

# The New England Journal of Medicine

Copyright © 2002 by the Massachusetts Medical Society

VOLUME 346

MAY 30, 2002

NUMBER 22



## EFFECTS OF INSULIN IN RELATIVES OF PATIENTS WITH TYPE 1 DIABETES MELLITUS

DIABETES PREVENTION TRIAL—TYPE 1 DIABETES STUDY GROUP\*

### ABSTRACT

**Background** It is unknown whether insulin therapy can delay or prevent diabetes in nondiabetic relatives of patients with diabetes.

**Methods** In a randomized, controlled, nonblinded clinical trial, we screened 84,228 first-degree and second-degree relatives of patients with diabetes for islet-cell antibodies; 3152 tested positive; 2103 of the 3152 underwent genetic, immunologic, and metabolic staging to quantify their risk; 372 of the 2103 had a projected five-year risk of more than 50 percent; 339 of the 372 (median age, 11.2 years) were randomly assigned to undergo either close observation or an intervention that consisted of low-dose subcutaneous ultralente insulin, administered twice daily for a total dose of 0.25 unit per kilogram of body weight per day, plus annual four-day continuous intravenous infusions of insulin. Oral glucose-tolerance tests were performed every six months. Median follow-up was 3.7 years. The primary end point was a diagnosis of diabetes.

**Results** Diabetes was diagnosed in 69 subjects in the intervention group and 70 subjects in the observation group. The annualized rate of progression to diabetes was 15.1 percent in the intervention group and 14.6 percent in the observation group. The cumulative incidence of diabetes was similar in the two groups (relative risk in the intervention group as compared with the observation group, 0.96). Most subjects in whom diabetes developed were asymptomatic. Progression to diabetes occurred at a faster rate among subjects with abnormal base-line glucose tolerance (22 percent per year) than among those with normal base-line glucose tolerance (10 percent per year,  $P < 0.001$ ). There were no episodes of severe hypoglycemia. The incidence of chemical hypoglycemia, assessed without ascertainment bias, was similar in the two groups.

**Conclusions** In persons at high risk for diabetes, insulin at the dosage used in this study does not delay or prevent type 1 diabetes. (N Engl J Med 2002; 346:1685-91.)

Copyright © 2002 Massachusetts Medical Society.

**T**YPE 1 diabetes mellitus occurs in genetically predisposed persons as a consequence of the immune-mediated destruction of pancreatic islet beta cells that secrete insulin.<sup>1</sup> The onset of clinically overt diabetes represents the end point of an insidious, progressive decline in the function of beta cells after the majority of beta cells have been damaged or destroyed. Risk can be predicted on the basis of immunologic markers and tests of beta-cell function.

Parenteral insulin therapy prevents diabetes in animal models.<sup>2-7</sup> Moreover, pilot studies have suggested that insulin therapy also delays diabetes in humans.<sup>8-10</sup> Animal studies have suggested that insulin may be acting metabolically<sup>7,11-13</sup> — by causing the beta cells to rest — or immunologically.<sup>8,14-16</sup> Such studies have been so convincing that many physicians have begun to use insulin in persons who are at high risk for diabetes.

We undertook a randomized, controlled clinical trial in order to determine whether insulin could prevent or delay the onset of overt diabetes in relatives of patients with diabetes. Relatives were studied because they have a risk of diabetes that is 10 to 20 times that in the general population. Our study, the Diabetes Prevention Trial—Type 1 Diabetes (DPT-1), included two separate trials. We report here the results of the parenteral insulin trial, involving relatives with a projected five-year risk of diabetes that was higher than 50 percent. A second trial studying the effect of oral insulin therapy in relatives with a projected five-year risk of 26 to 50 percent is ongoing.

The study chairman, Jay S. Skyler, M.D., takes responsibility for the content of this article. Address reprint requests to Dr. Skyler at the University of Miami, P.O. Box 016960 (D-110), Miami, FL 33101, or at [jskyler@miami.edu](mailto:jskyler@miami.edu).

\*The members of the study group are listed in the Appendix.

## METHODS

### Study Design

The study was divided into three parts: screening, staging, and intervention. Subjects were recruited from study clinics and through media campaigns.

#### Screening

First-degree relatives, 3 to 45 years of age, and second-degree relatives, 3 to 20 years of age, of patients with diabetes were screened for islet-cell antibodies. Those with an islet-cell antibody titer of 10 Juvenile Diabetes Foundation (JDF) units or higher were offered staging evaluations.

#### Staging

Staging confirmed the presence of islet-cell antibodies, measured insulin antibodies, assessed the first-phase insulin response to intravenous glucose, assessed oral glucose tolerance, and determined the presence or absence of HLA-DQA1\*0102,DQB1\*0602, a protective haplotype, the presence of which excluded subjects from further participation.<sup>17,18</sup> Islet-cell antibody-positive subjects were then defined as having a high risk of diabetes (a five-year risk of more than 50 percent) and were deemed eligible for the parenteral insulin trial if they had a first-phase insulin response below the threshold (as defined below) on two occasions, if their oral glucose-tolerance results were not completely normal, or both.<sup>19</sup> Relatives who tested positive for islet-cell antibodies and insulin antibodies and who had a first-phase insulin response above the threshold and normal glucose tolerance were defined as having intermediate risk (a five-year risk of 26 to 50 percent) and were deemed eligible for the ongoing oral insulin trial.

#### Intervention

Subjects identified as having a high risk were eligible for random assignment to the experimental intervention (parenteral insulin therapy) or to a control group that underwent close observation. Subjects were stratified according to glucose-tolerance status (normal vs. impaired or indeterminate) before randomization. Randomization was performed by a central, automated system, was stratified according to base-line glucose tolerance and clinical center, and used blocks of random, variable sizes.

#### Study Sites

Study coordination, laboratory assessment, and data management were performed centrally. Three types of clinical sites were involved in the study: there were nine clinical centers, each of which coordinated a network of affiliate and satellite sites throughout the United States and Canada. Screening occurred at any of these approximately 360 locations. Staging was performed at clinical centers and affiliates; clinical centers and many affiliates followed the randomized subjects. The protocol was approved by the institutional review boards at participating locations. Subjects (or their parents, or both) provided written informed consent before each step — screening, staging, and intervention — and yearly for continuation in the study. Written or oral assent was obtained from minor subjects.

#### Study Protocol

Subjects in the intervention group received parenteral insulin — subcutaneous injections twice daily, plus annual intravenous infusions. Subjects received subcutaneous injections of recombinant human ultralente insulin (Humulin U, Eli Lilly) in the morning when they awoke and in the evening at bedtime; the initial dose for each injection was 0.125 U per kilogram of body weight. Doses were adjusted as the subject's weight changed and in response to hypoglycemia. At base line and every 12 months ( $\pm 6$  weeks)

thereafter, subjects in the intervention group were hospitalized and received continuous intravenous infusions of insulin (recombinant human regular insulin [Humulin R, Eli Lilly]) for 4 days at an initial dose of 0.015 U per kilogram per hour, with an increased rate for meals. Doses were altered according to an algorithm. The target blood glucose level was 60 to 80 mg per deciliter (3.3 to 4.4 mmol per liter), and glucose levels were measured every hour when the subject was awake and every two hours when he or she was asleep. Because the interventions involved injections and infusions and because children were included in the study, the control group did not receive placebo.

#### Follow-up Assessments

All randomized subjects were seen every six months, at which time an oral glucose-tolerance test was administered to assess glycemic status, the primary study end point. Mixed-meal tolerance tests were performed at base line, at years 1, 3, and 5, and at the end of the study. Intravenous glucose-tolerance testing was performed at years 2, 4, and 6 and at the end of the study.

