Emerging Epidemic of Type 2 Diabetes in Youth

ARLAN L. ROSENBLOOM, MD
JENNIE R. JOE, PHD
ROBERT S. YOUNG, PHD
WILLIAM E. WINTER, MD

This review considers the epidemiologic evidence for an increasing incidence of type 2 diabetes in youth, the classification and diagnostic issues related to diabetes in young populations, pathophysiologic mechanisms relevant to the increasing incidence, the role of genetics and environment, and the community challenge for prevention and treatment. Type 2 diabetes in youth has been recognized to be frequent in populations of native North Americans and to comprise some 30 percent of new cases of diabetes in the 2nd decade of life, largely accounted for by minority populations and associated with obesity. Among Japanese schoolchildren, type 2 diabetes is seven times more common than type 1, and its incidence has increased more than 30-fold over the past 20 years, concomitant with changing food patterns and increasing obesity rates. The forms of diabetes seen in children and youth include typical type 1, occurring in all races; type 2, seen predominantly in minority youth; atypical diabetes, seen as an autosomal dominantly transmitted disorder in African-American populations; and maturity-onset diabetes of the young (MODY), seen rarely and only in Caucasians. Of the nonautoimmune forms of diabetes seen in youth, only type 2 diabetes is increasing in incidence. Proper classification requires consideration of onset (acute/severe versus insidious), ethnicity, family history, presence of obesity, and if necessary, studies of diabetes-related autoimmunity. Insulin resistance predicts the development of diabetes in Pima Indians, in offspring of parents with type 2 diabetes, and in other high-risk populations. African-American children and youth have greater insulin responses during glucose tolerance testing and during hyperglycemic clamp study than do whites. There is also evidence of altered β-cell function preceding the development of hyperglycemia. Of particular interest is the evidence that abnormal fetal and infantile nutrition is associated with the development of type 2 diabetes in adulthood. The thrifty phenotype hypothesis states that poor nutrition in fetal and infant life is detrimental to the development and function of the β-cells and insulin sensitive tissues, leading to insulin resistance under the stress of obesity. The thrifty genotype hypothesis proposes that defective insulin action in utero results in decreased fetal growth as a conservation mechanism, but at the cost of obesity-induced diabetes in later childhood or adulthood. The vast majority of type 2 diabetes in adults is polygenic and associated with obesity. Monogenic forms (MODY, maternally transmitted mitochondrial mutations) are rare, but are more likely to appear in childhood. Linkage studies of the common polygenic type 2 diabetes have emphasized the heterogeneity of the disorder. The prevention and treatment of type 2 diabetes in children and youth is a daunting challenge because of the enormous behavioral influence, difficulty in reversing obesity, and typical nonadherence in this age-group. The emerging epidemic of type 2 diabetes in the pediatric population, especially among minorities whose proportion in the U.S. population is increasing, presents a serious public health problem. The full effect of this epidemic will be felt as these children become adults and develop the long-term complications of diabetes.

Diabetes Care 22:345–354, 1999

From the Children's Medical Services Center (A.L.R.) and the Departments of Pathology and Pediatrics (W.E.W.), University of Florida College of Medicine, Gainesville, Florida; and the Native American Research and Training Center (J.R.J., R.S.Y.), Department of Family and Community Medicine, University of Arizona, Tucson, Arizona.

Address correspondence and reprint requests to Arlan L. Rosenbloom, MD, University of Florida College of Medicine, Children's Medical Services Center, 1701 SW 16th Ave., Gainesville, FL 32608. E-mail: rosenal@peds.ufl.edu.

Received for publication 20 May 1998 and accepted in revised form 9 October 1998.

Abbreviations: ADA, American Diabetes Association; ADM, atypical diabetes mellitus; HGNK, nonketotic severe hypoglycemia; HNF, hepatocyte nuclear factor; MODY, maturity-onset diabetes of the young; ND, NADH dehydrogenase subunit; OHA, oral hypoglycemic agents; VNTR, variable number of tandem repeats.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

RECOGNITION OF AN EPIDEMIC

— Pediatric diabetologists and other health workers involved with minority communities have recognized an emerging epidemic of type 2 diabetes among youth over the past 20 years, primarily affecting minorities. This phenomenon parallels increased prevalence of obesity in children and youth (1). Epidemiologic data from several ethnic populations are summarized in Table 1. The initial report of a high frequency of type 2 diabetes in young patients came from the carefully studied Pima Indian population, in which >1% of those 15–24 years of age (but none under this age) had diabetes that was associated with obesity and long-term diabetes complications. Five of the individuals had been treated with insulin, and four had experienced ketoacidosis (2).

Some 13 years after this initial report, numerous instances of type 2 diabetes were reported among native populations in Manitoba in the 5–14 years age-group, with a prevalence of 0.8:1000; 10–20% of new cases of diabetes in youth in Manitoba were in the type 2 category. This type 2 diabetes in youth occurred exclusively in the First Nation population (3,4). Similar observations were made in northwest Ontario in the <16 years age-group, but with a higher age-specific prevalence of 2.5:1000 (5). In all of these reports, the sex ratio was remarkably skewed, with 4–6 female patients for every male patient affected. In Cincinnati, Ohio, one-third of all new cases of diabetes in the 10–19 years age-group were classified as type 2 diabetes, giving an age-specific incidence of 7.2:100,000 per year. Type 2 diabetes comprised 2–4% of all childhood diabetes before 1992, but by 1994, type 2 diabetes accounted for 16% of all new cases in children (6). In the Cincinnati report, as well as in reports from Arkansas (7,8), African-Americans accounted for 70–75% of type 2 diabetes patients. Among Mexican-American children from Ventura, California, <17 years of age, 31% of those with diabetes have type 2 (9). The sex ratio in these African-American and Mexican-American youngsters is less skewed than that among the Native American population.

The phenomenon of a rapidly accelerating incidence of type 2 diabetes in young

Table 1—S*tudies of type 2 diabetes in young populations*

Location	Race/ethnicity	Age-group	Frequency		Sex ratio (M:F)	Ref.
			Incidence	Prevalence		
Arizona	Pima Indian	5–24	—	0 (<15 years) 9/1000 (15–24 years)	1:5	2
Manitoba, Canada	First Nation	5–14	—	0.8/1000	1:4	3,4
Ontario, Canada	First Nation	<16	—	2.5/1000	1:6	5
Cincinnati, Ohio	African-American (70%)	10–19	$7.2/10^5$	—	1:1.7	6
Ventura, California	Mexican American	<17	—	—	1:1.3	9
Libya	Arab	0–34	$19.6/10^5$ (male) $35.3/10^5$ (female)	—	1:1 (0–14 years) 1:2 (15–34 years)	10
Japan	Japanese	<15	$2.0/10^5$ (primary grades) $13.9/10^5$ (junior high)	—	1:2 1:1.2	11,12

Prevalence rates are given per 1,000, and incidence (annual), per 100,000 (10^5).

patients is not peculiar to North America. Among Libyan Arabs <34 years of age, the annual incidence of type 2 diabetes is 19.6:100,000 for male patients and 35.3:100,000 for female patients, compared with incidences for type 1 diabetes of 9.4 and 8.5, respectively. There is an even sex ratio in the <14 years age-group, but a twofold greater female incidence in the 15–34 years group (10). Among Japanese school children, the incidence of type 2 diabetes increased from 0.2 to 7.3:100,000 from 1976 to 1995. This increase was primarily among junior high school–aged youngsters, who have a type 2 diabetes incidence of 13.9:100,000, compared with grammar school children, who have an incidence of 2.0:100,000. The grammar school incidence of type 2 diabetes is comparable to that for type 1 diabetes, 1.65:100,000, whereas the junior high school incidence of type 2 diabetes is nearly seven times that for type 1 diabetes in that age-group (2.07:100,000). Japanese investigators have associated the increasing incidence of type 2 diabetes with changing food patterns and rising obesity rates among Japanese school children (11,12). They have also documented a high risk for early nephropathy among those developing type 2 diabetes before 30 years of age (13).

