Review article: food hypersensitivity and irritable bowel syndrome

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SUMMARY
Irritable bowel syndrome is a common condition but its pathophysiology remains poorly understood. Many irritable bowel syndrome patients give a history of food intolerance, but data from dietary elimination and re-challenge studies are inconclusive. Multiple aetiological mechanisms have been postulated. The gut has an extensive immune system but current understanding of processing of food antigens in health and disease is limited. There is no clinically useful marker available to test for food hypersensitivity in irritable bowel syndrome. Researchers have employed both skin tests and serum immunoglobulins (IgG and IgE) as markers of food hypersensitivity in various disorders including irritable bowel syndrome, but published data are equivocal.

In this article, the evidence for the role of food hypersensitivity in irritable bowel syndrome is reviewed and, based on the available data, a possible pathophysiological hypothesis has been formulated.

INTRODUCTION
Irritable bowel syndrome is a common disorder and accounts for 30–50% of referrals to gastroenterology clinics. However, its pathophysiology remains poorly understood. Historically, the diagnosis of irritable bowel syndrome has been based on the exclusion of identifiable pathology, but recently various symptom-based criteria have been introduced, encouraging clinicians to make a positive clinical diagnosis. Of these, the Manning and Rome criteria are used most frequently. Employing the Manning criteria, a 17–22% prevalence of irritable bowel syndrome has been reported in the general population. However, the Manning criteria have a low overall specificity and are more reliable in identifying irritable bowel syndrome in female patients.

In 1989, an international working party proposed the Rome Criteria for the diagnosis of irritable bowel syndrome (revised in 1992 and 1999) (Table 1). These symptom-based criteria are now widely used for clinical and research purposes. Using the Rome criteria in a stratified random population, prevalence rates of 5% in men and 13% in women have been reported.

Various hypotheses, including food hypersensitivity and psychosocial factors have been proposed as possible pathophysiological agents. Current data support a multifactorial aetiology, in which various agents acting either independently or in concert, result in sensorimotor dysfunction within the enteric nervous system (ENS). Despite recent technological advances, no consistent sensory and/or motor abnormality has been identified in irritable bowel syndrome.

FOOD INTOLERANCE, FOOD HYPERSENSITIVITY AND FOOD AVERSION
The term ‘food intolerance’ encompasses nonimmunologically mediated adverse reactions to food, which resolve following dietary elimination and are reproduced by food challenge. This includes the direct effects of pharmacologically active constituents of foodstuffs (e.g. tyramine in cheese, caffeine in coffee) and enzyme deficiencies (e.g. lactose and fructose intolerance). Food
allergy/hypersensitivity is used to describe conditions in which an immunological mechanism may be demonstrable (e.g. cow’s milk, peanut and soybean allergy). In contrast, food aversion is a psychological avoidance response.

Patients with food-induced symptoms, with no identifiable pathogenetic mechanism, are grouped under ‘food intolerance’. It is possible that a proportion of these patients have an immunopathological basis for their symptoms. It has been proposed that many irritable bowel syndrome patients with food intolerance have underlying food hypersensitivity. In some patients with Crohn’s disease, wheat and dairy products exacerbate symptoms.

PREVALENCE OF FOOD INTOLERANCE IN THE GENERAL POPULATION

Although food intolerance is a common perception amongst the general population, it can be demonstrated in only a small proportion of the population employing double-blind food elimination and challenge studies. A questionnaire study of 20,000 individuals reported food intolerance in 20%. The questionnaire assessed the relationship between food ingestion and the presence of skin allergy, asthma, angioedema, intestinal symptoms, headaches and behavioural changes. Of those reporting food intolerance, 93 patients entered a double-blind placebo-controlled food challenge study but only 18 (19.4%) tested positive. Based on these data, the prevalence of food intolerance in the general population is 1.4–1.8%. If anything, the true prevalence of food intolerance is probably higher, as patients with a history of severe reactions were excluded, many were lost to follow-up and data collection was restricted to only eight common foodstuffs. It is estimated that the true prevalence of food intolerance or food hypersensitivity is 5% in the general population.

Food hypersensitivity is a common perception amongst irritable bowel syndrome patients, with 20–65% attributing their symptoms to adverse food reactions. In fact, it is not uncommon for patients to experiment with a variety of elimination diets or alternative therapy before seeking medical help. Few clinicians recognize food hypersensitivity as a cause of irritable bowel syndrome, the majority considering it as a functional disorder. Although various studies have attempted to resolve this issue, the published data remain contradictory.