Subjects checked their blood glucose level if they had symptoms of hypoglycemia. Presumed hypoglycemia (without measurement of glucose) was defined by typical symptoms that resolved promptly with the intake of food. Definite hypoglycemia was defined as a blood glucose concentration of less than 50 mg per deciliter (2.8 mmol per liter) measured at the time symptoms appeared. Severe hypoglycemia was defined as loss of consciousness, convulsion, stupor, or hypoglycemia necessitating the assistance of another person or treatment with intravenous glucose or subcutaneous glucagon. Every three months, subjects obtained a capillary-blood glucose profile that consisted of five measurements (before breakfast, before lunch, before supper, two hours after supper, and at 3 a.m.); when two of these glucose values were less than 50 mg per deciliter, the subject was classified as having chemical hypoglycemia. To detect possible cognitive changes caused by hypoglycemia, the Wide Range Achievement Test was administered at base line, six months after enrollment, and annually thereafter to subjects who were 5 to 18 years of age at enrollment or who turned 5 during the study.<sup>20</sup>

#### Tolerance-Test Procedures

Tolerance tests were performed after an overnight fast and insertion of an intravenous cannula.

##### Intravenous Glucose-Tolerance Test

Intravenous glucose-tolerance tests were performed as described previously.<sup>21,22</sup> Insulin values at one and three minutes were added together to determine the first-phase insulin response. The first-phase insulin response in siblings, offspring, and second-degree relatives was considered to be below threshold if it was below the 10th percentile for this group ( $<100 \mu\text{U}$  per milliliter for subjects eight years of age or older;  $<60 \mu\text{U}$  per milliliter for subjects less than eight years of age); the response in parents was considered to be below threshold if it was below the first percentile for the group of parents ( $<60 \mu\text{U}$  per milliliter).

##### Oral Glucose-Tolerance Test

The dose of oral glucose was 1.75 g per kilogram (maximum, 75 g). Plasma glucose values were interpreted according to the guidelines of the American Diabetes Association<sup>19</sup>: a fasting plasma glucose level of 126 mg per deciliter (7.0 mmol per liter) or higher or a glucose level of 200 mg per deciliter (11.1 mmol per liter) or higher at 120 minutes was considered to be diagnostic of diabetes; a fasting plasma glucose level of 110 to 125 mg per deciliter (6.1 to 6.9 mmol per liter) was defined as impaired fasting glucose; a glucose level of 140 to 199 mg per deciliter (7.8 to 11.0 mmol per liter) at 120 minutes was defined as impaired glucose tolerance. If the level was 200 mg per deciliter or higher at 30,

60, or 90 minutes but the fasting plasma glucose level and the level at 120 minutes were below threshold for impaired fasting glucose and impaired glucose tolerance, the subject was classified as having indeterminate glucose tolerance. Subjects with oral glucose-tolerance results during the staging phase that were consistent with diabetes were excluded. After randomization, a diagnosis of diabetes required confirmation on a subsequent day by oral glucose-tolerance testing or the presence of an elevated fasting glucose level.<sup>19</sup>

#### Mixed-Meal Tolerance Test

Subjects consumed a liquid formula meal (Sustacal or Boost, Mead Johnson Nutritionals; 6 cal per kilogram; maximum, 360 kcal) for the mixed-meal tolerance test.

#### Laboratory Measures

The presence of islet-cell antibodies was determined by indirect immunofluorescence, and subjects with titers of 10 JDF units or higher were considered positive.<sup>23,24</sup> Insulin autoantibodies were measured by competitive liquid-phase radioassay, and 39 nU per milliliter (3 SD above normal) was considered the upper limit of normal.<sup>25,26</sup> The interassay coefficient of variation among assays with low positive values was 10.3 percent. In subjects under 30 years of age, the islet-cell antibody titer had 100 percent specificity and 74 percent sensitivity for the detection of new-onset diabetes, and the insulin antibody titer had 91 percent specificity and 49 percent sensitivity.<sup>27</sup>

Plasma glucose was measured by the glucose oxidase method. Insulin and C-peptide levels were determined by radioimmunoassay. The interassay coefficient of variation for the insulin assay was 4.5 percent in the high reference pool and 6.9 percent in the low reference pool. The interassay coefficient of variation for the C-peptide assay was 6.9 percent in a reference pool with relatively high values and 7.8 percent in a reference pool with relatively low values. For HLA-DQ typing, we used DNA extracted from the buffy coats of peripheral-blood leukocytes, and HLA-DQA1 and DQB1 alleles were amplified by polymerase chain reaction with the use of sequence-specific probes.

#### Statistical Analysis

The trial was designed on the basis of the following assumptions: a five-year cumulative incidence of diabetes of at least 50 percent (annual hazard rate, 21 percent), 80 percent power to detect a 35 percent reduction in incidence in the intervention group, and a two-tailed alpha level of 0.05. We planned to enroll subjects for 4 years, with 2 years of follow-up, and we anticipated an annual rate of loss to follow-up of 10 percent, yielding an estimated average duration of treatment of 2.8 years.

Data that were not normally distributed were log-transformed for analysis and back-transformed for presentation. Data were analyzed according to the intention-to-treat principle. Kaplan-Meier life tables were constructed and compared by means of the log-rank chi-square statistic. Categorical variables were compared by Pearson's chi-square test or Fisher's exact test. Differences in means were tested with the use of analysis of variance. Tests of significance were two-tailed. Statistical analyses were performed with SAS software. Data were monitored twice yearly by an independent data and safety monitoring board, which had been given predefined stopping rules.

## RESULTS

#### Enrollment

Screening began on February 15, 1994. The first subject underwent randomization on December 31,

1994. By the time randomization was completed (October 31, 2000), samples for screening for islet-cell antibodies had been obtained from 89,827 relatives. Of these, 84,594 samples were eligible for further study. The remaining samples were excluded because they came from persons without an identified relative with diabetes or persons whose age was outside the range defined by the protocol. By the end of the enrollment period, 84,228 samples had been analyzed for islet-cell antibodies, and 3152 of the subjects (3.7 percent) were found to be islet-cell antibody-positive. Of these, 354 (11.2 percent) were excluded before randomization because they had a fasting plasma glucose level of 126 mg per deciliter or higher or a glucose level of 200 mg per deciliter or higher two hours after oral glucose challenge — values that, if confirmed, are diagnostic of diabetes. A total of 2103 subjects (66.7 percent of those who were islet-cell antibody-positive) underwent staging. On initial intravenous glucose-tolerance testing, 535 subjects had a low first-phase insulin response. As staging continued, a total of 372 subjects were classified as having a high risk and were deemed eligible for randomization; of these, 339 underwent randomization (91.1 percent) — 169 were assigned to the intervention and 170 to observation. The base-line characteristics of the subjects are summarized in Table 1; there were no statistically significant differences between the treatment groups.

#### Outcomes

Subjects were followed for a median of 1345 days (3.7 years; interquartile range, 784 to 1737 days). The annual rate of loss to follow-up was 1.3 percent — lower than the 10 percent we had anticipated. The annual rate of noncompliance was 5.5 percent in the intervention group (i.e., subjects declined daily injections, infusions, or both) and 1.0 percent in the observation group (i.e., subjects began insulin therapy or other prophylactic therapy). Diabetes was diagnosed in 139 participants: 69 in the intervention group and 70 in the observation group. The majority of participants in whom diabetes was diagnosed were asymptomatic (102 of 139, 73.4 percent). The proportion of participants in whom diabetes developed, averaged over the duration of follow-up, was 15.1 percent per year in the intervention group and 14.6 percent per year in the observation group. The cumulative incidence of diabetes was similar in the two groups (hazard ratio in the intervention group as compared with the observation group, 0.96; 95 percent confidence interval, 0.69 to 1.34;  $P=0.80$ ) (Fig. 1A).