Children have hyperinsulinism as a result of obesity, as do adults, and childhood obesity is commonly associated with impaired glucose tolerance (14). The stress of obesity and the increased demand for insulin at the time of adolescence (15) explain the largely pubertal and postpubertal onset of type 2 diabetes in children.

Although type 2 diabetes in children and youth is increasingly recognized as a problem, the current American Diabetes Association (ADA) position statement on screening for type 2 diabetes makes no specific mention of children and adolescents at risk (16).

CLASSIFICATION ISSUES — The new classification recommendations of the ADA recognize major differences in prevalence of the forms of diabetes among various racial or ethnic groups (17). Table 2 summarizes distinguishing features of the forms of diabetes as seen in youth. These include the following: typical type 1 diabetes that occurs in all races but is relatively rare in Asians; type 2 diabetes seen predominantly in minority youth; atypical diabetes mellitus (ADM) that is seen as an autosomal dominant condition in African-American populations (18); and maturity-onset diabetes of the young (MODY), which is seen rarely and only in Cau-

Table 2—*Classification of diabetes seen in children and youth*

	Type 1 diabetes	Type 2 diabetes	ADM	MODY
Age	Throughout childhood	Pubertal	Pubertal	Pubertal
Onset	Acute, severe	Mild to severe, often insidious	Acute, severe	Mild, insidious
Insulin secretion	Very low	Variable	Moderately low	Variable
Insulin sensitivity	Normal	Decreased	Normal	Normal
Insulin dependence	Permanent	No	Variable	No
Genetics	Polygenic	Polygenic	Autosomal dominant	Autosomal dominant
Race/ethnic distribution	All (low frequency in Asians)	African-American, Hispanic, Asian, Native American	African-American	Caucasian
Frequency (of all diabetes in children and youth)	~80%	10–20%	5–10%	Rare
Association				
Obesity	No	Strong	Variable	No
Acanthosis nigricans	No	Yes	No	No
Autoimmunity	Yes	No	No	No

Insulin sensitivity is given as a pathogenic factor. Insulin dependence is assumed to be in the absence of acute illness or other stress.

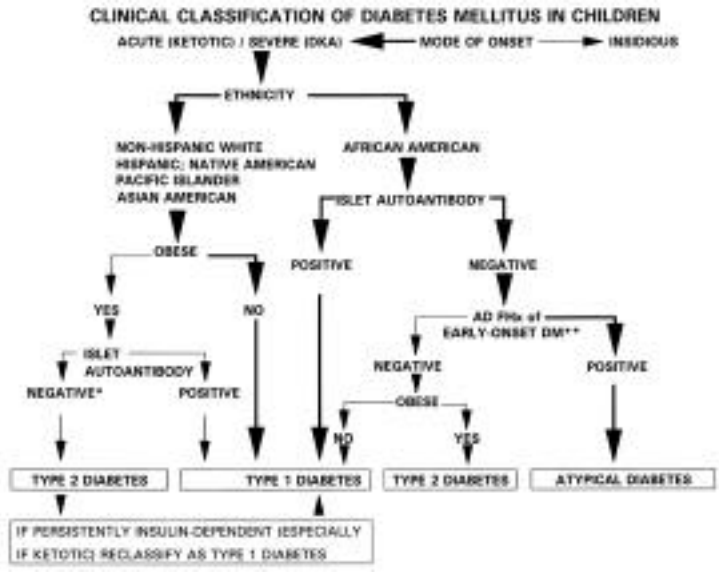

Figure 1—*Decision tree for classification of diabetes in children presenting with acute/severe symptoms. The bold arrows indicate the most likely pathway for this condition. *No specific autoimmunity. **Autosomal dominant (AD) family history (FHx) of diabetes (DM) with an onset <40 years of age.*

casians. The importance of atypical forms of diabetes in African-American youth has recently been emphasized by Arslanian and Danadian (19), who proposed the term "youth-onset atypical diabetes" (YOAD) for disorders that episodically display features of type 1 and type 2 diabetes. Of the three nonautoimmune forms of diabetes noted above, there is only evidence of increasing incidence in the pediatric population for type 2 diabetes.

In many reports, it is difficult to determine how many of the patients being reported as having type 2 diabetes, particularly among the African-American population, might meet the criteria of ADM. For example, ketoacidosis is common among African-American adolescents with type 2 diabetes in Cincinnati, Ohio (20). In ADM, there is acute onset of hyperglycemia, with ketosis or ketoacidosis as common features, followed by a clinical course more characteristic of type 2 diabetes (18). It is also unclear how many of the patients reported as type 1 might, in fact, have type 2 diabetes; a number of the youngsters reported from Chicago as having type 1 diabetes were noted to be obese (21). As noted in Table 2, obesity is not as common in ADM as it is in type 2 diabetes in youth. The background prevalence of obesity in the African-American population is high, however, and therefore some children with ADM will be significantly overweight.

The initial classification of the etiology of diabetes must occur at the time of diagnosis. The new ADA classification and diagnostic guidelines emphasize etiopathophysiologic classification, and not classification by clinical course (e.g., insulin-dependent versus non-insulin-dependent). Nevertheless, excluding islet autoantibody testing, the clinician remains dependent on clinical acumen and reasoning in classifying new-onset diabetes patients. In Figs. 1 and 2, the pathways in bold are the most likely outcomes for the majority of children. In some cases, the diagnosis of type 2 diabetes is made on the basis of the clinical course during follow-up.

The pragmatic first step in classification is to separate acute-onset diabetes (usually with ketosis or frank ketoacidosis) from insidious-onset diabetes and cases of nonketotic severe hyperglycemia (HGNK). In adults, HGNK is often referred to as hyperglycemic nonketotic coma (HGNK coma). For example, a child with new-onset diabetes who has a glucose level >750–1000 mg/dl in the absence of significant ketosis or ketoacidosis is unlikely to have type 1 diabetes.

In children with acute-onset diabetes, because ADM of African-Americans usually presents acutely, not unlike type 1 diabetes, the ethnic background of the patient must be considered. Nonobese non-Hispanic, Hispanic, Native, Pacific Islander, and Asian Americans with acute-onset diabetes are very likely to have type 1 diabetes and usually require no further testing. If the non-Hispanic, Hispanic, Native, Pacific Islander, or Asian American with acute-onset diabetes is obese, islet and thyroid autoantibody testing should be considered.