ELIMINATION DIETS AND FOOD CHALLENGE

In 1982, Jones et al. evaluated the role of food intolerance in irritable bowel syndrome. The effect of a 1-week elimination diet, comprising of both a single meat and fruit and distilled or spring water, followed by open challenge with the suspected foodstuff, was evaluated in 25 consecutive irritable bowel syndrome patients. Symptoms resolved in 14/21 (67%), recurring on food challenge. The foodstuffs commonly implicated were wheat, corn, dairy products, coffee, tea and citrus fruits. A double-blind provocation study was performed in six patients, who were symptom-free on a limited diet. Patients correctly identified 10 of the 12 test days and 11 of the 12 control days.

Since these initial observations, a number of studies have attempted to elucidate this relationship further. To date there have been seven studies in which the effect of dietary exclusion followed by food challenge has been investigated. Despite the methodological limitations (e.g. trial design, inadequate patient selection, duration of elimination diet and the methods of food challenge employed), 15–67% response rates to elimination diets were reported. The double-blind placebo-controlled challenges identified food intolerance in 6% to 58% of cases, with milk, wheat and eggs being the most commonly implicated foods.

In the largest study, the effect of an exclusion diet was evaluated in 200 irritable bowel syndrome patients (156 women and 44 men). Symptomatic improvement was reported in 91/189 (48%) patients and was maintained for a mean of 14.7 months. Following open dietary challenge, 73/91 (80.2%) of responders identified one or more food intolerances. In contrast, 95/98 (96.9%) nonresponders had persistent symptoms at final follow-up (mean 12.5 months). These data indicate that a significant proportion of irritable bowel

syndrome patients could benefit from therapeutic dietary manipulation.

Whilst food-induced symptoms may represent a hypersensitivity reaction, the role of psychological factors and/or a placebo response cannot be excluded. In three of the above studies, skin prick test and/or RAST test was used as evidence of food hypersensitivity, but positive correlation with dietary challenge was demonstrated in only one study.27 Double-blind placebo-controlled trials are considered as the gold standard in the diagnosis of food hypersensitivity but these are difficult to conduct and therefore most studies have used open dietary elimination and challenge design.

Disodium cromoglicate (DSCG) inhibits the release of inflammatory mediators (e.g. histamine, leukotrienes and slow reacting substance of anaphylaxis) by inhibiting degranulation of mast cells, following contact with an allergen. The role of topically administered DSCG in the treatment of various allergic conditions (e.g. asthma, allergic conjunctivitis and allergic rhinitis) is well established. The oral preparation of the drug has been used successfully in atopic patients with suspected ‘food induced’ exacerbation of symptoms.30–32

The hypothesis that food hypersensitivity may play a role in the pathogenesis of irritable bowel syndrome, has led to the evaluation of DSCG. Two, albeit small, double-blind placebo-controlled studies demonstrated that DSCG resulted in significant symptomatic improvement.33, 34 A larger study (428 patients) demonstrated that DSCG was as effective as an elimination diet in improving symptoms (67% vs. 60%).35 The response was greater in patients with a positive skin prick test to food allergens in both groups (75% vs. 54% in patients treated with elimination diet and 81% vs. 58% in the group treated with DSCG).

In clinical practice, poor patient compliance limits the effectiveness of elimination diets. Current data indicate that DSCG may prove to be a useful adjunct in the treatment and, possibly, even in the diagnosis of ‘food hypersensitivity’ induced irritable bowel syndrome.

FOOD HYPERSENSITIVITY AND EXTRA-INTESTINAL ALLERGIC CONDITIONS

In several common allergic disorders (e.g. atopic dermatitis, asthma and allergic rhinitis) and some cases of acute anaphylaxis, the role of food hypersensitivity is increasingly being recognized.16–19 An IgE mediated, type I hypersensitivity reaction, to a variety of inhaled allergens, is well recognized in atopic individuals. A similar mechanism has been proposed for various food-induced hypersensitivity reactions. Many atopic individuals, without clinical evidence of food hypersensitivity, exhibit an abnormal immunological response to food allergens.40 In patients with asthma and atopy, abnormal duodenal histology has been observed with features similar to bronchial mucosa.41 These data suggest that a more generalized abnormality in the mucosal immune system may exist.

