Specific food intolerance: its place as a cause of gastrointestinal symptoms

D A FARAH, I CALDER, LOUISE BENSON, AND J F MACKENZIE

From the Gastroenterology Unit and Departments of Pharmacy and Dietetics, Royal Infirmary, Glasgow

SUMMARY Thirteen out of 49 patients suspected of having specific food intolerance after withdrawal and reintroduction of specific foods, were further subjected to double blind placebo controlled food challenges. Only three of these subjects were thus shown to have proven specific food intolerance. Of the remaining 10, nine were strong 'placebo reactors'. The study suggests that a small number of patients with gastrointestinal symptoms have verifiable specific food intolerance but that a greater number have symptoms attributable to psychogenic causes.

Unpleasant reactions attributed to recently ingested foods may be termed specific food intolerance where specific foods are implicated. If an immunological mechanism is subsequently invoked, the term 'food allergy' may justifiably be used.1

Many and varied symptoms have been attributed to such food intolerances by previous workers.2-6 Irritable bowel syndrome, for instance, was recently reported to be largely a manifestation of food intolerance.7 Despite this, and the extravagant claims recently made for food allergy notwithstanding, it is likely that food allergy is an under-diagnosed condition.8 This may, however, be obscured by the exaggerated impression of prevalence gained from studies involving highly selected population samples. Without previous regard to the mechanism involved, we therefore proposed to seek specific food intolerance among patients with unexplained gastrointestinal symptoms.

One of the reasons for the scepticism surrounding the subject of food intolerance is the absence of simple and reliable tests for diagnosis. Double blind food challenges are required to establish diagnosis and a number of techniques using this approach are available. In view of the recognition that food induced symptoms may be delayed9 10 and to ensure, therefore, that chronic food intolerance sufferers with late onset of symptoms were not missed, we used food challenges over one week periods, repeated as necessary if more than one food was suspected. The challenges were double blind and placebo controlled.

Methods

PATIENTS
Over a two year period, the diagnosis of food intolerance was considered in 49 patients who were therefore selected for the study. There were 21 men and 28 women aged 19–55 years with a mean age of 39 years. They had all been referred to the General Medical and Gastroenterology Clinics for gastrointestinal disorders, mainly diarrhoea, nausea, vomiting, and abdominal pain. Detailed but relevant investigation was used to exclude the potential organic causes for their symptoms. Other criteria for inclusion, but present only in a small minority of patients, were a personal or family history of allergy related symptoms and a history of self imposed dietary restriction for the relief of symptoms.

CAPSULES
Identical, opaque, tartrazine free capsules containing 400 mg of either glucose as placebo (placebo capsules) or the test food in a freeze dried form (active capsules) were prepared specifically for each patient. The foods tested were eggs, milk, coffee, orange, and peas as only these were shown as 'provocants' in the first open challenge part of the study (see below). Before patient administration, samples of the capsules were tested blind by the four investigators who took them according to the same protocol as the patients. They all failed to recognise any of the contents.

RAST AND SKIN TESTS
Radioallergosorbent test (RAST), using the method...
Specific food intolerance

of Wide et al, and skin prick tests, using commercially available antigens (Bencard) and with 3 mm wheal accepted as positive, were carried out in the 13 patients who reached the double blind stage of the trial (see below).

Design of trial
A flow chart programme of an elimination diet and stepwise single food reintroduction was adopted as follows (Figure): a low allergenicity diet was prescribed for two weeks. This strictly excluded all potentially allergenic foods, allowing only the consumption of the following: rice and rice flour, lamb, bacon, lemons, grapefruit, pineapple, prunes, apricots, carrots, lettuce, potatoes, salt, sugar, vinegar, butter-free margarine, olive, corn and sunflower seed oil. Drinks except for plain water were all disallowed. All but those who reported complete remission of their symptoms on this diet (the 'responders') were excluded. The responders then had their offending foods identified by the single, weekly reintroduction, in an open fashion, of the potentially allergenic foods originally omitted from the low allergenicity diet. Only patients in whom definite offending foods were conclusively identified in this manner proceeded to the next stage of the trial, the double blind challenge. This consisted of the administration, with the patients still on a low allergenicity diet, of active and placebo capsules at a dose of three capsules three times a day one hour before meals. Each set of active and placebo capsules was taken for a full week with a 'rest' week during which no capsules were taken in between. The active capsules contained, for each patient, only the offending food identified in the first, open part of the trial. The order of placebo and active capsule administration was randomised. All symptoms were recorded daily in a diary card and scored, according to severity, on a 0–4 scale. In order to prevent the expectation of a change of symptoms in the second week the patients were told that during each pair of test weeks, they may get the test diets in any of the four possible combinations—that is, active, active; placebo, placebo; active, placebo; placebo, active.

