Inflammatory Bowel Disease and Food Intolerance

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Are the idiopathic inflammatory bowel diseases, ulcerative colitis and Crohn's disease, manifestations of food allergy? This question is often posed by patients, and increasingly by doctors. We do not know enough to give a short answer, so this article attempts to give a long one.

The Gut and Food Allergy

Various forms of food intolerance exist, and a distinction is usually drawn between adverse reactions that are allergic or immunological in origin, and those that are idiosyncratic, in which symptoms may be pharmacological in origin, or metabolic, reflecting, for example, a genetically determined enzyme defect[1]. Both allergy and idiosyncracy need to be considered in the context of inflammatory bowel disease, but the concept of allergy underlying the conditions has received most attention. Indeed, the gut would seem to be a highly likely site for the manifestation of food allergy. The antigens in food are present in high concentration at the surface of the gut mucosa, which is permeable to allow the gut to fulfil its absorbtive function, and within which there is a highly organised local immune system, encompassing both humoral and cell-mediated immunity. It might indeed be thought surprising that food-allergic manifestations, arising either within the gut or the rest of the body, are not universally present in the population. That this is not so reflects some of the specialised aspects of the gut immune system. There are two major features of importance.

The first is the local production within the gut mucosa of the specialised mucosal immunoglobulin, IgA. Secretory IgA, directed in part against antigens present in food, lines the mucosa of the intestine and helps prevent penetration of antigen into the gut mucosa. The combination of secretory IgA with its antigen appears to be an undramatic process, as the resulting antigen-antibody complex lacks the ability to fix complement readily, and therefore does not induce local inflammation[2].

The other major feature is that, experimentally, development of a local IgA immune response in the gut mucosa against specific antigen can often be shown to be linked with induction of systemic tolerance, i.e. specific non-responsiveness of the systemic immune system of the body to subsequent challenge with that antigen[3]. Teleologically this process would seem desirable in preventing major systemic allergic responses to food.

An abnormal gastrointestinal immune response to food might therefore lead in different ways to allergic manifestations. An inadequate local gastrointestinal immune response, without induction of systemic tolerance to food antigens, might underlie systemic forms of allergy. In contrast, an enhanced local immune response, in which mechanisms other than IgA production are recruited, might lead to local gut inflammation. Some form of this latter process is often cited in attempts to explain the chronic inflammatory bowel diseases.

Allergic Manifestations in the Gastrointestinal Tract

Acute gastrointestinal allergic disease is relatively common, usually recognised by patients themselves, and rarely a clinical problem. Oral oedema, abdominal pain and diarrhoea, sometimes associated with systemic manifestations such as asthma, may reflect an acute IgE-mediated response to specific food antigens, readily confirmed if necessary by prick testing or detection of specific IgE in the serum. The acuteness of this form of allergy makes it a poor model for ulcerative colitis and Crohn's disease, chronic conditions which often show continuous disease activity over many months or even years. There are, however, good examples of diseases that seem to be immunologically mediated which are characterised by chronic inflammation in the gut. These include coeliac disease (although an immunological basis is not universally accepted) and, most intriguingly for the purposes of this article, the milk allergic colitis recognised in infants. For example, studies at the Hospital for Sick Children, London, demonstrated a bimodal age of presentation of clinical 'colitis' with rectal bleeding and diarrhoea[4]. While older children followed the course of classical ulcerative colitis, those presenting at an early age had a colonic inflammatory infiltrate with a prominent eosinophilic component. These infants often had evidence of IgE-mediated reactions to cows' milk, and remitted on withdrawing this antigen from their diet. Is this condition a model for the chronic inflammatory bowel diseases seen in later life?

To try and answer this question, we shall first survey the evidence for abnormal reactions to food antigens in patients with ulcerative colitis and Crohn's disease, and then survey the evidence that removing or altering the ingestion of food antigens affects the disease. Both ulcerative colitis and Crohn's disease will be considered together, for the evidence of abnormal immune responses

in these diseases is virtually identical; indeed many of the family studies indicate that these conditions are variants of a single disease process[5].

Immune Responses to Food Antigens in Inflammatory Bowel Disease

There is strong evidence of immunity against food antigens among patients with inflammatory bowel disease. It is not this finding but its interpretation which is uncertain. The damaged intestinal mucosa in inflammatory bowel disease has an enhanced permeability, which presumably permits more, or larger size, antigenic particles derived from food to penetrate[6]. This mechanical breaking of the local immune barrier seems likely to enhance the local generation of immunity to food antigens, and to permit development of systemic immune responses. Evidence of immune responses to food might therefore be considered as secondary phenomena of no importance. However, an alternative interpretation is that locally-generated immune responses against food antigens perpetuate inflammation in the gut by, for example, persistent antigen-antibody complex-mediated tissue damage.

The evidence for immune response against food may be summarised as below, following the classical Gell and Coombs classification.