IgA production by the gut mucosa has been proposed to play a protective role in preventing food allergy by blocking mucosal exposure to food antigens.42, 43 Atopic individuals tend to produce IgE and IgG antibodies in response to antigenic food challenge, rather than IgA antibodies, as opposed to nonatopic individuals.43, 44 Pre-treatment with DSCG not only attenuates this response, but is also associated with a reduction in symptoms. These data support a causal relationship between IgE and IgG antibodies and food hypersensitivity.45 However, symptoms neither occur immediately after a food challenge nor are they temporally related to the appearance of serum IgE-complexes. This suggests an IgE-mediated late phase hypersensitivity reaction. This concept is supported by the fact that many of the features of atopic eczema do not resemble a type I hypersensitivity response. The skin histology in these patients shows a mixed picture with infiltration by mononuclear cells, suggesting a delayed hypersensitivity component.46 In patients with atopic dermatitis and hay fever, a large fraction of circulating IgE has been shown to be in the complexed form rather than in free form, which is involved in an immediate hypersensitivity response.47

PATHOGENESIS OF FOOD HYPERSENSITIVITY IN IRRITABLE BOWEL SYNDROME

The bowel mucosa acts as a physical barrier to a variety of intraluminal dietary and microbial antigens.48 In addition, the enzymatic breakdown of food by luminal and brush border enzymes to an elemental form helps in reducing total antigen exposure. However, even under normal physiological conditions, intact food antigens can penetrate the mucosal barrier via transcellular or paracellular routes.49, 50 The integrity of the mucosa is further compromised during episodes of gastroenteritis and in inflammatory bowel disease. The mechanism by which mucosal immune system maintains a state of
immunological tolerance to constant antigen exposure is not clear at present but will be crucial to an understanding of the pathogenesis of food hypersensitivity.

Despite an extensive immuno-regulatory system, only a few hypersensitivity disorders are recognized in the gastrointestinal tract. In direct contrast, extrinsic allergic disorders of the skin and respiratory system are frequently encountered in clinical practice. This may not represent the true picture, as the gastrointestinal symptoms are often vague and nondiscriminatory, whilst study of the target organ is limited by poor accessibility. Studies demonstrating a positive response to elimination diets and DSCG support the role of a ‘food hypersensitivity’ reaction in irritable bowel syndrome. The increased prevalence of atopic conditions seen in diarrhoea-predominant irritable bowel syndrome patients suggests the presence of a generalized immune hypersensitivity state. Similarly, increased airway responsiveness to inhaled methacholine has been demonstrated in irritable bowel syndrome patients, with no clinical evidence of atopic disease, in comparison to healthy controls or patients with inflammatory bowel disease. An immune-mediated food hypersensitivity response involving IgE and IgG antibodies has been postulated as the underlying mechanism in a proportion of irritable bowel syndrome patients.

**IgE MEDIATED FOOD HYPERSENSITIVITY**

**Immediate phase reaction**

IgE mediated immediate phase reactions involve the release of inflammatory mediators (e.g. histamine) from previously sensitized mast cells (Table 2). This results in increased vascular permeability, smooth muscle contraction and the classical weal and flare response. A similar mechanism may be involved in the mucosal hypersensitivity reaction. Food antigen induced degranulation of mast cells has been demonstrated both *in vitro* and *in vivo* in the rat intestine, with perturbation of both mucosal secretory and motor function. A similar immediate phase response has been demonstrated in food-induced perennial rhinitis, atopic dermatitis, urticaria, and in some cases of food-induced systemic anaphylaxis in humans. However, there is little evidence that an immediate phase reaction plays a role in the pathogenesis of irritable bowel syndrome.

**Delayed phase reaction**

Degranulation of mast cells releases a variety of immunomodulators and pro-inflammatory agents. These promote the migration and activation of granulocytes, lymphocytes and monocytes/macrophages, resulting in a more protracted hypersensitivity response, with the subsequent release of inflammatory and cytotoxic mediators (Table 2). The role of IgE-mediated delayed phase reaction in asthma and atopic eczema is well recognized. It has been suggested that similar mechanisms are involved in intestinal mucosa of humans causing symptoms of food allergy.