Results

Side effects
The Figure summarises the results. Of 49 patients originally selected as potential sufferers from food intolerance, 36 failed to improve on a low

Figure  Flow chart illustrating format of protocol. The figures in brackets indicate the number of patients at each stage of the study.
allergenicity diet and were therefore excluded from further follow up for the purposes of the study. Five of the 13 responders were eliminated at the next stage of the screening procedure as no specific offending foods could be identified on food reintroduction. The remaining eight patients underwent the double blind challenge. The Table shows the results expressed as active and placebo symptom scores for the eight patients. In order to minimise the incidence of false positive results, we decided at the beginning of the trial to attribute significance only to active scores which were at least twice the placebo scores. Only three patients satisfied this criterion and they were therefore accepted as sufferers from specific food intolerance. One of these (RE) was sensitive to eggs, one (KA) to peas and the other (RB) to coffee. Their symptoms varied: RE had abdominal pain and diarrhoea, KA complained of rash, irritability and diarrhoea and RB mostly suffered from nausea and diarrhoea. One patient (WM) achieved a slightly higher active than placebo score but this was not deemed significant. The rest were designated as placebo reactors.

Valid conclusions can obviously only be drawn from the comparison of placebo and active scores but scores during the rest weeks were also of some interest. Rest scores in the three food intolerance sufferers largely paralleled the placebo scores but with a tendency for them to be lower. Unlike the placebo reactors, moreover, there was no random week-to-week alteration of scores for these three patients as they achieved consistently higher figures for each of the individual active weeks when compared with the placebo and rest weeks.

**RAST AND SKIN TESTS**

These were negative in all 13 patients. It is noteworthy, however, that KA who was shown to be intolerant of peas, reportedly had a positive skin test to peas in the past but we were unable to confirm this.

**Table Symptom scores in the double blind food challenge**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Active score</th>
<th>Placebo score</th>
</tr>
</thead>
<tbody>
<tr>
<td>KA*</td>
<td>63</td>
<td>0</td>
</tr>
<tr>
<td>EB</td>
<td>84</td>
<td>165</td>
</tr>
<tr>
<td>AB*</td>
<td>33</td>
<td>8</td>
</tr>
<tr>
<td>RE*</td>
<td>25</td>
<td>8</td>
</tr>
<tr>
<td>MK</td>
<td>21</td>
<td>23</td>
</tr>
<tr>
<td>WM</td>
<td>68</td>
<td>64</td>
</tr>
<tr>
<td>HP</td>
<td>15</td>
<td>21</td>
</tr>
<tr>
<td>MS</td>
<td>0</td>
<td>8</td>
</tr>
</tbody>
</table>

* Positive response accepted as diagnostic of specific food intolerance.

**PATIENT FOLLOW UP**

The eight patients who reached the stage of double blind food challenge have now been followed up for between six and 18 months after the completion of the trial. All three specific food intolerance sufferers remain well and symptom free on diets excluding the offending foods. WM, on his own initiative, went on a high fibre diet with a consequent amelioration of symptoms. Of the placebo reactors, one patient continues to avoid eggs blaming them, with little objective evidence and despite uncertain results, for all her symptoms. The remaining three placebo reactors have been advised to resume normal diets. There has been no alteration in their presenting complaints.

