fulfilled the prediction were younger than those who did not. The younger the type 1 diabetic child at diagnosis, the more likely he/she is to carry high-susceptibility HLA genes (3), and so it is possible, even probable, that the proportion of children carrying high-susceptibility HLA genes was greater in the younger group than in the older group. Reactive HLA genes are the third accelerator of β-cell loss, and presenting the data in this way may serve to support the hypothesis for the entire group, rather than qualify it according to FCP.

The only difference between the behavior of the two groups in Fig. 2 may be one of tempo, and while the age range studied was sufficient to demonstrate the predicted inverse relationship in the younger group carrying more intensely reactive HLA genes, it may not have been wide enough to demonstrate the corresponding relationship for the older group carrying less reactive genes. An age range spanning many decades may be needed where the tempo is slower. DNA is available to the SEARCH study, and it will be interesting to learn in due course whether the distribution of HLA genotypes was indeed different between the two groups.

The accelerator hypothesis has now been subject to the scrutiny of several independent cohort studies. The Birmingham study mentioned by Dabelea et al. was small and of mixed race. (The relationship between BMI and insulin resistance is different between children of Asian and European descent [4].) The racial distribution of the children in Dabelea et al.'s study is not detailed but may be important. Two other U.K. studies of almost exclusively white children (5,6) and a large European study involving many thousands of predominantly white children (7) have all shown the predicted inverse relationship between age at onset and BMI on simple univariate regression. Furthermore, a German study involving 920 children with type 1 diabetes shows the same (8), and a study of pre–type 1 diabetic children from Australia suggests that the more insulin resistant the child, the more rapidly he/she progresses to type 1 diabetes (9). Longitudinal studies will be important to further elucidate the accelerator hypothesis, as Dabelea et al. suggest, but the real test will be a randomized controlled trial to reduce insulin resistance in at-risk children of type 1 diabetes.

Terence J. Wilkin, MD

From the Department of Endocrinology and Metabolism, Peninsula Medical School, Plymouth, U.K.
Address correspondence to Terence Wilkin, Professor of Endocrinology and Metabolism, Peninsula Medical School, University Medicine, Level 7, Derriford Hospital, Plymouth PL6b 8DH, U.K. E-mail: t.wilkin@pms.ac.uk.

● ●

References
1. Dabelea D, D'Agostino RB Jr, Mayer-Davis EJ, Pettitt DJ, Imperatore G, Dolan LM, Pihoker C, Hillier TA, Marcovina SM, Linder B, Ruggiero AM, Hamman RF, the SEARCH for Diabetes in Youth Study Group: Testing the accelerator hypothesis: body size, β-cell function, and age at onset of type 1 (autoimmune) diabetes. *Diabetes Care* 29:290–294, 2006
2. Wilkin TJ: The accelerator hypothesis: weight gain as the missing link between type I and type II diabetes. *Diabetologia* 44:914–922, 2001
3. Tait BD, Harrison LC, Drummond BP, Stewart V, Varney MD, Honeyman MC: HLA antigens and age at diagnosis of insulin-dependent diabetes mellitus. *Hum Immunol* 42:116–122, 1995
4. Ehtisham S, Crabtree N, Clark P, Shaw N, Barrett T: Ethnic differences in insulin resistance and body composition in United Kingdom adolescents. *J Clin Endocrinol Metab* 90:3963–3969, 2005
5. Kibirige M, Metcalf B, Renuka R, Wilkin TJ: Testing the accelerator hypothesis: the relationship between body mass and age at diagnosis of type 1 diabetes. *Diabetes Care* 26:2865–2870, 2003
6. Betts P, Mulligan J, Ward P, Smith B, Wilkin T: Increasing body weight predicts the earlier onset of insulin-dependant diabetes in childhood: testing the 'accelerator hypothesis' (2). *Diabet Med* 22:144–151, 2005
7. Knerr I, Wolf J, Reinehr T, Stachow R, Grabert M, Schober E, Rascher W, Holl RW, the DPV Scientific Initiative of Germany and Austria: The 'accelerator hypothesis': relationship between weight, height, body mass index and age at diagnosis in a large cohort of 9,248 German and Austrian children with type 1 diabetes mellitus. *Diabetologia* 48:2501–2504, 2005
8. Kordonouri O, Hartmann R: Higher body weight is associated with earlier onset of type 1 diabetes: confirming the accelerator hypothesis (Letter). *Diabet Med* 22:1783–1784, 2005
9. Fourlanos S, Narendran P, Byrnes GB, Colman PG, Harrison LC: Insulin resistance is a risk factor for progression to type 1 diabetes. *Diabetologia* 47:1661–1667, 2004

Testing the Accelerator Hypothesis: Body Size, β-Cell Function, and Age at Onset of Type 1 (Autoimmune) Diabetes

Response to Wilkin

We thank Dr. Wilkin (1) for his valuable comments. Overall, we (2) did not observe the hypothesized association between increasing BMI and younger age at onset of diabetes among U.S. youth with autoimmune diabetes. Our results were similar to a report from Birmingham, U.K. (3), and one from Philadelphia (4). They were in contrast to three previous European studies (5–7). However, we did observe the inverse association among youth with low residual insulin secretion at diagnosis (fasting C-peptide [FCP] <0.5 ng/ml). We hypothesize that obesity is "accelerating" the onset of the disease at a later stage in the natural history of the diabetes process, after substantial autoimmune destruction of β-cells has occurred.