Because this was not a blinded study, we also assessed progression to diabetes among only the subjects who were reported to have adhered to the treatment regimen (Fig. 1B) and again found no difference

**TABLE 1.** BASE-LINE CHARACTERISTICS OF THE 339 RANDOMIZED SUBJECTS.\*

CHARACTERISTIC	INTERVENTION GROUP (N=169)	OBSERVATION GROUP (N=170)
Age — yr		
Median	11.9	12.1
Interquartile range	7.1–16.7	7.6–16.6
First-phase insulin response — $\mu\text{U}/\text{ml}$	70.8 $\pm$ 40.4	72.8 $\pm$ 37.1
Impaired or indeterminate glucose tolerance — no. (%)	58 (34.3)	54 (31.8)
Race or ethnic group — no. (%)		
Non-Hispanic white	159 (94.1)	158 (92.9)
Non-Hispanic black	1 (0.6)	1 (0.6)
Hispanic	4 (2.4)	5 (2.9)
Other	5 (3.0)	6 (3.5)
Sex — no. (%)		
Male	87 (51.5)	89 (52.4)
Female	82 (48.5)	81 (47.6)
Relationship to index patient with diabetes — no. (%)		
Sibling	100 (59.2)	112 (65.9)
Parent	47 (27.8)	40 (23.5)
Offspring	8 (4.7)	5 (2.9)
Second-degree relative	14 (8.3)	13 (7.6)
Antibody levels		
Islet-cell antibodies — JDF units		
Median	160	160
Interquartile range	40–320	40–320
Insulin antibodies — nU/ml	365 $\pm$ 641	295 $\pm$ 552

\*Plus-minus values are means  $\pm$ SD. JDF denotes Juvenile Diabetes Foundation.

between the treatment groups. Progression to diabetes was also examined separately in two predetermined subgroups: subjects with normal glucose tolerance at base line (Fig. 1C) and those with abnormal glucose tolerance but not diabetes at base line (Fig. 1D). No differences were found between the groups. There was a higher rate of progression to diabetes among those with abnormal base-line glucose tolerance (22 percent per year) than among those with normal base-line glucose tolerance (10 percent per year,  $P<0.001$ ).

Insulin secretion before the diagnosis of diabetes was examined through the assessment of the C-peptide response during mixed-meal tolerance testing, oral glucose-tolerance testing, and intravenous glucose-tolerance testing. There were no differences between groups in terms of the peak values or the areas under the curve for any of the tests. The peak C-peptide values during mixed-meal tolerance testing, as representative of the data, are presented in Figure 2.

There was no difference in the level of glycemia between groups in the intention-to-treat analysis. Not surprisingly, a secondary regression analysis re-

vealed that, as compared with those in whom diabetes did not develop, those who had progression to diabetes had a slight progressive increase in both glycosylated hemoglobin ( $P<0.001$ ) and the area under the curve on serial glucose-tolerance tests ( $P<0.001$ ).

#### Side Effects

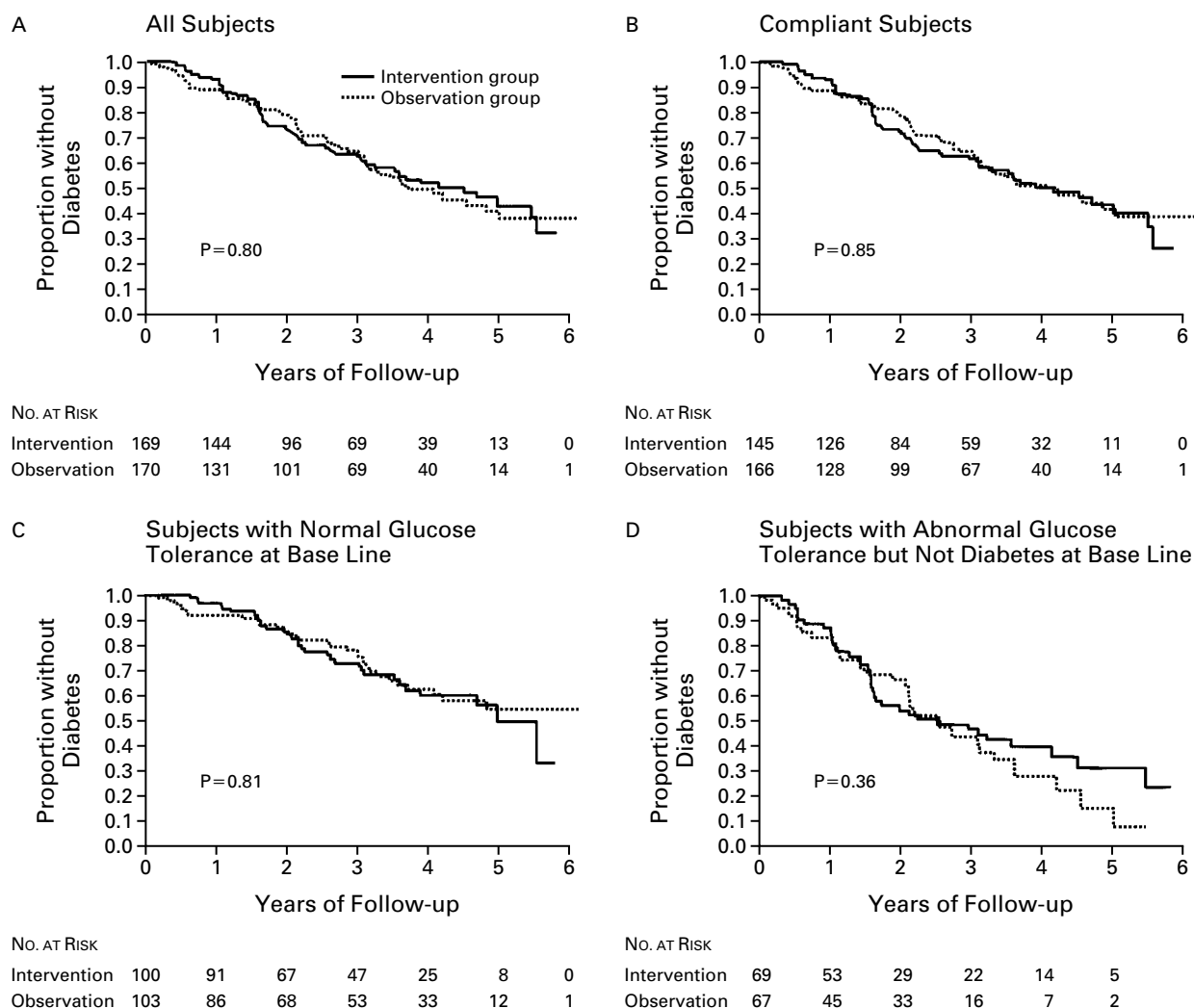
Hypoglycemic episodes during follow-up, excluding those that occurred during intravenous infusions of insulin, are summarized in Table 2. The rates of chemical hypoglycemia, assessed without ascertainment bias, were identical in the two groups. There were no reported episodes of severe hypoglycemia. As expected, more episodes of presumed and definite hypoglycemia were spontaneously reported in the intervention group than in the observation group. The Wide Range Achievement Test, used to ascertain major changes in cognitive function, showed no differences in any of the three subscales during serial evaluations; no subject had clinically important changes in scores; and there were no significant differences between the scores of subjects who had a definite hypoglycemic episode and the scores of those who did not (data not shown).

#### DISCUSSION

Insulin has been used for the treatment of diabetes since the 1920s. Investigators have long pondered whether insulin given before the onset of diabetes could alter the course of the disease. In 1940, Best and colleagues, in an article in the *Journal*, suggested testing insulin for the prevention of diabetes.<sup>28</sup> More than 50 years later, stimulated by contemporary studies of animal models of diabetes<sup>3,7,14,15</sup> and encouraged by small pilot studies,<sup>8,10</sup> we initiated such an investigation. Indeed, those pilot studies had motivated many clinicians to initiate insulin therapy in the relatives of patients with diabetes, particularly siblings, who were islet-cell antibody-positive.

The results demonstrate that insulin, in small doses, can indeed be administered safely to persons who are at risk for diabetes. Previous studies in children have shown that hypoglycemia may be associated with a decrease in cognitive function, especially in patients in whom diabetes is diagnosed at a young age.<sup>29,31</sup> In our trial, the increase in presumed and definite hypoglycemia among the subjects in the intervention group did not adversely affect cognitive function.

