Food allergy — fact or fiction: a review

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Summary

Food sensitivity is a common condition presenting with various clinical syndromes including migraine, urticaria, gluten enteropathy, Crohn's disease and irritable bowel syndrome. It is a heterogeneous condition affecting different organ systems and is also aetiologically diverse with subgroups due to allergy, pharmacological reactions, enzyme deficiencies and psychological causes. Clinical acceptance of food sensitivity has been delayed by the use of dubious diagnostic techniques by a minority of practitioners and the lack of laboratory diagnostic tests, but several double blind studies have now fully validated the existence of food sensitivity syndromes. More widespread recognition of food sensitivity would be cost effective for the National Health Service.

Introduction

The question 'Food Allergy - Fact or Fiction' was originally raised by Finn and Cohen in 1978. This article received extensive publicity and led to widespread public interest. More than 12 years have elapsed and food allergy continues to generate much public interest and medical scepticism. The question, therefore, arises as to why more than a decade later, food allergy still remains a controversial subject despite a major report from The Royal College of Physicians entitled 'Food Intolerance and Food Aversion'. This article explores the reasons for this situation and assesses the current state of knowledge in this field.

Diagnostic methods

Undoubtedly some of the techniques used to 'diagnose' food allergy in the last decade have done much to bring the subject and its practitioners into disrepute. Methods used have included symptom provocation by food extracts, hair analysis, dowsing, cytotoxic testing and various electrical methods including the Vega machine. None of these methods has been validated and most are scarcely credible. Patients who had previously seen a clinical ecologist and subsequently consulted an allergist might describe having been tested with one of these methods, and this has the effect of alienating the physician to the whole subject of food allergy. These techniques are mainly used by lay practitioners, but unfortunately a small number of medical practitioners have used similar methods.

An unfortunate side effect consequent on the use of these false diagnostic methods is the phenomenon of 'guilt by association' which to some degree affects all of those working in food allergy and to some extent general allergy, and tends to discourage young men from entering this field.

The only accepted method of diagnosis is an elimination diet followed by test reintroduction of foods. Practitioners of food allergy must restrict their diagnostic methods to those that are accepted and have a reasonable theoretical basis, if their subject is to escape the controversy that has surrounded it in the last decade. Elimination diets are troublesome and tedious and a continued search for more acceptable diagnostic methods must continue. Intradermal testing deserves further study and validation. It is a variation of the classic prick test which is only of value in IgE food allergies. Food antigens are injected intradermally and growth of the wheal over 10 min is defined as a positive reaction. It is an objective test which does not lend itself to placebo responses. It is used by many physicians particularly in the United States, and merits further validation, but at the present time, despite several trials, it has to be regarded as non-proven.

Scientific studies

In the past decade scientific studies have been carried out which should reduce the credibility gap for food allergy as a genuine clinical phenomenon.

Acute allergic reactions to such foods as eggs, nuts and shell fish are well recognized by appropriate diagnostic methods such as prick tests and RAST and have an accepted mechanism involving IgE antibody. These reactions are easily diagnosed by the patient himself and are uncommon. The problem is whether there are other food-related immunological conditions mediated by other immunoglobulins (IgG and IgA), immune complexes or cellular mechanisms.

Food allergy is common in paediatric practice with an incidence of up to 7%. This may be due to a poorly developed mucosal barrier in infants which normally protects against food antigens. Bovine serum albumin absorption from the gut is increased by achlorhydria and gastric acid is low in infants. Food antigens are complexed to secretory IgA in the gut and this limits absorption, and it is, therefore, significant that IgA levels in serum and gut are reduced in infancy. The extensive gut associated immune system is, however, continuously exposed to food antigens, but most produce oral tolerance induced by suppressor T cells derived from Peyer's Patches. Nevertheless IgG food antibodies are regularly found in adults. Our group has worked with ovalbumen, casein and lactalbumen and has established that the relevant IgG antibodies are commonly found in normal adults. The frequency of these antibodies is slightly increased in classical allergic conditions including eczema, but there is no definite evidence that these antibodies cause disease. Nevertheless, despite oral tolerance there is now no doubt that immunological reaction to foods as shown by the production of IgG antibodies is a common phenomenon.
Coeliac disease is an immunological reaction to gluten and there is a lymphoid infiltration of the intestinal mucosa with villous atrophy. Circulating IgA antibodies to gliadin can often be demonstrated. Possibly due to damage to the barrier function of the intestinal wall the frequency of other IgG food antibodies is increased. Milk allergy in infants causes diarrhoea with patchy areas of villous atrophy and some lymphoid infiltration. A protocollitis with bloody diarrhoea, eosinophilic infiltration and crypt abscesses is described. Milk allergy can cause rhinorrhoa and sneezing and Heiner’s syndrome comprises recurrent pneumonia, pulmonary haemosiderosis, anaemia, failure to thrive and intestinal blood loss. Milk allergy can also cause urticaria and atopic dermatitis. Breast-fed infants with milk allergy improve when the mother avoids milk.