Type 1, IgE-mediated Immune Responses

Some early studies suggested that the classical atopic disorders, which reflect a tendency to develop IgE-mediated immune responses to common extrinsic antigens to a greater degree than normal, were more common in patients with inflammatory bowel disease. Furthermore, in some patients, particularly those with localised proctitis, there may be a prominent eosinophilic component to the inflammatory infiltrate, and peripheral eosinophilia is not uncommon[7]. Some controlled therapeutic trials have reported beneficial responses to the local administration of cromoglycate, which inhibits IgE-mediated damage by preventing degranulation of mast cells[8]. However, the benefits of this treatment are minor, and have not always been confirmed. In addition the most meticulous studies on atopy in inflammatory bowel disease do not suggest that atopic disorders in general are more common than in the whole population[9]. They do, however, suggest that among atopic individuals with inflammatory bowel disease, evidence of immediate-type skin hypersensitivity to food is more common than among atopic individuals without gut disease. This would suggest merely that among individuals with a tendency to develop reaginic antibody, the presence of inflammatory bowel disease, and thus enhanced penetration of food antigens, is more likely to result in reaginic antibodies to food.

Type II

The search for circulating antibodies in inflammatory bowel disease has produced findings that have contributed significantly to the immunological theories of inflammatory bowel disease. However, they have been mainly concerned with antibodies to antigens other than food. The main findings can be summarised as follows:

1. Many patients have circulating autoantibodies to colonic epithelium[10].
2. Antibodies in the serum of patients with inflammatory bowel disease can initiate antibody-dependent lymphocyte cytotoxicity directed against colonic epithelial cells *in vitro*[11].
3. There are cross-reacting antigens between bacteria commonly present in the lumen of the colon, and colonic epithelium. This might result in immune responses initially directed against bacteria inflicting damage on the colon[12].

Some workers have felt that these events underlie the pathogenesis of inflammatory bowel disease. In contrast, the detection of circulating antibody against food protein has seemed of little relevance. For example, antibodies against bovine proteins are readily detected in inflammatory bowel disease, but they are also found in patients with other inflammatory lesions of the gut such as coeliac disease, and in apparently normal individuals[13].

Type III

The histological appearance of the inflammatory infiltrate in inflammatory bowel disease has been likened to the Arthus reaction, representing the inflammatory consequences of an antigen-antibody complex formation. This might well reflect the combination of antibody, either from the circulation or more likely produced locally within the mucosa, with antigens from the gut. The ability of antigen-antibody complexes to initiate chronic inflammation in the gut mucosa has been reproduced experimentally[14]. Again, however, bacterial antigens are better established as potential contributors to this process than food antigens, as there is evidence of local production of anti-bacterial antibody within the colonic mucosa[15], but theoretically food antigens could also act in this way. An attraction of this hypothesis is that deposition of immune complexes elsewhere in the body, perhaps from the circulation after being formed in the gastrointestinal mucosa, could explain those systemic complications of inflammatory bowel disease, such as iritis, arthritis and erythema nodosum that are strongly reminiscent of serum sickness[16].

Type IV

In contrast to the considerable work in defining antibody reactions to both food and bacterial proteins in inflammatory bowel disease, fewer studies have been made on cell-mediated immunity. There is little direct evidence of cell-mediated immunity to food antigens in man. However, experimentally cell-mediated immunity against extrinsic antigen introduced into the gut lumen has produced a chronic colitis[17].

Thus there is good evidence that patients are sensitised to food proteins, but little evidence to suggest that this

sensitisation plays a critical role in maintaining inflammation. Suggestive evidence, however, comes from a variety of clinical studies.

Clinical Studies of Food Antigen Withdrawal

The literature of the early half of this century contains many accounts of successful treatment of ulcerative colitis by withdrawal diet, remission being induced by withdrawal of potatoes, chocolates, milk, tomatoes, etc. All these observations were uncontrolled, and clearly unimpressive in a disease characterised by frequent spontaneous relapses and remissions. The controlled evidence for benefit from removal of specific allergens is very scarce.

The most quoted trial of withdrawal of a single foodstuff is that of Wright and Truelove, who tried the effect of milk withdrawal in ulcerative colitis[18]. The result of this trial is summarised as 'one patient in five had some benefit from milk withdrawal' — with the complex statistical appendix reflecting significance of some tests but not others. The details of this trial are worth emphasising. The main comparison was not between a milk-free diet and a normal diet, but between a milk-free diet and one in which patients were advised to drink milk liberally. Subsequent work has emphasised that patients with inflammatory bowel disease may be intolerant of milk, not on the basis of an allergy but of idiosyncracy[19]. Lactase deficiency resulting in unhydrolysed lactose reaching the colon, where it may initiate a fermentative diarrhoea, is more common in patients with inflammatory bowel disease, and some of the symptomatic differences between a low and a high milk diet could be explained on this basis. But it is also possible that this study did indeed reflect a beneficial immunological effect of removal of this particular antigen, and patients with the highest level of milk precipitins were more likely to do better, but it was not possible to correlate improvement with changes in circulating milk precipitin levels. In a different group of patients studied subsequently, immediate hypersensitivity to milk proteins was not more common in inflammatory bowel disease than in the general population[20].