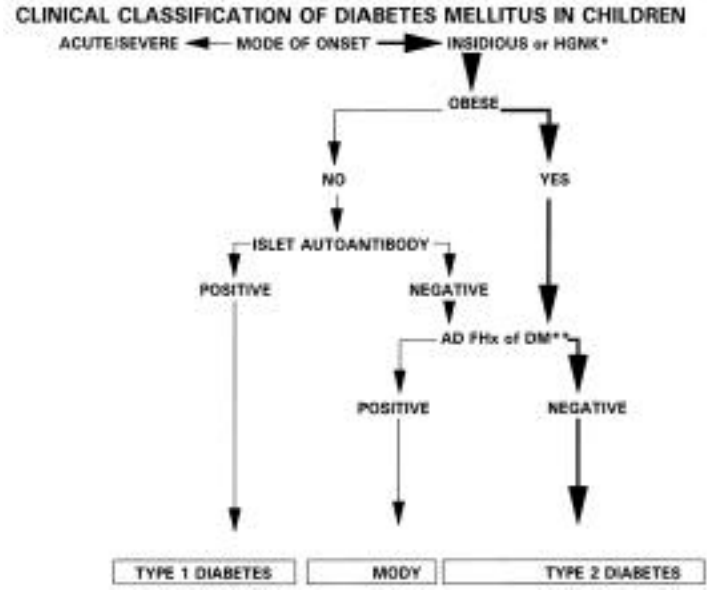

Figure 2—*Decision tree for classification of diabetes presenting with insidious or no symptoms or with hyperglycemia without significant ketosis. Bold arrows indicate the most likely pathway. Genetic studies of MODY genes and mitochondrial genes are not indicated. **Autosomal dominant (AD) family history (FHx) of diabetes (DM) in more than three generations.*

Table 3—*Genetic classification of non–type 1 diabetes*

Polygenic*
Monogenic
Mutations in nuclear DNA (nDNA)
MODY1: HNF-4α (chromosome 20q12-q13.1)
MODY2: Glucokinase (chromosome 7p15-p13)
MODY 3: HNF-1α (chromosome 12q24.3)
Atypical diabetes mellitus: glucokinase in one ADM family
Mutations in mitochondrial DNA (mDNA)†

Monogenic is classified as "other specific type" per 1997 ADA guidelines. For more information see *Table 5 and †Table 4.

If all are negative, the child may indeed have type 2 diabetes. Follow-up at 1 year may be helpful in such cases. If insulin is then continuously required or the child manifests ketosis, type 1 diabetes is likely.

In African-American children with new-onset acute-onset diabetes, islet autoantibody testing can identify most of the children who have type 1 diabetes. If islet and thyroid autoantibody studies are negative, a family history of early-onset diabetes in three or more generations suggests ADM. In the absence of such a family history, the absence of obesity suggests type 1 diabetes. Otherwise, the presence of obesity suggests type 2 diabetes.

For children with insidious-onset diabetes (Fig. 2), obese children without a three or more generation history of early-onset diabetes most likely have type 2 diabetes, which is not unlike type 2 diabetes in adults. If the child with insidious-onset diabetes is lean, islet autoantibody and thyroid testing may be helpful. The presence of such autoantibodies strongly argues in favor of type 1 diabetes. The absence of such autoantibodies and their family history would separate such children into MODY or type 2 diabetes. Because MODY is rare, there is no routine value in testing for hepatocyte nuclear factor (HNF)-4α, glucokinase, or HNF-1α mutations. Mitochondrial mutations account for <2% of clinical type 2 (non-insulin-dependent) diabetes in adults; therefore, studies of the mitochondrial genome remain research tools, as do HNF-4α, glucokinase, and HNF-1α studies.

PATHOPHYSIOLOGY — The deterioration of glucose tolerance and the development of type 2 diabetes reflect insulin resistance combined with relative insulin deficiency. Limited β-cell capacity would have little significance in the absence of obesity. The emergence of type 2 diabetes in all societies as rates of obesity increase and the strong familial tendency to develop type 2 diabetes indicate that there may have been an advantage to the metabolic phenotype that is now detrimental (22).

Insulin resistance, documented as either fasting hyperinsulinism or as the insulin response to oral glucose or to the hyperglycemic clamp, has been noted in the adult nondiabetic offspring of Pima Indians, Mexican Americans, and non-Hispanic whites with type 2 diabetes (23–26). In one longitudinal study of such individuals, a high cumulative incidence of type 2 diabetes was associated with earlier findings of insulin resistance on intravenous glucose tolerance testing and with increased first phase insulin release. Thus, in the prediabetic stage of the evolution of their diabetes, these normoglycemic individuals were maintaining an increased insulin secretion in the face of insulin resistance (27).

Several recent studies have explored the metabolic differences between African-American and white children. In the Bogalusa Heart Study, 5- to 17-year-old black children had higher insulin responses during an oral glucose tolerance test and higher insulin-to-glucose ratios than did white children. Among nearly 1,200 11- to 18-year-olds, black adolescents had higher insulin levels and lower glucose-to-insulin ratios than did whites, after correction for obesity, indicative of reduced insulin sensitivity among the black youngsters (28). Prepubertal black children also had lower resting energy expenditure and higher fasting and first phase insulin concentrations during glucose clamp studies than did white youngsters (29–31). Among pubertal subjects, lower insulin sensitivity was also seen in African-Americans (32). The lower resting energy expenditure in black prepubertal children in the Bogalusa Heart Study suggested a greater susceptibility to obesity. Nonetheless, there was little difference between black and white children in the increasing rates of adiposity documented over 2 decades (33).

There is also evidence for altered β-cell function as the initial lesion in type 2 diabetes. Lean patients with mild disease had impaired insulin release but normal insulin sensitivity in a Canadian and Swedish study (34). A British study found impaired pulsatile secretion in nondiabetic relatives of type 2 patients, indicative of a very early β-cell lesion (35).

The possibility that limited β-cell capacity and insulin resistance might be programmed in utero was initially suggested by studies associating impaired glucose tolerance or type 2 diabetes in adults with lower birth weight, smaller head circumference, and thinness at birth (36). The investigators proposed that reduced growth of the endocrine pancreas was a consequence of maternal undernutrition. It was subsequently demonstrated that glycemic response to insulin was also reduced in individuals who had been thin at birth (37). These observations led to the thrifty phenotype hypothesis, that poor nutrition in fetal and early infant life would be detrimental to the development and function of the β-cells and insulin-sensitive tissues, primarily muscle, leading to insulin resistance. With a surfeit of nutrients resulting in obesity in later life, type 2 diabetes would ensue.

These observations have been confirmed in a large study in Sweden, where reduced birth weight for length was associated with a threefold increased risk for type 2 diabetes by age 60 years, although at age 50 years, there was no evidence for decreased β-cell function, suggesting that the fetal undernutrition was primarily responsible for insulin resistance (38). In a cohort of 23,000 healthy men in the U.S., there was a nearly twofold increased risk for the development of diabetes in those with low birth weight (39). In Pima Indians, high birth weights (>4.5 kg) and low birth weights (<2.5 kg) are both associated with an increased risk for type 2 diabetes, suggesting that maternal diabetes, resulting in the higher birth weights, may have effects similar to fetal malnutrition (40).

