Evidence for Heterogeneous Pathogenesis of Insulin-Treated Diabetes in Black and White Children

INGRID M. LIBMAN, MD, PHD[1]
MASSIMO PIETROPAOLO, MD[2]
SILVA A. ARSLANIAN, MD[1]
RONALD E. LAPORTE, PHD[3]
DOROTHY J. BECKER, MBBCH, FCP[1]

OBJECTIVE — We have previously reported differences in the prevalence of β-cell autoantibodies (AAs) in black and white children with insulin-treated diabetes, suggesting that the disease pathogenesis may be more heterogeneous among racial groups than previously thought. To further explore this issue, we compared clinical, biochemical, and autoimmune characteristics at disease diagnosis and follow-up treatment in an expanded number of black and white children with and without the presence of AAs.

RESEARCH DESIGN AND METHODS — The study cohort of 130 black children and adolescents, aged <19 years, diagnosed with diabetes and treated with insulin at time of diagnosis (January 1979 to December 1998) were matched with an equal number of white children by age at onset, sex, and year of diagnosis.

RESULTS — The black children had a higher prevalence of obesity (43 vs. 11%) and acanthosis nigricans (21 vs. 1%) than white children and a lower prevalence of AAs. Compared with black children who had AAs, those with no AAs were older and had a higher prevalence of obesity, acanthosis nigricans, and parental diabetes. However, one of four of the black children with AAs was obese and/or had acanthosis nigricans. Among white children, the absence of AAs was not associated with any differences in terms of obesity or acanthosis nigricans compared with those with AAs. Similar to their black counterparts, white children without antibodies were older and had a higher prevalence of parental diabetes. Although treatment with an insulin sensitizer was used, insulin therapy was rarely discontinued on follow-up.

CONCLUSIONS — These pediatric subjects, irrespective of autoimmunity, often showed characteristics associated with type 2 diabetes. These characteristics were more frequently displayed in black than in white children. Our data suggest that childhood diabetes may constitute a spectrum of pathogenic mechanisms that may overlap, including those typically associated with both type 1 and type 2 diabetes. This finding could have therapeutic implications.

Diabetes Care 26:2876–2882, 2003

Immune-mediated type 1 diabetes is the most prevalent type of diabetes among children, and until recently only 1–2% of diabetic children were considered to have type 2 diabetes or other rare forms of the disease. However, recent reports have suggested that 8–45% of children with newly diagnosed diabetes have type 2 diabetes or another nonclassical type of diabetes (1–10). The majority of these children are classified as having type 2 diabetes according to clinical criteria, but increasingly more children are being identified with other types of diabetes. In particular, diagnoses of atypical diabetes and type 1.5 diabetes have been reported, especially in the black population, who seem to be disproportionately represented in this heterogeneous group (11). We and others reported an increase in the incidence of insulin-treated diabetes in black adolescents in the 1990s, based on the results of population-based studies (1–3). This observation raises the question of whether this rising incidence could be the result of an increasing incidence of type 1 diabetes or another type of insulin-requiring diabetes, possibly with mixed pathogenesis.

The Children's Hospital of Pittsburgh's (CHP's) Insulin-Dependent Diabetes Mellitus (IDDM) Registry includes all children aged <19 years treated with insulin at diabetes diagnosis since 1965 and has been shown to be representative of the larger population-based Allegheny County IDDM registry (12). The registry offers an invaluable opportunity to explore possible explanations for this increased incidence of insulin-treated diabetes in black children. Previous data in a small sample of this population demonstrated that, although >90% of white subjects had evidence of autoimmunity as measured by conventional islet cell antibody (ICA) assays, these antibodies were frequently undetected in black subjects (12). The objective of this study was to characterize and compare clinical, biochemical, and autoimmune characteristics at diagnosis and follow-up treatment of black and white children with insulin-requiring diabetes who did or did not have islet autoantibodies (AAs). All subjects were from the CHP's IDDM Registry and were diagnosed with diabetes between 1979 and 1998. The hypothesis to be tested was that black children had a higher prevalence of characteristics associated with insulin resistance/type 2 dia-

From the [1]Division of Pediatric Endocrinology, Department of Pediatrics, Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania; the [2]Division of Immunogenetics, Rangos Research Center, Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania; the [3]Diabetes Research Center, Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania.

Address correspondence and reprint requests to Ingrid M. Libman, MD, PhD, Department of Pediatric Endocrinology, Children's Hospital of Pittsburgh, 3705 Fifth Ave., Pittsburgh, PA 15213. E-mail: ingrid.libman@chp.edu.

