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EDITORIAL

IgG-Mediated Food Intolerance in Irritable Bowel Syndrome: A Real Phenomenon or an Epiphenomenom?

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Abnormal reactions to food probably contribute to the complex pathophysiology of irritable bowel syndrome, but the mechanisms involved remain unclear. Following the recent identification of subtle mucosal inflammation in at least some patients with the disorder, perhaps now is the time to revisit some of the immunological reactions to dietary antigens that, in the past, have been dismissed as irrelevant.

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It is commonplace for patients with gastrointestinal diseases in general and irritable bowel syndrome (IBS) in particular to question whether the food they consume might have some influence on the course of their disease. Unfortunately, physicians are often criticized for not paying enough attention to this problem although this is probably because the available scientific data on the subject are either insufficient or conflicting. However, to dismiss these concerns about diet serves to undermine the patient's confidence in conventional medicine, denies them a measure of control, and runs the risk of them being driven to seek other sources of help. Like other chronically ill patients, IBS sufferers are vulnerable to exploitation by commercial outlets offering expensive, unsubstantiated, and often dubious remedies, some of which may even be dangerous. In the pursuit of a dietary solution to their problem, patients with IBS seem to be especially willing to expend large sums of money on this approach, presumably because their symptoms are so often exacerbated by eating (1) as well as the fact that they see it as a natural and logical way of managing their problem.

Despite difficulties in the past in identifying environmental factors such as food that might influence the course of IBS, there are emerging examples of food-induced aggravation of symptoms. For instance, it has been shown that various carbohydrate substitutes appear to perturb gut function more in patients with IBS than those without (2), and it also seems reasonable to assume that some of these agents might have an effect beyond that for which they were intentioned. In addition, there is now increasing interest in the possibility that there may be a genetic component to a particular individual's response to various nutrients, which is part of the emerging field of nutrigenomics. Given the heterogeneity of IBS, it seems likely that there are subsets of patients waiting to be identified in whom the symptoms are aggravated by certain food components. The molecular basis for such interactions is likely to be varied, but an immunological basis for some of them is a distinct possibility. The gut-brain axis is now well accepted as a modulator of symptoms and perhaps now is the time for the role of the gut-immune axis to be taken more seriously.

An exclusion diet based on the presence of IgG antibodies to food has recently been shown to have possible utility in the management of IBS (3). However, IgG antibodies to various food components are detectable in healthy individuals although usually at rather low levels and thus the role of this class of antibody in the induction of symptoms remains highly controversial (4–6). One possible explanation for the presence of these antibodies is low-level absorption of macromolecules from the gut although it is unknown whether absorption could be more pronounced in certain individuals with IBS but such a possibility deserves further investigation. In addition, it would be of interest to know what levels of these IgG food antibodies exist in other groups of patients where permeability is known to be increased, such as in inflammatory bowel disease. In the current issue of this journal (7), Zar and colleagues have also examined IgG antibodies in patients with IBS although they confined themselves to assaying only the IgG4 subclass. They found increased titers of these antibodies to certain foods and speculate that this observation is unlikely to be due to increased permeability because of the finding of a differential increase in titer to different food antigens. An association between IgG4 and IgE antibodies has been noted in several settings but the relationship in allergy appears to be complex with IgG4 reactivity linked to inhibition of IgE-mediated responses (8). In the present study by Zar *et al.*, no evidence for the latter was found, which is in accord with the previous literature on IBS suggesting that classic allergy does not play an important role in IBS except possibly in a small group of diarrhea-predominant subjects where oral sodium cromoglycate may sometimes be helpful (9–11).

It is now well recognized that some patients with IBS appear to have an ongoing, low-grade inflammatory process in the gut mucosa (12), and this has traditionally been attributed to a previous dysenteric infection. However, not all patients give a history of a gastrointestinal infection and it is tempting

to speculate that an alternative mechanism might be based on IgG reactivity. It would be useful to know whether such serological responses could be reconciled with any markers of a subtle immuno-inflammatory disturbance. Identifying the level and source of immunological reactivity might also be helpful because if the IgG is elaborated systemically, it could be indicative of increased permeability, whereas mucosal production might suggest a more fundamental disorder of immune regulation. The latter situation is analogous to inflammatory bowel disease, where autoantibodies such as antineutrophil cytoplasmic antibodies (ANCA) and antisaccharomyces antibody (ASCA) are produced in the gut and appear to reflect mucosal immune dysregulation with loss of tolerance and cross-reactivity with components of the flora (13, 14).

Double-blind food challenges are currently regarded as the best way of identifying foods to which patients are intolerant and it would therefore be of interest to undertake some form of food rechallenge in patients where IgG antibodies are considered possibly to be important. However, it has to be borne in mind that if IgG reactions induce an inflammatory response, this may render the gut more susceptible to other perturbing influences rather than necessarily causing symptoms directly. Furthermore, IgG food antibodies might be harmful in IBS as a result of a completely different mechanism. For instance, they may crossreact with a host antigen in genetically predisposed IBS individuals thus explaining why they might be pathogenic in some but not other individuals.

To date, efforts have largely concentrated on trying to identify potential physiological markers for IBS with limited success. Perhaps a more fruitful line of inquiry might be a search for bio-markers that could have the potential to help us not only dissect out the heterogeneity of IBS, but also provide targets against which we may be able to assess therapeutic interventions. Immunological signals such as food-related antibodies or measures of intestinal permeability might be a useful beginning.

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