Unfortunately, in high-risk relatives of patients with diabetes who were selected by the criteria we used, the insulin regimen we used did not delay or prevent the development of diabetes. Long-term follow-up, to detect any effects on the course of diabetes, has begun. There are several potential explanations for the lack of effect. One is that we intervened too late

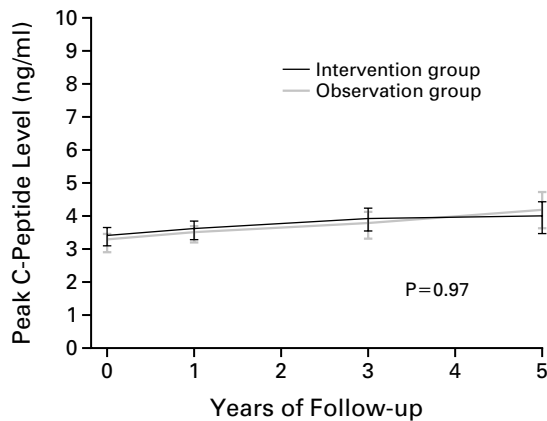


**Figure 1.** Kaplan–Meier Curves Showing the Proportion of Subjects without Diabetes, According to Treatment-Group Assignment. Panel A shows all subjects, Panel B compliant subjects, and Panel C subjects with normal glucose tolerance at base line. Subjects with abnormal glucose tolerance but not diabetes at base line (Panel D) included those with impaired glucose tolerance, those with impaired fasting glucose, and those with indeterminate glucose tolerance. P values were calculated by the log-rank test.

in the disease process to slow the progression of disease. Studies conducted earlier in the disease process — such as the ongoing DPT-1 oral-insulin trial in relatives of patients with diabetes who have a projected five-year risk of 26 to 50 percent — may be more successful. Moreover, oral insulin may have a greater immunologic effect but does not cause beta cells to rest. In fact, the low dose of insulin we used may have failed to have such an effect on beta cells,

but the dose was limited by the risk of hypoglycemia. With a different dosing scheme or a different regimen, insulin or insulin-like peptides might alter the course of development of diabetes.

The outcome of this large study was in stark contrast to those of the smaller pilot studies that preceded it. An important lesson is that clinical practice should not be altered solely on the basis of small pilot studies. During our study, a number of subjects,



No. AT RISK

Intervention	157	125	62	16
Observation	162	116	47	18

**Figure 2.** Mean ( $\pm 2$  SE) Peak C-Peptide Levels Measured during Mixed-Meal Tolerance Tests, According to Treatment-Group Assignment.

either of their own accord or because of the influence of their physicians, declined to undergo randomization, believing that pilot studies had already answered the question about the efficacy of prophylactic insulin therapy and that our trial was merely confirmatory. Well-designed, randomized, controlled clinical trials are crucial before the issuing of guide-

lines for clinical practice or the implementation of public health practices.

Nearly three quarters of the subjects in whom diabetes developed were asymptomatic at the time of diagnosis. Participation in a clinical trial makes persons more aware of their level of risk and more prone to test their blood glucose intermittently or when illness occurs. Moreover, having a routine oral glucose-tolerance test every six months increases the likelihood of early diagnosis and prevents ketoacidosis and other crises at the onset of diabetes. Thus, participation in this trial may have benefited all involved.

The values used to predict the development of diabetes in relatives of patients with diabetes were accurate. Moreover, persons with abnormal base-line glucose tolerance have more rapid progression to diabetes than those with normal base-line glucose tolerance. It should be understood, too, that diabetes is predicted to continue to develop in high-risk subjects in this trial at the rates we observed. Those with a projected 5-year risk of more than 50 percent have a 10-year risk of 90 percent and should maintain close contact with their physicians.

A large number of subjects were identified and followed in our study. A later analysis of this cohort may improve understanding of the course of development of diabetes and may refine predictive markers, facilitating the design of future intervention studies. Our data show that it is possible to identify a cohort of participants at high risk for diabetes and enroll them in a long-term intervention study involving a continent-wide group of investigators working cooperatively and collegially.

**TABLE 2.** HYPOGLYCEMIC EPISODES DURING FOLLOW-UP.\*

VARIABLE	INTERVENTION GROUP (N=169)		OBSERVATION GROUP (N=170)		P VALUE
	NO. OF EPISODES	RATE/100 PERSON-YEARS	NO. OF EPISODES	RATE/100 PERSON-YEARS	
No. of person-years of follow-up	438.7		428.1		
Hypoglycemia detected by quarterly glucose profiles	32	7.3	32	7.5	0.93
Spontaneously reported hypoglycemia					
Presumed hypoglycemia	591	134.7	243	56.8	<0.001
Definite hypoglycemia†	59	13.4	11	2.6	<0.001

\*Episodes that occurred during intravenous infusions of insulin are excluded.

†All definite hypoglycemic episodes were identified on the basis of a blood glucose level of less than 50 mg per deciliter; there were no episodes of severe hypoglycemia.

Supported by cooperative agreements with the Division of Diabetes, Endocrinology and Metabolic Diseases of the National Institute of Diabetes and Digestive and Kidney Diseases; the National Institute of Allergy and Infectious Diseases; the National Institute of Child Health and Human Development; the National Center for Research Resources; the American Diabetes Association; and the Juvenile Diabetes Research Foundation. Supplies were provided by Eli Lilly, Bayer, Becton Dickinson, International Technidyne, LifeScan, the Mead Johnson Nutritional Division of Bristol-Myers Squibb, the Medisense Division of Abbott Laboratories, MiniMed, and Roche Diagnostics.

Presented at the Annual Meeting of the American Diabetes Association, Philadelphia, June 22–26, 2001.

The DPT-1 protocol and manual of operations are available from the authors on request.

## APPENDIX

The members of the Diabetes Prevention Trial–Type 1 Diabetes (DPT-1) Study Group are as follows: *Steering Committee*: J.S. Skyler (University of Miami, Chair), D. Brown (University of Minnesota), H.P. Chase (University of Colorado), E. Collier (National Institute of Allergy and Infectious Diseases), C. Cowie (National Institute of Diabetes and Digestive and Kidney Diseases [NIDDK]), G.S. Eisenbarth (University of Colorado), J. Fradkin (NIDDK), G. Grave (National Institute of Child Health and Human Development), C. Greenbaum (Virginia Mason Research Center), R.A. Jackson (Joslin Diabetes Center), F.R. Kaufman (Children's Hospital Los Angeles), J.P. Krischer (University of South Florida), J.B. Marks (University of Miami), J.P. Palmer (University of Washington), A. Ricker (Children's Hospital, Boston), D.A. Schatz (University of Florida), D. Wilson (Stanford University), W.E. Winter (University of Florida), J. Wolfsdorf (Children's Hospital, Boston), A. Zeidler (University of Southern California); *Previous Members*: H. Dickler, R.C. Eastman, N.K. Maclaren, J.I. Malone, and P.R. Robertson; *Writing and Review Committee*: J.S. Skyler, J.P. Krischer, J. Wolfsdorf, C. Cowie, J.P. Palmer, C. Greenbaum, D. Cuthbertson (University of South Florida), L.M. Rafkin-Mervis (University of Miami), F.R. Kaufman, and H.P. Chase; *Planning Committee*: J.P. Palmer (Chair), H.P. Chase, C. Cowie, J. Fradkin, G.S. Eisenbarth, C. Greenbaum, K. Herold (Columbia University), F.R. Kaufman, J.P. Krischer, J.B. Marks, L. Rafkin-Mervis, D.A. Schatz, J.S. Skyler; *Trial Coordinators*: B. Aneju (Stanford University), D. Conboy (Joslin Diabetes Center), R. Cook (University of Florida), M.A. Dennis (University of Florida), L. Finney (University of Minnesota), S. Harris (University of Colorado), D. Matheson (University of Miami), M. McCulloch-Olsen (Virginia Mason Research Center), T. Smith (Joslin Diabetes Center), J. Valenzuela (Children's Hospital Los Angeles), N. Vega (University of Southern California); *Data Safety and Quality Monitoring Committee*: O.B. Crofford (Melbourne, Ark.), D. DeMets (University of Wisconsin), J.M. Lachin (George Washington University), J. Nerup (University of Copenhagen), A. Rossini (University of Massachusetts), A. Schiffrin (McGill University), M. Steffes (University of Minnesota), A. Tsiatis (North Carolina State University), B. Zinman (University of Toronto). A list of affiliates and satellites follows as Supplementary Appendix 1.