GENETIC MARKERS, LINKAGE, AND DEFECTS — The inheritance of non–type 1 diabetes can be classified as polygenic or monogenic (Table 3). The vast majority of type 2 diabetes cases are polygenic and occur in adults aged >40 years and in association with obesity (41). The

Table 4—*Mutations in mitochondrial DNA associated with diabetes*

Class of mutation	Gene	Mutation	Additional potential clinical features	Accompanied by the A3243G mutation
rRNA	12SrRNA	C946A	HC	Yes
		A1041G	HC	Yes
tRNA	$tRNA^{Leu(UUR)}$	A3243G	MELAS, DF	—
		A3252G	MM	No
		C3256T	MM, LHON	No
		A3260G	MM, CM	No
		T3271C	MELAS	No
	$tRNA^{Lys}$	A8344G	MERRF	No
	$tRNA^{Glu}$	T14709C	MM	No
NADH dehydrogenase				
	ND1	G3316A	—	No
		T3394C	HC, LHON	Yes
	ND2	G4491A	HC	Yes
	ND4	G11963A	HC	Yes

CM, cardiomyopathy; DF, sensorineural hearing loss; HC, hypertrophic cardiomyopathy; LHON, Leber's hereditary optic neuropathy; MELAS, mitochondrial myopathy/encephalopathy/lactic acidosis/stroke-like syndrome; MERRF, myoclonic epilepsy, ragged-red fibers; MM, mitochondrial myopathy.

autosomal dominant (MODY) and maternally inherited (mitochondrial) monogenic forms of type 2 diabetes are rare. Monogenic type 2 diabetes often presents in childhood or early adulthood, however. According to the 1997 ADA guidelines (17), the monogenic forms of type 2 diabetes have been classified as "other specific types of diabetes."

Studies of MODY and the mitochondrial diabetes syndromes have resulted in fascinating discoveries that provide insights for the study of the polygenic forms. The first locus (MODY1) mapped to the MODY phenotype was located on chromosome 20 near the adenosine deaminase gene in the large RW pedigree (42). In studies of French MODY families, the inheritance of glucokinase was linked to the inheritance of MODY, establishing glucokinase as the candidate gene for MODY2 (43,44). More than 30 distinct mutations in the glucokinase gene have subsequently been identified in various MODY pedigrees (45,46). In studies of MODY families that showed no linkage to either the MODY1 or MODY2 loci, a region of chromosome 12 (MODY3) was linked to the MODY phenotype (47,48). The gene for HNF-1α was located within the MODY3 region, and by sequencing the HNF-1α gene in subjects affected with MODY3 and control subjects, mutations were discovered in HNF-1α (49). This confirmed that HNF-1α was the MODY3 gene. Next, HNF-4α, which is located near the adenosine deaminase gene on chromosome 20, was sequenced. Indeed, affected individuals in the RW MODY1 pedigree displayed a consistent HNF-4α mutation (50). ADM is inherited as an autosomal dominant trait, similar to MODY, but as noted above, displays a different clinical phenotype than MODY (18). In 1 of 10 ADM families, a unique glucokinase mutation was identified (51).

Families with type 2 diabetes may rarely display maternal inheritance (Table 4) (52). In this situation, disease is passed to offspring exclusively from the mother, and never from the father. Mitochondria are inherited strictly from the mother via the cytoplasm of the ovum, and maternally inherited disease results when mutations occur in mitochondrial DNA. Individuals affected with the mitochondrial diabetes syndromes may display, in addition to diabetes, sensorineural hearing loss, cardiomyopathy, optic neuropathy, myopathy, encephalopathy, lactic acidosis, stroke-like syndrome, or epilepsy (53). All of the mitochondrial mutations involve tRNA mutations except for the NADH dehydrogenase subunit (ND) 1 mutation. Some patients with mitochondrial diabetes syndromes have displayed an acute-onset insulin-dependent form of diabetes, although in most individual patients, the monogenic forms are clinically indistinguishable from other type 2 diabetes.

Genetic studies of the common, polygenic form of type 2 diabetes have been carried out almost exclusively in adults. Multiple loci have demonstrated associations or linkages to type 2 diabetes (Table 5). It is apparent that these associations and linkages are not observed in all populations studied. The most important locus found thus far is on chromosome 2 (*NIDDM1*) (76). In the study group of Mexican-American sib pairs with type 2 diabetes from Starr County, Texas, *NIDDM1* accounted for ~30% of genetic susceptibility to type 2 diabetes. Researchers are working to identify the specific *NIDDM1* gene. Other loci that have been associated with type 2 diabetes are expressed in the β-cells (glucokinase, islet-associated polypeptide, insulin, sulfonylurea receptor, prohormone convertase 2), target cells (apolipoprotein A1/C3/A4 cluster, apolipoprotein B, β_3-adrenergic receptor, glucokinase, insulin receptor, insulin receptor substrate-1, muscle glycogen synthase 1, phosphoenolpyruvate carboxykinase 1, *Ras* associated with diabetes), and other sets of cells (cholycystokinin type B receptor, growth hormone). This field deserves further study, with emphasis on inheritance of early-onset polygenic type 2 diabetes.

There are exciting new data that have demonstrated an association between the VNTR (variable number of tandem repeats) region of the human insulin gene and size at birth (79). This may provide a biologic and genetic link between the insulin gene, small size at birth, and type 2 diabetes. This could explain the epidemiologic finding that small size at birth is associated with an increased risk for type 2 diabetes later in life (36–38). The association between the VNTR region and type 1 diabetes was provided by Bell et al. (61) more than 10 years ago. The association of small size at birth and the later development of type 2 diabetes is very strong. Unresolved, however, is whether this is the result of nature or nurture, i.e., whether the insulin resistance is primarily genetic or a consequence of poor intrauterine nutrition.

There is no evidence that viruses cause type 2 diabetes or insulin resistance. Of the more than 14 loci that have been linked or associated with type 1 diabetes, only IDDM2, the insulin gene, influences susceptibility to both type 1 and type 2 diabetes (61,79).

TREATMENT AND PREVENTION: THE COMMUNITY CHALLENGE

Treatment issues

Treatment of type 2 diabetes in the pediatric population is similar to treatment of

Table 5—*Loci linked to or associated with type 2 diabetes in adults*

Locus/abbreviation	Location	Populations studied (Ref.)
Expressed in the β-cell		
Amylin (islet-associated polypeptide; IAPP)	12p12.3–p12.1	Japanese (54)
β-cell K_{ATP} channel subunit		
Sulfonylurea receptor (SUR)	11p15.1	U.K./U.S. Caucasians (55); French (56)
Glucokinase (GCK)	7p15–p13	African-Americans (57); Mauritian Creoles (58); Japanese (59); South Indians (60)
Insulin (INS)	11p15.5	U.S. Caucasian (61)
Prohormone convertase 2 (PCSK2)	20p11.2	Japanese (62)
Expressed in target cells		
Apolipoprotein A1, C3, A4 loci (apoA1/C3/A4)	11q23	Chinese Americans (63)
Apolipoprotein B (apoB)	2p24	Chinese Americans (63)
β_3-Adrenergic receptor (ADRB2)	5q32–q34	Pimas (64); Japanese (65)
Insulin receptor (INSR)	19p13.2	U.S. Caucasians, Hispanics (66); Mexican Americans (67); Chinese Americans (63)
Insulin receptor substrate-1 (IRS-1)	2q36–q37	Mexican Americans (68)
Muscle glycogen synthase (GSY1)	19q13.3	Finns (69); Japanese (70)
Phosphoenolpyruvate carboxykinase (PCK1)	20q13.31	French (71)
Ras associated with diabetes (RAD)	16q	U.S. Caucasians (72)
Expressed in other sets of cells		
Cholycystokinin type B receptor (CCKBR)	11p15.5–p15.4	French (73)
Growth hormone (GH1)	17q22–q24	U.S. Caucasians (74)
Loci associated with type 2 diabetes where the specific gene etiology has not been identified		
Chromosome 1	1, D1S191	U.S. Caucasians (75)
Chromosome 2 (NIDDM1)	2, D2S125	Mexican Americans (76)
Chromosome 11	11, D11S935	Caucasians, North European ancestry (77)
Chromosome 20	20q, D20S197	U.S. Caucasians (78)

