Concordance for Islet Autoimmunity among Monozygotic Twins

TO THE EDITOR: The risk of type 1 diabetes among the monozygotic twins of patients with type 1 diabetes is reported to be as low as 30%; this percentage is usually based on the ascertainment of data at a single time point.[1-3] Less is known about the cumulative incidence of islet antibodies and diabetes among twins followed over time.[4,5] We analyzed the long-term risk of islet autoimmunity and type 1 diabetes in a cohort of twins of patients with type 1A diabetes as defined by the American Diabetes Association criteria (95% of the twins with a prediabetic condition who were initially discordant for diabetes were islet autoantibody–positive before diabetes developed). Eighty-three monozygotic twins without diabetes were prospectively followed for antibody expression (i.e., GAD65, ICA512, insulin, and cytoplasmic islet-cell antibodies),[5] progression to diabetes, or both for up to 43.8 years (mean, 12.8; median, 8.5; range, 0 to 43.8). Twins were identified at the Joslin Diabetes Center and the Barbara Davis Center for Childhood Diabetes and through the Diabetes Prevention Trial–Type 1 Diabetes.

As shown in Figure 1, by 60 years of age, the cumulative incidence of diabetes among monozygotic twins who were initially discordant for diabetes was 65% (95% confidence interval [CI], 39 to 91), and persistent autoantibody positivity, type 1 diabetes, or both had developed in 78% (95% CI, 61 to 95). Among 32 autoantibody-positive monozygotic twins, the risk of diabetes was 89% (95% CI, 72 to 100) within 16 years after the first positive antibody test. Because we

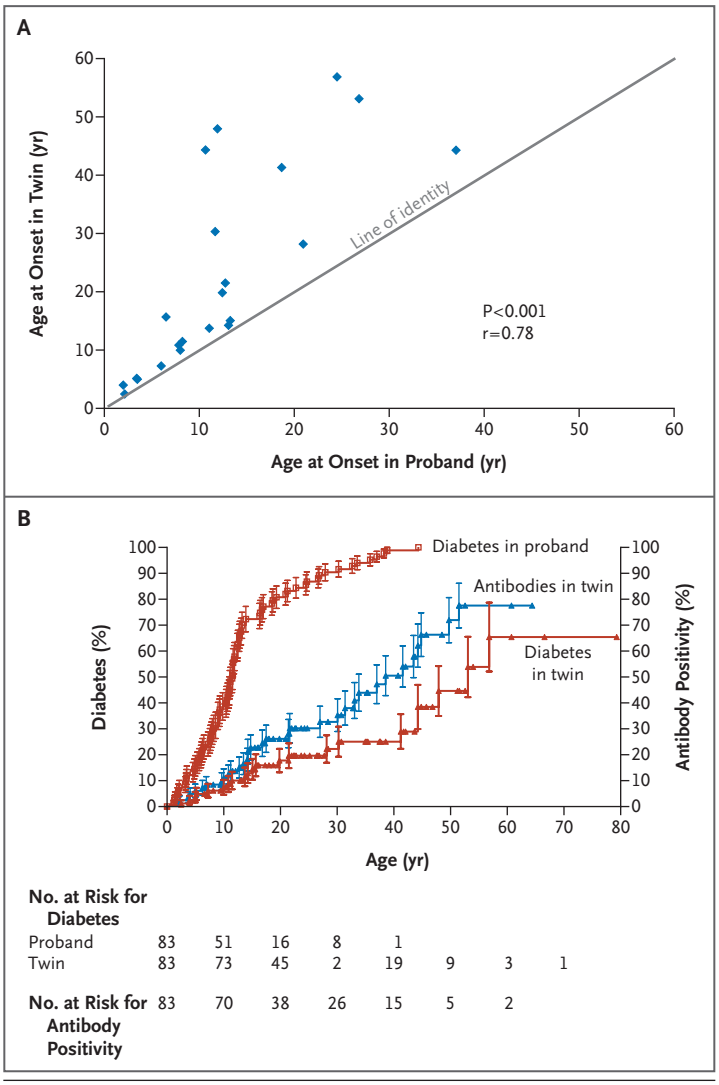

Figure 1. Progressive Development of Anti-Islet Autoimmunity and Diabetes.