**Evidence for IgE mediated food hypersensitivity in irritable bowel syndrome**

In several studies, skin prick tests and total serum IgE and food specific IgE (RAST) levels have been evaluated as markers of food hypersensitivity. Zwetchkenbaum *et al.* evaluated 10 irritable bowel syndrome patients using a skin prick test to common food antigens. None of the six patients who had a positive skin prick test reacted to dietary challenge following a period of open elimination diet. Petitpierre *et al.* evaluated total serum IgE titres, skin prick test and RAST test to various food antigens in 24 irritable bowel syndrome patients (12 atopic and 12 nonatopic). All patients underwent 3 weeks of dietary elimination followed by open challenge and the responders underwent blind dietary provocation. The total serum IgE levels were elevated in 9/12 atopic and 0/12 nonatopic individuals.

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<th>Onset and duration</th>
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<td>Immediate phase reaction</td>
<td>Develops in minutes and abates within 0.5–1 h</td>
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<td>Delayed phase reaction</td>
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This correlated well with clinical evidence of food allergy. The skin prick test was positive for 46 antigens in atopic patients and for five antigens in nonatopic individuals, but a positive correlation to blind dietary challenge was seen in response to only 18 of these antigens. A positive RAST test to 12 food allergens was seen in atopic individuals, which correlated to dietary manipulation in 10 instances. None of the nonatopic individuals had a positive RAST test. Barau et al. demonstrated increased intestinal permeability to food challenge in 9/17 children with irritable bowel syndrome. All of these children had personal and/or family history of allergy and/or raised total serum IgE levels. These observations suggest that irritable bowel syndrome symptoms in atopic individuals may be mediated by an IgE hypersensitivity reaction.

An IgE response to dietary antigens may be localized to the bowel mucosa and may therefore not correlate with serum levels of the antibody. An increased IgE excretion is seen in the faeces of children with evidence of gastrointestinal allergy, which does not correlate to total serum IgE levels. Andre et al. showed increased Fc fragment of IgE in faecal extracts of 236/312 patients who had food hypersensitivity based on history, positive skin prick test and RAST test, whilst all of the 95 healthy subjects had undetectable faecal IgE. In a subgroup analysis, 22/32 (68.8%) irritable bowel syndrome patients were found to have detectable faecal IgE fragments. The possibility that extravasation of IgE antibody from the serum was responsible for these findings was excluded by the simultaneous measurement of alpha-1-antitrypsin in the serum and faeces. The clinical implication of these findings has not been evaluated further and the role of IgE-based diagnostic tests remains to be determined.

Colonscopic allergen provocation test (COLAP test)

The COLAP test is a novel technique to assess mucosal evidence of food hypersensitivity in vivo. The basis of this test is the submucosal injection of ‘extracts’ of suspected foodstuffs and the subsequent measurement of the resulting weal and flare response. This permits a semiquantitative assessment of a food hypersensitivity response at the level of the target organ. In a study of 70 patients with chronic abdominal symptoms and suspected food allergy, Bischoff et al. reported a positive COLAP test in 77% (54/70), of which 74% (39/53) had a putative diagnosis of irritable bowel syndrome.

Biopsies taken from the site of the response in test-positive patients demonstrated both mast cell and eosinophil activation. Following the dietary elimination of suspected food agents in COLAP positive patients, 83% (29/35) reported a significant clinical improvement after 3 months. Interestingly, there was a strong relationship between the COLAP result and a history of food intolerance (P < 0.02), with a reported concordance of 56% (42 positive for both and 75 negative for both). On the other hand, the relationship between COLAP result, skin prick test and specific serum IgE levels was poor. The test was negative in response to 42% of antigens to which patients had significant IgE levels. Conversely, 40% of food antigens, against which IgE were not detected, induced a positive mucosal response. None of the five normal controls had a positive response to any antigen.

Whilst irritable bowel syndrome patients were not evaluated as a specific group, the findings of the Bischoff study suggest a possible role of food hypersensitivity in irritable bowel syndrome patients. Clearly, prospective studies are needed to confirm the relevance of these observations in irritable bowel syndrome patients.

IgG mediated food hypersensitivity

The role of IgG and IgA antigliadin antibodies in the management of coeliac disease is well established. Raised IgG levels are seen in patients with asthma, hayfever, eczema and atopic dermatitis. Whilst an IgG antibody mediated immune reaction, especially of the IgG4 subclass, has been suggested in food hypersensitivity, the published data are contradictory. In fact, several studies have suggested that IgG and IgG4 production may be a normal immunological response to dietary antigens.