the disease in adults: most patients can manage the disease by diet and exercise (4,80,81). Oral hypoglycemic agents (OHA), including sulfonylureas and biguanides, have been prescribed for youth unable to manage their diabetes by diet and exercise (4,80). Studies are needed that evaluate the long-term safety and efficacy of OHA in youth, particularly given recent reports of serious hepatic dysfunction in 1.9% of adult patients taking troglitazone (82,83). Side-effects of α-glucosidase inhibitors limit their use with youth (4,80). Some youths may require insulin when OHA are ineffective (81). The occasional patient presenting with diabetic ketoacidosis as a result of underlying infection may also require insulin, which can be stopped at a later time as blood sugar concentrations are stabilized (4,80,84).

Self-administration of insulin is a matter of survival for youth with type 1 diabetes and therefore becomes integrated into the daily routine. The situation is different for most youth with type 2 diabetes, however, and several studies comment on the nonadherence of the majority of patients in this age-group to recommended lifestyle modifications and medical treatment (4,8,80,81). Especially problematic are the youngsters with ADM who require insulin but do not become acutely ill when they fail to take their injections (18). Although adolescents begin to exert more control over their health behavior as they enter adulthood, studies indicate that most adolescents do not relate unhealthy behaviors with negative health outcomes (85,86). Studies of Mexican-American youth in California (80), Native American youth in Canada (4) and the U.S. (83), and Japanese youth (82) attribute nonadherence to several factors. These include lack of improvement in health status while on OHA, denial about their diabetes because they are asymptomatic, and peer pressure to consume high-caloric foods and beverages high in sugar content.

Numerous cultural and socioeconomic barriers interfere with the implementation of dietary changes in minority youth with diabetes. There may be lack of familiarity with recommended food items, which may be costly, difficult for families to obtain, and require special preparation (4,80). Finally, many youth who are obese find it difficult to engage in strenuous physical activity (87).

Prescribed lifestyle and behavioral changes for patients with type 2 diabetes are complex and of lifelong duration. Investigation is needed about how youth diagnosed with type 2 diabetes understand their disease and the treatment rationale. One recent study attributes poor compliance in African-American youth with type 2 diabetes to lack of understanding about the disease and its management (8). Self-care regimens need to be structured to enable the youth to critically analyze behavior choices in the context of their health. A recent study suggests that patient adherence may be facilitated if the health care provider actively involves the patient in developing the self-care regimen (88).

Prevention

Studies of programs of type 2 diabetes prevention that target African-American and

Mexican-American youth are unavailable. Because the disease has been recognized in Native American youth for >15 years, a number of summer camps and school-based education and prevention programs that focus on type 2 diabetes have been implemented for this population in the U.S. and Canada. School-based programs emphasize modification of the food supply in school meals, provide some classroom education about diabetes, and create a school environment that supports healthy lifestyle behaviors, including increased exercise (84,89,90). Programs for children in Headstart and K–6 encourage family involvement (84), whereas programs designed for high school children use social networks and peer pressure as a passive support system to promote behavior change and reduce health risk factors (88). Evaluations of these programs indicate that they are successful in promoting short-term behavior changes, but longitudinal studies need to be conducted to determine whether these programs induce persistent behavior changes that reduce health risks for type 2 diabetes in this age-group.

There are 1-week summer camps for Native American youth with type 2 diabetes or at high risk for the disease that provide a diabetes education program within a controlled environment that enables the participant to experience the benefits of exercise and good nutrition. Studies of camps in Canada and in the U.S. report normal glycemic levels in youth with type 2 diabetes after 5 days of controlled diet and increased physical activity (4,84,91). Behaviors learned at the camps are not maintained, however, and most youth experience poor glycemic control after returning home. One study reports that some youths participating in these camps in consecutive years do attempt to integrate the lifestyle changes into their home environments (84).

A number of school-based nutrition and exercise programs aimed at diabetes prevention exist on reservations across the U.S., but studies evaluating the effect of these programs have not been published. The Pathways program is in year 5 of a 9-year research effort to develop a culturally appropriate school- and family-based prevention program promoting increased physical activity and a healthy diet to prevent obesity and reduce risk for diabetes in grade 3–5 Indian children. A collaborative effort among universities, six Indian nations, reservation schools, and Indian families, the program draws on a social learning theory model similar to that used in the Child and Adolescent Trial for Cardiovascular Health (CATCH). The program stresses family participation as one key to program success (91,92).

Most diabetes prevention efforts in Indian communities have been secondary or tertiary prevention programs targeting adults with type 2 diabetes. The approaches often combine a number of strategies, including health education, health fairs, fitness programs, nutrition education, etc., and are delivered in a shotgun method with the expectation that one or two of the strategies will be effective. Prevention programs are often implemented with little or no pilot testing, assuring poor outcomes. Although many programs incorporate some culturally appropriate strategies, such as using cultural motifs in education pamphlets or the language of the target audience, they often neglect the sociocultural health beliefs of the target population.

Developing culturally relevant prevention programs necessitates analysis of sociocultural health beliefs and behaviors as well as the level of knowledge about the disease held by the program recipients. For example, one study of Indian youth who have family members with diabetes reports that, although the youth had some knowledge about the disease, they did not relate complications such as retinopathy or amputation to diabetes. Furthermore, over half of the study population expressed the belief that diabetes was contagious or was caused by "bad blood," and over a third of the group attributed the disease to "weakness" (93). This study highlights the necessity for health care providers to be informed about the attitudes, beliefs, and knowledge levels of the target population when designing education and prevention programs if these programs are to be meaningful, relevant, and effective.

CONCLUSIONS —

Nonautoimmune forms of youth-onset diabetes are becoming increasingly prevalent as rates of obesity in children and adolescents accelerate. This trend is particularly pronounced in minority populations. Research directed to an understanding of the basic biology of insulin production in youth deserves high priority. The development of therapy for non–type 1 diabetes that is safe and acceptable to youth is also important. Most importantly, behavioral and dietary programs that are able to effect long-term change and prevent obesity need to be developed within the communities affected.

