is there a relationship? *Am J Clin Nutr* 51:489-91, 1990

105. Virtanen SM, Rasanen L, Aro A, et al: Infant feeding in Finnish children yr of age with newly diagnosed IDDM. *Diabetes Care* 14:415-17, 1991

106. Metcalfe MA, Baum JD: Family characteristics and insulin-dependent diabetes. *Arch Dis Child* 67:731-36, 1992

107. Dahlquist G, Savilahti E, Landin-Olsson M: An increased level of antibodies to beta-lactoglobulin is a risk determinant for early-onset Type 1 (insulin-dependent) diabetes mellitus independent of islet cell antibodies and early introduction of cow's milk. *Diabetologia* 35:980-84, 1992

108. Savilahti E, Tuomilehto J, Savkkonen TT, et al: Increased levels of cow's milk and beta-lactoglobulin antibodies in young children with newly diagnosed IDDM. *Diabetes Care* 16:984-89, 1993

109. Karjalainen J, Martin JM, Knip M, et al: A bovine albumin peptide as a possible trigger of insulin-dependent diabetes mellitus. *New Engl J Med* 327:302-07, 1992

110. Wagenknecht LE, Roseman JM, Herman WH: Increased incidence of insulin-dependent diabetes mellitus following an epidemic of coxsackievirus B5. *Am J Epidemiol* 133:1024-31, 1991

111. King ML, Bidwell D, Shaikh A, et al: Coxsackie-B-virus-specific IgM responses in children with insulin-dependent diabetes mellitus. *Lancet* i:1397-99, 1983

112. Palmer JP, Cooney MK, Ward RH, et al: Reduced coxsackie antibody titres in Type I (insulin-dependent) diabetic patients presenting during an outbreak of Coxsackie B3 and B4 infection. *Diabetologia* 22:426-29, 1982

113. Yoon JW, Rayfield EJ: Two possible pathogenic mechanisms for virus-induced diabetes. In *The Immunology of Diabetes Mellitus*, Molinar GD, Jaworski MA, eds. Elsevier Science Publisher, 1986, p. 287-98

114. D'Alessio DJ: A case-control study of group B Coxsackie virus immunoglobulin M antibody prevalence and HLA-DR antigens in newly diagnosed cases of insulin-dependent dia-

betes mellitus. *Am J Epidem* 135:1331-38, 1992

115. Yoon JW: Role of viruses and environmental factors in induction of diabetes. In *Current Topics in Microbiology and Immunology*, Baekkeskov S, Hansen B, eds. Heidelberg, Springer-Verlag, 164:95-123, 1990.

116. Pak CY, Eun HM, McArthur RG, et al: Association of cytomegalovirus infection with autoimmune type 1 diabetes. *Lancet* ii:1-4, 1988

117. Nicoletti F, Scalia G, Lunetta M, et al: Correlation between islet cell antibodies and anti-cytomegalovirus IgM and IgG antibodies in healthy first-degree relatives of type 1 (insulin-dependent) diabetic patients. *Clin Immun and Immunopath* 55:139-47, 1990

118. Menser MA, Forrest JM, Bransky RO: Rubella infection and diabetes mellitus. *Lancet* i:57-60, 1978

119. Ginsberg-Fellner F, Witt ME, Yagihashi S, et al: Congenital rubella syndrome as a model for type 1 (insulin-dependent) diabetes mellitus: Increased prevalence of islet cell surface antibodies. *Diabetologia* 27:87-89, 1984

120. Ginsberg-Fellner F, Witt ME, Fedun B, et al: Diabetes mellitus and autoimmunity in patients with the congenital rubella syndrome. *Rev Inf Dis* 7 (Suppl.):S170-74, 1985

121. King RC: Mumps followed by diabetes. *Lancet* ii:1055, 1962

122. Messaritikas J, Karabula C, Kattamis C, et al: Diabetes following mumps in sibs. *Arch Dis Child* 46:561-62, 1971

123. Sultz HA, Hart BA, Zielezny M, et al: Is mumps virus an etiologic factor in juvenile diabetes mellitus? *J Peds* 86:654-56, 1975

124. West R, Colle E, Belmonte MM, et al: Prospective study of insulin-dependent diabetes mellitus. *Diabetes* 30:584-89, 1981

125. Kisch ES: Stressful events and the onset of diabetes mellitus. *Israel J Med Sci* 21:356-58, 1985

126. Robinson N, Fuller JH: Severe life events and their relationship to the etiology of insulin-dependent (Type I) diabetes mellitus. *Pediat Adolesc Endocr* 15:129-33, 1986

127. Leclere J, Wergha G: Stress and autoimmune endocrine diseases. *Horm Res* 31: 90-93, 1989

128. Surwit RS, Schneider MS, Feinglos MN: Stress and diabetes mellitus. *Diabetes Care* 15:1413-42, 1992

129. Flood TM, Brink SJ, Gleason RE: Increased incidence of Type I diabetes in children of older mothers. *Diabetes Care* 5:571-73, 1982

130. Wagener DK, LaPorte RE, Orchard TJ, et al: The Pittsburgh Diabetes Mellitus Study 3: An increased prevalence with older maternal age. *Diabetologia* 25:82-85, 1983

131. Ramachandran A, Snehalatha C, Joseph A, et al: Maternal age and birth order of young IDDM patients: A study from Southern India. *Diabetes Care* 16:636-37, 1993

132. Crow YJ, Alberti KG, Parkin JM: Insulin dependent diabetes in childhood and maternal deprivation in northern England. *Brit Med J* 303:158-60, 1991

133. Patterson CC, Waugh NR: Urban/rural and deprivational differences in incidence and clustering of childhood diabetes in Scotland. *Int J Epidemiol* 21:108-17, 1992

134. Colle E, Siemiatyckie J, West R, et al: Incidence of juvenile onset diabetes in Montreal: Demonstration of ethnic differences and socioeconomic class differences. *J Chron Dis* 14:611-16, 1981

135. Christau B, Kromann AH, Anderson O, et al: Incidence, seasonal and geographic patterns of juvenile onset insulin-dependent diabetes mellitus in Denmark. *Diabetologia* 12:281-89, 1977

136. West KM: *Epidemiology of Diabetes and Its Vascular Lesions*. Elsevier, New York, NY 1978