These conditions are usually transient and most infants will usually tolerate milk by one year.

It is generally accepted that food allergy defined as an immunologically mediated clinical syndrome that develops after the ingestion of a dietary product is less common in adults. Gluten enteropathy occurs in adults and the recent finding that IgA antibodies to baker’s and brewer’s yeast are found in Crohn’s disease, but not in ulcerative colitis or normal controls raises the possibility that Crohn’s disease may also be an allergic condition. Food allergy is not a common cause of adult rhinitis, asthma or eczema, but occasional cases respond to an elimination diet.

It has to be concluded that there is a gap between the experimental evidence and the claim that food allergy is common in adults. Well controlled clinical trials have, however, shown that elimination diets can be helpful in irritable bowel syndrome, Crohn’s disease, migraine, hyperkinesis and rheumatoid arthritis but this does not constitute evidence that these conditions are due to food allergy, rather than some other food-related reaction.

Terminology
Academic acceptance of the reality of food allergy has been delayed because of the blanket use by some practitioners of the term ‘Food allergy’ to cover all food-related reactions. The subject was clarified by the Royal College Physicians report on ‘Food Intolerance and Food Aversion’ which divided food reactions into defined aetiological groups. Food intolerance has been suggested as a general term to cover all types of reaction, but food sensitivity is probably preferable as food intolerance does not emphasize the critical fact that only a small number of sensitive subjects will develop food reactions.

Classification of food sensitivity
This classification of food sensitivity is based on the Royal College of Physicians Report:

**Food allergy**
Acute IgE mediated reactions are uncommon, but would include allergy to shellfish, eggs and nuts. They are usually acute urticarial or gastrointestinal reactions, but can, particularly with peanuts, cause fatal anaphylaxis. Non-IgE food allergy includes gluten enteropathy and possibly Crohn’s disease. Ecema, urticaria, asthma and rhinitis are occasionally due to food allergy in adults. There is little evidence that food allergy is responsible for other diseases, but this area requires further study. The gut associated immune system comprises the largest single collection of lymphocytes in the body and the potential must exist for other diseases caused by as yet unrecognized food induced immunological reactions. IgA nephropathy and gut associated arthropathies are possible candidates.

**Pharmacological reactions**
Certain foods, particularly those containing caffeine produce pharmacological reactions if taken in excessive quantities. Thus coffee, tea and cola can produce headaches, palpitations and anxiety in subjects predisposed to these symptoms. Headaches are particularly produced by caffeine withdrawal which may be a factor in weekend migraine, when the amount of coffee taken regularly at work is suddenly reduced. Other reactive amines such as tyramine in cheese, phenylethylamine in chocolate and octopamine in citrus fruits can exacerbate migraine.

Aspirin and salicylates in foods such as fruits can induce urticaria, rhinitis, nasal polyps and asthma in susceptible subjects. Aspirin causes a pseudo-allergic reaction by inhibiting the cyclo oxygenase enzyme leading to inhibition of prostaglandin formation. Certain food additives such as tartrazine, benzoate and ascorbic acid act in a similar fashion and can produce pseudo-allergic symptoms. These additives act synergistically and thus the effects of diet on symptoms are very variable, and testing of single substances may be misleading. Certain colouring agents and salicylates can cause hyperactivity in children, but the mechanism is obscure.