References

1. Glaser NS: Non-insulin-dependent diabetes mellitus in childhood and adolescence. *Pediatr Clin North Am* 44:307–337, 1997
2. Savage PJ, Bennett PH, Senter RG, Miller M: High prevalence of diabetes in young Pima Indians. *Diabetes* 28:937–942, 1979
3. Dean HE, Mundy RLL, Moffatt M: Non-insulin-dependent diabetes mellitus in Indian children in Manitoba. *Can Med Assoc J* 147:52–57, 1992
4. Dean H: NIDDM-Y in First Nation children in Canada. *Clin Pediatr* 39:89–96, 1998
5. Harris SB, Perkins BA, Whalen-Brough E: Non-insulin dependent diabetes mellitus among First Nations children: new entity among First Nations people of northwestern Ontario. *Can Fam Physician* 42:869–876, 1996
6. Pinhas-Hamiel O, Dolan LM, Daniels SR, Standiford D, Khoury PR, Zeitler P: Increased incidence of non-insulin-dependent diabetes mellitus among adolescents. *J Pediatr* 128:608–615, 1996
7. Scott CR, Smith JM, Cradock M, Pihoker C: Characteristics of youth-onset non-insulin-dependent diabetes mellitus and insulin-dependent diabetes mellitus at diagnosis. *Pediatrics* 100:84–91, 1997
8. Pihoker C, Scott CR, Lensing SY, Cradock MM, Smith J: Non-insulin dependent diabetes mellitus in African American youths of Arkansas. *Clin Pediatr* 37:97–102, 1998
9. Neufeld ND, Raffal LJ, Landon C, Chen Y-DI, Vadheim CM: Early presentation of type 2 diabetes in Mexican-American youth. *Diabetes Care* 21:80–86, 1998
10. Kadiki OA, Reddy MR, Marzouk AA: Incidence of insulin-dependent diabetes (IDDM) and non-insulin-dependent diabetes (NIDDM) (0–34 years at onset) in Benghazi, Libya. *Diabetes Res Clin Pract* 32:165–173, 1996
11. Kitagawa T, Owada M, Urakami T, Tajima N: Epidemiology of type 1 (insulin-dependent) and type 2 (non-insulin-dependent) diabetes mellitus in Japanese children. *Diabetes Res Clin Pract* 24 (Suppl.):S7–S13, 1994
12. Kitagawa T, Owada M, Urakami T, Yamauchi K: Increased incidence of non-insulin dependent diabetes mellitus among Japanese school children correlates with an increased intake of animal protein and fat. *Clin Pediatr* 37:111–115, 1998
13. Yokoyama H, Okudaira M, Otani T, Watanabe C, Takaike H, Miuira J, Yamada H, Mutou K, Satou A, Uchigata Y, Iwamoto Y: High incidence of diabetic nephropathy in early-onset Japanese NIDDM patients: risk analysis. *Diabetes Care* 21:1080–1085, 1998
14. Martin MM, Martin ALA: Obesity, hyperinsulinism, and diabetes mellitus in childhood. *J Pediatr* 82:192–201, 1973
15. Rosenbloom AL: Age-related plasma insulin

response to glucose ingestion in children and adolescents. *IRCS Metab Nutr: Pediatr* 2:1210, 1974
16. American Diabetes Association: Screening for type 2 diabetes. *Diabetes Care*21 (Suppl. 1): S20–S22, 1998
17. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care*20:1183–1197, 1997
18. Winter WE, Maclaren NK, Riley WJ, Clarke DW, Kappy MS, Spillar RP: Maturity onset diabetes of youth in Black Americans. *N Engl J Med*316:285–291, 1987
19. Arslanian S, Danadian K: Insulin secretion, insulin sensitivity and diabetes in black children. *Trends Endocrinol Metab*9:194–199, 1998
20. Pinhas-Hamiel O, Dolan LM, Zeitler PS: Diabetic ketoacidosis among obese African-American adolescents with NIDDM. *Diabetes Care*20:484–486, 1997
21. Lipton RB, Fivecoate JA: High risk of IDDM in African-American and Hispanic children in Chicago, 1985–1990. *Diabetes Care* 18:476–482, 1995
22. Neel JV: Diabetes mellitus: a thrifty genotype rendered detrimental by progress? *Am J Hum Genet*14:353–362, 1962
23. Lillioja S, Mott DM, Spraul M, Ferraro R, Foley JE, Ravussin E, Knowler WC, Bennett PH, Bogardus C: Insulin resistance and insulin secretory dysfunction as precursors of non-insulin-dependent diabetes mellitus: prospective studies of Pima Indians. *N Engl J Med*329:1988–1992, 1993
24. Haffner SM, Stern MP, Dunn J, Mobley M, Blackwell J, Bergman RN: Diminished insulin sensitivity and increased insulin response in non-obese, non-diabetic Mexican Americans. *Metabolism*39:842–847, 1990
25. Haffner SM, Miettinen H, Stern MP: Insulin secretion and resistance in non-diabetic Mexican Americans and non-Hispanic whites with a parental history of diabetes. *J ClinEndocrinol Metab*81:1846–1851, 1996
26. Groop L, Forsblom C, Lehtovirta M, Tuomi T, Karanko S, Nissén M, Ehrnstrõm B-O, Forsén B, Isomaa B, Snickars B, Taskinen N-R: Metabolic consequences of a family history of NIDDM (the Botnia Study): evidence for sex-specific parental effects. *Diabetes*45:1585–1593, 1996
27. Martin BC, Warram JH, Krolewski AS, Bergman RN, Soeldner JS, Kahn CR: Role of glucose and insulin resistance in development of type 2 diabetes mellitus: results of a 25-year follow-up study. *Lancet* 340:925–929, 1992
28. Svec F, Nastasi K, Hilton C, Bao W, Srinivasan SR, Berenson GS: Black-white contrasts in insulin levels during pubertal development: the Bogalusa Heart Study. *Diabetes*41:313–317, 1992
29. Arslanian S: Insulin secretion and sensitivity in healthy African-American vs American-white children. *Clin Pediatr*37:81–88, 1998