The discrepancy between our results and those of the European studies may be due to several factors. It is possible that youth in Europe are diagnosed at a later stage in their natural history, when most have low residual FCP. This cannot be addressed, since these studies did not measure FCP. In the U.S., diagnosis may occur at an earlier stage in the natural history, before complete β-cell destruction occurs. Evidence for this exists, since a lower proportion of cases now present in diabetic ketoacidosis than previously reported (8,9). In these youth, acceleration, as assessed using age at clinical diagnosis, may be impossible to document since the time of true disease onset is uncertain.

Dr. Wilkin suggests that the two groups of youth in our Fig. 2 have different HLA genes. According to Dr. Wilkin, a higher proportion of high-risk HLA genes would trigger a more intense insulin resistance–induced autoimmune destruction. This hypothesis is testable in longitudinal studies starting before the onset of autoimmunity. We have collected HLA genotype data in SEARCH; however, none of the previous cross-sectional reports, including the current

one, are able to address the impact of HLA genotype in acceleration if the true age of disease onset is uncertain. Even if Dr. Wilkin is correct in predicting that the low-FCP group has more high-risk HLA genes, then this would not provide evidence that insulin resistance triggers the autoimmune process. The two groups in Fig. 2 had identical autoantibody numbers and titers. If insulin resistance triggers an autoimmune response, then part of the acceleration induced by insulin resistance could be mediated through an increased autoimmune destruction. We did not find evidence for such mediation. No important associations between BMI and diabetes autoantibodies were noted. Our findings do not support the hypothesis that insulin resistance triggers the autoimmune process.

There is increasing evidence that obesity and insulin resistance accelerate the onset of type 1 diabetes. The increasing prevalence of childhood obesity (10) may substantially account for the younger age at diagnosis of type 1 diabetes. However, only longitudinal studies starting before the onset of autoimmunity will be able to address the mechanism(s) by which and critical period(s) when increased insulin resistance may accelerate the type 1 diabetes process.

DANA DABELEA, MD, PHD
FOR THE SEARCH FOR DIABETES IN YOUTH
STUDY GROUP

From the University of Colorado Health Sciences Center, Denver, Colorado.
Address correspondence to Dana Dabelea, MD, PhD, University of Colorado Health Sciences Center, Department of Preventive Medicine and Biometrics, 4200 East 9th Ave., Box C245, Denver, CO 80262. E-mail: dana.dabelea@UCHSC.edu.

● ●

References
1. Wilkin TJ: Testing the accelerator hypothesis: body size, β-cell function, and age at onset of type 1 (autoimmune) diabetes (Letter). *Diabetes Care* 29:1462–1463, 2006
2. Dabelea D, D'Agostino RB Jr, Mayer-Davis EJ, Pettitt DJ, Imperatore G, Dolan LM, Pihoker C, Hillier TA, Marcovina SM, Linder B, Ruggiero AM, Hamman RF, the SEARCH for Diabetes in Youth Study Group: Testing the accelerator hypothesis: body size, β-cell function, and age at onset of type 1 (autoimmune) diabetes. *Diabetes Care* 29:290–294, 2006
3. Porter JR, Barrett TJ: Braking the accelerator hypothesis? (Letter). *Diabetologia* 47:352–353, 2003
4. Libman IM, Brooke S, Balfour P, LaPorte R, Becker DJ: Is earlier age at onset of insulin-treated diabetes associated with higher body mass index? (Abstract). *Diabetologia* 48 (Suppl. 1):A276, 2005
5. Kordonouri O, Hartmann R: Higher body weight is associated with earlier onset of type 1 diabetes, confirming the accelerator hypothesis (Letter). *Diabet Med* 22:1783–1784, 2005
6. Knerr I, Wolf J, Reinehr T, Stachow R, Grabert M, Schober E, Rascher W, Holl RW, the SEARCH for Diabetes in Youth Study Group: The 'accelerator hypothesis': relationship between weight, height, body mass index and age at diagnosis in a large cohort of 9,248 German and Austrian children with type 1 diabetes mellitus. *Diabetologia* 48:2501–2504, 2005
7. Kibirige M, Metcalf B, Renuka R, Wilkin TJ: Testing the accelerator hypothesis: the relationship between body mass and age at diagnosis of type 1 diabetes. *Diabetes Care* 26:2865–2870, 2003
8. Jackson W, Hofman PL, Robinson EM, Elliot RB, Pilcher CC, Cutfield WS: The changing presentation of children with newly diagnosed type 1 diabetes mellitus. *Pediatr Diabetes* 2:154–159, 2001
9. Rewers A, Chase HP, Mackenzie T, Walravens P, Roback M, Rewers M, Hamman RF, Klingensmith G: Predictors of acute complications in children with type 1 diabetes. *JAMA* 287:2511–2518, 2002
10. Flegal KM: The obesity epidemic in children and adults: current evidence and research issues. *Med Sci Sports Exerc* 31:S509–S514, 1999