The syndrome of cyclical oedema with mental symptoms of fatigue and irritability is often mistaken for allergic angioedema. It almost invariably occurs in women on long-term diuretics who vary their food intake considerably with periods of partial fasting followed by binging on foods high in sodium and carbohydrate. Sodium retention following a large carbohydrate intake is well documented. Stopping diuretics and avoiding carbohydrate binges is usually effective, although the oedema is often worse for a short period.

**Partial enzyme deficiencies**
Lactase deficiency which is to some extent dose dependant can cause intestinal disorders. Poor sulphoxidation is common in subjects with food reactions and G-6-PD deficiency is associated with haemolytic anaemia caused by fava beans. It is likely that partial enzyme deficiencies will be shown to be an important cause of food sensitivity and further work in this area is indicated.

**Psychological reactions**
Psychological reactions include anorexia nervosa and bulimia.

It is now evident that food allergy is responsible for only a proportion of patients with food sensitivity. Pharmacological reactions are probably more common, and further work may show that partial enzyme deficiencies constitute the most important cause of food sensitivity.

**Diagnosis**
The only proven method of diagnosing food sensitivity is by elimination diet and challenge. An elimination
diet consists of a small number of safe foods which clinical experience has shown rarely produce reactions. Typical diets would exclude additives and salicylates; or the main food allergens such as milk, eggs and wheat. Alternatively a synthetic elemental diet can be used. The diet is given for about 10 days. Withdrawal symptoms may occur in the first 3 days, but the patient should be free of symptoms within 10 days. If symptoms persist, food sensitivity as a cause of the patients symptoms can be excluded and the patient should be informed of this fact and returned to a normal diet. If symptoms are relieved the omitted foods are reintroduced to the diet sequentially to determine which produce the initial symptoms. The rate of reintroduction is usually one food every 24 hours. If no reaction is produced the food is returned to the diet. A strong reaction may take several days to settle and further testing should be delayed. After avoiding a food for about 10 days, sensitivity is increased and a genuine reaction is usually very obvious.

Elimination dieting is tedious and requires enthusiasm by both patient and physician. Thus it should only be considered for severe, incapacitating and intractable symptoms which have failed to respond to other therapy. With minor symptoms the treatment is worse than the disease and patient compliance understandably is poor. With severe intractable symptoms the patient is usually only too anxious to attempt anything to obtain relief, and in these circumstances there is rarely anything less than total co-operation. Conversely the physician should be enthusiastic and knowledgeable and hence physicians who use the technique only occasionally and with some scepticism are less likely to be successful. This raises a logistic problem as to who should manage food sensitivity. As the symptoms of food sensitivity can affect many organ systems the appropriate specialist is a possibility, but they usually lack the clinical experience or interest to master a difficult clinical technique. Allergists are often only willing to treat specific IgE food allergy, which, as has been indicated only accounts for a small proportion of cases of food sensitivity; furthermore there are few allergists in the NHS, which has forced many patients into an uncontrolled private sector.

Elimination dieting is tedious and the search continues for objective laboratory tests for food sensitivity. It should be realized that no single test is possible as there are many different causes of food sensitivity. Acute IgE reactions can be confirmed by skin testing and RAST, but no reliable tests are available for non-IgE allergy. IgG and IgA antibodies to various foods can be detected11-16, but they do not correlate closely with symptoms. Intradermal testing has been used by some physicians38 but has not yet been fully validated. It is likely that investigations will become available to identify partial enzyme deficiencies leading to difficulty in handling certain foods, but these are now only available on an experimental basis.

The lack of objective laboratory tests has undoubtedly delayed the acceptance of food sensitivity as a genuine clinical phenomenon, and this has been compounded by the use of less than credible techniques by some alternative practitioners. Thus the diagnosis of food sensitivity remains dependant on clinical rather than laboratory methods, but it should be emphasized that this situation also applies in other specialties. There are no objective laboratory tests for various psychiatric disorders such as schizophrenia, but no one would doubt that they exist as genuine clinical entities.

**Treatment**

The treatment of food sensitivity is exclusion. Acute IgE sensitivities are permanent but do not present a problem as they usually only involve a single food. Allergy to dairy products or cereals involves avoiding a group of foods, but suitable alternatives can be advised. Many other forms of sensitivity are dose-related and simply reducing the quantity of a food eaten repetitively and to excess is often effective. This applies to most pharmacological reactions. Other food sensitivities are transient and will resolve after a short period on an elimination diet. Patients who claim to be allergic to multiple foods should be tested under double blind conditions as the problem is often psychological. Attempts to desensitize to foods have been made, particularly with low dosage regimens, but these methods require further validation39.