Received for publication 9 February 2003 and accepted in revised form 9 June 2003.

Abbreviations: AA, autoantibody; CHP, Children's Hospital of Pittsburgh; IA-2, insulinoma-associated protein 2; IAA, insulin autoantibody; ICA, islet cell antibody; MODY, maturity-onset diabetes of the young; RIA, radioimmunoassay; SDS, SD score.

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

See accompanying editorial, p. 2954.

betes and that these characteristics were present irrespective of autoimmune status.

RESEARCH DESIGN AND METHODS

Subjects

All 130 black patients diagnosed with diabetes between 1 January 1979 and 31 December 1998 at the CHP were matched by sex, age (within 1 year), and year of diagnosis (within 1 year) to an equal number of white patients who were also part of the CHP registry. Onset sera had been stored since 1979 from patients in this registry; the registry has previously been demonstrated to be representative of the population-based Allegheny County registry with 70% overlap (12). All newly diagnosed diabetic patients who presented to CHP were routinely admitted to the hospital during the 20 years of the study period. The criteria for study inclusion were as follows: *1*) new onset of insulin-requiring diabetes, as determined by a pediatric endocrinologist; 2) age <19 years at diagnosis; and *3*) on insulin therapy at hospital discharge. All cases of secondary diabetes were excluded. The general treatment philosophy was to start insulin therapy in all patients with clinically apparent insulin-requiring diabetes, irrespective of the presence of obesity, if the patients had ketosis and/or severe hyperglycemia and/or marked weight loss. If obese patients became euglycemic on small insulin dosages while on diet therapy, insulin therapy was stopped within a few days and the patients were treated with diet and oral agents. These patients, and those designated as having type 2 diabetes and treated without insulin at onset, were not included in the study. After informed consent was received, blood samples were obtained within 1 week of diagnosis for measurement of insulin autoantibodies (IAAs) and/or within 3 months of diagnosis for testing of other islet cell AAs.

Clinical and biochemical data

Demographic data, including sex, race, date and age at onset, family history (in parent or extended family member) of diabetes (type 1 or 2 or gestational diabetes), Tanner stage, height, weight, presence of acanthosis nigricans, serum glucose level, presence of urine and/or serum ketones, serum bicarbonate and cholesterol levels, and insulin dosage at discharge and follow-up at 2 years (±3 months), were obtained from a review of medical records. BMI was calculated (13), and obesity was defined as a BMI ≥85th percentile for age and sex. Follow-up treatment was categorized as being *1*) on insulin alone, *2*) on insulin plus an oral hypoglycemic agent, or *3*) off insulin (either on diet or oral hypoglycemic agent).

Table 1—*Demographic, clinical, biochemical, and autoimmune characteristics by race*

Variable	Black subjects	White subjects	*P*
n	113	117	—
Age at onset (years)	10 ± 4.1	10 ± 4.0	0.97
Male/female (%)	53/47	51/49	0.78
Obesity (BMI ≥85th percentile; %)*	43	11	0.00005
Tanner stage 4 or 5 (%)†	38	28	0.13
Acanthosis nigricans (%)‡	21	1	0.0003
Insulin dosage at discharge (units/kg)	0.91 ± 0.46	0.88 ± 0.39	0.61
Parent with diabetes (%)§	29	21	0.24
Family history of diabetes (%)§	81	75	0.35
Ketones (%)	71	79	0.2
Bicarbonate level (meq/l)	17.1 ± 7.9	17.4 ± 7.2	0.78
Acidosis (% bicarbonate <18 meq/l)	35	43	0.35
Cholesterol level (mg/dl)‖	184 ± 39	179 ± 43	0.42
≥1 conventional β-cell AA (%)	70	89	0.0002
ICA(H)+ (%)	58	77	0.001
GAD65 AA+ (%)	54	73	0.004
IA-2 AA+ (%)	38	65	0.0001
IAA+ (%)	20	35	0.21
GAD AA + IA-2 AA (%)¶	29	51	0.001
ICA(H)+ GAD65 AA+ IA-2 AA (%)¶	29	47	0.007

Data are means ± SD unless otherwise noted. Data available for indicated number of black and white subjects, respectively: *96 and 89; †105 and 103; ‡67 and 69; §89 and 84; ‖52 and 59; ¶109 and 106.

Autoantibody assays

Blood samples were obtained within 1 week of diagnosis for IAAs or within 3 months for AAs other than IAAs. Blood was stored frozen at −20°C before being tested for antibodies. Antibody positivity was defined as having at least one of the four conventional AAs: ICAs measured from human pancreas (n = 224), IAAs (n = 95), GAD65 AAs (n = 219), or insulinoma-associated protein 2 (IA-2) AAs (n = 229).