30. Morrison JA, Alfaro MP, Khoury P, Thornton BB, Daniels SR: Determinants of resting energy expenditure in young black girls and young white girls. *J Pediatr* 129:637–642, 1996
31. Kaplan AS, Zernel BS, Stallings VA: Differences in resting energy expenditure in prepubertal black children and white children. *J Pediatr* 129:643–647, 1996
32. Arslanian S, Suprasongsin C: Differences in the *in vivo*insulin secretion and sensitivity of healthy black versus white adolescents. *J Pediatr*12:440–443, 1996
33. Freedman DS, Srinivasan SR, Valdez RA, Williamson DF, Berenson GS: Secular increases in relative weight and adiposity among children over two decades: the Bogalusa Heart Study. *Pediatrics*99:420–426, 1997
34. Pigon J, Giacca A, Õstenson C-G, Lam L, Vranic M, Efendi S: Normal hepatic insulin sensitivity in lean, mild non-insulin-dependent diabetic patients. *J Clin Endocrinol Metab*81:3702–3708, 1996
35. O'Rahilly S, Turner RC, Matthew D: Impaired pulsatile secretion of insulin in relatives of patients with non-insulin-dependent diabetes. *N Engl J Med*318:1225–1230, 1988
36. Phipps K, Barker DJP, Hales CN, Fall CHD, Osmond C, Clark PMS: Fetal growth and impaired glucose tolerance in men and women. *Diabetologia*36:225–228, 1993
37. Phillips DIW, Barker DJP, Hales CN, Hirst S, Osmond C: Thinness at birth and insulin resistance in adult life. *Diabetologia* 37:150–154, 1994
38. Lithell HO, McKeigue PM, Berglund L, Mohsen R, Lithell UB, Leon DA: Relation of size at birth to non-insulin dependent diabetes and insulin concentrations in men aged 50–60 years. *BMJ*312:406–410, 1996
39. Curhan GC, Willett WC, Rimm EB, Spiegelman D, Ascherio AL, Stampfer MJ: Birth weight and adult hypertension, diabetes mellitus, and obesity in US men. *Circulation*94:3246–3250, 1994
40. Fowden AL: The role of insulin in prenatal growth. *J Dev Physiol*12:173–182, 1989
41. DeFronzo RA, Bonadonna RC, Ferrannini E: Pathogenesis of NIDDM: a balanced overview. *Diabetes Care*15:318–368, 1992
42. Bell GI, Xiang KS, Newman MV, Wu SH, Wright LG, Fajans SS, Spielman RS, Cox NJ: Gene for non-insulin-dependent diabetes mellitus (maturity-onset diabetes of the young) subtype is linked to DNA polymorphism on human chromosome 20q. *Proc Natl Acad Sci U S A*88:1484–1488, 1991
43. Velho G, Froguel P, Clement K, Pueyo ME, Rakotoambinina B, Zouali H, Passa P, Cohen D, Robert JJ: Primary pancreatic beta-cell secretory defect caused by mutations in glucokinase gene in kindreds of maturity onset diabetes of the young. *Lancet*340:444–448, 1992
44. Froguel P, Zouali H, Vionnet N, Velho G, Vaxillaire M, Sun F, Lesage S, Stoffel M, Takeda J, Passa P, Permutt MA, Beckmaan JS, Bell GI, Cohen D: Familial hyperglycemia due to mutations in glucokinase. Definition of a subtype of diabetes mellitus. *N Engl J Med*328:697–702, 1993
45. Permutt MA, Chiu KC, Tanizawa Y: Glucokinase and NIDDM: a candidate gene that paid off. *Diabetes*41:1367–1372, 1992
46. Hattersley AT, Turner RC: Mutations of the glucokinase gene and type 2 diabetes. *Q J Med*86:227–232, 1993
47. Lesage S, Hani EH, Philippi A, Vaxillaire M, Hager J, Passa P, Demenais F, Froguel P, Vionnet N: Linkage analysis of the MODY3 locus on chromosome 12q with late-onset NIDDM. *Diabetes*44:1243–1247, 1995
48. Menzel S, Yamagata K, Trabb JB, Nerup J, Permutt MA, Fajans S, Menzel R, Iwasaki N, Omori Y, Cox YO, Bell GI: Localization of MODY3 to a 5-cM region of human chromosome 12. *Diabetes* 44:1408–1413, 1995
49. Yamagata K, Oda N, Kaisaki PJ, Menzel S, Furuta H, Vaxillaire M, Southam L, Cox RD, Lathrop GM, Boriraj VV, Chen X, Cox NJ, Oda Y, Yano H, LeBeau MM, Yamada S, Nishigori H, Takeda J, Fajans SS, Hattersley AT, Iwasaki N, Hansen T, Pedersen O, Polonsky KS, Turner RC, Vellho G, Chèvre J-C, Froguel P, Bell GI: Mutations in the hepatocyte nuclear factor-1α gene in maturity-onset diabetes of the young (MODY3). *Nature* 384:455–458, 1996
50. Yamagata K, Ruruta H, Oda N, Kaisaki PJ, Menzel S, Cox NJ, Fajans SS, Signorini S, Stoffel M, Bell GI: Mutations in the hepatocyte nuclear factor-4-α gene in maturity-onset diabetes of the young (MODY 1). *Nature* 384:458–460, 1996
51. Nakamura M, House DV, Winter WE: Novel mutations identified in the glucokinase (GCK) genes of a patient with atypical diabetes mellitus (ADM) of African Americans (Abstract). *Diabetes* 45 (Suppl. 2):77A, 1996
52. van den Ouweland JM, Lemkes HHPJ, Trembath RC, Ross R, Velho G, Cohen D, Froguel P, Maassen JA: Maternally inherited diabetes and deafness is a distinct subtype of diabetes and associates with a single point mutation in the mitochondrial tRNA $^{Leu(UUR)}$ gene. *Diabetes*43:746–751, 1994
53. Gerbitz K-D, Gempel K, Brdiczka D: Mitochondria and diabetes: genetic, biochemical, and clinical implications of the cellular energy circuit. *Diabetes*45:113–126, 1996
54. Sakagashira S, Sanke T, Hanabusa T, Shimomura H, Ohagi S, Kumagaye KY, Nakajima K, Nanjo K: Missense mutation of

