Letters

important, and we thank Dr. Bell for his interest in our work.

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- References
- 1. Bell DSH: The effectiveness of β -blockers after myocardial infarction in patients with type 2 diabetes (Letter). Diabetes Care 29: 483, 2006
- Redelmeier D, Scales D, Kopp A: Beta blockers for elective surgery in elderly patients: population based, retrospective cohort study. *BMJ* 331:932, 2005
- Kjekshus J, Gilpin E, Cali G, Blackey AR, Henning H, Ross J Jr.: Diabetic patients and beta-blockers after acute myocardial infarction. *Eur Heart J* 11:43–50, 1990
- Jonas M, Reicher-Reiss H, Boyko V, Shotan A, Mandelzweig L, Goldbourt U, Behar S: Usefulness of beta-blocker therapy in patients with non-insulin-dependent diabetes mellitus and coronary artery disease: Bezafibrate Infarction Prevention (BIP) Study Group. Am J Cardiol 77:1273–1277, 1996
- 5. Jackevicius CA, Tu K, Filate WA, Brien SE, Tu JV: Trends in cardiovascular drug utilization and drug expenditures in Canada between 1996 and 2001. *Can J Cardiol* 19: 1359–1366, 2003
- Yusuf S, Peto R, Lewis J, Collins R, Sleight P: Beta blockade during and after myocardial infarction: an overview of the randomized trials. *Prog Cardiovasc Dis* 27:335– 371, 1985
- Freemantle N, Cleland J, Young P, Mason J, Harrison J: Beta blockade after myocardial infarction: systematic review and meta regression analysis. *BMJ* 318:1730–1737, 1999
- Malmberg K, Ryden L, Hamsten A, Herlitz J, Waldenstrom A, Wedel H: Mortality prediction in diabetic patients with myocardial infarction: experiences from the DIGAMI study. *Cardiovasc Res* 34:248– 253, 1997

Type 1 Diabetes and Autism: Is there a link?

Response to Freeman et al.

n a recent issue of *Diabetes Care*, Freeman et al. (1) discussed a possible link between type 1 diabetes and autism spectrum disorder (ASD). Their data suggested that the prevalence of ASD in nearly 1,000 children with type 1 diabetes may be greater than that in the general population.

We investigated the presence of ASD in 5,178 children diagnosed with type 1 diabetes at age ≤ 14 years from the Prospective Childhood Diabetes Registry of Finland. Children with type 1 diabetes were born between 1980 and 2000. The data were linked to the nationwide Hospital Discharge Register (HDR) by the end of the year 2003 using the unique personal identity number that is assigned to all residents of Finland. We included autism, Asperger disorder, pervasive developmental disorder-not otherwise specified, Rett's syndrome, and childhood disintegrative disorder in the diagnosis of ASD (2). We also linked the data of mothers of ASD cases to the HDR and reviewed hospital records in order to find out pregnancy and delivery complications related as potential risk factor for subsequent ASD in the child.

Seven cases with type 1 diabetes fulfilled the criteria of ASD, giving a cumulative incidence of 1.35/1,000 (95% CI 0.5-2.8). The cumulative incidence of ASD did not differ from that in the background population. The cumulative incidence of ASD was 1.39/1,000 (1.2-1.57) at age 18 years in northern Finland (3). There was male excess in ASD: five of seven cases were boys. Perinatal risk factors were present in five cases of ASD; some of them had several: asphyxia during delivery was present in two cases, umbilical cord around the neck in three cases, and excess bleeding during delivery in two cases, of which one had asphyxia and one had umbilical cord around neck.

Some studies have suggested that a family history of autoimmune disorders is more common among children with ASD than those healthy control children (4). However, there are many limitations in these studies, especially regarding sample sizes and study designs. A recent appro-

priately designed case-control study, much larger than those conducted earlier, found no overall association between ASD risk in children and autoimmune disorders in mothers; only psoriasis occurred more frequently (5).

Finland provides free or low-cost health service for all the habitants. Specialized health care like child neurological and psychiatric services are available in central hospitals and university hospitals that can all be found in the HDR. The HDR also covers central institutions for the mentally disabled. The HDR has nationwide coverage of inpatient treatment facilities. However, we were not able to capture cases who were diagnosed and treated as outpatient only; therefore, some mild cases of ASD may have remained unrecognized.

In conclusion, our observations do not support the suggestion about the link between type 1 diabetes and ASD. These findings, however, suggest that a subgroup of children developing autism suffered exposure to adverse prenatal and neonatal asphyxia (6) and unfavorable events in pregnancy, delivery, and the neonatal phase.

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References

- 1. Freeman SJ, Roberts W, Daneman D: Type 1 diabetes and autism: is there a link? *Diabetes Care* 28:925–926, 2005
- 2. Wing L: The autistic spectrum. Lancet 350:1761–1766, 1997
- 3. Kielinen M, Linna SL, Moilanen I: Autism in Northern Finland. *Eur Child Adolesc Psychiatry* 9:162–167, 2000
- Comi AM, Zimmerman AW, Frye VH, Law PA, Peeden JN: Familial clustering of autoimmune disorders and evaluation of medical risk factors in autism. *J Child Neu*rol 14:388–394, 1999
- Croen LA, Grether JK, Yoshida CK, Odouli R, Van de Water J: Maternal autoimmune diseases, asthma and allergies, and childhood autism spectrum disorders: a case-control study. Arch Pediatr Adolesc Med 159:151–157, 2005

6. Hultman CM, Sparen P, Cnattingius S: Perinatal risk factors for infantile autism. *Epidemiology* 13:417–423, 2002

Type 1 Diabetes and Autism: Is there a link?