ICAs were detected by a modification of an immunoperoxidase method on both human blood group 0 (ICA[H]) and cafeteria-fed rat (ICA[R]) fresh frozen pancreases to compare these assays (14,15). These assays are sensitive to 2 JDF units using the JDF serum as standard. The specificity of both of these assays was 90–100%; their sensitivity has varied between 70 and 100% in the JDF proficiency workshops conducted by the University of Florida in Gainesville since their inception. Specifically, ICA(R) was detected in 3% (5 JDF units) of 100 black and 70 white control subjects and in no subjects with multiple sclerosis (16) or Hashimoto thyroiditis.

The IAA assay was performed only in those subjects with serum available within 7 days of diagnosis. The radioimmunoassay (RIA) used ^{125}I monoiodinated insulin obtained from New England Nuclear and protein A separation using the assay described by Williams et al. (17). This assay detected 16% of blinded sera of type 1 diabetes with 100% specificity in the Immunology of Diabetes Workshop in 2000, which was average for participating laboratories. The intra-assay coefficient of variation (CV) was 8% and the interassay CVs were 8.9, 6.5, and 21.6% for low, medium, and high controls, respectively.

GAD65 AAs were detected by a radiobinding assay using ^{35}S-[Met]-labeled recombinant human GAD65 produced in vitro with the TNT reticulocyte R transcription/translation kit, as described by Grubin et al. (18). The intra- and interassay CVs were 12.2 and 13.2%, respectively. The GAD65 construct used for this

Table 2—*Demographic, clinical, and biochemical characteristics in black subjects by antibody status*

Variable	At least one conventional antibody	Absent conventional antibodies	*P*
n	79	34	
Age at onset (years)	9 ± 4.1	12 ± 3.6	0.001
Male/female (%)	49/51	41/59	0.42
Obesity (BMI ≥85th percentile; %)*	24	83	0.00001
BMI	19.2 ± 6.4	29.8 ± 11.7	0.0005
BMI SDS	0.014 ± 1.754	1.636 ± 1.152	0.005
BMI percentile (M/F)	87/85	>97/>97	
Tanner stage 4 or 5 (%)†	25	67	0.00004
Acanthosis nigricans (%)‡	5	48	0.00003
Insulin dosage at discharge (units/kg)	0.88 ± 0.36	0.93 ± 0.50	0.64
Parent with diabetes (%)§	19	48	0.004
Family history of diabetes (%)§	83	77	0.54
Ketones (%)	83	48	0.0006
Bicarbonate level (meq/l)	15.8 ± 7.6	19.6 ± 7.8	0.04
Acidosis (% bicarbonate <18 meq/l)	50	28	0.06
Cholesterol level (mg/dl)‖	157 ± 27	203 ± 51	0.01
ICA(R)+ (%)	69	29	0.0004
ICA(H)+ (%)	81	0	—
GAD65 AA+ (%)	75	0	—
IA-2 AA+ (%)	58	0	—
IAA+ (%)	33	0	—

Data are means ± SD unless otherwise noted. Data available for indicated number of black subjects with at least one or no antibodies, respectively: *65 and 31; †72 and 33; ‡42 and 25; §58 and 31; ‖35 and 17.

study was donated by Dr. Åke Lernmark, and the IA-2 construct (ICA512bdc) was provided by Dr. George Eisenbarth. The results were expressed as an index (index equals sample cpm − negative control cpm/positive control cpm − negative control cpm), as previously reported (19). Results of the proficiency workshops, organized by the University of Florida in Gainesville (1995, 1996, and 1997), and of the Diabetes Autoantibody Standardization Program (DASP 2000, 2002), organized by the World Health Organization, are summarized as follows: 76–100% sensitivity, 90–100% specificity (100% specificity three times), and 100% validity for GAD AAs, and 48–78.5% sensitivity, 98–100% specificity, 87.5% validity, and 91.6% consistency in the 1996 and 2000 for IA-2 AAs.

Statistical analysis

The *t* test was used to compare continuous variables, and the χ^2 test was used to compare proportions. In cases where the expected values were <5, Fisher's exact test was used. *P* values <0.05 were deemed statistically significant. Logistic regression analysis was used to examine the effect of the different variables on the absence of conventional AAs. Variables introduced into the regression analysis included those that had ≥60% of the information available (sex, age at diagnosis, obesity, Tanner stage, parental diabetes status, and presence of ketosis). Computations were done using the statistical software package SPSS (Chicago, IL).