There is little other controlled evidence on withdrawal of specific items of food in inflammatory bowel disease, but there are now a number of studies indicating that 'bowel rest', which involves removal of food and food antigens from the lumen, may be effective in inducing clinical remission. Most of this work pertains to Crohn's disease rather than ulcerative colitis, but it is not clear whether this reflects a true biological difference, or merely that frustration with the current treatment of Crohn's disease has led to continuing experimentation in treatment, whereas ulcerative colitis is usually readily controllable by current medical means.

Bowel rest has been achieved in a number of different ways. Colonic Crohn's disease has been treated by double-barrelled ileostomy, with diversion of the faecal stream, resulting in decreased inflammation within the excluded segment[21]. While removal of antigenic food residues might explain this, profound changes in the motility, the consistency of the intraluminal contents and the bacterial flora of the excluded colonic segment will also occur, and it is difficult to interpret these changes. Some evidence suggests that reintroduction of faecal filtrates into the excluded segments can reinitiate inflammation, with a particle smaller than a bacterium being responsible for this phenomenon, but clearly the bacterial products are still as likely to be responsible as food antigens[22].

Striking clinical improvement has been reported in Crohn's disease, particularly in adolescents, from the use of total parenteral nutrition, which rests both small and large gut[23]. An allied approach is the use of an elemental diet, which avoids the risks of central venous feeding and removes food antigens by providing food in the form of simple molecules of carbohydrate, fatty acids, and amino acids or peptides of a molecular size so small that they are unlikely to be antigenic. There seems little doubt now that these approaches can induce remission in Crohn's disease, and in a controlled trial the effects of an elemental diet, although slow, have been similar to those of conventional treatment with corticosteroids, with a fall in indices of inflammation as well as clinical improvement[24].

The interpretation of these findings is very difficult. The nutritional state of patients may well be of considerable importance. Many patients with inflammatory bowel disease are malnourished, and re-feeding malnourished patients alters their immune responsiveness[25]; in one small study an elemental diet appeared no better than tube feeding a normal diet[26]. Furthermore, both total parenteral nutrition and elemental diets alter bacterial flora within the gut, so potentially the expression of immune responses against bacterial products within the gut lumen is likely to be altered. In this context it is of interest that a combined approach (an elemental diet in combination with the administration of non-absorbable antibiotics to reduce the bacterial flora of the gut), was shown to equal systemic corticosteroids in inducing rapid remission in active Crohn's disease; remission was induced within ten days[27].

An alternative approach to the study of food withdrawal in inflammatory bowel disease is that used by Hunter and his colleagues in Addenbrooke's Hospital, in which a strictly regimented diet was tried to keep patients in remission. Initially patients with Crohn's disease achieved clinical remission by means of either total parenteral nutrition or an elemental diet. Patients subsequently reintroduced foods singly into their diets at intervals, attempting to identify the particular foodstuffs that initiated symptoms. Symptoms such as diarrhoea and pain returned with anything from one to more than ten different articles of diet, ranging from dairy products and wheat to tap water. Long-term remissions have been reported on subsequent maintenance of a restricted diet excluding those foods that in the dietary trial caused symptoms[28]. The difficulties in interpretation are obvious; in particular the attitude of the patients, and their own belief in the role that food may play in their disease, may well be important factors. Hunter and his colleagues are now undertaking the daunting task of a controlled evaluation of this approach.

Conclusion

No simple relationship between eating particular foods and disease activity in inflammatory bowel disease has emerged. It remains a field in which the cynical disbeliever in food allergy — whose own reactions may have become hypersensitive in response to media and patient exposure — remains confident. The data can best be summarised as follows. (a) Patients with inflammatory bowel disease have enhanced immune responses against food antigens, but also against other antigens in the gut, particularly bacteria and bacterial products. (b) Expression of these immune responses may contribute to inflammation, and dietary alterations can induce remission. It seems just as likely that changes in faecal consistency and bacterial content are responsible for improvement, as that the withdrawal of a specific food antigen is responsible.

Finally, however, there are striking geographical variations. Inflammatory bowel disease is a common problem in the West, and rare in the Third World. Epidemiological studies have shown that increasing westernisation leads to a higher incidence of these diseases: in Polynesians, Maoris and South African blacks ulcerative colitis is becoming more common, perhaps with westernisation of habits as previously rural people become urbanised[29]. The immigrant from India in the UK has an incidence of inflammatory bowel disease which approaches that of the native Briton, although he is more likely to have ulcerative colitis than Crohn's disease[30]. These emerging trends, as people of different races take up similar life-styles, point convincingly to environmental causes. While 'food allergy' remains the language of the enthusiast, a 'major influence of the constituents of the diet' seems likely to be an aetiological factor of great significance.

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