In healthy infants, there are high titres of IgG antibody to milk and egg proteins which diminish with time. In contrast, atopic children continue to produce IgG (and IgE) antibodies, suggesting an underlying disturbance of immune regulation. Raised titres of IgG4 antibodies have been reported in patients with eczema and asthma caused by milk intolerance. Increased levels of food-specific IgG4 antibodies have also been demonstrated in patients with atopic eczema and respiratory allergy.

It is probable that food hypersensitivity is a heterogeneous condition, and that more than one immunological abnormality may exist. In an individual patient, either

IgG4 or IgE may be the predominant antibody response, and measurement of one or both may be useful in the diagnosis of food allergy. Awazuhara et al. studied antibody responses in patients with atopic dermatitis and/or bronchial asthma caused by soyabean hypersensitivity. IgE antibodies of variable reactivity and specificity to different soyabean protein fractions were detected. In addition, strongly reactive IgG4 antibodies were also present in some patients, although these were not necessarily reactive to the same protein as the IgE antibodies. Five patients with strongly reactive IgG4 antibodies produced only weakly reactive IgE antibodies, suggesting a predominant role of IgG4 antibodies. El-Rafie et al. compared specific IgG4 and IgE levels to a double-blind food challenge in 25 patients with a history of food allergy. Raised IgE and IgG4 levels each correlated with a positive history of food hypersensitivity in 63% of patients, whereas the combination of IgE and IgG4 correlated in 91% of patients. Similar results have been reported in other studies. In a double-blind placebo-controlled food challenge study, IgG2 but not IgG4 antibody, was found to be significantly raised in shrimp-sensitive patients. However, these data were not reproduced in a further study.

The role of food specific IgG antibodies or its subclasses has not been evaluated in irritable bowel syndrome and further studies are needed to evaluate the role of IgG antibodies in this disorder.

DELAYED TYPE AND NON-IgE MEDIATED HYPERSENSITIVITY REACTION

Cell-mediated hypersensitivity reactions have been incriminated in food allergic disorders such as coeliac disease and cow milk allergy. There is no evidence to suggest that similar delayed hypersensitivity reactions are involved in the pathogenesis of irritable bowel syndrome. However, a non-IgE mediated release of histamine has been shown in patients with food allergy. This observation supports the possibility of hitherto unidentified immunological mechanisms in food hypersensitivity.

ROLE OF MAST CELLS

In 1962, Hiatt and Katz reported increased numbers of mast cells in the muscular layer of four surgical large bowel specimens of ‘spastic colitis’ (irritable bowel syndrome) patients. More recently, increased numbers of mast cells have been demonstrated in the terminal ileal mucosal biopsies of irritable bowel syndrome patients. Patients with diarrhoea-predominant irritable bowel syndrome were reported to have the highest mean value of terminal ileal mast cells. In another study, Yang et al. demonstrated increased numbers of mast cells closely related to unmyelinated nerves in the lamina propria at the ileo-caecal junction in irritable bowel syndrome patients. Pang et al. reported increased mucosal mast cells in close relationship to substance-P positive nerves, in the bladder and colonic biopsies of a patient with interstitial cystitis and irritable bowel syndrome. These two conditions commonly coexist, indicating a similar and possibly shared pathophysiological mechanism involving an interaction between mast cells and unmyelinated nerves.

Mast cells are capable of secreting numerous inflammatory mediators and bioactive chemicals which can perturb the gastrointestinal sensori-secretomotor function. By virtue of their location and secretory capabilities, mast cells are the ideal candidates to be able to mediate a two-way interaction between the gut immune system and the enteric nervous system. This interface may also modulate the effect of the central nervous system influences (e.g. stress and anxiety) in irritable bowel syndrome. An IgG or IgE-mediated immunological response to food allergens can activate mast cells, which in turn can perturb the enteric nervous system.