**Food sensitive conditions**

How important is food sensitivity in clinical medicine? Is the diagnosis of food sensitivity only helpful in a few rare cases or does it have wider relevance? Double blind studies36-30 in migraine, irritable bowel syndrome, Crohn's disease and rheumatoid arthritis have shown that food sensitivity does exist as a genuine entity.

In order to determine the spectrum of conditions due to Food Sensitivity a successful result has been defined as at least 70% improvement in symptoms using a visual analogue scale. To exclude a placebo effect which is usually transient the improvement had to be maintained for at least 6 months. Over the last decade a record has been kept of over 300 highly successful cases fulfilling these criteria and from this data it is now possible to state which conditions are likely to respond to dietary management (Table 1). It should be pointed out that many of these cases had been ill for many years and had seen several physicians, before seeking treatment for food sensitivity. Migraine occurs in 10% of the population and is severe in 1% causing much morbidity and loss of time from work comparable with industrial action. Severe irritable bowel syndrome probably occurs at about the same frequency, and is also responsible for much morbidity and cost due to repeated clinical investigations. If one simply considers

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<th>Table 1. Food sensitive conditions</th>
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<th>Group A</th>
<th>Group B</th>
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<tr>
<td>Headache including migraine</td>
<td>Asthma</td>
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<tr>
<td>Irritable bowel syndrome</td>
<td>Eczema</td>
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<tr>
<td>Urticaria and angio-oedema</td>
<td>Rheumatoid arthritis</td>
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<td>Crohn's disease</td>
<td>Rhinitis</td>
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<td>Gluten enteropathy</td>
<td>Hyperactivity</td>
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<td></td>
<td>Anxiety and depression</td>
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<td>Aphthous ulcers</td>
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In group A, food sensitivity is a common cause of the conditions listed, and at least 50% will improve with elimination diets. In group B, food sensitivity is a less common cause of the conditions listed, and the success rate with elimination diets is lower.
these two conditions, at least 2% or 100 000 of the UK population have a major food sensitivity which might be amenable to fairly simple dietary modification. It may, therefore, be concluded that food sensitivity is clinically important, and should be considered in intractable cases of the conditions shown in Table 1, when other methods of treatment have failed. It should also be emphasized that successful treatment of these cases would be highly cost effective to the NHS by preventing further morbidity and expensive investigations.

Short and long term reactions
By definition food sensitivity reactions occur acutely and can be reversed within a week by avoidance of the particular food or additive. These reactions, which are the subject of this review should be clearly distinguished from those that take longer to produce symptoms. Thus diet may produce heart disease and hypertension in genetically susceptible individuals with an incubation period of several decades, comparable to the tobacco induction of bronchial carcinoma. Subjects with motor neurone disease may have poor sulphur oxidizing and conjugating enzymes40, and this could make them sensitive to a food component or toxin over a prolonged period. There are more than half a million natural compounds in plant foods, and there is a suspicion that some may have long-term side effects in man41.

Food components or toxins could therefore be of considerable importance in late onset degenerative diseases, but by definition this is distinct from food sensitivity which is a more acute and reversible process.

Conclusions
Ten years on, the question posed in the original article 'Food Allergy - Fact or Fiction' can be answered in the affirmative, with the proviso that food sensitivity would be a better general description of the clinical phenomenon. Many patients with otherwise refractory symptoms can be helped by relatively limited dietary manipulation.

The scepticism associated with this subject has led to its rejection by many in the academic community, and this in turn has restricted research. The use of frankly dubious techniques by a small number of alternative practitioners, should not be allowed to negate the work of serious clinicians and investigators in this field. A more liberal view by the academic community could lead to the opening up of an important area of clinical science.

Finally, who should manage patients with food sensitivity? At the present time there are minimal facilities within the NHS and many patients are forced into an uncontrolled private sector. Perhaps clinical allergists should widen their horizon from IgE reactions and also accept responsibility for the management of food sensitivity in its broad sense.

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