Panel A shows the correlation between the age at the onset of type 1 diabetes in the probands and in their monozygotic twins. The line of identity shows the values if diabetes developed in a proband and his or her twin at the same time. In the nine monozygotic twin pairs with a twin in whom diabetes developed before 10 years of age, there was a close correlation in the age at onset ($r=0.78$, $P<0.001$), whereas if diabetes developed in the twin after 10 years of age, there was greater variability in the ages at onset between the twin pairs, with the age at onset differing by more than 30 years in many twin pairs ($r=0.55$, $P=0.05$). Panel B shows the cumulative incidence of diabetes among the probands and the cumulative incidence of diabetes and autoantibody positivity according to life-table analysis in the twins who were initially discordant for diabetes. Kaplan–Meier estimates of progression to diabetes and anti-islet autoimmunity according to age are shown. Survival analyses of progression to diabetes in patients (probands) and in their monozygotic twins who initially did not have diabetes are indicated by the red lines ($P<0.001$). Progression to anti-islet autoimmunity (i.e., development of positive anti-islet autoantibodies, diabetes, or both) in the monozygotic twins of patients is indicated by the blue line. The numbers of patients still followed at each time point are shown. I bars denote 95% confidence intervals.

studied only monozygotic twins who were initially discordant for diabetes, and a subgroup of twins before 1992 was not assessed with more recently available biochemical autoantibody assays (GAD65 and ICA512), the rates of progression to autoantibody positivity shown in the figure are probably underestimates.[5]

We conclude that with prospective long-term follow-up, both autoantibody positivity and diabetes frequently develop in monozygotic twins of patients with type 1 diabetes, even if the twins were initially discordant for diabetes. We believe that, at least in studies of autoimmune disorders, estimates of the concordance rate for diabetes among monozygotic twins should include long-term follow-up.

Maria J. Redondo, M.D., Ph.D.
Joy Jeffrey, B.S.
Pamela R. Fain, Ph.D.
George S. Eisenbarth, M.D., Ph.D.
Barbara Davis Center for Childhood Diabetes
Aurora, CO 80045
george.eisenbarth@uchsc.edu

Tihamer Orban, M.D.
Joslin Diabetes Center
Boston, MA 02215

Supported by grants from the Juvenile Diabetes Foundation (11-2002-696, to Dr. Redondo), the National Institutes of Health (DK32083), the Autoimmunity Prevention Center (AI50964), and the American Diabetes Association (1-04-RA-23, to Dr. Fain).

Dr. Eisenbarth reports receiving royalties from Kronus and Quest Laboratories. No other potential conflict of interest relevant to this letter was reported.

1. Barnett AH, Eff C, Leslie RD, Pyke DA. Diabetes in identical twins: a study of 200 pairs. Diabetologia 1981;20:87-93.
2. Redondo MJ, Yu L, Hawa M, et al. Heterogeneity of type I diabetes: analysis of monozygotic twins in Great Britain and the United States. Diabetologia 2001;44:354-62. [Erratum, Diabetologia 2001;44:927.]
3. Kaprio J, Tuomilehto J, Koskenvuo M, et al. Concordance for type 1 (insulin-dependent) and type 2 (non-insulin-dependent) diabetes mellitus in a population-based cohort of twins in Finland. Diabetologia 1992;35:1060-7.
4. Redondo MJ, Rewers M, Yu L, et al. Genetic determination of islet cell autoimmunity in monozygotic twin, dizygotic twin, and non-twin siblings of patients with type 1 diabetes: prospective twin study. BMJ 1999;318:698-702.
5. Verge CF, Gianani R, Kawasaki E, et al. Prediction of type I diabetes in first-degree relatives using a combination of insulin, GAD, and ICA512bdc/IA-2 autoantibodies. Diabetes 1996;45:926-33.

INSTRUCTIONS FOR LETTERS TO THE EDITOR

Letters to the Editor are considered for publication, subject to editing and abridgment, provided they do not contain material that has been submitted or published elsewhere. Please note the following: •Letters in reference to a *Journal* article must not exceed 175 words (excluding references) and must be received within 3 weeks after publication of the article. Letters not related to a *Journal* article must not exceed 400 words. All letters must be submitted over the Internet at http://authors.nejm.org. •A letter can have no more than five references and one figure or table. •A letter can be signed by no more than three authors. •Financial associations or other possible conflicts of interest must be disclosed. (Such disclosures will be published with the letters. For authors of *Journal* articles who are responding to letters, this information appears in the published articles.) •Include your full mailing address, telephone number, fax number, and e-mail address with your letter.

Our Web site: http://authors.nejm.org

We cannot acknowledge receipt of your letter, but we will notify you when we have made a decision about publication. Letters that do not adhere to these instructions will not be considered. Rejected letters and figures will not be returned. We are unable to provide prepublication proofs. Submission of a letter constitutes permission for the Massachusetts Medical Society, its licensees, and its assignees to use it in the *Journal*'s various print and electronic publications and in collections, revisions, and any other form or medium.