## SUPPLEMENTARY APPENDIX I

*Affiliates*: Akron, Ohio — A. Haider, J. Haas; Albany, N.Y. — R. Busch, K. Marshilok, N. Toleno; Albuquerque, N.M. — D. Schade, P. Katz, D. Hornbeck; Alexandria, La. — S. Foster, W.E. Roberts, M. Vercher; Ann Arbor, Mich. — C. Foster, C. Bower; Atlanta — I.L. Hansen, D. Burcell, S. Anderson, R. Shultz, C. Sparks; Austin, Tex. — J. Wray, L. Goldman, R.M. Holt; Baltimore — D. Counts, D. Ostrowski, L. Plotnick, P. Fechner, C. Donnelly; Baton Rouge, La. — P. Bourgeois, P.R. Prosser, B. Bowden; Billings, Mont. — F. Gunville, C. McClave, P. Heldt; Birmingham, Ala. — F. Ovalle, J.A. Atchison, P. Trull, A. Bottomlee; Bismarck, N.D. — S. Betting, T. Davis, J. Wetzstein; Boise, Idaho — C. Clinkingbeard, J. Davis, T.S. Roosevelt; Bronx, N.Y. — H. Shamoon, H. Duffy; Brooklyn, N.Y. — H. Anhalt, L. Brussard, J.V. Capotorto, P. Sheehan, S.A. Quyyumi, N.D. Cohen, B. Recker, S. Castells, W. Bastian, T.W. AvRuskin, V. Verdica; Buffalo, N.Y. — T. Quattrin, K. Dwigun; Burlington, Vt. — W. Cefalu, N. Clark, L. Tilton; Calgary, Alta. — B. Corenblum, S. Harries, A. Whitty; Camp Hill, Pa. — R. McInroy, S. Smith; Charleston, S.C. — S.M. Willi, L.A. Key, D.S. O'Rear; Charleston, W.Va. — S.R. Grubb, K. Taylor, P. Adams; Chattanooga, Tenn. — M. Reeves, P. Reeves, R. Marshall, E. Tessmann; Chicago Heights, Ill. — A. Dwarakanathan, C. Beebe, I. Weintraub-Yohay, P. O'Donnell; Chicago — B. Rich, J. Imperial, B. Silverman, D. Eddin, S. Goodman, I. Brodsky, L. Brodsky; Cincinnati — D. Klein, L. Dolan, D. Standiford; Cleveland — D. Rogers, C. Switzer; Columbia, Mo. — D.E.

Goldstein, D. Eichelberger, A. Smith; Columbus, Ohio — C. Ganong, J. Gernak, W.B. Zipf, M. Dyas, J.F. Sotos, C. Young; Corpus Christi, Tex. — W. Riley, S. Salai; Dallas — P. Raskin, J. Marks, M. Alford, R. Sachson, C. Lebowitz; Des Moines, Iowa — J. Cook, J. Stedman, D. Indra; Detroit — J. Gutai, B. Vinuya, M. McGraw-Maly; Duarte, Calif. — W. Feng, C. Williams, C.M. Krygsman, M. Pierce; Durham, N.C. — M. Freemark, J. Litton; Edmonton, Alta. — E.A. Ryan, K. Todd; El Paso, Tex. — D. Aboud, M. Pacillas; Erie, Pa. — J.H. Hines, A.F. Walczak, L.F. Aparicio, D. Harbaugh; Fairbanks, Alaska — M. Bergeson, M. Rozell; Fairfield, Alaska — E. Mahan; Folcroft, Pa. — H. Brooks; Fresno, Calif. — P. Ginier, P. Hensley; Glen Ellyn, Ill. — M. Heymann, B. Johnson, J. Tack; Grand Forks, N.D. — L. Sondrol, T. Hjelle; Grand Rapids, Mich. — D. Perry, J. Albert, L. Flory; Great Falls, Mont. — N.C. Gerrity, C. Naab, J. Heck; Greenville, S.C. — S. Weber, P. Mulhall; Gulfport, Miss. — B.G. Lansden; Halifax, N.S. — E. Cummings, S. Salisbury, C.A. Armour; Hartford, Conn. — S. Ratzan, M. Trahiotis; Hollywood, Fla. — R. Nemery, H. Carney, D. Shorkey; Honolulu — D. Fitz-Patrick, A.M.Y. Taniguchi; Houston — S. Gunn, K. Copeland, S. McGirk; Idaho Falls, Idaho — J. Liljenquist, C. Fielding, S. Richards, V. Best; Indianapolis — H. Rodriguez, G. Freidenberg, L. Amstutz, C. Weir; Iowa City, Iowa — E. Tsalikian, R. Hoffman, M. Bayless; Kalamazoo, Mich. — J.D. Hare, K. Hare; Kansas City, Kans. — J.L. Kyner, G. Eaks; Kansas City, Mo. — C.P. Howard, W. Moore, B. Woodford, T. Salyer; Kennewick, Wash. — N. Wannarachue, R. Meredith, D. Squires; Kiel, Wis. — D. Deubler; Kingsville, Tex. — H. Bruschetta; Knoxville, Tenn. — D.A. Nickels, C. Dohard, A. Courtney; Laguna Hills, Calif. — A.O. Marcus; Lebanon, N.H. — P.J. Leisswenger, S. Kairys, W. Boyle, A.S. Christiano, R. O'Dell, A. Touchette; Lexington, Ky. — K.M. Thraillkill, D. Karounos, S. Webb, L. Moore, P. Allweiss, F. Anderson; London, Ont. — J.L. Mahon, J. McCallum; Los Angeles — L. Raffel, J. Rotter, A. Verne, M.B. Davidson, G. Keppler; Madera, Calif. — S. Banerjee, M. Simon; Madison, Wis. — M.J. MacDonald, S. Mokrohisky; Manhasset, N.Y. — P.W. Speiser, P. Fort, J. Corrigan; Marquette, Mich. — S. Pelkola; Memphis, Tenn. — A.E. Kitabchi, M. Murphy, H. Lambeth, G. Burghen, P. McGlendon, J. Bondani, P. LeNoye; Milwaukee — R. Alemzadeh, M. Koppin; Mineola, N.Y. — J.A. Canas, M. Lamerson; Minneapolis — M. Spencer, D. Etzwiler, K. Reynolds; Missoula, Mont. — N. Eyer, P. Allen; Mobile, Ala. — B.A. Warner, K.R. Rettig, K.L. Levens, M.R. Davis; Montreal — C. Polychronakos, D. Laforêt; Naperville, Ill. — W.P. Zeller, J. McKernan, S. Finn; Nashville — A. Powers, J. Lipps; New Albany, Ind. — S. Raghavan, V. Broadstone, P. Raake, K. Weissberg; New Haven, Conn. — W.V. Tamborlane, P. Gatcomb; New Orleans — L. Blonde, T. Zimmerman, R. Zimmerman, C. Liebel, S. Chalew, A. Vargas, J. Rao, J. Ascani, T. Compton; New York City — B. Cerame, M.D. Harbison, R. Newfield, M. New, M. Wajnrajch, I. Vargas, K. Herold, H. Schachner, G. Feberes, N.K. Maclaren, D. Golub, R. Rappaport, R. McEvoy, N. Thomas, X. Pi-Sunyer, R. Saliel-Berzin; Newark, N.J. — R. Rappaport, J. Koblish; Oklahoma City — P. Blackett, C. Comp, J. Beck; Omaha, Nebr. — J. Hassing, L. Hahn, J.T. Lane, K. Corley, L. Larson; Orange, Calif. — R. Fiallo-Sharer, P. Lee, A. Cortez, N. Varni, H. Speer; Orlando, Fla. — S. Crockett, W. McDaniel, V. Roberts; Philadelphia — S.A. Weinzimer, P. Cohen, L. Baker, D. De Paul, E. Rebecca; Phoenix, Ariz. — R. Dolinar, M.B. Block, P. Krametbauer; Ponce, P.R. — T. Frazer, G. Veray; Portland, Oreg. — A. Ahmann, S. LaFranchi, P. Jennings, A. Kelleher, M. Kummer, J. Hansen, M.K. Hunter, K. LaMorticella, R. Bergstrom, M. Rigdon; Reno, Nev. — K. Eckert; Renton, Wash. — L.J. Klaff, R. Brazg, J. Springs; Richland, Wash. — B. Wilson, E. Isaacson, H. Kuhn; Richmond, Va. — D. Willis, P. Kaplowitz, K. Genther; Rio Piedras, P.R. — C. Bourdony, A. Rivera; Rochester, Minn. — R. Basu, R. Rizza, P. Whannel, N. Jospe, A. Uzman; Sacramento, Calif. — B. Sheikholisham, C. Hiner; Salt Lake City — D. Hardin, R. Lindsay, M. Swinyard, M. Rallison, L. Jarrett, J. Sirstins; San Antonio, Tex. — K. Pierson, S. Trevino, S. Schwartz, K. Dickens; San Bernardino, Calif. — S. Clark, P. Scroggin, G.R. Greene; San Diego, Calif. — L. Linarelli, E. Camuro, S. Hermsillo, R. Estrada, W. Bailey, J. Fuqua; San Francisco — S.E. Gitelman, M. Fountaine; San Juan, P.R. — G. Colon, L. Gonzalez de Pijem, F. Nieves-Rivera, A. Rivera, R. Perez; Santa Barbara, Calif. — L. Jovanovic, S. Vesterfelt; Santurce, P.R. — C.A. Saenz; Seattle — G. Kletter, K. Pihoker, S. Kearns; Sioux Falls, S.D. — L. Keppen, P. Johnson, E. Krell; Skokie, Ill. — S.C. Duck; Spokane, Wash. — M. Noble, S. Thompson, K. Wilson, P. Malody; Springfield, Ill. — N.G. Soler, L. McCall; Springfield, Mass. — H.F. Allen, G. Roumeliotis; Springfield, Mo. — L. Chase, D. Braden-Moll; St. Louis — N. White, L. Levandoski; St. Petersburg, Fla. — J.I. Malone, J. Steinbrueck; State College, Pa. — J.S. Ulbrecht, N. Lambert, P. Mulhall; Stony Brook, N.Y. — T.A. Wilson, A.H. Lane, A. Smaldone; Sylmar, Calif. — T. Modilevsky; Syracuse, N.Y. — R. Izquierdo, R. Weinstock, S. Mackowiak, K. Brindak; Toronto — D. Wherrett, D. Daneman, K. Pearlman, C. McLellan, A. Rogers; Torrance, Calif. — E. Ipp, C. Mao; Traverse City, Mich. — E.H. Rushovich, I. Thorne;