RESULTS

Demographic and clinical differences at onset

Data, including sera for antibody testing, were available from 230 (88.5%) of the 260 subjects, of whom 113 were black and 117 were white. The demographic, clinical, biochemical, and autoimmune characteristics for black and white children are shown in Table 1. No black/white differences were found with reference to family history of diabetes, parental diabetes status, Tanner stage, mean insulin dosage at discharge, prevalence of ketones, or mean bicarbonate or cholesterol levels. However, black subjects had a higher prevalence of obesity (43 vs. 11%; $P = 0.00005$) and acanthosis nigricans (21 vs. 1%; $P = 0.0003$) when compared with white subjects. Although most subjects had conventional β-cell AAs, the prevalence was lower in black than in white subjects (70 vs. 89%; $P = 0.0002$).

Obesity was present in both groups irrespective of autoimmune status. However, the prevalence of obesity was higher in black compared with white subjects in those with at least one ($P = 0.02$) or no AAs ($P = 0.0009$). A higher prevalence of acanthosis nigricans was seen in black compared with white subjects in those with at least one ($P = 0.16$) or no AAs ($P = 0.19$); this difference was not significant, most likely because of the small numbers studied, as this clinical sign was infrequently documented as present or absent until the last decade.

As expected, children who had at least one β-cell antibody had a lower mean BMI SD score (SDS) at diagnosis than those with no antibodies (−0.22 vs. 1.27; $P = 0.0005$). The mean BMI, BMI SDS, and BMI percentiles by race and autoimmune status are presented in Tables 2 and 3. The mean BMI SDS was higher in blacks than whites in each category, significant in those without conventional antibodies ($P = 0.0013$) and almost significant in those with AAs ($P = 0.078$). The mean BMI percentile was greater in those without AAs, irrespective of race. However, the mean BMI percentile was far greater in those without AAs, especially among blacks, in whom it was well over the 97th percentile. When examining the obese group (BMI >85th percentile) for age and sex, the BMI SDS was lower in those with evidence of autoimmunity ($n = 26$) compared with those without ($n = 25$) (1.63 vs. 2.12; $P = 0.12$). However, this difference did not reach statistical significance, likely due to small numbers.

Racial differences by antibody status

Onset characteristics in black and white subjects by conventional antibody status are shown in Tables 2 and 3. In black subjects (Table 2), there were no differences in sex distribution, family history of diabetes, or mean insulin dosage at discharge in those with and without these AAs. However, black subjects with no conventional AAs were older; had a higher prevalence of obesity, acanthosis nigricans, and parental diabetes; and had

Table 3—*Demographic, clinical, and biochemical characteristics in white subjects by antibody status*

Variable	At least one conventional antibody	Absent conventional antibodies	*P*
n	104	13	—
Age at onset (years)	10 ± 4.1	13 ± 2.6	0.01
Male/female (%)	49/51	46/54	0.84
Obesity (BMI ≥85th percentile; %)	10	20	0.31
BMI	17.6 ± 4.3	22.1 ± 8.1	0.015
BMI SDS	−0.419 ± 1.548	0.2351 ± 1.50	0.93
BMI percentile (M/F)	65/60	87/80	
Tanner stage 4 or 5 (%)†	25	60	0.02
Acanthosis nigricans (%)‡	0	14	0.10
Insulin dosage at discharge (units/kg)	0.64 ± 0.41	0.91 ± 0.38	0.04
Parent with diabetes (%)§	17	62	0.003
Family history of diabetes (%)§	72	100	0.19
Ketones (%)	82	62	0.35
Bicarbonate level (meq/l)	16.8 ± 7.3	23.5 ± 3.3	0.03
Acidosis (% bicarbonate <18 meq/l)	38	0	0.08
Cholesterol level (mg/dl)‖	175 ± 39	208 ± 66	0.33
ICA(R)+ (%)	71	15	0.00001
ICA(H)+ (%)	88	0	—
GAD65 AA+ (%)	82	0	—
IA-2 AA+ (%)	74	0	—
IAA+ (%)	34	0	—

Data are means ± SD unless otherwise noted. Data available for indicated number of white subjects with at least one or no antibodies, respectively: *79 and 10; †93 and 10; ‡62 and 7; §76 and 8; ‖54 and 5.

more advanced pubertal status. Despite the absence of these AAs, almost 50% of these subjects had ketosis, but the prevalence was lower than in those with AAs. Mean bicarbonate levels were higher in those without antibodies, suggesting less decompensation. In those with at least one conventional AA (i.e., those with type 1 diabetes), 24% were obese and/or had acanthosis nigricans.

