

Manipulating the Type 1 Diabetes Disease Process, Man Versus Mouse

In their article in this month's issue of *Diabetes Care*, Hummell et al. (1) tested the hypothesis that gluten is a driving antigen for type 1 diabetes-associated islet autoimmunity. They convincingly demonstrated that elimination of dietary gluten for 12 months in humans positive for at least two type 1 diabetes-associated autoantibodies does not consistently alter the titers of these antibodies. The study is well done and carefully analyzed. Their conclusion that gluten does not drive islet autoantibody production in type 1 diabetes, as it does in celiac disease, seems very appropriate. Yet, because the β -cell lesion of type 1 diabetes is T-cell and not antibody mediated, and because antibody and T-cell responses to the same antigen can be markedly different or even reciprocally related, they cannot conclude that the underlying type 1 diabetes disease process in humans is not altered by elimination of dietary gluten for 12 months.

Nonetheless, I feel that studies such as this are extremely important because they provide information that allows us to compare specific aspects of the type 1 diabetes disease process in man versus mouse. A tremendous amount has been learned about the molecular and cellular immunogenetic pathophysiology of type 1 diabetes in the NOD mouse, and in this animal model, a large number of manipulations can prevent type 1 diabetes (2), including a gluten-free diet (3). How the findings in the NOD mouse relate to type 1 diabetes in humans is a major question. This is especially important at this time because the diabetes community is eager to test ways to preserve β -cell function in recently diagnosed patients with type 1 diabetes and to prevent the development of clinical type 1 diabetes in subjects identified as high risk. To accomplish this goal in the U.S., the National Institutes of Health is funding TrialNet, a consortium of clinical centers, core laboratories, and a coordinating/biostatistical center specifically charged with evaluating ways to alter the type 1 diabetes disease process in humans. The potential relevance of observa-

tions in the NOD mouse to the design of such clinical trials in humans is unknown.

As mentioned above, a large number of interventions can alter the type 1 diabetes disease process in the NOD mouse (2). Because intervention studies provide much stronger evidence for cause-effect relationships than observational/association studies, studies in humans using interventions efficacious in the mouse will provide the best data to allow us to compare the pathophysiology of type 1 diabetes in man versus mouse. If several interventions that successfully alter the type 1 diabetes disease process in the NOD mouse are also successful in humans, then the concept that the underlying type 1 diabetes disease mechanisms in man and mouse are similar would be strongly supported. In contrast, failure in humans of interventions that clearly work in the NOD mouse suggests important difference in the pathogenesis of type 1 diabetes in man versus mouse that will be essential for us to understand. The recently reported failure of parenteral insulin to prevent progression of high-risk subjects to clinical type 1 diabetes in the Diabetes Prevention Trial (DPT-1) is an excellent example (4). In the NOD and other mouse models of type 1 diabetes, there is agreement by many investigators that parenteral insulin can prevent progression to clinical type 1 diabetes; in fact, much has been learned about the mechanism of this prevention in the mouse (5–9). It remains to be determined whether the difference between the results of the DPT-1 in humans and the observations in the NOD mouse are due to minor but important differences in experimental design, such as insulin dose or timing during the preclinical period of type 1 diabetes, or whether they are due to major differences in the importance of insulin as an antigen in the type 1 diabetes disease process in man versus mouse. Nevertheless, it is essential for investigators involved in intervention studies in humans to make this determination.

Although Hummell et al. did not show a consistent effect of dietary gluten on type 1 diabetes-associated islet autoantibodies, inspection of Fig. 1 in their article suggests more concordance between changes in antibodies than would be expected if the changes over time of the three antibodies were completely independent. In patients 1, 2, 3, and 5, the rises and falls of the antibody, especially for GAD and IA-2 antibodies, seem to be concordant for several time points over quite long periods of time. This concordance suggests that the fluctuations in autoantibodies are not random and, potentially, that the underlying disease process is being altered by something other than gluten in the environment. It is also important to note that type 1 diabetes was not diagnosed when antibodies were at their peak; in fact, in both cases, the most recent autoantibodies were decreasing in titer.

Islet cell antibodies, which provided the first solid evidence that human type 1 diabetes was autoimmune in nature, were discovered a little over 25 years ago (10). Partly based on data from the NOD mouse and other animal models of human type 1 diabetes, the field has rapidly advanced to the point where numerous interventions are being tested for their ability to alter the type 1 diabetes disease process in humans. Clearly these are exciting times for patients with or at risk for type 1 diabetes, for physicians caring for these patients, and for investigators in this field.

JERRY P. PALMER, MD

From the University of Washington, Department of Medicine, Division of Metabolism, Endocrinology and Nutrition; and the Department of Veterans Affairs Puget Sound Health Care System, Seattle, Washington.

Address correspondence and reprint requests to Jerry P. Palmer, MD, DVA Puget Sound Health Care System, Primary and Specialty Medical Care Service (111), 1660 S. Columbian Way, Seattle, WA 98108. E-mail: jpp@u.washington.edu.