Tulsa, Okla. — D.H. Jelly, D. Greer; Vancouver, B.C. — D. Metzger; Washington, D.C. — A. Austin, A. Glasgow, J. Turck, J. Archer, G. Nunlee-Bland, K. Johnson, J. Harris; White Plains, N.Y. — S. Driedbart, R. Noto, A. Romano, W. Herl; Wichita, Kans. — R. Guthrie, O. Tatpati, A. Brenner; Willmar, Minn. — D. Lippert; Wilmington, Del. — G. Reeves, C. Swenson; Winnipeg, Man. — L. Murphy, H. Dean, L. Berard; Winston-Salem, N.C. — S.S. Werbel, A. Bell-Farrow; Woodinville, Wash. — R. Mauseth, J. Hanson; Youngstown, Ohio — S.K. Mishr, L. DiCaria, B. Wilson.

*Satellites:* Aberdeen, S.D. — C. Wischmeier; Akron, Ohio — M.F. Moosa, R. Levy; Albany, N.Y. — J. Desemone; Albany, Oreg. — L. Bentson; Alexandria, Va. — H.M. Lando; Alton, Ill. — J. Hoelscher; Amarillo, Tex. — W.C. Biggs; Ames, Iowa — R. Carano; Anaheim, Calif. — P. Nosstrand; Anchorage, Alaska — C. Esquival, L. Achee, J. Kelly, P. Nolan; Apple Valley, Calif. — T. Otsuka; Appleton, Wis. — K. Heymann; Astoria, Oreg. — N. Autio, K. Gohl; Atherton, Calif. — J. Prendergast; Atlanta — B. Bode, H. Delcher, C.H. Reed; Atlantis, Fla. — M. Mellman; Augusta, Ga. — I.C. Herskowitz, W. Hoffman; Bangor, Me. — A. Boniface; Bassett, Nebr. — H. Leigh; Batavia, N.Y. — G. Ginsberg; Bedford, Ohio — D. Weiss; Belleville, Ill. — M. Rosecan; Bellevue, Wash. — P. Doyle; Bellingham, Wash. — J. McAfee, G. Goldfogel; Bend, Oreg. — J. Henschel; Bennington, Vt. — D.M. Gorson; Bethlehem, Pa. — J. Ramos; Beverly Hills, Calif. — M. Bush; Bismarck, N.D. — K. Martin; Blacksburg, Va. — B. Birch; Bremerton, Wash. — S. Reimer; Bristol, Tenn. — J.D. Neil; Bronx, N.Y. — P. Saenger, J. Dimartino-Nardi; Brooklyn, N.Y. — J.V. Capotorto, P. Sheehan, S.A. Quyyumi, N.D. Cohen; Burbank, Calif. — R. Stein; Burlingame, Calif. — D. Klonoff; Butte, Mont. — J. de Souza, D. McCarthy, J. Salisbury, C. Edstrom; Caguas, P.R. — M.F. William; Caldwell, Idaho — M. Brown; Camp Springs, Md. — R. Vigersky; Canton, Ohio — C.E. Smith, A. Krishna, R. Benson; Castaner, P.R. — F. Murphy; Cedar Rapids, Iowa — C. Pruchno; Chapel Hill, N.C. — M. Davenport; Charlottesville, Va. — W.L. Clarke, M. McDuffie; Cheyenne, Wyo. — G. Melinkovich, V. Bell; Chicago Heights, Ill. — A. Ravanam, W. Will; Clearwater, Fla. — D. Leonard; Cleveland — W. Dahms; Clinton, Mo. — K. Scott; Columbia, S.C. — F. Bowyer; Columbus, Ga. — S.B. Leichter; Concord, Calif. — R. Kaplan, S. Lewis; Coopers Mills, Me. — R. Miller; Corpus Christi, Tex. — M. Upmanyu; Culver City, Calif. — N. Goldberg; Danbury, Conn. — R. Savino; Danville, Ind. — S.M. Wentworth; Danville, Pa. — D.R. Langdon; Davenport, Iowa — C. Weideman; Dayton, Ohio — M. Urban; Detroit — D. Transue, F. Whitehouse, J. Cara; Downey, Calif. — S. Shaw; Drayton, S.C. — W. Price; Dubuque, Iowa — R. Iverson; Duluth, Minn. — M. Slag; Durango, Colo. — J. Hutt; Eau Claire, Wis. — N. McLean, R. Moore; El Paso, Tex. — R. Christenson; Elgin, Ill. — K. Valika; Englewood, Colo. — N. Nayak, C.A. Bloch; Englewood, N.J. — L. Strom; Escondido, Calif. — T.S. Bailey, C.P. Varma; Eugene, Oreg. — D. Calder, M. Bilger; Everett, Wash. — K. Larson, M. Papenhausen; Fairfield, Calif. — Y. Shlesinger; Fargo, N.D. — A. Kenien; Fayetteville, N.C. — E. Wright; Flint, Mich. — M.A. Jabbar; Flushing, N.Y. — D.L. Lorber; Fort Dodge, Iowa — J. Berkett; Fort Smith, Ark. — R.P. Robinson; Fort Wayne, Ind. — A. Kadambi; Framingham, Mass. — W. Sullivan; Fremont, Calif. — E. Meyer; Fresno, Calif. — J.L. Bautista, P.C. Norwood; Ft. Lauderdale, Fla. — E. Biederman, S. Nassberg, L. Goscin, M. Mata, N. Thompson, R.M. Harrell, J. Cabral; Ft. Myers, Fla. — A. Pietri; Ft. Worth, Tex. — C.R. Scott, T.K. Flannery, D.B. Wilson; Gainesville, Fla. — B. Rogers; Glendale, Calif. — M. Campos, M.N. Montero; Gorham, N.H. — B. Beals; Grand Junction, Colo. — D. Mair, A. Long; Grand Rapids, Mich. — R.S. Rood; Green Bay, Wis. — J. Taylor; Greensboro, N.C. — R. Sevier; Greenville, N.C. — G. Harris, M.A. Pfeifer; Hackensack, N.J. — M. Blechman, J. Giangola; Hermitage, Tenn. — R. Creech; Hershey, Pa. — M. Lathrop, A. Dunaf; Hollywood, Fla. — G. Miceli, L. Lewy-Alterbaum, P.S. Jellinger, S.B. Novak, K.M. Gellman, S. Lerman; Honolulu — S. Waxman; Houston — D.J. Hamilton; Huntington, W.Va. — H. Driscoll; Huntsville, Ala. — R. Schneier; Hutchinson, Kans. — J.L. Casey; Indianapolis — P. Boyce, J. Meachum; Irving, Tex. — J. Milburn; Issaquah, Wash. — D. Pomeroy; Jackson, Miss. — G. Moll; Jacksonville, Fla. — K. Macyko, L.A. Fox, N. Mauras; Jersey City, N.J. — P. Ledereich; Juneau, Alaska — D. Novotny; Kalispell, Mont. — C. Gill, B. Rossetto; Kingston, Ont. — R. Houlden; Klamath Falls, Oreg. — P. Heck; La Crosse, Wis. — J. Korducki; La Habra, Calif. — J. Winston, D. Geffner; La Jolla, Calif. — S. Edelman, B. Henry; La Mesa, Calif. — D. Einhorn, R. Fink, E. Gold; Lake Charles, La. — R.W. Calhoun; Lake Jackson, Tex. — J. Leidlein; Lancaster, Calif. — K. Arul; Lansing, Mich. — D. Henry; Las Vegas — D.L. Donaldson; Lebanon, Oreg. — K. Middlestadt; Lewiston, Idaho — L. Grande-Luke; Lincoln, Nebr. — J. Guest, R. Wermers, B. Bells; Little Rock, Ark. — P. Frindik; Livingston, N.J. — G. Gewirtz; Lompoc, Calif. — C. Blyfield;