**Discussion**

Food intolerance is probably a significantly under-diagnosed condition. Recent questionnaire based epidemiological surveys have suggested prevalence rates of 16–33%, although these figures would have been substantially reduced if confirmatory tests were used for definitive diagnosis. The issue has, however, been greatly clouded by extravagant claims which have only served to arouse scepticism. A further complication has been the paucity of simple and reliable tests for establishing the diagnosis. A number of investigative techniques are used for the diagnosis of food allergy. These include skin tests, RAST, basophil histamine test, leukocyte cytotoxic test, and sublingual skin provocation tests. Only the first two have proven their worth in the field although the sheer profusion of tests is a testimony to the reality that they too have shortcomings. We have found RAST and skin tests unhelpful in the diagnosis of specific food intolerance in our patients. We have, however, shown the diagnostic role of placebo controlled, double blind food challenge. Food and placebo during the food challenge may be administered within capsules, through a nasogastric tube or as part of a flavoured meal designed to disguise their taste. We chose the first method as the last two have limitations. The nasogastric method renders the investigation of nausea difficult and is, moreover, unsuitable for the detection of reactions delayed for, say, 48 hours or more. As for the last method, there is always the risk that the disguised food may be recognised, either by taste or smell.

The positive diagnostic yield in our study (6%) is substantially lower than figures quoted (25–30%) in previous reports. This must be largely because of patient selection although the limited test dose used in this study may be relevant. The subjects in earlier reports had been referred, mostly to allergy
clinics, with symptoms strongly suggestive of food sensitivity. By contrast, the major criterion for inclusion into our study was the presence of unexplained gastrointestinal disturbances, although a minority of our patients had other features, such as asthma and rhinitis, suggestive of an allergic aetiology. Direct comparison is, therefore, inappropriate but if this discrepancy in patient selection is adjusted for by considering the group of 13 patients in whom elimination diets and food reintroduction suggested a higher probability of food sensitivity, a more comparable figure of 23% is obtained. This would confirm the previous views that the positive yield from double blind food challenges in this condition is in the order of 25%.25 26 The same argument about patient selection is to a certain extent also applicable to the study of Jones et al who showed specific food intolerance in 14 out of 21 patients with the irritable bowel syndrome.7 These patients obviously comprised a more homogenous sample than ours but it is perhaps of more interest that nine out of the 14 were sensitive to wheat which, though not included in our repertoire of test diets, is a recognised inducer of gastrointestinal disturbances in susceptible individuals.27 28 Wheat was unlikely to have been an important cause of symptoms in our patients as this possibility was specifically excluded in the first part of the trial when they were all challenged openly with wheat based foods.

The relevance of the test dose is less easy to assess. In immunologically mediated food allergy, the size of the test dose is probably not crucial. In other forms of food intolerance, however, it may be critical. In the case of the capsule method, it has been suggested that if no reactions are elicited with small test doses, these should be increased in a stepwise fashion until a total dose of 8 g is reached.29 30 The daily test dose in our patients was a relatively modest 3-6 g and the cumulative weekly dose 25-2 g. We felt that this repeated and prolonged challenge was particularly appropriate as it would ensure the detection of these patients with delayed reactions and would minimise variables such as mood, psychological stress, and exercise which has been reported to influence response to food challenge.31 Nevertheless, the possibility still remains that some genuine sufferers from food intolerance might have slipped through the diagnostic net because of insufficient challenge dose. It was, however, felt that at this relatively early stage in the art of food intolerance diagnosis, it was a small price to pay in the quest for a method which avoids the potentially greater risks of over-diagnosis. It is conceivable that the capsule method lends itself better to the investigation of food allergy rather than food intolerance for which methods capable of delivering large test doses – for example, nasogastric intubation, may be more suitable.

Our insistence, as a diagnostic criterion, on a two-fold increase in the active as compared with placebo scores was also prompted by the desire to keep false positive responses to a minimum. Because of the prolonged nature of the food challenge, we deemed it unreasonable to expect zero placebo scores in a test situation where a variety of extraneous factors may help to provoke minor symptoms.

This study confirms Lessof's view that most forms of food reactions are due to causes, largely psychogenic, other than genuine specific food intolerance.32 It shows that specific food intolerance is a clinical entity which should be considered and sought in patients with unexplained gastrointestinal symptoms although the positive diagnostic yield among such a heterogenous population is likely to be low. Finally, it emphasises the need, recently stressed by May,24 for rigorous, placebo controlled food challenges for diagnosis if this condition is to be saved from falling into clinical disrepute.

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References


7 Jones VA, McLaughlan P, Shorthouse M, Workman...
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D A Farah, I Calder, L Benson and J F MacKenzie

Gut 1985 26: 164-168
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