Likewise, in white subjects (Table 3), there were no differences in sex distribution and family history of diabetes in those with and without conventional AAs. As in black subjects, the group with no AAs was older and had a more advanced pubertal status, higher prevalence of parental diabetes, and higher mean bicarbonate level, but frequent presentation with ketosis (62%). However, in contrast to black subjects, white subjects with no AAs received a higher mean insulin dosage at discharge, and there were no significant differences in prevalence of obesity, acanthosis nigricans, ketosis, or mean cholesterol level compared with those with AAs.

Using the above-described conventional measurement of AAs to islet antigens, 30% of black and 11% of white subjects would be designated as antibody negative. However, the presence of another measure of autoimmunity, demonstrated by antibodies to the islet antigens of cafeteria-fed rat pancreases, showed that almost 30% of black and 15% of white subjects without conventionally measured antibodies had autoimmune features that presumably reflected some degree of β-cell damage. This was in contrast to a prevalence of positive results of this rat ICA in <3% of both black and white control subjects using this assay.

In the logistic regression analysis, being obese was significantly associated with an absence of conventional AAs in black subjects (odds ratio [OR] 5.8; 95% CI 2.86–9.82) and having a parent with diabetes was significantly associated with the absence of AAs in white subjects (OR 13.9, 95% CI 2.51–76.9).

Follow-up therapy

Of the 230 subjects, data at follow up (2 years ± 3 months) were available for 176 (77%) subjects, of whom 87 were black and 89 were white (mean onset age 10 ± 4.2 and 10 ± 4.1 years, respectively; sex distribution [male/female] 45/55% in both groups). There was no difference in the continuation of insulin treatment at follow-up between groups (98% in both groups). Thus, insulin was stopped in only 2% in each group. However, of the children treated with insulin at follow-up, 17% of black subjects, compared with 2% of white subjects, were also treated with an oral hypoglycemic agent (metformin in all cases except one child who was on troglitazone) ($P = 0.001$). Black subjects treated with both insulin and an oral agent were older at onset, had a more advanced Tanner stage, and had a higher prevalence of parental diabetes, obesity, and acanthosis nigricans. However, a significant number of these subjects presented either with ketosis or in diabetes ketoacidosis, and almost half of them (43%) had at least one antibody (Table 4). Because of the small number of white sub-

Table 4—*Onset characteristics in black subjects by type of treatment*

Variable	Insulin alone	Insulin + oral agent	*P*
n	71	14	—
Age at onset (years)	9 ± 4.2	12 ± 3.1	0.003
Male/female (%)	45/55	42/58	0.69
Obesity (BMI ≥85th percentile; %)*	28	100	0.0001
Tanner stage 4 or 5 (%)†	28	68	0.005
Acanthosis nigricans (%)‡	4	70	0.0001
Parent with diabetes (%)§	17	58	0.0001
Ketones (%)	79	48	0.009
Acidosis (% bicarbonate <18 meq/l)	47	26	
At least one conventional β-cell AA (%)	90	43	0.0003

Data are means ± SD unless otherwise noted. Data available for indicated number of subjects treated insulin alone or insulin plus oral agent, respectively: *70 and 14; †69 and 14; ‡48 and 12; §65 and 14.

jects who were on both insulin and an oral agent ($n = 2$), no comparisons were made.

CONCLUSIONS — The data from this study support the observation that present day diabetes in children and adolescents involves more than one pathogenic mechanism. Children and adolescents, especially black youth, with type 1A diabetes (classified as such because of the presence of ICAs) frequently have features associated with insulin resistance and type 2 diabetes. It is probable that there is a spectrum of autoimmune damage and that its clinical presentation is influenced by the degree of β-cell damage, with multiple AAs at one end and the severity of insulin resistance, related to excess weight, at the other.

Overall, black children and adolescents had a higher prevalence of obesity (not unexpected as this is also seen in the general population) and acanthosis nigricans than their white counterparts, despite a similar frequency of ketosis and irrespective of whether they had evidence of ICAs. Thus, they were more likely to display characteristics that are usually associated with insulin resistance and type 2 diabetes (4) than white patients. Features of type 2 diabetes, such as parental history of diabetes and higher cholesterol levels, were even more likely to be found in those black subjects without detectable conventional AAs than in those with these antibodies, and these subjects were also older and had a more advanced pubertal stage. There are numerous reports of adolescent children, usually from minority groups, presenting with characteristics of type 2 diabetes, such as obesity, acanthosis nigricans, an absence of ICAs, and/or a significant family history of diabetes, but with ketoacidosis. These children are initially diagnosed with type 1 diabetes because of their clinical presentation, but later are designated as having type 2 diabetes because of their insulin independence (5,20,21). It is possible that some of the children in our study had a form of severe type 2 diabetes with a nonautoimmune pathogenesis of their β-cell damage and relative insulin deficiency. This could partially explain the increased incidence of insulin-treated diabetes in Allegheny County in the early 1990s (1).