Long Beach, Calif. — M. Brakin; Los Angeles — D. Borut, D. Geffner, J. Winston, M. Geffner, M. Rodriguez, V. Gura; Los Gatos, Calif. — C. Shough; Louisville, Ky. — H. Bays, H. Shenouda; Lubbock, Tex. — S. Varma, M.J. Bourgeois; Lufkin, Tex. — L.A. Sloan; Lynchburg, Va. — C.E. Guthrow; Lynwood, Calif. — S. Shaw; Manhattan Beach, Calif. — R. Ruby; Margate, Fla. — B. Motzkin-Kava; Marshalltown, Iowa — D. Jebson; Marshfield, Wis. — I. Zador, S. Maby; McLean, Va. — F. Crantz; Medford, Oreg. — D. Zietlow; Miami Beach, Fla. — D. Kudzma; Miami, Fla. — E. Levy, E.T. Shapiro, J. Jacobi, J. Pita, W. Ablove, J. Perez-Rodriguez, L. Gonzalez-Mendoza, S. Richton, P. Weissman; Middletown, N.Y. — N. Stein; Midland, Tex. — L. Sherman-Adcock; Milwaukie — D. Ferguson, M. Jacobson, J. Sennett, R. Jain; Minneapolis — D. Etwiler, R.C. Ramsay; Minot, N.D. — M. Holland; Miramar, Fla. — S. Carrington; Missoula, Mont. — S. Seagraves; Modesto, Calif. — G.M. Yue, J. Downs-Couba; Montebello, Calif. — H. Flores; Montgomery, Ala. — S. Weinrib; Morgantown, W.Va. — E. Jones; Morristown, N.J. — H. Starkman; Mount Vernon, Wash. — D. White; Mountain View, Calif. — L. Doberne, M. Greenfield; Muncie, Ind. — K. Alexander; Napa, Calif. — C. O'Sullivan; Naples, Fla. — R. Duncan; Naranja, Fla. — G. Barandiaran, J. Yunis, L. Nunez, V. Ramos; Nashua, N.H. — E. Holland; Natrona Heights, Pa. — W.R. Balash; Neptune, N.J. — J. Sher; New Brunswick, N.J. — R. Agrin; New Orleans — J. Frenzt; New York City — I. Fennoy; Newhall, Calif. — S. Baron; Nipomo, Calif. — J. Door; Norfolk, Va. — A. Vinik; North Las Vegas, Nev. — F. Savery; Oakland, Calif. — F. Gareis, R. Mack, D. Devoe, Y. Fan; Oklahoma City — D. Domek; Olympia, Wash. — D. Kelley; Onalaska, Wis. — T. Roberts; O'Neill, Nebr. — B. Gushall; Orange, Calif. — I. Madu, R. Poucher; Orlando, Fla. — M. Mengel, P. Desrosiers, R.A. Banks, B. Kopp; Pacific Grove, Calif. — I. Fishman; Pacific Palisades, Calif. — D. Geller, W. Smith; Palm Bay, Fla. — J.A. Duncan; Palm Beach Gardens, Fla. — O. Nyman, M. Vaccarello-Cruz; Parkersburg, W.Va. — F.L. Schwartz; Pasadena, Calif. — O. Olambiowonu; Paso Robles, Calif. — M. Ortiz; Pembroke Pines, Fla. — S. Freedman; Pendleton, Oreg. — S. Merrill; Peoria, Ill. — J. Wise; Philadelphia — I. Rezvani, D. Doyle, P. Hale, C. Singer-Granick, W. Fore; Phoenix, Ariz. — A. Perelman, R. Clemmons, R. Johnsonbaugh; Pittsburgh — A.R. Gonzalez; Pocatello, Idaho — M. Baker, C. Field, C. Shields, K. Walker; Port Huron, Mich. — S. Reddy, K. Pilote; Port St. Lucie, Fla. — M. Borchelt; Port Townsend, Wash. — D. Bommer; Portland, Oreg. — N. Curosch, D. Karl, B. Phillipson; Poway, Calif. — W.L. Iverson; Princeton, N.J. — A. Krosnick; Providence, R.I. — C.B. Kahn; Puyallup, Wash. — B. Blodgett, N. Iverson, C. Jacobson, M. Haynes, D. Moore, R. Alston, R. Eachempati; Raleigh, N.C. — D. Becker; Rapid City, S.D. — L. Weide; Red Wing, Minn. — M. Decker; Redding, Calif. — J. Greaves; Richburg, S.C. — M.J. Curry; Richmond, Va. — J. Radcliffe; Ridgecrest, Calif. — V. Schauf; Riverside, Calif. — D. Childs; Riverside, Ill. — R. Crawford, G. Charnogursky; Robbinsdale, Minn. — M. Stesin; Rockford, Ill. — M. Schneider; Rockville, Md. — H.W. Rodbard, M.A. Dempsey; Roseau, Minn. — R. Brummer; Roseburg, Oreg. — L. Elston, D. Marseters; Rutland, Vt. — P. Lapp; Sacramento, Calif. — N. Glaser, J.S. Soeldner; Safford, Ariz. — V. Chaurasia; Salem, Oreg. — R. Michaels; Salinas, Calif. — A. King, R. Olson; San Antonio, Tex. — D. Hale, M. Danney, S.S. Miller; San Carlos, Calif. — S. Madan; San Diego, Calif. — J.R. Dudl; San Francisco — N. Bohannon, M. Berlund, T. Jackson; San Jose, Calif. — J. Kitzmiller; Santa Rosa, Calif. — D. Price; Savannah, Ga. — K. Ehsanipoor; Sayre, Pa. — M.R. Homan; Scarborough, Me. — J. Olshan; Scottsbluff, Nebr. — T. Sorensen; Scranton, Pa. — A. Perry; Seattle — G.T. Nepom, D. McCulloch, I. Hirsch, R. Kanter, N. Niles; Shattuck, Okla. — M. Vogiatzi; Sheboygan, Wis. — V. Kerpe; Shreveport, La. — R. McVie; Sioux City, Iowa — J. Aniszewski, T. Carroll, R. Bacon; South Bend, Ind. — M. Hudson, A. Simpson; South Miami, Fla. — M. Fili, D. Krieger; South Windsor, Conn. — D. Golob; Southfield, Mich. — J. Carney; Springfield, Ill. — R. Khadori; St. Cloud, Minn. — M. Peitso; St. Louis — J.T. Lane; St. Paul, Minn. — H. Katz, R. Warhol; Staten Island, N.Y. — J. Rothman; Stockton, Calif. — D.F. Jensen, J. Rooke; Stoughton, Mass. — H. Fogel, L. Hotes; Sumter, S.C. — U. Lilavivat; Tacoma, Wash. — T. Gauthier; Tallahassee, Fla. — L. Deeb, T. Sherradan; Tarzana, Calif. — N. Lavin; Tecumseh, Nebr. — K. Shuey; Toledo, Ohio — J. Horner; Torrance, Calif. — J.M. Tsao; Traverse City, Mich. — A. Scrogin; Tuxedo, Pa. — C. Greenlee; Tucson, Ariz. — J. Insel, M. Wheeler; Tuscaloosa, Ala. — T. Kamal; Tyler, Tex. — L. Wiertz; Union, N.J. — H. Bucholtz, J. Dunn; Urbana, Ill. — K. Wilson; Valhalla, N.Y. — M. Frey, R. Noto; Ventura, Calif. — R. Chochinov; Vincennes, Ind. — J.M. Bridges; Waco, Tex. — M. Amar; Walnut Creek, Calif. — R. Weinstein, T.E. Poore; Waltham, Mass. — S. Brink, K. Moltz; Washington, D.C. — D. Sobel, G. Francis, R. Sveck, J. Ramey; Waterford, Mich. — N. Haque; Watseka, Ill. — A. Villafria, R.E. Villafria; Wausau, Wis. — J. Madagame; Wenatchee, Wash. — L. Stone; West Carrollton, Ohio — R. Cech; West Yellowstone, Mont. — J. Schnellbach; White Plains, N.Y. — S. Dreidbart, R. Noto, T. Lebinger, L. Shane; Whittier, Calif.