Response to Harjutsalo and Tuomilehto

e thank Harjutsalo and Tuomilehto (1) for their most informative comments. There can be no doubt that they have thoroughly investigated the potential association between type 1 diabetes and autism spectrum disorder (ASD) in a large population-based cohort of Finnish children and failed to find any suggestion of an association. Why might their data differ from ours?

Based on clinical experiences, we reported what had appeared to be a higherthan-expected prevalence of ASD in our clinic-based cohort of children with type 1 diabetes (2). Our report was submitted in the hope of stimulating further evaluation and discussion about possible links between these two common disorders of childhood. As discussed in our report, it is possible that our patient population is biased in that it is derived from a large tertiary care center rather than being population based as in the case of the Finnish analysis. Thus, our patient population may be more likely to suffer other serious chronic conditions in addition to type 1 diabetes than would a group receiving therapy in a more community-based diabetes program.

However, it is possible that the Finnish data mask the possible association between ASD and type 1 diabetes for one or more reasons. First, it is possible that ASD remains relatively underdiagnosed in their diabetic population. Second, it is more likely that there are significant differences between the two cohorts that make comparison difficult. For example, there are reports that suggest that the rising incidence of childhood type 1 diabetes is associated with reduced contributions of high-risk HLA haplotypes (3). These data suggest that, in a country with a very high incidence of type 1 diabetes such as Finland, the relative contribution of genetic susceptibility to the expression of the disorder is therefore diminished. If the relationship between ASD and type 1

diabetes is on the basis of shared genetic influences, then any possible relationship may be diluted out by the heavier contribution of environmental factors in high compared to medium or lower incidence countries.

The contribution of Harjutsalo and Tuomilehto is greatly appreciated in helping to facilitate a definitive answer to the question of disease association between type 1 diabetes and ASD. There may be other investigators willing to share their experiences on this issues.

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- 1. Harjutsalo V, Tuomilehto J: Type 1 diabetes and autism: is there a link? (Letter). *Diabetes Care* 29:484–485, 2005
- 2. Freeman SJ, Roberts W, Daneman D: Type 1 diabetes and autism: is there a link? *Diabetes Care* 28:925–926, 2005
- Gillespie KM, Bain SC, Barnett AH, Bingley PJ, Christie MR, Gill GV, Gale EA: The rising incidence of childhood type 1 diabetes and reduced contributions of highrisk HLA haplotypes. *Lancet* 364:1645– 1647, 2004

Metformin in Pregnancy

Its time has not yet come

The American Diabetes Association (ADA) responds to letters concerning published articles in Diabetes Care. It does not respond to letters concerning presentations at the ADA Annual Scientific Sessions or reports of such presentations. The ADA held an entire conference on the treatment of gestational diabetes in November 2005, in which the use of metformin was discussed.

n 12 June 2005, the ADA's newsletter from the 65th Annual Scientific Sessions, the *Bayside Tribune* (1), ran a piece entitled "Metformin Shown to be Safe and Effective in Pregnancy". The article erroneously stated that speakers at a symposium answered "with a resounding 'Yes'" to the question of whether metformin is safe and effective for diabetes in pregnancy. We are concerned with that message.

A symposium entitled "Metformin in Pregnancy-Is it Safe? Does it Work?" discussed metformin in pregnancy. Dr. Clifford Bailey reviewed cellular mechanisms of metformin in nonpregnant patients (2) and suggested applications in pregnancy. Professor Gerald Briggs discussed how to determine the teratogenic risk of drugs and suggested that metformin use in the first trimester may be low risk based on animal and human data. Dr. Charles Glueck presented data on the use of metformin with diet throughout three trimesters in patients with polycystic ovary syndrome (PCOS) (3,4). His data showed a decreased risk of first-trimester spontaneous abortions compared with previous pregnancies in the same women not on metformin. Compared with community control subjects, Dr. Glueck's study subjects had a decreased risk of gestational diabetes, decreased maternal weight gain, and decreased insulin resistance. There was no increase in infant birth weight compared with gestational age- and sexmatched norms from the Centers for Disease Control and Prevention. Dr. Glueck attributed the slight increase in prematurity to a higher BMI in the PCOS patients compared with community control subjects. Neonatal outcomes were good, with normal growth and development up to 4 years in exposed offspring. Dr. Rowan presented retrospective data on the use of metformin in women with type 2 diabetes during pregnancy. Although the results were reassuring, she emphasized caution until randomized data are available. She presented an outline of an Australasian randomized trial, comparing insulin with metformin in women with gestational diabetes. This study will be called Metformin in Gestational Diabetes (MiG) and the follow up of offspring (MiG:TOFU). It will finish recruiting during 2006.

Metabolic effects of metformin include enhanced hepatic insulin sensitivity and reduced hepatic glucose output (2). Metfomin might reduce insulin resistance in pregnancy, decrease maternal weight gain, reduce maternal glucose levels and fetal hyperinsulinemia, and, as a consequence, reduce neonatal adiposity and birth trauma. Long-term sequelae of neonatal adiposity, including childhood obesity and diabetes, might be diminished with metformin.