amylin gene (S20G) in Japanese NIDDM patients. *Diabetes* 45:1279–1281, 1996
55. Inoue H, Ferrer J, Welling CM, Elbein SC, Hoffman M, Mayorga R, Warren-Perry M, Zhang Y, Millns H, Turner R, Province M, Bryan J, Permutt MA, Aguilar-Bryan L: Sequence variants in the sulfonylurea receptor (SUR) gene are associated with NIDDM in Caucasians. *Diabetes* 45:825–831, 1996
56. Hani EH, Clément K, Velho G, Vionnet N, Hager J, Philippi A, Dina C, Inoue H, Permutt MA, Basdevant A, North M, Demenais F, Guy-Grand B, Froguel P: Genetic studies of the sulfonylurea receptor gene locus in NIDDM and in morbid obesity among French Caucasians. *Diabetes* 46:688–694, 1997
57. Chiu KC, Province MA, Permutt MA: Glucokinase gene is genetic marker for NIDDM in American Blacks. *Diabetes* 41:843–849, 1992
58. Chiu KC, Province MA, Dowse GK, Zimmet PZ, Wagner G, Serjeantson S, Permutt MA: A genetic marker at the glucokinase gene locus for type 2 (non-insulin-dependent) diabetes mellitus in Mauritian Creoles. *Diabetologia* 35:632–638, 1992
59. Noda K, Matsutani A, Tanizawa Y, Neuman R, Kaneko T, Permutt MA, Kaku K: Polymorphic microsatellite repeat markers at the glucokinase gene locus are positively associated with NIDDM in Japanese. *Diabetes* 42:1147–1152, 1993
60. McCarthy MI, Hitchins M, Hitman GA, Cassell P, Hawrami K, Morton N, Mohan V, Ramachandran A, Snehalatha C, Viswanathan M: Positive association in the absence of linkage suggests a minor role for the glucokinase gene in the pathogenesis of type 2 (non-insulin-dependent) diabetes mellitus amongst South Indians. *Diabetologia* 36:633–641, 1993
61. Bell GI, Horita S, Karam JH: A polymorphic locus near the human insulin gene is associated with insulin-dependent diabetes mellitus. *Diabetes* 33:176–183, 1984
62. Yoshida H, Ohagi S, Sanke T, Furuta H, Furtuta M, Nanjo K: Association of the prohormone convertase 2 gene (PCSK2) on chromosome 20 with NIDDM in Japanese subjects. *Diabetes* 44:389–393, 1995
63. Xiang K, Cox NJ, Sanz N, Huang P, Karam JH, Bell GI: Insulin-receptor and apolipoprotein genes contribute to development of NIDDM in Chinese Americans. *Diabetes* 38:17–23, 1989
64. Walston J, Silver K, Bogardus C, Knowler WC, Celi FS, Austin S, Manning B, Strosberg AD, Stern MP, Raben N, Sorkin JD, Roth J, Shuldiner AR: Time of onset of non-insulin-dependent diabetes mellitus and genetic variation in the β_3-adrenergic-receptor gene. *N Engl J Med* 333:343–347, 1995
65. Fujisawa T, Ikegami H, Yamato E, Takekawa K, Nakagawa Y, Hamada Y, Oga T, Ueda H, Shintani M, Fukuda M, Ogihara T: Association of Trp64Arg mutation of the beta3-adrenergic-receptor with NIDDM and body weight gain. *Diabetologia* 39:349–352, 1996
66. McClain DA, Henry RR, Ullrich A, Olefsky JM: Restriction-fragment length polymorphism in insulin-receptor gene and insulin resistance in NIDDM. *Diabetes* 37:1071–1075, 1988
67. Raboudi SH, Mitchell BD, Stern MP, Eifler CW, Haffner SM, Hazuda HP, Frazier ML: Type II diabetes mellitus and polymorphism of insulin-receptor gene in Mexican Americans. *Diabetes* 38:975–980, 1989
68. Stern MP, Mitchell BD, Blangero J, Reinhart L, Krammerer CM, Harrison CR, Shipman PA, O'Connell P, Frazier ML, MacCluer JW: Evidence for a major gene for type II diabetes and linkage analyses with selected candidate genes in Mexican-Americans. *Diabetes* 45:563–568, 1996
69. Groop LC, Kankuri M, Schalin-Jäntti C, Ekstrand A, Nikula-Ijäs P, Widén E, Kuismanen ESA, Eriksson J, Franssila-Kallunki A, Saloranta C, Koskimies S: Association between polymorphism of the glycogen synthase gene and non-insulin-dependent diabetes mellitus. *N Engl J Med* 328:10–14, 1993
70. Kuroyama H, Sanke T, Ohagi S, Furuta M, Furuta H, Nanjo K: Simple tandem repeat DNA polymorphism in the human glycogen synthase gene is associated with NIDDM in Japanese subjects. *Diabetologia* 37:536–539, 1994
71. Hani EH, Zouali H, Philippi A, Beaudoin JC, Vionnet N, Passa P, Demenais F, Froguel P: Indication for genetic linkage of the phosphoenolpyruvate carboxykinase (PCK1) gene region on chromosome 20q to non-insulin-dependent diabetes mellitus. *Diabete Metab* 22:451–454, 1996
72. Doria A, Caldwell JS, Ji L, Reynet C, Rich SS, Weremowicz S, Morton CC, Warram JH, Kahn CR, Krolewski AS: Trinucleotide repeats at the rad locus. Allele distributions in NIDDM and mapping to a 3-cM region on chromosome 16q. *Diabetes* 44:243–247, 1995
73. Vionnet N, Hani EH, Lesage S, Philippi A, Hager J, Varret M, Stoffel M, Tanizawa Y, Chiu KC, Glaser B, Permutt MA, Passa P, Demenais F, Froguel P: Genetics of NIDDM in France: studies with 19 candidate genes in affected sib pairs. *Diabetes* 46:1062–1068, 1997
74. Elbein SC, Chiu KC, Hoffman MD, Mayorga RA, Bragg KL, Leppert MF: Linkage analysis of 19 candidate regions for insulin resistance in familial NIDDM. *Diabetes* 44:1259–1265, 1995
75. Elbein SC, Hoffman MD, Mayorga RA, Barrett KL, Leppert M, Hasstedt S: Do non-insulin-dependent diabetes mellitus (NIDDM) and insulin-dependent diabetes mellitus (IDDM) share genetic susceptibility loci? An analysis of putative IDDM susceptibility regions in familial NIDDM. *Metabolism* 46:48–52, 1997
76. Hanis CL, Boerwinkle E, Chakraborty R, Ellsworth DL, Concannon P, Stirling B, Morrison VA, Wapelhorst B, Spielman RS, Gogolin-Ewens KJ, Shephard JM, Williams SR, Risch N, Hinds D, Iwasaki N, Ogata M, Omori Y, Petzold C, Rietzsch H, Schröder HE, Schulze J, Cox NJ, Menzel S, Boriraj VV, Chen X, Lim LR, Lindner T, Mereu LE, Wang YQ, Xiang K, Yamagata K, Yang Y, Bell GI: A genome-wide search for human non-insulin-dependent (type 2) diabetes genes reveals a major susceptibility locus on chromosome 2. *Nat Genet* 13:161–166, 1996
77. Elbein SC, Bragg KL, Hoffman MD, Mayorga RA, Leppert MF: Linkage studies of NIDDM with 23 chromosome 11 markers in a sample of whites of Northern European descent. *Diabetes* 45:370–375, 1996
78. Ji L, Malecki M, Warram JH, Yang Y, Rich SS, Krolewski AS: New susceptibility locus for NIDDM is localized to human chromosome 20q. *Diabetes* 46:876–881, 1997
79. Dunger DB, Ong KKL, Huxtable SJ, Sheriff A, Woods KA, Ahmed ML, Golding J, Pembrey ME, Ring S, the ALSPAC study team, Bennett ST, Todd JA: Association of *INS* VNTR with size at birth. *Nat Genet* 19:98–100, 1998
80. Jones KL: Non-insulin dependent diabetes in children and adolescents: the therapeutic challenge. *Clin Pediatr* 37:103–110, 1998
81. Owada M, Nitadori Y, Kitagawa T: Treatment of NIDDM in youth. *Clin Pediatr* 37:117–121, 1998
82. Imura H: A novel antidiabetic drug, troglitazone: reason for hope and concern. *N Engl J Med* 338:908–909, 1998
83. Watkins PB, Whitcomb RW: Hepatic dysfunction associated with troglitazone. *N Engl J Med* 338:916–917, 1998
84. Cook VV, Hurley JS: Prevention of type 2 diabetes in childhood. *Clinical Pediatr* 37:123–129, 1998
85. Gochman DS: Some correlates of children's health beliefs and potential health behavior. *J Health Soc Behav* 12:148–154, 1971
86. Radius SM, Dillman TE, Becker MH, Rosenstock IM, Horvath, WJ: Adolescent perspective on health and illness. *Adolescence* 15:375–384, 1980
87. Molnar D, Porszasz J: The effect of fasting hyperinsulinemia on physical fitness in obese children. *Eur J Pediatr* 149:570–573, 1990
88. McNabb WL: Adherence in diabetes: can we define it and can we measure it? *Diabetes Care* 20:215–218, 1997
89. Teufel NI, Ritenbaugh CK: Development of a primary prevention program: insight

gained in the Zuni Diabetes Prevention Program. *Clin Pediatr* 37:131–141, 1998
90. Macaulay AC, Paradis G, Potvin L, Cross EJ, Saad-Haddad C, McComber A, Desrosiers S, Kirby R, Montour LT, Lamping DL, Leduc N, Rivard M: The Kahnawake Schools Diabetes Prevention Project: intervention, evaluation and baseline results of a diabetes primary prevention program with a native community in Canada. *Prev Med* 26:779–790, 1997
91. Stone EJ, Perry CL, Luepker RV: Synthesis on cardiovascular behavioral search for youth health promotion. *Health Ed Q* 16:155–169, 1989
92. Perry CL, Stone EJ, Parcel GS, Ellison RC, Nader P, Webber LS, Luepker RV: School-based cardiovascular health promotion: the child and adolescent trial for cardiovascular health (CATCH). *J School Health* 60:406–413, 1990
93. Joe JR: Perceptions of diabetes by Indian adolescents. In *Diabetes as a Disease of Civilization: The Impact of Culture Change on Indigenous Peoples* Joe JR, Young RS, Eds. Berlin, Mouton de Gruyter, 1994, p. 329–356