However, our data also showed that many individuals presented with characteristics of both insulin resistance and autoimmunity. Obesity with or without acanthosis nigricans was not found exclusively in patients without AAs, but was seen in 25% of black children with autoimmunity detected by conventional antibody assays and in 10% of white children with these antibodies. In addition, almost 30% of black youngsters who did not have conventional AAs showed some degree of islet cell autoimmunity, demonstrated by ICAs detected on rat pancreas substrate. The presence of ICAs detected on cafeteria-fed rat pancreases seems to be specific to individuals with diabetes, and is seen in 70% of new onset patients (often in very high titer and/or together with at least one other AA) and in 10% of their first-degree relatives. ICAs are mostly absent in control black and white populations and in patients with other autoimmune diseases (16). Our data suggest that these antibodies are generated against known or unknown epitopes, presumably detected because of increased assay sensitivity by stimulation of the islet cell antigens in the fed state (as opposed to suppression in the starved state of most available autopsy human pancreases). These antibodies appear to be an early feature of autoimmunity in first-degree relatives with type 1 diabetes who may later develop conventional AAs and/or clinical diabetes (22). Further evidence of autoimmunity against β-cell antigens is our finding of T-cell responses to islet cell antigens in up to 50% of tested new-onset children with diabetes who do not have detectable AAs (22).

Our group has previously proposed the concept of "double diabetes" (23). This concept was initially conceived because of the high frequency of a family history of apparent type 2 diabetes in probands with type 1 diabetes in the CHP's IDDM Registry. Evidence for the coexistence of insulin resistance and insulin deficiency caused by autoimmune β-cell destruction was expanded in this population and proven by the performance of insulin-glucose clamps in a subset of subjects (24,25). A recent study from Hathout et al. (26) found that among children and adolescents diagnosed with type 2 diabetes, almost 35% had at least one conventional AA. Case reports have also been published describing adolescents who present with features of both type 1 and type 2 diabetes (27). Moreover, Palmer and colleagues (28,29) have suggested that there may be a group of individuals who present with typical type 2 diabetes, but who have some of the immunologic and clinical features of type 1 diabetes (type 1.5 diabetes), including T-cell responses to islet cell antigens. These reports, together with our data, suggest that some children, especially black youth, could have both disease processes.

The concept of the "accelerator hypothesis" recently reviewed by Wilkin (30) suggests that the weight gain that causes insulin resistance also increases the demands on β-cells damaged by autoimmunity. Such a process would accelerate the clinical presentation of autoimmune islet cell destruction and relative insulin deficiency, which otherwise might not appear until much later in life. Rather than being viewed as a misdiagnosis of type 2 diabetes, this could offer an alternative explanation for the increase in insulin-treated diabetes seen in adolescents, as there could have been a shift to a younger age at onset secondary to the increase in obesity.

The fact that the majority of our cohort continued to be treated with insulin 2 years after diagnosis is not surprising in view of the fact that almost 80% of the subjects presented with ketosis at onset of the disease. However, it is interesting that one in five black children, some with evidence of conventional autoimmunity, were also treated with an oral hypoglycemic agent, suggesting that their endocrinologist saw enough evidence of some degree of insulin resistance to require additional treatment. The efficacy of this approach has recently been confirmed in a formal trial (31).

There were a few subjects, more white than black, with no evidence of obesity or AAs but with a parent with diabetes, who may have had maturity-onset diabetes of the young (MODY) (32,33). These forms of diabetes, with manifestations of insulin deficiency without evidence of increased insulin resistance, are included in the American Diabetes Association classification of type 1B diabetes (34).

