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Letters to the Editor

RE: "DECREASED RISK OF CELIAC DISEASE IN PATIENTS WITH HELICOBACTER PYLORI *COLONIZATION"*

We read with interest the study by Lebwohl et al. (1) suggesting that colonization with *Helicobacter pylori* may be protective against the development of celiac disease (CD). The authors present a well-conducted study demonstrating a 4.4% prevalence of *H. pylori* in patients with CD compared with 8.8% of controls without CD. As with other autoimmune conditions, the prevalence of CD is increasing (2), and 1 theory explaining this is the so-called "hygiene hypothesis," in which reduced exposure to infective antigens in childhood as Western environments become cleaner leads to an increased risk of autoimmunity (3). The authors rightly postulate reasons why this may be the case with *H. pylori* and CD with an altered T-cell response as a result of chronic *H. pylori* infection.

Although their fascinating work supports this model, there may be other models to consider. It is not clear whether patients have CD from birth, but we do know that the most common age for presentation is during the fourth or fifth decade of life (4). Could infection play another role?

Our group conducted a 2-part study that may provide evidence to support the "second hit" hypothesis. This hypothesis postulates that, in addition to a genetic predisposition, an environmental trigger is required to initiate the autoimmune process (5). In the first part of the study, we investigated 101 patients (48 men; median age, 57 years) with stool culture–proven bacterial gastroenteritis (95% *Campylobacter* species) for CD. All patients underwent tissue transglutaminase and endomysial antibody testing, and if either test was positive, we performed a small-bowel biopsy. The prevalence of CD was higher in this group of patients than in a healthy control group (2.97% vs. 1%, $P = 0.10$).

In the second part of our study, we used a validated questionnaire (6) to assess patients with CD or inflammatory bowel disease, as well as healthy controls. A total of 69 of 233 (29.6%) patients with CD and 53 of 196 (27.1%) patients with inflammatory bowel disease self-reported having a gastrointestinal infection within the 12 months prior to diagnosis. In both diseases, this rate was significantly greater than in healthy controls (15 of 219 (6.8%) patients) ($P < 0.0001$).

The role of infection in the development of CD and other autoimmune conditions is complex (3). Circumstantial evidence exists for both the protective and deleterious consequences of gastrointestinal infection, and further work is required to delineate more clearly the role of different pathogens in the development of CD.

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THE AUTHORS REPLY

We appreciate the points made by Mooney et al. (1) regarding our study (2), and we agree that the pathogenesis of celiac disease (CD) likely involves more than 1 environmental exposure working in concert. Their findings regarding *Campylobacter* in particular are consistent with a recent study of US military enlistees, in which increased rates of CD were seen after *Campylobacter* infection but not after infection with *Salmonella, Shigella,* or *Yersinia* (3). The

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association between *Campylobacter* infection and Guillain-Barré syndrome likewise points to a parallel immune-based phenomenon (4). An increased risk of CD has also been associated with rotavirus infection (5) and antibiotic receipt (6), suggesting that there are multiple exposures through which the immune system can lose tolerance to gluten. In the data reported in the letter by Mooney et al. (1), it is uncertain whether the increased risk of developing CD was a consequence of *Campylobacter* infection itself or the antibiotics that were likely prescribed to treat this infection.

Indeed, the "2-hit hypothesis" and the "hygiene hypothesis" are not mutually exclusive. We found that *H. pylori* may be protective against the development of CD (2). Perhaps the presence of *H. pylori* prevents the "second hit," such as an enteric viral or bacterial infection, from triggering CD. Given the rise of CD seroprevalence over the past half-century (7), at least 1 of several interacting exposures must be changing over time, and *H. pylori* has had a rapid decline during the same period as the rise in CD (8).

To develop a full model of CD pathogenesis would require longitudinal measurement of exposures, with testing for effect modification. Such a model might also incorporate information regarding infant feeding practices (such as the timing of gluten introduction and duration of breastfeeding), as well as the use of other medications that have been proposed to increase the risk of CD, such as early-life antibiotic use, acid suppression drugs, and in utero exposure to iron supplements (9). As risk factors and their interactions become better characterized, efforts can then be made for risk stratification, in which patients at increased risk of CD can be targeted for interventions to prevent its development.

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RE: "TYPE 2 DIABETES AND THE RISK OF COLORECTAL ADENOMAS: BLACK WOMEN'S HEALTH STUDY"

Dash et al. (1) carried out a nested case-control study in 917 cases of colorectal adenoma and 2,751 controls without colorectal polyps. Contrary to their hypothesis, the authors found an unexpected inverse association between type 2 diabetes mellitus (DM) and colon adenoma risk among older African American women.

The authors suggested that the change in diet and lifestyle after diabetes diagnosis may be 1 possible explanation for the inverse association between DM and colon adenoma risk. This explanation was supported by their finding of a stronger association with increasing duration of DM. Results from other studies concur with this explanation (2, 3). The authors

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