ROLE OF GUT MICROBIAL FLORA AND INFECTION IN FOOD HYPERSENSITIVITY AND IRRITABLE BOWEL SYNDROME

There is no clear evidence to suggest that irritable bowel syndrome is an infective condition, but up to 30% of patients develop symptoms after an episode of gastroenteritis. Other workers have demonstrated the association between irritable bowel syndrome and a previous use of antibiotics for infective conditions. A number of possible mechanisms can explain these observations. Infective and inflammatory conditions of the bowel cause an increased mucosal permeability, thereby exposing the immune system to an increased load of dietary and microbial antigens. The concomitant production of a variety of pro-inflammatory and immunomodulatory cytokines may serve to prime the mucosal and submucosal immune system, thereby providing all the necessary ‘ingredients’ for a hypersensitivity
response. It is possible that the gastrointestinal microbial flora may be altered, either by the disease process or following the use of antibiotics. This alteration may modulate the immune system in a number of ways. Altered bowel flora has been reported in patients with irritable bowel syndrome with an increase in the proportion of facultative anaerobes and clostridium species and a decrease in coliforms and lactobacilli. Altered bowel flora has been reported in patients with irritable bowel syndrome with an increase in the proportion of facultative anaerobes and clostridium species and a decrease in coliforms and lactobacilli. Restoration of bowel flora, either by dietary manipulation or by the use of probiotics has been suggested as a treatment for irritable bowel syndrome and other bowel disorders.

STRESS, FOOD HYPERSENSITIVITY AND IRRITABLE BOWEL SYNDROME

Stress has frequently been reported as a precipitant cause of either the onset or relapse of irritable bowel syndrome symptoms. The magnitude of chronic life stress has been shown to correlate with symptomatic outcome in irritable bowel syndrome. The interaction between stress and irritable bowel syndrome in terms of 'help-seeking' behaviour goes beyond a simple modification in patients' illness behaviour. Both acute and chronic life stresses have been shown to affect intestinal motility and sensitivity. The pathogenic
mechanism underlying this brain–gut interaction in irritable bowel syndrome may involve both neural and hormonal pathways. With regard to the latter, corticotropin releasing hormone (CRH) has been shown to perturb bowel motility in animal models. Recently, Fukudo et al. demonstrated an increase in motility indices and symptoms in irritable bowel syndrome patients in response to intravenous CRH.

The mechanisms which initiate and potentiate the sensitization of brain-gut axis are likely to be mediated via the gastrointestinal immune system. It has been shown that stress can either activate or suppress the immune system via the release of various immune mediators and cytokines. Therefore, acute and/or chronic life stresses may induce an abnormal immunological milieu within the gastrointestinal tract, resulting in an inappropriate and exaggerated hypersensitivity response to intraluminal dietary or microbial antigens. This is supported by the observations of Gwee et al., who demonstrated that post-gastroenteritis irritable bowel syndrome patients report more life events and have higher hypochondriasis scores as compared to those who return to a normal bowel pattern. In the same study, irritable bowel syndrome patients also had persistent chronic inflammation on rectal biopsies at 3 months as compared to nonpatients.

Theoretically, the close proximity of mucosal mast cells to enteric neural components provides an interface whereby a primary immunological abnormality of the gut immune system can perturb neural activity within both the enteric and central nervous systems. Subsequent exposure to life stresses can induce an anamnestic response in the gut immune system through this ‘acquired’ association, without the need for a repeat exposure to the causative antigen. This hypothesis has been supported by a number of animal studies. Stress can induce mast cell degranulation in rat colon and small bowel. Using the rat model, MacQueen et al. reported mucosal mast cell degranulation following an audiovisual cue in animals sensitized to ovalbumin injections paired with the sensory stimulus.

CONCLUSIONS

Irritable bowel syndrome affects a large proportion of the general population and it can have a significant effect on quality of life. It carries a huge financial burden, both in terms of utilization of health resources and time lost at work. The inherent diagnostic uncertainty based on symptom criteria alone, the chronicity of the condition and an individual’s illness perception pressurizes the clinician to undertake extensive and often negative investigations. Recently, food hypersensitivity has re-surfaced as a possible approach in the diagnosis and management of many chronic disorders, including irritable bowel syndrome.

Data from dietary elimination and food challenge studies support the role of diet in the pathogenesis of a sub-group of irritable bowel syndrome patients. This hypothesis is supported by the response to disodium cromoglicate in such patients. Mast cells, with their ability to alter various aspects of gut physiology, are emerging as an integral component in this process. Firstly, their close anatomical proximity to the neurones of the Enteric Nervous System makes them ideally suited for this role. Secondly, gut mucosal mast cell degranulation has been observed following direct challenge with food antigen, as an objective measure of food hypersensitivity.

For the first time, a pathophysiological basis for irritable bowel syndrome is beginning to emerge (Figure 1), but further work is needed to advance current understanding of the exact mechanisms by which gastrointestinal immune system handles food and microbial antigens in health and disease. Newer drugs which can modify hypersensitivity response to food need to be developed. However, pending further scientific evidence, a cautious approach is advisable before the concept of food hypersensitivity can find a place in the routine clinical management of the irritable bowel syndrome.

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