In summary, these findings support the concept that clear, simple classifications separating type 1 and type 2 diabetes in children may not be appropriate for a large proportion of patients, as the pathoetiology of the disease may be more heterogeneous than previously thought. Even though type 1A diabetes remains the more prevalent form of the disease in childhood, other types such as type 1B and type 2 diabetes, MODY, and a possi-

ble form of diabetes with the coexistence of two overlapping pathogenic mechanisms (type 1.5 or "double" diabetes) need to be considered. Our data suggest that this latter subgroup of diabetes may be more prevalent in the black population and can be diagnosed on the basis of the association of autoimmunity (type 1A diabetes) with clinical characteristics of increased insulin resistance (type 2 diabetes). These results could have an impact on treatment and prevention strategies, as suggested by the recent report that clinical outcome in adults with atypical diabetes are better when insulin is continued in their treatment regimen (35). Our data also suggest that the interpretation of recent changes in the incidence of both insulin-treated and type 2 diabetes in childhood may be difficult and challenging, especially in the adolescent group. Neither clinical characteristics alone nor the choice of therapy clearly divide type 1 autoimmune and type 2 insulin-resistant diabetes.

Acknowledgments— This work was supported in part by National Institutes of Health Grants R01-DK-24021-20 (D.J.B.) and R01-DK-53456 and R01-DK-56200 (M.P.), a resident research grant from the American Academy of Pediatrics (I.M.L.), National Institutes of Health Grant T-32-DK-07729 (I.M.L.), and grants from the American Diabetes Association (career development award to M.P.), the General Clinical Research Center (5-M01-RR00084), the Renziehausen Trust Fund, and the Cochrane-Webber Trust Fund.

We thank Angela Darnley, Jamie Gay, Susan Pietropaolo, Karen Riley, and the general clinical research center nurses for their assistance.