— E. Reece, R. Harris, W.D. Welsh; Wilmington, N.C. — P.C. Whitesides; Winter Park, Fla. — A. Scoma; Woodland Hills, Calif. — F.H. Ziel; Worcester, Mass. — C. Alter, P. Lock; Yakima, Wash. — G. Trece.

## REFERENCES

1. Atkinson MA, Maclaren NK. The pathogenesis of insulin-dependent diabetes mellitus. *N Engl J Med* 1994;331:1428-36.
2. Gotfredsen GF, Buschard K, Frandsen EK. Reduction of diabetes incidence of BB Wistar rats by early prophylactic insulin treatment of diabetes-prone animals. *Diabetologia* 1985;28:933-5.
3. Like AA, Guberski DL, Butler L. Diabetic BioBreeding/Worcester (BB/Wor) rats need not be lymphopenic. *J Immunol* 1986;136:3254-8.
4. Vlahos WD, Seemayer TA, Yale JF. Diabetes prevention in BB rats by inhibition of endogenous insulin secretion. *Metabolism* 1991;40:825-9.
5. Gottlieb PA, Handler ES, Appel MC, Greiner DL, Mordes JP, Rossini AA. Insulin treatment prevents diabetes mellitus but not thyroiditis in RT6-depleted diabetes resistant BB/Wor rats. *Diabetologia* 1991;34:296-300.
6. Atkinson MA, Maclaren NK, Luchetta R. Insulinitis and diabetes in NOD mice reduced by prophylactic insulin therapy. *Diabetes* 1990;39:933-7.
7. Bowman MA, Campbell L, Darrow BL, Ellis TM, Suresh A, Atkinson MA. Immunological and metabolic effects of prophylactic insulin therapy in the NOD-scid/scid adoptive transfer model of IDDM. *Diabetes* 1996;45:205-8.
8. Keller RJ, Eisenbarth GS, Jackson RA. Insulin prophylaxis in individuals at high risk of type I diabetes mellitus. *Lancet* 1993;341:927-8.
9. Ziegler A, Bachmann W, Rabl W. Prophylactic insulin treatment in relatives at high risk for type I diabetes. *Diabetes Metab Rev* 1993;9:289-93.
10. Fuchtenbusch M, Rabl W, Grassl B, Bachmann W, Standl E, Ziegler AG. Delay of type I diabetes in high risk, first degree relatives by parenteral antigen administration: the Schwabing Insulin Prophylaxis Pilot Trial. *Diabetologia* 1998;41:536-41.
11. Aaen K, Rygaard J, Josefsen K, et al. Dependence of antigen expression on functional state of beta-cells. *Diabetes* 1990;39:697-701.
12. Bjork E, Kampe O, Andersson A, Karlsson FA. Expression of the 64 kDa/glutamic acid decarboxylase rat islet cell autoantigen is influenced by the rate of insulin secretion. *Diabetologia* 1992;35:490-3.
13. Bjork E, Kampe O, Karlsson FA, et al. Glucose regulation of the autoantigen GAD65 in human pancreatic islets. *J Clin Endocrinol Metab* 1992;75:1574-6.
14. Thivolet CH, Goillot E, Bedossa P, Durand A, Bonnard M, Orgiazzi J. Insulin prevents adoptive cell transfer of diabetes in the autoimmune non-obese diabetic mouse. *Diabetologia* 1991;34:314-9.
15. Bertrand S, de Paepe M, Vigeant C, Yale JF. Prevention of adoptive transfer in BB rats by prophylactic insulin treatment. *Diabetes* 1992;41:1273-7.
16. Karounos DG, Bryson JS, Cohen DA. Metabolically inactive insulin analog prevents type I diabetes in prediabetic NOD mice. *J Clin Invest* 1997;100:1344-8.
17. Pugliese A, Gianani R, Moromisato R, et al. HLA-DQB1\*0602 is associated with dominant protection from diabetes even among islet cell antibody-positive first-degree relatives of patients with IDDM. *Diabetes* 1995;44:608-13.
18. Greenbaum CJ, Schatz DA, Cuthbertson D, Zeidler A, Eisenbarth GS, Krischer JP. Islet cell antibody-positive relatives with human leukocyte antigen DQA1\*0102, DQB1\*0602: identification by the Diabetes Prevention Trial-type 1. *J Clin Endocrinol Metab* 2000;85:1255-60.
19. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 1997;20:1183-97.
20. Wilkinson GS. WRAT3 Wide Range Achievement Test. Wilmington, Del.: Wide Range, 1993.
21. Bingley PJ, Colman P, Eisenbarth GS, et al. Standardization of IVGTT to predict IDDM. *Diabetes Care* 1992;15:1313-6.
22. Chase HP, Cuthbertson DD, Dolan LM, et al. First-phase insulin release during the intravenous glucose tolerance test as a risk factor for type 1 diabetes. *J Pediatr* 2001;138:244-9.
23. Neufeld M, Maclaren NK, Riley WJ, et al. Islet cell and other organ specific antibodies in U.S. Caucasians and Blacks with insulin-dependent diabetes mellitus. *Diabetes* 1980;29:589-92.
24. Lernmark A, Molenaar JL, van Beers WAM, et al. The Fourth International Serum Exchange Workshop to standardize cytoplasmic islet cell antibodies. *Diabetologia* 1991;34:534-5.
25. Vardi P, Dib SA, Tuttleman M, et al. Competitive insulin autoantibody assay: prospective evaluation of subjects at high risk for development of type 1 diabetes mellitus. *Diabetes* 1987;36:1286-91.
26. Ziegler AG, Ziegler R, Vardi P, Jackson RA, Soeldner JS, Eisenbarth GS. Life-table analysis of progression to diabetes of anti-insulin autoantibody-positive relatives of individuals with type 1 diabetes. *Diabetes* 1989;38:1320-5.
27. Verge CF, Stenger D, Bonifacio E, et al. Combined use of autoantibodies (IA-2 autoantibody, GAD autoantibody, insulin autoantibody, cytoplasmic islet cell antibodies) in type 1 diabetes: Combinatorial Islet Autoantibody Workshop. *Diabetes* 1998;47:1857-66.
28. Haist RE, Campbell J, Best CH. The prevention of diabetes. *N Engl J Med* 1940;223:607-15.
29. Rovet JF, Ehrlich RM, Hoppe M. Specific intellectual deficits in children with early onset diabetes mellitus. *Child Dev* 1988;59:226-34.
30. Ryan C, Vega A, Drash A. Cognitive defects in adolescents who develop diabetes early in life. *Pediatrics* 1985;75:921-7.
31. Rovet J, Alvarez M. Attentional functioning in children and adolescents with IDDM. *Diabetes Care* 1997;20:803-10.

Copyright © 2002 Massachusetts Medical Society.