References

1. Libman I, LaPorte R, Becker D, Dorman J, Drash A, Kuller L: Was there an epidemic of diabetes in non-white adolescents in Allegheny County? *Diabetes Care* 21: 1278–1282, 1998
2. Lipman T, Chang YF, Murphy KM: The epidemiology of type 1 diabetes in children in Philadelphia 1990–1994: evidence of an epidemic. *Diabetes Care* 25: 1969–1975, 2002
3. Keenan H, el Deirawi K, Walsh M, Grover V, Alva E, Onyemere K, Lipton R: Are trends in diabetes incidence changing for minority children? *Ann Epidemiol* 10:459, 2000
4. Scott CR, Smith JM, Michaeleen Cradock M, Pihoker C: Characteristics of youth-onset noninsulin dependent diabetes mellitus and insulin-dependent diabetes mellitus at diagnosis. *Pediatrics* 100:84–91, 1997
5. Pinhas-Hamiel O, Zeitler P: The importance of a name. *N Engl J Med* 340:1418–1421, 1999
6. Fagot-Campagna A, Pettitt DJ, Engelgau MM, Burrows NR, Geiss LS, Valdez R, Beckles GL, Saaddine J, Gregg EW, Williamson DF, Narayan KM: Type 2 diabetes among North American children and adolescents: a epidemiologic review and a public health perspective. *J Pediatr* 36: 664–672, 2000
7. Glaser NS, Jones KL: Non-insulin dependent diabetes mellitus in Mexican-American children. *West J Med* 168:11–16, 1998
8. Neufeld N, Raffel L, Landon C, Chen Y, Valdheim C: Early presentation of type 2 diabetes in Mexican-American youth. *Diabetes Care* 21:80–86, 1998
9. Hale DE, Danney MM: Non-insulin dependent diabetes in Hispanic youth (type 2Y) (Abstract). *Diabetes* 47 (Suppl. 1): A82, 1998
10. Ehtisham S, Kirk J, McEvilly A, Shaw NI, Jones S, Matyka K, Lee T, Britton SB, Barrett T: Prevalence of type 2 diabetes in children in Birmingham. *BMJ* 322:1428, 2001
11. American Diabetes Association: Type 2 diabetes in children and adolescents. *Diabetes Care* 23:381–389, 2000
12. Libman I, Pietropaolo M, Trucco M, Dorman J, LaPorte RE, Becker D: Islet cell autoimmunity in white and black children and adolescents with IDDM. *Diabetes Care* 21:1824–1827, 1998
13. Barlow SE, Dietz WH: Obesity evaluation and treatment: Expert Committee recommendations. The Maternal and Child Health Bureau, Health Resources and Services Administration and the Department of Health and Human Services. *Pediatrics* 102:E29, 1998
14. Dib SA, Colman PG, Dotta F, Tautkus M, Rabizadeh A, Eisenbarth GS: Expression of cytoplasmic islet cell antigens by rat pancreas. *Diabetes* 36:982–985, 1987
15. Pilcher CC, Elliot RB: A sensitive and reproducible method for the assay of human islet cell antibodies. *J Immunol Methods* 129:111–117, 1990
16. Winer S, Astsatourov I, Cheung RK, Lakshman G, Kubiak V, Cortez MA, Moscarello M, O'Connor PW, McKerlie C, Becker DJ, Dosch HM: Type 1 diabetes and multiple sclerosis patients target islet plus central nervous system autoantigens: nonimmunized nonobese diabetic mice can develop autoimmune encephalitis. *J Immunol* 166:2831–2841, 2001
17. Williams AJK, Bingley PJ, Bonifacio E, Palmer JP, Gale EAM: A novel micro-assay for insulin autoantibodies. *J Autoimmun* 10:473–478, 1997
18. Grubin CE, Daniels T, Toivola B, Landin-Olsson M, Hagopian WA, Li L, Karlsen AE, Boel E, Michelsen B, Lernmark A: A novel radiobinding assay to determine diagnostic accuracy of isoform-specific glutamic acid decarboxylase antibodies in childhood. *Diabetologia* 37:344–350, 1994
19. Pietropaolo M, Peakman M, Pietropaolo S, Zanone M, Foley T, Becker D, Trucco M: Combined analysis of GAD65 and ICA512 (IA-2) autoantibodies in organ and non-organ specific autoimmune diseases confers high specificity for insulin-dependent diabetes mellitus. *J Autoimmun* 11:1–10, 1998
20. Fagot-Campagna A, Imperatore G, Narayan V, Engelgau M: Diabetes mellitus: type 1 or type 2? (Letter). *J Pediatr* 138:612–613, 2001
21. Pinhas-Hamiel O, Dolan LM, Zeitler PS: Diabetic ketoacidosis among obese African-American adolescents with NIDDM. *Diabetes Care* 20:484–486, 1997
22. Becker DJ, Libman I, Pietropaolo M, Dosch M, Arslanian S, LaPorte R: Changing phenotype of IDDM: is it type 1 or type 2? *Pediatr Res* 49:93A, 2001
23. Orchard TJ: From diagnosis and classification to complications and therapy. DCCT II? Diabetes Control and Complications Trial. *Diabetes Care* 17:326–338, 1994
24. Erbey J, Kuller L, Becker D, Orchard T: The association between a family history of type 2 diabetes and coronary artery disease in a type 1 diabetes population. *Diabetes Care* 21:610–614, 1998
25. Williams K, Erbey J, Becker D, Arslanian S, Orchard T: Can clinical factors estimate insulin resistance in type 1 diabetes? *Diabetes* 49:626–632, 2000
26. Hathout EH, Thomas W, El-Shahawy M, Nahab F, Mace J: Diabetic autoimmune markers in children and adolescents with type 2 diabetes. *Pediatrics* 107:E102, 2001
27. Rapaport R, Wallach E, Greig F, Iazzetti L: Diabetes mellitus: type 1 or type 2? *J Pediatr* 138:612, 2001
28. Juneja R, Palmer JP: Type 1½ diabetes: myth or reality? *Autoimmunity* 29:65–83, 1999
29. Pihoker C, Brooks-Worrell B, Greenbaum C, Palmer J: Impact of islet reactive T-cells and autoantibodies in clinical diagnosis of type 1, type 2, or atypical diabetes in children (Abstract). *Diabetes* 49 (Suppl.1): A409, 2000
30. Wilkin TJ: The accelerator hypothesis: weight gain as the missing link between type 1 and type 2 diabetes. *Diabetologia* 44:914–922, 2001
31. Hamilton J, Cummings E, Zdravkovic D, Finegood D, Daneman D: Metformin as an adjunct therapy in adolescents with type 1 diabetes and insulin resistance: a randomized controlled trial. *Diabetes Care* 26:138–143, 2003

32. Herman WH, Fajans SS, Oritz FJ, Smith MJ, Sturis J, Bell GI, Polonsky KS, Halter JF: Abnormal insulin secretion, not insulin resistance, is the genetic or primary defect of MODY in the RW pedigree. *Diabetes* 43:40–46, 1994
33. Byrne MM, Sturis J, Menzel S, Yamagata K, Fajans SS, Dronsfield MJ, Bain SC, Hattersley AT, Velho G, Froguel P, Bell GI, Polonsky KS: Altered insulin secretory response to glucose in diabetic and nondiabetic subjects with mutations in the diabetes susceptibility gene MODY3 on chromosome 12. *Diabetes* 45:1503–1510, 1996
34. American Diabetes Association: 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* 25:S5–S20, 2002
35. Pinero-Pilona A, Litonjua P, Aviles-Santa L, Raskin P: Idiopathic type 1 diabetes in Dallas, Texas: a 5-year experience. *Diabetes Care* 24:1014–1018, 2001